UNIVERSITAT DE BARCELONA

Consecuencias psicológicas y neurobiológicas del maltrato infantil: alteraciones neuroendocrinas en la regulación del estrés e implicaciones en la salud mental infantojuvenil

Psychological and neurobiological consequences of childhood maltreatment: neuroendocrine alterations in stress regulation and implications for child and adolescent mental health

Laia Marqués Feixa

Consecuencias **psicológicas** y **neurobiológicas** del **maltrato infantil:**

alteraciones neuroendocrinas en la regulación del estrés e implicaciones en la salud mental infantojuvenil

Tesis doctoral **Laia Marqués Feixa**

Consecuencias psicológicas y neurobiológicas del maltrato infantil: alteraciones neuroendocrinas en la regulación del estrés e implicaciones en la salud mental infantojuvenil

Psychological and neurobiological consequences of childhood maltreatment: neuroendocrine alterations in stress regulation and implications for child and adolescent mental health

Memoria presentada por
Laia Marqués Feixa

Para optar al grado de
Doctora por la Universidad de Barcelona

Barcelona, abril del 2022

Programa de Doctorado en Biomedicina - Neurociencias
Departamento de Biología Evolutiva, Ecología y Ciencias Ambientales
Facultad de Biología, Universidad de Barcelona

Directora y tutora	Co-director	Doctoranda
Lourdes Fañanás Saura	Jorge Moya Higueras	Laia Marquès Feixa
Catedrática UB	Profesor titular UdL	Investigadora predoctoral UB

"It is easier to build strong children than to repair broken men"

-Frederick Douglass-

"Quizás olvidaré lo que has hecho, quizás olvidaré lo que has dicho,
pero nunca olvidaré cómo me has hecho sentir"
–Maya Angelou-

"Para educar a un niño hace falta la tribu entera"

-Proverbio Africano-

"Si nadie lo ve, nadie lo sabe. Si nadie lo sabe todos lo ocultan.
Si todos lo ocultan, nadie lo ve. Y así, es como nace el tabú."

Agradecimientos

Sembla impossible que aquest moment hagi arribat. Sento l'impuls i la necessitat d'agrair a moltíssimes persones que han format part d'aquest període de la meva vida. Sento que tanca una etapa important com a "estudiant" i marca el principi d'un altre cicle. Tant de bo que aquesta tesi no només aporti coneixement científic, sinó que pugui fer reflexionar i donar suport a persones que treballen al seu dia a dia amb persones víctimes de violència i, en última instància, aporti un gra d'arena més a l'evidència científica a la qual aferrar-se perquè es promoguin canvis de transformació política i social, on el benestar dels infants sigui realment una prioritat.

M'agradaria començar compartint el profund agraïment i admiració que sento cap a tots els nens, nenes i adolescents que han participat en l'estudi Epi_young_stress (que sento com un fillet meu). Heu sigut sens dubte el motor que en moments d'indecisió m'ha fet seguir. Gràcies a vosaltres (i a la vostra família) per la generositat i entrega, per obrir-vos i deixar-me entrar en moments tan vulnerables de les vostres vides. M'heu fet sentir una gran gamma d'emocions que m'han ajudat a créixer molt personalment i professionalment. M'heu fet connectar i replantejar amb els valors i els perquès més profunds de l'existència humana. A la vegada que m'heu fet connectar amb una part de mi que em dona llum i m'il·lusiona, recordant-me que el món de la infància i l'adolescència és meravellós. Veure les ganes i la disposició que teníeu en explicar les vostres experiències, em fa reafirmar que no sou prou escoltats. I que necessiteu persones que us preguntin sobre els vostres fantasmes i el vostre món intern, més enllà dels símptomes que expresseu i que sovint s'emporten el protagonisme. De vegades penso en vosaltres i en com deveu estar. Espero que estigueu bé i confiant en la vida, tot i que sé que no és fàcil.

Lourdes, toda esta aventura no hubiera existido sin ti. Apareciste en un momento de mi formación académica donde la inmensidad del mundo intracelular me oprimía, y me recordaste que en el mundo Neurocientífico también hay lugar para una investigación a escala más humana. Creo que todos los que hemos sido alumnos tuyos aprendemos una gran lección; lo más importante es hacerse buenas preguntas. A lo largo del doctorado me he dado cuenta de que, en momentos de crisis o saturación, cuando uno se pierde en el caos o en lo concreto, no hay mejor solución que parar y volver al inicio. Conectar con la curiosidad innata de uno mismo y definir esa pregunta. Gracias por esta gran enseñanza que me llevo tanto en el campo científico como personal, porque a partir de ahí pueden suceder cosas mágicas. También quería reconocer la inmensa confianza que siempre has depositado en mí, en todos los sentidos. Siento que siempre has tenido una mirada muy positiva hacia mí, y has sido muy generosa a la hora de presentarme al mundo científico, favoreciendo siempre mi inquietud para divulgar la ciencia. También agradezco la oportunidad que nos has dado de viajar e ir a tantos congresos y cursos. Sin duda, son alicientes que nos cargan las pilas a lo largo de esta etapa tan intensa.

Jorge, em va fer molta il·lusió saber que podria compartir amb tu aquesta nova etapa de la meva formació acadèmica. Encara que hàgim connectat des de la distància, infinites gràcies

per posar llum al meu caos en moments clau. Després de les trobades amb tu sempre he sortit amb una espurna d'il·lusió, sentint com la meva energia es focalitzava de nou i podia seguir encaminada amb un propòsit clar. Tant de bo haver pogut compartir i aprendre més de tu. Com ja ens vas demostrar com a professor de la primera promoció de Psicologia de Lleida, gràcies per la teva proximitat, naturalitat, eficiència i capacitat resolutiva.

I sobretot volia agrair-vos-ho a vosaltres, a tots els companys i companyes. Una embarcada com aquesta hagués estat impossible sense una bona tribu al meu costat. Molts de vosaltres vau començar sent companys de feina, però heu acabat sent amics i amigues que estic segura que ens acompanyarem en moltes més aventures de la vida.

Recordo que quan vaig entrar al grup era un pou de dubtes i vaig agrair infinit la teva rebuda Anna. Amb la teva energia, les teves anècdotes i sempre disposada a ajudar amb el que fes falta. La mare lleona que ens protegia i cuidava amb entrega. Gràcies per ajudar a tirar endavant els inicis del projecte (havent-te de saltar els teus horaris i rutines tan apreciades). També a tu Helen, que has estat una peça imprescindible en el meu doctorat. Gràcies per recordar-nos què és la passió per la ciència i la il·lusió que hi pot haver darrere d'un "paper". Sempre et recordaré com la postdoc que m'ha donat temps per pensar, per tenir dubtes, debatre obertament i posar solucions eficaces i rigoroses als problemes. Tant de bo t'haguéssim pogut tenir més a prop en aquesta última etapa. Tot i això, encara que estiguis a milers de kilòmetres, continues sent un pilar científic i de referència per a nosaltres. Arribaràs on vulguis si t'ho proposes (però t'ho has de proposar, i posar data!). La pandèmia ha fet que finalment no hagi pogut realitzar l'estada a USA amb tu, però qui si sap si et vindré a fer una visita. També gràcies a vosaltres, Ma José i Clàudia Pla, per facilitar molts processos durant aquesta etapa. La vostra presència (i paciència) feien les coses més fàcils. I a molts altres predocs que heu format part del departament i hem compartit el nostre dia a dia: Marta, Bya, Miguel, Patri i Aldo.

Si penso en la primera etapa del doctorat, a l'antiga sala, us recordo també a vosaltres. Flowers, quina sort conèixer-nos i poder seguir-ho fent en aquesta etapa de la uni. No podria imaginar els inicis sense tu: cafés, congressos, viatges, nits... Va ser una època realment molt divertida. Vas ser un suport immens i crec que ho continuaràs sent durant molts anys, per la forma en que entenem el món, les persones i la vida. També a tu Clàudia, gràcies per les mirades de complicitat. Per donar-me energia positiva contagiosa en aquelles tardes (quasi nits) a la universitat, ja fos amb una abraçada, una aventura de nenes petites o una filosofada sobre l'existència humana. Gràcies per fer que sense parlar ens puguem dir tantes coses. Ets de les poques persones que només mirant-me ja saps com estic realment. Com tu dius, he de fer sortir la llum que porto dins i amb persones com vosaltres al voltant és molt més fàcil. I a tu "George", el meu company de taula durant molts anys. Sempre amb les coses tan clares, sense complicar-te i anant al gra. Ha sigut un plaer poder compartir amb tu moments tan divertits, sobretot fora de la facultat (per què enganyar-nos): avions, congressos (o més aviat bars, terrasses, nits,

platges...), masies, sopars i *lasertags* per Barcelona. Has estat sens dubte l'organitzador d'esdeveniments del grup! Gràcies també per haver-me apropat a la Natàlia i al Wahi.

Àlex, recordo que quan vas aparèixer al grup vas renovar les energies amb aire fresc, humor i molt amor. M'agrada la capacitat que tens de crear debats i fer replantejar moltes coses a les persones que t'envolten. Gràcies per haver-nos trencat els esquemes moltes vegades i haver-nos regalat noves maneres d'entendre el món. Tant de bo el món de la ciència no funcionés com funciona actualment i haguéssim pogut compartir molt més temps amb tu. Maria, va ser molt guai que poguessis entrar a l'equip. He pogut conèixer-te molt més en aquesta nova etapa i compartir experiències i moments molt còmplices. T'hem trobat a faltar en aquesta última etapa. Gràcies també per les *pijamades* en pandèmia i els caps de setmana dels quatre.

Nora no sé què hagués fet sense el teu suport en aquesta última etapa del doctorat. Ets un exemple de vocació per la ciència, constància i superació personal. Sento que ens hem descobert amb el temps. Ets immensament generosa, i t'he sentit molt a prop fos l'hora que fos, i hi hagués la pandèmia que hi hagués al món. Em sento afortunada d'haver pogut fer un "mano a mano" amb tu en moments on s'havien de fer "clics" molt importants. Gràcies per tot.

I també als que heu format part del que sento la meva segona etapa del doctorat, a la nova sala. A ti Águeda, que has sido un comodín desde que llegaste. Gracias por tu templanza cuando de repente me venía un ataque de saturación y lo veía todo al revés (literal, desde mi pelota yogui). Por tu rigurosidad, paciencia, disposición y tu mirada positiva hacia mí (siendo tu postdoc menos postdoc de la historia). Compartiendo las penas uno se siente menos raro, graciñas. También a ti José Luís, que con tu inmensa generosidad y paciencia nos has acompañado en momentos clave, y con un toque de humor indispensable. Mi tejido adiposo y yo también te agradecemos el millón de galletas y empanadas que han subido el triptófano en momentos de bajón. Gracias a los dos por vuestro trabajazo en el lab, que han hecho posible que hoy pueda presentar parte de esta tesis. Y a ti Nerea, que recién llegada ya estás involucrada en todo. Mil gracias por tu compañerismo y disposición a ayudar siempre en lo que sea, ¡eres un Sol y tus feedbacks me han ayudado mucho en esta recta final!

També us volia agrair a totes les que heu estat al dia a dia al voltant de la nostra "cafetera ecofriendly". Natalia, mi compañera risueña a la hora del café, me encantó la forma tan rápida y natural en la que entraste y te convertiste en una más. Paula és admirable la teva espontaneïtat i bondat. Gràcies per brindar esperança i veure que altres maneres de fer i sentir la ciència són possibles, qualsevol persona et voldria al seu equip. També a vosaltres, Mireia, Alba i Nerea Moreno, que formant-vos com a estudiants a l'equip ens heu ensenyat molt a nosaltres també.

Gràcies a les que esteu més des de la distància, però com a referents i veteranes. Mar, per la confiança que em vas dipositar en el moment de presentar el TFM i convidar-me a venir al grup. Sovint penso on seria ara si no haguessis estat en aquell tribunal. Gràcies per la proximitat que sempre m'has mostrat. A tu Bàrbara, per ser tan transparent, realista i currante.

Per estar disposada a donar un cop de mà quan fes falta. A tu Araceli, per la teva senzillesa, bondat i perseverança. T'estic molt agraïda pel suport emocional en moments clau de l'última etapa, donant-me un toc de realitat amb molta tendresa i confiança: "ara Laia toca fer-se gran, pa'lante". I a tu Marina per la teva energia positiva. Gràcies per seure't al meu costat aquell dia quan l'estadística se'm feia costa amunt. En aquests moments de desesperació tenir algú al costat que t'acompanya s'agraeix moltíssim.

També volia agrair a tots els psiquiatres i psicòlegs implicats en aquest estudi i als infermers, tècnics, residents que s'han involucrat en aquest projecte de manera tan generosa. A tot l'equip de la UCA, i en especial a vosaltres Ma José Muñoz, Maria Martín, Laura Magallón i María Giralt. Gràcies per l'oportunitat de conèixer als nois i noies que ateneu al vostre dia a dia, i descobrir la realitat i la complexitat de l'assistència clínica pública. Eulàlia, infinitament gràcies per aparèixer quan la recerca bàsica em saturava. Gràcies per obrir-me un món de possibilitats amb la teràpia familiar sistèmica. Crec que no n'ets conscient, però gràcies a tu vaig endinsar-me en aquest nou món que ja forma part de mi i de la manera en com entenc la Psicologia infantil. Gràcies per deixar-me aprendre tant de tu, del teu ull clínic i les teves pacients i famílies. Estic segura que més endavant tornarem a compartir espai, no és fàcil trobar professionals amb una mirada tan humana, holística i curiosa com la teva. También al resto de clinicos del Epi_young_stress: Sole, Pilar, Ari, Marisol, Iñaki, Maite, Hilario, Marta, Mireia, etc. En especial, a vosotras, Sole y Pilar, por vuestro apoyo en los artículos finales, trabajar con vosotras da gusto.

Sens dubte, una part important que m'emporto del doctorat és haver pogut donar classes i xarrades. Volia agrair als alumnes del màster en Neurociències i del màster en Psicologia General Sanitària, la seva curiositat. M'heu fet recordar durant aquests anys que ensenyar m'il·lusiona. Que si la ciència es queda als articles científics no serveix de res. I que sovint quan la sindrome de la impostora s'apoderava de mi, el contacte amb vosaltres em feia veure que compartint el que sabia tenia més ganes de saber. També agrair al gran nombre de professionals amb els quals m'he topat en congressos o cursos. Gràcies a tots els que heu tingut curiositat i interès per la feina feta i us heu acostat amb paraules d'elogi i agraïment.

I sobretot, a tots els meus amics, amigues que no enteneu molt bé què és fer el doctorat, però sense entendre-ho m'heu ajudat a connectar i desconnectar. Gràcies per entendre que quan us deia que era una tema tabú, s'havia de deixar de preguntar sobre quan acabaria el doctorat. Paula gràcies per ser-hi sempre, també en els dalts i baixos de l'última etapa del doctorat, on hem conegut una Laia poc habitual. Assegudes al terra d'un rooftop amb vistes a Barcelona, fent un pícnic al parc, amb unes braves a plaça osca, a l'entrada d'un portal plovent o amb àudios de 10 minuts. Si juntes ens n'hem sortit de bronques al director amb tamagochis, autopistes sense tiquet, atacs de riure enmig de classe i la metacognició, ens en podem sortir de tot. També a tu Judith, que des de la distància sempre ens regales paraules d'amor i estima. Elisenda i Paula, gràcies pels sopars entre setmana i els vermuts de diumenge al Sol, que fan que tot sigui més

fàcil. Meri i Núria per la vostra escalfor des de la distància i l'humor amb què ho impregneu tot. Èlia gràcies per tot el suport durant aquests anys, tot descobrint nous racons i activitats per Barcelona. A tu Gonzalo, per contagiar-me la teva energia quan arribava a casa a la nit. Compartir amb vosaltres moments del doctorat i convertir-ho en anècdota fa que sigui alliberador.

Ara semblarà que vagi molt enrere, però gràcies al cau i a tots els que n'heu format part. Allí vaig conèixer i formar part d'una de les millors tribus. Des de ben petita vaig aprendre a confiar, a fer introspecció, a gaudir i a ser curiosa. I ja de gran, vaig descobrir que m'encanta treballar en equip, i que quan les coses es fan amb dedicació i molta il·lusió surten coses màgiques. Gràcies a tots els dinos. També a vosaltres, Ventu, Riki, Pons, Cris, Rai, les escapades junts a la muntanya són per a mi moments especials, que fan que tot es vegi diferent i més fàcil. Gràcies per ser-hi. També gràcies a vosaltres Anaïs, Núria, Miriam, per ser-hi i confiar tant en mi. En aquesta última etapa heu viscut la meva desaparició més que mai, però heu format part de moments importants dels cinc anys que ha durat aquesta aventura, i me'n sento afortunada.

Raqui, ya lo hiciste en Chile, gracias por sembrar semillas en mí y que sea tan fácil regarlas. Te agradezco mucho la oportunidad que me has dado de formar parte de tu proyecto. No sé si eres consciente de las alas y seguridad que entregas a las personas con tu mirada llena de amor y confianza. Aunque estemos con un océano de por medio, gracias a ti y a Pietro por el apoyo en todos los sentidos. También a ti Luis, por tu curiosidad insaciable.

Els que em coneixeu sabeu que tantes hores davant l'ordinador han sigut possible gràcies a les meves "activitats extraescolars". Mario i Javi, no sereu mai prou conscients de com fer-me posar de cap per avall m'ha ajudat tant a trobar l'equilibri. Carola, Jordi, Ana i Marina heu sigut un gran descobriment dels últims anys a Barcelona. Heu celebrat amb mi les petites alegries i feu que tot sigui fàcil, fluid i que valgui la pena. Fer acrobàcies em dona llum i fa que pugui veure les coses molt més clares, i que qualsevol dia acabi amb bon sabor. Laura gràcies per la teva entrega i l'amor amb què fas les coses, m'encanta que la portada d'aquesta tesi estigui feta per tu i fruit d'aquest petit món que ens dona tantes ales. Ets una crack (@lgir23art). També al rugbi i "les cocodriles", que vau permetre que en plena pandèmia, després d'hores asseguda davant la pantalla acabés corrent i gaudint d'aquest esport.

I a tu Sergi, perquè t'estimo com mai hagués imaginat. Gràcies per fer-me descobrir l'amor lliure i sincer. Perquè crec que amb els anys finalment has anat entenent (i vivint en primera pell) què significa la muntanya russa de fer un doctorat. Gràcies per ser el millor company de vida que pogués imaginar. Per fer-me riure com mai. Per treure'm la nena petita que porto dins. Per acompanyar-me en les aventures. Per treure el sac taronja en moments d'excés d'adrenalina. Per acollir tan bé el "knock-knock". Per parlar durant hores sobre la vida, nosaltres i el món. Part del que he après durant l'etapa del doctorat és fruit de les nostres converses on la curiositat ens pot fer divagar durant hores. Gràcies per fer que un confinament

es convertís en una etapa divertida i de felicitat. Gràcies per fer que la vida al teu costat sigui tan fàcil, i jo, sigui tan jo.

A vosaltres família, per ensenyar-me diferents maneres de ser i fer. Per haver-me despertat la curiositat des de ben petita per entendre per què som com som, actuem com actuem i sentim com sentim. Gràcies per haver-me regalat una infància i una adolescència bonica, que han permès que pugui confiar en mi i en la vida. Mare, gràcies per la mirada tan positiva que tens cap a mi, per ensenyar-me sense paraules l'amor a la diversitat, el compromís, la valentia, la solidaritat i la importància de compartir. Pare, gràcies per ensenyar-me a viure al present, a saber gaudir dels petits detalls, i fer les coses des de l'amor i la llibertat. Alba gràcies per tenir aquestes antenes que em detecten a km lluny. Perquè els últims mesos de la tesi m'han permès entendre't molt. I tu m'has pogut entendre molt. Gràcies pels moments de sofà on els minuts es fan hores i fluir ens fa tan bé. No sé què faríem sense els teus ulls que ens veuen a tots tan guapos sempre. Tu, tu ets casa. Maite, Didac gràcies pels diumenges en què fluïm, i sabem com comencen però no com acaben. També a vosaltres Miquel, Pili i Maria per cuidar tant els petits detalls de la vida i estimar tan generosament com ho feu. I a la resta de la família també; àvia, iaia, cosins, Fàtima, Awa, Oudya, Bye, Daouda i altres, per haver-me ensenyat tant, cadascú a la vostra manera.

Tinc clar que la resiliència d'una persona no ve donada per la seva voluntat, sinó per la mirada positiva que rep de la tribu que estima. Si una persona et fa sentir valorada, recolzada i capaç poden passar coses extraordinàries. Per això, part d'aquesta tesi és gràcies a tots vosaltres. Estic profundament agraïda de la tribu on he nascut i de la tribu que he anat escollint amb el temps. Només desitjo que tothom pugui sentir-se així a la vida, i que si no, com a societat siguem capaços de crear espais perquè qualsevol criatura al món pugui sentir que mereix, que val i que pot, donant-los l'oportunitat de ser resilients.

Laia.

Barcelona, 2022.

Sinopsis

El maltrato infantil es un fenómeno muy complejo que afecta de manera integral al individuo y se asocia con diferentes problemas de salud mental en la infancia, adolescencia y adultez.

Aunque el estudio del trauma relacional y sus consecuencias sobre la salud mental es de máxima actualidad en la literatura científica, son todavía escasas las investigaciones en población infantojuvenil. Estudiar su impacto en etapas de maduración cerebral y psíquica tan sensibles sería de gran relevancia para comprender los mecanismos neurobiológicos de sensibilización temprana y su relación con la psicopatología infantil.

En primer lugar, el metaanálisis realizado en el contexto de esta tesis doctoral, confirma la relación entre la agregación de estresores durante la adolescencia y la presencia de sintomatología clínica internalizante (ansiedad, depresión, somatización) y externalizante (impulsividad, trastornos de la conducta, agresividad, consumo de drogas), demostrando que la acumulación de acontecimientos estresantes puede ser tanto una causa como una consecuencia de sufrir psicopatología.

Para poder minimizar los efectos dañinos de las adversidades tempranas es imprescindible el desarrollo de herramientas útiles que permitan identificarlas y medirlas adecuadamente en los niños/as y adolescentes, facilitando la detección e intervención precoz por parte de los profesionales. En la presente tesis se ha diseñado y validado un nuevo instrumento con el que valorar de forma completa los acontecimientos vitales estresantes vividos en el último año por los adolescentes, el *Life Events Inventory for Adolescents* (LEIA). Este trabajo demuestra la relevancia de explorar la naturaleza de los eventos sufridos (si dependen o no de uno mismo, que involucren directamente a otras personas o no, etc.), así como la afectación subjetiva para el sujeto, ya que estas variables van a tener un impacto diferencial en la sintomatología expresada por el adolescente.

Por otro lado, el estudio llevado a cabo en una muestra de niños/as y adolescentes, con y sin diagnósticos psiquiátricos (proyecto *Epi_young_stress*), pone de manifiesto que los traumas relacionales afectan de manera compleja y sistémica a la salud de los menores.

Nuestros hallazgos indican que las experiencias de maltrato infantil se relacionan con la presencia de rasgos de la personalidad disfuncionales, como la desregulación emocional, la irritabilidad y la impulsividad. Estos rasgos, y la historia de maltrato en sí misma, se asocian a una mayor exposición a situaciones de estrés, incrementando el riesgo de revictimización. Considerando este complejo entramado, nuestro estudio apoya que la exposición a acontecimientos estresantes recientes y la desregulación emocional serían los elementos finales clave para explicar los comportamientos suicidas observados en niños/as y adolescentes.

El maltrato infantil es un factor de riesgo transdiagnóstico en enfermedad mental. El proyecto *Epi_young_stress*, demuestra que el trauma relacional aumenta el riesgo de presentar sintomatología internalizante, externalizante y también se relaciona con la alteración del pensamiento, problemas de atención y dificultades en las relaciones interpersonales. En este contexto, y considerando la gran dificultad de los profesionales para definir el cuadro clínico que presentan los menores que han sufrido maltrato, este trabajo respalda el nuevo diagnóstico psiquiátrico incluido en la Clasificación Internacional de Enfermedades (CIE-11): el Trastorno por Estrés Postraumático Complejo (TEPT-C). Esta entidad diagnóstica incluye los síntomas postraumáticos clásicos además de alteraciones en la auto-organización (desregulación emocional, autoconcepto negativo y dificultades interpersonales), aspectos clave que merecen priorizarse en el tratamiento clínico. También se profundiza en los diferentes tipos de maltrato y el periodo ontogénico de exposición como factores de vulnerabilidad para desarrollar esta sintomatología compleja.

Por último, se investiga el impacto del maltrato infantil en dos sistemas neurobiológicos esenciales en la respuesta al estrés psicosocial: el eje Hipotalámico-Hipofisario-Adrenal (HHA) y el sistema inmune. La aplicación de un paradigma experimental que permite estudiar la respuesta al estrés psicosocial agudo, el *Trier Social Stress Test* (TSST), y la recogida de muestras salivares, han permitido explorar el funcionamiento de estos sistemas biológicos en la muestra del proyecto *Epi_young_stress*.

Los niños/a y adolescentes con historia de maltrato muestran una desregulación del eje HHA caracterizada por una hiporeactividad frente estrés agudo, así como elevados niveles de cortisol en condiciones basales, especialmente por la noche. También se ha detectado una relación dosis-efecto entre la frecuencia o severidad del maltrato y la desregulación del eje HHA. Además, existe una disociación entre su percepción subjetiva de estrés (elevada) y su respuesta biológica (aplanada). Por otro lado, se ha explorado, por primera vez en población infantojuvenil, la relevancia del maltrato en la reactividad frente estrés de la inmunoglobulina A secretora (s-IgA), un biomarcador del sistema inmune. Los hallazgos apuntan a que el estrés psicosocial agudo estimula la secreción de s-IgA, pero solo después de la pubertad. Sin embargo, los niños/as con historia de maltrato muestran una respuesta similar a los adolescentes, sugiriendo que el trauma complejo podría adelantar la maduración del sistema inmune de estos niños/as.

En definitiva, esta tesis doctoral demuestra la importancia de evaluar tempranamente e integralmente las experiencias de trauma relacional vividas por los niños/as o adolescentes, ya que la tipología del maltrato, la comorbilidad, la severidad, la duración, así como la ventana ontogénica en la que ocurren, tendrán un papel fundamental en las expresiones psicopatológicas asociadas y en la sensibilización de los sistemas neurobiológicos implicados en la respuesta al estrés.

Abstract

Childhood maltreatment is a complex phenomenon that affects individuals systemically, and is associated with different mental health problems during childhood, adolescence and adulthood.

Although relational trauma and its consequences on adult mental health have been extensively studied, there are few investigations based on child and adolescent populations. Studying its impact on such on such sensitive maturation stages for brain and psychic development would be of great relevance to understand the neurobiological mechanisms of early sensitization and its relationship with child psychopathology.

Firstly, the meta-analysis carried out confirms the relationship between the aggregation of stressors during adolescence and the presence of internalizing symptoms (anxiety, depression, somatization) and externalizing symptoms (impulsivity, behavioral disorders, aggressiveness, drug use), demonstrating that the accumulation of stressful events can be both a cause and a consequence of suffering psychopathology.

Furthermore, in order to minimize the harmful effects of early adversities, it is essential to develop useful tools that allow to properly identify and measure them in children and adolescents, facilitating early detection and intervention by professionals. Accodingly, a new instrument for the assessment of recent stressful life events in adolescents has been designed and validated in this thesis: the Life Events Inventory for Adolescents (LEIA). This work demonstrates the relevance of exploring the nature of the suffered events (whether they depend on oneself or not, whether they directly involve other people or not, etc.), and their subjective impact on each subject, since these factors will have a differential impact on the symptomatology expressed by the adolescent.

On the other hand, the study conducted in our sample of children and adolescents, with and without psychiatric diagnoses (*Epi_young_stress* project), shows that relational trauma affects in a complex and systemic manner to the health of youth.

Our findings indicate that childhood maltreatment experiences are related to the presence of dysfunctional personality traits, such as emotional dysregulation, irritability and impulsivity. These traits, and the history of maltreatment itself, are associated with a greater exposure to stressful situations, increasing the risk of re-victimization. Considering this complex framework, our study supports that exposure to recent stressful events and emotional dysregulation would be the final key elements to explain the suicidal behaviors observed in children and adolescents.

Childhood maltreatment is a transdiagnostic risk factor for mental illness. The *Epi_young_stress* project demonstrates that relational trauma increases the risk of presenting internalizing and externalizing symptoms and is also related to altered thinking, attention problems and difficulties in interpersonal relationships. In this context, and considering the great difficulty of professionals to define the clinical picture presented by maltreated youth, this thesis supports the new psychiatric diagnosis included in the International Classification of Diseases (ICD-11): Complex Post Traumatic Stress Disorder (PTSD-C). This diagnostic entity includes the post-traumatic classic symptoms, but also self-organization disturbances (emotional dysregulation, negative self-concept and interpersonal difficulties), which are key aspects to prioritize during clinical treatment. In addition, the different types of maltreatment and the developmental period of exposure are explored as vulnerability factors to explain this complex symptomatology.

Finally, the impact of childhood maltreatment on two essential neurobiological systems involved in the psychosocial stress response has been explored: the Hypothalamic-Pituitary-Adrenal (HPA) axis and the immune system. The application of an experimental paradigm to study the responses to acute psychosocial stress, the Trier Social Stress Test (TSST), and the collection of different salivary samples have enabled to study the functioning of these biological systems in the entire sample of the *Epi_young_stress* project.

Children and adolescents with history of maltreatment show a deregulation of the HPA axis, characterized by hyporeactivity during acute stress, as well as increased cortisol levels in basal conditions, especially at night. Besides, a dose-effect relationship between frequency and severity of maltreatment suffered and HPA axis dysregulation was detected. In addition, there is a dissociation between their subjective perception of stress (elevated) and their biological response (flattened). On the other hand, the relevance of maltreatment on the reactivity of secretory immunoglobulin A (s-IgA), a biomarker of the immune system functioning, has been explored for the first time in a child and adolescent population. The findings suggest that acute psychosocial stress stimulates s-IgA secretion, but only after puberty. However, children with history of maltreatment show a similar response to adolescents, suggesting that complex trauma could lead to earlier maturation of the immune system in affected children.

In summary, this PhD thesis underscores the importance of an early and comprehensive evaluation of the experiences of relational trauma suffered by children or adolescents. The type, comorbidity, severity, and duration of maltreatment, as well as the ontogenic window in which it occurs, will play a fundamental role in the associated psychopathological expressions and in the degree of sensitization of the neurobiological systems involved in the stress response.

Fuentes de financiación que han hecho posible esta tesis doctoral

Financiación de proyectos y del grupo:

- "Estudio multicéntrico del maltrato infantil en niños y adolescentes con trastornos psiquiátricos: modificaciones epigenéticas y correlatos con marcadores periféricos de inmunidad innata". Proyecto multicéntrico financiado por el Instituto de Salud Carlos III (FIS PI15-20/00097) del 2015-2019 (ampliado a 2020). IP: Lourdes Fañanás. Universidad de Barcelona.
- "Función del eje HHA y modificaciones epigenéticas como predictores del curso clínico en menores con psicopatología expuestos a maltrato infantil e investigados en la transición puberal-adolescente". Proyecto coordinado financiado por la Fundación Alicia Koplowitz 2021 (PI047268). IP: Soledad Romero. Hospital Clinic de Barcelona.
- Grupo G08 del Centro de Investigación Biomédica en red en Salud Mental (CIBERSAM). Instituto de Salud Carlos III, Ministerio de Ciencia e Innovación, Gobierno de España. IP: Lourdes Fañanás. Universidad de Barcelona.
- *Comissionat per a Universitats i Recerca del DIUE*. Grupo SGR1577-2017 "Gens, ambient i desenvolupament: una visió longitudinal en la comprensió de l'origen de les malalties mentals i la diversitat de la conducta humana". IP: Lourdes Fañanás.
- Instituto de Biomedicina de la Universidad de Barcelona (IBUB). IP: Lourdes Fañanás. Universidad de Barcelona.

Becas personales:

- Beca para investigadores predoctorales de la "Agència de Gestió d'Ajuts Universitaris i de Recerca" (AGAUR) de la Generalitat de Catalunya (FI_100023). Marzo 2017- febrero 2020.
- Contrato de apoyo a la investigación por parte del proyecto 2017SGR1577, por parte de la Universidad de Barcelona. Marzo 2020 – diciembre 2020.
- Contrato de personal investigador adscrito al proyecto "Investigación aplicada en el campo de la genética de carácteres complejos en poblaciones humanas y la etiopatogencia de las enfermedades mentales", financiado por la *Fundació Bosch i Gimpera* de la Universidad de Barcelona. Enero 2021 – actualidad.

ÍNDICE

1. Introducción 1

1.1. Infancia y salud mental 3

1.1.1. La importancia de la infancia 3

1.1.2. Etapas del desarrollo psicológico humano 4

1.1.3. El apego como base fundamental del desarrollo 6

1.1.4. Infancia y emociones humanas 7

1.2. Las experiencias adversas en las primeras etapas de la vida 9

1.2.1. Acontecimientos vitales estresantes 11

1.2.1.1. Evaluación de los acontecimientos vitales estresantes 11

1.2.2. Trauma complejo y maltrato infantil 13

1.2.2.1. Evaluación del maltrato en la infancia o adolescencia 15

1.3. Implicaciones psicológicas y psiquiátricas del maltrato infantil 19

1.3.1. Maltrato infantil y personalidad 22

1.3.2. Maltrato infantil y sintomatología durante la infancia y adolescencia 24

1.3.3. Exposición a maltrato infantil y la relación dosis-efecto sobre los fenotipos clínicos 26

1.4. La neurobiología del maltrato infantil 29

1.4.1. El estrés como respuesta fisiológica 32

1.4.2. Sistemas de conservación de la homeostasis frente estrés psicosocial 32

1.4.2.1. El eje hipotalámico-hipofisario-adrenal (HHA) 34

1.4.2.2. Sistema inmunitario y respuesta al estrés 40

1.4.2.2.1. La inmunoglobulina A secretora (s-IgA) 40

2. Hipótesis y objetivos 43

3. Publicaciones 47

Informe del director sobre el factor de impacto 49

Sección I: Acontecimientos vitales estresantes en adolescentes y sintomatología internalizante y externalizante asociada 53

3.1. Stressful life events during adolescence and the development of externalizing and internalizing psychopathology: a meta-analysis 55

Informe del director sobre la contribución del doctorando al artículo 71

3.2. Recent stressful life events (SLE) and adolescent mental health: initial validation of the LEIA, a new checklist for SLE assessment according to their severity, interpersonal, and dependent nature 73

Informe del director sobre la contribución del doctorando al artículo 94

Sección II: Maltrato infantil, estresores recientes y alteraciones en la salud mental infantojuvenil.....95

3.3. Risk of suicidal behavior in children and adolescents exposed to maltreatment: the mediating role of borderline personality traits and recent stressful life events 97

Informe del director sobre la contribución del doctorando al artículo..... 117

3.4. Reinforcing the new diagnosis of Complex Post-Traumatic Stress disorder (CPTSD) of ICD-11 in children and adolescents exposed to relational trauma: developmental stage at exposure and its associated clinical outcomes 119

Informe del director sobre la contribución del doctorando al artículo..... 155

Sección III: La neurobiología del maltrato infantil en niños/as y adolescentes..... 157

3.5. Childhood maltreatment disrupts HPA-axis activity under basal and stress conditions in a dose–response relationship in children and adolescent..... 159

Informe del director sobre la contribución del doctorando al artículo..... 175

3.6. Secretory immunoglobulin A (s-IgA) reactivity to acute psychosocial stress in children and adolescents: the influence of pubertal development and history of maltreatment 177

Informe del director sobre la contribución del doctorando al artículo..... 187

4. Resumen global de los resultados 189

5. Discusión 193

6. Conclusiones..... 219

7. Referencias 223

8. Currículum vitae 239

1. Introducción

1.1. Infancia y salud mental

1.1.1. La importancia de la infancia

La infancia es el periodo más sensible y prolongado de la vida de las personas. A diferencia de otras especies, los humanos nacemos indefensos y con una gran inmadurez neurológica, siendo totalmente dependientes del cuidado de nuestros progenitores para sobrevivir a corto y largo plazo.

La maduración cerebral es lenta y compleja (Lenroot and Giedd, 2006); de hecho, se estima que nuestro cerebro no alcanza su máxima madurez hasta los 20 o 23 años de edad (Giedd et al., 1999). Esta condición particular de nuestra especie está estrechamente vinculada a la aparición y maduración de funciones cognitivas complejas como el lenguaje, el pensamiento abstracto, la cognición social, la creatividad o la planificación; todas ellas funciones relacionadas con la cohesión social de los grupos y su supervivencia.

Aunque el desarrollo cerebral tiene lugar bajo un estricto control genético, los factores ambientales van a ser transcendentales a la hora de permitir y dirigir dicha expresión génica. En este sentido, parece que nuestro cerebro, un órgano muy sensible al entorno, habría sido diseñado a lo largo de la evolución para nutrirse del entorno social más próximo e incorporar, durante la infancia, funciones claves para las futuras relaciones sociales del adulto y su éxito reproductor. Por tanto, el estilo de crianza y los estímulos ambientales recibidos durante la niñez serán cruciales para la maduración de funciones cognitivas y emocionales complejas, fundamentales para el desarrollo de recursos internos que permitan a la persona adaptarse, con mayor o menor facilidad, a la realidad social de su entorno.

Desde esta perspectiva, se puede entender la relevancia del ambiente social temprano en el neurodesarrollo infantil (De Bellis and Zisk, 2014). La violencia y las experiencias de maltrato en la infancia no solo modificarán nuestra manera de ser e interpretar la realidad, sino que, por los momentos ontogénicos de maduración en los que se encuentra el cerebro, también cambiarán su estructura y función (Teicher and Samson, 2016).

Puesto que el desarrollo cerebral comienza en el ambiente intrauterino y continúa hasta bien entrada la veintena, las etapas del desarrollo infantil constituirán una oportunidad para la acción positiva y protectora del ambiente o, por el contrario, para la acción desestabilizadora o de riesgo para la enfermedad (Clark et al., 2020). De acuerdo

con la Figura 1, el diálogo entre factores protectores (en verde) y factores de vulnerabilidad (en rojo) irá configurando el riesgo final de enfermedad. Esta espiral de desarrollo alterado puede tener claras repercusiones en la salud mental del individuo y manifestarse, ya en etapas infantiles y juveniles, en forma de alteraciones conductuales o psicopatológicas de diferente naturaleza o gravedad.

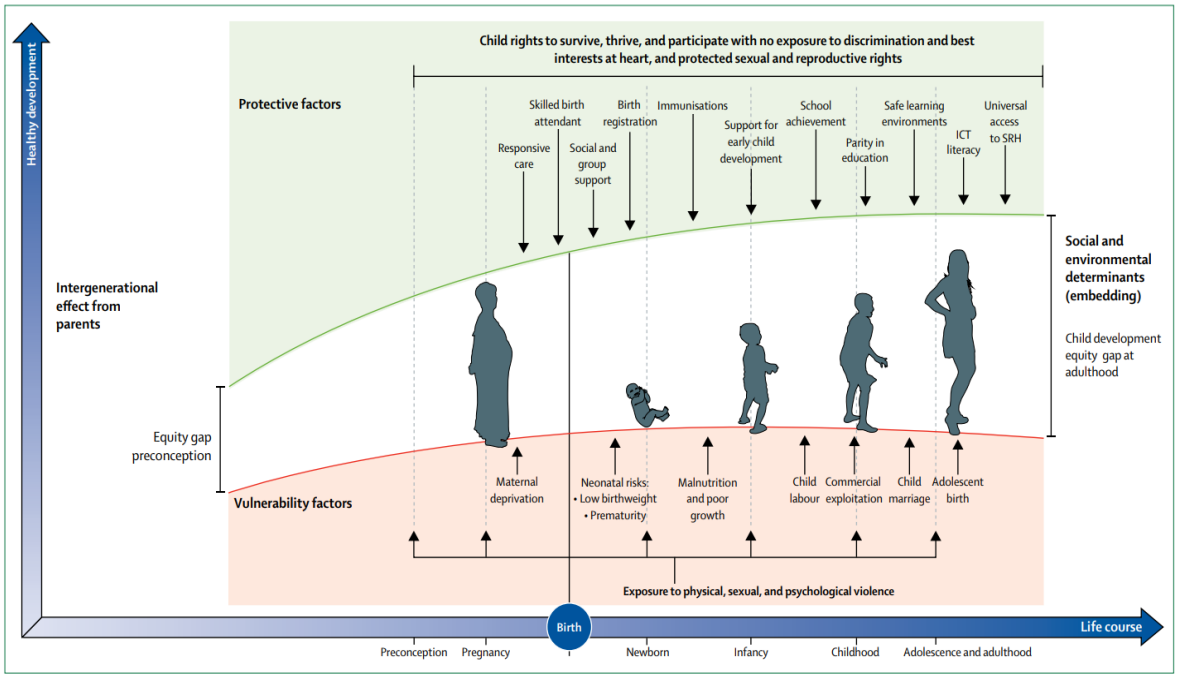


Figura 1. Factores protectores (en verde) y de vulnerabilidad (en rojo) relacionados con la salud a lo largo de la vida. Obsérvese la perspectiva dinámica de la configuración del estado salud-enfermedad infantil y juvenil dentro del desarrollo ontogénico prolongado (desde su inicio en etapas prenatales hasta la adolescencia). Imagen reproducida del artículo de Clark et al., de la revista Lancet (2020).

En este sentido, y como veremos extensamente más adelante, en estas etapas tempranas puede emerger sintomatología psiquiátrica más inespecífica, de la esfera internalizante (síntomas ansioso-depresivos), de la esfera externalizante (impulsividad-agresividad) o de otro tipo (alteración del pensamiento o problemas de relación). Cabe mencionar que en estas etapas también pueden emerger trastornos del neurodesarrollo, como el trastorno del espectro autista (TEA), en los que los factores genéticos son bien reconocidos (Bai et al., 2019). Sin embargo, estos últimos trastornos no serán el foco de esta tesis.

1.1.2. Etapas del desarrollo psicológico humano

Existen múltiples teorías formuladas por psicólogos a la hora de clasificar las distintas etapas del desarrollo psíquico del ser humano. De todas ellas se podrían extraer fundamentos interesantes y matices diferentes para comprender su complejidad. Sin

embargo, en esta tesis se va a tomar como referencia la teoría psicosocial de Erik Erikson (1968).

Erikson elaboró la teoría del desarrollo de la personalidad redefiniendo y expandiendo la teoría de los estadios de Freud y enfatizando mucho más el impacto de la sociedad y de la cultura sobre el individuo en crecimiento. Este autor propuso, por primera vez, que el desarrollo duraba toda la vida y que podía ser clasificado en ocho etapas determinadas, en gran medida, por la naturaleza genética de nuestra especie (ver Tabla 1).

Tabla 1. Teoría psicosocial de Erikson: las ocho etapas del ciclo vital.

	Estadio	Edad	Crisis psicosocial	Características	Relaciones significativas
1	Infancia	0 - 1½ años	Confianza o desconfianza	Sentimiento sobre si el mundo es un lugar seguro y se puede confiar en los otros	Madre
2	Niñez temprana	1½ - 3 años	Autonomía o vergüenza y duda	Independencia, autocontrol, uso de sus propios juicios y decisiones	Padres
3	Edad preescolar	3 - 5 años	Iniciativa o culpa	Iniciativa ante nuevos retos, balance entre lo que es permitido y no	Familia
4	Edad escolar	6 - 12 años	Laboriosidad o inferioridad	Aprender habilidades de su cultura, comparación, autoestima	Escuela y vecindad
5	Adolescencia	12 - 20 años	Identidad o confusión de roles	Crisis de identidad (valores, sexualidad, compromiso, rol), reavivará conflictos de etapas anteriores	Pares, grupo, modelos de roles
6	Adultez temprana	20 - 40 años	Intimidad o aislamiento	Compromiso con otros, amor	Amigos y afiliación
7	Adultez media	40 - 60 años	Generatividad o estancamiento	Crianza, creatividad, productividad, utilidad	Hogar, compañeros de trabajo
8	Adultez tardía	>60 años	Integridad o desesperación	Aceptación de la vida o desesperación por la incapacidad de revivirla	Especie humana

De acuerdo con esta teoría, los seres humanos con un desarrollo sano pasan a través de las ocho etapas del ciclo vital. En cada una de ellas, el individuo se deberá enfrentar a nuevos conflictos o crisis propias (ver Tabla 1). Si los retos no se completan con éxito en cada fase, es de esperar que reaparezcan como problemas o crisis en el futuro.

Según Erikson, para superar los conflictos propios de cada estadio, serán especialmente significativas algunas relaciones interpersonales concretas de cada etapa (ver Tabla 1 para detalles). Comprender la importancia y el especial cuidado que debe ejercer cada una de estas figuras a lo largo de cada etapa es imprescindible para favorecer un óptimo desarrollo. Como se puede observar, los cuidadores principales y la familia próxima representan figuras esenciales en las primeras etapas de la vida, por lo que serán el principal foco de interés del presente trabajo.

1.1.3. El apego como base fundamental del desarrollo

El apego se refiere al vínculo emocional que desarrollan los bebés con su cuidador principal desde el momento del nacimiento (Bowlby, 1969). Esta tendencia innata del bebé a desarrollar una atracción emocional hacia quien lo rodea es compartida con muchas otras especies y favorece la adaptación, ya que garantiza la cobertura tanto de sus necesidades físicas como psicológicas (Ainsworth et al., 2015). La calidad del apego dependerá principalmente del tipo de atención y respuesta que reciba el bebé por parte de la persona adulta responsable de su cuidado, habitualmente la madre.

Las personas pueden desarrollar un apego seguro o inseguro en base a la sensibilidad, disponibilidad y previsibilidad que van a mostrar los cuidadores frente a sus necesidades. Un apego seguro se desarrollará de modo gradual a medida que los cuidadores aprendan a interpretar las señales del pequeño y a reaccionar pronto y adecuadamente a ellas (con afecto positivo, tranquilo y focalizado). Sin embargo, aunque biológicamente el ser humano esté preparado para crear vínculos estrechos, estos no se adquirirán si las personas adultas no han aprendido previamente a reaccionar adecuadamente ante la conducta del otro. Así, puede haber muchas desviaciones que hagan que las señales del infante se interrumpan y no provoquen una reacción adecuada en la persona cuidadora, estableciéndose un apego inseguro.

En este sentido, Bowlby (1969) subrayó que el apego entre progenitor-infante es una relación recíproca. Es decir, el infante se apega al progenitor y este a él. Así, no hay que perder de vista que además de la calidad de los cuidados, el temperamento propio del bebé influirá en esta interacción (Groh et al., 2017). Es decir, aquellos niños/as que por su base genética nacen con rasgos más inquietos, impulsivos y reactivos podrán suponer un reto añadido para sus cuidadores a la hora de regular sus estados emocionales. También el estado de salud, tanto del bebé como de los cuidadores, o el clima emocional en el hogar influirán en el estilo de apego desarrollado. Si el infante

crece en un ambiente de violencia y malos tratos, es probable que se construya un apego inseguro desorganizado, con las repercusiones que este tipo de vínculo puede acarrear a corto y largo plazo.

Es importante señalar que, a través del estilo de apego que se establezca con el principal cuidador, se van a modular numerosos mecanismos neurobiológicos esenciales para la futura regulación emocional del sujeto (Tarullo and Gunnar, 2006; Brown et al., 2019).

Es decir, los lazos emocionales que se establezcan en las primeras etapas del desarrollo serán importantes durante toda la vida. El tipo de apego desarrollado va a influir en las configuraciones mentales que constituyen los sentimientos de seguridad y protección, así como en la regulación emocional, la personalidad y el ajuste psicológico general de la persona (Cassidy et al., 2013). Tanto es así que la asociación entre el estilo de apego y la sintomatología psiquiátrica posterior ha sido ampliamente reportada. Se ha revelado que los niños/as con apego inseguro son más propensos a desarrollar sintomatología externalizante (Fearon et al., 2010) e internalizante (Brumariu and Kerns, 2010), así como trastornos de la personalidad en edades más avanzadas (Levy, 2005).

1.1.4. Infancia y emociones humanas

Como se ha comentado anteriormente, en el momento de nacer, los bebés ya muestran su propio temperamento (determinado por su genética) y la crianza, el vínculo de apego y la cultura ejercerán un papel muy importante en la manera de interpretar y responder en el mundo, regulando sus emociones y en definitiva definiendo su forma de ser. En este sentido, para comprender el impacto de las experiencias tempranas adversas en la salud mental de la persona, es importante conocer cómo maduran y se expresan las emociones a lo largo del desarrollo humano.

Algunas de las emociones fundamentales, como el interés, la angustia, el rechazo o la alegría, están ya presentes de forma innata en el momento de nacer. Sin embargo, no será hasta los 2-7 meses de vida cuando el bebé empezará a mostrar otras emociones básicas, también programadas biológicamente, tales como la ira, la tristeza, el miedo o la sorpresa (Izard et al., 1995). La manera en la que los cuidadores gestionen estas emociones primarias durante los primeros dos años de vida del bebé será esencial en la capacidad que tendrá esta persona para regular sus propias emociones en etapas futuras.

La incipiente capacidad de reconocer e interpretar emociones ajenas se desarrolla alrededor de los 10-12 meses y constituye un logro decisivo que permite al infante saber lo que debería sentir o cómo comportarse en diferentes situaciones según el entorno que lo rodea. Así, el cerebro del niño/a empezará en este periodo a almacenar y a asociar aquellas experiencias o comportamientos propios que desencadenan, por ejemplo, emociones de rechazo, rabia, o aceptación. En consecuencia, esta etapa será un periodo altamente sensible e importante, ya que las experiencias vividas serán esenciales para asentar los estímulos desencadenantes de estas emociones que, a su vez, irán forjando el autoconcepto del infante.

A partir de los dos años, cuando el cerebro ya es mucho más maduro, el bebé ya puede reconocerse (en una foto o en el espejo) y es capaz de integrar reglas para evaluar su propia conducta. Es en este momento cuando empiezan a manifestarse también otras emociones más complejas y autoconscientes como la vergüenza, la culpa, la envidia o el orgullo (Lewis et al., 1989). Todas estas emociones se configuran en base a la mirada del otro. De hecho, en la etapa preescolar estas emociones autoevaluativas suelen mostrarse solo cuando un adulto observa su conducta. Por lo tanto, a partir de los dos años, los mensajes (verbales y no verbales) de apoyo, rechazo o ignorancia que el niño/a recibe por parte de sus cuidadores, influirán directamente en la experiencia y expresión de estas emociones. Así, comprender la asociación que pudo hacer cada persona entre su comportamiento y las emociones o atención recibida por sus figuras de apego será esencial para comprender cómo se va a relacionar y a comportar en sociedad. A partir de los 6 años, el niño/a ya habrá internalizado estas pautas de evaluación y experimentará todas estas emociones sin necesidad de la presencia de un adulto.

A partir de los 12 años, coincidiendo con la máxima maduración del córtex prefrontal, los niños/as ya serán capaces de reprimir sus emociones y esconder su enfado, decepción o tristeza frente algunas situaciones. La adolescencia será un momento clave en el desarrollo para asentar todo lo vivido en etapas previas (Nivard et al., 2017). En esta etapa podremos observar que, niños/as que mostraban dificultades previas, durante la adolescencia definitivamente empeoran o, por el contrario, algunos, gracias a la maduración cerebral y los nuevos procesos cognitivos establecidos, se ordenan y mejoran.

En definitiva, los infantes aprenderán a autorregularse emocionalmente en función de lo que hayan vivido previamente con sus cuidadores (lo que se conoce como «co-regulación»). No hay que perder de vista, sin embargo, que el temperamento, y los

factores genéticos implicados en su naturaleza van a influir en este proceso complejo. Sea como sea, un mal manejo final de estas emociones puede acarrear un bloqueo o incluso la aparición de sintomatología psiquiátrica, siendo la desregulación emocional uno de los factores de base transdiagnóstico más reportados en numerosos trastornos mentales (Sloan et al., 2017; Paulus et al., 2021).

1.2. Las experiencias adversas en las primeras etapas de la vida

Desde la perspectiva de un adulto, resulta evidente que la vida es una sucesión de dificultades y de cambios, algunos con repercusión emocional, a los que la mayoría de las personas se enfrentan con éxito. El ambiente en el que vivimos será siempre un contexto de cambio permanente que desestabilizará la homeostasis de los sistemas psíquicos y biológicos del individuo, requiriendo un reajuste para una correcta adaptación. Sin embargo, sabemos que determinadas situaciones de violencia extrema y mantenida son capaces de dañar la salud física y mental de cualquier ser humano.

Por tanto, aunque todas las personas pueden verse involucradas en situaciones de estrés o sufrir experiencias adversas, la naturaleza de estas experiencias (cómo y quién las ejerce) y la manera de presentarse (intensidad, frecuencia, momento del desarrollo) pueden conllevar un impacto diferente, tanto a nivel psicológico como biológico.

Las vivencias adversas y el maltrato infantil están presentes en todas las sociedades humanas y ocurren con mayor frecuencia de lo que cabría esperar. Sin embargo, el riesgo de exposición a estresores o eventos traumáticos varía según el país y la disponibilidad de recursos personales, materiales y económicos (Brown et al., 2019).

Para empezar, es necesario mencionar que actualmente no existe una definición operativa del concepto «trauma». De hecho, la palabra trauma a menudo se relaciona con las consecuencias psicopatológicas de haber sufrido la exposición a un evento catastrófico (lo que en realidad sería un Trastorno por Estrés Postraumático (TEPT)). En cambio, en otras ocasiones se habla de trauma para referirse a las experiencias potencialmente traumáticas en sí mismas, que según el Manual Diagnóstico y Estadístico de los Trastornos Mentales (DSM-5) serían la exposición a muerte, lesión grave o ser víctima de violencia sexual (APA, 2013). Discernir entre estos dos significados es importante, ya que no todas las personas que viven eventos potencialmente traumáticos acaban desarrollando un TEPT, mientras que otras pueden experimentar un TEPT a

consecuencia de experiencias no reconocidas como traumáticas en los manuales diagnósticos actuales.

En referencia a las experiencias que podrían considerarse potencialmente adversas para la salud, en algunos estudios el concepto de trauma lo engloban con sucesos que realmente podrían considerarse eventos puntuales traumáticos y experiencias de violencia extrema (Shields and Slavich, 2017). En cambio, otros autores combinan estresores menores con otras experiencias de trauma (Haller and Chassin, 2012). Por tanto, ponerse de acuerdo en la línea que separa lo que debe considerarse una experiencia vital estresante o un evento traumático es verdaderamente complicado.

Según la perspectiva dimensional, las adversidades psicosociales y sus consecuencias en un niño o adolescente podrían situarse en una escala continua que iría desde las dificultades diarias más cotidianas, pasando por eventos vitales estresantes (acontecimientos o cambios vitales relevantes), eventos puntuales traumáticos, hasta llegar a experiencias extremas y continuadas de maltrato o violencia (ver Figura 2).

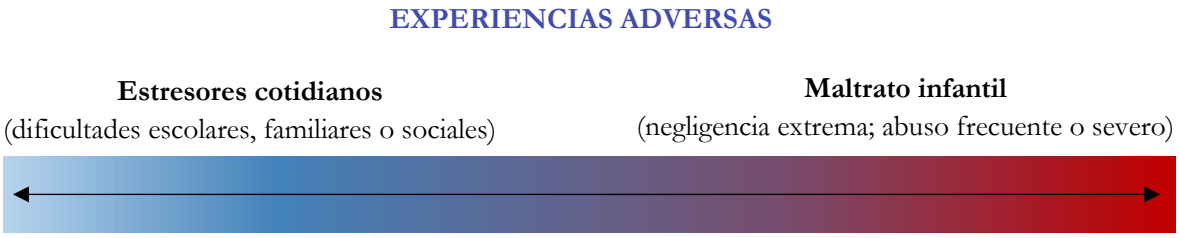


Figura 2. Rango de variación de la severdiad de las experiencias adversas en un modelo contínuum.

Desde esta perspectiva, respecto a los sucesos que se situarían en el extremo izquierdo (estresores diarios o menos severos), se necesitaría la acumulación de muchos de ellos para ocasionar daño psicológico. Por el contrario, las experiencias situadas en el extremo derecho (maltrato infantil) serían eventos que por sí mismos ya serían dañinos y dejarían una fuerte huella en la persona.

En este trabajo se ha optado por diferenciar y evaluar estas experiencias adversas de manera distinta, situando los acontecimientos vitales estresantes y el maltrato infantil como factores de riesgo naturalmente distintos. En el próximo apartado se va a detallar y discutir en profundidad la naturaleza distinta de estas dos experiencias.

1.2.1. Acontecimientos vitales estresantes

Algunos de los eventos vitales estresantes más descritos como acontecimientos concretos que pueden alterar el equilibrio y la vida de una persona serían: la muerte de un miembro de la familia, una enfermedad grave, un divorcio, una separación, una mudanza o una ruptura amorosa, entre otras (Shields and Slavich, 2017).

Curiosamente, algunos autores refieren que los sucesos que dependen de las acciones de uno mismo, los cuales reciben el nombre de «eventos controlables o dependientes» (p. ej. el encarcelamiento, un cambio de trabajo, repetir curso, etc.), podrían tener un mayor impacto en la salud mental de la persona (Wichers et al., 2012). Por el contrario, aquellos sucesos que son impredecibles por naturaleza y no dependen del comportamiento de la persona para que ocurran, denominados «eventos incontrolables o independientes» (p. ej. la muerte o la enfermedad de un familiar, vivir un terremoto, etc.) podrían ser menos dañinos. Los estudios también demuestran que podrían impactar de forma distinta a la salud de la persona en función de si son eventos interpersonales (que involucran a otras personas) o no (Rudolph et al., 2000). Sin embargo, falta mucha investigación sobre el impacto diferencial de este tipo de eventos, sobre todo en población infantojuvenil, y conocer qué eventos podrían ser más perjudiciales a la hora de predecir sintomatología psiquiátrica, tanto a corto como a largo plazo.

Los acontecimientos vitales estresantes, al no ser muy intensos, necesitan la acumulación de muchos de ellos, en relativamente poco tiempo, para que impacten en la salud (Wildschut et al., 2020; Low et al., 2012). Sin embargo, hay eventos puntuales e intensos que pueden provocar un fuerte impacto por sí mismos, con vivirlos solo una vez. Desde la Psicología focalizada en el trauma esto se denominaría «Trauma» (con T mayúscula), como por ejemplo un atentado, un accidente, un desastre natural o una violación. Estos eventos traumáticos son tan intensos que ponen al organismo en una situación de amenaza extrema donde la supervivencia está en un claro peligro. Estas experiencias traumáticas, al situar a la persona cerca de la muerte, dejan un fuerte impacto en la memoria emocional.

1.2.1.1. Evaluación de los acontecimientos vitales estresantes

Existen diversos instrumentos o entrevistas para evaluar la presencia actual o biográfica de acontecimientos vitales estresantes. Sin embargo, las propiedades

psicométricas, en general, tienen pocas garantías (Joana-Santiveri et al., 2018). Además, hay una gran disparidad en los constructos que evalúan estos instrumentos, ya que algunos incluyen solo estresores menores, mientras que otros también incluyen acontecimientos traumáticos o experiencias de maltrato más severas sufridas durante la infancia (Young-Wolff et al., 2012). Esto conlleva que la información reportada en los estudios que evalúan los estresores vitales pueda estar sesgada.

A día de hoy, por tanto, son escasos los instrumentos disponibles para valorar las situaciones estresantes desde la perspectiva de la sociedad actual del siglo XXI en nuestro contexto y en población infantojuvenil. De hecho, cuando empezó el proyecto de esta tesis solo existían cinco instrumentos en población infantojuvenil en España y algunos fueron diseñados hace casi 40 años (ver Cuadro 1). Además, la mayoría de ellos no cumplen los estándares psicométricos óptimos que debe garantizar un instrumento (Dohrenwend, 2006).

CUADRO 1: Instrumentos disponibles para valorar los acontecimientos vitales estresantes en adolescentes

A continuación, se detallan los instrumentos disponibles en España para valorar los acontecimientos vitales estresantes recientes en adolescentes, según la revisión sistemática de Joana-Santiveri et al. (2018):

1. Adaptación Toro-Coddington (Toro et al., 1983): entre los 3 y 6 años (41 ítems), entre los 6 y 10 años (46 ítems) y entre los 10 y 14 años (45 ítems).
2. Escala de Acontecimientos vitales de Coddington (CLES) (Villalonga-Olives et al., 2008): de 12 a 20 años (53 ítems)
3. Escala de Acontecimientos Vitales (EAV) (Mardomingo et al., 1986; Mardomingo and Gonzalez-Garrido, 1990): 6 a 12 años (40 ítems) y de 12 a 18 años (47 ítems)
4. Acontecimientos Vitales Estresantes (AVE)(Oliva et al., 2008): para adolescentes (29 ítems)
5. *Adolescent Life Change Event Scale* (ALCES)(Voltas et al., 2015): para adolescentes (31 ítems)

Asimismo, ninguno de los instrumentos reflejados en el Cuadro 1 separa los acontecimientos estresantes de otras adversidades naturalmente distintas, como el maltrato infantil. Por otro lado, estos instrumentos solo valoran la presencia de estos acontecimientos de forma dicotómica (presencia o ausencia) sin incluir la vivencia particular de la persona (a excepción del AVE y el ALCES), con el posible sesgo de interpretación que esto puede conllevar (Kessler, 1997).

1.2.2. Trauma complejo y maltrato infantil

Comúnmente, cuando se habla de trauma, se suele pensar en una experiencia emocional intensa concreta, vivida o presenciada, que no ha sido procesada y que influye en la vida presente (lo que hemos definido anteriormente como Trauma con T mayúscula). Sin embargo, además de esta faceta, existe otro tipo de trauma que está relacionado directamente con las relaciones interpersonales, conocido como «trauma complejo» (trauma con t minúscula, trauma del desarrollo o trauma relacional). El trauma complejo se produce cuando crecemos en un entorno familiar (o institucional) en el que hay falta de afecto o escasa atención a las necesidades emocionales, ya sea porque los cuidadores están ausentes física o emocionalmente (negligencia) o porque ejercen violencia psicológica o física directa (maltrato o abuso)(van der Kolk, 2005).

El trauma complejo, sin ser un evento puntual intenso, deja una huella incalculable en la persona (Herman, 1992). De hecho, sabemos que, debido a nuestra condición social como especie, serán particularmente relevantes aquellas experiencias que derivan de las relaciones interpersonales, especialmente en el seno familiar. Al mismo tiempo, cuanto más cerca del inicio de la vida ocurra el evento, mayor es la vulnerabilidad, y más impacto puede tener la dinámica relacional traumática en el organismo.

En este sentido, existe una gran variabilidad de conductas y actitudes por parte de los adultos o cuidadores que podrían ser perjudiciales para el menor y que impedirían su óptimo desarrollo psíquico y físico. Sin embargo, ponerse de acuerdo entre profesionales para determinar y especificar estas conductas resulta mucho más difícil; aunque algunas de ellas estén más definidas y son claramente inherentes a los valores, costumbres o periodos históricos en los que se valoren como tales, teniendo un impacto profundo en la persona (Moody et al., 2018).

Comúnmente, a la hora de explicar las diferentes experiencias de violencia sufridas durante la crianza podemos clasificarlas según el momento de exposición (prenatal o posnatal), según el contexto en el que tiene lugar (intrafamiliar o extrafamiliar) así como según la conducta en sí ejercida. A este respecto, la clasificación más utilizada suele diferenciar entre: i) el maltrato activo o violencia por acción (como comportamientos y discursos que implican el uso de la fuerza psicológica, física o sexual y provocan daños directos), y ii) el maltrato pasivo, violencia por omisión o negligencia

(caracterizado por la falta de intervenciones y/o discursos necesarios para asegurar el bienestar del menor) (ver Tabla 2).

Tabla 2. Clasificación más común de los tipos de maltrato infantil.

	Activo	**Pasivo**
Visible	Maltrato físico o abuso sexual	Negligencia física
Invisible	Maltrato psicológico	Abandono o negligencia emocional

Stoltenborgh y colaboradores (2015) revisaron los estudios disponibles en la literatura sobre la prevalencia del maltrato infantil en el mundo y concluyeron que, según los datos extraídos mediante autoinformes, un 36% de las personas han sufrido maltrato emocional, un 23% maltrato físico, un 16-18% negligencia física o emocional, y un 18% de las chicas y un 7.6% de los chicos abuso sexual. Aunque el maltrato infantil es una realidad para demasiados niños/as o adolescentes, a menudo pasa desapercibida. De hecho, hay una infraestimación del fenómeno y es difícil calcular la prevalencia, ya que según las definiciones empleadas, o si se capturan de forma retrospectiva, actual, o mediante cuestionarios, entrevistas o informes oficiales, las conclusiones pueden ser dispares (Tingskull et al., 2015). Además, los diferentes tipos de maltrato en pocas ocasiones se presentan de forma aislada o puntual, si no que coexisten y, en muchas ocasiones, se experimentan de forma crónica (Vachon et al., 2015).

Cabe señalar que las experiencias que provocan un trauma relacional no son únicamente aquellas que recaen directamente sobre el individuo, sino que ya son muchos los estudios que demuestran que ser testigo y convivir con situaciones de violencia doméstica tiene un efecto dañino directo sobre la persona. Por lo tanto, cuando un menor convive con situaciones de violencia en el domicilio, ya representa en sí mismo un tipo de maltrato hacia él, y afecta a su desarrollo y bienestar óptimo (Osofsky, 2018).

Más recientemente, también se han incorporado las experiencias de violencia en el ámbito escolar (Moore et al. 2017) o la violencia de género (Dillon et al., 2013) como otro tipo de traumas relacionales que afectan gravemente a la salud física y mental de la persona (ver Cuadro 2 para más detalle).

CUADRO 2. Otros traumas relacionales: acoso escolar y violencia de género

Normalmente, el trauma complejo ocurre en el entorno familiar y tiene sus inicios al principio de la vida. Sin embargo, la violencia severa entre iguales, como el acoso escolar (*Bullying* en inglés) o la violencia de género, también son en sí mismas un tipo de trauma complejo o relacional que pueden dejar una huella profunda a nivel psicobiológico.

El acoso escolar es un comportamiento agresivo (verbal o físico) que se da de forma repetida por parte de un individuo o grupo de iguales con desequilibrio de poder. Se estima que una tercera parte la población infantojuvenil en España puede ser víctima de alguna conducta relacionada con acoso escolar. Uno de los factores de riesgo para sufrir experiencias de violencia es ser percibido como diferente, sobre todo si esta diferencia posiciona al individuo en una situación de desventaja social (como una discapacidad intelectual o física).

Por otra parte, la violencia de género es aquella que se ejerce sobre las mujeres por parte de quienes estén o hayan estado ligados a ellas por relaciones de afectividad (parejas o exparejas). El objetivo del agresor es producir daño y conseguir el control sobre la mujer, por lo que se produce de manera continuada y sistemática, como parte de una misma estrategia, siendo una de las manifestaciones más claras de la desigualdad y subordinación de la relación de los hombres sobre las mujeres.

Ambas experiencias afectan directamente a aspectos esenciales del desarrollo psicológico y físico de la persona (Moore et al., 2017; Dillon et al., 2013). Aunque estos tipos de maltrato no serán el foco de la presente tesis, sabemos que muchas veces previamente a estos traumas relacionales entre iguales, puede subyacer un trauma complejo en la infancia que pudo influir en la manera en como la persona aprendió a situarse en el mundo y a relacionarse con los demás (Wolfe, 2009). Por ello, es importante intervenir lo más pronto posible y minimizar la posible revictimización de estas personas.

1.2.2.1. Evaluación del maltrato en la infancia o adolescencia

Si la definición de trauma ya es compleja y ambigua, todavía es más difícil diseñar herramientas útiles y validadas para capturar esta realidad. En este sentido, es importante tener previamente un constructo al cual aferrarse, ya que en función de la teoría o modelo al cual se vincule cada investigación, se capturará de forma distinta la realidad y, por lo tanto, se van a extraer conclusiones dispares.

Un manual reciente sobre prácticas éticas a la hora de evaluar las experiencias de violencia infantil en menores de edad (Pereda et al., 2018), manifiesta que realizar estudios sobre temas tan sensibles y, además, con participantes que se encuentran en momentos del desarrollo tan vulnerables, posiciona al investigador ante un dilema. Por un lado, el interés del investigador en obtener información fiable y completa de los propios protagonistas, en un intento de fomentar la detección y la intervención precoz. Por otro lado, garantizar que la investigación no dañe a los participantes y no provoque una revictimización. Ante este dilema, los científicos habitualmente se han decantado por estudios en adultos que evalúen el maltrato de manera retrospectiva (ver Cuadro 3). Sin embargo, la evidencia empírica ha demostrado que preguntar a los niños/as y

adolescentes sobre sus experiencias no los daña; se trata de una falsa creencia que los investigadores deberían desterrar (Pereda et al., 2018). Es más, excluirlos de estas iniciativas respondería más bien a una tendencia adultocentrista de la sociedad, en lugar de concebirlos como ciudadanos de pleno derecho.

CUADRO 3. Instrumentos para valorar el maltrato infantil de manera retrospectiva en adultos

Una revisión sistemática reporta 54 entrevistas existentes a la hora de recoger las experiencias de maltrato infantil de manera retrospectiva en adultos (Hovdestad et al., 2015). Sin embargo, hay grandes limitaciones, ya que algunas de ellas solo valoran subtipos de maltrato específicos o no incluyen distintos ítems para valorar cada subdominio de maltrato correctamente. De hecho, solo existen 7 entrevistas que estén realmente validadas. Algunas de las entrevistas semiestructuradas más usadas son el *Early Trauma Inventory* (ETI) o *Children's Life Events Scale* (CLES)(Bremner, 2004).

En adultos existe también un gran número de cuestionarios autoinformados muy utilizados en investigación, entre las cuales destacarían:

1) *Childhood Trauma Questionnaire* (CTQ) (Bernstein et al., 1997), presenta 28 ítems que engloban 5 tipos de maltrato.
2) *Early Trauma Inventory* (ETI-SR) (Bremner et al., 2007) formado por 56 ítems que incluyen la valoración de las experiencias de abuso y otros traumas, así como la frecuencia, la edad y el perpetrador.
3) *Traumatic Life Events Questionnaire* (TLEQ) (Kubany et al., 2000) valora 16 posibles eventos traumáticos más allá del maltrato infantil, valorando su frecuencia y severidad.
4) *Adverse Childhood Experiences* (ACE) (Felitti et al., 1998), consta de 17 ítems dicotómicos sobre experiencias de abuso y disfunciones en el hogar.

Sin embargo, existen limitaciones importantes en todos estos instrumentos, ya que gran parte de ellos no valoran experiencias como la negligencia, la violencia intrafamiliar, ni las condiciones en las que se dan estas experiencias (frecuencia, severidad, perpetrador, respuesta del ambiente, etc.). Por tanto, aunque a día de hoy existen algunas herramientas disponibles, es una necesidad evidente desarrollar instrumentos bien validados que permitan trazar una línea de vida útil parta investigar las experiencias de maltrato sufridas tanto en población adulta como infantil.

Se estima que solo el 10% de los casos de violencia infantil llegan a revelarse mientras están ocurriendo (WHO, 2003). En la mayoría de los casos no es hasta bien entrada la edad adulta cuando se conocen o se rebelan por parte de la persona. En este sentido, es importante señalar que tanto los infantes como los adolescentes tienen dificultades y no suelen reportar las situaciones de abuso o maltrato a menos que se les pregunte sobre ellas, debido a la incomprensión, el secretismo, la vergüenza, la culpa o el miedo asociado a las experiencias que sufren. Además, no hay que olvidar que el 80% de las veces el maltrato ocurre dentro del seno familiar, por lo que preguntar a sus padres o cuidadores principales, en lugar de al propio niño/a, puede suponer una subestimación de la presencia de estas experiencias (Tingskull et al., 2015).

Aunque evaluar a los infantes directamente resulta a menudo la fuente de información más precisa para explorar sobre su propia vida (Achenbach et al., 1987), no exime a los profesionales de su responsabilidad moral en el uso de buenas herramientas, velando siempre por el bienestar último del menor.

Sin embargo, en muchas ocasiones los profesionales que quieren valorar estas experiencias adversas (tanto en el ámbito clínico, educativo, social, judicial o en investigación) refieren que no disponen de instrumentos válidos y fiables para recoger adecuadamente esta información. Es evidente que, en comparación con otras áreas de interés en psiquiatría infantojuvenil, existe un gran vacío de herramientas o protocolos para valorar las experiencias de maltrato adecuadamente según los estándares internacionales y éticos (Harkness and Monroe, 2016). Por tanto, la creación y disponibilidad de instrumentos fiables para valorar las experiencias adversas en la infancia es una necesidad emergente en nuestra sociedad, que permitiría a los profesionales recoger información fiable y útil para detectar e intervenir acordemente. Asimismo, disponer de puntos de corte que puedan situar al niño/a en un nivel de riesgo permitiría al profesional activar recursos de protección antes de que se desarrolle sintomatología psiquiátrica o conductas de riesgo (fracaso escolar, delincuencia, suicidio, etc.).

Es difícil encontrar protocolos que permitan valorar las experiencias de maltrato en población infantil y juvenil, y que además engloben tanto la perspectiva subjetiva como la valoración objetiva por parte de un adulto, incluyendo aspectos más cualitativos como la severidad, frecuencia o impacto que la vivencia ha podido tener en cada persona.

De hecho, a menudo se estudia la exposición a estresores con cuestionarios generales no validados para la población que se quiere estudiar, recogiendo la información de forma muy sesgada. Por ejemplo, a la hora de valorar la exposición a estresores deben tenerse en cuenta muchos otros factores que a menudo no se consideran en las investigaciones. En primer lugar, se ha de investigar adecuadamente la población que se pretenda evaluar, tanto en el contenido como en la forma (Turner and Wheaton, 1997). Por ejemplo, la aproximación que se deberá usar para obtener información de niños/as, adolescentes o adultos será muy diferente. Además, los instrumentos usados deben ser representativos de la población que se quiere estudiar, ya que según la cultura o el país donde se encuentre la persona, el género, ámbito laboral, nivel socioeconómico o el grado de adaptación social, los estresores a considerar serán

distintos. Además, se deben valorar algunas características importantes como la frecuencia, severidad, edad de exposición, figuras protectoras, etc. (Barnett et al., 1993).

Concretamente, existen algunas entrevistas semiestructuradas o cuestionarios autoreportados validados para valorar las posibles situaciones de maltrato en adolescentes (ver Cuadro 4). No hay que olvidar que la adolescencia se ha descrito como una etapa de la vida donde la posibilidad o el riesgo de sufrir diferentes tipos de maltrato se hace mayor, especialmente en el caso de los abusos sexuales o del *bullying* (Arseneault, 2018), por lo que es una etapa importante en la cual valorar posibles situaciones de victimización.

CUADRO 4. Instrumentos para valorar el maltrato infantil en adolescentes

Existen algunos cuestionarios o entrevistas para valorar experiencias de violencia o maltrato en adolescentes. Sin embargo, algunos de ellos contemplan también otras experiencias traumáticas que no son de índole relacional, o no valoran de forma completa las experiencias vividas. Además, muchos de los cuestionarios existentes recogen más bien la sintomatología postraumática, siendo una limitación para detectar experiencias de maltrato en jóvenes resilientes.

Algunos de los cuestionarios disponibles en español para valorar en adolescentes las experiencias de maltrato sufridas son:

1) *Childhood Trauma Questionnaire short form* (CTQ-SF) (Bernstein, 2003). Es el mismo test que en adultos. Incluye 28 ítems y engloba cinco tipos de maltrato y su frecuencia.
2) *Childhood Experience of Care and Abuse Questionnaire* (CECA-Q2) (Kaess, 2011), evalúa de forma separada la figura materna y paterna. Incluye el grado de parentesco, el tipo de crianza recibida, edad y motivos de abandono, frecuencia o figuras de apoyo. Evalúa posible negligencia o invalidación emocional, maltrato emocional, físico o sexual.
3) *UCLA-PTSD for children and adolescents* (UCLA) (Steinberg et al., 2013). Evalúa diferentes eventos traumáticos (incluido el maltrato infantil). Pregunta sobre si la persona fue testigo/víctima, se concreta la edad de exposición y la sintomatología TEPT asociada (DSM-5).
4) *Juvenil Victimization Questionnaire* (JVQ) (Finkelhor et al., 2005; Pereda, Gallardo-Pujol, and Guilera, 2018), valora 36 experiencias de victimización más allá de las experiencias de maltrato convencionales.
5) *Maltreatment Abuse Chronology of Exposure Scale* (MACE) (Teicher and Parigger, 2015). Permite evaluar diferentes tipos de traumas relacionales de forma autoreportada y su edad de exposición.

Por otro lado, los niños/as muestran una inmadurez cognitiva que no permite evaluar las experiencias a partir de este tipo de herramientas, por lo que debe abarcarse desde otras perspectivas. En población infantil, las técnicas narrativas (como las historias incompletas) o proyectivas (como dibujos o juegos) constituyen procedimientos útiles para explorar posibles situaciones de maltrato, ya que permiten abrir una ventana desde la que acceder al mundo interno del niño/a. Las técnicas narrativas se basan en las

experiencias de interacción que los niños/as establecen con los principales cuidadores o adultos de su entorno, generando la construcción de modelos mentales basados en las expectativas que el niño/a tiene sobre cómo responderán sus cuidadores a sus necesidades.

Durante muchos años estos instrumentos dirigidos a niños/as, como por ejemplo el *Macarthur Story Stem Battery* (MSSB) (Bretherton et al., 2003), han carecido de protocolos sistematizados. Sin embargo, actualmente existen instrumentos de aplicación infantil validados, como el *Story Stem Assessment Profile* (SSAP) (Hodges et al., 2007) también traducido al español (Roman et al., 2018). Esta herramienta resulta eficaz para evaluar las representaciones mentales y expectativas de los roles familiares en niños/as de 4-9 años, y se ha descrito como una herramienta útil para predecir posibles experiencias de maltrato del menor (Hillman et al., 2020). La investigación sobre el estilo de apego mediante la evaluación de la situación del extraño (Ainsworth et al., 1978), también se ha usado ampliamente como un método para identificar estilos de apego seguro o inseguro en la primera infancia.

En definitiva, tanto la práctica clínica como los estudios científicos sugieren que la mejor información para valorar posibles situaciones de maltrato proviene de diferentes fuentes (niño/a o adolescente, familiares, informes de los profesores o servicios sociales, etc.), ya que es la que mejor informa el riesgo infantil al que está expuesto el menor (Sierau et al., 2016).

1.3. Implicaciones psicológicas y psiquiátricas del maltrato infantil

Es importante recordar que, desde un punto de vista epidemiológico y de la historia natural de la enfermedad mental, la mayoría de los trastornos psiquiátricos se manifiestan en las primeras etapas de la vida, habitualmente durante la pubertad, adolescencia o inicio de la juventud (Solmi et al., 2021). Muchos procesos del neurodesarrollo culminan también en este periodo, permitiendo al cerebro expresar algunos síntomas de mayor complejidad relacionados con diagnósticos psiquiátricos específicos en la edad adulta (Figura 3).

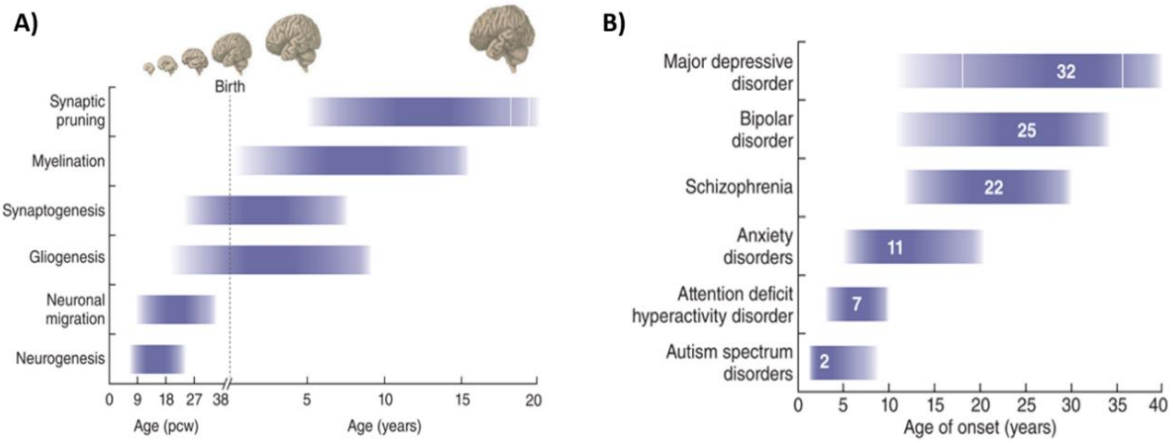


Figura 3. A) Procesos clave del desarrollo cerebral humano antes y después del nacimiento. B) Edad de inicio media de los diferentes trastornos psiquiátricos. Imagen reproducida con los permisos de Marín O. *Developmental timing and critical windows for the treatment of psychiatric disorders. Nature Medicine 22, 1229-1238 (2016).*

El abandono, la negligencia y el maltrato producen en los niños/as heridas profundas que condicionan su desarrollo neuropsicológico, su autoestima, su autoconcepto y también la forma de relacionarse consigo mismo, con los demás y con el mundo.

Cuando los propios cuidadores ejercen maltrato, el niño/a se encuentra en una situación sin salida; las figuras que le provocan miedo y rechazo son las mismas que en principio le tienen que dar protección y seguridad, dejándole en una situación ambivalente y sin la posibilidad de encontrar refugio ante las situaciones de temor.

Diferentes teorías y estudios en los últimos cuarenta años han intentado describir y explicar las alteraciones psicológicas y neurobiológicas que se observan en los niños/as o adultos que viven estas situaciones de maltrato en el ambiente familiar.

Cuando el evento se ha producido de manera abrupta, aguda y violenta (como, por ejemplo, un abuso sexual) a menudo es posible reconocer en la persona síntomas compatibles con el TEPT (Yehuda et al., 2015) (ver Cuadro 5). Sin embargo, la mayor parte de los individuos expuestos a acontecimientos traumáticos no desarrollan un TEPT, sugiriendo que esta sintomatología es solamente una de las numerosas respuestas posibles frente a un evento traumático (Tolin and Foa, 2006). Además, la exposición a trauma complejo, como el maltrato infantil, se ha asociado con sintomatología diversa mucho más amplia que la recogida por los criterios diagnósticos del TEPT (Messman-Moore and Bhuptani, 2017).

CUADRO 5. Trastorno por estrés postraumático (TEPT)

El riesgo de exposición a acontecimientos vitales traumáticos varía según el país y la disponibilidad de recursos materiales, personales y económicos, que serán cruciales tanto para predecir la aparición como la persistencia de la sintomatología por estrés postraumático. El diagnóstico TEPT fue creado inicialmente para capturar los síntomas que observaron en adultos que habían sufrido traumas puntuales como una violación o experiencias de guerra.

Los síntomas del TEPT se caracterizan principalmente por presentar:

1) Intrusión: recuerdos o sueños recurrentes angustiosos como si estuviera sucediendo otra vez el hecho traumático, provocando malestar psicológico y/o fisiológico intenso.
2) Evitación: evasión persistente de pensar o hablar sobre al suceso traumático o evitar estímulos o lugares asociados a él.
3) Hiperalerta: sensación continuada de hiperactivación o sensación de peligro.

Los estudios han demostrado que la sintomatología TEPT está directamente relacionada con la severidad de los eventos traumáticos a los que se ha estado expuesto (Tollin and Foa, 2006). Debería ser una prioridad apoyar y luchar por políticas sociales y de salud pública que protejan y defiendan a las personas con TEPT, que permitan prevenir la cascada en el ciclo de pérdidas que prolongan sus efectos (Yehuda et al 2015).

En este sentido, la Clasificación Internacional de las Enfermedades (CIE-11) (World Health Organization, 2019) ha propuesto un nuevo diagnóstico que pretende abarcar la clínica observada en pacientes expuestos a trauma complejo, el TEPT-complejo (TEPT-C). Esta nueva entidad diagnóstica se define por los síntomas característicos de un TEPT y también por la presencia de alteraciones en la autoorganización de la persona (desregulación emocional, autoconcepto negativo y dificultades interpersonales). Estas últimas características se asemejan a algunos de los rasgos clínicos observados en personas con trastorno límite de la personalidad (TLP), otro diagnóstico también muy vinculado al trauma complejo (Giourou et al., 2018).

Sin embargo, aunque algunos estudios vinculan ciertos tipos de maltrato con diagnósticos psiquiátricos específicos, la evidencia científica sugiere que cualquier forma de maltrato (desde la negligencia al abuso emocional, físico o sexual) tiene efectos generalizados y sistémicos sobre la salud física y mental de la persona. Es decir, el maltrato es un factor de riesgo transdiagnóstico (Teicher and Samson, 2013). De hecho, solo hay que preguntar a las personas que acuden a los servicios de salud mental para darse cuenta de que un gran porcentaje de ellos relatan infancias complejas con padres ausentes, fríos y/o violentos (Read et al., 2005).

Uno de los estudios más relevantes en este campo fue el desarrollado por Anda y colaboradores (2006), basado en una amplia muestra de adultos evaluados

retrospectivamente. Este trabajo demostró que las experiencias adversas durante la infancia (acontecimientos familiares estresantes o maltrato) eran relevantes para explicar el riesgo de desarrollar distintos trastornos mentales en la edad adulta. Los diagnósticos que más riesgo acumularon fueron los trastornos por consumo de sustancias y los trastornos del espectro ansioso-depresivo.

Sin embargo, esta asociación incluye también aquellos diagnósticos en los que se ha reportado una importante carga genética, como el trastorno bipolar o la esquizofrenia. En este sentido, un estudio que revisó 46 artículos científicos sobre maltrato en pacientes con episodios psicóticos (con un total de 4.140 participantes), observó que casi el 70% de las mujeres y casi el 60% de los hombres referían haber sufrido maltrato físico y/o abuso sexual durante su infancia (Read et al., 2005). Estos números hablan por sí solos. Además, hay que tener en cuenta que estos datos no incluyen otros tipos de maltrato como la negligencia o el maltrato emocional, por lo que las cifras serían aún más altas.

Algunos autores estiman que casi la mitad de los trastornos mentales que se manifiestan en la infancia o adolescencia están directamente relacionados con experiencias de maltrato, y más del 35% en el caso de los trastornos diagnosticados en la edad adulta (Kessler et al., 2010). Además, parece que los pacientes psiquiátricos con historia de maltrato constituyen un subtipo de pacientes clínicamente distinto, con una sintomatología más compleja, de inicio más temprano, con más comorbilidad y con una peor adherencia y respuesta al tratamiento psicológico y farmacológico (Nanni et al., 2012).

1.3.1. Maltrato infantil y personalidad

Para construir una personalidad madura, un niño/a necesita percibirse y ser reconocido como un individuo independiente y dotado de necesidades propias distintas a las de sus padres. Sobre la base de este bagaje fundamental, el niño/a organiza y construye su experiencia relacional dando sentido a lo que le sucede y construyendo así su identidad que, si es sana y madura, le servirá de anclaje adecuado en la realidad. Una falta de reconocimiento o una descalificación constante de sus cualidades personales por parte de figuras relevantes del entorno puede comportar, por tanto, serios hándicaps para la construcción de una personalidad sana (Linehan, 1993).

Entendemos por rasgos de la personalidad aquellos patrones persistentes del modo en que percibimos, pensamos y nos relacionamos con el entorno y nosotros mismos, y que se muestran en una amplia gama de contextos sociales y personales.

Cuando los rasgos de personalidad son inflexibles, desadaptativos y causan malestar subjetivo o deterioro funcional, hablamos de trastornos de la personalidad. La manifestación más habitual de los trastornos de la personalidad se produce en la adolescencia o en la edad adulta temprana, cuando el sujeto debe enfrentarse al mundo social de manera independiente y autónoma.

A la hora de comprender cómo se constituye y se establece un trastorno de la personalidad, es importante destacar que, como en la mayoría de los trastornos mentales, existen factores genéticos y factores ambientales implicados; estos últimos, de tipo relacional y claramente enmarcados en un contexto cultural. Es decir, la genética juega un papel importante en la transmisión de rasgos temperamentales y la cultura enmarca y determina esta personalidad, influyendo decisivamente en su definición o interpretación (por ejemplo, no significa lo mismo ser introvertido en un país Oriental que en el Caribe).

Por último, el ambiente familiar próximo tiene un papel fundamental en la construcción de un trastorno de la personalidad. Los factores familiares de riesgo más reportados son la exposición a maltrato, los estilos de crianza invalidantes, la negligencia, el abuso sexual y la exposición a situaciones adversas y conflictivas o violentas.

Debido a su complejidad, los trastornos de la personalidad han despertado mucha controversia y existen numerosos puntos de vista sobre cómo definirlos, clasificarlos y tratarlos. Actualmente, el DSM-5, manual diagnóstico de referencia en el campo de la salud mental, define los trastornos de la personalidad desde una perspectiva categorial, entendiéndolos como síndromes clínicos cualitativamente distintos entre sí (APA, 2013).

Aunque hay evidencia científica (Kaess et al., 2014) que demuestra que los trastornos de la personalidad son tan fiables y válidos entre los adolescentes como en los adultos, siguen siendo diagnósticos controvertidos a la hora de aplicarlos en población infantojuvenil. De hecho, la adolescencia, en su propia naturaleza, es una etapa vital compleja que abarca grandes cambios psíquicos y biológicos caracterizados por alteraciones en la cognición, la afectividad, el funcionamiento interpersonal y el control de los impulsos (Soto and Tackett, 2016). Por tanto, en esta etapa evolutiva son bastante frecuentes los patrones desadaptativos que podrían asociarse a rasgos característicos de los trastornos de la personalidad, especialmente el TLP y el trastorno de la personalidad antisocial (Fossati et al., 2014).

Sin embargo, la propuesta del DSM-5 que establece los trastornos de la personalidad como tipos diferenciados en entidades diagnósticas, es muy criticada por

algunos autores (Polek et al., 2018). Así, existen enfoques alternativos basados en una perspectiva dimensional que los consideran como variaciones desadaptativas y disfuncionales de los rasgos de la personalidad que se mezclan imperceptiblemente con la normalidad. Estas últimas aproximaciones han ido tomando cuerpo en los últimos años y se han incorporado en la nueva clasificación de la CIE-11 propuesta por la OMS (World Health Organization, 2019).

Este nuevo enfoque, que rompe con la visión tradicional categorial, y junto con la idea de que estos trastornos son la expresión de una desorganización generalizada del sistema personal, resulta más útil y productiva, ya que permite pensar en ellos como una entidad diagnóstica única que se expresa de modos diferentes en cada individuo (Livesley, 2021). Además, incluye la valoración de su gravedad en base a las disfunciones que provoca en las relaciones interpersonales y en la vida cotidiana de la persona (Bach and First, 2018). De acuerdo con esta visión, los rasgos desadaptativos de la personalidad se pueden encontrar presentes en la población general distribuidos a lo largo de un contínuum de gravedad.

1.3.2. Maltrato infantil y sintomatología durante la infancia y adolescencia

Como hemos visto, las consecuencias psicopatológicas de las adversidades tempranas pueden manifestarse tanto de manera proximal al evento, durante la propia infancia, como años más tarde durante la vida adulta.

Sin embargo, en la mayoría de los niños/as las manifestaciones clínicas asociadas a las experiencias de maltrato infantil son globales, dispares e inespecíficas, lo que dificulta habitualmente la detección e intervención por parte de los especialistas (Winter et al., 2022).

Algunos de los síntomas descritos más frecuentemente relacionados con las experiencias de maltrato en población infantojuvenil serían los siguientes (García and Noguerol, 2007):

- Problemas emocionales: Miedos y fobias, desconfianza, depresión, ansiedad, baja autoestima, culpabilidad, vergüenza, estigmatización, estrés postraumático (pesadillas, sueños recurrentes, hipervigilancia, respuestas exageradas y sobresalto), rechazo al cuerpo, retraso en el desarrollo, conductas autolesivas, ideación o conductas suicidas.

- Problemas cognitivos: conductas hiperactivas, problemas de atención o concentración, bajo rendimiento académico.
- Problemas de relación: círculo de amistades reducido, menor tiempo de juego con iguales, aislamiento, déficit de habilidades sociales, círculo de amistades solo superficiales.
- Problemas funcionales: problemas del sueño, cambios en los hábitos alimenticios, problemas en el control de esfínteres (enuresis o encopresis), quejas somáticas (dolor de cabeza, estómago…)
- Problemas de conducta:
    - Conductas disruptivas o disociales: hostilidad, rabia, agresividad, oposición, desafiante, fugas del hogar.
    - Conductas sexualizadas o erotizadas: masturbación compulsiva, imitación de actos sexuales, uso de vocabulario sexual inapropiado, curiosidad sexual excesiva, juegos y dibujos de naturaleza sexual, conductas exhibicionistas o seductoras, promiscuidad exagerada.
    - Conductas adictivas: Abuso de sustancias, adicción a las nuevas tecnologías.

Como se ha descrito, puede existir una gran dificultad en el proceso de diagnóstico del cuadro clínico que presentan los niños/as que sufren experiencias de maltrato y, por lo tanto, también para seleccionar las intervenciones más adecuadas (Lippard and Nemeroff, 2020). Además, la sintomatología que presentan en estas edades tiende a concurrir (Kessler et al., 2012).

Debido a esta inespecificidad diagnóstica, se ha observado que en población infantojuvenil la sintomatología puede agruparse en dos grandes espectros: internalizante y externalizante. Aquellos sujetos que suelen expresar el malestar emocional "hacia dentro", en forma de ansiedad, tristeza, aislamiento, dolores abdominales o miedo, formarían parte del espectro internalizante. En cambio, aquellos que lo manifiestan "hacia fuera", con agresividad, impulsividad o conductas antinormativas, se considerarían externalizantes.

De acuerdo con algunos autores, estos síntomas internalizantes o externalizantes expresados en la infancia o la adolescencia podrían considerarse como estados prodrómicos de cuadros clínicos más específicos de aparición tardía (Fryers and Brugha, 2013). La sintomatología internalizante se considera un riesgo general para desarrollar trastornos mentales caracterizados por el afecto negativo, desregulación del estado de

ánimo y la ansiedad. En cambio, los síntomas externalizantes serían un factor de riesgo para los trastornos de desinhibición, como los trastornos por uso de sustancias y los trastornos del comportamiento antisocial (Krueger and Markon, 2006).

Usar esta conceptualización en población infantojuvenil permite englobar los síntomas tan difusos y generales que se observan habitualmente en niños/as o adolescente y que a menudo son difíciles de encajar completamente en un diagnóstico categorial específico (Cicchetti and Rogosch, 2002).

1.3.3. Exposición a maltrato infantil y la relación dosis-efecto sobre los fenotipos clínicos

Un gran número de fenómenos biológicos de causalidad de enfermedad han sido relacionados con el modelo de dosis-efecto. Quizás el más conocido y replicado sea el del uso del tabaco y el riesgo de cáncer de pulmón (Ruano-Ravina et al., 2003). Estos modelos de causalidad ponen de relevancia la capacidad limitada de los sistemas biológicos para reponer la homeostasis y responder de manera adaptativa a la agresión ambiental continuada. En este sentido, parece que el cerebro y los mecanismos neurobiológicos operarían de un modo semejante frente a los estresores psicosociales para preservar la integridad psíquica del individuo.

Asimismo, algunos autores describen la relevancia que tiene el periodo evolutivo en el que tiene lugar cada tipo de maltrato, señalando la etapa media de la niñez (6-10 años) como uno de los periodos del desarrollo más sensibles y críticos para acabar desarrollando problemas de desregulación emocional o sintomatología psiquiátrica (Dunn et al., 2018). Dado que el desarrollo cerebral es distinto en cada etapa evolutiva, determinar cuándo ocurrieron las experiencias adversas será crucial a la hora de entender el impacto que han podido tener en el desarrollo cerebral de la persona y en los síntomas con los que se asocia (Schalinski et al., 2016).

Son varios los trabajos que demuestran que existe una relación dosis-efecto entre la agregación de vivencias adversas y el riesgo de presentar sintomatología psiquiátrica. Una de las investigaciones más relevantes en este campo fue desarrollada por Anda y colaboradores (2006). Específicamente, este estudio puso de manifiesto que, a partir de cuatro o más eventos adversos vividos durante la infancia, aumentaba significativamente el riesgo de sufrir un trastorno mental en la edad adulta (ver Figura 4).

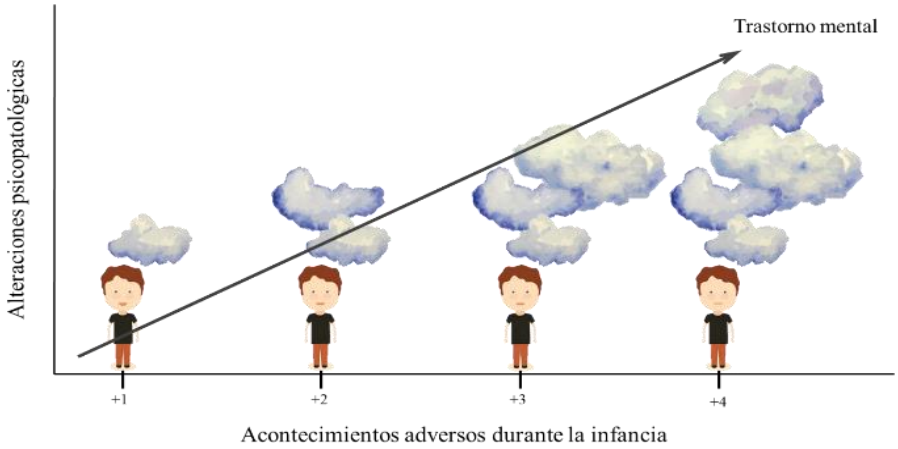


Figura 4. Propuesta de relación dosis-efecto entre las experiencias adversas vividas en la infancia y sus consecuencias psicopatológicas más tempranas.

En la misma línea, otro estudio reciente basado en niños/as, demuestra que aquellos que han experimentado múltiples tipos de maltrato de forma crónica tienen mayor riesgo de desarrollar problemas psicológicos y emocionales en comparación con los niños/as que han vivido un tipo de maltrato de forma puntual (Warmingham et al., 2019). Sin embargo, cabe mencionar que la mayoría de las personas no viven las experiencias de maltrato de manera aislada y puntual, sino que los diferentes tipos de maltrato coexisten y se experimentan de forma continuada (Vachon et al., 2015). Por tanto, a la hora de comprender los efectos del maltrato en el organismo y sus repercusiones psicopatológicas es de gran relevancia considerar esta condición habitual de agregación y cronicidad.

También los abordajes longitudinales desarrollados en poblaciones infantiles de escolares británicos (Arseneault et al., 2011), han confirmado la existencia de esta relación dosis-efecto entre las experiencias de maltrato familiar y/o *bullying* y los síntomas del espectro psicótico (*Psychosis like experiences* en inglés). En concreto, este estudio demuestra que la agregación de los dos tipos de traumas relacionales aumentaría más de seis veces el riesgo de tener experiencias psicóticas a los 12 años de edad, un riesgo muy superior que si el maltrato o el *bullying* aparecían de forma aislada.

Este modelo dosis-efecto centrado en la edad infantil podría ser corroborado desde el estudio de nuevas poblaciones infantiles y de adolescentes bien caracterizadas en su historia de maltrato infantil y en sus perfiles psicopatológicos. Profundizar en el estudio de estas asociaciones sería, por tanto, uno de los principales objetivos de la presente tesis.

En este contexto, es importante señalar que la ideación y las conductas suicidas podrían representar la punta más alta de la pirámide que representa el malestar y la indefensión de un ser humano. Aunque, tanto el suicidio como sus conductas asociadas son un fenómeno multifactorial, el trauma relacional es un factor clásicamente relacionado con el riesgo de autolesiones, gestos suicidas, intentos autolíticos y la muerte por suicidio (Angelakis et al., 2019; Miller et al., 2013). La asociación entre las experiencias adversas sufridas, los rasgos de personalidad disfuncionales y las conductas suicidas está bastante bien establecida (Allen et al., 2013) (Ver Cuadro 6). Sin embargo, la interacción entre estas variables (rasgos de personalidad, trauma relacional, acontecimientos estresantes recientes y conductas suicidas) en población infantojuvenil es menos conocida.

CUADRO 6. Conductas suicidas y autolesiones en personas con historia de trauma

Actualmente, el suicidio supone un grave problema de salud pública en Europa, ya que, en 2019 un total de 3.671 personas fallecieron por esta causa (los accidentes de tráfico suponen menos de la mitad). Además, en los últimos años ha aumentado el número de autolesiones o conductas suicidas en población infantojuvenil (Mortier et al., 2021; Cousien et al., 2021).

Este tipo de conductas se han asociado, entre otros factores, a experiencias de trauma complejo en la familia o acoso escolar (o ciberbullying), tanto de manera proximal como en la edad adulta (Winsper et al., 2012; Van Geel et al., 2014). De hecho, el maltrato podría suponer un riesgo añadido, pero los estresores próximos podrían ser los desencadenantes de estas conductas (Liu and Miller, 2014).

Desde el punto de vista de la investigación hemos de pensar, por tanto, que la tipología de maltrato, su comorbilidad, la severidad, la duración, así como la ventana ontogénica en la que ocurre jugarán un papel fundamental en las expresiones psicopatológicas y neurobiológicas futuras. Por tanto, explorar la historia de maltrato de manera dicotómica puede comportar muchos sesgos en su interpretación, siendo mucho más informativo y coherente un abordaje dosis-efecto.

En el último apartado de esta introducción se describen, brevemente, algunas de las características esenciales que definen estos sistemas biológicos de regulación de la respuesta al estrés y se hace también hincapié en los métodos empíricos para el estudio de su funcionamiento, tanto en estado basal como frente a la exposición a un estrés agudo de naturaleza psicosocial.

1.4. La neurobiología del maltrato infantil

La infancia temprana constituye un periodo crítico para establecer la biología de una mente sana. La relevancia del ambiente para moldear el cerebro en estos periodos tan incipientes del desarrollo ha sido reconocida desde multitud de estudios (Teicher et al., 2018).

Aunque durante mucho tiempo se ha asumido en la comunidad científica que el cerebro humano es innatamente social, una investigación reciente sugiere que no todas las capacidades mentales y sociales son universales y que existen diferencias culturales profundas entre los grupos. Es decir, numerosos conceptos emocionales y sociales se construyen ambientalmente en cada cultura y estas diferencias culturales se integran biológicamente en la estructura del cerebro (Atzil et al., 2018).

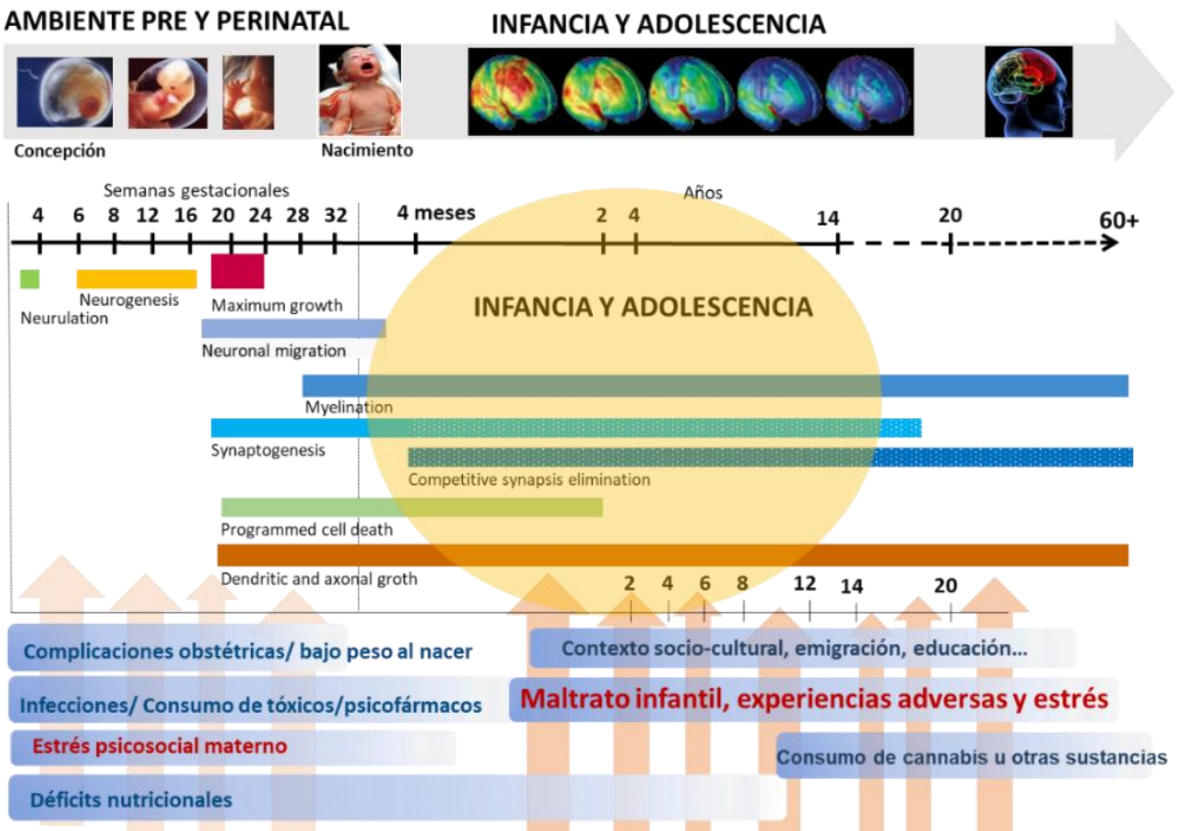


Figura 5. Desarrollo cerebral desde la fecundación hasta la edad adulta e impacto de diversos factores ambientales (pre y posnatales).

Esto implicaría, entre otras cosas, que las experiencias de crianza de los hijos y la infancia temprana son más importantes de lo que pensábamos en relación con la forma y función cerebral. Las experiencias tempranas no solo darían forma a nuestra

personalidad y valores, también crearían el cableado que gobernará nuestra percepción social del mundo. La habilidad de un cerebro adulto para responder a las situaciones de estrés psicosocial en su contexto cultural estará, por tanto, muy relacionada con las experiencias más tempranas y, de alguna manera, esta habilidad o dificultad estará inscrita en la función neurobiológica del cerebro desde etapas muy tempranas.

Aunque la mayoría de neuronas estén formadas antes del nacimiento, el crecimiento y maduración del cerebro se sigue produciendo a nivel posnatal, adquiriendo el 80% del volumen total de materia gris en los primeros dos años de vida, y el 80% del volumen de la materia blanca en la niñez avanzada (Groeschel et al., 2010).

Por tanto, durante los primeros años de vida se van a producir numerosos cambios estructurales, funcionales y de conectividad entre las neuronas del córtex cerebral, así como entre las neuronas y las células gliales que las acompañan (astrocitos, oligodendrocitos y microglía). La formación de sinapsis neuronales se extiende aceleradamente durante la primera infancia, y más lentamente a partir de los diez años de edad. Específicamente, se producen un gran número de sinapsis excitatorias (mediadas por el sistema glutamatérgico) y se incrementa de forma progresiva el volumen de materia blanca, reforzando así la conectividad entre diferentes áreas cerebrales. Paralelamente, a lo largo de la infancia, se produce una lenta sinaptogénesis inhibitoria (mediada por el sistema gabaérgico). En la pubertad, con la aparición de las hormonas sexuales, comenzará un proceso conocido como «poda neuronal» (*pruning* en inglés) mediante el cual se eliminarán las sinapsis sobrantes y se afianzarán las otras. Aunque el patrón que regirá este proceso está dirigido por los genes, como hemos comentado anteriormente, algunas funciones esenciales relacionadas con la cognición social y la comunicación social serán expectantes del ambiente. Así, las experiencias vividas en esos momentos podrán determinar las vías de respuesta más comunes en cada individuo.

En este contexto es fácil reconocer la importancia que pueden tener algunos estresores sociales a la hora de dirigir este proceso madurativo fundamental para determinar la arquitectura cerebral de cada persona (Santos and Noggle, 2011).

Por otro lado, está claramente demostrada la importancia que tienen diferentes factores ambientales de riesgo, tanto biológicos como sociales, en el posterior desarrollo de un trastorno mental. La Figura 5 recoge una síntesis de los principales factores ambientales de riesgo y los sitúa en un esquema del neurodesarrollo cerebral. Esta imagen nos permite identificar factores biológicos, tales como infecciones, consumo de

tóxicos o déficits vitamínicos, actuando durante procesos incipientes de gran relevancia para el cerebro como son la migración neuronal al córtex cerebral o los procesos de sinaptogénesis.

Es interesante señalar la relevancia que puede tener el estrés psicosocial sufrido por la mujer ya durante el embarazo en la formación y funcionamiento de algunas estructuras cerebrales del futuro bebé (Palma-Gudiel et al., 2015). Como se ha ido señalando a lo largo de esta introducción, entre los factores postnatales de mayor importancia asociados al trastorno mental se encontrarían las experiencias de maltrato infantil, coincidiendo con procesos de desarrollo de la interconectividad entre áreas cerebrales distantes (mielinización) y la selección competitiva de sinapsis (*pruning*).

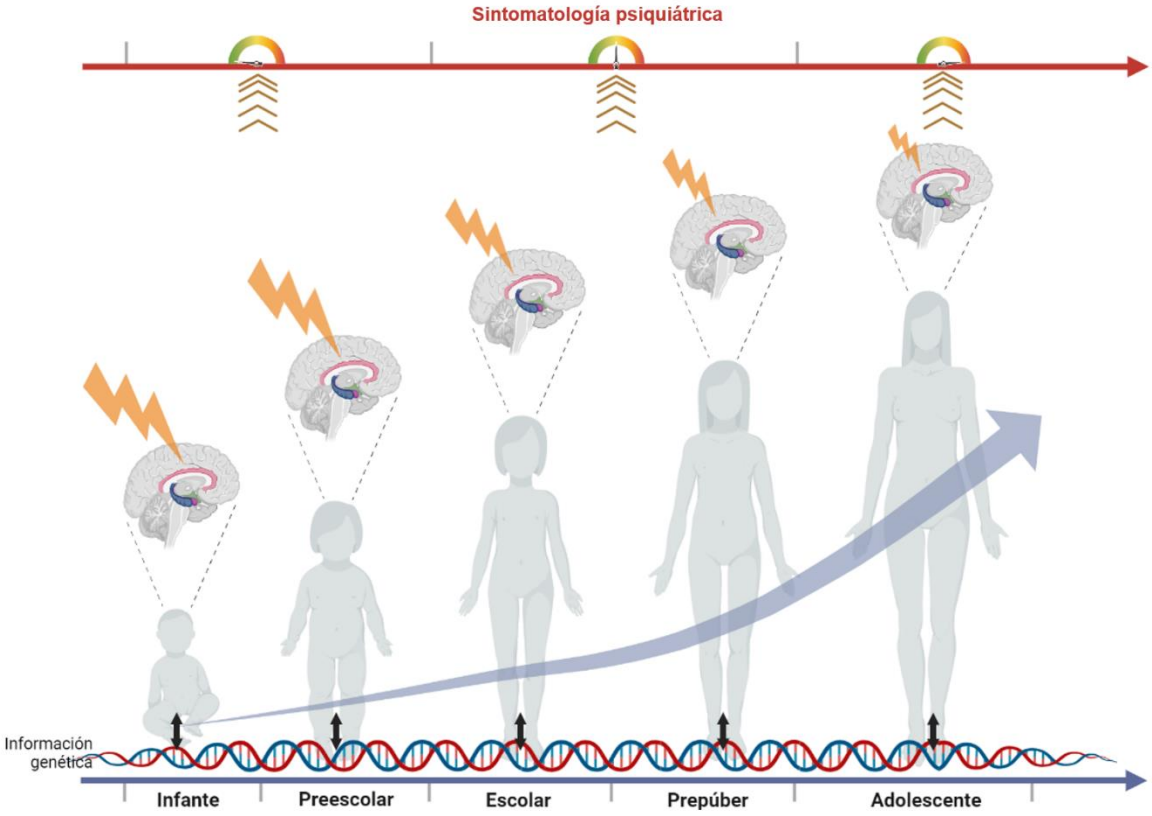


Figura 6. Impacto del estrés sobre el neurodesarrollo a lo largo de la infancia y adolescencia. El trauma relacional afecta directamente sobre la maduración del sistema límbico y del eje Hipotalámico-Hipofisario-Adrenal (HHA). Las flechas en naranja indican la capacidad del estrés psicosocial de alterar el funcionamiento de estos sistemas neurobiológicos, lo cual puede aumentar el riesgo de sintomatología psiquiátrica. Las alteraciones podrán ser distintas en función de la etapa del desarrollo cerebral en la que tenga lugar el maltrato. Los genes y las hormonas sexuales durante la pubertad jugarán un papel fundamental en este complejo entramado. Imagen creada con BioRender.com.

Por tanto, el momento ontogénico del desarrollo cerebral en el que tienen lugar las experiencias de maltrato va a tener una gran relevancia sobre las estructuras del

cerebro afectadas (Schalinski et al., 2016; Teicher et al., 2016). Por ejemplo, mientras que las consecuencias del maltrato o negligencia grave en los primeros meses de vida se encontraran principalmente en las áreas subcorticales del cerebro (como el hipocampo o el hipotálamo), el maltrato sufrido en etapas posteriores se refleja fundamentalmente en cambios corticales asociados con una disminución del volumen de materia gris en áreas prefrontales o la pérdida de integridad en la interconectividad entre áreas cerebrales (ver Figura 6).

1.4.1. El estrés como respuesta fisiológica

Según el modelo fisiológico del estrés establecido por Selye en 1936, el estrés se describe como "la respuesta fisiológica de un organismo caracterizada por un síndrome de adaptación general que resulta de la activación orquestada de los sistemas nervioso, endocrino e inmunológico".

Años más tarde, Lazarus y Folkman (1986) definieron el modelo psicológico del estrés como "una relación con el entorno que la persona evalúa como significativa para su bienestar y en la que las demandas ponen a prueba o superan los recursos de afrontamiento disponibles".

A día de hoy podemos asegurar que la respuesta al estrés es tanto un mecanismo biológico como un proceso cognitivo que incluye una amplia gama de cambios fisiológicos y psicológicos que se desencadenan para hacer frente al estresor físico o social (Folkman, 2013; Mendelson, 2013). Cuando los estresores poseen una duración y amplitud limitadas (estresor agudo), facilitan que el organismo vuelva a niveles homeostáticos rápidamente (van Oort et al., 2017). Sin embargo, la exposición continuada a un estresor conduce a una activación crónica de la respuesta al estrés, provocando que el organismo ya no sea capaz de volver rápidamente al estado homeostático, produciendo un empeoramiento de la salud (McEwen, 2017).

1.4.2. Sistemas de conservación de la homeostasis frente estrés psicosocial

Existen numerosos mecanismos biológicos involucrados en la respuesta al estrés que se activan paralelamente para que el organismo se adapte a la nueva situación.

Para comprender este complejo entramado que enmarca la respuesta al estrés psicosocial, es necesario recordar que cuando el cerebro humano detecta una señal de

alerta se activan de forma innata numerosos mecanismos psiconeurobiológicos, provocando una activación global del organismo para sobrevivir. Sin embargo, el cerebro es un órgano diseñado para afrontar situaciones de estrés puntuales y, por lo tanto, frente adversidades crónicas o de una intensidad extrema, como es el caso del maltrato infantil o el abuso sexual, se pueden desregular diferentes sistemas neurobiológicos que afectaran a la salud mental y física de la persona, aumentando aún más su vulnerabilidad frente futuras situaciones de estrés (Carr et al., 2013).

Aunque algunos mecanismos específicos de respuesta al estrés los veremos más adelante, es interesante recordar la importancia del Sistema Nervioso Autónomo (SNA) para producir cambios fisiológicos rápidos y adaptativos en todo el organismo. Clásicamente, el SNA se subdivide en una rama excitatoria, el sistema nervioso simpático (SNS), y otra inhibitoria, el sistema nervioso parasimpático (SNP) (Figura 7).

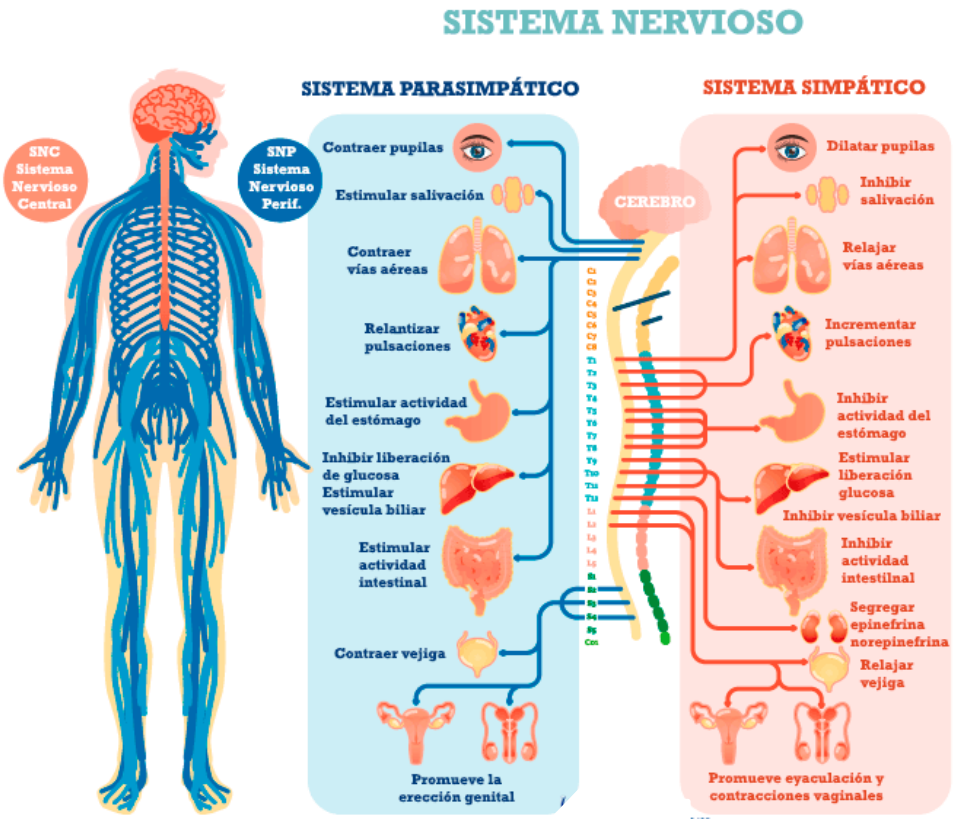


Figura 7. El sistema nervioso autónomo (SNA) forma parte del sistema nervioso que controla las acciones involuntarias. El SNA se divide en el sistema nervioso simpático (SNS) y el sistema nervioso parasimpático (SNP). En rojo se muestran algunas de las funciones que desencadena el SNS para hacer frente al estresor y en azul algunas de las funciones que desempeña el SNP para restaurar la homeostasis.

Cuando un estresor aparece en escena, se activa el SNS, que produce una activación fisiológica adaptativa rápida, conocida como de "lucha o huida", que permite

preparar al sistema para enfrentarse al peligro y proporcionar la energía necesaria para sobrevivir. Así, la activación del SNS permite al organismo reaccionar frente al desafío ambiental en cuestión de minutos u horas, aumentando el ritmo cardíaco, la frecuencia respiratoria, la presión arterial, dilatando las pupilas y disminuyendo los jugos digestivos, entre otros (Sapolsky et al., 2000; Segerstrom and Miller, 2004).

Por otro lado, el SNP se activa cuando ya ha culminado y finalizado el peligro, y conduce al organismo a un estado de calma y estabilidad, desacelerando el ritmo cardíaco, relajando los músculos, aumentando los jugos digestivos, etc. En condiciones óptimas, ambos sistemas interaccionan de forma antagónica para encontrar un equilibrio entre la activación fisiológica adaptativa y la homeostasis en el reposo basal.

La facilidad con la que un individuo puede oscilar entre estados de activación elevada o reducida depende de la habilidad del SNA para generar fluctuaciones rápidas en su respuesta biológica. Un SNA flexible permite la modulación rápida de los estados fisiológicos y emocionales de acuerdo a las demandas de la situación. En cambio, la rigidez del SNA resulta en una capacidad mermada de generar o alterar respuestas fisiológicas en sincronía con los cambios en el ambiente.

Por tanto, las emociones que los humanos experimentan a raíz de sus interacciones sociales se pueden asociar con distintos grados de activación fisiológica (Levenson, 2003). Tanto la regulación emocional que muestra un individuo como la capacidad de ajustar el funcionamiento de los sistemas fisiológicos se establece, en gran parte, durante los primeros años de vida mediante los vínculos de apego (Gross, 1998).

1.4.2.1. El eje hipotalámico-hipofisario-adrenal (HHA)

Uno de los principales y más tempranos mecanismos de regulación del estrés en humanos es el eje Hipotalámico-Hipofisario-Adrenal (HHA) (Tarullo and Gunnar, 2006). Como se representa en la Figura 8, en condiciones habituales, cuando el cerebro detecta una señal de estrés se activa el núcleo paraventricular del hipotálamo que estimula, a su vez, la liberación de la hormona adrenocorticotrópica (CRH) que se dirige a la adenohipófisis donde se va a promover la liberación de corticotropina (ACTH). A su vez, la ACTH llega a través de la sangre a las glándulas suprarrenales, ubicadas en la parte superior de los riñones, donde finalmente se desencadenará la secreción de los glucocorticoides, siendo el cortisol el más importante en humanos.

Una vez liberado el cortisol al torrente sanguíneo, se unirá a los receptores de glucocorticoides ubicados en el citoplasma celular de los diferentes tejidos y células diana (muscular, cerebral, células del sistema inmune, etc.). La unión del cortisol al receptor permitirá finalmente su translocación al núcleo, donde ejercerá un amplio rango de acciones mediante la activación y el silenciamiento de distintos genes. Esto permitirá activar diferentes procesos celulares en cascada para ayudar a lidiar con la situación de estrés percibida (aumento de la circulación sanguínea, gluconeogénesis, disminución de la acción del sistema inmune, aumento de la capacidad de concentración, etc.).

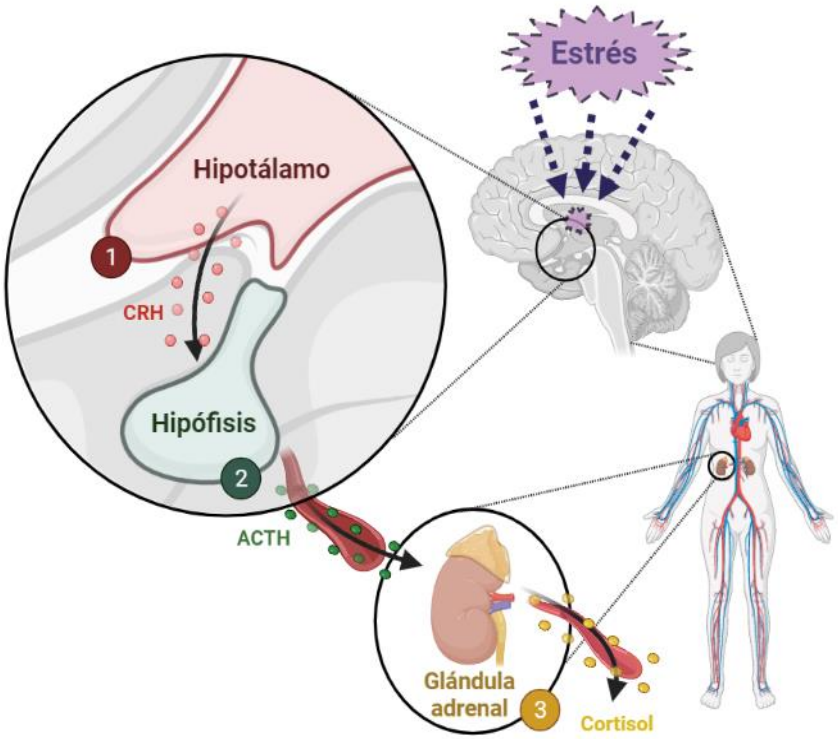


Figura 8. Eje Hipotalámico-Hipofisario-Adrenal (HHA). Cuando el cerebro detecta una señal de estrés, el hipotálamo estimula la liberación de la hormona adrenocorticotrópica (CRH) (1) que se dirige a la adenohipófisis, donde se va a promover la liberación de corticotropina (ACTH) (2). A su vez, la ACTH llega a través de la sangre a las glándulas adrenales ubicadas en la parte superior de los riñones, donde desencadenará la secreción del cortisol (3). Imagen creada con BioRender.com.

El cortisol es, por tanto, una hormona natural y adaptativa que frente a estresores agudos permitirá la activación de distintos procesos neurobiológicos. En paralelo, el organismo pondrá en marcha el sistema de retroalimentación negativa con el fin de restaurar la homeostasis. Es decir, una vez el cortisol liberado llegue al cerebro, se unirá a los receptores de glucocorticoides situados en el hipotálamo y la hipófisis que, en consecuencia, inhibirán la producción de CRH y ACTH para frenar la activación del eje HHA.

Es importante señalar que el funcionamiento del eje HHA todavía no ha madurado del todo cuando nacemos. Así, este mecanismo se va a modular durante las primeras etapas de la vida en función de diferentes factores ambientales, entre ellos el estilo de apego con el cuidador principal (Tarullo and Gunnar, 2006).

Como se ha mencionado previamente, si el organismo se encuentra sometido a periodos de estrés muy prolongados durante la infancia, este mecanismo adaptativo podría verse alterado y desregulado (Bernard et al., 2017; Bunea, Szentágotai-t, and Miu, 2017). De hecho, bajo situaciones de estrés crónico, como puede ser el maltrato infantil, el eje HHA podría estar hiperactivado durante demasiado tiempo. En este caso, el exceso de cortisol en sangre puede provocar, a largo plazo, una desensibilización de los receptores de glucocorticoides. Es decir, el sistema de retroalimentación negativa se vería alterado, provocando una producción de cortisol sin freno.

Niveles altos y prolongados de cortisol son neurotóxicos, modifican el perfil proinflamatorio y dañan otros sistemas biológicos. El organismo, para poder mantener el equilibrio y favorecer la homeostasis, puede dar lugar al mecanismo de desensibilización del funcionamiento del eje HHA. Por tanto, aquellas personas que han sufrido situaciones adversas durante largos periodos de su vida podrían presentar, a largo plazo, un eje HHA poco reactivo ante situaciones de estrés, caracterizado por una baja producción de cortisol frente a las situaciones de demanda o estrés. Se hipotetiza que, aunque esta desensibilización preservaría al organismo de la neurotoxicidad del cortisol, implicaría también una pérdida de la capacidad adaptativa del eje HHA frente situaciones de estrés agudo, aumentando, en última instancia, el riesgo de revictimización y aparición de psicopatología (Wesarg et al., 2020).

El estudio de la función del eje HHA puede hacerse en circunstancias basales, es decir, valorando sus cambios a lo largo de un día en el que el sujeto desarrolla su actividad normal (ritmo circadiano) o cuando el sujeto se expone a una situación aguda de alto estrés psicosocial (frente a estrés psicosocial agudo).

Desde el punto de vista de la investigación de las consecuencias del maltrato infantil sobre la función del eje HHA, ambas aproximaciones pueden tener un gran interés, ya que reflejan estados fisiológicos con potenciales consecuencias sobre la salud del individuo y sus conductas de riesgo. De hecho, las alteraciones en la funcionalidad del eje HHA tienen una gran relevancia en la salud mental de la persona. Por ejemplo, se han relacionado niveles atenuados de cortisol frente situaciones de estrés con

sintomatología de la esfera internalizante y externalizante en la adolescencia (Conradt et al., 2014; Bae et al., 2015). Además, estas alteraciones en las fluctuaciones del cortisol asociadas al maltrato pueden mantenerse hasta la vida adulta y relacionarse con distintos diagnósticos psiquiátricos (Zorn et al., 2017; Kudielka et al., 2004).

A continuación, se explican brevemente los métodos mejor validados que habitualmente son aplicados en la investigación de la función del eje HHA tanto en población sana como en poblaciones de riesgo.

Previamente, cabe mencionar que los niveles de cortisol en sangre correlacionan altamente con los descritos en saliva (Vining et al., 1983). Poder estudiar los niveles de cortisol en el organismo a través de muestras de saliva permite al investigador acceder más fácilmente y sin métodos invasivos a los patrones de respuesta de este biomarcador en diferentes contextos.

Estudio del eje HHA en situación basal: el ritmo circadiano

El ritmo circadiano del cortisol está regulado por la glándula pineal, el hipotálamo y la hipófisis. Estas estructuras regulan la secreción diaria de cortisol de manera adaptativa a la actividad diaria de un individuo. Como puede verse en la Figura 9, en la primera media hora después de despertarnos se observa un rápido incremento de los niveles de cortisol en sangre. Este fenómeno, conocido como respuesta del cortisol al despertar (c*ortisol awakening response* (CAR) en inglés), nos permite enfrentarnos al inicio del día y comenzar la actividad diaria. Con posterioridad, el cortisol ira disminuyendo progresivamente a lo largo del día hasta alcanzar los valores más bajos al anochecer, facilitando así la entrada en las horas de descanso y sueño.

Dado que el eje HHA continúa madurando durante las primeras etapas de la vida, los factores ambientales podrán inducir también cambios duraderos en el funcionamiento diurno del eje HHA (Tarullo and Gunnar, 2006). Sin embargo, los hallazgos sobre las alteraciones este patrón basal del eje HHA asociados a las adversidades sufridas en la infancia son inconsistentes (Fogelman and Canli, 2018). Además, los expertos manifiestan la gran relevancia que tiene la metodología utilizada a la hora de recoger la información biológica (muestras de saliva) y la historia de maltrato sufrida, sugiriendo que, puede haber variaciones importantes y que es necesaria una mayor investigación en este campo (Bernard et al., 2017).

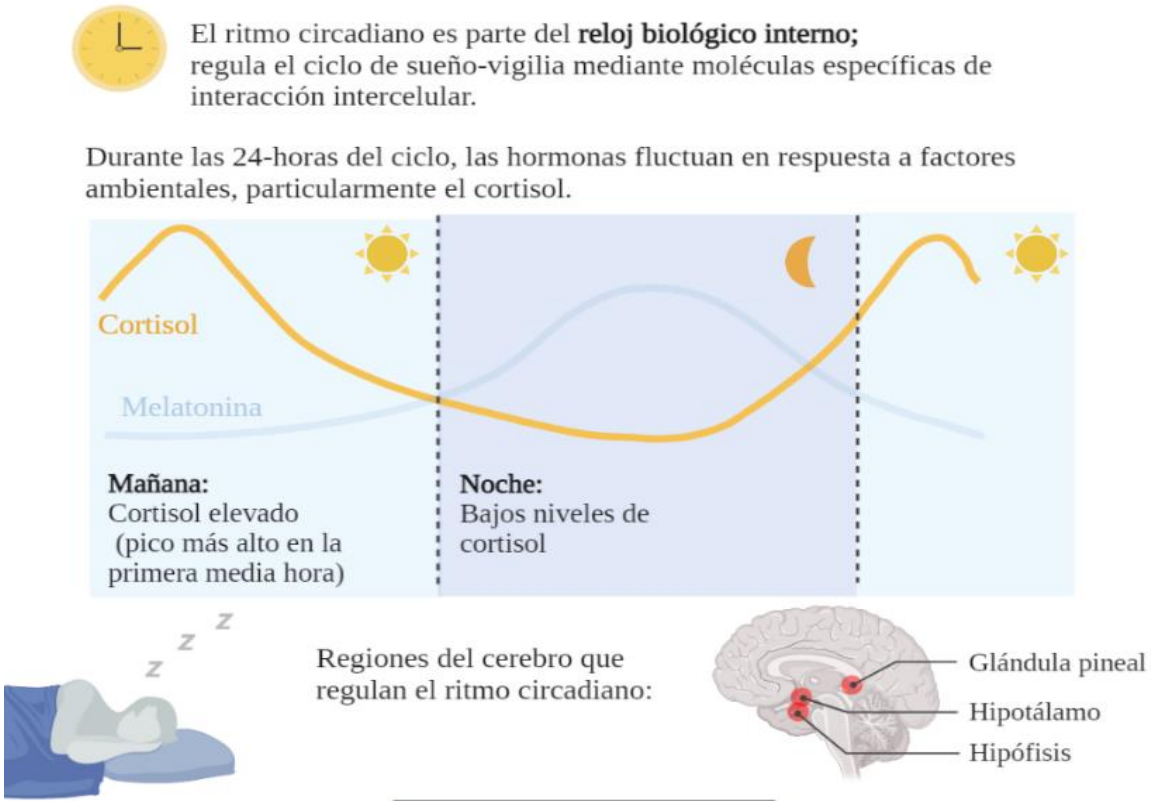


Figura 9. Ritmo circadiano del eje HHA. Por la mañana se observan altos niveles de cortisol que van disminuyendo a lo largo del día hasta medianoche. Imagen creada con BioRender.com.

Estudio del eje HHA bajo situaciones de estrés psicosocial agudo: el TSST-C

Desde el punto de vista de la investigación, existen protocolos validados empíricamente para valorar las respuestas biológicas frente situaciones de estrés agudo (Gunnar et al., 2009). En este sentido, uno de los paradigmas más utilizados es la prueba de estrés social de Trier (TSST, por sus siglas en inglés *Trier Social Stress Test*) (Buske-Kirschbaum et al., 1997). El TSST resulta especialmente interesante, ya que permite obtener una medida cuantitativa y continua del funcionamiento del eje HHA y otros sistemas biológicos, bajo una situación de estrés psicosocial controlada (Allen et al., 2017; Wu et al., 2019)(Ver cuadro 7). Este protocolo ha sido utilizado en los últimos años por distintos grupos de investigación tanto en sujetos infantiles como adultos, sanos o afectados por diversas patologías, y expuestos o no a maltrato.

Aunque algunos autores han podido estudiar la reactividad del eje HHA en personas que han sufrido maltrato infantil, sigue habiendo hallazgos contradictorios que podrían explicarse, entre otras variables, por la gravedad del maltrato, su frecuencia o la etapa del desarrollo de exposición (Fogelman and Canli, 2018; Bunea et al., 2017).

Además, son escasos los estudios basados en población infantojuvenil que valoren cuantitativamente y cualitativamente las experiencias de maltrato sufridas y su impacto en la funcionalidad del eje HHA frente el *Trier Social Stress Test for Children* (TSST-C). La utilización de este paradigma en una muestra representativa de niños/as y adolescentes con historias diferentes de maltrato infantil ha supuesto uno de los principales retos de esta tesis doctoral.

CUADRO 7. Trier Social Stress Test for Children (TSST-C)

Aunque a la hora de aplicar el TSST cada estudio puede mostrar pequeñas peculiaridades, para llevar a cabo la situación experimental de estrés psicosocial, los participantes son citados en el centro de investigación donde se les aplicará. En el momento de la llegada, los participantes tendrán un periodo de descanso en una habitación tranquila, para asegurar una situación basal comparable entre todos los sujetos. Después de este período de descanso (que puede variar entre estudios), el participante ingresa a una segunda sala (la sala experimental) donde dos personas desconocidas, una mujer y un hombre sentados tras una mesa, le esperarán con una actitud neutra (evitando dar refuerzo positivo). A continuación, este tribunal explicará a la persona las tareas que deberá llevar a cabo, destacando que serán grabadas en video para que los expertos puedan analizarlas posteriormente y calificar su desempeño (con el fin de situar al participante en un estado de evaluación y presión social).

En el TSST de adultos la tarea experimental suele ser la de simular una entrevista de trabajo. Sin embargo, en la versión para niños/as y adolescentes, *Trier Social Stress Test for Children* (TSST-C), la tarea de estrés consiste en inventar el final de un cuento lo más interesante posible. Normalmente, el participante dispone de 5 minutos para preparar mentalmente el discurso, mientras el tribunal permanece presente en silencio, antes de narrar su historia durante 5 minutos. Por último, la persona debe realizar una tarea aritmética durante cinco minutos, que normalmente consistente en una resta en serie. En la mayoría de estudios, la situación de estrés que tiene lugar en la sala experimental dura unos 15 o 20 minutos.

Una vez finalizadas las tareas, el participante regresa de nuevo a la habitación tranquila donde permanece un tiempo que permitirá evaluar su capacidad de recuperación tras un estresor. Este protocolo brinda la oportunidad de recoger distintos parámetros biológicos o psicológicos durante la sesión (muestras de saliva o sangre para explorar biomarcadores, frecuencia cardíaca, percepción de estrés, etc.) y compararlos en paralelo con la percepción subjetiva de la persona (cuestionarios cognitivos).

Figura 10. Diseño del protocolo *Trier Social Stress Test* para niños/as (TSST-C).

1.4.2.2. Sistema inmunitario y respuesta al estrés

Dado que en el pasado evolutivo de nuestra especie las situaciones amenazantes podían conllevar el riesgo de heridas, lesiones e infecciones, el SNS activa el sistema inmunitario cuando el individuo se enfrenta a situaciones de peligro. De esta forma, a la vez que aparece el cortisol en escena, se liberan también diferentes proteínas inflamatorias tanto en el torrente sanguíneo como en las superficies de las mucosas, facilitando la rápida reparación de heridas y la prevención de infecciones (Godoy et al., 2018).

Actualmente, aunque nuestros entornos mayoritariamente urbanos carecen de patógenos infecciosos continuados, están plagados de tensiones psicológicas que desafían el bienestar de la persona (Miller and Raison, 2016). El estrés psicosocial, por tanto, inducirá cambios psicobiológicos semejantes a los que se producirían si el individuo estuviera en una situación de peligro físico (Herr et al., 2018). Como se ha mencionado anteriormente, si esta situación estresante se experimenta de forma crónica, puede llevar, igualmente, a una desregulación del sistema inmunológico (McEwen, 2017; Tonhajzerova and Mestanik, 2017).

La respuesta inmunitaria se compone de dos partes: la innata (general) y la adaptativa (especializada). La inmunidad innata se activa en poco tiempo, minutos u horas después de la agresión, mediante la liberación de diferentes moléculas como las citocinas o el factor del complemento (Maier and Watkins, 1998). Por otro lado, la inmunidad adaptativa se activa normalmente unos días después de la exposición al factor de riesgo con la activación de linfocitos B y T y la producción de anticuerpos.

Cuando las funciones de la inmunidad innata no son suficientes para controlar el factor de estrés, normalmente una infección, se activan las células de la inmunidad adaptativa, los linfocitos. Los linfocitos van a liberar inmunoglobulinas (Ig), un conjunto de proteínas en forma de Y que se van a unir específicamente al antígeno del agente infeccioso, induciendo la fagocitosis y previniendo el desarrollo de un cuadro clínico (Segerstrom and Miller, 2004).

1.4.2.2.1. La inmunoglobulina A secretora (s-IgA)

Hay diferentes tipos de Ig que difieren en sus características biológicas, estructura, especificidad de destino y distribución. La inmunoglobulina A secretora (s-IgA), es la Ig predominante en la mucosa y ha emergido como un biomarcador

prometedor debido a su papel clave en la primera línea de defensa inmunológica y la protección oral contra patógenos (Nurkka et al., 2003; Staley et al., 2018). La secreción de s-IgA se encuentra bajo un fuerte control neuroendocrino desencadenado por el SNS (Brandtzaeg, 2007) y parece aumentar sus niveles después de una exposición a estrés agudo (ver Figura 11) (Campisi et al., 2012; Trueba et al., 2012).

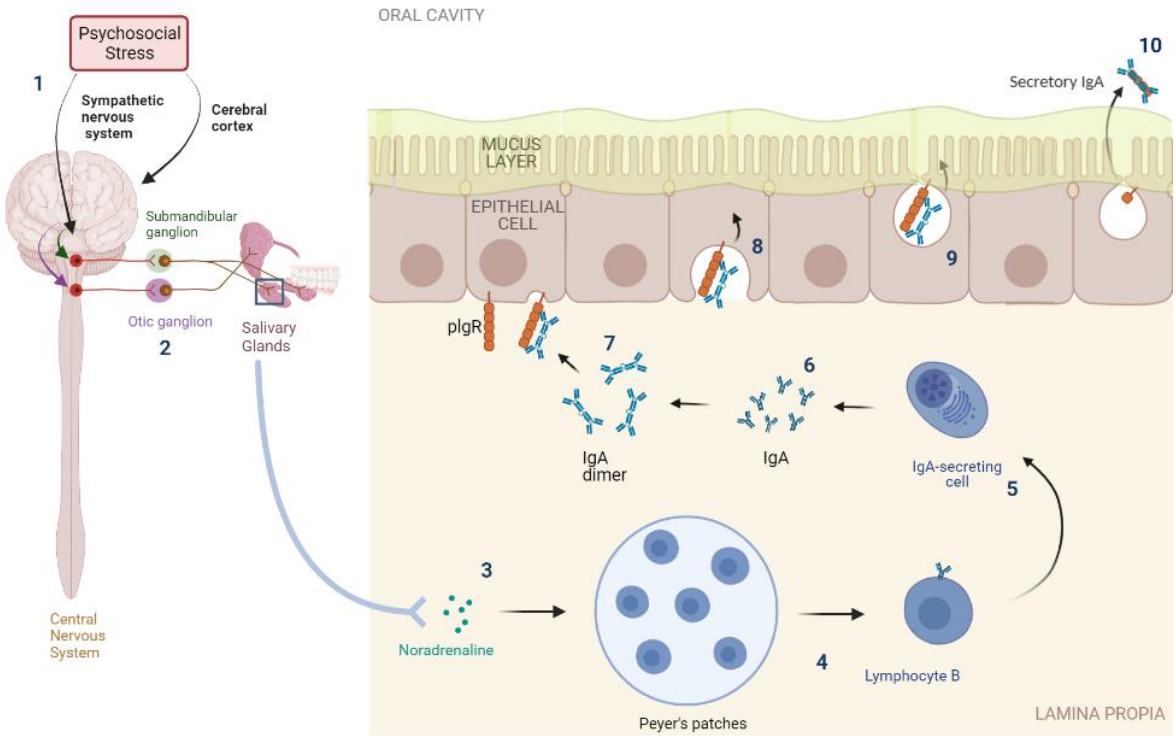


Figura 11. Secreción de la inmunoglobulina A en la mucosa salivar una vez se ha activado el SNS a causa de el estrés psicosocial. La noradrenalina en las glándulas salivares desencadena la respuesta inmunitaria en las placas de Peyer, activando los linfocitos B que inducirán la secreción de IgA. La s-IgA está constituida por dos moléculas de IgA y un componente secretor. Este componente se agrega cuando la IgA dimérica se lleva a cabo a través del epitelio antes de la liberación del lumen de la mucosa. Imagen cedida por Castro-Quintas (2022) y creada con BioRender.com.

El sistema inmunitario tampoco está completamente formado al nacer, sino que continúa madurando en respuesta al entorno. Por tanto, nuevamente, el ambiente temprano será determinante para el óptimo funcionamiento de este sistema. En esta línea, la interacción bidireccional entre el cerebro y el sistema inmunitario hace posible que los factores psicosociales estresantes tengan un gran impacto en el sistema inmunitario y en la función del cerebro, lo que a su vez puede provocar alteraciones duraderas en su maduración y funcionamiento (McCrory et al., 2010). De hecho, está bien reportado que las personas con historia de maltrato tienen un funcionamiento inmunitario menos efectivo, asociado a una mayor susceptibilidad a diferentes patologías, incluidas las enfermedades mentales (Kerr et al., 2021; Entringer, 2021).

A pesar del interés potencial de la s-IgA como un buen marcador del funcionamiento del sistema inmune frente al estrés psicosocial, solo aparece un estudio en la literatura explorando su reactividad frente estrés psicosocial agudo en población infantojuvenil (Laurent et al., 2015). Sin embargo, los autores no incluyen en su diseño una variable del máximo interés para nosotros: la historia de maltrato previa. Por este motivo, se consideró de gran interés estudio de este marcador en el presente proyecto, considerando los niveles de s-IgA en saliva un potencial biomarcador de interés en el ámbito de las consecuencias biológicas asociadas al maltrato infantil.

2. Hipótesis y objetivos

La infancia y la adolescencia constituyen un periodo de alta sensibilidad al ambiente familiar y social. Las adversidades vividas durante estos periodos, especialmente las de índole relacional, pueden incrementar el riesgo de psicopatología durante la infancia o adolescencia, sensibilizando algunos sistemas neuroendocrinos de respuesta al estrés.

Sin embargo, son escasos los instrumentos psicométricos que permitan valorar adecuadamente las experiencias de maltrato y otros eventos vitales en etapas tan tempranas de la vida.

Hipótesis General: Las adversidades y eventos traumáticos vividos durante la infancia se relacionan con la aparición de una amplia variedad de síntomas psicopatológicos y conductas de riesgo en niños/as y adolescentes. La naturaleza, severidad y cronicidad de estas experiencias adversas puede impactar de manera diferencial en los sistemas neurobiológicos, aumentando la vulnerabilidad para el desarrollo de síntomas psiquiátricos más graves.

Específicamente, se proponen las siguientes hipótesis:

> **Hipótesis I:** Vivir acontecimientos estresantes entre los 10 y 17 años aumenta el riesgo de presentar sintomatología internalizante y externalizante durante la adolescencia.
>
> **Hipótesis II:** Las adversidades sufridas durante la infancia, especialmente el trauma complejo, se asocian con distintos rasgos de personalidad desadaptativos como la impulsividad, la irritabilidad y la desregulación emocional, afectando a dimensiones esenciales como el autoconcepto y la capacidad de establecer relaciones interpersonales. Estas disfunciones empeoran el funcionamiento global del menor, aumentando el riesgo de revictimización, de sintomatología psiquiátrica y, en última instancia, el riesgo de comportamientos suicidas.
>
> **Hipótesis III:** Los niños/as y adolescentes con historia de maltrato muestran alteraciones en distintos sistemas neurobiológicos implicados en la regulación del estrés, como el eje Hipotalámico-Hipofisario-Adrenal (HHA) y el sistema inmune.

Con el fin de explorar estas hipótesis se establecieron los siguientes objetivos específicos, divididos en tres secciones y seis artículos científicos:

Objetivos específicos:

> **Sección I – Acontecimientos vitales estresantes en adolescentes y sintomatología internalizante y externalizante asociada:**

1. Revisar la literatura científica y meta-analizar el impacto de los acontecimientos estresantes vividos durante la adolescencia en la sintomatología internalizante o externalizante expresada en esta etapa de la vida.
2. Desarrollar y validar un instrumento para valorar adecuadamente los acontecimientos vitales estresantes en adolescentes y estudiar el impacto diferencial en la salud mental según la naturaleza de estos estresores.

Sección II – Maltrato infantil, estresores recientes y alteraciones en la salud mental infantojuvenil:

3. Estudiar la relación entre el maltrato infantil, los acontecimientos estresantes recientes y algunos rasgos del trastorno límite de la personalidad (TLP) como factores de riesgo para las conductas suicidas en población infantojuvenil.
4. Explorar el impacto de las experiencias de maltrato infantil en el funcionamiento global y el pronóstico clínico de los niños/as o adolescentes afectados. Estudiar el efecto de la edad de exposición a los distntos tipos de maltrato en la sintomatología del menor de acuerdo con el nuevo diagnóstico de Trastorno por Estrés Postraumático complejo (TEPT-C) propuesto por la CIE-11.

Sección III – La neurobiología del maltrato infantil en niñas/os y adolescentes:

5. Evaluar el impacto de las experiencias de maltrato infantil (su severidad y frecuencia) en el funcionamiento del eje HHA mediante el estudio de: i) las oscilaciones de cortisol diurnas y, ii) su reactividad frente una situación de estrés psicosocial agudo inducido experimentalmente mediante el protocolo *Trier Social Stress Test for Children* (TSST-C).
6. Explorar la reactividad de la Inmunoglobulina A secretora (s-IgA) frente al estrés psicosocial agudo, explorado mediante el TSST-C. Determinar el impacto del estadio de desarrollo puberal de los niños/as y de las experiencias de maltrato sufridas sobre dicha reactividad.

3. Publicaciones

Informe del director sobre el factor de impacto

La tesis doctoral "Consecuencias psicológicas y neurobiológicas del maltrato infantil: alteraciones neuroendocrinas en la regulación del estrés e implicaciones en la salud mental infantojuvenil" se basa en los resultados originales conseguidos por Laia Marqués Feixa. Estos resultados se han publicado, o han sido enviados para ser publicados, a revistas científicas internacionales revisadas por pares. El factor de impacto de estas revistas demuestra la calidad de la investigación realizada, según se detalla a continuación:

1. **Stressful life events during adolescence and the development of externalizing and internalizing psychopathology: a meta-analysis**, publicado en *European Child and Adolescent Psychiatry*. Esta revista científica publica artículos de alta calidad sobre neuropsiquiatría, neurociencia cognitiva, genética, neuroimagen, farmacología y campos de interés relacionados. Tiene como objetivo principal promover la comprensión de la psicopatología en niños y adolescentes. La investigación empírica es su fundamento y la relevancia clínica es su sello distintivo. Esta revista está indexada en *Journal Citation Reports* con un factor de impacto actual de 4.785 y clasificada según *Science Edtion* en el primer decil en el área de Pediatría (clasificada 10/129) y según *Social Science Edtion* en el primer cuartil del área de Psiquiatría (clasificada 27/144) y de Psicología y desarrollo (clasificada 12/77).

2. **Recent stressful life events (SLE) and adolescent mental health: initial validation of the LEIA, a new checklist for SLE assessment according to their severity, interpersonal, and dependent nature,** publicado en *Assessment*. Esta revista científica publica artículos de alta calidad centrados en el uso de medidas de evaluación clínica aplicada; incluyendo el desarrollo de pruebas, la validación y las prácticas de interpretación. Cubre áreas de evaluación del funcionamiento cognitivo y neuropsicológico, la personalidad y la psicopatología, así como la evaluación empírica de fenómenos clínicamente relevantes, como comportamientos, características de personalidad y diagnósticos. Esta revista está indexada en *Journal Citation Reports* (*Science Edtion*) con un factor de impacto actual de 4.667 y clasificada en el primer decil del área de Psicología clínica (clasificada 15/173).

3. **Risk of suicidal behavior in children and adolescents exposed to maltreatment: the mediating role of borderline personality traits and recent stressful life events**, publicada en *Journal of Clinical Medicine.* Esta revista internacional de acceso abierto tiene como objetivo publicar resultados experimentales detallados y teóricos sobre investigación clínica y preclínica en diversas áreas de la Medicina: Neurología, Psicología clínica y Psiquiatría, Farmacología, Inmunología, Epidemiología y Cardiología entre otras. Se diferencia de otras revistas por su predisposición a publicar artículos con resultados negativos, apoyando compartir estos hallazgos para no tener que repetir en el futuro estos experimentos. Particularmente, el artículo fue publicado dentro del número especial "Dissecting the Relationship between Personality Disorders and Suicide", que tuvo como objetivo proporcionar información actualizada sobre trastornos de la personalidad y suicidio. Esta revista está indexada en *Journal Citation Reports* (*Science Edtion*) con un factor de impacto actual de 4.242 y clasificada en el primer cuartil del área de Medicina general interna (clasificada 35/315).

4. **Reinforcing the new diagnosis of Complex Post-Traumatic Stress disorder (CPTSD) of ICD-11 in children and adolescents exposed to relational trauma: developmental stage at exposure and its associated clinical outcomes**, enviado para ser publicado a *Psychological Medicine.* Esta revista es líder internacional en los campos de la Psiquiatría, Psicología y ciencias básicas. Tiene como objetivo difundir investigaciones científicas novedosas que permitan comprender las causas de la enfermedad mental, mejorar la práctica clinica y los servicios relacionados con la salud mental. Se caracteriza por su enfoque en la Psiquiatría clínica, la salud mental infantojuvenil y la historia de la Psiquiatría. Esta revista está indexada en *Journal Citation Reports* (*Social science Edtion*) con un factor de impacto actual de 7.723 y clasificada en el primer decil del área de Psiquiatría (clasificada 10/144) y del área de Psicología Clínica (3/130).

5. **Childhood maltreatment disrupts HPA-axis activity under basal and stress conditions in a dose–response relationship in children and adolescents**, publicado en *Psychological Medicine.* Esta revista es líder internacional en los campos de la Psiquiatría, Psicología y ciencias básicas. Tiene como objetivo difundir investigaciones científicas novedosas que permitan comprender las causas de la enfermedad mental, mejorar la práctica clínica y los servicios relacionados con la salud mental. Se caracteriza por su enfoque en la Psiquiatría clínica, la salud mental

infantojuvenil y la historia de la Psiquiatría. Esta revista está indexada en *Journal Citation Reports* (*Social science Edtion*) con un factor de impacto actual de 7.723 y clasificada en el primer decil del área de Psiquiatría (clasificada 10/144) y del área de Psicología Clinica (3/130).

6. **Secretory immunoglobulin A (s-IgA) reactivity to acute psychosocial stress in children and adolescents: the influence of pubertal development and history of maltreatment** publicada en *Brain, Behavior, and Immunity*. Esta revista internacional está interesada en estudios experimentales y clínicos relacionados con las alteraciones del sistema inmunológico, endocrino, neural y conductual en humanos y animales. Es una revista interdisciplinaria dedicada a la investigación original en neurociencia, inmunología, fisiología integradora, biología del comportamiento, psiquiatría, psicología y medicina clínica que incluye investigaciones a nivel molecular, celular, social y de todo el organismo. Esta revista está indexada en *Journal Citation Reports* (*Science Edtion*) con un factor de impacto actual de 7.217 y clasificada en el primer decil del área de Psiquiatría (clasificada 16/156) y primer cuartil del área de Neurociencias (37/273) e Inmunología (31/162).

Por la presente, confirmo la calidad de los artículos publicados, o presentados para ser publicados, en las revistas científicas previamente mencionadas.

Signado por Prof. Lourdes Fañanás,

Barcelona, 12 abril 2022

Sección I: Acontecimientos vitales estresantes en adolescentes y sintomatología internalizante y externalizante asociada

3.1. Stressful life events during adolescence and the development of externalizing and internalizing psychopathology: a meta-analysis

Jaume March-Llanes, **Laia Marqués-Feixa**, Laura Mezquita, Lourdes Fañanás, Jorge Moya-Higueras

European Child and Adolescent Psychiatry (2017), 26:1409–1422.

DOI: 10.1007/s00787-017-0996-9

Eur Child Adolesc Psychiatry (2017) 26:1409–1422
https://doi.org/10.1007/s00787-017-0996-9

REVIEW

Stressful life events during adolescence and risk for externalizing and internalizing psychopathology: a meta-analysis

Jaume March-Llanes[1] · Laia Marqués-Feixa[2] · Laura Mezquita[3] · Lourdes Fañanás[2,4] · Jorge Moya-Higueras[1,4]

Received: 9 September 2016 / Accepted: 8 May 2017 / Published online: 13 May 2017

Abstract The main objective of the present research was to analyze the relations between stressful life events and the externalizing and internalizing spectra of psychopathology using meta-analytical procedures. After removing the duplicates, a total of 373 papers were found in a literature search using several bibliographic databases, such as the PsycINFO, Medline, Scopus, and Web of Science. Twenty-seven studies were selected for the meta-analytical analysis after applying different inclusion and exclusion criteria in different phases. The statistical procedure was performed using a random/mixed-effects model based on the correlations found in the studies. Significant positive correlations were found in cross-sectional and longitudinal studies. A transactional effect was then found in the present study. Stressful life events could be a cause, but also a consequence, of psychopathological spectra. The level of controllability of the life events did not affect the results. Special attention should be given to the usage of stressful life events in gene–environment interaction and correlation studies, and also for clinical purposes.

Keywords Stressful life events · Externalizing spectrum · Internalizing spectrum · Meta-analysis · Transaction

Introduction

Adolescence is a period of change. Pubertal maturation mixed with social demands leads adolescents to assume adult roles [1, 2]. These vital changes are often experienced as stressful [1]. During adolescence, stressors increase stress reactivity, decrease hippocampal volumes, and alter neural plasticity [3, 4]. Changes in neurobiological stress should be a natural response to properly adapt the organism to the challenges of adolescence [5]. However, the consequence of these brain changes in adolescents with individual and/or genetic predispositions for heightened affective processing could be a stress dysregulation process, increasing their vulnerability to psychopathology [1, 3, 5].

According to most recent reviews, the prevalence of mental disorders, without specifying which, during adolescence ranges from 25 to 45% [6–8]. Some mental disorders begin their prodromal phase or show an increase in prodromal symptoms at this stage of life [9–12]. Identifying adolescents with prodromic symptoms is crucial for proper intervention and prevention programs [10].

One difficulty for the diagnostic process and also for selecting proper interventions according to evidence-based guidelines is that some disorders tend to co-occur in a non-random fashion [13, 14]. Epidemiological studies estimate that comorbidity tends to occur in around 40% of affected

Electronic supplementary material The online version of this article (doi:10.1007/s00787-017-0996-9) contains supplementary material, which is available to authorized users.

✉ Jorge Moya-Higueras
jmoya@pip.udl.cat

[1] Department of Psychology, Faculty of Education, Psychology, and Social Work, University of Lleida, Avda. de l'Estudi General, 4, 25221 Lleida, Spain

[2] Department of Evolutionary Biology, Ecology, and Environmental Sciences, Faculty of Biology, University of Barcelona, Biomedicine Institute of the University of Barcelona (IBUB), Barcelona, Spain

[3] Department of Basic and Clinical Psychology and Psychobiology, Jaume I University, Avda. de Vicent Sos Baynat, s/n, 12701 Castelló De La Plana, Spain

[4] Instituto De Salud Carlos III, Centro De Investigación Biomédica en Red de Salud Mental (CIBERSAM), Madrid, Spain

adolescents [6, 7]. For example, social phobia, specific phobias, and depression are common co-occurring disorders with other mental illnesses [6, 7]. Although the concomitance of different affections has been considered a conceptual problem and a clinical difficulty [15], there is now evidence to confirm that, at least in mental disorders, some cases of comorbidity could be explained by common latent liability factors [16]. The most prevalent mental disorders can be grouped into two clusters of symptomatology [16–18]: the internalizing and externalizing spectra. The internalizing spectrum is considered a general liability toward the disorders characterized by negative affect, while the externalizing spectrum should be understood as a liability toward disinhibitory disorders [16]. With a few exceptions [19, 20], the externalizing/internalizing categorization has been found in children and adolescents [18, 21, 22]. In addition, the psychopathological spectra are important in clinical settings. When such symptomatology emerges during childhood and/or adolescence, it can evolve into adult psychiatric disorders [23, 24]. Such symptoms could also be considered as prodromic states of emotional and impulsive mental disorders. Hence, research to identify the risk factors for externalizing and internalizing spectra during childhood and adolescence is essential.

Regarding the association between stress and psychopathology, some of the stressors that an adolescent can experience are derived from adverse life events. The death of a family member, a divorce or a separation, or a romantic breakup are specific life events that have been found to increase the likelihood of developing psychiatric symptoms [25–27]. The effect of stressful life events seems to be strengthened when some of them are lived in an aggregated fashion. Swartz et al. [28] found that adolescents who had experienced more life events with a severe negative impact during the last 12 months showed a long-term alteration in amygdala reactivity, influencing their risk for depression. Besides its neurobiological implications, the aggregation of life events has proved to be clinically relevant. In healthy adolescents and clinical samples, a significantly higher number of stressful life events, during a short period of time, increased the likelihood of developing depression and emotional disorders [29, 30], substance use behaviors and addictions [27, 31], hyperactivity and conduct problems [30], and suicide attempts [2]. Furthermore, experiencing stressful life events during adolescence can predict psychopathology in adult life, for example, by disrupting the reward circuit function [32, 33]. Hence, the association between stressful life events and psychopathology has been consistently replicated in one direction: stress may induce the symptomatology; this effect is the one tested in gene–environment interaction studies [34–36].

However, exposure to certain life events is partly under genetic control for depression [37], and impulsive and aggressive behavior [38]. This is known as the gene–environment correlation [35, 39]. Commonly, the directionality of the association between stressful life events and psychopathology has been studied by separating the effects of "dependent" and "independent" life events [37]. The life events that are dependent on one's actions are considered controllable or dependent life events. On the contrary, those life events that are unpredictable by nature, that do not rely on the behavior of the person in order to happen, are considered uncontrollable or independent. In a systematic review, Kendler and Baker [39] showed that the heritability of dependent negative life events was higher than that of independent life events. This effect has since been replicated [40]. In addition, McAdams et al. [38] found that the same genes that affect dependent stressful life events are involved in delinquency, physical aggression, and depression. On the other hand, it seems that, in interaction with other environmental variables, a stress sensitization effect on psychopathology is caused by independent life events rather than by dependent ones [41, 42]. Hence, independent life events could causally affect psychopathology, while people with certain psychopathological symptoms and other intrinsic characteristics would show increased exposure to dependent life events. In other words, independent life events are involved in gene–environment interactions, while dependent life events are associated with psychopathology through gene–environment correlations [36, 39]. The experience of stressful dependent life events could increase the chronicity of some disorders, such as depression [43, 44], and also increase the risk of suicide in adolescents [45].

The directionality of the association between stressful life events and psychopathology has also been tested using longitudinal designs [37]. With this methodology, Hammen [46] introduced the concept of stress generation to describe the finding that people with past episodes of depression were more likely to be exposed to stressful life events than people with a lack of past depressive states. Stress generation has been replicated in different studies involving depression [47], and also in other mental disorders [48]. Taking into account the controllability of the life events in a longitudinal study, Kercher et al. [49] found that exposure to dependent negative life events partially mediated the relation between depressive symptomatology between time 1 and time 2, while independent stressful life events predicted depressive symptoms at time 2 but were not predicted by the depressive symptoms at time 1. Hence, the directionality of the relation between the psychopathological spectra and stressful life events is controversial nowadays. Moreover, as far as we know, no studies in this field have been performed using a meta-analytical methodology. The main aim of the present study was to systematically review all available studies concerning the relation between

the aggregated experience of stressful life events and the internalizing and externalizing spectra during adolescence. The internalizing spectrum is understood as "a general liability toward negative-affect-laden mood and anxiety disorders" [16]; and externalizing spectrum as "a general liability toward disinhibitory disorders such as substance use disorders and antisocial behavior disorders" [16]. In the present study, aggregate stressful life events are considered to be the sum of incidents that could occur during adolescence (our target stage of life) which have a negative impact on the person, because they potentially increase stress. Moreover, we tried to test the directionality in this relation, paying particular attention to longitudinal studies and the dependent/independent stressful life events classification. Moderators accounting for systematic variations were also analyzed.

Methods

The present study was performed following the MOOSE guidelines [50]. Two independent researchers selected the studies found in a systematic review of the literature by applying pre-specified inclusion and exclusion criteria. Heterogeneity and sensitivity analyses were performed to assess different biases in the studies. Proper meta-analytical statistics were applied to test the hypotheses.

Selection of studies

Literature search

We carried out a literature search using four bibliographic databases: PsycINFO, Medline, Scopus, and Web of Science. The search items were limited to the title, abstract, and keywords. Search terms were generated from the synonyms found in the MeSH and Cochrane Library databases and by inspecting the common terminology used in the stressful life events literature. The keyword combination was: (life event OR adolescent adverse* OR social adverse OR lifetime trauma OR traumatic event* OR life-history calendar OR life history calendar OR Event*, Life Change OR Life Change Event* OR Event*, Stressful OR Stressful Event* OR Analys*, Event History OR Event History Analys* OR Experience*, Life OR Life Experience*) AND (externalizing behavi* OR externalizing symptom* OR externalizing psychopath* OR externalizing path* OR externalizing disorder* OR externalizing problem* OR externalizing difficult* OR internalizing behavi* OR internalizing symptom* OR internalizing psychopath* OR internalizing path* OR internalizing disorder* OR internalizing problem* OR internalizing difficult*) AND (adolescen*). The same equation was repeated with the British form of 'externalising'/'internalising' terms. Reference lists of available reviews were also screened.

Phases of the study

Three basic screenings (phases 1–3) were carried out in the present study. First, after eliminating duplicated articles found in the different databases, a screening by titles was performed. Second, the abstract was screened to look for the inclusion and exclusion criteria. Finally, the full text was analyzed. Figure 1 is a flow diagram of the present study, reporting the number of studies included and excluded in each phase.

Inclusion and exclusion criteria

In phase 1 and 2, the strategy used to select the papers was conservative. We found that the main objective of a study was rarely to analyze the relations between externalizing/internalizing psychopathology and life events. However, some studies in which the main objective was not to test the association between psychopathological clusters and life events presented a correlation matrix that was suitable for the analysis that we conducted in the present study. Hence, in phase 1 and 2, the only papers that were excluded were those that completely matched the exclusion criteria and did not meet the inclusion criteria. Any ambiguities were resolved in phase 3, after reading the full text. Therefore, in the third phase, the strategy was rigid, and only those studies that completely fitted the inclusion criteria were selected for further analysis.

The inclusion criteria were as follows: (a) externalizing and internalizing clusters were assessed by means of a validated methodology. If a paper reported the assessment of the spectra with measures that did not use specific scales to assess them, then only if that paper estimated the externalizing and internalizing factors empirically, it was included. (b) Aggregated major life events were assessed. Daily hassles were not taken into account. (c) The study contained empirical data on the association between the stressful life events and the externalizing/internalizing spectra. (d) The sample was between 10 and 19 years of age, the period of time defined by the WHO as demarcating adolescence [51]. (e) Cross-sectional and longitudinal studies were included. Studies that focused on the effect of stressful life events on the externalizing/internalizing spectra or vice versa that began before 10 years of age or finished after 19 years of age were excluded. However, if a study with these characteristics included empirical data at different time points in the range of 10–19 years of age, then these data were included.

The exclusion criteria were as follows: (a) the topic of the paper was not concerned with either externalizing/

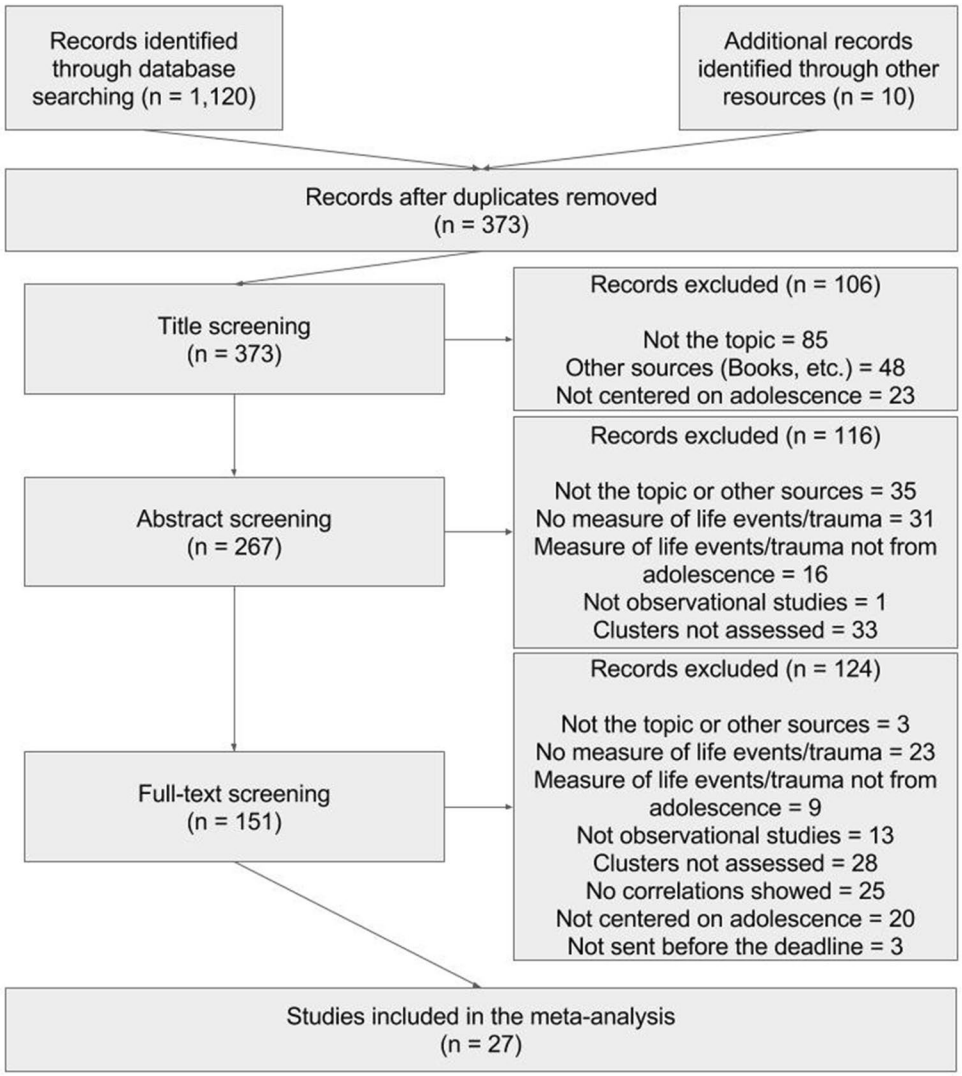


Fig. 1 Flowchart for study selection

internalizing symptoms or with stressful life events. (b) The reports were dissertations, books or book chapters, conference abstracts, and reviews. (c) The study did not report data about adolescence, such as life events assessed before the adolescent period or a longitudinal analysis of the prediction of young adult outcomes. (d) There is currently the lack of an operational definition of trauma. In some studies [52, 53], the concept of trauma was used as a synonym of stressful life events. However, the standard measures of life events mix major life events (e.g., the death of a parent) that could be really considered as traumatic events with minor life events (e.g., new partner moved into the home) that should not be considered traumatic. Moreover, some papers [54] restricted the usage of this terminology to major stressful life events, often making reference to sexual abuse, etc. Hence, another exclusion criterion was that no life event was measured in the study. Measures of daily hassles were also excluded. (e) Regarding the measures of psychopathology, the only studies that were accepted were those that assessed the internalizing and/or externalizing spectra. Although some papers argue that they assessed the internalizing/externalizing spectra, some of them only related the life events to separate disorders, and not with the cluster of disorders. These papers were excluded. (f) Studies that were not based on correlations, or on simple statistics suitable for transformation into correlations (e.g., simple odds ratios), were also excluded. (g) Finally, we tried to contact several authors to clarify some aspects of their studies. Four of them replied and the studies were thus included in the meta-analysis; the three that did not reply were excluded from the meta-analysis.

Problem of multiplicity

When different papers based on the same study were found, the key article referring to the main results was selected.

Coding

Two independent raters, the first and the last authors of the present study, coded the study features and extracted the effect-size data. The coding procedure was blind. In each phase of the study, both raters worked separately. They pooled their conclusions and if there was any substantial discrepancy, the other authors of the paper, experts in this field, were consulted. The final decision depended on a consensus on all parts of the study. The percentage of agreement between the two raters was 80% in phase one ($\kappa = 0.57$; 95% CI 0.48, 0.65; $p < 0.001$), 86% in phase two ($\kappa = 0.72$; 95% CI 0.64, 0.81; $p < 0.001$), and 95% in phase three ($\kappa = 0.83$; 95% CI 0.71, 0.94; $p < 0.001$). There were more inconsistencies between the raters in the first two phases due to the ambiguity and unclear information of some titles and abstracts.

For the purpose of the present study, the papers were classified into nine categories. (a) The type of stressful life events. Studies that did not assess subtypes of life events were coded as studies on general stressful life events. Those that assessed only the impact of life events uncontrolled by the subject were labeled as studies on independent stressful life events. Life events controlled by the subjects were coded as dependent stressful life events. Some studies separated those life events that can occur because of relations with other people (coded as interpersonal stressful life events), from life events that happen without the intervention of others (coded as non-interpersonal stressful life events). (b) The measure used to assess the life events: by interviewing and by administering a checklist. Another classification was attempted based on the specific measure used. However, only four studies used the same methodology to assess life events. (c) The time duration assessed by the measure of life events (number of months in which the life events could happen). (d) Who reported the life events: self-reports by the adolescents, hetero-evaluation by the parents or the teachers, or multi-informant assessment (self-report plus hetero-evaluations). (e) Regarding the psychopathological measures, the type of externalizing/internalizing spectra assessed. Most of the studies assessed both externalizing and internalizing symptoms, although some of them only presented data on one of them. (f) The specific measure used to assess the spectra was coded. (g) Who reported the psychopathology: self-report, hetero-evaluation, and multi-informant. (h) Regarding the design, the studies were coded as cross-sectional if they included measures of the stressful life events and the clusters of psychopathology at the same time, or as longitudinal if the basic measures were separated in time. In some cases, the same study contained cross-sectional and longitudinal data. These articles were coded as both designs, but the cross-sectional data were used in the cross-sectional analyses and the longitudinal data were used in the longitudinal analyses. (i) The longitudinal studies were also classified according to the classic distinction between the two main directional hypotheses described: the stress-generation hypothesis [46, 48, 55–57] and the sensitivity-stress hypothesis [58, 59]. In some longitudinal designs, the clusters of psychopathology were assessed at Time 1 and the life events at Time 2. In these cases, the time lapse reported for the life events was from the first to the second assessment. These studies were coded as relating to the stress-generation hypothesis. On the contrary, in other longitudinal studies, the stressful life events were assessed at Time 1 and the psychopathological clusters were assessed at Time 2. These studies were coded as relating to the sensitivity-stress hypothesis. As the cross-sectional studies were merely correlational, they were not suitable for testing the directionality of the association. These studies were coded as correlational.

In addition to this process, each study was assessed using a quality assessment tool. Seven criteria were formulated to judge the quality of the research articles: (a) operationalization of negative life events: if negative life events were measured and described in the paper by a standardized procedure, the study received two points; if the measure used was an ad hoc instrument, not validated previously, or a non-validated modification of a standardized procedure, the study received one point; if there was not enough information to deduce the quality, the study received zero points; (b) continuity of the life events measure: if the study used the sum of life events in a continuous measure, the study received two points; if the study categorized the measure into more than two categories, the study received one point; if the study dichotomized the measure, the study received zero points; (c) time period for which life events were reported: if the paper clearly described the time period that the participants had to think about, to report whether the life events had occurred or not, the study received one point; if this time period was not specified, the study received zero points (in such cases, the data were obtained by inspecting the stressful life events measure or by asking the authors); (d) appropriate statistical analyses: if the researchers used adequate analyses to answer the research question and a correlation matrix was clearly depicted, the study received one point; if the statistical procedure was not appropriate or the correlations were derived from latent variables despite the inclusion of observational variables, the study received zero points; (e) continuity of the psychopathological measure: if the study used the standard estimation of the externalizing/internalizing spectra that entailed a continuous measure, the study received two points; if the study categorized the measure into more than two categories, for example, by dividing the sample according to the standard deviations, the study received one point; if the study dichotomized the measure, for example,

by applying a percentile criterion, the study received zero points; (f) description of the sample: if the sample description was complete, by reporting at least the mean age with the standard deviation, the percentage of girls and boys, and the ethnicity of the sample, the study received two points; if there were missing data on the above descriptors, the study received one point; if no descriptors were reported, the study received zero points; (g) selection of the sample: if the authors performed a selection procedure resulting in a representative group of participants and the differences between the sample of participants who agreed to participate and those who declined was analyzed (or the attrition process), the study received two points; if the sample assessed was a representative group, but no analysis of the differences between those who participated and those who declined was described (or the attrition process), the study received one point; if the sample selection procedure was not explained, the study received 0 points. The quality score ranged from 0 to 12. According to the MOOSE proposal [50], a sensitivity analysis was performed rather than weighting the studies or not including some of them due to the quality score. The quality assessment was performed separately by two researchers. There was 95% agreement between them ($\kappa = 0.80$; 95% CI 0.69, 0.91; $p < 0.001$). The discrepancies were solved by consensus. In most cases, the discrepancies were due to unclear information in the papers.

Effect-size computation

The present meta-analysis was based on correlations. Most of the papers reported the exact values of the *r* measures. If the study described beta values of simple, not multiple, regressions, then the square root of the R^2 was used. This was required in one study. No studies presented simple, rather than multiple, odds ratios, so no transformation was needed to estimate the *r* value.

Decisions were made about four types of multiplicity: multiple assessment points, multiple measures for the externalizing/internalizing clusters, multiple measures for negative life events, and multiple stressful life events individually estimated. With respect to the first type, a multivariate meta-analysis model of estimation was performed, as will be described in the next section. Regarding the other types of multiplicity, the multiple associations were averaged.

Statistical analysis

We applied a random/mixed-effects model that provided unconditional inference about a larger set of studies from which the k studies included in the meta-analysis were assumed to be a random sample [60]. The outcome was the Fisher's *r*-to-*z* transformation, a variance stabilizing transformation for correlation coefficients with the added benefit of also being a rather effective normalizing transformation [61].

Procedure to fit meta-analytical model

All analyses were conducted using the metafor package, a comprehensive collection of functions in R for fitting meta-analytical multivariate random models with or without moderators via linear (mixed-effects) models. We used the rma.mv function to specify the correlated structure between samples derived from the same study. The rma.mv function assumes that outcomes with different values in the grouping factor come from independent studies, while effects or outcomes with the same value in the grouping factor share correlated random effects.

To properly test the hypotheses of the present study, three main analyses for each psychopathological spectrum were performed: one with the correlational (cross-sectional design) studies, one with the sensitivity-stress hypothesis (longitudinal design), and the third with the stress-generation hypothesis (longitudinal design). In addition, different meta-regressions were performed to test the effect of nine covariates: (a) the quality score, to test the sensitivity analysis according to the design specifications in the studies, (b) the female ratio, (c) the differences between samples from the general population versus samples with special characteristics, such as ADHD, etc., (d) the type of life events, tested by comparing those studies that evaluated non-specific general stressful life events versus those based on the independent life events and the interpersonal life events (dependent life events and non-interpersonal life events were not taken into account, because there were too few studies evaluating them), (e) interview methodologies to assess the life events versus checklists, (f) comparisons were also performed taking into account who reported the stressful life events (self-reports, hetero-evaluation, and multi-informant), (g) the same comparisons were performed regarding the reports of the psychopathology (self-reports, hetero-evaluation, and multi-informant), (h) the time (in months) referred to in the life events measure, (i) the number of life events that appeared in the life event checklists/interviews used in each study. Moreover, for longitudinal studies only, time between assessments was tested.

Finally, to analyze whether life events correlated better with externalizing or internalizing spectra, we performed the Hotelling–Williams test [62]. As the Williams test is only an approximation as it is not based on a mean difference, we did not carry out a meta-analysis (conversion of *t* values into outcomes accepted by the metafor package involves repeating a transformation similar to Fisher *r*-to-*z*

normalization). Instead, we determined a bootstrap confidence. We only performed this statistical test on the papers ($n = 24$) that assessed both externalizing and internalizing spectra in the same sample and in the same study with cross-sectional designs. This analysis was not performed on the longitudinal studies, because very few papers met the criteria of reporting the correlations with both spectra (4 regarding the stress-generation hypothesis and 3 for the stress-sensitivity hypothesis).

Results

Description of study features

Twenty-seven publications fulfilled the inclusion criteria (see Table S1 of the supplementary material for an overview of the studies and their features). Eleven contained cross-sectional and longitudinal data, fifteen studies were only cross-sectional and one contained only longitudinal data. The earliest studies were published in 1995, and the most recent was published in 2015. The quality of studies was good, ranging from 8 to 12 (mean = 10.2, SD = 1.21). The meta-analysis was performed in an aggregated sample of 13,340 participants.

Eighteen studies included general population samples. The non-general population samples included children of alcoholics, children with ADHD and referred samples, and adolescents who lived in particular environments such as violent neighborhoods. Eighteen studies assessed non-specific life events, five assessed independent life events only, one assessed dependent life events only, one assessed interpersonal life events only, one assessed both interpersonal and non-interpersonal life events, and one study assessed non-specific, dependent, and independent life events. Twenty-one studies used checklists, five studies used interviews, and one study used both methods. Twenty studies used a self-report measure, two studies used a hetero-evaluation measure, and five studies used a multi-informant measure of life events. Regarding the measurement of the psychopathological spectra, 16 studies used a self-report measure, one study used a hetero-evaluation measure, and ten studies used a multi-informant measure. Two studies included two different samples (the life events and the psychopathological variables were assessed with different measures in each sample). The mean time period asked about in the life events measure was 15.23 months (SD = 16.64).

Twenty-seven studies had cross-sectional data with the externalizing spectrum. Eleven included more than one correlation. Regarding the internalizing spectrum, 20 studies had cross-sectional data, six of them including more than one correlation. Seven studies were included in the sensitivity-stress hypothesis longitudinal analysis with the externalizing spectrum, two of them with more than one correlation, while four studies included longitudinal data to test this hypothesis with the internalizing spectrum, all of them with a single correlation. Finally, ten studies were included in the stress-generation hypothesis longitudinal analysis regarding the externalizing spectrum, four of them with more than one correlation. The internalizing spectrum analysis of this hypothesis was performed with seven studies, only one reporting more than one correlation.

Correlational and longitudinal hypothesis analysis

All the analyses showed high levels of heterogeneity, ranging from $Q(41) = 311.01$ ($p < 0.001$) for the cross-sectional analysis with the externalizing spectrum to $Q(8) = 21.08$ ($p = 0.007$) for the stress-generation longitudinal analysis with the internalizing spectrum. These results justified the use of random models to perform the statistical analyses.

The effect sizes estimated were significant in the six analyses (see Fig. 2 for the Forest plots of the cross-sectional studies. See the supplementary material, Figures S1 and S2, for the Forest plots of the longitudinal analyses). All of them were positive, indicating that the greater the number of life events experienced, the higher the level of the psychopathological spectrum found. The highest effect sizes were found in the cross-sectional correlational studies (externalizing spectrum: $r = 0.35$, $z = 14.59$, $p < 0.0001$, 95% CI 0.30, 0.40; internalizing spectrum: $r = 0.33$, $z = 14.92$, $p < 0.0001$, 95% CI 0.29, 0.38), and the lowest effect sizes were found in the stress-generation hypothesis analyses (externalizing spectrum: $r = 0.28$, $z = 6.41$, $p < 0.0001$, 95% CI 0.19, 0.37; internalizing spectrum: $r = 0.23$, $z = 7.98$, $p < 0.0001$, 95% CI 0.18, 0.29). The effect size regarding the externalizing spectrum in the sensitivity-stress hypothesis analysis was 0.28 ($z = 6.41$, $p < 0.0001$, 95% CI 0.19, 0.37), while in the internalizing spectrum, it was 0.29 ($z = 3.92$, $p < 0.0001$, 95% CI 0.14, 0.43).

By means of a bootstrapping procedure applied to the Hotteling–Williams t test, the correlations between life events and both psychopathological spectra were compared in 24 cross-sectional studies. The average correlation between life events and the externalizing spectrum was 0.34 (95% CI 0.29, 0.38), and the average correlation between life events and the internalizing spectrum was 0.31 (95% CI 0.26, 0.35). The difference between both correlations was not significant ($t = 0.439$, $p = 0.332$, 95% CI −0.521, 1.334).

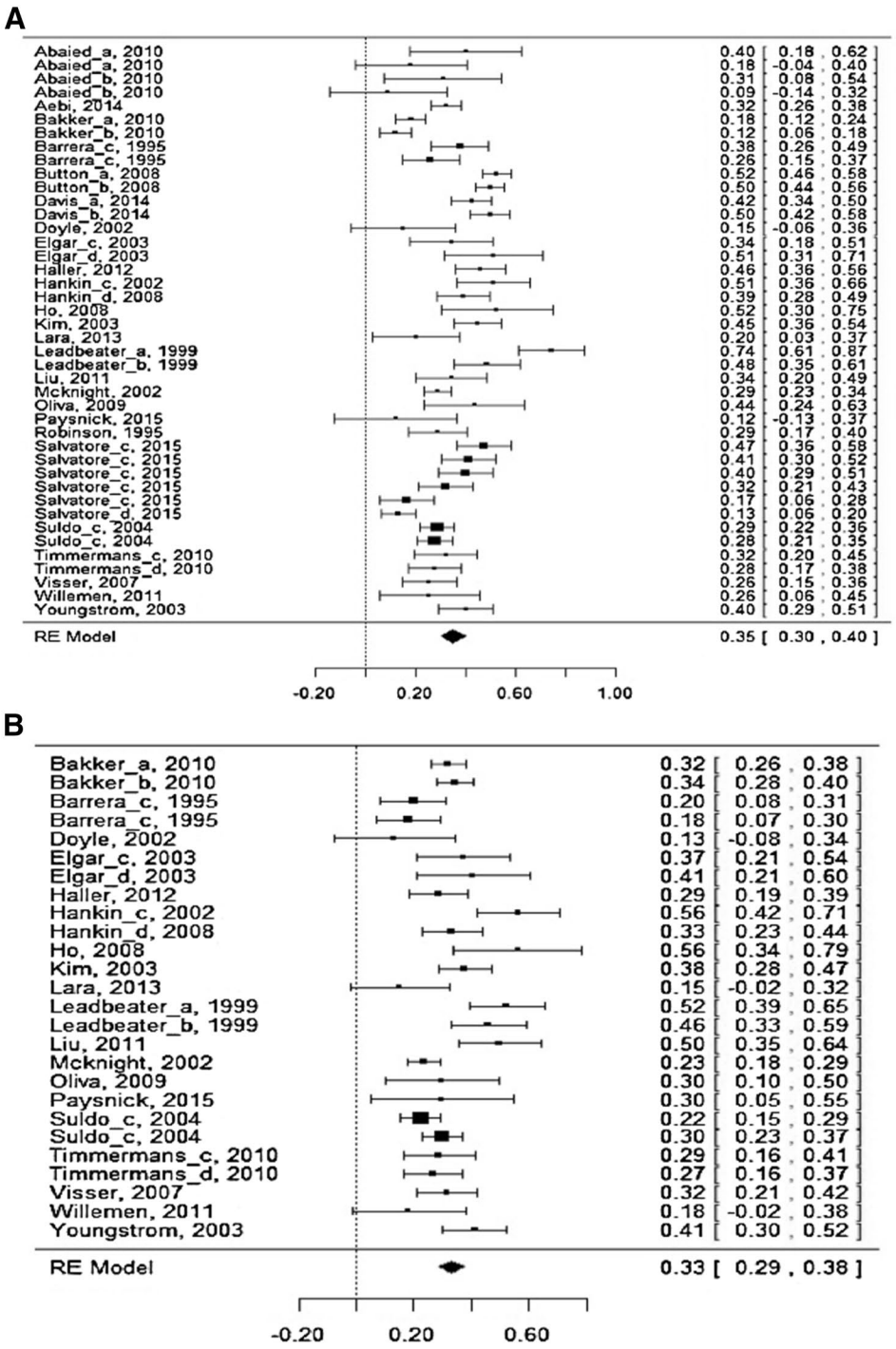


Fig. 2 Forest plot for the externalizing spectrum (**a**) and internalizing spectrum (**b**) of cross-sectional studies. Forest plot of average effect size and 95% confidence interval of each individual study (represented by a *square*) and summary effect (represented by a *diamond*)

Symmetric and sensitivity analyses

All the Funnel plots were symmetrical (see Fig. 3 for the Funnel plots of the cross-sectional studies. See the supplementary material, Figures S3 and S4, for the Funnel plots of the longitudinal analyses). The tau values ranged from $\tau = 0.33$ ($p = 0.75$) for the internalizing spectrum sensitivity-stress hypothesis longitudinal analysis to $\tau = -0.08$ ($p = 0.75$) for the internalizing spectrum stress-generation hypothesis longitudinal analysis. Hence, no bias of publication was found.

According to the MOOSE standards [50], the sensitivity analysis could be performed by controlling the effect of the quality score. The studies were divided into two groups, those considered to be of higher quality (more than 10 in the quality score) and those of lower quality (less than or equal to 10 in the quality score). A meta-regression was performed by introducing the dichotomous variable

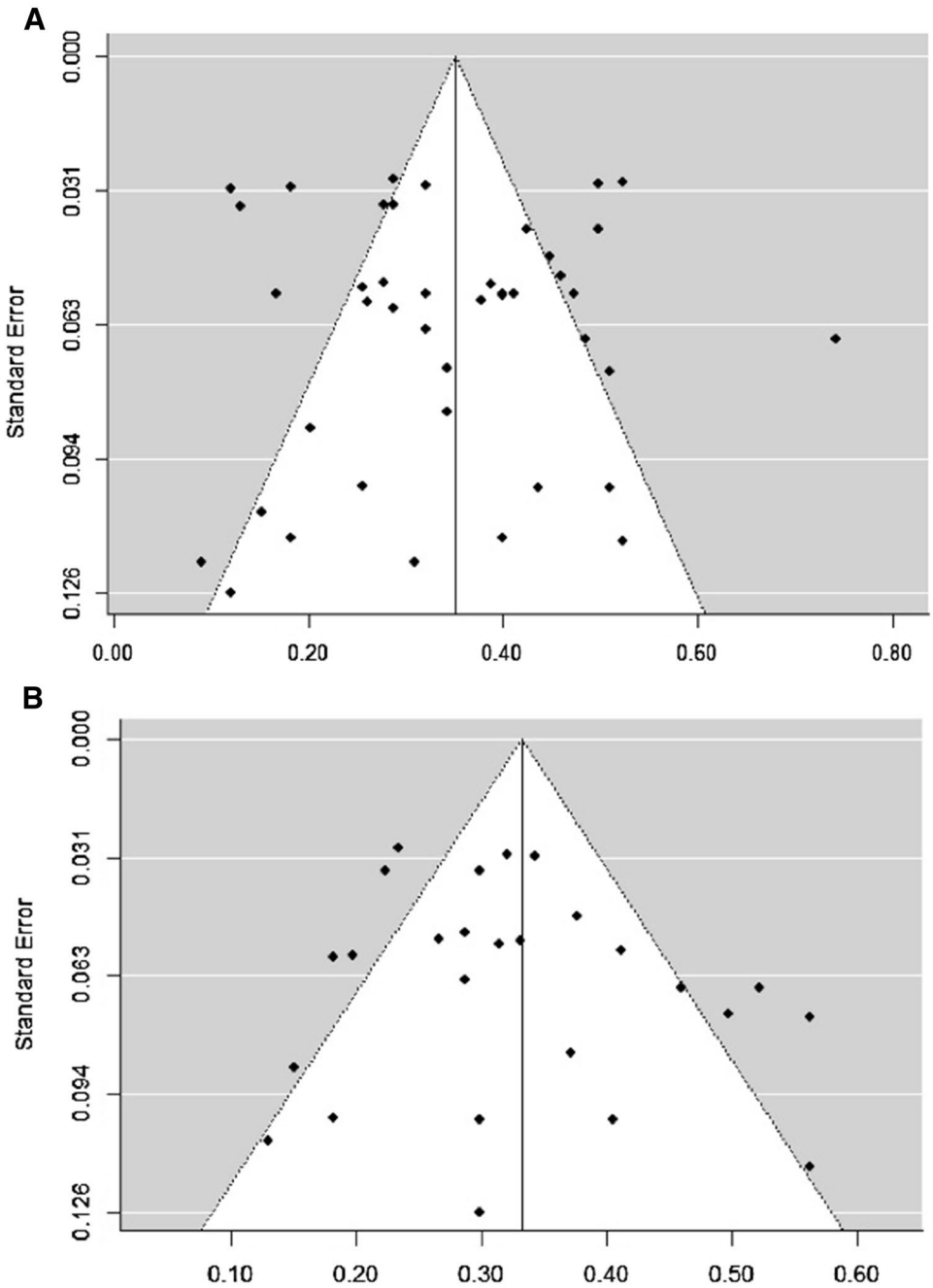


Fig. 3 Funnel plot of standard error by effect size for all cross-sectional studies (**a** externalizing spectrum; **b** internalizing spectrum)

as a covariate. In all analyses, the effect size estimated was independent of the studies' quality (highest value: $Z = 1.62$, $p = 0.11$; lowest value: $Z = -0.31$, $p = 0.75$).

Analyses of possible confounders

Nine extra meta-regressions were performed in the six basic analyses to test the effect of different confounders. No significant differences were found in any analysis regarding gender (highest value: $Z = -1.79$, $p = 0.07$; lowest value: $Z = 0.12$, $p = 0.90$). The comparison between the general population samples versus those with special characteristics also showed no significant differences (highest value: $Z = -1.72$, $p = 0.08$; lowest value: $Z = -0.26$, $p = 0.79$). This analysis could not be performed for the sensitivity-stress hypothesis with the internalizing spectrum, because all the studies included were based on general population samples. In line with the other analyses, the interviewing methodology used to assess the life events did not change the results significantly compared to the use of checklists (highest value: $Z = 0.77$, $p = 0.44$; lowest value: $Z = -0.60$, $p = 0.55$). Furthermore, the time period asked

about in the life events assessment was also not significant in any analysis (highest value: $Z = -1.72$, $p = 0.09$; lowest value: $Z = -0.68$, $p = 0.50$).

The analysis of the effect of the type of life events assessed was restricted only to those studies that used an independent life events measure. This was because none of the other types of life events were found in a minimum number of studies ($n = 4$) to have reliable data. Therefore, the effect-size reference was the general non-specific life events measures. No analysis showed significant differences between the use of a specific independent life events measure and a general non-specific life events measure (highest value: $Z = -1.50$, $p = 0.13$; lowest value: $Z = -0.17$, $p = 8.87$).

Significant differences were found when taking into account the reporter of the life events measure. In the cross-sectional studies regarding the externalizing spectrum, lower effect sizes were found in those studies with multiple reporters compared with the self-report method ($Z = -3.94$, $p < 0.0001$). However, in the cross-sectional studies of the internalizing spectrum, the lowest effect sizes were found in the studies with a single hetero-reporter ($Z = -2.19$, $p < 0.05$). In the longitudinal analyses, no significant differences were found regarding the reporter of the life events.

In line with the previous findings, a significant effect of the reporter was found for the assessment of the psychopathological clusters. In the cross-sectional studies, those studies that used multiple reporters to estimate the externalizing spectrum resulted in lower correlations than those that used only self-reports ($Z = -3.94$, $p < 0.0001$). The same result (lower correlations in studies with multiple reporters) was found in the stress-generation hypothesis analysis regarding the externalizing spectrum ($Z = -2.13$, $p < 0.05$). The other analyses showed no significant differences between the ways in which the psychopathology was evaluated.

Furthermore, for the longitudinal studies only, the time between the two assessments was introduced as a covariate. In the sensitivity-stress hypothesis analysis for the externalizing spectrum, a significant effect was found ($Z = -3.51$, $p < 0.001$). The longer the time between the two evaluations, the lower was the correlation coefficient. In the other three longitudinal analyses, no significant effect was found.

Finally, the number of life events in the checklists/interviews was also introduced as a covariate. Only for the externalizing spectrum a significant effect was found in cross-sectional studies ($Z = 2.82$, $p < 0.01$) and in the stress-generation hypothesis ($Z = 2.98$, $p < 0.01$). As more life events were questioned, the higher was the correlation coefficient.

Discussion

The main aim of the present study was to study the relation between stressful life events during adolescence and externalizing/internalizing spectra using a meta-analytical methodology. Twenty-seven studies were included in the meta-analysis. Population effect sizes were estimated based on the correlations using a random/mixed-effects model. In each study, the effect of aggregated stressful life events, rather than specific life events, was analyzed. Moreover, the life events investigated were those that occurred during adolescence, so no effects from other life periods were investigated. Hence, the present study focused only on recent life events during adolescence.

Some of the studies included were cross-sectional, while others used longitudinal designs. According to the empirical guidelines of Hemphill [63], the meta-analytical correlations found in cross-sectional studies could be interpreted as high. This is consistent with past research focused on individual disorders [29, 31].

As longitudinal designs are useful to deduce which variable precedes the other in correlational analyses, the present meta-analysis also used longitudinal data. Theoretically, the directional relation between stressful life events and psychopathology can be understood according to two hypotheses. The first one, the sensitivity-stress hypothesis, implies that the aggregation of stressful experiences should be a risk factor for psychopathology [58, 59]. Those studies that showed correlations between the stressful life events assessed at Time 1 and the psychopathological clusters evaluated at Time 2 were selected to test the sensitivity-stress hypothesis. According to Hemphill [63], the correlations found for the externalizing and internalizing spectra could be interpreted as a medium effect size. The second directional association between the stressful life events and the psychopathology is described by the stress-generation hypothesis. This suggests that a mental disorder increases exposure to more stressful life events or could lead to a more stressful interpretation of the life events experienced [46, 48, 55–57]. Hence, studies in which psychopathological clusters were assessed at Time 1 and stressful life events were assessed at Time 2 were selected to test the stress-generation hypothesis. According to Hemphill [63], the two correlations found could be interpreted as medium effect size. Hence, in line with past research [55, 64, 65], the directional association between the aggregation of stressful life events and the externalizing/internalizing spectra could be considered as transactional. The psychopathological spectra could be a consequence but also a cause of the stressful situations that could be experienced during adolescence. This developmental process of reciprocal relations

should evolve due to mutual interactions with other biopsychosocial factors [56].

According to the definition of the psychopathological spectra [16], the present study suggests that the aggregation of stressful life events must be considered as a general risk factor (and sometimes a consequence) for the common liability factors that underlie impulsive and emotional disorders, and not for specific mental problems. This could be important in clinical settings. For example, if a patient has a diagnosis of a specific phobia and the psychiatrist or psychologist detects that in recent months, this patient has experienced a significant increase in stressful life events; it should be pointed out that the patient will have an increased likelihood of developing another internalizing disorder, such as depression. On the other hand, which specific life events have been experienced could be important when hypothesizing which particular mental disorder could develop. For example, the death of a family member predicted major depression but not general anxiety syndrome [66]. This could also be applicable for gene–environment interaction/correlation studies.

One objective of the present study was to analyze the directionality of the association between the stressful life events and psychopathology, taking into account the difference between dependent and independent life events. The heritability component of independent life events is estimated to be lower than that of dependent life events [39]. Thus, it could be assumed that independent life events influence the individual through gene–environment interactions (sensitivity-stress hypothesis), whereas dependent life events are related to psychopathology through gene–environment correlation effects (stress-generation hypothesis) [36, 39]. However, when meta-regressions controlling the type of life events were performed, no significant results were found. Those studies that assessed life events using an undifferentiated measure showed the same pattern of relations as those studies that assessed independent life events only. One problem with the studies accepted for the meta-analysis is that most of them analyzed the effect of life events using an undifferentiated measure or they only assessed independent life events. As the undifferentiated measures mixed dependent and independent life events, we could not rule out the possibility that the main results of the present study were due exclusively to independent life events. Future studies in this field should differentiate more frequently between the types of life events.

In addition, only 4 out of the 27 studies assessed stressful life events using the same measure as any of the other 27 studies (2 using the Adolescent Life Events Questionnaire (ALEQ [67]) and 2 using a selection of items from the Life Events Checklist (LEC [68]). As all four of these studies did not use the same instrument, they did not reach the minimum number of studies ($n = 4$) necessary to provide reliable data for subgroup analysis. Hence, we could not test the effect of specific tests on the results directly. This heterogeneity in the measurement of life events makes it difficult to perform adequate meta-analysis, as not all the measures consider the same life events or use the same questions. This problem is also typical in meta-analysis focused on single disorders [69]. Taking into account that the life events considered by these measures are intended to be a representative sample of the most likely life events that a person could experience, not enquiring about a specific life event that was significant to the respondent means underestimating the real stress lived through by that person. Thus, a test of the effect of the number of life events measured in each study was performed to gain indirect information concerning the significance of using one measure or another. We found that the number of life events included in the tests moderated the associations between the aggregate life events and the externalizing spectrum. Hence, the checklist/interview that a researcher decides to use is relevant when estimating the effect of life events on some mental disorders. Therefore, a suggestion for the scientific community in this field would be to standardize the measurement of stressful life events, conceptually but also technically.

Another limitation of the present study is related to the outcome used. The fact that the meta-analysis was performed with the correlations of the studies presents two main drawbacks. The first is that we could not control confounders in the relations between life events and psychopathology. Some of the confounders tested in past studies have been the family's socioeconomic position, gender, and the parental psychopathology [70–72]. In non-meta-analytic studies, controlling these confounders is usually done by performing regressions. However, it is very difficult to carry out a meta-analysis by taking the standardized betas of regressions as the unit of measurement. This could be done if a sufficient number of studies performed the same regression methodology with the same dependent, independent, and confounder variables. However, there are very few studies with these characteristics in the literature. However, the empirical studies that have controlled for confounders found that the relation between the stressful life events and the psychopathological spectra remained stable and significant [70–72]. Another problem derived from using the correlations as the unit to perform the meta-analysis is that we could not control for the baseline levels of the variables of interest in the longitudinal studies. For example, if we wanted to test whether the stressful life events at Time 1 predicted the psychopathological spectra levels at Time 2, we would have to control the effect of the psychopathological spectra levels at Time 1. This methodological control is the basic step necessary to ensure assessment of

causation in a longitudinal design, while also performing regressions in empirical studies. In line with the first limitation, the longitudinal studies that have controlled this effect also found that the transactional relations between the stressful life events and the psychopathological spectra remained significant [64, 65].

In conclusion, the present study assessed the relations between stressful life events and the externalizing/internalizing spectra of psychopathology using a meta-analytical methodology. In cross-sectional studies, the association between these variables was significant and empirically high. From a longitudinal perspective, both the sensitivity-stress hypothesis and the stress-generation hypothesis were supported. These results would mean that the aggregation of stressful life events during adolescence should be considered as a risk factor for externalizing or internalizing symptoms, which increase the likelihood of developing specific psychiatric disorders. At the same time, having high levels of the liability to develop externalizing or internalizing disorders would increase exposure to more stressful life experiences. Hence, the relation between the variables studied seems to be reciprocal and transactional. More research in this field should be performed to show whether different types of life events (dependent vs. independent) explain the associations found in the present study.

Acknowledgements Thanks to the Comissionat per a Universitats i Recerca del DIUE, Generalitat de Catalunya (2014SGR1636); the Centre for Biomedical Research in the Mental Health Network (CIBERSAM) Intramural Project (SAM15PI12); the Spanish Ministry of Economy and Competitivity (ES-EUEpiBrain project, Grant SAF2015-71526-REDT); the Spanish Ministry of Economy and Competitivity, Instituto de Salud Carlos III (PI15/00097)—Ayuda cofinanciada por el Fondo Europeo de Desarrollo Regional (FEDER). "Una manera de hacer Europa". Thanks to the Secretaria d'Universitats i Recerca del Departament d'Empresa i Coneixement de la Generalitat de Catalunya (expedient 2017FI-B00258).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The manuscript does not contain clinical studies or patient data.

References

1. Dahl RE, Gunnar (2009) Heightened stress responsivity and emotional reactivity during pubertal maturation: implications for psychopathology. Dev Psychopathol 21:1–6
2. Serafini G, Muzio C, Piccinini G, Flouri E, Ferrigno G, Pompili M, Girardi P, Amore M (2015) Life adversities and suicidal behavior in young individuals: a systematic review. Eur Child Adolesc Psychiatry 24:1423–1446
3. Holder MK, Blaustein JD (2014) Puberty and adolescence as a time of vulnerability to stressors that alter neurobehavioral processes. Front Neuroendocrinol 35:89–110
4. Gee DG, Casey BJ (2015) The impact of developmental timing for stress and recovery. Neurobiol Stress 1:184–194
5. Spear LP (2009) Heightened stress responsivity and emotional reactivity during pubertal maturation: implications for psychopathology. Dev Psychopathol 21:87–97
6. Kessler RC, Avenevoli S, Costello J, Green JG, Gruber MJ, McLaughlin KA, Petukhova M, Sampson NA, Zaslavsky AM, Merikangas KR (2012) Severity of 12-month DSM-IV disorders in the national comorbidity survey replication adolescent supplement. Arch Gen Psychiatry 69:381–389
7. Merikangas K, Jian-ping H, Burstein M, Swanson S, Avenevoli S, Lihong C, Benjet C, Georgiades K, Swendsen J (2011) Lifetime prevalence of mental disorders in US adolescents: results from the National Comorbidity Study-Adolescent Supplement. J Am Acad Child Adolesc Psychiatry 49:980–989
8. Wittchen HU, Jacobi F, Rehm J et al (2011) The size and burden of mental disorders and other disorders of the brain in Europe 2010. Eur Neuropsychopharmacol 21:655–679
9. Trotman HD, Holtzman CW, Ryan AT, Shapiro DI, MacDonald AN, Goulding SM, Brasfield JL, Walker EF (2013) The development of psychotic disorders in adolescence: a potential role for hormones. Horm Behav 64:411–419
10. Yung ARAR, McGorry PD (1996) The prodromal phase of first-episode psychosis: past and current conceptualizations. Schizophr Bull 22:353–370
11. Caouette JD, Guyer AE (2014) Gaining insight into adolescent vulnerability for social anxiety from developmental cognitive neuroscience. Dev Cogn Neurosci 8:65–76
12. Pérez-Edgar KE, Guyer AE (2014) Behavioral Inhibition: temperament or prodrome? Curr Behav Neurosci Rep 1:182–190
13. Lingford-Hughes AR, Welch S, Nutt DJ (2004) Evidence-based guidelines for the pharmacological management of substance misuse, addiction and comorbidity: recommendations from the British Association for Psychopharmacology. J Psychopharmacol 18:293–335
14. Kelly TM, Daley DC, Douaihy AB (2013) Treatment of substance abusing patients with comorbid psychiatric disorders. Addict Behav 37:11–24
15. Valderas JM, Starfield B, Sibbald B, Salisbury C, Roland M (2009) Defining comorbidity: implications for understanding health and health services. Ann Fam Med 7:357–363
16. Krueger RF, Markon KE (2006) Reinterpreting comorbidity: a model-based approach to understanding and classifying psychopathology. Annu Rev Clin Psychol 2:111–133
17. Achenbach TM, Rescorla LA (2001) Manual for the ASEBA school-age forms & profiles. University of Vermont, Research Center for Children, Youth, & Families, Burlington, VT
18. Lahey BB, Rathouz PJ, Van Hulle C, Urbano RC, Krueger RF, Applegate B, Garriock HA, Chapman DA, Waldman ID (2008) Testing structural models of DSM-IV symptoms of common forms of child and adolescent psychopathology. J Abnorm Child Psychol 36:187–206
19. Verona E, Javdani S, Sprague J (2011) Comparing factor structures of adolescent psychopathology. Psychol Assess 23:545–551
20. Beesdo-baum K, Höfler M, Gloster AT, Klotsche J, Lieb R, Beauducel A, Bühner M, Kessler RC, Hans-Ulrich W (2009) The structure of common mental disorders: a replication study in a community sample of adolescents and young adults. Int J Methods Psychiatr Res 18:204–220
21. Cosgrove VE, Rhee SH, Gelhorn HL, Boeldt D, Corley RC, Ehringer M, Young SE, Hewitt JK (2011) Structure and etiology of co-occurring internalizing and externalizing disorders in adolescents. J Abnorm Child Psychol 39:109–123

22. Witkiewitz K, King K, Mcmahon RJ, Va BC, Wu J (2013) Evidence for a multi-dimensional latent structural model of externalizing disorders. J Abnorm Child Psychol 41:223–237
23. Fryers T, Brugha T (2013) Childhood determinants of adult psychiatric disorder. Clin Pract Epidemiol Ment Health 9:1–50
24. Copeland WE, Shanahan L, Costello EJ, Angold A (2009) Which childhood and adolescent psychiatric disorders predict which young adult disorders? Arch Gen Psychiatry 66:764–772
25. Low NC, Dugas E, O'Loughlin E, Rodriguez D, Contreras G, Chaiton M, O'Loughlin J (2012) Common stressful life events and difficulties are associated with mental health symptoms and substance use in young adolescents. BMC Psychiatry 12:116
26. Stikkelbroek Y, Bodden DHM, Reitz E, Vollebergh WAM, van Baar AL (2016) Mental health of adolescents before and after the death of a parent or sibling. Eur Child Adolesc Psychiatry 25:49–59
27. Fröjd S, Kaltiala-Heino R, Pelkonen M, Von Der Pahlen B, Marttunen M (2009) Significance of family life events in middle adolescence: a survey on finnish community adolescents. Nord J Psychiatry 63:78–86
28. Swartz JR, Williamson DE, Hariri AR (2015) Developmental change in amygdala reactivity during adolescence: effects of family history of depression and stressful life events. Am J Psychiatry 172:276–283
29. Fernandez Castelao C, Kröner-Herwig B (2013) Different trajectories of depressive symptoms in children and adolescents: predictors and differences in girls and boys. J Youth Adolesc 42:1169–1182
30. Flouri E, Kallis C (2011) Adverse life events and mental health in middle adolescence. J Adolesc 34:371–377
31. Charles NE, Ryan SR, Acheson A, Mathias CW, Liang Y, Dougherty DM (2015) Childhood stress exposure among preadolescents with and without family histories of substance use disorders. Psychol Addict Behav 29:192–200
32. King KM, Chassin L (2008) Adolescent stressors, psychopathology, and young adult substance dependence: a prospective study. J Stud Alcohol Drugs 69:629–638
33. Casement MD, Shaw DS, Sitnick SL, Musselman SC, Forbes EE (2013) Life stress in adolescence predicts early adult reward-related brain function and alcohol dependence. Soc Cogn Affect Neurosci 10:416–423
34. Rutter M, Moffitt TE, Caspi A (2006) Gene–environment interplay and psychopathology: multiple varieties but real effects. J Child Psychol Psychiatry Allied Discip 47:226–261
35. Plomin R, DeFries JC, Loehlin JC (1977) Genotype–environment interaction and correlation in the analysis of human behavior. Psychol Bull 84:309–322
36. Tsuang MT, Bar JL, Stone WS, Faraone SV (2004) Gene–environment interactions in mental disorders. World Psychiatry 3:73–83
37. Wichers M, Maes HH, Jacobs N, Derom C, Thiery E, Kendler KS (2012) Disentangling the causal inter-relationship between negative life events and depressive symptoms in women: a longitudinal twin study. Psychol Med 42:1801–1814
38. McAdams T, Gregory AM, Eley TC (2013) Genes of experience: explaining the heritability of putative environmental variables through their association with behavioural and emotional traits. Behav Genet 43:314–328
39. Kendler KS, Baker JH (2007) Genetic influences on measures of the environment: a systematic review. Psychol Med 37:615–626
40. Johnson DP, Rhee SH, Whisman MA, Corley RP, Hewitt JK (2013) Genetic and environmental influences on negative life events from late childhood to adolescence. Child Dev 84:1823–1839
41. Young-Wolff KC, Kendler KS, Prescott C (2012) Interactive effects of childhood maltreatment and recent stressful life events on alcohol consumption in adulthood. J Stud Alcohol Drugs 73:559–569
42. Harkness KL, Bruce AE, Lumley MN (2006) The role of childhood abuse and neglect in the sensitization to stressful life events in adolescent depression. J Abnorm Psychol 115:730–741
43. Fandiño-Losada A, Bangdiwala SI, Lavebratt C, Forsell Y (2016) Path analysis of the chronicity of depression using the comprehensive developmental model framework. Nord J Psychiatry 9488:1–12
44. Goodyer IM, Park RJ, Herbert J (2001) Psychosocial and endocrine features of chronic first-episode major depression in 8–16 year olds. Biol Psychiatry 50:351–357
45. Stone LB, Liu RT, Yen S (2014) Adolescent inpatient girls′ report of dependent life events predicts prospective suicide risk. Psychiatry Res 219:137–142
46. Hammen C (1991) Generation of stress in the course of unipolar depression. J Abnorm Psychol 100:555–561
47. Liu RT, Alloy LB (2011) Stress generation in depression: a systematic review of the empirical literature and recommendations for future study. Clin Psychol Rev 30:582–593
48. Bender RE, Alloy LB, Sylvia LG (2010) Generation of life events in bipolar spectrum disorders: a re-examination and extension of the stress generation theory. J Clin Psychol 66:907–926
49. Kercher AJ, Rapee RM, Schniering CA (2009) Neuroticism, life events and negative thoughts in the development of depression in adolescent girls. J Abnorm Child Psychol 37:903–915
50. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB (2008) Meta-analysis of observational studies. JAMA 283:2008–2012
51. World Health Organization (2014) Health for the world's adolescents: a second chance in the second decade. http://www.who.int/adolescent/seconddecade. Accessed 02 Sept 2016
52. Haller M, Chassin L (2012) A test of adolescent internalizing and externalizing symptoms as prospective predictors of type of trauma exposure and posttraumatic stress disorder. J Trauma Stress 25:691–699
53. Jenkins EJ, Wang E, Turner L (2009) Traumatic events involving friends and family members in a sample of African American early adolescents. Am J Orthopsychiatry 79:398–406
54. McMullen JD, O'Callaghan PS, Richards JA, Eakin JG, Rafferty H (2012) Screening for traumatic exposure and psychological distress among war-affected adolescents in post-conflict northern Uganda. Soc Psychiatry Psychiatr Epidemiol 47:1489–1498
55. Hammen C (2005) Stress and depression. Annu Rev Clin Psychol 1:293–319
56. Harkness KL, Hayden EP, Lopez-Duran NL (2015) Stress sensitivity and stress sensitization in psychopathology: an introduction to the special section. J Abnorm Psychol 124:1–3
57. Rudolph KD, Constance H, Burge D, Lindberg N, Herzberg D, Daley SE (2000) Toward an interpersonal life-stress model of depression: the developmental context of stress generation. Dev Psychopathol 12:215–234
58. Hankin BL, Abela (2005) Depression from childhood through adolescence and adulthood: a developmental vulnerability stress perspective. In: Hankin BL, Abela JRZ (eds) Dev. Psychopathol. a vulnerability Stress Perspect. Sage Publications, Thousand Oaks, pp 245–288
59. Cohen JR, Hankin BL, Gibb BE, Hammen C, Hazel NA, Ma D, Yao S, Zhu XZ, Abela JRZ (2013) Negative attachment cognitions and emotional distress in mainland Chinese adolescents: a prospective multiwave test of vulnerability-stress and stress generation models. J Clin child Adolesc Psychol 42:531–544
60. Hedges LV, Vevea JL (1998) Fixed- and random-effects models in meta-analysis. Psychol Methods 3:486–504
61. Viechtbauer W (2015) Package "metafor". https://cran.r-project.org/web/packages/metafor/index.html. Accessed 11 Feb 2016

62. Williams EJ (1959) The comparison of regression variables. J R Stat Soc Ser B 21:396–399
63. Hemphill JF (2003) Interpreting the magnitudes of correlation coefficients. Am Psychol 58:78–79
64. Kim KJ, Conger RD, Elder GH, Lorenz FO (2003) Reciprocal influences between stressful life events and adolescent internalizing and externalizing problems. Child Dev 74:127–143
65. Shapero B, Hankin BL, Barrocas AL (2013) Stress generation and exposure in a multi-wave study of adolescents: Transactional processes and sex differences. J Soc 32:1–17
66. Kendler KS, Hettema JM, Butera F, Gardner CO, Prescott CA (2003) Life event dimensions of loss, humiliation, entrapment, and danger in the prediction of onsets of major depression and generalized anxiety. Arch Gen Psychiatry 60:789–796
67. Hankin BL, Abramson LY (2002) Measuring cognitive vulnerability to depression in adolescence: reliability, validity, and gender differences. J Clin Child Adolesc Psychol 31:491–504
68. Johnson J, McCutcheon S (1980) Assessing life stress in children and adolescents: preliminary findings with the life events checklist. Stress Anxiety (Vol 7) 7:111–126
69. Karg K, Burmeister M, Shedden K, Sen S (2011) The serotonin transporter promoter variant (5-HTTLPR), stress, and depression meta-analysis revisited: evidence of genetic moderation. Arch Gen Psychiatry 68:444–454
70. Amone-P'Olak K, Ormel J, Huisman M, Verhulst FC, Oldehinkel AJ, Burger H (2009) Life stressors as mediators of the relation between socioeconomic position and mental health problems in early adolescence: the TRAILS study. J Am Acad Child Adolesc Psychiatry 48:1031–1038
71. Bakker MP, Ormel J, Verhulst FC, Oldehinkel AJ (2010) Peer stressors and gender differences in adolescents' mental health: the TRAILS study. J Adolesc Health 46:444–450
72. Barrera M, Li SA, Chassin L (1995) Effects of parental alcoholism and life stress on hispanic and non-hispanic caucasian adolescents: a prospective study. Am J Community Psychol 23:479–507

UNIVERSITAT DE BARCELONA

Dr. Lourdes Fañanás Saura
Unitat de Zoologia i Antropologia Biològica
Dept. Biologia Evolutiva, Ecologia i Ciències Ambientals
Facultat de Biologia, Universitat de Barcelona

Informe del director sobre la contribución del doctorando al artículo.

La Prof. Lourdes Fañanás Saura, profesora del Departamento de Biología Evolutiva, Ecologia y Ciencias Ambientales de la Facultad de Biología (Universitat de Barcelona) y directora de la presente tesis doctoral de Laia Marques Feixa, por la presente certifica que ninguno de los coautores del articulo *"Stressful life events during adolescence and the development of externalizing and internalizing psychopathology: a meta-analysis",* ha utilizado esta publicacion para una tesis doctoral, y que la participación del solicitante en este artículo incluyó las siguientes tareas:

- Participación en la concepción y diseño del estudio.
- Resumen de la evidencia e interpretación de los datos.
- Revisión crítica del artículo por contenido intelectual.

Signado por Prof. Lourdes Fañanás

Barcelona, abril 2022

3.2. Recent stressful life events (SLE) and adolescent mental health: initial validation of the LEIA, a new checklist for SLE assessment according to their severity, interpersonal, and dependent nature

Jorge Moya-Higueras, Andrea Cuevas, **Laia Marques-Feixa**, Laura Mezquita, María Mayoral, Lourdes Fañanás, Generós Ortet y Manuel I. Ibáñez

Assessment (2020), Dec; 27(8):1777-1795 (Epub 2018 Dec 12).

DOI: 10.1177/1073191118817648

Article

Assessment
1–19

DOI: 10.1177/1073191118817648
journals.sagepub.com/home/asm
SAGE

Recent Stressful Life Events (SLE) and Adolescent Mental Health: Initial Validation of the LEIA, a New Checklist for SLE Assessment According to Their Severity, Interpersonal, and Dependent Nature

Jorge Moya-Higueras[1,2], Andrea Cuevas[3], Laia Marques-Feixa[2,4], Laura Mezquita[2,3], María Mayoral[2,5], Lourdes Fañanás[2,4], Generós Ortet[2,3], and Manuel I. Ibáñez[2,3]

Abstract

The main aim of the present study was to develop and validate a checklist for adolescents, the Life Events Inventory for Adolescents (LEIA), for screening stressful life events (SLEs) of different nature (major–minor, dependent–independent, and personal–interpersonal). The LEIA was administered together with another SLE checklist (Escala de Acontecimientos Vitales [Life Events Scale], EAV), and with measures of life satisfaction and externalizing and internalizing symptoms. The results showed that the kappa and the percentage agreement reliability indices were adequate. Regarding validity evidences, the correlations found between the LEIA and the EAV ranged from .65 to .69, and between the LEIA and the psychopathological symptoms ranged from .26 to .38. Specifically, major dependent noninterpersonal SLEs were the best predictors of externalizing psychopathology; while major independent noninterpersonal SLEs were the best predictors of internalizing symptoms and low life satisfaction. To conclude, the LEIA could be considered an adequate checklist to screen for SLEs in adolescents.

Keywords

stressful life events, dependent, interpersonal, externalizing, internalizing, life satisfaction, adolescence

Adolescence is a key period of transition from childhood to adulthood. Adolescents have to adapt to multiple biological and physical changes that pubertal maturation involves, and they face new social challenges within the family, among their peers and at school (Crone & Dahl, 2012; Hollenstein & Lougheed, 2013). These changes lead to cognitive transformations, mood disruption, and personality changes in self-regulation, disinhibition, and conflictiveness (Denissen, van Aken, Penke, & Wood, 2013; Ibáñez et al., 2016). Therefore, adolescence has been conceptualized as a period of vulnerability during which some mental disorders present their prodromal phase (Casey, Jones, & Hare, 2008; Patton et al., 2014; Wittchen et al., 2011). Accordingly, the prevalence of common mental disorders during adolescence tends to be high, with estimations in the range of 25% to 45% (Merikangas et al., 2011; Patton et al., 2014; Wittchen et al., 2011). Moreover, episodes of mental disorder in adolescence seem to increase the risk of disorders later, in adulthood (Clark, Rodgers, Caldwell, Power, & Stansfeld, 2007; Copeland, Shanahan, Costello, & Angold, 2009; Patton et al., 2014)

An important factor in the initiation and chronification of mental disorders during this sensitive developmental period is stress (Gee & Casey, 2015; Grant, Compas, Thurm, McMahon, & Gipson, 2004; Holder & Blaustein, 2014). It have been proposed that the experience of multiple stressors in adolescence increases the likelihood of developing psychiatric symptoms through their action on psychobiological systems involved in emotional and coping responses

[1]Universitat de Lleida, Lleida, Spain
[2]Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Madrid, Spain
[3]Universitat Jaume I, Castelló, Spain
[4]Universitat de Barcelona, Barcelona, Spain
[5]Instituto de Investigación Sanitaria Gregorio Marañón (IiSGM), Madrid, Spain

Corresponding Author:
Manuel I. Ibáñez, Department of Basic and Clinical Psychology and Psychobiology, Universitat Jaume I, Av de Vicent Sos Bynat s/n, 12071 Castelló de la Plana, Spain.
Email: iribes@uji.es

to threats. Such systems include the amygdala (Swartz, Williamson, & Hariri, 2015), serotonergic neurotransmission (Caspi, Hariri, Holmes, Uher, & Moffitt, 2010) and the hypothalamic-pituitary-adrenal axis (Miller, Chen, & Zhou, 2007), and the action would be in part through epigenetic mechanisms linked to them (Palma-Gudiel, Córdova-Palomera, Leza, & Fañanás, 2015; van der Knaap et al., 2014).

Stress involves an organism's adaptation to any challenging situation or set of external demands that requires expending resources to cope with its circumstances (Monroe, 2008; Shields & Slavich, 2017). Research on stressful events has explored from extreme traumatic experiences (Gilbert et al., 2009; Van Der Kolk, Roth, Pelcovitz, Sunday, & Spinazzola, 2005) to mild to severe negative life incidents, or stressful life events (SLE; Grant et al., 2004; Monroe, 2008; Shields & Slavich, 2017); until minor quotidian disturbances, or daily hassles (Kanner, Coyne, Schaefer, & Lazarus, 1981; Trianes et al., 2009).

For SLE, the most common study estimating their relevance on psychopathology focuses on short-term effects of acute life events, typically a recall period of no more than 1 year, and their assessment has been performed through two main methods: interviews and checklists (Kessler, 1997; Shields & Slavich, 2017; Turner & Wheaton, 1997). Interviews are considered to be more accurate and effective in predicting outcomes than self-report checklists; but they have to be individually administered, demand much time of researchers and participants, and involve a high cost in personnel (Dohrenwend, 2006; Harkness & Monroe, 2016; Shields & Slavich, 2017; Wethington, Brown, & Kessler, 1997). Conversely, self-report checklists, demand little time of researcher and participant, are easy to administer and score, and can be administered collectively (Dohrenwend, 2006; Grant et al., 2004; Turner & Wheaton, 1997). Thus, when time and personnel are limited, such as in research involving large samples and a wide battery of tests, the checklists constitute a cost-effective tool for SLE screening (Duggal et al., 2000; Lewinsohn, Rohde, & Gau, 2003; Wagner, Abela, & Brozina, 2006).

There is compelling evidence that SLEs are related to adolescent mental health (Grant et al., 2004). A meta-analysis performed by March-Llanes, Marqués-Feixa, Mezquita, Fañanás, and Moya-Higueras (2017) confirmed that during adolescence, SLEs were strongly associated with internalizing pathology and its symptoms (such as depression, anxiety, or somatic complaints), but also with externalizing disorders (such as attention problems, aggressive behavior, or conduct problems), both in cross-sectional and longitudinal studies. Interestingly, the authors did not find significant differences in the magnitude of these associations as a function of the assessment method, interview versus checklist, in agreement with some previous findings (Duggal et al., 2000; Lewinsohn et al., 2003; Wagner et al., 2006).

However, the role of proximal SLEs in other areas is not so clear. For example, their connection with psychosis (Beards et al., 2013) or alcohol use (Veenstra et al., 2006) is far from completely consistent; and their moderator role on some mental disorders reported in gene–environment interaction studies (e.g., Caspi et al., 2003; Covault et al., 2007) has not always been replicated (Risch et al., 2009; Todkar, Nilsson, Oreland, Hodgins, & Comasco, 2013). One of the possible explanations of these and other inconsistencies is the psychometric deficiencies that SLE checklists often present (Beards et al., 2013; Compas, Davis, Forsythe, & Wagner, 1987; Grant et al., 2004; Monroe & Reid, 2008). Thus, the use of standardized checklists with reliable scores and adequate sources or validity evidences for the assessment of SLEs would increase the reliability of results, would facilitate replication and comparability of studies, and would help disentangle more specific issues regarding the association of SLEs and health (Grant et al., 2004; Turner & Wheaton, 1997).

Some recommendations for increasing the psychometric quality of SLE checklists can be derived from reviews of the topic (e.g., Dohrenwend, 2006; Grant et al., 2004; Hammen, 2005; Harkness & Monroe, 2016; Kessler, 1997; Rabkin & Struening, 1976; Turner & Wheaton, 1997; Zimmerman, 1983a). A basic psychometric requirement when dealing with SLEs is to report the scores' reliability properly, but most studies either do not test the reliability of the scores or use traditional reliability methodologies (such as the Cronbach alpha or test–retest coefficients) that are inadequate in the case of SLEs. Measures of internal consistency are inappropriate because there is no underlying assumption that items should covary (Harkness & Monroe, 2016); whereas test–retest reliabilities of aggregated SLEs do not guarantee that a same score in test and retest can be attributed to the aggregation of the same events on both occasions (Zimmerman, 1983a). A more adequate alternative is to administer the checklist at two different moments and to evaluate the appearance of each specific SLE (Turner & Wheaton, 1997) using kappa values together with the percentage of agreement (McHugh, 2012). Some validation studies of SLE checklists in adults have reported both statistics (e.g., Gray, Litz, Hsu, & Lombardo, 2004), but we are not aware of any checklist for adolescents that has used this procedure.

Another important question in the assessment of SLEs is how to estimate and quantify their degree of impact. The simplest and most usual way is to calculate the total number of SLEs experienced. However, one problem with this procedure is that it implies that each event has the same impact potential; for example, the death of one's mother is considered to have the same potential impact as an argument with a friend (Zimmerman, 1983a). So checklists that include *weighted* SLEs have been proposed as a better option (Compas et al., 1987; Kessler, 1997). The most commonly

used procedures to weight the SLEs in checklists are their objective and subjective weighting (Harkness & Monroe, 2016; Kessler, 1997; Turner & Wheaton, 1997). In the objective or consensual procedure, a panel of raters generates weights for each event (Holmes & Rahe, 1967); whereas in the subjective procedure, each respondent assigns a subjective weight to his or her own events (Sarason, Johnson, & Siegel, 1978). Regarding the objective procedure, an important criticism is that all life events of a given type are treated as equivalent for any person (Kessler, 1997); for example, the death of an adolescent's father would have the same weight irrespective of if he lived with the child or if he abandoned the home years ago. One strategy to tackle this problem is to ask participants to rate subjectively the emotional impact each SLE had on them (Kessler, 1997; Zimmerman, 1983a). This procedure assumes that the subjective emotional reactivity to stressors, or appraisal, constitutes a more relevant risk factor for certain disorders than the mere occurrence of the stressful experience (Conway, Hammen, & Brennan, 2012; Espejo, Hammen, & Brennan, 2012; Holtzman et al., 2013), in accordance with cognitive theories of vulnerability to mental disorders such as depression (Alloy, Abramson, & Francis, 1999). Accordingly, several studies have reported higher associations between adverse psychological outcomes and the subjective scoring procedure than the objective weighting or the simple count procedure (Calvete, Villardón, Estévez, & Espina, 2007; Espejo et al., 2012; Sarason et al., 1978); although these findings have not always been replicated (Ferreira, Granero, Noorian, Romero, & Domènech Llaberia, 2012; King, Pedersen, Louie, Pelham, & Molina, 2017; Zimmerman, 1983b).

Finally, another important recommendation for increasing the validity evidence for an SLE assessment is to take into account different typologies of life events (Grant et al., 2004; Hammen, 2005; Vrshek-Schallhorn et al., 2015). A relevant distinction between SLEs is their dependent versus independent nature; which refers to those life events that occur (in part) because of a person's own characteristics or behaviors (dependent or controllable) and events whose occurrence is most likely unrelated to the respondent's own behavior (independent or incontrollable). It has been found that dependent SLEs have a substantially higher heritability estimate than independent SLEs in adult and adolescent samples (D. P. Johnson, Rhee, Whisman, Corley, & Hewitt, 2013; Kendler & Baker, 2007). This indicates that genetical-based personal characteristics may be involved in the seeking out, creation or evocation of dependent SLEs. In addition, the interpersonal dimension (those that directly affect relationships with others vs. those that are experienced mainly by the respondent) also seems to be significant in SLE analysis, especially with regard to certain mental disorders such as depression (Hammen, 2005). Last, another relevant SLE typology is their moderate-to-severe negative impact (*major* SLEs) versus those with less than moderate impact (*minor* SLEs; Compas, 1987; Kendler et al., 1995).

Despite the importance of systematically examining which types of life events may be more relevant for different mental health outcomes, research on this topic is relatively scarce and has almost exclusively focused on the dependent interpersonal SLE combination. Dependent interpersonal SLEs are consistently associated with depressive symptoms and disorders in adolescents (Cohen et al., 2013; Espina & Calvete, 2017; Flynn, Kecmanovic, & Alloy, 2010; Flynn & Rudolph, 2011; Hankin, Stone, & Wright, 2010; Krackow & Rudolph, 2008; Rudolph et al., 2000; Shapero, Hankin, & Barrocas, 2013); and, according to the *stress generation theory* (Hammen, 1991, 2005), they are predicted by prior depression (Conway et al., 2012; Espina & Calvete, 2017; Hamilton et al., 2014; Harkness & Stewart, 2009). However, research examining the role of other types of SLEs on mental health outcomes is almost nonexistent. One noteworthy exception is the work of Vrshek-Schallhorn et al. (2015), which examined the predictive role of different types of SLE on the onset of depression disorders in emerging adulthood, categorizing them as a function of their interpersonal–noninterpersonal, dependent–independent, major–minor, and chronic–episodic characteristics. The main results of that study indicated that major interpersonal dependent and independent SLEs, together with chronic interpersonal SLEs, predicted the onset of depression. As far as we know, the issue of whether this pattern of results is replicated in other samples, in other lifespan stages such as adolescence, or in other mental health outcomes beyond depression, has not been explored.

Hence, the main aim of the present study was to develop a new SLE checklist, the Life Events Inventory for Adolescents (LEIA), following the recommendations aforementioned. The LEIA is intended to be a suitable screening instrument for large-scale research that offers advantages over other SLE checklists for adolescents. Past checklists were developed to give two main scores: (a) the aggregated occurrence of the SLEs and (b) an objective or a subjective score of the impact of each SLE, but not both of them. The LEIA allows the assessment of the occurrence of SLEs and their subjective impact for each adolescent, and it also generates an estimate of objective severity based on the mean impact of each event in the sample. These different scoring procedures may allow empirical testing of which SLE scoring method better predicts different mental health outcomes in adolescence. In addition, past checklists did not categorize properly the SLEs according to their interpersonal–noninterpersonal and dependent–independent nature. The LEIA gives open information about this classification, thereby allowing us to replicate in adolescence the findings of Vrshek-Schallhorn et al. (2015), and to extend the exploration of the differential impact that these types of SLEs

may have on other mental health outcomes. To this end, here we examine their associations with internalizing symptoms such as depression, anxiety, and somatization; with externalizing symptoms such as aggressivity, attention problems and antisocial behavior; and with subjective life satisfaction. Furthermore, we examine convergent validity by means of its association with another checklist that has been validated in Spanish adolescents: the Escala de Acontecimientos Vitales [Life Events Scale] (EAV; Mardomingo & González Garrido, 1990). Finally, we estimate the reliability of the LEIA's scores using the percentage of congruence between test and retest, and by estimating the kappa and the linear weighted kappa statistics (Fleiss, Levin, & Cho, 2003). To the best of our knowledge, no previous SLE validation study has used this methodology to examine the reliability in the reporting of both the occurrence of SLEs and their subjective impact.

Method

Participants

Of the 1,106 students invited to participate from two public high schools in the urban area of Castellón de la Plana, a city in eastern Spain, 835 returned signed written parental consent. Of these, 51 participants did not attend the two assessment sessions or did not respond to all the questionnaires. Thus, the final sample consisted on 784 adolescents (49.9% were girls), and the mean age of the sample was 14.31 years (SD = 1.59; age range = 12-17 years old). Moreover, 27.8% were 8th year students (48.1% girls, mean age = 12.59, SD = .70); 22% were 9th year students (52.6% girls, mean age = 13.68, SD = .83); 19.2% were 10th year students (43.6% girls, mean age = 14.62, SD = .76); 16.6% were 11th year students (50.4% girls, mean age = 15.70, SD = .83); 2.8% were vocational training students (60.9% girls, mean age = 16.61, SD = .66); and 11.6% were students of further education, preparing for university (56.7% girls, mean age = 16.41, SD = .63).

Around half of their fathers and mothers (56.3% and 55.9%, respectively) had successfully completed high school, but not continued on to higher education; whereas 26.3% of the fathers and 28.9% of the mothers had a university degree. The mean income was equivalent to that of a middle-class Spanish family and 24.1% of the sample were not from Spain (all of them showed an appropriate level of Spanish according to teacher's reports). All the questionnaires were administered in Spanish.

The LEIA checklist was readministered 1 month later, to determine the test–retest reliability in a subsample of 365 adolescents. This subsample was sociodemographically equivalent to the subgroup of adolescents who did not participate in the retest, age: $t(782) = 1.01$, $p = .31$; gender: $t(782) = 1.04$, $p = .30$; estimated family income: $t(782) = -.88$, $p = .38$; studies of the mother: $t(782) = -1.66$, $p = .10$; academic marks: $t(782) = .50$, $p = .62$, except for the level of education of the father, which was lower in the adolescents who did not participate in the retest, $t(782) = -5.30$, $p = .00$. Some significant differences were found between the subsamples in health outcome scales and some LEIA scores, although the effect size of these differences was trivial or very small (see Table 1). As this subsample was only used to assess the test–retest reliability, these differences should not affect the results.

Instruments

Life Events Inventory for Adolescents. This instrument for 12 to 17 years old adolescents includes 75 SLEs, plus an open-ended question. Specific items were created via inspection of some of the most used SLE instruments (most of them with a validation study in Spain or developed for Spanish populations), and their formulation was adapted to adolescents and updated to contemporary language when necessary: Social Readjustment Rating Scale (SRRS; Holmes & Rahe, 1967; Spanish adaptation of González de Rivera & Morera Fumero, 1983), Life Experiences Survey (LES; Sarason et al., 1978), Adolcescent Life Change Event Scale (ALCES; Spanish adaptation of Voltas, Aparicio, Arija, & Canals, 2015), Life Events Scale for Students (LESS; Clements & Turpin, 1996), Life Events Questionnaire (LEQ; Newcomb, Huba, & Bentler, 1981), List of Threatening Experiences Questionnaire (LTE-Q; Brugha & Cragg, 1990; Spanish adaptation of Motrico et al., 2013), Life Events Checklist (LEC; J. Johnson & McCutcheon, 1980), EAV (Mardomingo & González Garrido, 1990), Inventario de Acontecimientos Vitales Estresantes [Stressful Life Events Inventory] (IAVE; Oliva, Jiménez, Parra, & Sánchez-Queija, 2008) and Cuestionario de Sucesos Vitales [Questionnaire of Life Events] (CSV; Sandín & Chorot, 2017). As positive desirable SLEs tend to show nonsignificant associations with mental disorders (Kessler, 1997; Sarason et al., 1978), and following the recommendations in Turner and Wheaton (1997), only negative life events were included. In addition, other SLEs traditionally not assessed in SLE checklists were also incorporated, such as items related to bullying victimization. The respondents had to mark whether each SLE had occurred during the previous 12 months, in line with most of the checklists reviewed. If an SLE was experienced, then participants had to rate the magnitude of the negative impact, on a 5-point Likert-type scale (0 = *nothing* to 4 = *extremely*) with a pictographic aid (a representation of gradually sadder faces). The Spanish full version of the instrument is showed in the supplemental material (available in the online version of the article).

Table 1. Descriptions of Age and the Main Outcomes of the Study.

		Total sample ($N = 784$)		Boys ($n = 393$)		Girls ($n = 391$)				Subsample 1 retest ($n = 365$; 48.2% girls)			
	α	*M*	*SD*	*M*	*SD*	*M*	*SD*	*t*	*d*	*M*	*SD*	*t*	*d*
Age	—	14.31	1.59	14.32	1.61	14.30	1.57	0.17	.01	14.24	1.62	1.01	.07
LEIA Q	—	9.36	6.77	9.18	6.56	9.55	6.98	−0.88	.06	8.89	6.61	3.05**	.22
LEIA SS	—	28.61	24.00	26.37	20.34	30.87	27.00	−2.67**	.19	23.74	21.67	−1.37	.10
LEIA OS	—	28.50	20.34	27.74	19.61	29.26	21.05	−1.15	.08	27.08	19.80	3.09**	.22
SLE Q													
Independent interpersonal	—	4.15	3.46	4.05	3.37	4.25	3.55	−0.89	.06	4.09	3.49	2.12*	.15
Independent noninterpersonal	—	1.03	1.00	0.91	0.95	1.14	1.04	−3.24**	.23	1.02	0.95	1.23	.09
Dependent noninterpersonal	—	1.47	1.44	1.68	1.53	1.26	1.32	3.85***	.28	1.42	1.38	1.46	.11
Dependent interpersonal	—	2.58	2.65	2.47	2.60	2.70	2.69	−1.29	.09	2.33	2.60	2.85**	.21
SLE SS													
Independent interpersonal	—	12.46	11.76	11.43	10.09	13.49	13.17	−2.44*	.18	10.75	11.31	−2.02*	.15
Independent noninterpersonal	—	3.23	3.59	2.69	3.01	3.76	4.02	−4.20***	.30	2.72	3.16	−1.74	.12
Dependent noninterpersonal	—	4.51	4.99	4.85	4.88	4.16	5.08	1.77	.13	3.75	4.24	−1.60	.12
Dependent interpersonal	—	7.92	9.09	7.02	7.96	8.83	10.03	−2.80**	.20	6.42	8.40	−0.75	.05
AGG	.76	2.97	3.77	3.49	4.24	2.45	3.16	3.88***	.28	2.50	3.52	2.28*	.16
ATE	.89	14.04	8.67	13.67	8.58	14.41	8.74	−1.17	.08	12.96	8.63	3.04**	.22
ANT	.75	2.54	4.08	3.14	4.90	1.94	2.92	4.12***	.30	2.10	3.70	2.58*	.18
DEP	.91	10.92	9.74	8.87	7.75	13.03	11.05	−6.06***	.44	10.00	9.86	2.37*	.17
ANX	.89	14.38	9.08	11.33	7.80	17.47	9.25	−9.98***	.72	13.49	9.07	2.42*	.17
SOM	.79	10.20	6.12	8.64	7.75	11.78	6.30	−7.41***	.53	9.64	6.21	2.25*	.16
Intern.	.94	35.26	22.25	28.69	18.45	42.13	23.79	−8.67***	.63	33.23	22.51	2.39*	.17
Extern.	.89	19.31	13.28	20.03	14.50	18.59	11.90	1.50	.11	17.79	13.02	2.99**	.22
Life satisfaction	.77	22.45	6.21	23.39	5.56	21.51	6.68	4.24***	.31	23.00	6.43	−2.25*	.16

Note. *t* = student's *t* test; *d* = Cohen's *d* for effect size ($d < .20$ = trivial effect size; $.20 < d < .50$ = small effect size; $.50 < d < .80$ = medium effect size; $d > .80$ = large effect size); LEIA = Life Events Inventory for Adolescents; SLE = stressful life event; Q = quantity; SS = subjective severity; OS = objective severity; AGG = aggression; ATE = attention problems; ANT = antisocial behavior; DEP = depression; ANX = anxiety; SOM = somatic complaints; Extern = externalizing spectrum; Intern = internalizing spectrum.
*$p < .05$. **$p < .01$. ***$p < .001$.

Three different principal scores were calculated with the LEIA. First, a quantity score was calculated by adding up the SLEs that occurred for the participants (*LEIA quantity*). Second, a subjective weighted score was obtained by adding the subjective negative impact of each SLE (*LEIA subjective severity*). Last, an "objective" weighted score was derived by summing each SLE experienced weighted by the mean of the subjective negative impact for that SLE in the sample (*LEIA objective severity*). The mean impact for each event is presented in the Table 2.

To determine SLE typologies, 10 researchers, experts in the field, rated each life event in three dimensions. First, using a 5-point Likert-type scale (0 = *completely independent* to 4 = *completely dependent*), they estimated whether a life event was more or less dependent of the behavior of the respondent. When a life event had a mean score equal to or greater than 2 in this dependent–independent dimension, it was considered dependent. Second, the raters decided the social nature of the life event (0 = *noninterpersonal* to 1 = *interpersonal*). When a life event had a mean score equal or greater than .5 in the social dimension, it was considered interpersonal. These procedures were similar to those usually applied in studies that explore the combination of dependent interpersonal SLEs (e.g., Krackow & Rudolph, 2008). Last, we used the mean impact ratings of the adolescents to estimate the major versus minor category. When a life event had a mean score lower than 2.5, it was designated as minor ($n = 9$), whereas SLEs scoring greater than 2.5 were coded as major (severe and moderate; $n = 66$). The cut-off criterion of 2.5 follows the procedure used in Vrshek-Schallhorn et al. (2015). Due to the small number of minor events, and the fact that minor SLEs were not associated with mental health outcomes when controlling for major events (see Results section), we decided to combine only major events with the dependent versus independent and interpersonal versus noninterpersonal domains. Thus, a

Table 2. Test–Retest Reliability of the Occurrence and Impact of Stressful Life Events Over 1 Month.

				LEIA SLE		LEIA emotional impact	
	Type	Items	Percentage of people affected	Percentage agreement	Kappa	Weighted kappa	Mean impact (*SD*)
1a	IIM	Has your father died?	0.9	99.18	.57***	.21	3.14 (1.54)
1b	IIM	Has your mother died?	0.3	99.73	NA	NA	5.00 (.00)
1c	IIM	Have any of your siblings died?	1.1	98.63	.44***	.30	3.78 (1.30)
1d	IIM	Have any of your close relatives died?	31.8	82.74	.59***	.55	4.20 (1.00)
1e	IIM	Have any of your close friends died?	5.5	95.34	.58***	.58	4.26 (.88)
2a	INM	Have you suffered from any serious physical illness, accident, or assault?	12.4	90.36	.43***	.35	3.02 (1.11)
2b	IIM	Has your father suffered from any serious physical illness, accident, or assault?	9.8	91.74	.21***	.16	3.22 (1.27)
2c	IIM	Has your mother suffered from any serious physical illness, accident, or assault?	11.9	92.31	.52***	.48	3.62 (1.21)
2d	IIM	Have any of your siblings suffered from any serious physical illness, accident, or assault?	8	95.60	.37***	.24	3.43 (1.40)
2e	IIM	Have any of your close relatives suffered from any serious physical illness, accident, or assault?	26	77.81	.34***	.31	3.74 (1.15)
2f	IIM	Has any close friend suffered from any serious physical illness, accident, or assault?	10.2	92.56	.27***	.21	3.00 (1.36)
3a	DNM	Have you suffered from any psychological or psychiatric problem (excluding alcohol or drug-related problems)?	8	96.15	.65***	.62	3.54 (1.35)
3b	IIM	Has your father suffered from any psychological or psychiatric problem (excluding alcohol or drug-related problems)?	2.4	98.63	.44***	.21	3.42 (1.31)
3c	IIM	Has your mother suffered from any psychological or psychiatric problem (excluding alcohol or drug-related problems)?	3.2	96.71	.56***	.51	3.60 (1.19)
3d	IIM	Have any of your siblings suffered from any psychological or psychiatric problem (excluding alcohol or drug-related problems)?	2.4	98.63	.54***	.42	3.05 (1.43)
3e	IIM	Have any of your close relatives suffered from any psychological or psychiatric problem (excluding alcohol or drug-related problems)?	8.4	93.15	.39***	.30	3.24 (1.34)
3f	IIM	Have any of your close friends suffered from any psychological or psychiatric problem (excluding alcohol or drug-related problems)?	7	95.07	.16***	.16	3.09 (1.18)
4a	DNM	Have you had any alcohol or drug-related problems?	6.8	97.53	.46***	.43	2.49 (1.23)
4b	IIM	Has your father had any alcohol or drug-related problems?	4.2	97.26	.53***	.53	3.36 (1.30)
4c	IIM	Has your mother had any alcohol or drug-related problems?	2.2	99.45	.80***	.69	3.18 (1.43)
4d	IIM	Have any of your siblings had any alcohol or drug-related problems?	3.4	97.80	.32***	.16	2.63 (1.28)
4e	IIM	Have any of your close relatives had any alcohol or drug-related problems?	8.2	91.78	.38***	.26	2.91 (1.32)
5a	DNM	Have you had any legal problems?	7.7	96.16	.61***	.46	2.75 (1.36)
5b	IIM	Has your father had any legal problems?	4.7	96.70	.52***	.46	2.78 (1.40)
5c	IIM	Has your mother had any legal problems?	1.9	98.37	.39***	.45	2.87 (1.46)
5d	IIM	Have any of your siblings had any legal problems?	3.1	98.35	.66***	.57	2.96 (1.52)

(continued)

Table 2. (continued)

				LEIA SLE		LEIA emotional impact	
	Type	Items	Percentage of people affected	Percentage agreement	Kappa	Weighted kappa	Mean impact (*SD*)
5e	IIM	Have any of your close relatives had any legal problems?	5.4	95.62	.41***	.39	2.69 (1.32)
5f	IIM	Have any of your close friends had any legal problems?	7.4	95.61	.51***	.27	2.84 (1.41)
6a	DIM	Have you had any arguments with your father?	24.4	85.48	.50***	.41	3.14 (1.23)
6b	DIM	Have you had any arguments with your mother?	28.8	81.10	.46***	.42	3.15 (1.20)
6c	DIM	Have you had any arguments with any of your siblings?	28.7	80.82	.38***	.33	2.98 (1.35)
6d	DIM	Have you had any arguments with any of your close friends?	25.5	81.87	.31***	.24	2.98 (1.30)
6e	DIM	Have you had any arguments with your boyfriend/girlfriend?	10.7	92.86	.59***	.51	3.46 (1.30)
6f	DIM	Have you had any arguments with your teacher?	12.1	90.14	.45***	.32	2.56 (1.29)
6g	DIM	Have you had any arguments with any of your classmates?	26	75.82	.23***	.24	2.70 (1.25)
7a	DIM	Have you had a fight with your father?	2.7	95.34	.34***	.37	3.62 (1.20)
7b	DIM	Have you had a fight with your mother?	0.8	97.81	.19***	.10	2.55 (1.19)
7c	DIM	Have you had a fight with any of your siblings?	14.7	88.46	.31***	.27	2.90 (1.30)
7d	DIM	Have you had a fight with any of your close friends?	8.4	92.58	.31***	.30	3.08 (1.32)
7e	DIM	Have you had a fight with your boyfriend/girlfriend?	1.8	98.08	.21***	.09	2.64 (1.39)
7f	DIM	Have you had a fight with one of your teachers?	0.6	98.36	.24***	.33	2.80 (1.64)
7g	DIM	Have you had a fight with any of your classmates?	10.3	91.51	.33***	.23	2.68 (1.16)
8a	IIM	Has your father left home?	6.3	96.16	.59***	.47	3.24 (1.51)
8b	IIM	Has your mother left home?	1	98.90	.28***	.12	3.00 (1.77)
8c	IIM	Have any of your siblings left home?	5.2	95.07	.55***	.51	2.98 (1.41)
9	IIM	Have your parents got divorced or separated?	19.1	91.79	.66***	.64	3.27 (1.50)
10	IIM	Have your parents had a heated argument?	33.2	82.14	.49***	.45	3.34 (1.31)
11	IIM	Do you live with your father or mother's new partner?	11.7	94.25	.68***	.65	2.53 (1.33)
12	IIm	Do you live with of your father or mother's new partner's children?	4.7	96.71	.58***	.58	2.16 (1.21)
13	IIm	Has a new sibling been born?	3.7	95.89	.46***	.38	2.03 (.94)
14a	IIM	Has your father lost his job?	9.6	90.68	.45***	.43	3.24 (1.27)
14b	IIM	Has your mother lost her job?	10.1	91.23	.47***	.46	3.22 (1.30)
14c	IIm	Have any of your siblings lost their job?	2.6	97.26	.36***	.32	2.70 (1.26)
14d	IIM	Have any of your close relatives lost their jobs?	14.2	83.84	.32***	.28	2.69 (1.25)
15a	IIm	Has your father changed jobs?	13.4	85.16	.32***	.23	2.04 (1.03)
15b	IIm	Has your mother changed jobs?	13.1	92.33	.57***	.54	2.05 (1.04)
15c	IIm	Have any of your siblings changed jobs?	5.2	95.89	.46***	.43	1.71 (1.08)
15d	IIm	Have any of your close relatives changed jobs?	13.8	87.67	.43***	.32	1.99 (1.03)
16	INM	Have you had serious financial problems at home?	16.2	87.67	.54***	.49	3.13 (1.25)
17	INM	Have you changed school?	21.3	85.48	.47***	.43	2.80 (1.35)
18	DNM	Have your school marks dropped significantly?	46.4	76.99	.52***	.47	3.41 (1.30)
19	DNM	Have you been put back a year at school?	27.2	90.96	.75***	.61	3.39 (1.38)
20	DNM	Have you been suspended from school?	34.4	83.01	.62***	.49	2.54 (1.19)
21	DNM	Have you been expelled from school?	5	96.99	.63***	.45	2.92 (1.56)

(continued)

Table 2. (continued)

	Type	Items	Percentage of people affected	LEIA SLE		LEIA emotional impact	
				Percentage agreement	Kappa	Weighted kappa	Mean impact (*SD*)
22	IIM	Has a classmate picked on you, insulted you or made fun of you?	30.6	76.92	.37***	.33	2.78 (1.36)
23	IIM	Has a classmate threated you or hit you?	10.2	90.96	.25***	.28	2.84 (1.62)
24	IIM	Have your classmates excluded you from any activity?	11.6	89.32	.31***	.28	2.77 (1.31)
25	IIM	Has a classmate forced you to do things that you did not want to (give them your money, your packed lunch, etc.)?	0.8	97.26	−.01	−.01	3.5 (1.43)
26	INM	Have you felt bad about your physical appearance?	31.6	79.73	.48***	.52	3.23 (1.30)
27	DNM	Have you run away from home?	8.2	95.89	.63***	.49	2.67 (1.32)
28	INM	Have you lost anything of personal value or has it been stolen?	18.2	84.11	.37***	.36	3.48 (1.32)
29	DIM	Have you lost a friendship that was important to you?	34.9	82.04	.56***	.49	3.51 (1.33)
30	DIM	Have you had a break up?	20.8	90.03	.65***	.58	3.19 (1.44)
31	INm	Have you had to move to a relative's home?	8.5	93.97	.39***	.34	2.30 (1.29)
32	Ilm	Have any of your relatives had to move to your home?	13	89.50	.37***	.38	2.31 (1.20)

Note. SLE = stressful life events; NA = not applicable because the variable was a constant; II = independent interpersonal; IN = independent noninterpersonal; DI = dependent interpersonal; DN = dependent noninterpersonal; M = major events; m = minor events. Strength of agreement using the kappa statistic (Landis & Koch, 1977): <.00 = poor; .00-.20 = slight; .21-.40 = fair; .41-.60 = moderate; .61-.80 = substantial; .81-1.00 = almost perfect.

total of 37 life events were classified as major independent interpersonal, 5 were considered major independent noninterpersonal, 16 were considered major dependent interpersonal, and 8 were major dependent noninterpersonal (see Table 2).

Life Events Scale (Mardomingo & González Garrido, 1990). The EAV is an SLE scale frequently used in clinical psychology and psychiatric settings in Spain. This instrument was created following the SRRS of Holmes and Rahe (1967) and consists of 47 SLEs. Participants indicate whether the life event had occurred during the previous 12 months. The outcome of the checklist results from the weighted sum of each SLE experienced, multiplied by its life change unit score (*EAV total score*).

Assessment System of Children and Adolescents (SENA; Sánchez-Sánchez, Fernández-Pinto, Santamaría, Carrasco, & Barrio, 2016). The SENA is a self-report instrument for assessing some of the most common psychopathological problems that occur during adolescence. Participants indicate the frequency of the appearance of different behavior descriptions on a 5-point Likert-type scale (0 = *never or almost never* to 4 = *always or almost always*). For the present research, only some SENA scales were used: depression (14 items), anxiety (10 items), somatic complaints (9 items), aggressive behavior (7 items), attention problems (10 items), and antisocial behavior (8 items). We also obtained the internalizing and externalizing spectra scores by summing the scores of the first three scales and the second three, respectively. The reliability scores obtained in present sample were adequate (see Table 1).

Student's Life Satisfaction Scale (SLSS; Huebner, 1991; Spanish Adaptation of Galindez & Casas, 2010). The SLSS asks the extent to which the adolescents agree with seven general statements about their life, on a 6-point Likert-type scale (0 = *strongly disagree* to 5 = *strongly agree*). A total score that estimates global life satisfaction, a core component of subjective well-being or happiness, is calculated by summing the responses. SLSS alpha scores' reliability in our sample was adequate (see Table 1), and similar to the original coefficient.

Procedure

This study was part of broader research into psychosocial risk and protective factors affecting mental health during adolescence. After obtaining the approval of the two school boards, research leaders GO and MII presented the study to the teachers and parents at the first meeting of the school year. In this meeting, consent information documents were handed out to

parents or legal guardians. Once the consent documents were returned, trained research assistants administered, in groups, in the classrooms, a sociodemographic survey together with the rest of the battery of questionnaires in two sessions separated by 1 week. Research assistants gave detailed instructions to the students, highlighted the confidentiality of the data and the importance of giving honest responses, and helped the students whenever necessary. The questionnaires were voluntarily completed by those students authorized by their parents or legal guardians. The LEIA checklist was readministered together with the EAV 1 month later, to study the test–retest reliability and their convergent validity in a subsample of students.

Ethics

This research was approved by the ethical committee from the Universitat Jaume I, and authorized by the school board of the participating high schools as well as by the regional Valencian authorities. The parents or legal guardians of the participants gave written informed consent in accordance with the Declaration of Helsinki.

Analysis

The test–retest reliability of the total score was assessed by the percentage of agreement between the two occasions and by means of the kappa coefficient, in accordance with Landis and Koch (1977). The reliability of the weighted score was calculated by the linear weighted kappa statistic (Fleiss et al., 2003), which assumes that categories are ordered (i.e., from low to high impact) and it accounts for how far apart the two ratings are.

The convergent validity of the LEIA was assessed using Pearson correlations. Also, to compare the magnitude of the correlations between the three LEIA scores (SLE quantity, SLE subjective severity, and SLE objective severity), we performed Williams–Hotelling t tests (Williams, 1959). Last, the predictive power of the four combinations of life events assessed using the LEIA on different mental health outcomes was estimated by performing hierarchical linear regression analysis in two steps. The first included age and gender, while the second consisted of the SLE types estimated with each of the three scoring methods.

Results

Descriptives

Descriptives and gender differences for age and the main outcomes of the study can be seen in Table 1. Boys and girls did not differ in the occurrence of SLEs, or in the objective LEIA scores, but they presented small differences in subjective and noninterpersonal LEIA scores. In reference to mental health outcomes, boys showed more aggressive and antisocial symptoms than girls, although the effect sizes were small. Conversely, girls showed more internalizing symptoms at the spectrum level and at the scale of each symptom, with a medium effect size. This pattern of gender differences in psychopathological symptoms is similar to what could be expected from prevalence studies during adolescence (Merikangas et al., 2011; Ormel et al., 2015).

Reliability

Table 2 shows the percentage of agreement between the two administration occasions and the kappa statistics for each SLE (Table 2). The median percentage of agreement was 82.04% (79.67% of SLEs had an agreement greater than 90%). The median kappa value for the occurrence of the SLEs was .45 (61.97% of the items showed a moderate to almost perfect kappa value). However, one item (Item 25; see Table 2) showed very poor kappa values, so this SLE was not selected for posterior statistical analysis. Applying the Landis and Koch (1977) criteria, globally, the strength of agreement of the LEIA could be considered moderate. Last, the weighted kappa statistic also revealed adequate levels for the emotional impact assessment, although the values were slightly lower than the occurrence score.

Validity

The correlations of the LEIA scores with the EAV and with mental health outcomes can be seen in Table 3. In brief, LEIA total scores presented high to very high correlations with the EAV (from .65 to .69), indicating good convergent validity.

In addition, and as expected, experiencing more SLEs was associated with more internalizing and externalizing symptoms, as well as to a lower well-being. However, certain scoring procedures presented slightly higher correlations with mental health outcomes than others. According to the Williams–Hotelling tests for comparing pairs of correlations, the correlations found with the LEIA subjective severity score were significantly higher than the LEIA quantity for internalizing scales, except for depression, $t_{SOM}(781) = -2.19, p = .029$; $t_{ANX}(781) = -2.21, p = .027$; $t_{internalizing}(781) = -2.25, p = .025$.

Meanwhile, the LEIA quantity score tended to be higher than the LEIA subjective severity score for externalizing and aggressivity scales, $t_{AGG}(781) = 2.20, p = .028$; $t_{externalizing}(781) = 2.26, p = .024$. No differences between scores existed in life satisfaction, except for a higher correlation with the LEIA subjective severity score than the LEIA quantity score in major dependent noninterpersonal SLEs, $t_{life\ satisfaction}(781) = 2.04, p = .04$.

Table 3. Correlations Between Stressful Life Event Measures From the LEIA With the EAV Symptom and Life Satisfaction Assessments.

	EAV, total score (n = 365)	DEP	ANX	SOM	AGG	ATE	ANT	Extern.	Intern.	Life satisfaction
LEIA										
Q	.69	.34	.29	.26	.31	.29	.35	.38	.33	−.34
SS	.65	.36	.32	.29	.28	.27	.33	.35	.36	−.34
OS	.68	.34	.30	.27	.31	.29	.35	.37	.34	−.35
Independent interpersonal SLE										
Q	.62	.25	.22	.18	.19	.16	.19	.21	.25	−.24
SS	.58	.27	.26	.23	.19	.16	.18	.21	.28	−.23
OS	.61	.25	.23	.18	.19	.16	.20	.21	.25	−.24
Independent noninterpersonal SLE										
Q	.46	.34	.33	.27	.20	.20	.21	.23	.35	−.32
SS	.48	.40	.37	.32	.22	.22	.22	.25	.41	−.34
OS	.46	.34	.34	.27	.20	.20	.21	.23	.35	−.32
Dependent noninterpersonal SLE										
Q	.58	.22	.09	.16	.34	.35	.47	.46	.18	−.22
SS	.55	.25	.14	.19	.33	.31	.44	.43	.22	−.25
OS	.57	.22	.10	.17	.33	.35	.45	.45	.19	−.23
Dependent interpersonal SLE										
Q	.51	.30	.26	.24	.29	.25	.31	.34	.30	−.30
SS	.49	.32	.29	.26	.26	.22	.28	.30	.33	−.31
OS	.51	.30	.26	.24	.28	.25	.30	.34	.30	−.30
Severity										
Major SLE (Q)	.70	.37	.31	.29	.34	.31	.38	.40	.36	−.34
Major SLE (SS)	.67	.39	.34	.32	.32	.28	.35	.37	.39	−.34
Minor SLE (Q)	.41	.07	.04	.03	.11	.05	.06	.09	.05	−.12
Minor SLE (SS)	.41	.11	.09	.09	.09	.05	.08	.09	.11	−.12

Note. Q = quantity; SS = subjective severity; OS = objective severity; AGG = aggression; ATE = attention problems; ANT = antisocial behavior; DEP = depression; ANX = anxiety; SOM = somatic complaints; Extern = externalizing spectrum; Intern = internalizing spectrum. All correlations were significant at $p < .05$. Minor SLE (Q) and Minor SLE (SS) were not significantly correlated to any outcome when controlled by Major SLE. All correlations >.07 were significant at the .001 level.

In addition, when we divided the SLEs into minor versus major, major events were significantly more closely related to mental health outcomes than minor SLEs. Indeed, minor SLEs were not predictive of any outcome when they were controlled for major SLEs (data not presented but available on request from the corresponding author).

Finally, a regression analysis was performed on each mental health outcome to test the role of the four types of SLEs on mental health outcomes, controlling for age and gender as well as for the intercorrelations between SLE types.

Initially, major independent interpersonal SLEs did not predict any psychopathological outcome (data not presented but available on request from the corresponding author). However, most research on SLEs has focused on this kind of events (e.g., death of parents, health problems of relatives, parental divorce, etc.). On closer post hoc inspection, regressing each major independent interpersonal SLE on all mental health outcomes, this detailed examination revealed that Item 10 (*have your parents had a heated argument*), and those SLEs related to bullying (Items 22 to 24) were predictive of depression, anxiety, somatization, and internalizing symptoms (data not presented but available on request from the corresponding author). Consequently, we decided to subdivide major independent interpersonal events into two categories, one including SLEs concerning bullying victimization, and the other with the rest of the major independent interpersonal events.

As can be seen in Table 4, the percentage of variance explained by the SLEs for specific psychopathological symptoms ranged from 11% for somatic symptoms to 20% for depression symptoms and antisocial behavior. The main type of SLEs that predicted the internalizing scales was major independent noninterpersonal SLEs. In addition, major independent interpersonal SLEs related to bullying victimization and, to a lesser extent, major dependent interpersonal SLEs, also predicted internalizing behavior. Regarding the externalizing symptoms, major dependent SLEs, both noninterpersonal and interpersonal, were significant predictors, together with major independent

Table 4. Regression Analyses With Types of Life Events as Independent Variables and Psychopathologic Symptoms and Life Satisfaction as Dependent Variables.

	DEP		ANX		SOM	
	β	ΔR^2	β	ΔR^2	β	ΔR^2
	Q/SS/OS	Q/SS/OS	Q/SS/OS	Q/SS/OS	Q/SS/OS	Q/SS/OS
Age	**.12**	**.06**	**.17**	**.15**	**.10**	**.07**
Gender	**.22**		**.35**		**.25**	
Major independent interpersonal SLE						
Victimization	**.19/.20/.18**	**.17/.20/.17**	**.12/.12/.12**	**.11/.12/.11**	**.12/.12/.12**	**.10/.11/.10**
Others	−.04/−*.09*/−.04		.04/.01/.04		−.03/−.04/−.03	
Major independent noninterpersonal SLE	**.20/.25/.21**		**.19/.22/.19**		**.15/.19/.16**	
Major dependent noninterpersonal SLE	*.10/.09*/**.11**		−.06/−.05/−.05		*.08/.07/.09*	
Major dependent interpersonal SLE	**.13/.14/.13**		**.13/.13/.12**		**.12/.11/.11**	
	AGG.		ATE.		ANT.	
	β	ΔR^2	β	ΔR^2	β	ΔR^2
	Q/SS/OS	Q/SS/OS	Q/SS/OS	Q/SS/OS	Q/SS/OS	Q/SS/OS
Age	.07	**.02**	**.16**	**.03**	**.16**	**.04**
Gender	−.13		.03		**−.13**	
Major independent interpersonal SLE						
Victimization	.06/.03/.06	**.15/.14/.15**	.01/−.02/.01	**.13/.10/.13**	−.05/−.08/−.05	**.20/.19/.19**
Others	−*.07*/−.04/−.06		−.02/−.01/−.02		−.01/.01/.01	
Major independent noninterpersonal SLE	**.12/.14/.12**		*.09/.11/.09*		*.10/.10/*.**10**	
Major dependent noninterpersonal SLE	**.25/.25/.24**		**.30/.25/.29**		**.37/.36/.35**	
Major dependent interpersonal SLE	**.16/.11/.15**		*.09*/.06/*.09*		**.13**/*.10*/**.13**	
	Intern.		Extern.		Life satisfaction	
	β	ΔR^2	β	ΔR^2	β	ΔR^2
	Q/SS/OS	Q/SS/OS	Q/SS/OS	Q/SS/OS	Q/SS/OS	Q/SS/OS
Age	**.15**	**.11**	**.18**	**.04**	**−.20**	**.07**
Gender	**.30**		−.06		**−.16**	
Major independent interpersonal SLE						
Victimization	**.17/.17/.16**	**.16/.18/.16**	.01/−.02/.01	**.22/.19/.21**	*−.09/−.07/−.08*	**.12/.12/.12**
Others	−.01/−.05/−.01		−.05/−.03/−.05		−.01/.03/−.01	
Major independent noninterpersonal SLE	**.20/.24/.21**		*.10*/**.12/**.11*		**−.19/−.22/−.19**	
Major dependent noninterpersonal SLE	.05/.05/.06		**.38/.35/.36**		−.04/−.04/−.05	
Major dependent interpersonal SLE	**.14/.14/.14**		**.15**/*.11*/**.15**		**−.15/−.15/−.14**	

Note. AGG = aggression; ATE = attention problems; ANT = antisocial behavior; DEP = depression; ANX = anxiety; SOM = somatic complaints; Extern = externalizing spectrum; Intern = internalizing spectrum; LEIA = Life Events Inventory for Adolescents; SLE = stressful life event; Q = quantity; SS = subjective severity; OS = objective severity. Values in bold are significant associations at the .01 level. Values in italics are significant associations at the .05 level.

noninterpersonal SLEs. Life satisfaction presented a similar but inverse pattern of indicators to that of internalizing symptoms, with major independent noninterpersonal SLEs, followed by major dependent interpersonal SLEs and by major independent interpersonal SLEs related to bullying victimization as predictors.

Discussion

The main aim of the present study was to develop a sound psychometric checklist, the LEIA, to assess SLEs in Spanish adolescents, following the main recommendations of different reviews of the topic (Compas, 1987; Dohrenwend,

2006; Grant et al., 2004; Hammen, 2005; Harkness & Monroe, 2016; Kessler, 1997; Rabkin & Struening, 1976; Turner & Wheaton, 1997; Zimmerman, 1983a). The present research found that the LEIA is adequate for research, and could also be useful in clinical settings (although more research is needed). In relation to the reliability of the scores, more than 60% of the items presented a moderate to almost perfect kappa and weighted kappa statistic (Landis & Koch, 1977), while most SLEs showed levels of agreement higher than 90%. Thus, and interpreting the results as a whole, the scores of the LEIA showed an adequate level of reliability.

However, one item presented very poor kappa statistics (Item 25), although it also showed elevated agreement (98.90%). This could be a good example of how the agreement coefficient tends to overestimate interrater reliability, whereas the kappa statistic tends to underestimate interrater reliability, as noted by McHugh (2012). This kind of results are often found when a life event affects a very low percentage of people (Gray et al., 2004), as is the case here (Item 25 affected less than 0.8% of the sample in the retest subsample at T1). Another possible reason for this low kappa reliability could be the intracategory variability (Dohrenwend, 2006). This is a typical problem for checklists and is related to how the respondent understands the description of each item; it especially affects items that are formulated in a too general or somewhat ambiguous manner. Probably, Item 25, "has a classmate forced you to do things that you did not want to (give them your money, your packed lunch, etc.)," could be improved with more precise wording in the future, so its use is not recommended in its current form.

In reference to sources of validity, the correlations between the EAV and LEIA scores were high to very high, indicating good convergent validity. Taking into consideration that the EAV is based on consensual or objective weightings, it is not surprising that the EAV correlated more closely to the LEIA objective severity score than to the subjective severity score. In addition, the LEIA quantity score and LEIA objective severity score presented an almost identical pattern of associations with EAV and all mental health outcomes assessed in the present study (see Table 3). This supports some initial findings in the field that pointed to there not being much difference between simply counting the number of SLEs and readjusting each SLE using objective weights (Zimmerman, 1983b).

However, our data also showed that different scoring procedures presented small but significant differences in their association with distinct psychopathological symptoms. Thus, the LEIA subjective severity score presented significantly higher correlations with all internalizing scales, while the LEIA quantity score (and LEIA objective severity score) showed slightly higher associations with all externalizing symptoms. Therefore, our data seem to suggest that the adequate question is not which scoring procedure is best at predicting health outcomes, as the research literature has usually discussed (e.g., Dohrenwend, 2006; Turner & Wheaton, 1997; Zimmerman, 1983b), but which scoring procedure is the best for a specific type of health outcome. Accordingly, a simple count of the number of life events would be more adequate when examining externalizing disorders; whereas measures that are weighted by the subjective impact of SLEs, or appraisal, would be more appropriate for internalizing psychopathology, in agreement with cognitive theories of depression and other emotional disorders (Alloy et al., 1999).

However, more relevant than the scoring procedure for predicting mental health outcomes, is the consideration of different types of SLEs. Our results show important differences in the predictive value of SLEs when the major–minor, dependent–independent, and interpersonal–noninterpersonal SLE categories were considered. Hence, we found that major, but not minor, SLEs, showed a moderate to high association with adolescent mental health, in line with previous findings (Vrshek-Schallhorn et al., 2015). Consequently, we explored the combination of major interpersonal–noninterpersonal and dependent–independent SLEs.

One main finding of the present study is that the most relevant events for all kinds of internalizing symptoms are major independent noninterpersonal SLEs (e.g., "Have you had serious financial problems at home?" or "Have you felt bad about your physical appearance?"), in agreement with the few studies that have assessed this combination of SLEs (Rudolph et al., 2000; Vrshek-Schallhorn et al., 2015). Our study also supports the relevance for depression and anxiety of the most commonly studied typology of SLEs: major dependent interpersonal SLEs (e.g., "Have you had a fight with any of your close friends?" or "Have you lost a friendship that was important to you?" J. R. Cohen et al., 2013; Espina & Calvete, 2017; Flynn & Rudolph, 2011; Hamilton et al., 2014; Hankin et al., 2010; Krackow & Rudolph, 2008; Rudolph et al., 2000; Shapero, Hamilton, Liu, Abramson, & Alloy, 2013; Vrshek-Schallhorn et al., 2015). Moreover, our findings expand the importance of this type of SLEs to other symptoms such as somatization, and internalizing behavior, in line with Hankin et al. (2010). We also found that major independent interpersonal SLEs were not associated with any internalizing symptoms; at least when we controlled for the other SLEs. This last finding, although not unusual (e.g., Flynn et al., 2010; Rudolph et al., 2000; Stange, Hamilton, Abramson, & Alloy, 2014) is somewhat intriguing because major independent interpersonal SLEs include events typically linked to depression, such as the death of parents or serious mental or physical illness of relatives (Fröjd, Kaltiala-Heino, Pelkonen, Von Der Pahlen, & Marttunen, 2009; Kessler et al., 2010; Low et al., 2012; Stikkelbroek, Bodden, Reitz, Vollebergh, & van Baar, 2016). However, a more detailed inspection of each of the

major independent interpersonal SLEs in the LEIA revealed that a subgroup of events related to bullying victimization (Items 22, 23, and 24, e.g., Item 22: "Has a classmate threated you or hit you?") were predictive of internalizing symptoms and life satisfaction, as expected (Reijntjes, Kamphuis, Prinzie, & Telch, 2010; Rigby, 2003).

To sum up, and in relation to internalizing symptoms, our study offers novel and somewhat unexpected findings that deserve further replication. On one hand, the most relevant life events were the scarcely studied typology of major independent noninterpersonal SLEs. On the other hand, the most commonly studied typology, dependent interpersonal SLEs, were also associated with mental health outcomes, but to a much lesser extent than independent noninterpersonal SLEs. Last, major independent interpersonal SLEs, a typology that includes the most classic SLEs (such as death or serious illness of parents and other relatives) seemed irrelevant to the mental health of adolescents, with the notable exception of those SLEs related to bullying victimization.

The present study also explored the association of SLEs with positive aspects of adolescent mental health, such as life satisfaction: a core component of subjective well-being or happiness (Diener, Suh, Lucas, & Smith, 1999). Although this topic is frequently studied in adulthood (see the meta-analysis: Luhmann, Hofmann, Eid, & Lucas, 2012), only in the past few decades has it begun to be more intensely explored in adolescents (Bendayan, Blanca, Fernández-Baena, Escobar, & Trianes, 2013; Huebner, 2004; Ortuño-Sierra, Aritio-Solana, Chocarro de Luis, Nalda, & Fonseca-Pedrero, 2017). Our study confirms that experiencing negative events may have a significant impact on adolescence life satisfaction, with a moderate effect size similar to those reported in other studies (e.g., Ash & Huebner, 2001; Chappel, Suldo, & Ogg, 2014; McCullough, Huebner, & Laughlin, 2000; Mcknight, Huebner, & Suldo, 2002; Suldo & Huebner, 2004). However, and as far as we know, no previous study has examined the role of different types of SLEs on life satisfaction or subjective well-being. As expected, we found a similar but inverse pattern of results to that for internalizing symptoms. Thus, our data suggest that negative experiences that directly affect the adolescent, such as independent negative events that youngsters experience (e.g., health, physical, or financial family problems), or that others cause to the adolescent (e.g., being bullied or involved in fights), reduce their life satisfaction. Conversely, negative experiences that happened to others, or those that adolescents perform intentionally (usually antinormative and problematic behavior), do not seem to affect very strongly in their well-being.

Last, the present study also offers relevant information about the externalizing spectrum; more specifically, regarding problems related to aggressivity, antisocial behavior, and attention problems. SLEs have been consistently associated with these symptoms and disorders (March-Llanes et al., 2017), but only a few studies have examined the role of dependent–independent and interpersonal–noninterpersonal SLEs on externalizing symptoms in adolescents. Rudolph et al. (2000) found, in a reduced sample of clinic-referred participants, that the most relevant events for externalizing symptoms were the dependent noninterpersonal SLEs for both boys and girls, and the dependent interpersonal SLEs only for girls. Independent SLEs, both interpersonal and noninterpersonal, were not associated with externalizing disorders. Our results mostly replicate those findings. Thus, in our large sample of nonclinical adolescents, major dependent noninterpersonal SLEs (e.g., "Have you had alcohol or drug-related problems?" or "Have you been expelled from school?") and, to a lesser extent, major dependent interpersonal SLEs, presented relevant associations with externalizing scores. We also found that major independent noninterpersonal SLEs were significantly associated with externalizing spectrum symptoms, although the effect sizes were low to very low.

However, we think that the moderate to strong association between dependent SLEs and externalizing symptoms found in the present study should be treated cautiously. One problem usually leveled at SLE assessment is the possible confounding of stressors and symptoms of psychopathology, due to similar items appearing in measures of both constructs (Grant et al., 2004; Harkness & Monroe, 2016; Turner & Wheaton, 1997). We believe that this drawback especially affects dependent SLEs and externalizing symptoms. Most dependent SLEs during adolescence refer to interpersonal conflicts, behavioral problems, and antinormative behavior (i.e., arguments and fights with others, school suspensions, failing a grade, running away from home, and legal or drug problems), caused in part by personality characteristics of the adolescent. Such disruptive and conflictive behavior is also often a core symptom of externalizing symptoms, such as aggressivity and antisocial behavior (Achenbach & Edelbrock, 1984; Young et al., 2009). Although some researchers have opted to remove these potentially confounding SLEs from their studies, we consider that by doing so a relevant source of stress for mental health is omitted. In our opinion, a better alternative is to control for personality characteristics that underlie both dependent SLEs and externalizing symptoms. Specifically, low agreeableness and low conscientiousness personality traits are strongly associated with externalizing symptoms and disorders (Mezquita et al., 2015; Ruiz, Pardo, & San Martin, 2008), and also with dependent SLEs (Shiner, Allen, & Masten, 2017). Thus, studies that include the assessment of basic personality traits could control for their effect on both SLEs and psychopathology. This is not the case with our study, so this would be a first limitation of the present research and an interesting line of future work.

A second limitation, and also related to content issues, is that LEIA could be affected by the intracategory variability problem, as discussed previously. To overcome this potential problem, and in accordance with Dohrenwend (2006), a refined wording of the few items with lower kappa statistics is desirable. A third limitation is that we did not control whether any SLE occurred between the T1 and T2 assessments. A fourth limitation is that our results are restricted to a specific type of episodic SLEs, while a systematic study of relevant threats during adolescence should include other forms of stress, such as chronic SLEs (Kessler, 1997; Vrshek-Schallhorn et al., 2015) or daily hassles (Kanner et al., 1981; Trianes et al., 2009). However, our findings that only major, but not minor, SLEs are associated with mental health outcomes may suggest that daily problems may be of little importance, at least during adolescence. In addition, other important sources of adversity were not included in the LEIA because of problems in obtaining parental and school board permission, such as life events of a sexual nature (i.e., negative sexual experiences, sexual harassment, pregnancy, abortion, etc.), negative parenting styles, or childhood maltreatment, such as negligence, abuse, or family violence (Gershoff, 2002; Gilbert et al., 2009; McMaster, Connolly, Pepler, & Craig, 2002; Norman et al., 2012; Repetti, Taylor, & Seeman, 2002; Tolan, Gorman-Smith, & Henry, 2006). Hence, if a researcher or clinician needs to assess traumatic experiences besides acute SLEs, he or she should administer a specific trauma history questionnaire in addition to the LEIA. A fifth limitation, linked to the previous one, is that the present study only assessed the effects of the SLEs that occurred within the past 12 months, and the significant life events experienced more than 12 months ago could also affect the respondent. A sixth limitation is that the present study used a screening instrument to assess psychopathological symptoms, so the results should only be generalized to diagnosed mental disorders with caution. A last limitation is that the design of the present study was cross-sectional, so we have no evidence about the directionality of the relationship between SLEs and psychopathology. Specifically, during adolescence, SLEs may predict, but also may be predicted by, externalizing and internalizing spectrum symptoms (March-Llanes et al., 2017). The directionality of these associations could be better studied with prospective designs; so future longitudinal studies should be performed to test which types of SLEs are the predictors of psychopathology and which types of SLEs are predicted by psychopathological symptoms.

To conclude, this study presented the psychometric properties of a new checklist to assess SLEs during adolescence. We have tried to follow high-quality standards in the assessment of reliability and validity indices, following proposals in relevant reviews on the topic. In addition, and as far as we know, LEIA is the first SLE checklist to include the distinctions of major–minor, dependent–independent, and interpersonal–noninterpersonal categories in the validation process. LEIA showed moderate reliability kappa and weighted kappa indices, and elevated agreement. Regarding validity indicators, LEIA presented adequate evidence of convergent validity, as indicated by its elevated associations with the EAV, and criterion validity, according to the relationships with psychopathological symptoms and life satisfaction. Furthermore, the present study shows the relevance of assessing both the number of life events and their subjective appraisal, especially in relation to externalizing and internalizing symptoms, respectively. More important than the scoring procedure, however, is the distinction between different types of SLEs. We found that the main predictors of externalizing symptoms were major dependent SLEs; whereas major independent noninterpersonal SLEs and those major independent interpersonal SLEs related to bullying victimization were the main predictors of internalizing symptoms. Life satisfaction followed a similar, though inverse, pattern to that found for internalizing symptoms. Thus, our data suggest that not all types of proximal SLEs are equally relevant for mental health, in line with Vrshek-Schallhorn et al. (2015), and that different types of SLEs may be differentially linked to specific psychopathology. We think that these are promising findings that deserve more research. Consequently, the use of instruments that allow these (and other) SLE typologies to be assessed would be of great interest for the advance of research in the field of SLEs and mental (and physical) health, but also for clinical settings. Thus, assessing the different types of SLEs that have occurred in the past 12 months with the LEIA could help clinicians better estimate the risk of developing specific mental disorders in adolescents, from 12 to 17 years of age. To sum up, different sources of evidence support that the LEIA provide reliable and valid scores for the screening of different types of SLEs during adolescence in Spain and in a galaxy far, far away.

Acknowledgments

The authors wish to thank the students, parents, and teachers of the high schools *El Caminàs* and *Bovalar* for making this study possible.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Banco de Instrumentos Cibersam, SAM15PI01/2015; PSI2015–67766-R,

from the Spanish Ministry of Economy and Competitiveness (MINECO/FEDER); GV/2016/158, from the Autonomous Government of Valencia; UJI-A2017-18 and UJI-B2017-74, from the Universitat Jaume I; FIS PI15/00097, from the Instituto de Salud Carlos III; and 2014SGR1636 and 2017SGR1577, from the Comissionat per a Universitats i Recerca Del DIUE of the Generalitat de Catalunya. LMF was supported by a PhD grant from the AGAUR; AC was supported by a predoctoral grant from the MEC.

Supplemental Material

Supplemental material for this article is available online.

ORCID iDs

Jorge Moya-Higueras https://orcid.org/0000-0001-7017-3087
Generós Ortet https://orcid.org/0000-0002-3576-5316

References

Achenbach, T. M., & Edelbrock, C. S. (1984). Psychopathology of childhood. *Annual Review of Psychology*, *35*, 227-256. doi:10.1146/annurev.ps.35.020184.001303

Alloy, L. B., Abramson, L. Y., & Francis, E. L. (1999). Do negative cognitive styles confer vulnerability to depression? *Current Directions in Psychological Science*, *8*, 128-132. doi:10.1111/1467-8721.00030

Ash, C., & Huebner, E. S. (2001). Environmental events and life satisfaction reports of adolescents. *School Psychology International*, *22*, 320-336. doi:10.1177/0143034301223008

Beards, S., Gayer-Anderson, C., Borges, S., Dewey, M. E., Fisher, H. L., & Morgan, C. (2013). Life events and psychosis: A review and meta-analysis. *Schizophrenia Bulletin*, *39*, 740-747. doi:10.1093/schbul/sbt065

Bendayan, R., Blanca, M. J., Fernández-Baena, J. F., Escobar, M., & Trianes, M. V. (2013). New empirical evidence on the validity of the Satisfaction with Life Scale in early adolescents. *European Journal of Psychological Assessment*, *29*, 36-43. doi:10.1027/1015-5759/a000118

Brugha, T. S., & Cragg, D. (1990). The list of threatening experiences: The reliability and validity of a brief life events questionnaire. *Acta Psychiatrica Scandinavica*, *82*, 77-81.

Calvete, E., Villardón, L., Estévez, A., & Espina, M. (2007). La desesperanza como vulnerabilidad cognitiva al estrés: Adaptación del cuestionario de estilo cognitivo para adolescentes [Hopelessness as cognitive vulnerability to stress: Adaptation of the Cognitive Style Questionnaire for Adolescents]. *Ansiedad y Estrés*, *13*, 215-227.

Casey, B. J., Jones, R. M., & Hare, T. A. (2008). The adolescent brain. *Annals of the New York Academy of Sciences*, *1124*, 111-126. doi:10.1196/annals.1440.010

Caspi, A., Hariri, A. R., Holmes, A., Uher, R., & Moffitt, T. E. (2010). Genetic sensitivity to the environment: The case of the serotonin transporter gene and its implications for studying complex diseases and traits. *American Journal of Psychiatry*, *167*, 509-527. doi:10.1176/appi.ajp.2010.09101452

Caspi, A., Sugden, K., Moffitt, T. E., Taylor, A., Craig, I. W., Harrington, H., . . . Poulton, R. (2003). Influence of life stress on depression: Moderation by a polymorphism in the 5-HTT gene. *Science*, *301*, 386-389. doi:10.1126/science.1083968

Chappel, A. M., Suldo, S. M., & Ogg, J. A. (2014). Associations between adolescents' family stressors and life satisfaction. *Journal of Child and Family Studies*, *23*, 76-84. doi:10.1007/s10826-012-9687-9

Clark, C., Rodgers, B., Caldwell, T., Power, C., & Stansfeld, S. (2007). Childhood and adulthood psychological ill health as predictors of midlife affective and anxiety disorders: The 1958 British birth cohort. *Archives of General Psychiatry*, *64*, 668-678. doi:10.1001/archpsyc.64.6.668

Clements, K., & Turpin, G. (1996). The life events scale for students: Validation for use with British samples. *Personality and Individual Differences*, *20*, 573-576.

Cohen, J. R., Hankin, B. L., Gibb, B. E., Hammen, C., Hazel, N. A., Ma, D., . . . Abela, J. R. Z. (2013). Negative attachment cognitions and emotional distress in mainland Chinese adolescents: A prospective multiwave test of vulnerability-stress and stress generation models. *Journal of Clinical Child & Adolescent Psychology*, *42*, 531-544. doi:10.1080/15374416.2012.749787

Compas, B. E. (1987). Stress and life events during childhood and adolescence. *Clinical Psychological Review*, *7*, 275-302. doi:10.1016/0272-7358(87)90037-7

Compas, B. E., Davis, G. E., Forsythe, C. J., & Wagner, B. M. (1987). Assessment of major and daily stressful events during adolescence: The Adolescent Perceived Events Scale. *Journal of Consulting and Clinical Psychology*, *55*, 534-541. doi:10.1037/0022-006X.55.4.534

Conway, C. C., Hammen, C., & Brennan, P. A. (2012). Expanding stress generation theory: Test of a transdiagnostic model. *Journal of Abnormal Psychology*, *121*, 754-766. doi:10.1037/a0027457

Copeland, W. E., Shanahan, L., Costello, E. J., & Angold, A. (2009). Childhood and adolescent psychiatric disorders as predictors of young adult disorders? *Archives of General Psychiatry*, *66*, 764-772. doi:10.1001/archgenpsychiatry.2009.85

Covault, J., Tennen, H., Armeli, S., Conner, T. S., Herman, A. I., Cillessen, A. H. N., & Kranzler, H. R. (2007). Interactive effects of the serotonin transporter 5-HTTLPR polymorphism and stressful life events on college student drinking and drug use. *Biological Psychiatry*, *61*, 609-616. doi:10.1016/j.biopsych.2006.05.018

Crone, E. A., & Dahl, R. E. (2012). Understanding adolescence as a period of social-affective engagement and goal flexibility. *Nature Reviews Neuroscience*, *13*, 636-650. doi:10.1038/nrn3313

Denissen, J. J. A., van Aken, M. A. G., Penke, L., & Wood, D. (2013). Self-regulation underlies temperament and personality: An integrative developmental framework. *Child Development Perspectives*, *7*, 255-260. doi:10.1111/cdep.12050

Diener, E., Suh, E. M., Lucas, R. E., & Smith, H. L. (1999). Subjective well-being: Three decades of progress. *Psychological Bulletin*, *125*, 276-302. doi:10.1037/0033-2909.125.2.276

Dohrenwend, B. P. (2006). Inventorying stressful life events as risk factors for psychopathology: Toward resolution of the problem of intracategory variability. *Psychological Bulletin*, *132*, 477-495. doi:10.1037/0033-2909.132.3.477

Duggal, S., Malkoff-Schwartz, S., Birmaher, B., Anderson, B. P., Matty, M. K., Houck, P. R., . . . Frank, E. (2000). Assessment of life stress in adolescents: Self-report versus interview methods. *Journal of the American Academy of Child & Adolescent Psychiatry*, *39*, 445-452. doi:10.1097/00004583-200004000-00013

Espejo, E. P., Hammen, C., & Brennan, P. A. (2012). Elevated appraisals of the negative impact of naturally occurring life events: A risk factor for depressive and anxiety disorders. *Journal of Abnormal Child Psychology*, *40*, 303-315. doi:10.1007/s10802-011-9552-0

Espina, M., & Calvete, Y. E. (2017). Estilos de afrontamiento y generación de estrés interpersonal en adolescentes [Coping styles and interpersonal stress generation in adolescents]. *Revista de Psicopatologia y Psicologia Clinica*, *22*, 21-32. doi:10.5944/rppc.vol.22.num.1.2017.16825

Ferreira, E., Granero, R., Noorian, Z., Romero, K., & Domènech Llaberia, E. (2012). Acontecimientos vitales y sintomatologia depresiva en poblacion adolescente [Life events and depressive symptoms in adolescent population]. *Revista de Psicopatologia y Psicologia Clinica*, *17*, 123-136. Retrieved from http://revistas.uned.es/index.php/RPPC/article/view/11209/pdf

Fleiss, J., Levin, B., & Cho, M. (2003). *Statistical methods for rates and proportions* (3rd ed.). New York, NY: Wiley.

Flynn, M., Kecmanovic, J., & Alloy, L. B. (2010). An examination of integrated cognitive-interpersonal vulnerability to depression: The role of rumination, perceived social support, and interpersonal stress generation. *Cognitive Therapy and Research*, *34*, 456-466. doi:10.1007/s10608-010-9300-8

Flynn, M., & Rudolph, K. D. (2011). Stress generation and adolescent depression: Contribution of interpersonal stress responses. *Journal of Abnormal Child Psychology*, *39*, 1187-1198. doi:10.1007/s10802-011-9527-1

Fröjd, S., Kaltiala-Heino, R., Pelkonen, M., Von Der Pahlen, B., & Marttunen, M. (2009). Significance of family life events in middle adolescence: A survey on Finnish community adolescents. *Nordic Journal of Psychiatry*, *63*, 78-86. doi:10.1080/08039480802533754

Galindez, E., & Casas, F. (2010). Adaptación y validación de la *Students' Life Satisfaction Scale (SLSS) con adolescents* [Adaptation and validation of the Students' Life Satisfaction Scale (SLSS) with adolescents]. *Estudios de Psicología*, *31*, 79-87. doi:10.1174/021093910790744617

Gee, D. G., & Casey, B. J. (2015). The impact of developmental timing for stress and recovery. *Neurobiology of Stress*, *1*, 184-194. doi:10.1016/j.ynstr.2015.02.001

Gershoff, E. T. (2002). Corporal punishment by parents and associated child behaviors and experiences: A meta-analytic and theoretical review. *Psychological Bulletin*, *128*, 539-579. doi:10.1037/0033-2909.128.4.539

Gilbert, R., Widom, C. S., Browne, K., Fergusson, D., Webb, E., & Janson, S. (2009). Burden and consequences of child maltreatment in high-income countries. *Lancet*, *373*, 68-81. doi:10.1016/S0140-6736(08)61706-7

González de Rivera, J. L., & Morera Fumero, A. (1983). La valoración de sucesos vitales : Adaptación española de la escala de Holmes y Rahe [Life events assessment: the Spanish version of the Holmes-Rahe rating scale]. *Psiquis*, *4*(1), 7-11.

Grant, K. E., Compas, B. E., Thurm, A. E., McMahon, S. D., & Gipson, P. Y. (2004). Stressors and child and adolescent psychopathology: Measurement issues and prospective effects. *Journal of Clinical Child & Adolescent Psychology*, *33*, 412-425. doi:10.1207/s15374424jccp3302_23

Gray, M. J., Litz, B. T., Hsu, J. L., & Lombardo, T. W. (2004). Psychometric properties of the life events checklist. *Assessment*, *11*, 330-341. doi:10.1177/1073191104269954

Hamilton, J. L., Stange, J. P., Kleiman, E. M., Hamlat, E. J., Abramson, L. Y., & Alloy, L. B. (2014). Cognitive vulnerabilities amplify the effect of early pubertal timing on interpersonal stress generation during adolescence. *Journal of Youth and Adolescence*, *43*, 824-833. doi:10.1007/s10964-013-0015-5

Hammen, C. (1991). Generation of stress in the course of unipolar depression. *Journal of Abnormal Psychology*, *100*, 555-561.

Hammen, C. (2005). Stress and depression. *Annual Reviews in Clinical Psychology*, *1*, 293-319. doi:10.1146/annurev.clinpsy.1.102803.143938

Hankin, B. L., Stone, L., & Wright, P. A. (2010). Corumination, interpersonal stress generation, and internalizing symptoms: Accumulating effects and transactional influences in a multiwave study of adolescents. *Development and Psychopathology*, *22*, 217-235. doi:10.1017/S0954579409990368

Harkness, K. L., & Monroe, S. M. (2016). The assessment and measurement of adult life stress: Basic premises, operational principles, and design requirements. *Journal of Abnormal Psychology*, *125*, 727-745. doi:10.1037/abn0000178

Harkness, K. L., & Stewart, J. G. (2009). Symptom specificity and the prospective generation of life events in adolescence. *Journal of Abnormal Psychology*, *118*, 278-287. doi:10.1037/a0015749

Holder, M. K., & Blaustein, J. D. (2014). Puberty and adolescence as a time of vulnerability to stressors that alter neurobehavioral processes. *Frontiers in Neuroendocrinology*, *35*, 89-110. doi:10.1016/j.yfrne.2013.10.004

Hollenstein, T., & Lougheed, J. P. (2013). Beyond storm and stress: Typicality, transactions, timing, and temperament to account for adolescent change. *American Psychologist*, *68*, 444-454. doi:10.1037/a0033586

Holmes, T. H., & Rahe, R. H. (1967). The social readjustment rating scale. *Journal of Psychosomatic Research*, *11*, 213-218. doi:10.1016/0022-3999(67)90010-4

Holtzman, C. W., Trotman, H. D., Goulding, S. M., Ryan, A. T., MacDonald, A. N., Shapiro, D. I., . . . Walker, E. F. (2013). Stress and neurodevelopmental processes in the emergence of psychosis. *Neuroscience*, *249*, 172-191. doi:10.1016/j.neuroscience.2012.12.017

Huebner, E. S. (1991). Initial development of the Student's Life Satisfaction Scale. *School Psychology International*, *12*, 231-240. doi:10.1177/0143034391123010

Huebner, E. S. (2004). Research on assessment of life satisfaction of children and adolescents. *Social Indicators Research*, *66*, 3-33. doi:10.1023/B:SOCI.0000007497.57754.e3

Ibáñez, M. I., Viruela, A. M., Mezquita, L., Moya, J., Villa, H., Camacho, L., & Ortet, G. (2016). An investigation of five types of personality trait continuity: A two-wave longitudinal study of Spanish adolescents from age 12 to age 15. *Frontiers in Psychology*, *7*, 1-7. doi:10.3389/fpsyg.2016.00512

Johnson, D. P., Rhee, S. H., Whisman, M. A., Corley, R. P., & Hewitt, J. K. (2013). Genetic and environmental influences

on negative life events from late childhood to adolescence. *Child Development*, *84*, 1823-1839. doi:10.1111/cdev.12055

Johnson, J., & McCutcheon, S. (1980). Assessing life stress in children and adolescents: Preliminary findings with the Life Events Checklist. In I. G. Sarason & C. D. Spielberger (Eds.), *Stress and anxiety* (pp. 111-126). Washington, DC: Hemisphere.

Kanner, A. D., Coyne, J. C., Schaefer, C., & Lazarus, R. S. (1981). Comparison of two modes of stress measurement: Daily hassles and uplifts versus major life events. *Journal of Behavioral Medicine*, *4*, 1-39. doi:10.1007/BF00844845

Kendler, K. S., & Baker, J. H. (2007). Genetic influences on measures of the environment: A systematic review. *Psychological Medicine*, *37*, 615-626. doi:10.1017/S0033291706009524

Kendler, K. S., Kessler, R. C., Waiters, E. E., MacLean, C., Neale, M. C., Heath, A. C., & Eaves, L. J. (1995). Stressful life events, genetic liability, and onset of an episode of major depression in women. *American Journal of Psychiatry*, *152*, 833-842. doi:10.1176/ajp.152.6.833

Kessler, R. C. (1997). The effects of stressful life events on depression. *Annual Review of Psychology*, *48*, 191-214. doi:10.1146/annurev.psych.48.1.191

Kessler, R. C., McLaughlin, K. A., Green, J. G., Gruber, M. J., Sampson, N. A., Zaslavsky, A. M., . . .Williams, D. R. (2010). Childhood adversities and adult psychopathology in the WHO world mental health surveys. *British Journal of Psychiatry*, *197*, 378-385. doi:10.1192/bjp.bp.110.080499

King, K. M., Pedersen, S. L., Louie, K. T., Pelham, W. E., & Molina, B. S. G. (2017). Between- and within-person associations between negative life events and alcohol outcomes in adolescents with ADHD. *Psychology of Addictive Behaviors*, *31*, 699-711. doi:10.1037/adb0000295

Krackow, E., & Rudolph, K. D. (2008). Life stress and the accuracy of cognitive appraisals in depressed youth. *Journal of Clinical Child & Adolescent Psychology*, *37*, 376-385. doi:10.1080/15374410801955797

Landis, J. R., & Koch, G. G. (1977). The measurement of observer agreement for categorical data. *Biometrics*, *33*, 159-174. doi:10.2307/2529310

Lewinsohn, P. M., Rohde, P., & Gau, J. M. (2003). Comparability of self-report checklist and interview data in the assessment of stressful life events in young adults. *Psychological Reports*, *93*, 459-471. doi:10.2466/PR0.93.6.459-471

Low, N. C., Dugas, E., O'Loughlin, E., Rodriguez, D., Contreras, G., Chaiton, M., & O'Loughlin, J. (2012). Common stressful life events and difficulties are associated with mental health symptoms and substance use in young adolescents. *BMC Psychiatry*, *12*, 116. doi:10.1186/1471-244X-12-116

Luhmann, M., Hofmann, W., Eid, M., & Lucas, R. E. (2012). Subjective well-being and adaptation to life events. *Journal of Personality and Social Psychology*, *102*, 592-615. doi:10.1037/a0025948

March-Llanes, J., Marqués-Feixa, L., Mezquita, L., Fañanás, L., & Moya-Higueras, J. (2017). Stressful life events during adolescence and risk for externalizing and internalizing psychopathology: A meta-analysis. *European Child & Adolescent Psychiatry*, *26*, 1409-1422. doi:10.1007/s00787-017-0996-9

Mardomingo, M., & González Garrido, S. (1990). Escala de acontecimientos vitales para adolescentes [Life Events Scale for adolescents]. *Revista de Psiquiatria Infanto-Juvenil*, *2*, 123-125.

McCullough, G., Huebner, E. S., & Laughlin, J. E. (2000). Life events, self-concept, and adolescents' positive subjective well-being. *Psychology in the Schools*, *37*, 281-290. doi:10.1002/(SICI)1520-6807(200005)37:3<281::AID-PITS8>3.0.CO;2-2

McHugh, M. L. (2012). Interrater reliability: The kappa statistic. *Biochemia Medica*, *22*, 276-282.

Mcknight, C. G., Huebner, E. S., & Suldo, S. (2002). Relationships among stressful life events, temperament, problem behavior, and global life satisfaction in adolescents. *Psychology in the Schools*, *39*, 677-687. doi:10.1002/pits.10062

McMaster, L., Connolly, J., Pepler, D., & Craig, W. (2002). Peer to peer sexual harassment in early adolescence: A developmental perspective. *Development and Psychopathology*, *14*, 91-105. doi:10.1017/S0954579402001050

Merikangas, K., Jian-ping, H., Burstein, M., Swanson, S., Avenevoli, S., Lihong, C., . . . Swendsen, J. (2011). Lifetime prevalence of mental disorders in U.S. adolescents: Results from the National Comorbidity Study–Adolescent Supplement (NCS-A). *Journal of the American Academy Children Adolescent Psychiatry*, *49*, 980-989. doi:10.1016/j.jaac.2010.05.017

Mezquita, L., Camacho, L., Ibáñez, M. I., Villa, H., Moya-higueras, J., & Ortet, G. (2015). Five-factor model and alcohol outcomes: Mediating and moderating role of alcohol expectancies. *Personality and Individual Differences*, *74*, 29-34.

Miller, G. E., Chen, E., & Zhou, E. S. (2007). If it goes up, must it come down? Chronic stress and the hypothalamic-pituitary-adrenocortical axis in humans. *Psychological Bulletin*, *133*, 25-45. doi:10.1037/0033-2909.133.1.25

Monroe, S. M. (2008). Modern approaches to conceptualizing and measuring human life stress. *Annual Review of Clinical Psychology*, *4*, 33-52. doi:10.1146/annurev.clinpsy.4.022007.141207

Monroe, S. M., & Reid, M. W. (2008). Gene-environment interactions in depression research. *Psychological Science*, *19*, 947-957. doi:10.1111/j.1467-9280.2008.02181.x

Motrico, E., Moreno-Küstner, B., De Dios Luna, J., Torres-González, F., King, M., Nazareth, I., . . . Bellón, J. Á. (2013). Psychometric properties of the List of Threatening Experiences—LTE and its association with psychosocial factors and mental disorders according to different scoring methods. *Journal of Affective Disorders*, *150*, 931-940. doi:10.1016/j.jad.2013.05.017

Newcomb, M., Huba, G., & Bentler, P. (1981). A multidimensional assessment of stressful life events among adolescents: Derivation and correlates. *Journal of Health and Social Behavior*, *22*, 400-415.

Norman, R. E., Byambaa, M., De, R., Butchart, A., Scott, J., & Vos, T. (2012). The long-term health consequences of child physical abuse, emotional abuse, and neglect: A systematic review and meta-analysis. *PLoS Medicine*, *9*, 349. doi:10.1371/journal.pmed.1001349

Oliva, A., Jiménez, J. M., Parra, Á., & Sánchez-Queija, I. (2008). Acontecimientos vitales estresantes, resiliencia y ajuste adolescente [Stressful life events, resilience and adjustment in adolescence]. *Revista de Psicopatología y Psicología Clínica*, *13*(1), 53-62.

Ormel, J., Raven, D., van Oort, F., Hartman, C. A., Reijneveld, S. A., Veenstra, R., . . . Oldehinkel, A. J. (2015). Mental health in Dutch adolescents: A TRAILS report on prevalence, severity, age of onset, continuity and co-morbidity of DSM disorders. *Psychological Medicine*, *45*, 345-360. doi:10.1017/S0033291714001469

Ortuño-Sierra, J., Aritio-Solana, R., Chocarro de Luis, E., Nalda, F. N., & Fonseca-Pedrero, E. (2017). Subjective well-being in adolescence: New psychometric evidences on the satisfaction with life scale. *European Journal of Developmental Psychology*, *5629*, 1-9. doi:10.1080/17405629.2017.1360179

Palma-Gudiel, H., Córdova-Palomera, A., Leza, J. C., & Fañanás, L. (2015). Glucocorticoid receptor gene (NR3C1) methylation processes as mediators of early adversity in stress-related disorders causality: A critical review. *Neuroscience and Biobehavioral Reviews*, *55*, 520-535. doi:10.1016/j.neubiorev.2015.05.016

Patton, G. C., Coffey, C., Romaniuk, H., Mackinnon, A., Carlin, J. B., Degenhardt, L., . . . Moran, P. (2014). The prognosis of common mental disorders in adolescents: A 14-year prospective cohort study. *Lancet*, *383*, 1404-1411. doi:10.1016/S0140-6736(13)62116-9

Rabkin, J., & Struening, E. (1976). Live events, stress, and illness. *Science*, *194*, 1013-1020. doi:10.1126/science.790570

Reijntjes, A., Kamphuis, J. H., Prinzie, P., & Telch, M. J. (2010). Peer victimization and internalizing problems in children: A meta-analysis of longitudinal studies. *Child Abuse & Neglect*, *34*, 244-252. doi:10.1016/j.chiabu.2009.07.009

Repetti, R. L., Taylor, S. E., & Seeman, T. E. (2002). Risky families: Family social environments and the mental and physical health of offspring. *Psychological Bulletin*, *128*, 330-366. doi:10.1037//0033-2909.128.2.330

Rigby, K. (2003). Consequences of bullying in schools. *Canadian Journal Psychiatry*, *48*, 583-590. doi:10.1177/070674370304800904

Risch, N., Herrell, R., Lehner, T., Liang, K.-Y., Eaves, L., Hoh, J., . . . Merikangas, K. R. (2009). Interaction between the serotonin transporter gene (5-HTTLPR), stressful life events, and risk of depression: A meta-analysis. *JAMA*, *301*, 2462-2471. doi:10.1001/jama.2009.878

Rudolph, K. D., Hammen, C., Burge, D., Lindberg, N., Herzberg, D., & Daley, S. E. (2000). Toward an interpersonal life-stress model of depression: The developmental context of stress generation. *Development and Psychopathology*, *12*, 215-234.

Ruiz, M. A., Pardo, A., & San Martin, R. (2008). Modelos de ecuaciones estructurales [Structural equation models]. *Papeles Del Psicólogo*, *31*(1), 34-45.

Sánchez-Sánchez, F., Fernández-Pinto, I., Santamaría, P., Carrasco, M. A., & Barrio, V. (2016). SENA, Sistema de Evaluación de Niños y Adolescentes: Proceso de desarrollo y evidencias de fiabilidad y validez. *Revista de Psicología Clínica Con Niños y Adolescentes*, *3*, 23-34.

Sandín, B., & Chorot, P. (2017). Cuestionario de Sucesos Vitales (CSV): Estructura factorial, propiedades psicométricas y datos normativos [Life events questionnaire (CSV): factor structure, psychometric properties and normative data]. *Revista de Psicopatologia y Psicologia Clinica*, *22*, 95-115. doi:10.5944/rppc.vol.22.num.2.2017.19729

Sarason, I., Johnson, J., & Siegel, J. (1978). Assessing the impact of life changes: Development of the life experiences survey. *Journal of Consulting and Clinical Psychology*, *46*, 932-946. doi:10.1037//0022-006x.46.5.932

Shapero, B. G., Hamilton, J. L., Liu, R. T., Abramson, L. Y., & Alloy, L. B. (2013). Internalizing symptoms and rumination: The prospective prediction of familial and peer emotional victimization experiences during adolescence. *Journal of Adolescence*, *36*, 1067-1076. doi:10.1016/j.adolescence.2013.08.011

Shapero, B., Hankin, B. L., & Barrocas, A. L. (2013). Stress generation and exposure in a multi-wave study of adolescents: Transactional processes and sex differences. *Journal of Social and Clinical Psychology*, *32*, 989-1012. doi:10.1521/jscp.2013.32.9.989

Shields, G. S., & Slavich, G. M. (2017). Lifetime stress exposure and health: A review of contemporary assessment methods and biological mechanisms. *Social & Personality Psychology Compass*, *11*, e12335. doi:10.1111/spc3.12335

Shiner, R. L., Allen, T. A., & Masten, A. S. (2017). Adversity in adolescence predicts personality trait change from childhood to adulthood. *Journal of Research in Personality*, *67*, 171-182. doi:10.1016/j.jrp.2016.10.002

Stange, J. P., Hamilton, J. L., Abramson, L. Y., & Alloy, L. B. (2014). A vulnerability-stress examination of response styles theory in adolescence: Stressors, sex differences, and symptom specificity. *Journal of Clinical Child & Adolescent Psychology*, *43*, 813-827. doi:10.1080/15374416.2013.812037

Stikkelbroek, Y., Bodden, D. H. M., Reitz, E., Vollebergh, W. A. M., & van Baar, A. L. (2016). Mental health of adolescents before and after the death of a parent or sibling. *European Child & Adolescent Psychiatry*, *25*, 49-59. doi:10.1007/s00787-015-0695-3

Suldo, S. M., & Huebner, E. S. (2004). Does life satisfaction moderate the effects of stressful life events on psychopathological behavior during adolescence? *School Psychology Quarterly*, *19*, 93-105. doi:10.1521/scpq.19.2.93.33313

Swartz, J. R., Williamson, D. E., & Hariri, A. R. (2015). Developmental change in amygdala reactivity during adolescence: Effects of family history of depression and stressful life events. *American Journal of Psychiatry*, *172*, 276-283. doi:10.1176/appi.ajp.2014.14020195

Todkar, A., Nilsson, K. W., Oreland, L., Hodgins, S., & Comasco, E. (2013). Serotonin transporter genotype by environment: Studies on alcohol use and misuse in non-human and human primates. *Translational Neuroscience*, *4*, 241-250. doi:10.2478/s13380-013-0121-6

Tolan, P., Gorman-Smith, D., & Henry, D. (2006). Family violence. *Annual Review of Psychology*, *57*, 557-583. doi:10.1146/annurev.psych.57.102904.190110

Trianes, M. V., Blanca, M. J., Fernández, F. J., Escobar, M., Maldonado, E. F., & Muñoz, A. M. (2009). Assessment of stress in childhood: Children's Daily Stress Inventory (Inventario Infantil de Estresores Cotidiano, IIEC). *Psicothema*, *21*, 598-603.

Turner, R., & Wheaton, B. (1997). Checklist measurement of stressful life events. In S. Cohen, R. Kessler & L. Underwood (Eds.), *Measuring stress: A guide for health*

and social scientists (pp. 29-51). New York, NY: Oxford University Press.

van der Knaap, N. J. F., El Marroun, H., Klumpers, F., Mous, S. E., Jaddoe, V. W. V., Hofman, A., . . . Fernandez, G. (2014). Beyond classical inheritance: The influence of maternal genotype upon child's brain morphology and behavior. *Journal of Neuroscience*, *34*, 9516-9521. doi:10.1523/JNEUROSCI.0505-14.2014

Van Der Kolk, B. A., Roth, S., Pelcovitz, D., Sunday, S., & Spinazzola, J. (2005). Disorders of extreme stress: The empirical foundation of a complex adaptation to trauma. *Journal of Traumatic Stress*, *18*, 389-399. doi:10.1002/jts.20047

Veenstra, M. Y., Lemmens, P. H. H. M., Friesema, I. H. M., Garretsen, H. F. L., Knottnerus, J. A., & Zwietering, P. J. (2006). A literature overview of the relationship between life-events and alcohol use in the general population. *Alcohol and Alcoholism*, *41*, 455-463. doi:10.1093/alcalc/agl023

Voltas, N., Aparicio, E., Arija, V., & Canals, J. (2015). Association study of monoamine oxidase: A gene promoter polymorphism (MAOA-uVNTR) with self-reported anxiety and other psychopathological symptoms in a community sample of early adolescents. *Journal of Anxiety Disorders*, *31*, 65-72. doi:10.1016/j.janxdis.2015.02.004

Vrshek-Schallhorn, S., Stroud, C. B., Mineka, S., Hammen, C., Zinbarg, R. E., Wolitzky-Taylor, K., & Craske, M. G. (2015). Chronic and episodic interpersonal stress as statistically unique predictors of depression in two samples of emerging adults. *Journal of Abnormal Psychology*, *124*, 918-932. doi:10.1037/abn0000088

Wagner, C., Abela, J. R. Z., & Brozina, K. (2006). A comparison of stress measures in children and adolescents: A self-report checklist versus an objectively rated interview. *Journal of Psychopathology and Behavioral Assessment*, *28*, 251-261. doi:10.1007/s10862-005-9010-9

Wethington, E., Brown, G., & Kessler, R. (1997). Interview measurement of stressful life events. In S. Cohen, R. Kessler & L. Underwood (Eds.), *Measuring stress: A guide for health and social scientists* (pp. 59-79). New York, NY: Oxford University Press.

Williams, E. J. (1959). The comparison of regression variables. *Journal of the Royal Statistical Society: Series B*, *21*, 396-399.

Wittchen, H. U., Jacobi, F., Rehm, J., Gustavsson, A., Svensson, M., Jönsson, B., . . . Steinhausen, H. C. (2011). The size and burden of mental disorders and other disorders of the brain in Europe 2010. *European Neuropsychopharmacology*, *21*, 655-679. doi:10.1016/j.euroneuro.2011.07.018

Young, S. E., Friedman, N. P., Miyake, A., Willcutt, E. G., Corley, R. P., Haberstick, B. C., & Hewitt, J. K. (2009). Behavioral disinhibition: Liability for externalizing spectrum disorders and its genetic and environmental relation to response inhibition across adolescence. *Journal of Abnormal Psychology*, *118*, 117-130. doi:10.1037/a0014657

Zimmerman, M. (1983a). Methodological issues in the assessment of life events: A review of issues and research. *Clinical Psychology Review*, *3*, 339-370. doi:10.1016/0272-7358(83)90019-3

Zimmerman, M. (1983b). Weighted versus unweighted life event scores: Is there a difference? *Journal of Human Stress*, *9*, 30-35. doi:10.1080/0097840X.1983.9935028

UNIVERSITAT DE BARCELONA

Dr. Lourdes Fañanás Saura
Unitat de Zoologia i Antropologia Biològica
Dept. Biologia Evolutiva, Ecologia i Ciències Ambientals
Facultat de Biologia, Universitat de Barcelona

Informe del director sobre la contribución del doctorando al artículo.

La Prof. Lourdes Fañanás Saura, profesora del Departamento de Biología Evolutiva, Ecologia y Ciencias Ambientales de la Facultad de Biología (Universitat de Barcelona) y directora de la presente tesis doctoral de Laia Marques Feixa, por la presente certifica que Andrea Cuevas incorporó también este artículo *"Recent stressful life events (SLE) and adolescent mental health: initial validation of the LEIA, a new checklist for SLE assessment according to their severity, interpersonal, and dependent nature",* en su tesis doctoral presentada en la Universidad Jaume I. La participación de Laia Marquès Feixa en este artículo incluyó las siguientes tareas:

- Participación en la concepción y diseño del instrumento.
- Revisión crítica del artículo por contenido intelectual.

Signado por Prof. Lourdes Fañanás

Barcelona, abril 2022

Sección II: Maltrato infantil, estresores recientes y alteraciones en la salud mental infantojuvenil

3.3. Risk of suicidal behavior in children and adolescents exposed to maltreatment: the mediating role of borderline personality traits and recent stressful life events

Laia Marques-Feixa, Jorge Moya-Higueras, Soledad Romero, Pilar Santamarina-Pérez, Marta Rapado-Castro, Iñaki Zorrilla, María Martín, Eulalia Anglada, María José Lobato, Maite Ramírez, Nerea Moreno, María Mayoral, María Marín-Vila, Bárbara Arias, Lourdes Fañanás y EPI-Young Stress GROUP

Journal of Clinical Medicine (2021), Nov 14; 10(22):5293

DOI: 10.3390/jcm10225293

Journal of
Clinical Medicine

MDPI

Article

Risk of Suicidal Behavior in Children and Adolescents Exposed to Maltreatment: The Mediating Role of Borderline Personality Traits and Recent Stressful Life Events

Laia Marques-Feixa [1,2], Jorge Moya-Higueras [2,3], Soledad Romero [2,4,5], Pilar Santamarina-Pérez [4,5], Marta Rapado-Castro [2,6,7], Iñaki Zorrilla [2,8], María Martín [9], Eulalia Anglada [10], María José Lobato [11], Maite Ramírez [12], Nerea Moreno [1], María Mayoral [2,6], María Marín-Vila [11], Bárbara Arias [1,2], Lourdes Fañanás [1,2,*] and EPI-Young Stress GROUP [†]

1 Department of Evolutionary Biology, Ecology and Environmental Sciences, Faculty of Biology, University of Barcelona, Biomedicine Institute of the University of Barcelona (IBUB), Av Diagonal 643, 2n A, 08028 Barcelona, Spain; laiamarques@ub.edu (L.M.-F.); nereamorenog711@gmail.com (N.M.); barbara.arias@ub.edu (B.A.)
2 Network Centre for Biomedical Research in Mental Health (CIBER of Mental Health, CIBERSAM), Av. Monforte de Lemos, 3-5, 28029 Madrid, Spain; jorge.moya@udl.cat (J.M.-H.); sromero@clinic.cat (S.R.); mrapado@iisgm.com (M.R.-C.); inaki.zorrillamartinez@osakidetza.eus (I.Z.); maria.mayoral@iisgm.com (M.M.)
3 Department of Psychology, Faculty of Education, Psychology and Social Work, University of Lleida, Av. de l'Estudi General, 4, 25001 Lleida, Spain
4 Department of Child and Adolescent Psychiatry and Psychology, 2017SGR88, Institute of Neuroscience, Hospital Clínic de Barcelona, C/Villarroel, 170, 08036 Barcelona, Spain; psantama@clinic.cat
5 Institut d'Investigacions Biomediques August Pi i Sunyer (IDIBAPS), C/Rosselló, 149, 08036 Barcelona, Spain
6 Department of Child and Adolescent Psychiatry, Institute of Psychiatry and Mental Health, Hospital General Universitario Gregorio Marañón, IiSGM, C. Dr. Esquerdo, 46, 28007 Madrid, Spain
7 Melbourne Neuropsychiatry Centre, Department of Psychiatry, The University of Melbourne & Melbourne Health, C/Alan Gilbert, 161, Carlton, VIC 3053, Australia
8 Department of Psychiatry, Hospital Santiago Apostol, Olagibel Kalea, 29, 01004 Vitoria-Gasteiz, Spain
9 Adolescent Crisis Unit, Hospital Benito Menni, C/Pablo Picasso, 12, 08830 Sant Boi de Llobregat, Spain; mmartin.hbmenni@hospitalarias.es
10 Hospital for Adolescents, Fundació Orienta, c/Sant Lluís, 64, 08850 Gavà, Spain; eanglada@fundacioorienta.com
11 Department of Psychiatry, Puerta de Hierro University Hospital-Majadahonda, C/Joaquín Rodrigo, 1, 28222 Majadahonda, Spain; mjose.lobato@salud.madrid.org (M.J.L.); mmvila@salud.madrid.org (M.M.-V.)
12 Galdakao Mental Health Services, Child and Adolescent Mental Health, C/Ibaizabal, 6, 48960 Galdakao, Spain; maite.ramireztrapero@osakidetza.eus
* Correspondence: lfananas@ub.edu
† The investigators of the EPI-Young Stress GROUP are listed in Appendix A.

Abstract: Childhood maltreatment (CM) is associated with increased non-suicidal self-injury (NSSI) and suicidal behavior (SB), independently of demographic and mental health conditions. Self-Trauma Theory and Linehan's Biopsychosocial Model might explain the emergence of Borderline Personality Disorder (BPD) symptoms as mediators of the association between CM and the risk of SB. However, little is known regarding such relationships when the exposure is recent for young persons. Here, we study 187 youths aged 7–17, with or without mental disorders. We explore CM experiences (considering the severity and frequency of different forms of neglect and abuse), recent stressful life events (SLEs), some BPD traits (emotion dysregulation, intense anger and impulsivity), and the risk of SB (including NSSI, suicide threat, suicide ideation, suicide plan and suicide attempt). We study the direct and mediating relationships between these variables via a structural equation analysis using the statistical software package EQS. Our findings suggest that youths exposed to more severe/frequent CM have more prominent BPD traits, and are more likely to have experienced recent SLEs. In turn, BPD traits increase the risk of SLEs. However, only emotion dysregulation and recent SLEs were found to be correlated with SB. Therefore, targeted interventions on emotion dysregulation are necessary to prevent NSSI or SB in children and adolescents exposed to CM, as is the minimization of further SLEs.

Citation: Marques-Feixa, L.; Moya-Higueras, J.; Romero, S.; Santamarina-Pérez, P.; Rapado-Castro, M.; Zorrilla, I.; Martín, M.; Anglada, E.; Lobato, M.J.; Ramírez, M.; et al. Risk of Suicidal Behavior in Children and Adolescents Exposed to Maltreatment: The Mediating Role of Borderline Personality Traits and Recent Stressful Life Events. *J. Clin. Med.* **2021**, *10*, 5293. https://doi.org/10.3390/jcm10225293

Academic Editors: Hilario Blasco-Fontecilla and Giovanni Abbate-daga

Received: 28 August 2021
Accepted: 9 November 2021
Published: 14 November 2021

Keywords: childhood maltreatment; stressful life event (SLE); borderline personality disorder traits; emotion dysregulation; non-suicidal self-injury (NSSI); suicidal behavior (SB); youth; complex trauma

1. Introduction

Childhood is one of the most sensitive and neuroplastic periods of human development, as the stimuli and upbringing experienced during this stage is crucial for the maturation of brain systems and cognitive functions [1,2]. Early adversities, such as childhood maltreatment (CM), can be of detriment to neurodevelopment and can disturb intrapsychic and interpersonal patterns [3,4]. More specifically, when an individual has experienced multiple, severe and pervasive traumatic events during childhood (complex trauma), the psychological outcomes are often also multiple and severe. In this regard, it is not surprising that people with psychiatric disorders and a history of CM represent a clinically distinct subtype of patients, who have a worse clinical prognosis. They are characterized by earlier onset, more severe symptoms and comorbidity, the need for a higher medication dosage, and more frequent and longer hospitalizations [5,6]. Moreover, it seems that the timing, chronicity and the severity of the CM may play a role in clinical outcomes [7,8], establishing a dose–response relationship between multiplicity, severity or frequency of CM exposure on the one hand, and disease outcomes on the other [9,10].

Death by suicide could be one of the most devastating consequences of suffering from CM. Nowadays, suicide is the leading cause of death among young people (15–29 years old) in Spain and the second leading cause of death in Europe [11,12]. Throughout the last year (in the context of COVID-19 pandemic), it seems that suicide attempts began to increase among adolescents aged 12–17 years, especially in girls [13,14]. Although suicide is a multifactorial phenomenon, recent systematic reviews that focused on adolescents [15] and young adults [16] supported the finding that all types of CM are associated with an increased risk of SB. More specifically, Angelakis et al. [16] performed a meta-analysis concluding that complex trauma increased 5-fold the risk of suicide attempts in adults. Moreover, if after their experience of CM, there is an escalation of new stressful life events (SLEs), an increase in suicidal behavior (SB) might emerge [17]. This aspect could be especially relevant in stage in life that is as volatile as adolescence, during which brain regions associated with impulse control are still undergoing development [18].

Experts have also found higher rates of non-suicidal self-injury (NSSI), suicide ideation and other SB among individuals who have suffered CM [16,19]. NSSI is behavior that is not intended to result in the death of the individual and is often related to attempts to temporally alleviate overwhelming negative emotion or to a form of self-directed anger [20]. NSSI and SB can occur in the same individual [21]. In fact, a review on this topic proposes an integrated model with specific testable predictions about this link [22]. Some experts support the idea that NSSI is specifically associated with the transition from suicidal thinking to action in adolescents [23], and it is one of the main predictors of suicide attempts [24]. Thus, it is important to assess a broad spectrum of risk of SB, across the entire range it encompasses, from NSSI, suicide ideation, suicide threat and suicide plans to suicide attempts [25].

Nevertheless, there is a major gap in the literature regarding the mechanisms underlying the relationship between CM and SB risk, especially concerning young populations [26,27]. In this regard, a comprehensive theory was provided by Myers and colleagues to provide an understanding of the myriad self-damaging behaviors observed in individuals exposed to CM [28]. This model, called the Self-Trauma Model, proposes that complex trauma results in the maladaptive development of the following three primary capacities: affect regulation, identity, and interpersonal relatedness [29]. Consequently, when the individual with a history of CM is confronted with new stressful circumstances, she or he may be unable to rely on these internal resources and may resort to maladaptive tension-reducing behaviour, such as aggression, substance abuse, risky sexual behaviour,

self-injury or SB. Complementarily, Linehan's Biopsychosocial Model proposed that personality dysfunctions emerge when there is a biological predisposition (impulsivity followed by heightened emotional sensitivity) combined with an emotionally invalidating form of caregiving, CM being one of the most severe forms of emotional invalidation [30]. From a neuropsychological perspective of suicide risk, Allen et al. [31] proposed emotional dysregulation as a "multi-final common pathway" through which disparate diatheses (including CM) operate to influence varied adverse clinical outcomes.

In fact, some studies in an adult population have already described that the Self-Trauma Model provides support for the emergence of Borderline Personality Disorder (BPD) symptoms (affective dysregulation, identity problems or paranoia), a significant mediator of this relationship between CM and risk of SB [32]. Moreover, there seems to be a dose–effect relationship whereby the greater the exposure to early adversities, the more severe the Personality Disorders (PDs) [33], with increasing disturbances in the functioning of aspects of the self and interpersonal dysfunction across various contexts and relationships, such as a high risk of NSSI or SB. Therefore, considering that individuals with BPD are almost 14 times more likely to report a history of CM [27] and present higher rates of NSSI and SB [34,35], it would be interesting to consider, especially in the young population, BPD traits as possible mediators between CM and the risk of SB [30].

The diagnosis of PDs in childhood and in adolescence remains controversial [36,37] and many clinicians are reluctant to apply such diagnoses in younger individuals [38]. Nevertheless, previous research demonstrates that a considerable proportion of individuals with BPD traits prior to the age of 19 continue to manifest those symptoms for up to 20 years (from 14% to 40%) and that such traits at a young age predict long-term deficits in functioning [39]. Furthermore, considering that personality traits that increase the likelihood to risky behaviours are found in the general population, especially during adolescence, the use of a continuum of PD traits could be more effective. For instance, some authors support the claim that the traits most frequently exhibited by those who meet the criteria for BPD are emotion dysregulation, intense anger, impulsivity, and indirect aggression [40–42]. Along these themes, the literature shows that CM leads to experiences of chronic emotion dysregulation that might provide the basis of impairment and further exposure to trauma, as well as potentiating NSSI [43] and suicide ideation and suicide attempts [44]. In fact, emotion dysregulation is widely reported to be a transdiagnostic link between CM with general psychopathology [45,46].

To summarise, prior research focused on the mediating role of BPD traits in the association between CM and risk of SB, rarely included children and adolescents. In this study, we are particularly interested in elucidating the relationship between some BPD traits (emotion dysregulation, intense anger and impulsivity) and the risk of SB during the important life-cycle transition that is adolescence. In addition, we aim to assess CM experiences and disease outcomes carefully in an approach based on a continuum of severity, dispensing of classification dichotomies that fail to reflect the complexities of reality. We hypothesize that youths with more severe CM experiences manifest higher levels of related BPD traits and are less capable of buffering the impact of negative SLEs. Thus, BPD traits and SLEs mediate the correlation between CM and risky mental states or behavior, such as NSSI or SB (see Figure 1).

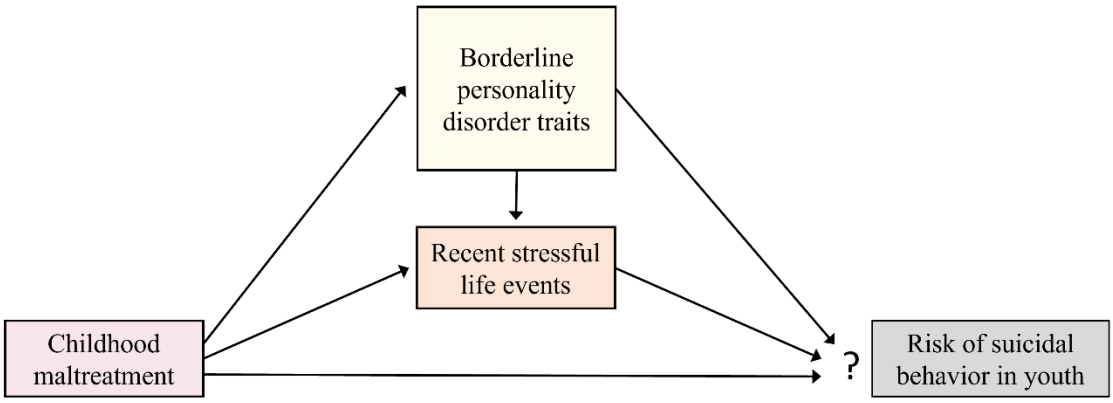


Figure 1. Our hypothesized model consisted of the following direct relationships: CM predicts BPD traits and is also related with recent SLEs and SB. Moreover, recent SLEs and BPD traits mediate the correlation between CM and SB. In turn, BPD traits are associated with exposure to recent SLEs and thereby also indirectly predict risk of SB.

2. Material and Methods

2.1. Participants

A total of 187 children and adolescents aged 7 to 17 years participated in our multicentre study of the psychoneurobiological consequences of CM (EPI_young_stress project) [47]. Of these participants, 116 had been diagnosed with a current psychiatric disorder and 71 were healthy controls (see Table 1). Psychopathology was ascertained using the Spanish version of the Schedule for Affective Disorders and Schizophrenia for School-Age Children: Present and Lifetime Version DSM-5 (K-SADS-PL-5) [48,49]. In order to better characterize the sample, the main diagnosis was later classified into the following dimensions: attention-deficit/hyperactivity disorder, affective disorders, trauma and stress-related disorders, anxiety disorders, behavioural disorders, psychotic disorders and eating disorder (see Table 1). Youths with a current psychopathology were recruited from six child and adolescent psychiatry departments in Spain. The healthy controls were recruited at the University of Barcelona or psychiatric centres via advertisements, primary healthcare centres, schools and other community facilities. The recruitment period lasted from April 2016 to March 2020. The exclusion criteria for all participants included the diagnosis of an autism spectrum disorder, an eating disorder with BMI < 18.5, intellectual disability (IQ < 70), current drug dependence, not being fluent in Spanish, extreme premature birth (<1500 g), head injury with loss of consciousness, and severe neurological or other pathological conditions (such as epilepsy, cancer or autoimmune diseases).

Table 1. Demographic and clinical descriptive data of our sample (n = 187).

Variables		Value
Age—mean (Sd) [range]		13.62 (2.59) [7–17]
Sex	Female—*n* (%)	108 (58%)
	Male—*n* (%)	79 (42%)
Ethnicity	European—*n* (%)	154 (82%)
	Others [a]—*n* (%)	33 (18%)
Socioeconomic status (SES) [b]—mean (Sd) [range]		40 (18) [8–66]
Current psychiatric diagnosis status	Without current psychiatric diagnosis—*n* (%)	71 (38%)
	With current psychiatric diagnosis—*n* (%)	116 (62%)

Table 1. *Cont.*

Variables	Value
Primary psychiatric diagnosis dimensions:	
ADHD [c]—*n* (%)	30 (26%)
Affective disorders—*n* (%)	29 (25%)
Trauma and stress-related disorders—*n* (%)	19 (16%)
Anxiety disorders—*n* (%)	15 (13%)
Behavioural disorders—*n* (%)	13 (11%)
Psychotic disorders—*n* (%)	7 (6%)
Eating disorders—*n* (%)	3 (3%)

[a] Other ethnicities were: Latin American (66%), Maghrebin (16%), sub-Saharan (9%), and others (9%). [b] SES is based on the Hollingshead Four-Factor Index of socioeconomic status (Hollingshead, 1975); higher scores reflect higher SES. [c] ADHD, attention-deficit/hyperactivity disorder.

Details of the assessment of the subjects have been reported elsewhere [47]. Briefly, all the participants and their parents/legal guardians were interviewed separately, face to face, by a trained psychologist or psychiatrist to obtain sociodemographic data, and their medical and psychiatric history, and to explore their CM history.

The study was approved by the Ethical Review Board of each participating hospital and university. Families were explicitly informed of the voluntary nature of the study, their rights, and the procedures, risks and potential benefits involved. Written consent was required from all parents or legal guardians; the children provided written assent after the nature of the procedure had been fully explained.

2.2. Measures and Final Scores

2.2.1. Childhood Maltreatment (CM)

CM Assessment

According to the recommendations of the National Child Traumatic Stress Network (NCTSN) [50], some key steps for conducting a comprehensive evaluation of complex trauma include the assessment for a wide range of traumatic events, and the gathering of information using a variety of techniques (clinical interviews, standardized measures, and behavioural observations) and a variety of perspectives (that of the child, caregivers, teachers, other providers, etc.). Thus, in this study, the participants and their parents/legal guardians were evaluated by trained psychologists by means of an exhaustive interview following the criteria of the instrument "Tool for assessing the severity of situations in which children are vulnerable" (TASSCV) [51] (available online in Spanish); and adolescents who were older than 12 answered self-reports such as the short version of the Childhood Trauma Questionnaire (CTQ-SF) [52] and the Childhood Experience of Care and Abuse Questionnaire (CECA-Q2) [53], while participants aged 7–11 answered an adapted ad-hoc hetero-administered questionnaire (for details see Supplementary Material in Marques-Feixa, 2021 [47]). Finally, reports from social services or teachers were reviewed by trained psychologists where applicable. After this, considering the information from the different sources, clinicians filled in a summary table, based on TASSCV criteria, regarding different forms of CM perpetrated by caregivers or other adults. Both confirmed (with clear evidence of a CM history) and suspected (if significant signs of neglect or abuse appeared during the evaluation) subjects were included. For the present report, data concerning five main types of CM were included in our analysis, which are emotional neglect, physical neglect, emotional abuse, physical abuse and sexual abuse. In our sample, 94 participants (50%) reported CM. Figure 2 shows the overlap of these CM subtypes. Additionally, clinicians assigned a severity and a frequency value to each subtype of CM, rated on a 4-point Likert scale, following TASSCV criteria. Specifically, for each subtype of CM, the severity was coded as low (1), moderate (2), severe (3) or extreme (4); while the frequency of CM

exposure was coded according to whether it occurred once (1), sometimes (2), often (3) or frequently (4).

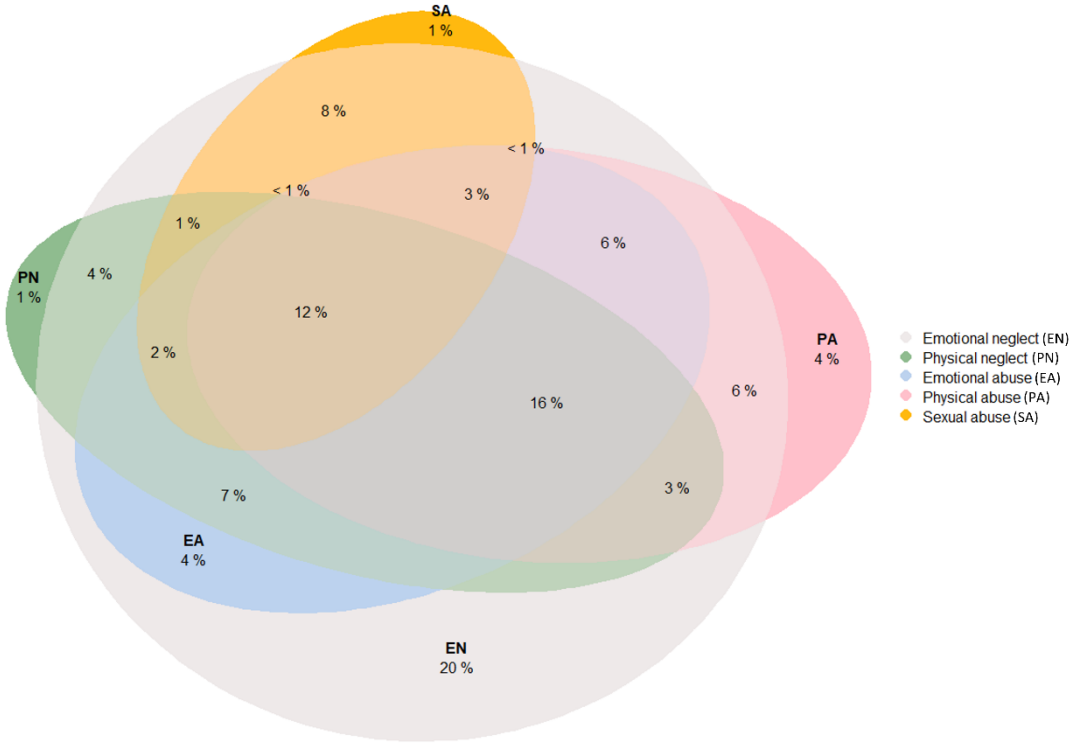


Figure 2. Overlap of childhood maltreatment (CM) subtypes in our sample. As can be seen, participants with a history of CM had rarely been exposed to only one type of CM. The form of CM that most often occurred in isolation was emotional neglect, accounting for 20% of the youths exposed to CM (although 94% of participants exposed to CM reported emotional neglect). Only 6% of the youth with a history of CM reported in isolation physical neglect, physical abuse or sexual abuse. Meanwhile, 74% of the individuals reported multiple forms of CM. Specifically, 16% reported four CM subtypes: emotional neglect, physical neglect, emotional abuse, and physical abuse. Furthermore, 12% of the children and adolescent exposed to CM manifested having suffered all five forms of CM, including sexual abuse.

CM Score

Assessing the experiences of CM on a continuum spectrum allows for a more complete and accurate understanding of the CM experiences suffered by each participant, beyond a simple presence/absence classification. Thus, a CM score was created by considering the severity and frequency of the CM: for each CM subtype, the reported severity (from 1 to 4) was multiplied by the reported frequency (from 1 to 4), to obtain a score for each subtype from 1 to 16. Finally, to obtain a global CM score, the five subtype scores were summed, thus obtaining a total CM score for each participant ranging from 0 (absence of CM) to 80 (for reports of extreme and frequent CM in all the subtypes) (see Figure 3). This CM score was included in our subsequent analysis.

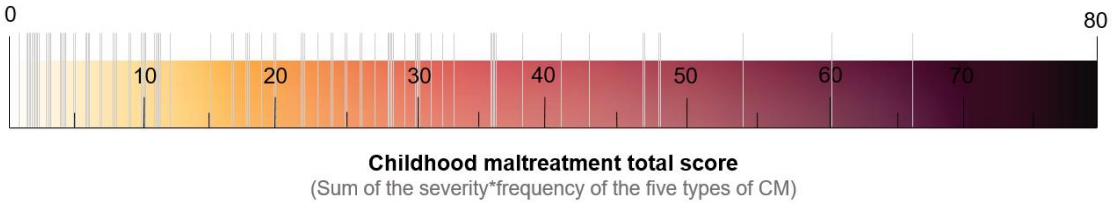


Figure 3. Distribution of subjects with a history of CM in the CM score (ranging from 1 to 80), considering the severity and frequency of each form of CM (emotional neglect, physical neglect, emotional abuse, physical abuse and sexual abuse).

2.2.2. Borderline Personality Disorder (BPD) Traits

BPD Trait Assessment

We explored BPD traits in our sample using two different questionnaires: the Trait Emotional Intelligence Questionnaire (TEIQue) and Child Behaviour Checklist 6–18, (CBCL). On the one hand, the TEIQue test provides comprehensive coverage of facets of child personality relating to emotions (adaptability, addictive disposition, emotion expression, emotion perception, emotion regulation, low impulsivity, peer relations, self-esteem and self-motivation) [54]. More specifically, the short form of the TEIQue for children answered by parents/guardians (TEIQue-CSF) was administered to our sample, which includes 36 short statements that the participant responds to on a 5-point Likert scale (1 = completely disagree, 2 = disagree, 3 = neither agree nor disagree, 4 = agree, 5 = agree completely) [55,56]. Secondly, the CBCL is an inventory for parents of the Achenbach System of Empirically Based Assessment (ASEBA) School-Age Forms and Profiles, which assesses the competencies, behavioural and emotional problems in children and adolescents aged 6 to 18 years [57,58]. The original questionnaire contains 113 items with three response options (0 = not true, 1= somewhat or sometimes true, 2 = very true or often true).

BPD Trait Score

In order to obtain BPD trait scores for all the participants, ten items from the TEIQue-CSF and eight from the CBCL were selected (see Table 2). Previously, the TEIQue-CSF scores were recoded as comparable with CBCL scores (1–2 = 0, 3 = 1, 4–5 = 2). According to the literature [59] and by reference to psychiatrists who were questioned, we chose items related to constructs that seem to be especially relevant in patients with BPD, including dysregulation and low levels of emotional control (such as affective instability, intense anger and impulsivity). To identify the relationship between items and the underlying empirical structure, we performed an exploratory factor analysis (EFA) of the principal axes with varimax rotation using SPSS. The Kaiser-Meyer-Olkin (KMO) value was 0.916, indicating the adequacy of the sampling. A parallel analysis (Monte Carlo PA software) suggested a three-factor structure for the BPD traits (see Table 2). A content analysis of the items revealed that one factor referred to the affective instability and difficulties of understanding and managing emotions. Therefore, this factor was named "emotion dysregulation". The second factor concerned the behaviour associated with irritability, inappropriate/explosive anger and trouble controlling such anger, and was named "intense anger". The third factor included items that relate to impulsivity of actions, and was named "impulsivity". The three-factor composite scores were extracted (as continuous regression scores) to be used as main BPD traits. The internal consistency can be seen in Table 2.

Table 2. Borderline personality trait scores.

Borderline Personality Disorder Traits	Item	Original Test (Item)	Loading Factor	Cronbach Alpha
Emotion Dysregulation	She/he can't find the right words to tell others how she/he feels	TEIQue-CSF (29)	0.720	0.804
	She/he is often confused about the way she/he feels	TEIQue-CSF (33)	0.711	
	She/he feels great about her/himself	TEIQue-CSF (4)	−0.641	
	Refuses to talk	CBCL (65)	0.625	
	It's easy for her/him to understand how she/he feels	TEIQue-CSF (16)	−0.618	
	Often, she/he is not happy with her/himself	TEIQue-CSF (12)	0.578	
	She/he is not good at controlling the way she/he feels	TEIQue-CSF (27)	0.530	

Table 2. *Cont.*

Borderline Personality Disorder Traits	Item	Original Test (Item)	Loading Factor	Cronbach Alpha
Intense Anger	Stubborn, sullen or irritable	CBCL (86)	0.845	0.915
	Temper tantrums or hot temper	CBCL (95)	0.790	
	Sulks a lot	CBCL (88)	0.758	
	Whining	CBCL (109)	0.752	
	Sudden changes in mood or feelings	CBCL (87)	0.710	
	Argues a lot	CBCL (3)	0.667	
	She/he often feels angry	TEIQue-CSF (5)	0.587	
Impulsivity	She/he thinks very carefully before she/he does anything	TEIQue-CSF (26)	−0.846	0.853
	Many times, she/he doesn't think before she/he does something	TEIQue-CSF (13)	0.806	
	Impulsive or acts without thinking	CBCL (41)	0.716	
	Usually, she/he thinks very carefully before she/he talks	TEIQue-CSF (36)	−0.715	

Note: CBCL: Child Behavior Checklist 6-18. TEIQue-CSF: Short form of the Trait Emotional Intelligence Questionnaire for children answered by parents/guardians.

2.2.3. Recent Stressful Life Events (SLEs)

The Life Events Inventory for Adolescents (LEIA) is a validated Spanish checklist used to screen for SLEs that occurred in youths in the last year [60]. Here, we used this instrument to assess 75 negative SLEs, including a loss or serious illness, family difficulties (financial, legal, divorce, moving address, etc.), peer problems (fights, losing a friend, breakup, etc.), academic problems (change of school, expulsion, repeating a year, etc.) and bullying or victimization, among others. The instrument showed an adequate level of reliability and good validity [60]. To avoid any interference in the main outcomes of the study, two items from the LEIA relating to one's own mental psychopathology were excluded ("Have you suffered from any psychological or psychiatric problem?" and "Have you had any alcohol or drug-related problems?"). The LEIA "quantity score" (calculated by adding up the total SLEs (0–73)) was used in this study.

2.2.4. Risk of Suicidal Behavior (SB)

Risk of SB Assessment

Since K-SADS-PL5 includes a section addressing suicide, which assesses past and current self-injurious thought and behaviour, after the interview the researchers reported information about the presence/absence of the following constructs: NSSI, suicide ideation, suicide threat, suicide plans and suicide attempts. In our sample 63 participants (33%) manifested some form of risk of SB (see Table 3 for details).

Risk of SB Score

The five suicide constructs previously described were considered to increase the risk of an SB score. We verified the relationships and underlying empirical structure between the five items by applying EFA with Varimax rotation via SPSS. The KMO measure of the sampling adequacy was 0.833. An inspection of the eigenvalues and screen plots suggested only one factor to be a variable. Thus, a single factor was included in main analyses as a continuous variable named "risk of SB".

Table 3. Main variables studied.

Variable			Value
CM	Absence (*n*, %)		93 (50%)
	Presence (*n*, %)		94 (50%)
	Types of CM:	Emotional neglect (*n*, %)	84 (44%)
		Physical neglect (*n*, %)	43 (23%)
		Emotional abuse (*n*, %)	49 (26%)
		Physical abuse (*n*, %)	50 (27%)
		Sexual abuse (*n*, %)	28 (15%)
	CM total score—mean (Sd) [range]		9.50 (14.26) [0—66]
Recent SLEs	**Total SLEs**—mean (Sd) [range]		6.60 (5.77) [0—25]
BPD trait score	Emotion dysregulation—mean (Sd) [range]		0.00 (1.0) [−1.96–2.91]
	Intense Anger mean (Sd) [range]		0.00 (1.0) [−1.89–2.26]
	Impulsivity mean (Sd) [range]		0.00 (1.0) [−2.28–2.15]
SBs	Absence (*n*, %)		124 (67%)
	Presence (*n*, %)		63 (33%)
	Subtypes ofSBs:	Non-suicidal self-injury (NSSI) (*n*, %)	48 (26%)
		Suicide ideation (*n*, %)	45 (24%)
		Suicide threat (*n*, %)	33 (18%)
		Suicide plans (*n*, %)	18 (10%)
		Suicide attempt (*n*, %)	30 (16%)
	Risk of SB score—mean (Sd) [range]		0.0 (1.0) [−0.58–2.63]

Note: BPD: borderline personality disorder. CM: childhood maltreatment. SBs: suicidal behaviours. SLEs: stressful life events.

2.3. Statistical Analysis

We analysed the descriptive statistics using SPSS version 26 (IBM, Chicago, IL, USA). Figure 2 was created through the use of R statistical software through the Euler diagram package. To identify relationships in our hypothesized model, we tested a path analysis model (see Figure 1) using the statistical software package EQS 6.1 [61]. Mardia's coefficient was calculated to assess overall normality. As the model was non-normal, we used the Satorra-Bentler robust indexes [61]. To evaluate the model's goodness-of-fit (capacity to reproduce the data), several indices were reported, including the Satorra-Bentler Chi-Square, Comparative fit index (CFI), Bollen's fit index (IFI), McDonalad's fit index (MFI) and the Root Mean Square Error of Approximation (RMSEA). Using standard criteria [62,63], values higher than 0.90 in CFI, IFI and MFI, and values lower than 0.08 in RMSEA, were considered as an acceptable model fit. As we needed to respecify the initial model, we used the Lagrange multiplier test (which provides information on what types of new associations could be included in the model) and the Wald test (indicating which fixed parameters or constraints might be released), according to Bentler [61]. The threshold applied for the Lagrange and Wald tests was $p < 0.05$. In addition, in order to compare the better fit of the two competing models, a Standardized Mean-square-Residual (SRMR) value was explored. When the SRMR value is found to be considerably small, the model fits the data well regardless of the other measures of fit. To compare the magnitude of each variable to predict the outcome, standardized regression coefficients were included in the arrows of path diagram (Figure 4).

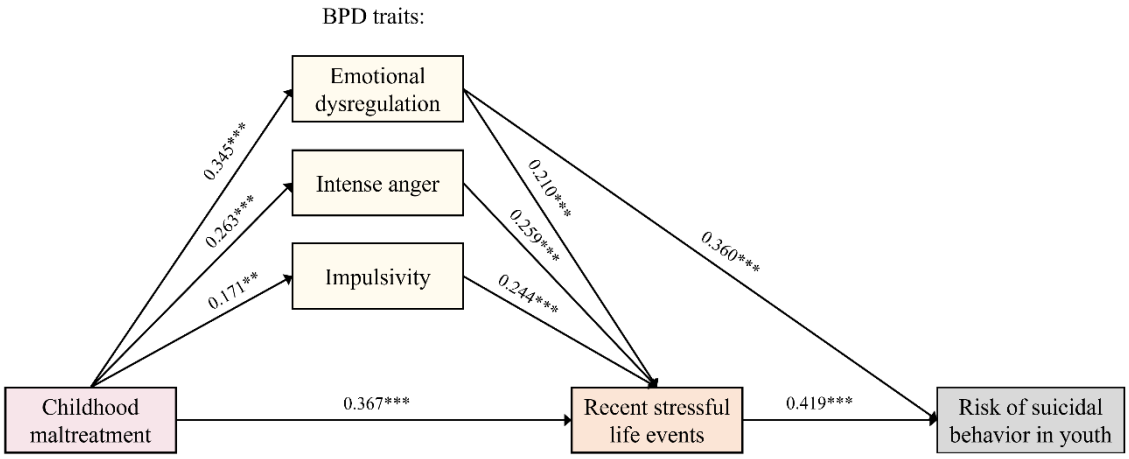


Figure 4. Final model obtained by path analysis. Our results support the hypothesis that youths with a more severe/frequent history of CM present a higher risk to recent SLEs. Furthermore, we found that youths with greater CM exposure had more BPD traits (emotion dysregulation, intense anger and impulsivity), which, in turn, directly predict higher incidence of recent SLEs. Nevertheless, SB was only correlated with emotion dysregulation and recent SLEs, but not with CM or the other BPD traits (impulsivity or intense anger) as we hypothesized. p values: ** $p \leq 0.01$, and *** $p \leq 0.001$.

3. Results

The descriptive data of the main variables included in the analysis can be seen in Table 3. Of the 94 participants with a history of CM, 79 (84%) have a current psychiatric disorder and 15 (16%) do not. Of the subjects without CM, 37 (40%) have a current psychiatric diagnosis and 56 (60%) do not have a psychiatric disorder. Since this is a cross-sectional study with a perspective of continue variables, the case/control differentiation was not included. Due to missing information for some of the main variables, the data obtained from nine subjects were excluded from the analysis, resulting in a final sample of 178 subjects. The attrition analysis showed no significant differences in sociodemographic factors when comparing the participants who were excluded and the subjects who were included in the path analysis.

The goodness-of-fit statistics showed that the initial model (see Figure 1) was almost overfitted (χ^2 (3) = 2.636, p = 0.45, CFI = 1.00, IFI = 1.00, MFI = 1.00, RMSEA < 0.001). Hence, we decided to respecify the model. We generated an alternative model, according to the Wald test, and excluded the direct effect of CM on the risk of SB and the direct effect of intense anger and impulsivity on the risk of SB.

The alternative model fitted the data similarly to the initial model (χ^2 (3) = 2.172, p = 0.53, CFI = 1.00, IFI = 1.00, MFI = 1.00, RMSEA < 0.001). Thus, we also explored the SRMR fitting statistic. According to Bentler (2006), when we compare two competing models, the one with lower SRMR should indicate the best fitting model [61]. The SRMR suggests that the best model was the respecified one, since the SRMR value of the initial model was 0.030, while that of the respecified model was 0.021. Therefore, this was used as our final model. As can be seen in Figure 4, CM had a significant positive correlation with BPD traits (emotion dysregulation (ß (0.004) = 0.345, p < 0.00001), intense anger (ß (0.005) = 0.263, p < 0.001) and impulsivity (ß (0.005) = 171, p = 0.009). Additionally, CM increased the risk of SLEs over the last year (ß (0.031) = 0.367, p < 0.00001). In turn, BPD traits are associated with higher SLE exposure (emotion dysregulation (ß (0.369) = 0.210, p < 0.001), intense anger (ß (0.367) = 0.259, p < 0.0001) and impulsivity (ß (0.333) = 0.244, p < 0.0001). However, only emotion dysregulation (ß (0.064) = 0.360, p < 0.00001) and recent SLEs (ß (0.013) = 0.419, p < 0.00001) showed a significant correlation with SB. This model explained 40% of the variance in the risk of SB.

4. Discussion

The present study examines the impact of CM on the risk of SB in a young population, exploring the mediating role of BPD traits and SLEs during the previous year. According to our results, emotional dysregulation and recent SLEs may indirectly help to explain the links between CM and the risk of SB (including NSSI, suicide threat, suicide ideation, suicide plan and suicide attempts).

On the one hand, in line with Self-Trauma Theory [28], it seems that CM (specifically, complex trauma characterized by multiple, severe and pervasive traumatic events) affects core personality domains in the early stages of life. It is hypothesised that CM may impact personality by altering the way we perceive and interpret the world around us, consequently affecting the way we respond to and manage future stressful situations [32]. From Linehan's Biopsychosocial Model, BPD may begin with early biological vulnerability, expressed initially as impulsivity and followed by heightened emotional sensitivity, potentiated across development via environmental risk factors that give rise to more extreme emotional, behavioural, and cognitive dysregulations [29]. Specifically, as previous studies report, our findings show that CM increases the emergence of some maladaptive personality traits typically associated with BPD, such as emotion dysregulation [64], intense anger [65] and impulsivity [66]. Additionally, the emergence of other maladaptive personality dimensions has been reported in the literature, such as self-criticism [67] interpersonal difficulties [64], reduced agreeableness or openness to experience, and increased neuroticism [68]. Consequently, these types of learned adaptations could lead to a large range of dysfunctional coping behaviours over time, such as greater exposure to destructive risks (aggression, substance abuse, delinquency, risky sexual behaviour, and also SB or NSSI). Furthermore, it seems that a greater personality disturbance in those who attempt suicide seems to be associated with repeated SB [69].

In this regard, in our study, only emotion dysregulation appears as a BPD trait associated with SB. This is in accordance with a recent review of an adult population [70]. The study suggested that previous experiences of trauma should always be included as a main moderator in the association between the regulation of one's emotions and suicide ideation or SB [70]. According to the neuroscience-based literature, CM might dysregulate neurobiological mechanisms involved in the stress response early in life, which may influence the ability to regulate emotions, resulting in reduced available internal resources to manage and respond effectively to new SLEs [47,71]. However, genetic and environmental protective factors could also lead to resilience and explain why not all people who experience such difficult starts in life experience such lifelong disability. In fact, a recent longitudinal study, based on adult psychiatric inpatients, also supports that CM was unrelated to SB, suggesting poor emotional response inhibition (a proposed behavioral marker of emotional dysregulation) as a predictor of SB [72].

Unlike other studies, the present study found intense anger and impulsivity to not be directly associated with SB [73]. Varied results have been found in past studies about this complex relationship [31]. However, the present study also agrees that emotion regulation is an importance mechanism to understand general psychopathology [46]. In fact, an inadequate emotion regulation has been associated with a wide range of both internalizing and externalizing disorders [74]. On this basis, our study adopted a transdiagnostic approach, including a wide range of mental health problems.

On the other hand, our findings also suggest that children and adolescents with higher severity/frequency of CM are more likely to experience new SLEs, thereby supporting a tendency towards revictimization [45]. Moreover, we found that the aggregation of recent SLEs are significant predictors (and indeed the main ones) of a risk of SB. Hence, the present study favours the Sensitivity–Stress Hypothesis, which states that the experience of numerous SLEs in a short period of time triggers psychopathology [75]. In addition, according to Allen et al. [25], the three BPD traits evaluated (emotion dysregulation, intense anger and impulsivity) positively correlated with exposure to further SLEs. Thus, we also offer confirmation of the Stress Generation Hypothesis of SLEs [75]. This hypothesis, first

expounded by Hammen [76], proposes that some psychological characteristics (especially those related to psychopathology) could function as significant predictors of SLEs. Overall, the present study supports the existence of a self-reinforcing cycle between maladaptive traits or psychopathology and exposure to stress [75].

It is important to highlight that adolescence is a life-cycle transition and a sensitive period that often triggers overwhelming and impulsive responses to a changing environment. Therefore, youths who have been maltreated or neglected may be prone to easily triggered trauma memories that potentially bring with them great emotional pain in new circumstances—which, in the absence of sufficient emotional regulation skills, may lead the youth to engage in behaviour that reduces awareness of extreme distress, such as NSSI or SB. Interestingly, Angelakis [16] propose that while children may present high rates of suicide ideation, it is not until adolescence that SB appears. In fact, the transition to suicide attempts among adolescents with suicide ideation or NSSI may also be predicted by other variables such as cannabis and other illicit drug abuse, sleep problems and a lower extraversion score [23]. Thus, it would be interesting to evaluate subjects based on a continuum, ranging from suicide ideation to suicide attempts, during childhood and adolescence. Furthermore, considering the dose–response effect reported in the literature, a more trait-specific approach based on the multi-dimensional nature of PDs could be more useful when studying young populations [77]. Indeed, predictive personality traits in the general population, which have not yet been diagnosed or treated by mental health services, could prove useful to reducing the likelihood of risky behaviours.

4.1. Clinical Implications

Given that we did not find a direct association between CM and the risk of SB, the presence of mediators, such as emotion dysregulation or SLEs, provides a greater margin for intervention, thereby allowing clinicians to work on these intermediate and modifiable traits. Firstly, targeting psychotherapy towards emotion dysregulation soon after trauma (rather than prioritizing other aspects such intense anger or impulse control) would improve victims' lives and reduce the risk of further traumatization and, ultimately, decrease the risk of SB. Secondly, it is important to consider recent SLEs in youths who have a CM history to prevent NSSI or SB [78,79]. Moreover, it is crucial to highlight that traumatized youth, although they may present other associated psychiatric disorders, often manifest disturbances in their self-organization, severe emotion dysregulation, and high levels of guilt, shame, self-harm and interpersonal problems. Thus, they require specific forms of intervention [80–83].

4.2. Limitations and Future Directions

Certain limitations of this study should be borne in mind. First, the present study is cross-sectional, so we cannot infer any directionality from the data. Only well-controlled longitudinal studies reveal whether the directions of the associations tested are real or spurious [84]. In addition, the study of BPD traits relied exclusively on questionaries designed to assess other variables, so we created a proxy for the main BPD features such as emotional dysregulation, intense anger and impulsivity, which did not allow for the analysis of other BPD traits. Additionally, we cannot discount the influence of genetically transmitted temperamental factors that may also influence BPD features and increase vulnerability to stress [85]. Similarly, other variables can also increase the risk of SB, such as associated mental disorders, family and socio-cultural environment or the absence of social support [73].

Furthermore, we did not include the nature of SLEs in this study. In this regard, some authors suggest that there is an association between particular stressor subtypes and suicide ideation or SB [86]; so, for future studies, it would be interesting to assess whether a particular type of SLE increases the risk of SB (e.g., SLEs with a dependent/independent nature, interpersonal or none, perpetrated by peers, or other) [17]. In addition, for distal and proximal stress factors that predispose individuals to experience problems with the

regulation of their affective/cognitive or social experiences, it would be interesting to consider social learning. This may lead to self-injury over other means of self-regulation, especially in young individuals.

For future studies it would be interesting to include indirectly harmful behaviour (e.g., alcohol and substance use), since these patters commonly co-occur with directly self-injurious behaviour, and it may be useful to consider them on a continuum of self-harm behaviour. Finally, the overlap in symptomatology between different PDs, especially in younger individuals, creates a boundary problem for clinicians when making differential diagnoses. Thus, when planning appropriate and effective interventions, a more trait-specific approach based on different dimensions might be more useful than applying a dichotomous classification of PDs, widening the gap between those just above the diagnostic threshold and those at subclinical levels [87].

5. Conclusions

It is well understood that CM is a highly complex phenomenon that affects the individual systemically. Furthermore, it constitutes a major risk factor for the development of a large range of mental disorders, including suicide ideation, NSSI or other forms of SB. A better understanding of the mechanisms that give rise to the risk of SB, especially in children and adolescents, may have the potential to guide the development of more efficient preventative treatments and interventions. In this regard, the present study provides support for the clinical use of gathering information on specific BPD traits, such as emotion dysregulation, intense anger and impulsivity in youths with adverse childhood experiences. Our findings may suggest that, to prevent suicide ideation, NSSI and SB in young people proximally exposed to CM, it would be crucial to target interventions against emotion dysregulation and to reduce, as far as possible, their exposure to new SLEs. Additional longitudinal investigations are required to confirm this hypothesis. In any case, interventions with children and adolescents exposed to CM who manifest BPD traits requires commitment from parents, a well-coordinated medical team, and a coherent treatment schedule.

Author Contributions: Conceptualization, L.M.-F., J.M.-H., S.R., P.S.-P., N.M., M.M.-V. and L.F.; methodology, L.M.-F., S.R., M.J.L. and M.M. (María Mayoral); software, L.M.-F. and J.M.-H.; validation, L.M.-F., J.M.-H.; formal analysis, L.M.-F. and J.M.-H.; investigation, L.M.-F., S.R., P.S.-P., M.M. (María Martín), E.A., M.J.L., M.R., M.M. (María Mayoral) and M.R.; resources, S.R., M.R.-C., I.Z., M.M. (María Martín), E.A. and L.F.; data curation, L.M.-F.; writing—original draft preparation, L.M.-F. and J.M.-H.; writing—review and editing, L.M.-F., J.M.-H., S.R., P.S.-P., B.A. and L.F.; visualization, L.M.-F., J.M.-H., S.R. and L.F.; supervision, L.M.-F., J.M.-H., S.R. and L.F.; project administration, L.M.-F., S.R., M.R.-C., I.Z., M.R. and L.F.; funding acquisition, L.M.-F., S.R., M.R.-C., I.Z. and L.F. The EPI-Young Stress GROUP members facilitate the study. All authors have read and agreed to the published version of the manuscript.

Funding: Supported by the Spanish Ministry of Economy and Competitiveness Instituto de Salud Carlos III through the University of Barcelona multicentre project (PI15/00097): PI L. Fañanas; Hospital Universitario Araba (PI15/00793): PI I. Zorrilla; Hospital Gregorio Marañón (PI15/00723): PI M. Rapado; and Hospital Clinic (PI15/00685): PI S. Romero. Co-financed by the European Regional Development Fund project, "A way of making Europe". We thank the Network Centre for Biomedical Research in Mental Health (CIBERSAM). This study was facilitated by a pre-doctoral research grant from the Catalonian authorities to Laia Marques-Feixa (AGAUR- FI_B100023-2018) and the Bosch i Gimpera Foundation. The work is also supported by the Comissionat per a Universitats i Recerca del DIUE, of the Generalitat de Catalunya regional authorities (2017SGR1577) and by the Spanish Ministry of Science, Innovation and Universities (RTI2018-099800-B-I00). Rapado-Castro was supported by a Ramon y Cajal Research Fellowship (RYC-2017-23144), from the Spanish Ministry of Science, Innovation and Universities.

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) of University of Barcelona (code IRB00003099, on 1 March 2016), Hospital Benito Menni (PR-2015-09, on 30 April 2015), Hospital Clinic-Barcelona (HCB/2015/0358, on 12 July 2016), Hospital Universitario de Araba (PI2016009SO, on 25 May 2016), Hospital General Universitario Gregorio Marañón (CPMP/1CH/135/95, on 25 April 2016), Hospital Universitario Puerta de Hierro Majadahonda (HPH2016/12.16, on 21 July 2016) and Hospital de día Orienta-Gavà (CPMP/ICH/135/95, on 30 November 2018).

Informed Consent Statement: Families were explicitly informed of the voluntary nature of the study, their rights, and the procedures, risks and potential benefits involved. Written consent was required from all parents or legal guardians; the children provided written assent after the nature of the procedure had been fully explained.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to restrictions in privacy and ethical.

Acknowledgments: We are indebted to all the participants and their families for taking part in a study with such deep emotional involvement. We also thank the nurses and lab technicians who made this research possible.

Conflicts of Interest: The authors declare no conflict of interest.

Appendix A

EPI-Young Stress GROUP: Helena Palma-Gudiel [1,2], María José Muñoz [3], Águeda Castro-Quintas [1,4], José Luis Monteserín-García [1,4], Iría Méndez [1,5,6], Ariadna Mas [5], Patricia Rubio [7], Dolores Moreno [1,7], María Ramos [7], Jorge Vidal [7], Juanjo Carballo [7], Elena Font [1,5,6], Lydia Gayubo [8], Laura Colino [8], María Rodrigo-Yanguas [8], Maddi Laborde [9] and Jaume March-Llanes [10]

1 Network Centre for Biomedical Research in Mental Health (CIBER of Mental Health, CIBERSAM), Av. Monforte de Lemos, 3-5, 28029 Madrid, Spain; helena.palma.gudiel@gmail.com (H.P.-G.); aguedacastro@ub.edu (Á.C.-Q.); monteserin@ub.edu (J.L.M.-G.); imendez@clinic.cat (I.M.); lolamoreno@hggm.es (D.M.); efont@clinic.ub.es (E.F.)

2 Department of Epidemiology, College of Public Health and Health Professions, University of Florida, Gainesville, FL 32611, USA

3 Adolescent Crisis Unit, Hospital Benito Menni, C/Pablo Picasso, 12, 08830 Sant Boi de Llobregat, Spain; mmunoz.hbmenni@hospitalarias.es

4 Department of Evolutionary Biology, Ecology and Environmental Sciences, Faculty of Biology, University of Barcelona, Biomedicine Institute of the University of Barcelona (IBUB), Av Diagonal 643, 2n A, 08028 Barcelona, Spain

5 Department of Child and Adolescent Psychiatry and Psychology, 2017SGR88, Institute of Neuroscience, Hospital Clínic de Barcelona, C/ Villarroel, 170, 08036 Barcelona, Spain; arimasmusons@gmail.com

6 Department of Child and Adolescent Psychiatry, Institut d'Investigacions Biomediques August Pi i Sunyer (IDIBAPS), C/Rosselló, 149, 08036 Barcelona, Spain

7 Department of Child and Adolescent Psychiatry, Institute of Psychiatry and Mental Health, Hospital General Universitario Gregorio Marañón, IiSGM, C. Dr. Esquerdo, 46, 28007 Madrid, Spain; patricia.rubiof@gmail.com (P.R.); mariaramosrdguez@yahoo.es (M.R.); jorge.vidal@salud.madrid.org (J.V.); juacarba@ucm.es (J.C.)

8 Department of Psychiatry, Puerta de Hierro University Hospital-Majadahonda, C/ Joaquín Rodrigo, 1, 28222 Majadahonda, Spain; lydiagayubo@yahoo.es (L.G.); mariarodrigopsi@gmail.com (M.R.-Y.)

9 Department of Psychiatry, Hospital Santiago Apostol, Olagibel Kalea, 29, 01004 Vitoria-Gasteiz, Spain; maddi.labordezufiaurre@osakidetza.eus

10 Department of Psychology, Faculty of Education, Psychology and Social Work, University of Lleida, Av. de I'Estudi General, 4, 25001 Lleida, Spain; jaume.march@udl.cat

References

1. McCrory, E.J.; Gerin, M.I.; Viding, E. Annual Research Review: Childhood maltreatment, latent vulnerability and the shift to preventative psychiatry—The contribution of functional brain imaging. *J. Child Psychol. Psychiatry Allied Discip.* **2017**, *58*, 338–357. [CrossRef] [PubMed]
2. Nemeroff, C.B. Paradise Lost: The Neurobiological and Clinical Consequences of Child Abuse and Neglect. *Neuron* **2016**, *89*, 892–909. [CrossRef] [PubMed]
3. Schalinski, I.; Teicher, M.H.; Nischk, D.; Hinderer, E.; Müller, O.; Rockstroh, B. Type and timing of adverse childhood experiences differentially affect severity of PTSD, dissociative and depressive symptoms in adult inpatients. *BMC Psychiatry* **2016**, *16*, 1–15. [CrossRef]
4. McCrory, E.; De Brito, S.A.; Viding, E. Research review: The neurobiology and genetics of maltreatment and adversity. *J. Child Psychol. Psychiatry Allied Discip.* **2010**, *51*, 1079–1095. [CrossRef] [PubMed]
5. Read, J.; Van Os, J.; Morrison, A.P.; Ross, C.A. Childhood trauma, psychosis and schizophrenia: A literature review with theoretical and clinical implications. *Acta Psychiatr. Scand.* **2005**, *112*, 330–350. [CrossRef] [PubMed]
6. Teicher, M.H.; Samson, J.A. Childhood maltreatment and psychopathology: A case for ecophenotypic variants as clinically and neurobiologically distinct subtypes. *Am. J. Psychiatry* **2013**, *170*, 1114–1133. [CrossRef]
7. Jonson-Reid, M.; Kohl, P.L.; Drake, B. Child and adult outcomes of chronic child maltreatment. *Pediatrics* **2012**, *129*, 839–845. [CrossRef]
8. Hughes, K.; Bellis, M.A.; Hardcastle, K.A.; Sethi, D.; Butchart, A.; Mikton, C.; Jones, L.; Dunne, M.P. The effect of multiple adverse childhood experiences on health: A systematic review and meta-analysis. *Lancet Public Health* **2017**, *2*, e356–e366. [CrossRef]
9. Anda, R.F.; Felitti, V.J.; Bremner, J.D.; Walker, J.D.; Whitfield, C.; Perry, B.D.; Dube, S.R.; Giles, W.H. The enduring effects of abuse and related adverse experiences in childhood: A convergence of evidence from neurobiology and epidemiology. *Eur. Arch. Psychiatry Clin. Neurosci.* **2006**, *256*, 174–186. [CrossRef] [PubMed]
10. Janssen, I.; Krabbendam, L.; Bak, M.; Hanssen, M.; Vollebergh, W.; Graaf, D. Childhood abuse as a risk factor for psychotic experiences. *Acta Psychiatr. Scand.* **2004**, *109*, 38–45. [CrossRef]
11. Paniagua, A. El Suicidio se Convierte en la Primera Causa de Muerte Entre los Jóvenes. Heraldo, 2021. Available online: https://www.heraldo.es/noticias/nacional/2021/07/25/el-suicidio-se-convierte-en-la-primera-causa-de-muerte-entre-los-jovenes-1508739.html?autoref=true (accessed on 25 July 2021).
12. Eurostat Statistics Explained. Being Young in Europe Today—Health. 2020. Available online: https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Being_young_in_Europe_today_-_health (accessed on 5 August 2021).
13. Yard, E.; Radhakrishnan, L.; Ballesteros, M.F.; Sheppard, M.; Gates, A.; Stein, Z.; Hartnett, K.; Kite-Powell, A.; Rodgers, L.; Adjemian, J.; et al. Emergency Department Visits for Suspected Suicide Attempts Among Persons Aged 12–25 Years Before and During the COVID-19 Pandemic—United States, January 2019–May 2021. *MMWR Recomm. Rep.* **2021**, *70*, 888–894. [CrossRef]
14. Gracia, R.; Pamias, M.; Mortier, P.; Alonso, J.; Pérez, V.; Palao, D. Is the COVID-19 pandemic a risk factor for suicide attempts in adolescent girls? *J. Affect. Disord.* **2021**, *292*, 139–141. [CrossRef] [PubMed]
15. Miller, A.B.; Esposito-Smythers, C.; Weismoore, J.T.; Renshaw, K.D. The Relation between Child Maltreatment and Adolescent Suicidal Behavior: A Systematic Review and Critical Examination of the Literature. *Clin. Child Fam. Psychol. Rev.* **2013**, *16*, 146–172. [CrossRef] [PubMed]
16. Angelakis, I.; Gillespie, E.L.; Panagioti, M. Childhood maltreatment and adult suicidality: A comprehensive systematic review with meta-analysis. *Psychol. Med.* **2019**, *49*, 1057–1078. [CrossRef] [PubMed]
17. Liu, R.T.; Miller, I. Life events and suicidal ideation and behavior: A systematic review. *Clin. Psychol. Rev.* **2014**, *34*, 181–192. [CrossRef] [PubMed]
18. Steinberg, L. A Social Neuroscience Perspective on Adolescent Risk-Taking. *Dev. Rev.* **2008**, *28*, 78–106. [CrossRef]
19. Lang, C.M.; Sharma-Patel, K. The relation between childhood maltreatment and self-injury: A review of the literature on conceptualization and intervention. *Trauma Violence Abus.* **2011**, *12*, 23–37. [CrossRef] [PubMed]
20. Klonsky, E.D.; Victor, S.E.; Saffer, B.Y. Nonsuicidal self-injury: What we know, and what we need to know. *Can. J. Psychiatry.* **2014**, *59*, 565–568. [CrossRef] [PubMed]
21. Grandclerc, S.; De Labrouhe, D.; Spodenkiewicz, M.; Lachal, J.; Moro, M.-R. Relations between Nonsuicidal Self-Injury and Suicidal Behavior in Adolescence: A Systematic Review. *PLoS ONE* **2016**, *11*, e0153760. [CrossRef] [PubMed]
22. Hamza, C.A.; Stewart, S.L.; Willoughby, T. Examining the link between nonsuicidal self-injury and suicidal behavior: A review of the literature and an integrated model. *Clin. Psychol. Rev.* **2012**, *32*, 482–495. [CrossRef]
23. Mars, B.; Heron, J.; Klonsky, D.E.; Moran, P.; O'connor, R.C.; Tilling, K.; Wilkinson, P.; Gunnell, D. Predictors of future suicide attempt among adolescents with suicidal thoughts or non-suicidal self-harm: A population-based birth cohort study. *Lancet Psychiatry* **2019**, *6*, 327–337. [CrossRef]
24. Asarnow, J.R.; Porta, G.; Spirito, A.; Emslie, G.; Clarke, G.; Wagner, K.D.; Vitiello, B.; Keller, M.; Birmaher, B.; McCracken, J.; et al. Suicide attempts and nonsuicidal self-injury in the treatment of resistant depression in adolescents: Findings from the TORDIA study. *J. Am. Acad. Child Adolesc. Psychiatry* **2011**, *50*, 772–781. [CrossRef] [PubMed]
25. Nock, M.K. Self-Injury. *Annu. Rev. Clin. Psychol.* **2010**, *6*, 339–363. [CrossRef] [PubMed]
26. Johnson, J.G.; Cohen, P.; Brown, J.; Smailes, E.M.; David, M.; Bernstein, P. Childhood Maltreatment Increases Risk for Personality Disorders During Early Adulthood. *Arch. Gen. Psychiatry* **1999**, *56*, 600–606. [CrossRef] [PubMed]

27. Porter, C.; Palmier-Claus, J.; Branitsky, A.; Mansell, W.; Warwick, H.; Varese, F. Childhood adversity and borderline personality disorder: A meta-analysis. *Acta Psychiatr. Scand.* **2020**, *141*, 6–20. [CrossRef] [PubMed]
28. Myers, J.; Berliner, L.; Briere, J.; Hendrix, C.; Reid, T.; Jenny, C. *The APSAC Handbook on Child Maltreatment*, 2nd ed.; Sage Publications: Thousand Oaks, CA, USA, 2002.
29. Ford, J.D.; Courtois, C.A. Complex PTSD and borderline personality disorder. *Borderline Personal. Disord. Emot. Dysregul.* **2021**, *8*, 1–21. [CrossRef] [PubMed]
30. Crowell, S.E.; Beauchaine, T.P.; Linehan, M.M. A Biosocial Developmental Model of Borderline Personality: Elaborating and Extending Linehan's Theory NIH Public Access. *Psychol. Bull.* **2009**, *135*, 495–510. [CrossRef] [PubMed]
31. Allen, K.J.D.; Bozzay, M.L.; Edenbaum, E.R. Neurocognition and Suicide Risk in Adults. *Curr. Behav. Neurosci. Rep.* **2019**, *6*, 151–165. [CrossRef]
32. Allen, B.; Cramer, R.J.; Harris, P.B.; Katrina, A. Archives of Suicide Research Borderline Personality Symptomatology as a Mediator of the Link between Child Maltreatment and Adult Suicide Potential. *Arch. Suicide Res.* **2013**, *17*, 37–41. [CrossRef]
33. Charak, R.; Koot, H.M. Severity of maltreatment and personality pathology in adolescents of Jammu, India: A latent class approach. *Child Abuse Negl.* **2015**, *50*, 56–66. [CrossRef]
34. Paris, J. Suicidality in Borderline Personality Disorder. *Medicina* **2019**, *55*, 223. [CrossRef] [PubMed]
35. Yen, S.; Weinstock, L.M.; Andover, M.S.; Sheets, E.S.; Selby, E.A.; Spirito, A. Prospective predictors of adolescent suicidality: 6-month post-hospitalization follow-up. *Psychol. Med.* **2013**, *43*, 983–993. [CrossRef]
36. Krueger, R.F.; Carlson, S.R. Personality Disorders in Children and Adolescents. *Curr. Psychiatry Rep.* **2001**, *3*, 46–51. [CrossRef] [PubMed]
37. Miller, A.L.; Muehlenkamp, J.J.; Jacobson, C.M. Fact or fiction: Diagnosing borderline personality disorder in adolescents. *Clin. Psychol. Rev.* **2008**, *28*, 969–981. [CrossRef] [PubMed]
38. Laurenssen, E.M.P.; Hutsebaut, J.; Feenstra, J.; Jurgen, J.; Busschbach, V.; Luyten, P. Diagnosis of Personality Disorders in Adolescents: A Study among Psychologists. *Child Adolesc. Psychiatry Mental Health* **2013**, *7*, 3. [CrossRef] [PubMed]
39. Winsper, C.; Marwaha, S.; Lereya, S.T.; Thompson, A.; Eyden, J.; Singh, S.P. Clinical and psychosocial outcomes of borderline personality disorder in childhood and adolescence: A systematic review. *Psychol. Med.* **2015**, *45*, 2237–2251. [CrossRef] [PubMed]
40. Looper, K.J.; Paris, J. What dimensions underlie cluster B personality disorders? *Compr. Psychiatry* **2000**, *41*, 432–437. [CrossRef] [PubMed]
41. Yen, S.; Frazier, E.; Hower, H.; Weinstock, L.M.; Topor, D.R.; Hunt, J.; Goldstein, T.R.; Goldstein, B.I.; Gill, M.K.; Ryan, N.D.; et al. Borderline personality disorder in transition age youth with bipolar disorder. *Acta Psychiatr. Scand.* **2015**, *132*, 270–280. [CrossRef] [PubMed]
42. Guilé, J.M.; Boissel, L.; Alaux-Cantin, S.; de La Rivière, S.G. Borderline personality disorder in adolescents: Prevalence, diagnosis, and treatment strategies. *Adolesc. Health Med. Ther.* **2018**, *9*, 199–210. [CrossRef] [PubMed]
43. Thomassin, K.; Shaffer, A.; Madden, A.; Londino, D.L. Specificity of childhood maltreatment and emotion deficit in nonsuicidal self-injury in an inpatient sample of youth. *Psychiatry Res.* **2016**, *244*, 103–108. [CrossRef] [PubMed]
44. Hatkevich, C.; Penner, F.; Sharp, C. Difficulties in emotion regulation and suicide ideation and attempt in adolescent inpatients. *Psychiatry Res.* **2019**, *271*, 230–238. [CrossRef]
45. Weissman, D.G.; Bitran, D.; Miller, A.B.; Schaefer, J.D.; Sheridan, M.A.; McLaughlin, K.A. Difficulties with emotion regulation as a transdiagnostic mechanism linking child maltreatment with the emergence of psychopathology. *Dev. Psychopathol.* **2019**, *31*, 899–915. [CrossRef]
46. Carver, C.S.; Johnson, S.L.; Timpano, K.R. Toward a Functional View of the P Factor in Psychopathology. *Clin. Psychol. Sci. Pract.* **2017**, *5*, 880–889. [CrossRef] [PubMed]
47. Marques-Feixa, L.; Palma-Gudiel, H.; Romero, S.; Moya-Higueras, J.; Rapado-Castro, M.; Castro-Quintas, Á.; Zorrilla, I.; José Muñoz, M.; Ramírez, M.; Mayoral, M.; et al. Childhood maltreatment disrupts HPA-axis activity under basal and stress conditions in a dose-response relationship in children and adolescents. *Psychol. Med.* **2021**, *16*, 1–14. [CrossRef]
48. De la Peña, F.R.; Villavicencio, L.R.; Palacio, J.D.; Félix, F.J.; Larraguibel, M.; Viola, L.; Ortiz, S.; Rosetti, M.; Abadi, A.; Montiel, C.; et al. Validity and reliability of the kiddie schedule for affective disorders and schizophrenia present and lifetime version DSM-5 (K-SADS-PL-5) Spanish version. *BMC Psychiatry* **2018**, *18*, 1–7. [CrossRef]
49. APA: American Psychiatric Association. *DSM-5: Diagnostic and Statistical Manual of Mental Disorders*, 5th ed.; American Psychiatric Publishing: Washington, DC, USA, 2013.
50. Spinazzola, J.; Habib, M.; Blaustein, M.; Knoverek, A.; Kisiel, C.; Stolbach, B.; Abramovitz, R.; Kagan, R.; Lanktree, C.; Maze, J. *What Is Complex Trauma: A Resource Guide for Youth and Those Who Care about Them*; National Center for Child Traumatic Stress: Los Angeles, CA, USA; Durham, NC, USA, 2017.
51. CARM Instrumento para la valoración de la gravedad de las situaciones de desprotección infantil (Tool for assessing the severity of situations in which children are vulnerable- TASSCV). *Serv. Soc. Atención Primaria y Espec. la Región Muricia*. 2012. Available online: https://www.carm.es/web/pagina?IDCONTENIDO=9415&IDTIPO=246&RASTRO=c886$m5855 (accessed on 5 August 2021).
52. Bernstein, D.P.; Stein, J.A.; Newcomb, M.D.; Walker, E.; Pogge, D.; Ahluvalia, T.; Stokes, J.; Handelsman, L.; Medrano, M.; Desmond, D.; et al. Development and validation of a brief screening version of the Childhood Trauma Questionnaire. *Child Abus. Negl.* **2003**, *27*, 169–190. [CrossRef]

53. Kaess, M.; Parzer, P.; Mattern, M.; Resch, F.; Bifulco, A.; Brunner, R. Childhood Experiences of Care and Abuse (CECA)—Validation of the German version of the questionnaire and interview, and results of an investigation of correlations between adverse childhood experiences and suicidal behaviour. *Z. Kinder. Jugendpsychiatr. Psychother.* **2011**, *39*, 243–252. [CrossRef] [PubMed]
54. Petrides, K.V. Psychometric properties of the Trait Emotional Intelligence Questionnaire (TEIQue). In *Advances in the Assessment of EI*; Stough, C., Saklofske, D.H., Park, J.D., Eds.; Springer: New York, NY, USA, 2009. [CrossRef]
55. Mavroveli, S.; Petrides, K.V.; Shove, C.; Whitehead, A. Investigation of the construct of trait emotional intelligence in children. *Eur. Child Adolesc. Psychiatry* **2008**, *17*, 516–526. [CrossRef] [PubMed]
56. Benito, S.; Perez-Gonzalez, J. Adaptación Española del Cuestionario Para Niños de Inteligencia Emocional Como Rasgo (TEIQue-CSF) en Forma Corta Para Padres [Internet]. Facultad de Educación, UNED, 2011. Available online: https://dialnet.unirioja.es/servlet/tesis?codigo=26929 (accessed on 20 April 2016).
57. Lacalle Sistere, M.; Domenech Massons, J.M.; Granero Perez, R.; Ezpeleta Ascaso, L. Validity of the DSM-Oriented Scales of the Child Behavior Checklist and Youth Self-Report. *Psicothema* **2014**, *26*, 364–371. [CrossRef] [PubMed]
58. Achenbach, T.M.; Rescorla, L. *Manual for the ASEBA School-Age Forms & Profiles: An Integrated System of Multi-Informant Assessment*; University of Vermont, Research Center for Children, Youth, & Families: Burlington, VT, USA, 2001; ISBN 0176085890/9780176085896.
59. McGonigal, P.T.; Dixon-Gordon, K.L. Anger and Emotion Regulation Associated with Borderline and Antisocial Personality Features within a Correctional Sample. *J. Correct. Health Care* **2020**, *26*, 215–226. [CrossRef] [PubMed]
60. Moya-Higueras, J.; Cuevas, A.; Marques-Feixa, L.; Mezquita, L.; Mayoral, M.; Fañanás, L.; Ortet, G.; Ibáñez, M.I. Recent Stressful Life Events (SLE) and Adolescent Mental Health: Initial Validation of the LEIA, a New Checklist for SLE Assessment According to Their Severity, Interpersonal, and Dependent Nature. *Assessment* **2020**, *27*, 177–1795. [CrossRef] [PubMed]
61. Bentler, P. *EQS Structural Equations Program Manual*; Multivariate Software: Encino, CA, USA, 2006.
62. Barrett, P. Structural equation modelling: Adjudging model fit. *Pers. Individ. Dif.* **2007**, *42*, 815–824. [CrossRef]
63. Schweizer, K. Some guidelines concerning the modeling of traits and abilities in test construction. *Eur. J. Psychol. Assess.* **2010**, *26*, 1–2. [CrossRef]
64. Lemaigre, C.; Taylor, E.P. Mediators of childhood trauma and suicidality in a cohort of socio-economically deprived Scottish men. *Child Abus. Negl.* **2019**, *88*, 159–170. [CrossRef]
65. Sigfusdottir, I.D.; Asgeirsdottir, B.B.; Gudjonsson, G.H.; Sigurdsson, J.F. Suicidal ideations and attempts among adolescents subjected to childhood sexual abuse and family conflict/violence: The mediating role of anger and depressed mood. *J. Adolesc.* **2013**, *36*, 1227–1236. [CrossRef] [PubMed]
66. Braquehais, M.D.; Oquendo, M.A.; Baca-García, E.; Sher, L. Is impulsivity a link between childhood abuse and suicide? *Compr. Psychiatry* **2010**, *51*, 121–129. [CrossRef] [PubMed]
67. Falgares, G.; Marchetti, D.; Manna, G.; Musso, P.; Oasi, O.; Kopala-Sibley, D.C.; De Santis, S.; Verrocchio, M.C. Childhood Maltreatment, Pathological Personality Dimensions, and Suicide Risk in Young Adults. *Front. Psychol.* **2018**, *9*, 806. [CrossRef] [PubMed]
68. Rogosch, F.A.; Cicchetti, D. Child maltreatment and emergent personality organization: Perspectives from the five-factor model. *J. Abnorm. Child Psychol.* **2004**, *32*, 123–145. [CrossRef] [PubMed]
69. Laget, J.; Plancherel, B.; Stéphan, P.; Bolognini, M.; Corcos, M.; Jeammet, P.; Halfon, O. Personality and repeated suicide attempts in dependent adolescents and young adults. *Crisis* **2006**, *27*, 164–171. [CrossRef]
70. Turton, H.; Berry, K.; Danquah, A.; Pratt, D. The relationship between emotion dysregulation and suicide ideation and behaviour: A systematic review. *J. Affect. Disord. Rep.* **2021**, *5*, 100136. [CrossRef]
71. Braquehais, M.D.; Picouto, M.D.; Casas, M.; Sher, L. Hypothalamic-pituitary-adrenal axis dysfunction as a neurobiological correlate of emotion dysregulation in adolescent suicide. *World J. Pediatr.* **2012**, *8*, 197–206. [CrossRef] [PubMed]
72. Allen, K.J.D.; Bozzay, M.L.; Armey, M.F.; Nugent, N.R.; Miller, I.W.; Schatten, H.T. Childhood Maltreatment, Emotional Response Inhibition, and Suicide in Psychiatric Inpatients. *Behav. Ther.* **2021**, *52*, 1529–1542. [CrossRef]
73. Paul, E.; Ortin, A. Psychopathological mechanisms of early neglect and abuse on suicidal ideation and self-harm in middle childhood. *Eur. Child Adolesc. Psychiatry* **2019**, *28*, 1311–1319. [CrossRef]
74. Lavi, I.; Katz, L.F.; Ozer, E.J.; Gross, J.J. Emotion Reactivity and Regulation in Maltreated Children: A Meta-Analysis. *Child Dev.* **2019**, *90*, 1503–1524. [CrossRef] [PubMed]
75. March-Llanes, J.; Marques-Feixa, L.; Mezquita, L.; Fañanás, L.; Moya-Higueras, J. Stressful life events during adolescence and risk for externalizing and internalizing psychopathology: A meta-analysis. *Eur. Child Adolesc. Psychiatry* **2017**, *26*, 1409–1422. Available online: http://www.ncbi.nlm.nih.gov/pubmed/28502034 (accessed on 28 August 2021). [CrossRef] [PubMed]
76. Hammen, C. Stress and depression. *Annu. Rev. Clin. Psychol.* **2005**, *1*, 293–319. [CrossRef] [PubMed]
77. Wildschut, M.; Swart, S.; Langeland, W.; Smit, J.H.; Draijer, N. An Emotional Neglect-Personality Disorder Approach: Quantifying a Dimensional Transdiagnostic Model of Trauma-Related and Personality Disorders. *J. Pers. Disord.* **2020**, *34*, 250–261. [CrossRef] [PubMed]
78. You, Z.; Chen, M.; Yang, S.; Zhou, Z.; Qin, P. Childhood adversity, recent life stressors and suicidal behavior in Chinese college students. *PLoS ONE* **2014**, *9*, e86672. [CrossRef]

79. Duprey, E.B.; Handley, E.D.; Manly, J.T.; Cicchetti, D.; Toth, S.L. Child maltreatment, recent stressful life events, and suicide ideation: A test of the stress sensitivity hypothesis. *Child Abuse Negl.* **2021**, *113*, 104926. [CrossRef] [PubMed]
80. Moreno-Alcázar, A.; Treen, D.; Valiente-Gómez, A.; Sio-Eroles, A.; Pérez, V.; Amann, B.L.; Radua, J. Efficacy of Eye Movement Desensitization and Reprocessing in Children and Adolescent with Post-traumatic Stress Disorder: A Meta-Analysis of Randomized Controlled Trials. *Front. Psychol.* **2017**, *8*, 1750. [CrossRef] [PubMed]
81. Santamarina-Perez, P.; Mendez, I.; Singh, M.K.; Berk, M.; Picado, M.; Font, E.; Moreno, E.; Martínez, E.; Morer, A.; Borràs, R.; et al. Adapted Dialectical Behavior Therapy for Adolescents with a High Risk of Suicide in a Community Clinic: A Pragmatic Randomized Controlled Trial. *Suicide Life-Threat. Behav.* **2020**, *50*, 652–667. [CrossRef] [PubMed]
82. Bohus, M.; Priebe, K. DBT–PTSD: A treatment Programme for complex PTSD after childhood abuse. In *The Oxford Handbook of Dialectical Behaviour Therapy*; Swales, M.A., Ed.; Oxford University Press: Oxford, UK, 2018.
83. Choi, H.; Lee, W.; Heo, S.; Kim, J. The Efficacy of Psychological Interventions for Complex Trauma: A Systematic Review and Meta-Analysis. *Korean J. Clin. Psychol.* **2020**, *39*, 164–199. [CrossRef]
84. Taris, T.W. Work & Stress Cause and effect: Optimizing the designs of longitudinal studies in occupational health psychology. *J. Occup. Health Psychol.* **1996**, *1*, 145. [CrossRef]
85. Kaess, M.; Brunner, R.; Chanen, A. Borderline Personality Disorder in Adolescence. *Pediatrics* **2014**, *134*, 782–793. [CrossRef] [PubMed]
86. Blasco-Fontecilla, H.; Delgado-Gomez, D.; Legido-Gil, T.; de Leon, J.; Perez-Rodriguez, M.M.; Baca-Garcia, E. Can the Holmes-Rahe Social Readjustment Rating Scale (SRRS) Be Used as a Suicide Risk Scale? An Exploratory Study. *Arch. Suicide Res.* **2012**, *16*, 13–28. [CrossRef] [PubMed]
87. Smith Benjamin, L. *Interpersonal Diagnosis and Treatment of Personality Disorders*, 2nd ed.; University of UTAH. Guilford Press: New York, NY, USA; London, UK, 2003; ISBN 1-57230-860-5.

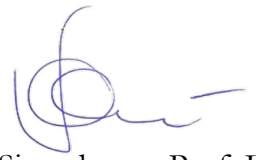
UNIVERSITAT DE BARCELONA

Dr. Lourdes Fañanás Saura
Unitat de Zoologia i Antropologia Biològica
Dept. Biologia Evolutiva, Ecologia i Ciències Ambientals
Facultat de Biologia, Universitat de Barcelona

Informe del director sobre la contribución del doctorando al artículo.

La Prof. Lourdes Fañanás Saura, profesora del Departamento de Biología Evolutiva, Ecologia y Ciencias Ambientales de la Facultad de Biología (Universitat de Barcelona) y directora de la presente tesis doctoral de Laia Marques Feixa, por la presente certifica que ninguno de los coautores del articulo *"Risk of suicidal behavior in children and adolescents exposed to maltreatment: the mediating role of borderline personality traits and recent stressful life events",* ha utilizado esta publicacion para una tesis doctoral, y que la participación del solicitante en este artículo incluyó las siguientes tareas:

- Participación en la concepción y diseño del estudio.
- Reclutamiento y evaluación de los sujetos incluidos.
- Coordinación del proyecto.
- Preparación de los datos.
- Análisis estadísticos e interpretación de los datos.
- Redacción del manuscrito.
- Revisión crítica del artículo por contenido intelectual.



Signado por Prof. Lourdes Fañanás

Barcelona, abril 2022

3.4. **Reinforcing the new diagnosis of Complex Post-Traumatic Stress disorder (CPTSD) of ICD-11 in children and adolescents exposed to relational trauma: developmental stage at exposure and its associated clinical outcomes**

Laia Marques-Feixa, Jorge Moya-Higueras, Soledad Romero, Pilar Santamarina-Pérez, Nerea San Martín-González, María José Muñoz, Eulalia Anglada, Hilario Blasco-Fontecilla, Marta Rapado-Castro, Iñaki Zorrilla, Maite Ramírez, Lourdes Fañanás y EPI-Young Stress GROUP.

Psychological medicine (submitted)

Reinforcing the new diagnosis of Complex Post-Traumatic Stress Disorder (CPTSD) of ICD-11 in children and adolescents exposed to relational trauma: developmental stage at exposure and its associated clinical outcomes

Laia Marques-Feixa[1, 2], Jorge Moya-Higueras [2, 3], Soledad Romero [2, 4, 5], Pilar Santamarina-Perez [4], Nerea San Martín-Gonzalez[1], María José Muñoz [6], Eulalia Anglada[7], Hilario Blasco-Fontecilla [2, 8], Marta Rapado-Castro [2, 9, 10], Iñaki Zorrilla[2, 11], Maite Ramírez [12], Lourdes Fañanás[1, 2]** and EPI-Young Stress GROUP

[1] Department of Evolutionary Biology, Ecology and Environmental Sciences, Faculty of Biology, University of Barcelona. Biomedicine Institute of the University of Barcelona, Barcelona, Spain.
[2] Network Centre for Biomedical Research in Mental Health (CIBER of Mental Health, CIBERSAM), Spain.
[3] Department of Psychology, Faculty of Education, Psychology and Social Work, University of Lleida. Spain
[4] Department of Child and Adolescent Psychiatry and Psychology, 2017SGR88, Institute of Neuroscience, Hospital Clínic de Barcelona, Barcelona, Spain
[5] Institut d'Investigacions Biomediques August Pi i Sunyer (IDIBAPS), Barcelona, Spain.
[6] Hospital Benito Menni, Adolescent Crisis Unit, Sant Boi de Llobregat, Spain.
[7] Day Hospital for Adolescents, Fundació Orienta, Gavà, Spain
[8] Department of Psychiatry, Puerta de Hierro University Hospital-Majadahonda, Autonoma University, ITA Mental Health, Madrid, Spain.
[9] Department of Child and Adolescent Psychiatry, Hospital General Universitario Gregorio Marañón, School of Medicine, Universidad Complutense, IiSGM, Madrid, Spain.
[10] Melbourne Neuropsychiatry Centre, Department of Psychiatry, The University of Melbourne & Melbourne Health, Victoria, Australia
[11] Hospital Santiago Apostol, Department of Psychiatry, Vitoria-Gasteiz, Spain.
[12] Day Hospital for Adolescents OSI Barrualde-Galdakao, Mental Health Services, Child and Adolescent Mental Health, Galdakao, Spain.
[13] College of Public Health and Health Professions, Department of Epidemiology, University of Florida, United States of America
[14] Department of Psychiatry, Hospital Universitari Vall d'Hebron, Barcelona, Spain.

Corresponding author **:
Lourdes Fañanás Saura
Faculty of Biology, University of Barcelona
Av Diagonal 643, 2n A, Barcelona
lfananas@ub.edu

ABSTRACT

Background: Children and adolescents exposed to childhood maltreatment (CM) show an increased risk of psychiatric morbidity. The new Complex Post-Traumatic Stress Disorder (CPTSD) diagnosis of the ICD-11 captures the heterogeneity and complexity of clinical outcomes observed in subjects exposed to early relational trauma. This study aims to explore CPTSD symptomatology of youth exposed to CM and its association with clinical outcomes, considering the impact of CM subtypes and the age of exposure.

Methods: 187 youth aged 7-17 were studied (116 with current psychiatric disorder and 71 healthy controls). Different types of CM were evaluated following TASSCV structured interview criteria. CPTSD symptomatology was explored by a confirmatory factor analysis, considering four subdomains: stress post-traumatic symptoms, emotion dysregulation, negative self-concept and interpersonal problems. Youth's current and past clinical outcomes were also explored.

Results: Youth exposed to CM (with or without current psychiatric disorders) showed greater internalizing, externalizing and other symptomatology, worst premorbid adjustment and poorest overall functioning. Patients exposed to CM reported more psychiatric comorbidity, CPTSD symptomatology, greater polypharmacy prescription and earlier onset of illegal drug abuse. Secondary analyses showed that different subtypes of CM and developmental period of exposure have a differential impact on all CPTSD subdomains.

Conclusion: CM negatively affects the mental health of children and adolescents with diverse psychiatric diagnosis, although alterations are also present in healthy subjects. The inclusion of the CPTSD diagnosis in mental disorders manuals should increase the implementation of early specific relational trauma interventions, improving victims' lives and reducing the risk of worse clinical outcomes.

KEYWORDS: childhood maltreatment (CM), complex trauma, Complex PTSD (CPTSD), age of CM exposure, poor outcomes, internalizing, externalizing, youth psychopathology.

INTRODUCTION

Exposure to childhood adverse experiences might predispose individuals to an increased vulnerability to develop different psychiatric disorders, soon after traumatic experiences but also throughout lifespan (Heim et al., 2010; Scott et al., 2010; Teicher and Samson, 2013). Indeed, adverse childhood experiences are associated with up to 45% of all childhood onset psychiatric disorders and with around 30% of later-onset non-specific psychiatric disorders (Green et al., 2010). Furthermore, the evidence suggests that the psychological outcomes observed may depend upon the nature, timing, chronicity and severity of the adverse experiences (Hughes et al., 2017; Jonson-Reid et al., 2012).

Although childhood maltreatment (CM) is considered a severe problem worldwide, with remarkably high prevalence rates (Akmatov, 2011), a noteworthy number of cases remain unreported, since victims are typically reluctant to disclose their CM experiences (Radford et al., 2011). In addition, clinicians often report not being sufficiently prepared to capture and adequately respond to these situations or revelations. For that reason, trauma histories remain unnoticed for many years, leading to misdiagnosis that cause noticeable stress in victims, since they are catalogued with diagnostic labels which are not sufficient to support the person with an integrative and holistic view.

Recent studies estimated that 70% of the world's population has experienced at least one

traumatic event (Kessler et al., 2017). Some people, after suffering or witnessing a terrifying event characterized for being intense and acute (defined as Trauma with capital T, e.g., serious injury accidents, sexual violence or witnessing of death), may experience post-traumatic symptoms, such as unwanted and upsetting memories or flashbacks, avoidance of any reminder of the event, as well as various mood and functional impairments (APA: American Psychiatric Association, 1980). However, numerous clinicians soon realized that the Post-traumatic Stress Disorder (PTSD) diagnosis did not quite fit in explaining the complex symptoms expressed by people exposed to severe prolonged, multiple or repeated traumatic events (Van der Kolk and Najavits, 2013). In this regard, complex trauma (also named interpersonal trauma or little "t" trauma) refers to multiple traumatic events of a long-lasting, invasive and primarily interpersonal nature, of which escaping is difficult or impossible, since they usually arise as a result of close relationships (e.g., neglect, child abuse or intimate domestic violence) (Cook et al., 2012). The literature on this topic highlights the wide-ranging and long-lasting consequences of complex trauma, which interfere with child's ability to form a secure attachment and alter many aspects of child's development that rely on this primary source of safety, stability and the formation of a sense of self (De Bellis and Zisk, 2014). In fact, according to official data, after exposure to complex trauma, the percentage of youth who develop PTSD is low since most of them meet criteria for many other diagnoses (Jaffee, 2017).

In this regard, in 1992, Herman introduced the concept of Complex-PTSD (CPTSD) (Herman, 1992) and Van der Kolk (2005) also proposed the concept Complex Developmental Trauma to refer the particular effects of relational trauma in children, highlighting the diagnostic problem of these youths who often received inaccurate diagnoses. Although in the last decades many investigations of trauma-related symptoms demonstrated different empirical CPTSD models (Cloitre et al., 2013; Karatzias et al., 2017; Knefel et al., 2015), this diagnosis was not recognized in the last version of DSM-5 (APA, 2013). However, the World Health Organization (WHO) finally recognized CPTSD as a diagnostic entity distinct from the PTSD, and it will appear in the latest version of the ICD-11 manual (WHO, 2019). Briefly, CPTSD has been defined as the presence of the three domains of classic PTSD (traumatic re-experiencing, avoidance of traumatic reminders and hypervigilance), along with three self-organization disturbances (SOD): emotional dysregulation, negative self-concept and interpersonal problems. Nevertheless, studies addressing CPTSD in child and adolescent populations are still scarce (Elliott et al., 2021; Haselgruber et al., 2021; Sachser et al., 2017; Villalta et al., 2020).

This new approach may elucidate and improve diagnoses and treatments in patients with CM history, especially of those who have been primarily treated for other comorbid psychiatric disorders with poor outcomes. In fact, different studies support that adult psychiatric patients with a history of CM show a distinct ecophenotype characterized by an earlier onset, worse symptom severity and comorbidity, the need for higher medication dosage, increased suicidal behaviours, and more frequent and longer hospitalizations (Read et al., 2005; Teicher and Samson, 2013). It could be hypothesized that this worse prognostic could be due to the self-organization disturbances (SOD) described by

the new CPTSD diagnosis. Furthermore, it is of great interest to explore whether the nature of CM (e.g., neglect versus abuse; and physical versus emotional or sexual) and the developmental period of exposure may produce differential alterations on brain development and CPTSD subdomains. Elucidating these mechanisms may enhance the development of new target interventions for children and adolescents with mental health problems and CM history.

The aims of this study have been designed in order to answer the following questions:

Aim I: Do youths with a history of CM, regardless of whether they have a psychiatric diagnosis, show higher internalizing, externalizing and other symptomatology and worst global functioning? Have youths with CM a more severe symptomatology, higher diagnostic comorbidity, more drug prescriptions, and earlier onset of illegal drug use?

Aim II: Is the new CPTSD diagnosis present in children and adolescents with other psychiatric disorders with a CM history? Specifically, (a) do all CM subtypes (emotional neglect, physical neglect, emotional abuse, physical abuse and sexual abuse) increase the symptomatology of CPTSD? and (b) Is the developmental stage in which CM takes place relevant to the manifestation of each CPTSD subdomain?

MATERIALS AND METHODS

Participants

The sample was recruited as a part of a cohort study exploring the psycho-neuro-biological consequences of CM (EPI_young_stress project), carried out from April 2016 to March 2020. Participants were 187 children and adolescents aged 7-17 years: 116 were diagnosed with a current psychiatric disorder and 71 were healthy controls (see Table 1). Healthy controls were recruited via advertisements, primary healthcare centers, schools and other community facilities. Youths with a current psychiatric diagnosis were recruited from six child and adolescent psychiatry departments in Spain (inpatients, outpatients and partial programs). Due to the complex and heterogeneous symptomatology observed in people exposed to trauma during nurture, our study adopted a transdiagnostic approach, including a wide range of mental health problems. The exclusion criteria for all participants included the diagnosis of an autism spectrum disorder, underweight anorexia nerviosa, intellectual disability (IQ < 70), current drug dependence (not abuse), not being fluent in Spanish, extreme premature birth (<1500 g), head injury with loss of consciousness, and severe neurological or other pathological conditions (such as epilepsy, cancer or autoimmune diseases). The Ethical Review Board of each hospital and university involved in the project approved this study. Further details about the nature of the study have been described elsewhere (Marques-Feixa et al., 2021b).

Assessment measures

Sociodemographic and anthropometric

The interview package comprised basic demographic information, including socioeconomic status (SES) based on the Hollingshead Four-Factor Index of SES (Hollingshead, 1975). Developmental stage was assessed using the Tanner staging questionnaire (Morris and Udry, 1980) and participants were later classified as either children (Tanner stages 1–3) or adolescents (Tanner stages 4–5).

Childhood maltreatment (CM) experiences

To assess features of CM, we used the instrument "Tool for assessing the severity of situations in which children are vulnerable" (TASSCV), which is a semi-structured interview that has been validated by professionals working in child and adolescent care in Spain. This instrument is detailed elsewhere (Marques-Feixa et al., (2021b) and available online in Spanish (CARM, 2012). For the present report, data concerning five main types of CM were included: emotional neglect, physical neglect, emotional abuse, physical abuse and sexual abuse. The timing of exposure to each CM subtype was later classified as experienced (absence/presence) during early childhood (0-5 years), school-aged childhood (6-12 years) or adolescence (13-17 years). Additionally, since assessing the history of CM on a continuum spectrum allows a more complete understanding of participants' complex trauma, a CM-score was created. Thus, for each CM subtype, the reported severity (from 1 to 4) was multiplied by the reported frequency (from 1 to 4), obtaining a final CM-score for each participant ranging from 0 (absence of CM) to 80 (extreme and frequent CM in all the subtypes) (see Figure 1).

Internalizing and externalizing symptomatology (CBCL)

The Child Behavior Checklist 6–18 (CBCL) is a parent-reported inventory, which assesses the competencies, behavioral, emotional and social problems in children and adolescents aged 6 to 18 years (Achenbach and Rescorla, 2001; Lacalle Sistere et al., 2014). The CBCL scores comprise several subscales. In the present study, we included the following scales: Internalizing, Externalizing and Others, encompassed in a Total problems score.

Premorbid adjustment and general functioning

The Premorbid Adjustment Scale (PAS), which evaluates the degree of achievement of different developmental goals, includes rating scales about five domains of functioning: sociability and withdrawal, peer relationships, scholastic performance, adaptation to school and social-sexual aspects of life (Cannon-Spoor et al., 1982). The PAS included in the present study covers two periods of development: childhood (up to age 11) and early adolescence (12 to 15).

The global level of functioning and impairment was measured by the Children's Global Assessment Scale (CGAS) (Shaffer et al., 1983). CGAS provides a single score (1-100), based on a clinician's assessment of a variety of aspects related to a child's psychological and social functioning (adaptation at school and at home, social life, hobbies, self-confidence, aggressiveness, autonomy, emotional distress, etc.).

Current psychiatric diagnostics and clinical outcomes

Present and lifetime psychopathology was ascertained using the Spanish version of the Kiddie-Schedule for Affective Disorders and Schizophrenia for School- Age Children Version DSM-5 (K-SADS-PL-5) (APA, 2013; De la Peña et al., 2018).

Psychiatric diagnoses of each participant, both currently and throughout lifespan, were reported by clinicians (or confirmed by caregivers in control subjects). The number of diagnoses obtained during lifetime was coded as "lifetime psychiatric diagnosis" (ranged from 0 to 7). The total number of current psychiatric disorders of each participant was called "Psychiatric comorbidity" (ranged from 0 to 5). Additionally, information about current prescribed psychiatric medication was collected (labeled as antipsychotics, antidepressants, anxiolytics, mood stabilizers,

psychostimulants or others). Besides the dichotomized variable of "use of psychiatric drugs" (absence/presence), the term "polypharmacy" was included as the combined use of psychiatric drugs from different classes, calculated according to the sum of six types of psychotropic drugs prescribed daily. Moreover, first age of use of any illegal drug was extracted from K-SADS-PL5.

Complex post-traumatic stress disorder (CPTSD) symptomatology

Since CPTSD is a psychiatric diagnosis recently included in ICD-11 and, at the time of the current study, there was not a valid and reliable instrument for CPTSD, additional analyses were performed to obtain a proxy of these symptomatology (details in supplementary material). Briefly, following ICD-11 criteria, in the present study 28 items from two different measures were collected as a proxy of CPTSD (14 items for PTSD and 14 items for SOD). For detailed information about the questionnaires used and statistics of the confirmatory factorial analysis (CFA), see supplementary material. In summary, to clarify the CPTSD multidimensional structure and examine the internal and external validity of the construct, a Confirmatory Factor Analysis (CFA) was conducted using the statistical software package EQS 6.1 (Bentler, 2006). Finally, the model created with an excellent fit was the 4-factor first order, which includes the following domains: PTSD, emotional dysregulation, negative self-concept and interpersonal problems.

Statistical analysis

Statistical analyses were performed using SPSS version 26 (IBM, Chicago, IL, USA). Student's t test for continues variables and chi-square test ($\chi 2$) for categorical variables were performed to compare cases and controls regarding demographic variables, CM history and CPTSD symptomatology (Table 1).

To explore our first aim, hierarchical regression analyses were performed to study the impact of CM-score in global functioning, symptomatology and clinical variables. Two levels were introduced as predictor variables: i) first level included: development stage, age, sex and SES, and ii) second level included the CM-score. Externally observed variables were considered as outcomes (PAS, CGAS, CBCL, lifetime psychiatric diagnosis, current psychiatric comorbidity, polypharmacy and first age of illegal drug use). To explore the differences in psychiatric drug prescription (absence/presence) predicted by CM-score, logistic regression analyses were conducted, also including as predictors the development stage, age, sex and SES.

To explore our second aim, an additional regression path was conducted to study the association between different forms of CM, periods of the exposure of each CM subtype, and CPTSD symptomatology. The four domains extracted for CPTSD (PTSD, emotional dysregulation, negative self-concept and interpersonal problems) were entered into the hierarchical regression analyses as outcomes. The predictive variables introduced in the first level were development stage, age, sex and SES. Then, CM variables (CM-score and CM subtypes (absence/presence of physical neglect, emotional neglect, emotional abuse, physical abuse, sexual abuse)) were introduced in the second level of the regression. Finally, we performed separated analyses introducing in different CM subtypes the absence/presence on each developmental period (0-5 years, 6-12 years, 13-17 years) in the second step. Due to the small percentage of CM experiences referred by control

participants (n=15), the statistics of the impact of CM and the period of exposure in CPTSD symptoms in this subgroup are detailed in supplementary material.

RESULTS

In our sample, 94 participants (50%) reported CM. Figure 1 shows the overlap of these CM subtypes. Participants with a current psychiatric disorder had lower SES, more CM experiences and increased CPTSD symptomatology compared to control subjects (see Table 1 for further details).

Aim I: CM, symptomatology and poor clinical outcomes and functioning

As can be seen in Table 2, patients exposed to CM showed worse premorbid adjustment before 11 years, which was maintained until adolescence. However, controls with CM history showed a worse premorbid adjustment only from adolescence on (12-15 years). The CGAS analysis indicated that participants with severe CM history (both cases and controls), showed a worst global functioning.

Our results indicate that between 12% and 15% of the general symptomatology assessed by CBCL was directly explained by CM history. Specifically, participants with psychiatric disorders exposed to CM showed statistically significant increased internalizing, externalizing and other symptomatology when compared with those without CM. Interestingly, similar results were obtained in the healthy control group, revealing that, although they did not fulfil diagnostic criteria for mental disorders, those with CM history showed statistically significant increased internalizing, externalizing and other symptomatology.

Furthermore, youth with worst CM history showed an increased number of different lifetime psychiatric diagnoses. Additionally, in cases, having a higher CM-score increased the number of current psychiatric comorbidity. Although there was not an effect of CM on psychiatric drugs intake (Wald = .371, p =.54; Exp (B) = 1.010, 95% CI (0.978, 1.044)), an increase of polypharmacy was observed in youth exposed to CM, consuming up to four different families of psychotropic. Results also showed an earlier age of onset of illegal drug use (cannabis in all subjects) in youth cases exposed to CM.

Aim II a: CPTSD symptomatology in subjects with psychiatric disorders exposed to CM

The second regression analyses explore the impact of CM on CPTSD domains (Table 3; control's data reported in supplementary material). Participants with current psychiatric disorders with greater CM-scores showed significantly higher punctuations in all CPTSD subdomains: PTSD symptoms, emotion dysregulation, negative self-concept and interpersonal problems. Particularly, all CM subtypes increased the probability of suffering from all CPTSD subdomains. Exceptionally, physical neglect and sexual abuse did not increase the risk of emotional dysregulation (see Table 3 and Figure 2).

Aim II b: The impact of developmental stage of CM exposure in CPTSD symptomatology: infancy, childhood or adolescence

The stage of development (0-5 years, 6-12 years or 13-17 years) in which CM subtypes occur might have a main effect in CPTSD subdomains (see Table 3 and Figure 2). The only CM subtype that constantly remains harmful, regardless of the developmental stage in which it occurs, is emotional neglect. Moreover, regarding PTSD symptomatology subdomain, physical neglect affects only if it

occurs during the first 5 years of life. In contrast, although physical, emotional and sexual abuse affect during all developmental periods, physical abuse is especially devastating if it occurs in the first 5 years of development, emotional abuse is especially critical during childhood (6-12 years) and sexual abuse when it occurs from age 6 to 17.

Regarding SOD subdomains, emotional neglect and abuse, and physical abuse had a strong impact on the emotional dysregulation, without detecting any particular stage of sensitivity during development. Neither physical neglect nor sexual abuse showed a significant impact on this domain. Secondly, regarding the negative self-concept, all subtypes of CM had a strong effect. Specifically, physical neglect appears to be of greater risk when it occurs during the first five years of life. However, no effects were found for a specific development stage of exposure in other CM subtypes (emotional neglect, emotional abuse, physical abuse and sexual abuse). Finally, all subtypes of CM produced disturbances on interpersonal problems. Physical neglect and emotional neglect produced interpersonal problems regardless of the age of exposure, while physical abuse especially affected when it occurred between 0-5 years, and emotional and sexual abuse when they occurred during childhood (6-12 years).

DISCUSSION

The present study demonstrates that CM experiences increase the expression of psychiatric symptomatology in a dose-response effect and worsen the global functioning of children and adolescents, independently of their current diagnostic status. Our findings also reinforce ICD-11's new diagnosis of CPTSD in youth with psychiatric disorders exposed to CM, as a useful label to detect underlying SOD of great relevance for the prognosis.

Regarding our fist aim, this study shows that, both for cases and control subjects, CM is associated with all types of symptomatology: internalizing (anxious-depressive and somatization), externalizing (behavioral disorders, aggressiveness, impulsiveness) and other (thought disturbances, social difficulties and attention problems).

This is in line with previous literature supporting that early maltreatment is a transdiagnostic risk factor that increases from 2 to 10-fold the risk for a wide range of mental disorders (Heim et al., 2010; Scott et al., 2010; Vachon et al., 2015). Furthermore, an increase in the number of lifetime and current psychiatric diagnoses has been detected in all participants with CM, highlighting the difficulty of clinicians to fit within conventional diagnostic boundaries in exposed youth. Thereby, CM might be a nonspecific amplifying factor that would "tip the balance" of inherited genetic susceptibilities for internalizing or externalizing spectra (Teicher and Samson, 2013). These findings also reveal that youth with CM, who do not still fulfil diagnostic criteria, already show greater global symptomatology than their non-exposed peers, bringing to light the importance of establishing preventive measures prior to psychiatric disorders onset. This highlights the relevance of training health professionals in the detection of CM and in intervention strategies focused on the aftermath of relational trauma.

As other authors point out, psychiatric patients with CM history might be the most resistant to conventional treatments and might present the worst outcomes (Lippard and Nemeroff, 2020; Teicher and Samson, 2013). This could be

already observed in both child and adolescent population, since this study shows that youth with CM history (especially those with more overlapping, severity and chronicity of CM) are characterized by having an earlier onset of worst premorbid adjustment, a worst global functioning and greater current psychiatric comorbidity compared to those without CM history. This is in agreement with the dose-response relationship between multiplicity of exposure to CM and disease outcomes that has been previously described (Anda et al., 2006; Janssen et al., 2004). Interestingly, our study also suggests that suffering CM does not determine the use of psychiatric drugs during treatment, but is associated with polypharmacy prescription. Thus, young people with a history of CM tend to be prescribed more drugs from different families when compared with other patients without CM, which is relevant in pediatric populations due to the consequences it may entail on their health (Horace and Ahmed, 2015). Polypharmacy is probably due to the difficulty of psychiatrists to treat the diverse and complex symptomatology expressed by youth, without being aware that these serious symptoms may actually hide the origin of their suffering. This would explain why psychiatric treatment often does not work with these patients, suggesting to prioritize the re-processing of complex trauma and associated SOD, beyond the symptoms or the forms that the expression of discomfort takes (Heim et al., 2010).

According to previous literature, childhood abuse, neglect and attachment disturbances create a "perfect storm" that can lead youths to be flooded with unwanted emotions, thoughts, and memories, which could lead to a wide range of dysfunctional avoidance or destructive behaviors in order to cope with distress and regulate their negative internal states (substance abuse, aggression, delinquency or suicidal behaviors (Briere and Scott, 2013; Herman, 1997; van der Kolk, 2005). In this line, this study supports that one of the most common avoidance behaviors carried out by adolescents, the illegal drug use, might appear earlier in youth exposed to CM. Cannabis abuse may be interpreted as an attempt to reduce the global internal discomfort, as a form of self-medication to "anesthetize" suffering. Additionally, that would suppose another risk factor for the onset of other serious psychopathological problems such as psychotic disorders (Forti et al., 2019), supporting the beginning of a self-reinforcing cycle between CM, maladaptive personality traits and exposure to new stressors or risk factors (Marques-Feixa et al., 2021a).

Secondly, the present study demonstrates that the four dimensions of the new CPTSD diagnosis are present in children and adolescents exposed to relational trauma with a great disparity of psychiatric disorders (behavioral, mood, anxious, psychotic, ADHD and others). These results go in line with the literature on this topic, which highlights the wide-ranging and long-lasting consequences of complex trauma as opposed to a single traumatic incident (Brewin et al., 2017; Redican et al., 2021). In fact, this new diagnosis may remark Self-Trauma Theory (Myers et al., 2002), which supports that CM affects core personality domains, altering the way we perceive and interpret the world around us, consequently affecting the way we respond to and manage future stressful situations (Allen et al., 2013). This set of symptoms (SOD) affects to essential aspects to live and adapt in society, which could underlie the worse global functioning previously described. The degree

to which SOD affect survivors' lives, more than PTSD itself, has a direct impact on clinical practice, since it facilitates diagnostic precision and the design of more personalized and effective treatments (Cloitre, 2020).

Finally, we aimed to explore whether the different types of CM could have a differential impact on the alteration of CPTSD domains, also depending of the developmental period of exposure (Hughes et al., 2017; Jonson-Reid et al., 2012). In our sample, emotional neglect seems to be the most prevalent CM subtype and contributes to all CPTSD subdomains throughout the entire development. Taken together within the broader CM literature, current findings support the notion that emotional violence (neglect or abuse) is equally potent, if not more, than physical or sexual abuse (e.g., (McGee et al., 1997; Spinazzola et al., 2014).

Although post-traumatic stress symptomatology was increased with all CM subtypes, the significant effect for physical neglect only appears when exposure occurred during infancy (0-5 years). Physical abuse seems to be detrimental throughout development in predicting PTSD, but appears to be especially harmful when it occurs also during 0-5 years, contrary to popular beliefs which state that events during first stages of life are less important. Interestingly, emotional abuse seems to be the type of CM that most explains the variability of PTSD symptoms (Hoeboer et al., 2021), contrary to the idea that it is more linked to sexual or physical abuse (Luthra et al., 2009). Besides, emotional abuse is especially sensitive to produce PTSD from the age of six (6-12 years), when language acquisition is already developed, and children can understand the meaning of hurtful words. As some studies also point out, childhood is a sensible stage of development for the intimate partner violence, considered a subtype of emotional abuse (Castro et al., 2017). In contrast, sexual abuse seems to be harmful and induce PTSD when occurs after 5 years and during adolescence, as other studies have previously described (Adams et al., 2018). This emphasizes the importance of introducing the study of developmental stage of CM exposure in clinical practice and future research.

On the other hand, we observed that almost all types of CM seem to be associated with SOD subdomains. Emotional violence (both neglect and abuse) and physical abuse affect the individual's ability to regulate their emotions during the entire development. Youths might feel emotionally overwhelmed when trauma - related distress exceeds their relative ability to handle that much situations, and they do not have healthy and safe role models to help them learn adaptive skills. In addition, physical abuse are often unpredictable behaviors from abuser caregivers that place the child in a feeling of uncertainty, generating also greater emotional destabilization. This goes in line with a recent meta-analysis which showed a strong association between complex trauma and emotion regulation difficulties in children and adolescents (Villalta et al., 2020). Furthermore, difficulties with emotional regulation are also associated with a wide range of both internalizing and externalizing disorders, increasing the risk of suffering from other mental health problems (Turton et al., 2021).

Regarding negative self-concept and interpersonal problems, they seem to be affected by all forms of CM, early modifying the mental representations that the person has about himself and the others. Interestingly, physical neglect and abuse seem to be sensitive during the first 5 years of life, while emotional abuse and sexual abuse are sensitive during

childhood (6-12 years). In summary, SOD reinforce that children can learn adaptations to cope with CM, which are useful when physical or emotional threats are present, but can turn counterproductive as they grow up and encounter situations and relationships that are safe, producing interferences with the capacity to live, love, and be loved (Spinazzola et al., 2017).

Supported by considerable scientific evidence (Hyland et al., 2018; Yehuda and Wong, 2007), identification of CPTSD is important so that people suffering from more complex consequences of their traumatic experiences can be recognized and targeted intervention can be offered in order to avoid inaccurate and inadequate diagnoses and treatments (Karatzias et al., 2019). The inclusion of this new diagnoses may provide the opportunity to detect and focus treatment on the processing of complex trauma, instead of being trapped in interventions focused on comorbid symptomatology that could hide the root of the problem (Briere and Hedges, 2010; Sachser et al., 2017). In these periods, quality interventions can make an important difference in shifting the balance between risk and protective factors (Chinitz et al., 2017).

To interpret the whole picture, we must take into account that CM may dysregulate neurobiological mechanisms related to the stress response which may influence the ability to regulate emotions and result in reduced neurobiological resources to cope with adverse experiences and respond effectively (Keding et al., 2021; Marques-Feixa et al., 2021b). However, genetic and environmental protective factors could also lead to resilience and explain why not everyone who experiences such difficulties in early life develop lifelong disabilities.

The present study has limitations to be considered. Firstly, there is a high percentage of psychiatric diagnoses in the sample; therefore, it has not been possible to study the specific interaction between these disorders and the history of CM to explore further associations. In addition, there is a small percentage of resilient youth, defined as children with a history of CM but without current psychopathology. Exploring the presence of other biopsychological protective or risk factors, such as the close relationship with the aggressor, genetics, temperament, parent-child attachment and the support received could elucidate their contribution to mental health outcomes (Myers et al., 2002). This is a cross-sectional study, so, direct inference cannot be assumed and longitudinal studies would be of great interest to assess the evolution of the CPTSD symptomatology. As borderline personality disorder (BPD) shares similar features to dysfunctions in self-organization and is commonly associated with PTSD, further studies are needed to disentangle whether and how CPTSD is distinct from PTSD comorbid with BPD (Jowett et al., 2020).

Moreover, the definition of CM is complex, while the methods available to evaluate it and the criteria for classifying the victims greatly differ across different cultures. For that reason, is necessary to promote studies of CM based on child's populations, when carrying out interventions is still possible. Furthermore, as childhood and adolescence are considered key developmental periods for emotion regulation, self-concept and interpersonal abilities, developing a gold standard measure adapted to general young populations would be of paramount usefulness. In this regard, Haselgruber et al. (2020) have recently validated the International Trauma Questionnaire (ITQ) to asses CPTSD in

children and adolescents. However, deeper exploratory instruments should be design to address complex trauma and CPTSD symptomatology in young population.

CONCLUSIONS

CM is a highly complex phenomenon that affects the individual systemically and is a major risk factor for the development of dysfunctionality and a huge range of psychiatric disorders and comorbidity. The present study provides support for the clinical utility of gathering information of violence and adverse childhood experiences to understand the complexity of psychiatric symptoms observed in children and adolescents exposed to relational trauma. The new diagnosis accepted by ICD-11, CPTSD, may partly help to explain the worse clinical prognostic observed in these patients, and may have the potential to guide the development of more efficient preventive treatments and interventions focused on trauma, emotional dysregulation, negative self-concept and interpersonal problems, which are fundamental aspects, especially during development.

Role of funding sources

This study was supported by grants from the Spanish Ministry of Economy and Competitiveness, Instituto de Salud Carlos III through the University of Barcelona multicenter project (PI15/00097)-PI L. Fañanas, Hospital Universitario Araba (PI15/00793)-PI I. Zorrilla, Hospital Gregorio Marañón (PI15/00723)-PI M. Rapado and Hospital Clinic (PI15/00685)-PI S. Romero, co-financed by the European Regional Development Funds from the European Comission, "A way of making Europe" and Alicia Koplowitz Foundation. We thank the Network Centre for Biomedical Research in Mental Health (CIBERSAM). This study was facilitated by a pre-doctoral research grant from the Catalonian authorities to Laia Marques-Feixa (AGAUR-FI_B100023-2018). Supported by a NARSAD Distinguished Investigator Grant awarded to Professor Lourdes Fañanas (26887) and by the Comissionat per a Universitats i Recerca del DIUE, of the Generalitat de Catalunya regional authorities (2017SGR1577). Dr. Rapado-Castro was supported by a Ramon y Cajal Research Fellowship (RYC-2017-23144).

Acknowledgments

We are indebted to all the participants and their families for taking part in a study with such deep emotional involvement.

Conflict of interest

The authors do not have any conflict of interest regarding the publication of this manuscript.

Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Figure 1. Overlap of CM subtypes in EPI_young_stress cohort. The most common CM subtype was emotional neglect (EN), present in 94% of individuals. Noticeably, 74% of individuals reported multiple forms of CM, while isolated forms were largely less frequent. Specifically, isolated EN was present in 20% of participants and only 6% of subjects reported isolated physical neglect (PN), physical abuse (PA) or sexual abuse (SA). CM-score is a continuum index considering the severity, frequency and overlapping of different types of the history of CM (ranging from 0 to 80).

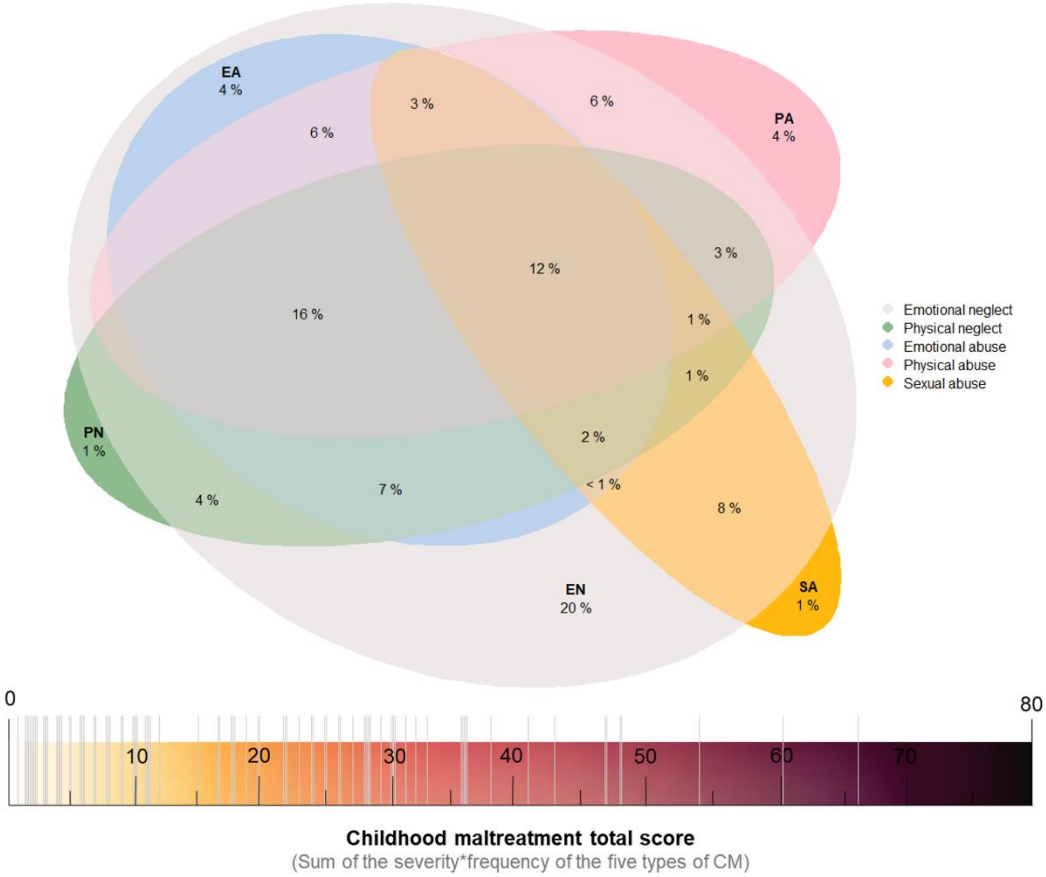


Table 1: Sociodemographic, CM and CPTSD symptoms of participants with (cases) and without (controls) current psychiatric disorders.

	CASES n=116 (62%) n (%) / mean (sd) [range]	**CONTROLS** n=71 (38%) n (%) / mean (sd) [range]	t/χ2	*p*	*d/kappa*
Developmental stage (adolescents)	63 (54%)	30 (42%)	2.561	.110	-0.117
Age	13.78 (2.37) [7-17]	13.35 (2.92) [7-17]	1.052	.270	-0.166
Sex (female)	68 (58%)	40 (56%)	0.094	.759	-0.022
Family socioeconomic status (SES)	35.42 (17.75) [8-66]	48.11 (15.38) [14-66]	-5.119	<.001***	0.751
Childhood maltreatment (CM) history	79 (68%)	15 (21%)	38.879	<.001***	-0.456
Emotional neglect	73 (63%)	11 (16%)	40.059	<.001***	-0.463
Physical neglect	41 (34%)	2 (3%)	26.317	<.001***	-0.375
Emotional abuse	43 (37%)	6 (9%)	18.654	<.001***	-0.316
Physical abuse	42 (36%)	8 (11%)	13.984	<.001***	-0.273
Sexual abuse	25 (22%)	3 (4%)	10.385	.001***	-0.236
CM-score	13.90 (15.79) [0-66]	2.31 (6.82) [0-36]	6.926	<.001***	-0.882
PTSD score	10.17 (5.41) [0-28]	2.54 (2.67) [0-13]	12.754	<.001***	-1.669
Emotional dysregulation score	8.74(3.68) [0-14]	4.23 (3.30) [0-12]	8.399	<.001***	-1.274
Negative concept score	3.47 (2.28) [0-8]	1.07 (1.46) [0-6]	8.691	<.001***	-1.194
Disturbance relationships score	2.13 (1.77) [0-6]	0.41 (0.77) [0-3]	9.061	<.001***	-1.167

Note: CM-score (childhood maltreatment score was calculated adding severity*frequency of each CM subtype, ranging from 0 to 80). Family socioeconomic status (SES) raw scores range from 8 to 66, with higher scores reflecting higher SES. p values: *$p \leq 0.05$, **$p \leq 0.01$, and ***$p \leq 0.001$.

Table 2: Regression analysis of childhood maltreatment score (CM-score) and premorbid adjustment, global functioning, psychiatric symptomatology and other clinical outcomes (comorbidity, polypharmacy and onset of illegal drug use).

		Cases						Controls					
			95% CI						95% CI				
STEP	**Effect**	**Beta**	**LL**	**UL**	**t**	**p**	**ΔR^2 (*100)**	**Beta**	**LL**	**UL**	**t**	**p**	**ΔR^2 (*100)**
	Premorbid adjustment 0-11 years [1]												
1	Development stage [a]	-.316	-5.097	-0.379	2.303	.023*	13.2%**	-.163	-2.498	1.123	0.758	.451	6.5%
	Age	.028	-0.406	0.509	0.224	.823		.284	-0.100	0.508	1.339	.185	
	Sex	.103	-1.048	2.850	0.917	.361		.055	-0.798	1.263	0.450	.654	
	Socioeconomic status	-.295	-0.117	-0.026	3.097	.003**		-.177	-0.057	0.008	1.484	.142	
2	CM-score	.218	0.004	0.116	2.141	.035*	3.8%*	.163	-0.036	0.136	1.164	.249	1.9%
	Premorbid adjustment 12-15 years [2]												
1	Development stage [a]	-.057	-4.688	3.096	0.407	.685	12.2%*	-.262	-6.184	2.094	0.996	.325	6.8%
	Age	.026	-0.896	1.106	0.209	.835		.256	-0.593	1.695	0.971	.337	
	Sex	.031	-3.054	3.906	0.244	.808		-.034	-2.651	2.119	0.225	.823	
	Socioeconomic status	-.345	-0.203	-0.048	3.221	.002**		-.208	-0.129	0.023	1.413	.165	
2	CM-score	.248	0.007	0.198	2.138	.036*	4.7*	.409	0.064	0.545	2.558	.014*	12.6%*
	Current CGAS [3]												
1	Development stage [a]	-.166	-15.541	3.431	1.265	.208	17.7%***	.054	-4.524	5.909	0.265	.792	16.0%*
	Age	-.039	-2.130	1.534	0.323	.747		.006	-0.864	0.889	0.028	.978	
	Sex	-.036	-9.058	6.458	0.332	.740		-.124	-4.555	1.385	1.065	.291	
	Socioeconomic status	.325	0.151	0.517	3.617	<.001***		.370	0.060	0.247	3.267	.002**	
2	CM-score	-.372	-0.644	-0.224	4.101	<.001***	11.4***	-.361	-0.575	-0.102	2.859	.006**	9.4%**
	CBCL total [4]												
1	Development stage [a]	.156	-7.582	27.372	1.123	.264	10.4%*	.152	-8.004	18.249	0.779	.439	23.7%***
	Age	.040	-2.823	3.885	0.314	.754		-.494	-5.059	-0.629	-2.564	.013*	
	Sex	.100	-8.120	20.858	0.872	.385		.113	-3.713	11.318	1.011	.316	
	Socioeconomic status	-.156	-0.613	0.059	1.635	.105		-.276	-0.537	-0.063	-2.532	.014*	
2	CM-score	.374	0.366	1.141	3.861	<.001***	11.5%***	.454	0.547	1.680	3.928	<.001***	14.8%***

	CBCL Internalizing [4]												
1	Development stage [a]	.003	-5.380	5.493	0.020	.984	26.4%***	.448	0.528	8.752	2.254	.028*	20.5%**
	Age	.321	0.411	2.498	2.766	.007**		-.595	-1.746	-0.358	3.029	.004**	
	Sex	.261	1.210	10.224	2.516	.013*		.177	-0.519	4.190	1.557	.124	
	Socioeconomic status	-.068	-0.146	0.063	0.781	.437		-.224	-0.149	-0.001	2.019	.048*	
2	CM-score	.239	0.041	0.290	2.629	.010**	4.7%**	.349	0.076	0.449	2.816	.006**	8.8%**
	CBCL Externalizing [4]												
1	Development stage [a]	.308	.780	15.341	2.196	.030*	8.3%	.067	-4.055	5.655	0.329	.743	16.2%*
	Age	-.197	-2.471	0.323	1.525	.130		-.366	-1.563	0.075	1.813	.074	
	Sex	-.094	-8.508	3.564	0.812	.418		.106	-1.519	4.041	.906	.368	
	Socioeconomic status	-.199	-0.286	-0.006	2.062	.042*		-.228	-0.175	0.000	1.997	.050*	
2	CM-score	.353	0.130	0.455	3.564	.001***	10.2%***	.563	0.289	0.687	4.893	<.001***	22.8%***
	CBCL Others [4]												
1	Development stage [a]	.058	-4.820	7.306	0.407	.685	4.2%	.014	-4.328	4.664	0.074	.941	26.1%***
	Age	.029	-1.035	1.292	0.219	.827		-.421	-1.603	-0.086	2.224	.030*	
	Sex	.091	-3.082	6.970	0.767	.445		-.008	-2.669	2.479	0.073	.942	
	Socioeconomic status	-.115	-0.85	0.048	1.161	.248		-.277	-0.186	-0.024	2.583	.012*	
2	CM-score	.338	0.092	0.365	3.319	.001***	9.4%***	.272	0.024	0.440	2.225	.030*	5.3%*
	Lifetime psychiatric diagnosis [5]												
1	Development stage [a]	-.023	-0.945	0.794	0.173	.863	9.6%*	-.035	-0.380	0.324	0.161	.872	5.1%
	Age	.224	-0.018	0.322	1.771	.079		.153	-0.038	0.080	0.714	.478	
	Sex	.039	-0.585	0.840	0.354	.724		.086	-0.131	0.270	0.695	.489	
	Socioeconomic status	-.172	-0.033	0.001	1.837	.069		-.157	-0.010	0.002	1.306	.196	
2	CM-score	.238	0.004	0.045	2.409	.018*	4.7%*	.431	0.010	0.041	3.265	.002**	13.4%**
	Current psychiatric comorbidity [6]												
1	Development stage [a]	-.085	-0.723	0.389	0.596	.553	2.0%	NA	NA	NA	NA	NA	NA
	Age	.147	-0.047	0.168	1.115	.267		NA	NA	NA	NA	NA	
	Sex	.017	-0.422	0.487	0.142	.887		NA	NA	NA	NA	NA	
	Socioeconomic status	-.070	-0.015	0.007	0.710	.479		NA	NA	NA	NA	NA	
2	CM-score	.234	0.002	0.028	2.246	.027*	4.5%*	NA	NA	NA	NA	NA	NA

	Polypharmacy [7]												
1	Development stage [a]	.048	-0.469	0.670	0.349	.727	9.3%*	NA	NA	NA	NA	NA	NA
	Age	.275	0.010	0.230	2.158	.033*		NA	NA	NA	NA	NA	
	Sex	-.059	-0.588	0.343	0.523	.602		NA	NA	NA	NA	NA	
	Socioeconomic status	-.063	-0.015	0.007	0.670	.504		NA	NA	NA	NA	NA	
2	CM-score	.201	0.000	0.027	2.000	.048*	3.3%*	NA	NA	NA	NA	NA	NA
	Age of first use of illegal drugs [8]												
1	Development stage [a]	.023	-2.627	2.850	0.084	.933	33.4%*	NA	NA	NA	NA	NA	NA
	Age	.455	0.117	0.939	2.660	.014*		NA	NA	NA	NA	NA	
	Sex	-.360	-3.653	0.768	1.350	.190		NA	NA	NA	NA	NA	
	Socioeconomic status	-.011	-0.041	0.039	0.061	.952		NA	NA	NA	NA	NA	
2	CM-score	-.457	-0.084	-0.005	2.325	.030*	13.1%*	NA	NA	NA	NA	NA	NA

Note: 95 % CI (95% confidence interval, where LL is the lower limit and UL the upper limit).

[1] Premorbid adjustment scores for children range from 0-24, with higher scores indicating a worse global adjustment.

[2] Premorbid adjustment scores during early adolescence range from 0-30, with higher scores indicating a worse global adjustment.

[3] CGAS: Children's Global Assessment Scale, provides a single score, between 1 'extremely impaired' to 100 'doing very well".

[4] CBCL: Child Behavioural Check-List scores comprise several subscales: Internalizing (Anxious/Depressed, Withdrawn, Somatic Complaints), Externalizing (Rule-Breaking Behaviour and Aggressive Behaviour) and Other symptomatology (Social Problems, Thought Problems and Attention Problems).

[5] Lifetime psychiatric diagnosis lifetime: Total number of different diagnosis received though lifespan (ranged from 0 to 7).

[6] Psychiatric comorbidity: Number of current psychiatric diagnosis (ranged from 0 to 5).

[7] Polypharmacy: considered as multimorbidity use of psychiatric drugs, calculated according to the sum of six types of psychotropic drugs prescribed daily (antipsychotics, antidepressants, anxiolytics, mood stabilizers, psychostimulants or others), ranging from 0 to 4.

[8] Age of first use of illegal drugs: In our sample, cannabis was always the first used drug (between 9 and 16 years old). Not sufficient affirmative subjects in control group to perform this analysis.

Table 3. Regression analyses of the impact of CM (each subtype and period of exposure) on CPTSD symptomatology (PTSD, emotional dysregulation, negative self-concept and interpersonal problems) in participants with current psychiatric diagnosis

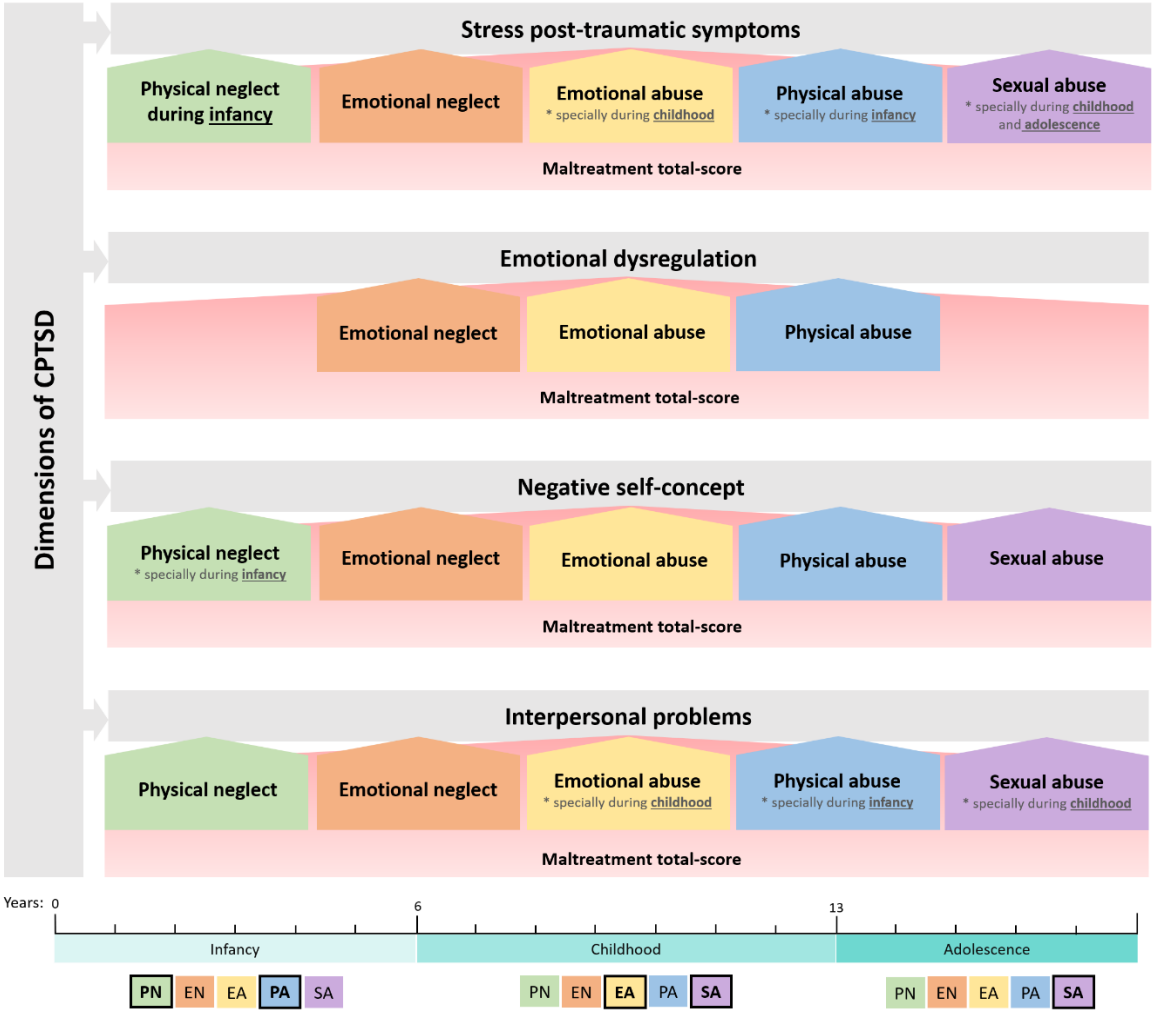
		Cases					
		95% CI					
STEP	**Effect**	**Beta**	**LL**	**UL**	**t**	**p**	**ΔR^2 (*100)**
Outcome: PTSD							
1	Development stage [a]	.159	-0.994	4.444	1.258	.211	23.8%***
	Age	.200	-0.072	0.978	1.711	.090	
	Sex	.194	-0.107	4.340	1.887	.062	
	Socioeconomic status	-.089	-0.080	0.025	1.025	.308	
2	CM-score	.309	0.046	0.169	3.465	.001***	7.8%***
2.1a	Physical neglect	.103	-0.922	3.258	1.108	.270	0.9%
2.1b	PN 0-5 years	.234	0.068	6.156	2.028	.045*	7.1%*
	PN 6-12 years	.029	-2.862	3.588	0.223	.824	
	PN 13-17 years	-.123	-5.157	1.150	1.260	.211	
2.2a	Emotional neglect	.259	0.963	4.802	2.977	.004**	5.9%**
2.2b	EN 0-5 years	.048	-1.941	3.020	0.431	.667	6.5%*
	EN 6-12 years	.218	-0.393	5.110	1.700	.092	
	EN 13-17 years	.045	-2.012	3.009	0.394	.695	
2.3a	Emotional abuse	.421	2.867	6.554	5.066	<.001***	15.0%***
2.3b	EA 0-5 years	-.098	-4.152	1.461	0.951	.344	13.9%***
	EA 6-12 years	.488	2.752	8.418	3.909	<.001***	
	EA 13-17 years	-.065	-3.539	1.830	0.631	.529	
2.4a	Physical abuse	.290	1.437	5.079	3.547	.001***	8.2%***
2.4b	PA 0-5 years	.201	0.012	5.520	1.992	.049*	9.8%**
	PA 6-12 years	.157	-0.806	4.435	1.373	.173	
	PA 13-17 years	.013	-2.957	3.391	0.136	.892	
2.5a	Sexual abuse	.350	2.386	6.925	4.068	<.001***	10.4%***
2.5b	SA 0-5 years	-.141	-12.791	1.320	1.612	.110	9.9%**
	SA 6-12 years	.250	1.188	7.204	2.767	.007**	
	SA 13-17 years	.194	0.389	6.108	2.253	.026*	
Outcome: Emotional dysregulation							
1	Development stage [a]	.199	-0.567	3.417	1.419	.159	6.2%
	Age	-.217	-0.710	0.059	1.678	.096	
	Sex	.048	-1.287	1.971	0.416	.678	
	Socioeconomic status	-.176	-0.074	0.003	1.830	.070	
2	CM-score	.225	00.005	0.098	2.206	.030*	4.2%*
2.1a	Physical neglect	.169	-0.258	2.783	1.646	.103	2.4%
2.1b	PN 0-5 years	.230	-0.274	4.324	1.747	.084	3.4%
	PN 6-12 years	-.091	-3.179	1.694	0.604	.547	
	PN 13-17 years	.009	-2.482	2.283	0.083	.934	
2.2a	Emotional neglect	.200	0.036	2.909	2.033	.045*	3.6%*
2.2b	EN 0-5 years	.059	-1.435	2.309	0.463	.644	2.6%
	EN 6-12 years	-.005	-2.116	2.038	0.037	.971	
	EN 13-17 years	.171	-0.647	3.143	1.306	.194	

2.3a	Emotional abuse	.217	.124	3.073	2.150	.034*	4.0%*
2.3b	EA 0-5 years	.205	-0.349	4.073	1.670	.098	5.0%
	EA 6-12 years	-.044	-2.562	1.902	0.294	.770	
	EA 13-17 years	.126	-1.024	3.206	1.023	.309	
2.4a	Physical abuse	.312	0.974	3.652	3.426	.001***	9.4%***
2.4b	PA 0-5 years	.151	-0.691	3.436	1.319	.190	8.2%*
	PA 6-12 years	.110	-1.126	2.802	0.847	.399	
	PA 13-17 years	.126	-1.029	3.728	1.125	.263	
2.5a	Sexual abuse	.098	-.920	2.641	0.958	.340	0.8%
2.5b	SA 0-5 years	-.064	-7.215	3.808	0.613	.541	1.0%
	SA 6-12 years	.109	-1.139	3.559	1.022	.309	
	SA 13-17 years	.003	-2.195	2.272	0.034	.973	
Outcome: Negative Self concept							
1	Development stage [a]	.074	-0.880	1.554	0.549	.584	13.3%**
	Age	.166	-0.076	0.394	1.338	.184	
	Sex	.204	-0.063	1.856	1.928	.066	
	Socioeconomic status	.048	-0.017	0.030	0.525	.600	
2	CM-score	.340	0.022	0.077	3.600	<.001***	9.5%***
2.1a	Physical neglect	.218	0.116	1.955	2.232	.028*	3.9%*
2.1b	PN 0-5 years	.250	0.027	2.768	2.023	.046*	7.2%*
	PN 6-12 years	.042	-1.233	1.671	0.299	.765	
	PN 13-17 years	-.051	-1.764	1.075	0.481	.631	
2.2a	Emotional neglect	.268	0.392	2.115	2.885	.005**	6.4%**
2.2b	EN 0-5 years	.070	-0.794	1.459	0.585	.560	5.0%
	EN 6-12 years	.136	-0.631	1.868	0.982	.328	
	EN 13-17 years	.097	-0.693	1.588	0.779	.438	
2.3a	Emotional abuse	.309	0.574	2.327	3.280	.001***	8.1%***
2.3b	EA 0-5 years	.043	-1.079	1.572	0.368	.713	7.7%*
	EA 6-12 years	.234	-0.216	2.461	1.663	.099	
	EA 13-17 years	.059	-0.942	1.594	0.510	.611	
2.4a	Physical abuse	.289	0.543	2.186	3.294	.001***	8.1%***
2.4b	PA 0-5 years	.141	-0.443	2.080	1.287	.201	7.6%*
	PA 6-12 years	.109	-0.674	1.726	0.869	.387	
	PA 13-17 years	.122	-0.621	2.286	1.135	.259	
2.5a	Sexual abuse	.210	0.105	2.243	2.178	.032*	3.7%*
2.5b	SA 0-5 years	-.089	-4.820	1.802	0.904	.368	3.9%
	SA 6-12 years	.161	-0.277	2.545	1.593	.114	
	SA 13-17 years	.116	-0.528	2.156	1.203	.232	
Outcome: Interpersonal problems							
1	Development stage [a]	.163	-0.386	1.541	1.189	.237	10.6%*
	Age	.037	-0.159	0.213	0.293	.770	
	Sex	.120	-0.359	1.217	1.080	.283	
	Socioeconomic status	-.131	-0.032	0.005	1.402	.164	
2	CM-score	.423	0.027	0.069	4.540	<.001***	14.7%***
2.1a	Physical neglect	.206	0.031	1.491	2.066	.041*	3.5%*
2.1b	PN 0-5 years	.162	-0.394	1.807	1.274	.206	5.0%
	PN 6-12 years	.091	-0.795	1.537	0.631	.529	
	PN 13-17 years	-.087	-1.605	0.675	0.808	.421	
2.2a	Emotional neglect	.264	0.276	1.643	2.785	.006**	6.1%**
2.2b	EN 0-5 years	-.038	-1.029	0.749	0.313	.755	5.7%

	EN 6-12 years	.186	-0.327	1.645	1.325	.188	
	EN 13-17 years	.139	-0.398	1.401	1.106	.271	
2.3a	Emotional abuse	.407	0.821	2.159	4.417	<.001	14.0%***
2.3b	EA 0-5 years	.079	-0.666	1.381	0.693	.490	11.9%**
	EA 6-12 years	.314	0.142	2.208	2.256	.026*	
	EA 13-17 years	.003	-0.966	0.992	0.0236	.979	
2.4a	Physical abuse	.336	0.589	1.876	3.837	<.001***	11.0%***
2.4b	PA 0-5 years	.246	0.131	2.089	2.249	.027*	10.9%**
	PA 6-12 years	.068	-0.675	1.188	0.547	.586	
	PA 13-17 years	.126	-0.456	1.800	1.182	.240	
2.5a	Sexual abuse	.272	0.351	2.019	2.818	.006**	6.3%**
2.5b	SA 0-5 years	-.067	-3.465	.684	0.686	.494	6.9%*
	SA 6-12 years	.261	0.333	2.528	2.586	.010**	
	SA 13-17 years	.101	-0.487	1.600	1.058	.292	

Note: The effect in participants without psychiatric disorders in supplementary material.

Figure 2: The impact of CM-score (in red), CM subtypes (other colors) and the respectively age of exposure on CPTSD subdomains (in grey) in children and adolescents with current psychiatric disorders (cases, n=116). At the bottom the figure, it is shown how all types of CM contribute to CPTSD during all developmental stages. The bold boxes indicate the stage of development in which each type of CM has the greatest impact. PN: physical neglect, EN: emotional neglect, EA: emotional abuse, PA: physical abuse, SA: sexual abuse.



REFERENCES

Achenbach, T.M., Rescorla, L., 2001. Manual for the ASEBA school-age forms & profiles : an integrated system of multi-informant assessment. Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families (USA).

Adams, J., Mrug, S., Knight, D.C., 2018. Characteristics of child physical and sexual abuse as predictors of psychopathology. Child Abuse Negl.

Akmatov, M.K., 2011. Child abuse in 28 developing and transitional countries-results from the multiple indicator cluster surveys. Int. J. Epidemiol. 40, 219–227.

Allen, B., Cramer, R.J., Harris, P.B., Katrina, A., 2013. Archives of Suicide Research Borderline Personality Symptomatology as a Mediator of the Link Between Child Maltreatment and Adult Suicide Potential 37–41.

Anda, R.F., Felitti, V.J., Bremner, J.D., Walker, J.D., Whitfield, C., Perry, B.D., Dube, S.R., Giles, W.H., 2006. The enduring effects of abuse and related adverse experiences in childhood: A convergence of evidence from neurobiology and epidemiology. Eur. Arch. Psychiatry Clin. Neurosci. 256, 174–186.

APA: American Psychiatric Association, 1980. DSM-III: Diagnostic and statistical manual of mental disorders (3th edition). American Psychiatric Association, Washington.

APA, 2013. Guía Criterios Dx DSMV español.

Bentler, P., 2006. EQS Structural Equations Program Manual. Encino, CA: Multivariate Software.

Brewin, C.R., Cloitre, M., Hyland, P., Shevlin, M., Maercker, A., Bryant, R.A., Humayun, A., Jones, L.M., Kagee, A., Rousseau, C., Somasundaram, D., Suzuki, Y., Wessely, S., van Ommeren, M., Reed, G.M., 2017. A review of current evidence regarding the ICD-11 proposals for diagnosing PTSD and complex PTSD. Clin. Psychol. Rev. 58, 1–15.

Briere, J., Hedges, M., 2010. Trauma Symptom Inventory. Corsini Encycl. Psychol., Major Reference Works.

Briere, J.N., Scott, C., 2013. Principles of trauma therapy: A guide to symptoms, evaluation, and treatment, 2nd ed., revised and expanded, Principles of trauma therapy: A guide to symptoms, evaluation, and treatment, 2nd ed., revised and expanded. Sage Publications, Inc, Thousand Oaks, CA, US.

Cannon-Spoor, H.E., Potkin, S.G., Wyatt, R.J., 1982. Measurement of premorbid adjustment in chronic schizophrenia. Schizophr. Bull. 8, 470–484.

CARM, 2012. Instrumento para la valoración de la gravedad de las situaciones de desprotección infantil (Tool for assessing the severity of situations in which children are vulnerable- TASSCV). Serv. Soc. Atención Primaria y Espec. la Región Muricia.

Castro, M., Alcántara-López, M., Martínez, A., Fernández, V., Sánchez-Meca, J., López-Soler, C., 2017. Mother's IPV, Child Maltreatment Type and the Presence of PTSD in Children and Adolescents. Int. J. Environ. Res. Public Health 14.

Chinitz, S., Guzman, H., Amstutz, E., Kohchi, J., Alkon, M., 2017. Improving outcomes for babies and toddlers in child welfare: A model for infant mental health intervention and collaboration. Child Abus. Negl. 70, 190–198.

Cloitre, M., 2020. ICD-11 complex post-traumatic stress disorder: simplifying diagnosis in trauma populations. Br. J. Psychiatry.

Cloitre, M., Garvert, D.W., Brewin, C.R., Bryant, R.A., Maercker, A., 2013. Evidence for proposed ICD-11 PTSD and complex PTSD: A latent profile analysis. Eur. J. Psychotraumatol.

Cook, E.C., Chaplin, T.M., Sinha, R., Tebes, J.K., Mayes, L.C., 2012. The Stress Response and Adolescents' Adjustment: The Impact of Child Maltreatment. J. Youth Adolesc. 41, 1067–1077.

De Bellis, M.D., Zisk, A., 2014. The Biological Effects of Childhood Trauma. Child Adolesc. Psychiatr. Clin. N. Am. 23, 185–222.

De la Peña, F.R., Villavicencio, L.R., Palacio, J.D., Félix, F.J., Larraguibel, M., Viola, L., Ortiz, S., Rosetti, M., Abadi, A., Montiel, C., Mayer, P.A., Fernández, S., Jaimes, A., Feria, M., Sosa, L., Rodríguez, A., Zavaleta, P., Uribe, D., Galicia, F., Botero, D., Estrada, S., Berber, A.F., Pi-Davanzo, M., Aldunate, C., Gómez, G., Campodónico, I., Tripicchio, P., Gath, I., Hernández, M., Palacios, L., Ulloa, R.E., 2018. Validity and reliability of the kiddie schedule for affective disorders and schizophrenia present and lifetime version DSM-5 (K-SADS-PL-5) Spanish version. BMC Psychiatry 18, 193.

Elliott, R., McKinnon, A., Dixon, C., Boyle, A., Murphy, F., Dahm, T., Travers-Hill, E., Mul, C.-L., Archibald, S.-J., Smith, P., Dalgleish, T., Meiser-Stedman, R., Hitchcock, C., 2021. Prevalence and predictive value of ICD-11 post-traumatic stress disorder and Complex PTSD diagnoses in children and adolescents exposed to a single-event trauma. J. Child Psychol. Psychiatry. 62, 270–276.

Forti, M. Di, Quattrone, D., Freeman, T.P., Tripoli, G., Gayer-anderson, C., Quigley, H., Rodriguez, V., Jongsma, H.E., Bernardo, M., Delben, C.M., Menezes, P.R., Selten, J., Jones, P.B., Kirkbride, J.B., Rutten, B.P.F., Haan, L. De, 2019. The contribution of cannabis use to variation in the incidence of psychotic disorder across Europe (EU-GEI): a multicentre case-control study 427–436.

Green, J.G., McLaughlin, K.A., Berglund, P.A., Gruber, M.J., Sampson, N.A., Zaslavsky, A.M., Kessler, R.C., 2010. Childhood Adversities and Adult Psychiatric Disorders in the National Comorbidity Survey Replication I. Arch. Gen. Psychiatry 67, 113–123.

Haselgruber, A., Knefel, M., Sölva, K., Lueger-Schuster, B., 2021. Foster children's complex psychopathology in the context of cumulative childhood trauma: The interplay of ICD-11 complex PTSD, dissociation, depression, and emotion regulation. J. Affect. Disord. 282, 372–380.

Haselgruber, A., Sölva, K., Lueger-Schuster, B., 2020. Validation of ICD-11 PTSD and complex PTSD in foster children using the International Trauma Questionnaire. Acta Psychiatr. Scand. 141, 60–73.

Heim, C., Shugart, M., Craighead, W.E., Nemeroff, C.B., 2010. Neurobiological and psychiatric consequences of child abuse and neglect. Dev. Psychobiol. 52, 671–690.

Herman, J.L., 1997. Trauma and recovery: The aftermath of violence – from domestic abuse to political terror, Basic Book. ed. New York.

Herman, J.L., 1992. Complex PTSD: A syndrome in survivors of prolonged and repeated trauma. J. Trauma. Stress 5, 377–391.

Hoeboer, C., de Roos, C., van Son, G.E., Spinhoven, P., Elzinga, B., 2021. The effect of parental emotional abuse on the severity and treatment of PTSD symptoms in children and adolescents. Child Abuse Negl. 111, 104775.

Hollingshead, A.B., 1975. Four Factor Index of Social Status. New Haven, CT Yale Univ. Dep. Psychol.

Horace, A.E., Ahmed, F., 2015. Polypharmacy in pediatric patients and opportunities for pharmacists' involvement. Integr. Pharm. Res. Pract. 4, 113–126.

Hughes, K., Bellis, M.A., Hardcastle, K.A., Sethi, D., Butchart, A., Mikton, C., Jones, L., Dunne, M.P., 2017. The effect of multiple adverse childhood experiences on health: a systematic review and meta-analysis. Lancet Public Heal. 2, e356–e366.

Hyland, P., Shevlin, M., Fyvie, C., Karatzias, T., 2018. Posttraumatic Stress Disorder and Complex Posttraumatic Stress Disorder in DSM-5 and ICD-11: Clinical and Behavioral Correlates. J. Trauma. Stress 31, 174–180.

Jaffee, S.R., 2017. Child Maltreatment and Risk for Psychopathology in Childhood and Adulthood. Annu. Rev. Clin. Psychol. 13, 525–551.

Janssen, I., Krabbendam, L., Bak, M., Hanssen, M., Vollebergh, W., Graaf, D., 2004. Childhood abuse as a risk factor for psychotic experiences 38–45.

Jonson-Reid, M., Kohl, P.L., Drake, B., 2012. Child and adult outcomes of chronic child maltreatment. Pediatrics 129, 839–845.

Jowett, S., Karatzias, T., Shevlin, M., Albert, I., 2020. Differentiating symptom profiles of ICD-11 PTSD, complex PTSD, and borderline personality disorder: A latent class analysis in a multiply traumatized sample. Personal. Disord. Theory, Res. Treat. 11, 36–45.

Karatzias, T., Murphy, P., Cloitre, M., Bisson, J., Roberts, N., Shevlin, M., Hyland, P., Maercker, A., Ben-Ezra, M., Coventry, P., Mason-Roberts, S., Bradley, A., Hutton, P., 2019. Psychological interventions for ICD-11 complex PTSD symptoms: systematic review and meta-analysis. Psychol. Med. 49, 1761–1775.

Karatzias, T., Shevlin, M., Fyvie, C., Hyland, P., Efthymiadou, E., Wilson, D., Roberts, N., Bisson, J.I., Brewin, C.R., Cloitre, M., 2017. Evidence of distinct profiles of Posttraumatic Stress Disorder (PTSD) and Complex Posttraumatic Stress Disorder (CPTSD) based on the new ICD-11 Trauma Questionnaire (ICD-TQ). J. Affect. Disord. 207, 181–187.

Keding, T.J., Heyn, S.A., Russell, J.D., Zhu, X., Cisler, J., McLaughlin, K.A., Herringa, R.J., 2021. Differential Patterns of Delayed Emotion Circuit Maturation in Abused Girls With and Without Internalizing Psychopathology. Am. J. Psychiatry 178, 1026–1036.

Kessler, R.C., Aguilar-Gaxiola, S., Alonso, J., Benjet, C., Bromet, E.J., Cardoso, G., Degenhardt, L., de Girolamo, G., Dinolova, R. V, Ferry, F., Florescu, S., Gureje, O., Haro, J.M., Huang, Y., Karam, E.G., Kawakami, N., Lee, S., Lepine, J.-P., Levinson, D., Navarro-Mateu, F., Pennell, B.-E., Piazza, M., Posada-Villa, J., Scott, K.M., Stein, D.J., Ten Have, M., Torres, Y., Viana, M.C., Petukhova, M. V, Sampson, N.A., Zaslavsky, A.M., Koenen, K.C., 2017. Trauma and PTSD in the WHO World Mental Health Surveys. Eur. J. Psychotraumatol. 8, 1353383.

Knefel, M., Garvert, D.W., Cloitre, M., Lueger-Schuster, B., 2015. Update to an evaluation of ICD-11 PTSD and complex PTSD criteria in a sample of adult survivors of childhood institutional abuse by Knefel & Lueger-Schuster (2013): a latent profile analysis. Eur. J. Psychotraumatol. 6, 25290.

Lacalle Sistere, M., Domenech Massons, J.M., Granero Perez, R., Ezpeleta Ascaso, L., 2014. Validity of the DSM-Oriented Scales of the Child Behavior Checklist and Youth Self-Report. Psicothema 26, 364–371.

Lippard, E.T.C., Nemeroff, C.B., 2020. The Devastating Clinical Consequences of Child Abuse and Neglect : Increased Disease Vulnerability and Poor Treatment Response in Mood Disorders.

Luthra, R., Abramovitz, R., Greenberg, R., Schoor, A., Newcorn, J., Schmeidler, J., Levine, P., Nomura, Y., Chemtob, C.M., 2009. Relationship between type of trauma exposure and posttraumatic stress disorder among urban children and adolescents. J. Interpers. Violence 24, 1919–1927.

Marques-Feixa, L., Moya-Higueras, J., Romero, S., Santamarina-Pérez, P., Rapado-Castro, M., Zorrilla, I., Martín, M., Anglada, E., Lobato, M.J., Ramírez, M., Moreno, N., Mayoral, M., Marín-Vila, M., Arias, B., Fañanás, L., Stress, E.-Y., 2021a. Risk of Suicidal Behavior in Children and Adolescents Exposed to Maltreatment: The Mediating Role of Borderline Personality Traits and Recent Stressful Life Events. J. Clin. Med 10, 5293.

Marques-Feixa, L., Palma-Gudiel, H., Romero, S., Moya-Higueras, J., Rapado-Castro, M., Castro-Quintas, Á., Zorrilla, I., José Muñoz, M., Ramírez, M., Mayoral, M., Mas, A., José Lobato, M., Blasco-Fontecilla, H., Fañanás, L., 2021b. Childhood maltreatment disrupts HPA-axis activity under basal and stress conditions in a dose-response relationship in children and adolescents. Psychol. Med. 16, 1–14.

McGee, R.A., Wolfe, D.A., Wilson, S.K., 1997. Multiple maltreatment experiences and adolescent behavior problems: adolescents' perspectives. Dev. Psychopathol. 9, 131–149.

Morris, N.M., Udry, J.R., 1980. Validation of a self-administered instrument to assess stage of adolescent development. J. Youth Adolesc. 9, 271–280.

Myers, J., Berliner, L., Briere, J., Hendrix, C., Reid, T., Jenny, C., 2002. The APSAC Handbook on child maltreatment, Second edi. ed, Thousand Oaks (CA). Sage Publications.

Radford, L., Corral, S., Bradley, C., Fisher, H., Bassett, C., Howat, N., Collishaw, S., 2011. Child abuse and neglect in the UK today. London.

Read, J., Van Os, J., Morrison, A.P., Ross, C.A., 2005. Childhood trauma, psychosis and schizophrenia: A literature review with theoretical and clinical implications. Acta Psychiatr. Scand. 112, 330–350.

Redican, E., Nolan, E., Hyland, P., Cloitre, M., McBride, O., Karatzias, T., Murphy, J., Shevlin, M., 2021. A systematic literature review of factor analytic and mixture models of ICD-11 PTSD and CPTSD using the International Trauma Questionnaire. J. Anxiety Disord. 79, 102381.

Sachser, C., Keller, F., Goldbeck, L., 2017. Complex PTSD as proposed for ICD-11: validation of a new disorder in children and adolescents and their response to Trauma-Focused Cognitive Behavioral Therapy. J. Child Psychol. Psychiatry. 58, 160–168.

Scott, J., Varghese, D., McGrath, J., 2010. As the Twig Is Bent, the Tree Inclines. Arch. Gen. Psychiatry 67, 111.

Shaffer, D., Gould, M.S., Brasic, J., Ambrosini, P., Fisher, P., Bird, H., Aluwahlia, S., 1983. A Children's Global Assessment Scale (CGAS). Arch. Gen. Psychiatry 40, 1228–1231.

Spinazzola, J., Habib, M., Blaustein, M., Knoverek, A., Kisiel, C., Stolbach, B., Abramovitz, R., Kagan, R., Lanktree, C., Maze, J., 2017. What is complex trauma: a resource guide for youth and those who care about them, Los Angeles, CA, and Durham, NC: National Center for Child Traumatic Stress.

Spinazzola, J., Hodgdon, H., Liang, L.-J., Ford, J.D., Layne, C.M., Pynoos, R., Briggs, E.C., Stolbach, B., Kisiel, C., 2014. Unseen wounds: The contribution of psychological maltreatment to child and adolescent mental health and risk outcomes. Psychol. Trauma Theory, Res. Pract. Policy 6, S18–S28.

Teicher, M.H., Samson, J.A., 2013. Childhood maltreatment and psychopathology: A case for ecophenotypic variants as clinically and neurobiologically distinct subtypes. Am. J. Psychiatry 170, 1114–1133.

Turton, H., Berry, K., Danquah, A., Pratt, D., 2021. The relationship between emotion dysregulation and suicide ideation and behaviour: A systematic review. J. Affect. Disord. Reports 5, 100136.

Vachon, D.D., Krueger, R.F., Rogosch, F.A., Cicchetti, D., 2015. Assessment of the harmful psychiatric and behavioral effects of different forms of child maltreatment. JAMA Psychiatry 72, 1135–1142.

Van der Kolk, B., Najavits, L.M., 2013. Interview: What is PTSD Really? Surprises, Twists of History, and the Politics of Diagnosis and Treatment. J. Clin. Psychol. 69, 516–522.

van der Kolk, B.A., 2005. Developmental Trauma Disorder: Toward a rational diagnosis for children with complex trauma histories. Psychiatr. Ann. 35, 401–408.

Villalta, L., Khadr, S., Chua, K.C., Kramer, T., Clarke, V., Viner, R.M., Stringaris, A., Smith, P., 2020. Complex post-traumatic stress symptoms in female adolescents: the role of emotion dysregulation in impairment and trauma exposure after an acute sexual assault. Eur. J. Psychotraumatol. 11.

Yehuda, R., Wong, C.M., 2007. Acute Stress Disorder and Posttraumatic Stress Disorder. Encycl. Stress 4, 1–6.

Supplementary material

1. Definition of Complex Posttraumatic Stress Disorder (CPTSD)

According to ICD-11, CPTSD includes two sections, PTSD and Self-Organization Disturbances (SOD). Specifically, PTSD clusters three types of symptoms: (1) nightmares or flashbacks as re-experiencing symptoms; (2) avoidance of internal or external reminders of traumatic experience; and (3) hypervigilance or startle reactions as a current sense of threat. The second section includes symptoms of three Self-organization domains: (1) hyper- (heightened emotional reactions) or hypo-activation (emotional numbing or dissociation) as affective dysregulation when confronted with minor stressors; (2) persistent feelings of being a failure or worthless as negative self-concept; and (3) persistent feelings of being distant from others or having difficulties in maintaining close relationships as disturbances in relationships.

2. Instruments used to assess CPTSD symptomatology and confirmatory factor analysis

At the time of designing our study, it was not available an instrument to measure CPTSD. Thus, we explored a proxy of CPTSD symptomatology using two different questionnaires: the Trait Emotional Intelligence Questionnaire (TEIQue) and Child Behaviour Checklist 6–18, (CBCL) (see Table S1).

On the one hand, the TEIQue short form for children (TEIQue-CSF), answered by parents/guardian, provides comprehensive coverage of child personality facets relating to emotion (1). It includes 36 short statements responded on a 5-point Likert scale (1= disagree completely, 2= Disagree, 3= Neither agree nor disagree, 4= agree, 5= agree completely) (2,3). Six items from this questionnaire were selected to be included in the CPTSD construct (see Table S1). Previously, the TEIQue-CSF scores were recoded to be comparable with CBCL scores (1-2 =0, 3=1, 4-5=2). On the other hand, CBCL is an inventory for parents of the Achenbach System of Empirically Based Assessment (ASEBA) School-Age Forms and Profiles, which assesses the competencies, behavioral and emotional problems in children and adolescents aged 6 to 18 years (4,5). The original questionnaire contains 113 items with three response options (0 = not true, 1= somewhat or sometimes true, 2 = very true or often true). Twenty-two items from the CBCL were selected to be included in CPTSD factorial analysis. The internal consistency can be seen in Table S1.

To identify the relationship between the items and the underlying empirical structure, we performed a confirmatory factor analysis (CFA) using the statistical software package EQS 6.1 (6). Mardia's coefficient was calculated to assess overall normality. As the model was non-normal, we used the Satorra-Bentler robust indexes. To evaluate the model's goodness-of-fit (capacity to reproduce the data), several indices were reported, including the Satorra-

Bentler Chi-Square, Comparative fit index (CFI), Bollen's fit index (IFI), McDonalad's fit index (MFI) and the Root Mean Square Error of Approximation (RMSEA). Using standard criteria (7,8), values higher than 0.90 in CFI, IFI and MFI, and values lower than 0.08 in RMSEA, were considered as an acceptable model fit (see Table S2).

As we needed to respecify the initial model, according to Bentler (6), we used the Wald test and Lagrange multiplier test. Wald test indicate which fixed parameters or constraints might be released. Lagrange multiplier test provides information on what types of new associations could be included in the model.

We compared three nested models: A) a unidimensional 1-factor model for CPTSD and two multidimensional models; B) a first-order model with four factors (PTSD, emotion dysregulation, negative self-concept and interpersonal problems) and, C) a second-order model for CPTSD as an overriding construct subtended by previous four factors.

Table S1: Included items included representing the symptoms of Post-Traumatic Stress Disorder (PTSD), and self-organization disturbances characterized by ICD-11's Complex Post-Traumatic Stress Disorder (CPTSD) diagnosis.

Factor		Item	Test (item)	Loading factor	Cronbach alpha
PTSD symptoms (F1)	*Intrusion*	Can't get his/her mind off certain thoughts; obsessions	CBCL (9)	.527	.873
		Confused or seems to be in a fog	CBCL (13)	.432	
		Stares blankly	CBCL (80)	.349	
		Underactive, slow moving, or lacks energy	CBCL (102)	.292	
		Daydreams or gets lost in his/her thoughts	CBCL (17)	.279	
		Nightmares	CBCL (47)	.226	
		Hears sound or voices that aren't there	CBCL (40)	.216	
	Avoidance	Withdrawn, doesn't get involved with others	CBCL (111)	.374	
		Refuses to talk	CBCL (65)	.190	
	Sense of threat	Worries a lot	CBCL (112)	.480	
		Fears she/he might think or do something bad	CBCL (31)	.439	
		Nervous, high-strung, or tense	CBCL (45)	.368	
		Overtired without good reason	CBCL (54)	.350	
		Fears certain animals, situations, or places, other than school	CBCL (29)	.220	
Self-organization	Emotion dysregulation (F2)	Sudden changes in mood or feelings	CBCL (87)	.784	.823
		Stubborn, sullen, or irritable	CBCL(86)	.573	
		She/he gets angry very easily	TEIQue-SF (18)	.454	
		She/he is not good at controlling the way she/he feels.	TEIQue-SF (27)	.352	

		She/he is often confused about the way she/he feels	TEIQue-SF (33)	.343	
		She/he thinks very carefully before she/he does anything (inverse)	TEIQue-SF (26)	-.198	
		She/he can't find the right words to tell others how she/he feels	TEIQue-SF (29)	.181	
	Negative self-concept (F3)	Feels worthless or inferior	CBCL (35)	.622	.738
		Feels or complains that no one loves him/her	CBCL (33)	.599	
		Often, she/he is not happy with her/himself	TEIQue-SF (12)	.279	
		Feels too guilty	CBCL (52)	.273	
	Disturbance relationships (F4)	Feels others are out to get him/her	CBCL (34)	.489	.702
		Complains of loneliness	CBCL (12)	.474	
		Suspicious, distrustful	CBCL (89)	.350	

Abbreviations: PTSD = Post-Traumatic Stress Disorder; CBCL= Child Behavior checklist 6-18; TEIQue-SF = Trait Emotional Intelligence Questionnaire-Short Form answered by parents/guardians

Table S2. Fit indices and model comparison of Complex Post-Traumatic Stress Disorder (CPTSD) competing models

CPTSD models	X^2	df	p	BBNNI	CFI	MFI	RMSEA
A) 1-factor 1st order (CPTSD)	664.846	347	<.001	.822	.836	.403	.073
B) 4-factor 1st order (PTSD, ED, NSC, IP)	345.819	340	.402	.997	.997	.984	.010
C) 4-factor 2n order (CPTSD: PTSD, ED, NSC, IP)	567.648	341	<.001	.871	.883	.523	.062

Abbreviations: BBNNI= Bentler-Bonett nonnormed fit index; CFI = comparative fit index; MFI = Mcdonald's fit index; RMSEA = root-mean-square error of approximation**;** CPTSD = Complex Post-Traumatic Stress Disorder symptoms; PTSD = Post-Traumatic Stress Disorder symptoms; ED: emotional dysregulation; NSC=negative self-concept; IP= interpersonal problems.

Table S3. Regression analysis of the impact of CM (each subtype and period of exposure) on CPTSD symptomatology (PTSD, emotional dysregulation, negative self-concept and interpersonal problems) in participants with (cases) and without (controls) current psychiatric diagnostic

		Cases						Controls					
			95% CI						95% CI				
STEP	**Effect**	**Beta**	**LL**	**UL**	**t**	**p**	**ΔR^2 (*100)**	**Beta**	**LL**	**UL**	**t**	**p**	**ΔR^2 (*100)**
Outcome: PTSD													
1	Development stage [a]	.159	-0.994	4.444	1.258	.211	23.8%***	.310	-0.558	3.887	1.496	.140	13.6%*
	Age	.200	-0.072	0.978	1.711	.090		-.520	-0.852	-0.102	2.538	.014*	
	Sex	.194	-0.107	4.340	1.887	.062		.080	-0.844	1.701	0.672	.504	
	Socioeconomic status	-.089	-0.080	0.025	1.025	.308		-.163	-0.068	0.012	1.406	.165	
2	Maltreatment score	.309	0.046	0.169	3.465	.001***	7.8%***	.314	0.020	0.225	2.395	.020*	7.1%*
2.1a	Emotional neglect	.259	0.963	4.802	2.977	.004**	5.9%**	.272	-0.003	3.986	1.995	.050*	5.1%*
2.1b	EN 0-5 years	.048	-1.941	3.020	0.431	.667	6.5%*	.312	-1.735	6.948	1.200	.235	6.4
	EN 6-12 years	.218	-0.393	5.110	1.700	.092		-.036	-5.123	4.577	0.113	.911	
	EN 13-17 years	.045	-2.012	3.009	0.394	.695		-.011	-3.099	2.909	0.063	.950	
2.2a	Physical neglect	.103	-0.922	3.258	1.108	.270	0.9%	.330	1.485	9.052	2.782	.007**	9.3%**
2.2b	PN 0-5 years	.234	0.068	6.156	2.028	.045*	7.1%*	.561	3.773	14.135	3.454	.001***	14.0%**
	PN 6-12 years	.029	-2.862	3.588	0.223	.824		NA	NA	NA	NA	NA	
	PN 13-17 years	-.123	-5.157	1.150	1.260	.211		-.318	-14.138	-0.104	2.028	.047*	
2.3a	Emotional abuse	.421	2.867	6.554	5.066	<.001***	15.0%***	.309	0.575	5.302	2.483	.016*	7.6*
2.3b	EA 0-5 years	-.098	-4.152	1.461	0.951	.344	13.9%***	.540	2.136	10.233	3.054	.003**	13.2%*
	EA 6-12 years	.488	2.752	8.418	3.909	<.001***		-.487	-10.196	-0.972	2.421	.018*	
	EA 13-17 years	-.065	-3.539	1.830	0.631	.529		.301	0.217	7.689	2.115	.038*	
2.4a	Physical abuse	.290	1.437	5.079	3.547	.001***	8.2%***	.225	-0.103	3.872	1.895	.063	4.6%
2.4b	PA 0-5 years	.201	0.012	5.520	1.992	.049*	9.8%**	.337	0.093	6.866	2.054	.044*	9.7%
	PA 6-12 years	.157	-0.806	4.435	1.373	.173		.065	-2.133	3.283	0.424	.673	
	PA 13-17 years	.013	-2.957	3.391	0.136	.892		-.233	-11.108	0.667	1.773	.081	

2.5a	Sexual abuse	.350	2.386	6.925	4.068	<.001***	10.4%***	-.110	-4.590	1.692	0.922	.360	1.1%
2.5b	SA 0-5 years	-.141	-12.791	1.320	1.612	.110	9.9%**	.012	-7.391	7.918	0.069	.945	1.7%
	SA 6-12 years	.250	1.188	7.204	2.767	.007**		-.056	-6.290	4.497	0.332	.741	
	SA 13-17 years	.194	0.389	6.108	2.253	.026*		-.126	-8.290	2.595	1.040	.302	
Outcome: Emotional dysregulation													
1	Development stage [a]	.199	-0.567	3.417	1.419	.159	6.2%	.131	-1.553	3.280	0.714	.478	32.6%***
	Age	-.217	-0.710	0.059	1.678	.096		-.550	-1.029	-0.213	3.042	.003**	
	Sex	.048	-1.287	1.971	0.416	.678		.084	-0.828	1.939	0.802	.425	
	Socioeconomic status	-.176	-0.074	0.003	1.830	.070		-.327	-0.113	-0.026	3.199	.002**	
2	Maltreatment score	.225	00.005	0.098	2.206	.030*	4.2%*	.276	0.021	0.244	2.378	.020*	5.5%*
2.1a	Emotional neglect	.200	0.036	2.909	2.033	.045*	3.6%*	.409	1.644	5.717	3.610	.001***	11.4%***
2.1b	EN 0-5 years	.059	-1.435	2.309	0.463	.644	2.6%	.221	-1.954	6.511	1.076	.286	17.2%***
	EN 6-12 years	-.005	-2.116	2.038	0.037	.971		.003	-4.705	4.753	0.010	.992	
	EN 13-17 years	.171	-0.647	3.143	1.306	.194		.346	0.844	6.702	2.575	.012*	
2.2a	Physical neglect	.169	-0.258	2.783	1.646	.103	2.4%	.081	-2.749	5.925	0.732	.467	0.6%
2.2b	PN 0-5 years	.230	-0.274	4.324	1.747	.084	3.4%	-.031	-6.686	5.472	0.200	.842	1.7%
	PN 6-12 years	-.091	-3.179	1.694	0.604	.547		NA	NA	NA	NA	NA	
	PN 13-17 years	.009	-2.482	2.283	0.083	.934		.154	-3.991	12.475	1.030	.307	
2.3a	Emotional abuse	.217	.124	3.073	2.150	.034*	4.0%*	.299	.949	6.040	2.742	.008**	7.1%**
2.3b	EA 0-5 years	.205	-0.349	4.073	1.670	.098	5.0%	.106	-2.949	5.934	0.672	.504	9.2%*
	EA 6-12 years	-.044	-2.562	1.902	0.294	.770		-.046	-5.711	4.408	0.257	.798	
	EA 13-17 years	.126	-1.024	3.206	1.023	.309		.324	1.145	9.343	2.557	.013*	
2.4a	Physical abuse	.312	0.974	3.652	3.426	.001***	9.4%***	.109	-1.085	3.321	1.014	.314	1.1%
2.4b	PA 0-5 years	.151	-0.691	3.436	1.319	.190	8.2%*	.414	1.603	8.932	2.873	.006**	8.1%*
	PA 6-12 years	.110	-1.126	2.802	0.847	.399		-.190	-5.001	0.859	1.413	.163	
	PA 13-17 years	.126	-1.029	3.728	1.125	.263		-.154	-10.630	2.112	1.336	.186	
2.5a	Sexual abuse	.098	-.920	2.641	0.958	.340	0.8%	.094	-1.888	4.944	0.893	.375	0.8%
2.5b	SA 0-5 years	-.064	-7.215	3.808	0.613	.541	1.0%	.011	-8.037	8.658	0.074	.941	0.9%
	SA 6-12 years	.109	-1.139	3.559	1.022	.309		.086	-4.185	7.578	0.577	.566	
	SA 13-17 years	.003	-2.195	2.272	0.034	.973		.032	-5.013	6.787	0.301	.765	

Outcome: Negative Self concept													
1	Development stage [a]	.074	-0.880	1.554	0.549	.584	13.3%**	-.001	-1.239	1.236	0.003	.998	10.8%
	Age	.166	-0.076	0.394	1.338	.184		-.187	-0.303	0.115	0.897	.373	
	Sex	.204	-0.063	1.856	1.928	.066		.124	-0.345	1.073	1.026	.309	
	Socioeconomic status	.048	-0.017	0.030	0.525	.600		-.238	-0.045	0.001	2.020	.047*	
2	Maltreatment score	.340	0.022	0.077	3.600	<.001***	9.5%***	.464	0.045	0.153	3.666	.001***	15.5%***
2.1a	Emotional neglect	.268	0.392	2.115	2.885	.005**	6.4%**	.554	1.218	3.221	4.428	<.001***	20.9%***
2.1b	EN 0-5 years	.070	-0.794	1.459	0.585	.560	5.0%	.133	-1.420	2.643	0.602	.550	30.9%***
	EN 6-12 years	.136	-0.631	1.868	0.982	.328		.194	-1.462	3.077	0.711	.479	
	EN 13-17 years	.097	-0.693	1.588	0.779	.438		.428	2.958	0.674	3.486	.004**	
2.2a	Physical neglect	.218	0.116	1.955	2.232	.028*	3.9%*	.208	-0.366	4.002	1.663	.101	3.7%
2.2b	PN 0-5 years	.250	0.027	2.768	2.023	.046*	7.2%*	.090	-2.274	3.856	0.516	.608	4.9%
	PN 6-12 years	.042	-1.233	1.671	0.299	.765		NA	NA	NA	NA	NA	
	PN 13-17 years	-.051	-1.764	1.075	0.481	.631		.162	-2.166	6.135	0.956	.343	
2.3a	Emotional abuse	.309	0.574	2.327	3.280	.001***	8.1%***	.520	1.507	3.909	4.505	<.001***	21.5%***
2.3b	EA 0-5 years	.043	-1.079	1.572	0.368	.713	7.7%*	.227	-0.617	3.473	1.396	.168	27.0%***
	EA 6-12 years	.234	-0.216	2.461	1.663	.099		-.126	-3.120	1.539	0.679	.500	
	EA 13-17 years	.059	-0.942	1.594	0.510	.611		.562	2.159	5.934	4.286	<.001***	
2.4a	Physical abuse	.289	0.543	2.186	3.294	.001***	8.1%***	.356	0.570	2.693	3.069	.003**	11.5%**
2.4b	PA 0-5 years	.141	-0.443	2.080	1.287	.201	7.6%*	.555	1.349	4.930	3.505	.001***	17.8%**
	PA 6-12 years	.109	-0.674	1.726	0.869	.387		-.073	-1.787	1.076	0.497	.621	
	PA 13-17 years	.122	-0.621	2.286	1.135	.259		-.148	-4.932	1.293	1.168	.247	
2.5a	Sexual abuse	.210	0.105	2.243	2.178	.032*	3.7%*	.023	-1.594	1.926	0.188	.851	0.0%
2.5b	SA 0-5 years	-.089	-4.820	1.802	0.904	.368	3.9%	.159	-2.323	6.216	0.911	.366	1.5%
	SA 6-12 years	.161	-0.277	2.545	1.593	.114		-.119	-4.048	1.968	0.691	.492	
	SA 13-17 years	.116	-0.528	2.156	1.203	.232		.058	-2.310	3.725	0.469	.641	
Outcome: Disturbance relationships													
1	Development stage [a]	.163	-0.386	1.541	1.189	.237	10.6%*	.033	-0.581	0.682	0.160	.873	15.9%*
	Age	.037	-0.159	0.213	0.293	.770		-.386	-0.208	0.005	1.908	.061	
	Sex	.120	-0.359	1.217	1.080	.283		.068	-0.257	0.466	0.577	.566	
	Socioeconomic status	-.131	-0.032	0.005	1.402	.164		-.156	-0.019	0.004	1.370	.175	

2	Maltreatment score	.423	0.027	0.069	4.540	<.001***	14.7%***	.286	0.003	0.061	2.194	.032*	5.9%*
2.1a	Emotional neglect	.264	0.276	1.643	2.785	.006**	6.1%**	.287	0.039	1.167	2.136	.036*	5.6%*
2.1b	EN 0-5 years	-.038	-1.029	0.749	0.313	.755	5.7%	.364	-0.314	2.063	1.471	.146	11.7%*
	EN 6-12 years	.186	-0.327	1.645	1.325	.188		.061	-1.195	1.461	0.200	.842	
	EN 13-17 years	.139	-0.398	1.401	1.106	.271		-.143	-1.188	0.456	0.889	.377	
2.2a	Physical neglect	.206	0.031	1.491	2.066	.041*	3.5%*	.055	-0.881	1.390	0.448	.655	0.3%
2.2b	PN 0-5 years	.162	-0.394	1.807	1.274	.206	5.0%	.192	-0.707	2.471	1.110	.271	1.9%
	PN 6-12 years	.091	-0.795	1.537	0.631	.529		NA	NA	NA	NA	NA	
	PN 13-17 years	-.087	-1.605	0.675	0.808	.421		-.188	-3.364	0.940	1.126	.265	
2.3a	Emotional abuse	.407	0.821	2.159	4.417	<.001***	14.0%***	.171	-0.225	1.160	1.348	.182	2.3%
2.3b	EA 0-5 years	.079	-0.666	1.381	0.693	.490	11.9%**	.281	-0.250	2.100	1.574	.121	9.6%
	EA 6-12 years	.314	0.142	2.208	2.256	.026*		.051	-1.171	1.506	0.250	.803	
	EA 13-17 years	.003	-0.966	0.992	0.0236	.979		-.211	-1.880	0.289	1.467	.147	
2.4a	Physical abuse	.336	0.589	1.876	3.837	<.001***	11.0%***	.142	-0.232	0.915	1.189	.239	1.8%
2.4b	PA 0-5 years	.246	0.131	2.089	2.249	.027*	10.9%**	-.034	-1.084	0.880	0.208	.838	6.2%
	PA 6-12 years	.068	-0.675	1.188	0.547	.586		.275	-0.083	1.487	1.787	.079	
	PA 13-17 years	.126	-0.456	1.800	1.182	.240		-.204	-3.021	0.393	1.539	.129	
2.5a	Sexual abuse	.272	0.351	2.019	2.818	.006**	6.3%**	.032	-0.777	1.017	0.268	.789	0.1%
2.5b	SA 0-5 years	-.067	-3.465	.684	0.686	.494	6.9%*	.229	-0.677	3.628	1.370	.176	3.2%
	SA 6-12 years	.261	0.333	2.528	2.586	.010**		-.086	-1.913	1.121	0.522	.603	
	SA 13-17 years	.101	-0.487	1.600	1.058	.292		-.042	-1.789	1.254	0.352	.726	

UNIVERSITAT DE BARCELONA

Dr. Lourdes Fañanás Saura
Unitat de Zoologia i Antropologia Biològica
Dept. Biologia Evolutiva, Ecologia i Ciències Ambientals
Facultat de Biologia, Universitat de Barcelona

Informe del director sobre la contribución del doctorando al artículo.

La Prof. Lourdes Fañanás Saura, profesora del Departamento de Biología Evolutiva, Ecologia y Ciencias Ambientales de la Facultad de Biología (Universitat de Barcelona) y directora de la presente tesis doctoral de Laia Marques Feixa, por la presente certifica que ninguno de los coautores del articulo *""Reinforcing the new diagnosis of Complex Post-Traumatic Stress disorder (CPTSD) of ICD-11 in children and adolescents exposed to relational trauma: developmental stage at exposure and its associated clinical outcomes",* ha utilizado esta publicacion para una tesis doctoral, y que la participación del solicitante en este artículo incluyó las siguientes tareas:

- Participación en la concepción y diseño del estudio.
- Reclutamiento y evaluación de los sujetos incluidos.
- Coordinación del proyecto.
- Procesamiento de los datos.
- Análisis estadísticos e interpretación de los datos.
- Redacción del manuscrito.
- Revisión crítica del artículo por contenido intelectual.

Signado por Prof. Lourdes Fañanás

Barcelona, abril 2022

Sección III: La neurobiología del maltrato infantil en niños/as y adolescentes

3.5. Childhood maltreatment disrupts HPA-axis activity under basal and stress conditions in a dose–response relationship in children and adolescent

Laia Marques-Feixa, Helena Palma-Gudiel, Soledad Romero, Jorge Moya-Higueras, Marta Rapado-Castro, Águeda Castro-Quintas, Iñaki Zorrilla, María José Muñoz, Maite Ramírez, María Mayoral, Ariadna Mas, María José Lobato, Hilario Blasco-Fontecilla, Lourdes Fañanás y EPI-Young Stress GROUP

Psychological Medicine (2021), Jul 16;1-14.

DOI: 10.1017/S003329172100249X.

Psychological Medicine

cambridge.org/psm

Original Article

*List of authors is provided at the end of document.

Cite this article: Marques-Feixa L *et al* (2021). Childhood maltreatment disrupts HPA-axis activity under basal and stress conditions in a dose–response relationship in children and adolescents. *Psychological Medicine* 1–14. https://doi.org/10.1017/S003329172100249X

Received: 10 November 2020
Revised: 31 March 2021
Accepted: 3 June 2021

Key words:
Anxiety perception; child abuse; childhood maltreatment (CM); cortisol; dose–response; hypothalamic–pituitary–adrenal (HPA)-axis; Trier Social Stress Test for children (TSST-C); youth psychopathology

Author for correspondence:
Lourdes Fañanás, E-mail: lfananas@ub.edu

CAMBRIDGE UNIVERSITY PRESS

Childhood maltreatment disrupts HPA-axis activity under basal and stress conditions in a dose–response relationship in children and adolescents

Laia Marques-Feixa[1,2], Helena Palma-Gudiel[1,2], Soledad Romero[2,3,4], Jorge Moya-Higueras[2,5], Marta Rapado-Castro[2,6,7], Águeda Castro-Quintas[1,2], Iñaki Zorrilla[2,8], María José Muñoz[9], Maite Ramírez[10], María Mayoral[2,6], Ariadna Mas[3], María José Lobato[11], Hilario Blasco-Fontecilla[2,11], Lourdes Fañanás[1,2] and EPI-Young Stress GROUP*

[1]Department of Evolutionary Biology, Ecology and Environmental Sciences, Faculty of Biology, University of Barcelona, Biomedicine Institute of the University of Barcelona (IBUB), Barcelona, Spain; [2]Network Centre for Biomedical Research in Mental Health (CIBER of Mental Health, CIBERSAM), Spain; [3]Department of Child and Adolescent Psychiatry and Psychology, Institute of Neuroscience, Hospital Clínic de Barcelona, 2017SGR88, Barcelona, Spain; [4]Institut d'Investigacions Biomediques August Pi i Sunyer (IDIBAPS), Barcelona, Spain; [5]Department of Psychology, Faculty of Education, Psychology and Social Work, University of Lleida, Spain; [6]Department of Child and Adolescent Psychiatry, Institute of Psychiatry and Mental Health, Hospital General Universitario Gregorio Marañón, School of Medicine, Universidad Complutense, IiSGM, Madrid, Spain; [7]Department of Psychiatry, Melbourne Neuropsychiatry Centre, The University of Melbourne & Melbourne Health, Victoria, Australia; [8]Department of Psychiatry, Hospital Santiago Apostol, Vitoria-Gasteiz, Spain; [9]Hospital Benito Menni, Adolescent Crisis Unit, Sant Boi de Llobregat, Spain; [10]Galdakao Mental Health Services, Child and Adolescent Mental Health, Galdakao, Spain; [11]Department of Psychiatry, Puerta de Hierro University Hospital-Majadahonda, Autonoma University, ITA Mental Health, Madrid, Spain and [12]Day Hospital for Adolescents, Fundació Orienta, Gavà, Spain

Abstract

Background. This study investigates the impact of childhood maltreatment (CM) on hypothalamic–pituitary–adrenal (HPA)-axis functioning and on anxiety perception. Moreover, the influence of CM severity and frequency was also explored.

Methods. In total, 187 participants aged 7–17 were assessed for CM history using validated questionnaires and *ad hoc* interviews to be classified according to the criteria of the Tool for Assessing the Severity of Situations in which Children are Vulnerable (TASSCV). Psychopathology was ascertained using the K-SADS-PL5. To assess HPA-axis functioning, salivary cortisol samples were collected throughout a normal day and during an acute psychosocial stressor, the Trier Social Stress Test for children (TSST-C). Subjective anxiety was evaluated using STAI/-C.

Results. Youth with a CM history had higher overall diurnal cortisol levels ($p = 0.001$), blunted cortisol response to acute psychosocial stress ($p = 0.002$) and greater perceived anxiety ($p = 0.003$), than those without CM. Specifically, participants exposed to moderate/severe or often/frequent CM showed the greater diurnal cortisol output ($p_{severity} = 0.002$; $p_{frequency} = 0.003$), and blunted cortisol response during the TSST-C ($p_{severity} = 0.006$; $p_{frequency} = 0.008$). Meanwhile, youth with low CM severity/frequency exhibited a similar cortisol response to those without CM. However, perceived anxiety was higher in those exposed to CM ($p < 0.001$), regardless of its severity/frequency.

Conclusions. Disturbances in HPA-axis functioning are already evident early after CM exposure, while psychological and physiological responses to an acute stressor are dissociated in youth exposed to CM. The dose–response relationship described in this paper highlights the need to comprehensively evaluate CM so that vulnerable children can be identified and assigned to proper interventions.

Introduction

Experiences of childhood maltreatment (CM) are one of the main contributors to mental illness (Brown, Harris, & Craig, 2019; Hughes et al., 2017). However, CM is non-specifically associated with psychiatric disorders, i.e. several types of CM can increase vulnerability for a specific disorder in different patients (Vachon, Krueger, Rogosch, & Cicchetti, 2015). CM has been associated with early onset of psychiatric illness, increased symptom severity and comorbidity, and poor clinical outcomes characterized by requiring higher medication

dosages, increased suicidal behavior, and more and longer hospitalizations (Lippard & Nemeroff, 2020). Furthermore, factors such as time of exposure, chronicity, and severity of childhood abuse or neglect play a role in clinical outcomes. Studies indicate a dose–response relationship between multiplicity of exposure, severity or frequency, and risk of mental disorders (Anda et al., 2006).

CM is associated with dysregulation of stress-mediating systems, thereby increasing the risk of mental and physical health problems. Specifically, disruptions in hypothalamic–pituitary–adrenal (HPA)-axis regulation have been studied as a potential mediator of this association (Koss & Gunnar, 2018; Kudielka & Wüst, 2010). The HPA-axis is one of the main stress response systems; cortisol, its final effector, released in direct response to acute stressors, triggers a wide range of actions by regulating gene transcription and epigenetic modifications in several brain areas (Provençal, Arloth, Cattaneo, Anacker, & Cattane, 2019). Furthermore, HPA-axis maintains a diurnal rhythm, with the highest cortisol levels in the morning which decrease progressively during the day until reaching the lowest at midnight. Since the HPA-axis continues to mature during early stages of life, environmental factors such as early-life stress may induce long-lasting changes in its functioning, resulting in the emergence of different disorders (Tarullo & Gunnar, 2006). However, findings regarding alterations in the patterns of cortisol associated with early-life stress have been inconsistent (Fogelman & Canli, 2018).

A recent meta-analysis focusing on CM and diurnal HPA-axis activity in children and adults reported no overall effect on diurnal cortisol slope (Bernard, Frost, Bennett, & Lindhiem, 2017). However, a moderate association was found between CM and blunted awakening cortisol concentrations when considering only sufferers of CM who were referred from child welfare system agencies. In contrast, another recent meta-analysis showed that CM affects HPA-axis reactivity during stressful situations as evidenced by a flattened cortisol pattern during an acute psychosocial stress task in children and adults who faced early-life adversities (Bunea, Szentágotai-t, & Miu, 2017). Interestingly, the effects were more pronounced in studies focused on adults and CM. These findings suggest a pattern of blunted cortisol response during the peak and recovery phases of acute stress, and overall hypocortisolism in individuals exposed to CM. However, some studies report hypercortisolism in subjects exposed to early-life stress, childhood trauma, or insensitive interactions with caregivers (Hunter, Minnis, & Wilson, 2011). Besides, it has been suggested that distinct patterns of cortisol responses may be partially explained by CM severity and frequency (Ouellet-Morin et al., 2019), pubertal stage (King et al., 2017), or sex (Trickett, Gordis, Peckins, & Susman, 2014).

Notably, HPA-axis dysregulation, both hyperactivity and hypoactivity, has been associated with different psychiatric disorders and other disease outcomes (Turner et al., 2020). Although infancy is a sensitive period for HPA-axis regulation, this system remains plastic and it can be recalibrated during specific ontogenic periods, if the environmental conditions improve. In fact, recent studies support puberty as a key recalibration period to trigger shifts in HPA-axis functioning in postinstitutionalized children (DePasquale, Donzella, & Gunnar, 2019).

Thus, the main aim of the current research was to establish the proximal effects of CM on HPA-axis regulation and anxiety perception in children and adolescents, under basal conditions and in response to a psychosocial stressor, as compared with youth without CM. In addition, the differential impact of the severity and frequency of the CM experiences was also analyzed to better dissect the relationship between CM and HPA-axis dysfunction. Finally, anxiety perception was assessed throughout the experimental stress paradigm to verify that all participants underwent a subjective experience of stress (regardless of their CM history); thus, the potential differences in stress perception with regard to CM can be disentangled from actual differences in HPA-axis functioning. Complementarily, anxiety trait was also assessed in relationship with basal diurnal cortisol output. Specifically, we hypothesized that exposure to CM would be associated with blunted HPA-axis functioning and higher anxiety perception. Moreover, more severe and frequent exposure to CM would be associated with greater dysregulation of the HPA-axis following a dose–response relationship.

Methods

The EPI-Young-Stress project is a multi-center study which aims to evaluate HPA-axis functioning, associated epigenetic signatures, and immunological biomarkers involved in the association between CM and youth mental disorders. The research was conducted at the University of Barcelona and six child and adolescent psychiatry departments in Spain: Hospital Benito Menni, Hospital Clínic Barcelona, Hospital Gregorio Marañón, Hospital Puerta de Hierro, Hospital Santiago Apóstol, and Day Hospital Orienta Gavà.

The study was approved by the Ethical Review Board of each participating hospital and university. Families were explicitly informed about the voluntary nature of the study, their rights, and the procedures, risks, and potential benefits involved. Written consent was required from all parents or legal guardians; the children provided written assent after the nature of the procedure had been fully explained.

Participants

A total of 187 children and adolescents aged 7–17 years participated in this study. Children without psychopathology were recruited from advertisements, primary healthcare centers, schools, and other community facilities. Children with current psychopathology were recruited from the above-mentioned hospitals (inpatient clinics, partial hospitalization programs, and outpatient clinics) (see Table 1). Recruitment lasted from April 2016 to March 2020. Exclusion criteria for all participants included diagnosis of autism spectrum disorder, eating disorder with body mass index (BMI)<18.5, intellectual disability (IQ < 70), current drug dependence, non-fluency in Spanish, extreme premature birth (<1500 g at birth), head injury with loss of consciousness, and severe neurological or other pathological conditions likely to affect HPA-axis functioning (such as cancer or autoimmune diseases).

Procedures

Sociodemographic and clinical measures

The interview package included basic demographic information including socioeconomic status (SES) based on the Hollingshead Four-Factor Index of SES (Hollingshead, 1975). Pubertal development was assessed using the Tanner staging questionnaire (Morris & Udry, 1980) and participants were classified as either children (Tanner stages 1–3) or adolescents (Tanner stages 4–5). The Global Family Environment Scale

Table 1. Sociodemographic and anthropometric data of participants with and without a history of CM

Variable			Total sample ($n = 187$)	Youth without CM ($n = 93$, 50%)	Youth with CM ($n = 94$, 50%)	t/χ^2	p	d/κ
Age (M, S.D.)[a]			13.62 (2.59)	13.20 (2.69)	14.03 (2.44)	−2.204	**0.029***	0.323
Sex[b]	Female (*n*, %)		108 (58%)	48 (52%)	60(64%)	2.860	0.091	0.122
	Male (*n*, %)		79 (42%)	45 (48%)	34 (36%)			
Pubertal stage[b]	Child (Tanner stage 1–3) (*n*, %)		94 (50%)	53 (57%)	41 (44%)	3.344	0.067	0.134
	Adolescent (Tanner stage 4–5) (*n*, %)		93 (50%)	40 (43%)	53 (56%)			
Ethnicity[b]	European (*n*, %)		154 (82%)	87 (93%)	67 (71%)	15.956	**<0.001*****	0.222
	Others[c] (*n*, %)		33 (18%)	6 (7%)	27 (29%)			
Socioeconomic status (SES) (M, S.D.)[a,d]			40.34 (17.93)	47.49 (14.77)	33.12 (18.03)	5.893	**<0.001*****	0.872
CGAS (M, S.D.)[a]			72.07 (21.66)	84.26 (14.37)	59.88 (20.89)	9.270	**<0.001*****	1.359
Current psychiatric diagnosis status[b]	Subjects without current psychiatric diagnosis (*n*, %)		71 (38%)	56 (60%)	15 (16%)	38.879	**<0.001*****	−0.442
	Subjects with current psychiatric diagnosis (*n*, %):		116 (62%)	37 (40%)	79 (84%)			
	Primary psychiatric diagnosis dimensions[b,e]	ADHD	30 (26%)	18 (49%)	12 (15%)	32.235	**<0.001*****	0.119
		Affective disorders	29 (25%)	6 (16%)	23 (29%)			
		Trauma and stress-related disorders	19 (16%)	0 (0%)	19 (24%)			
		Anxiety disorders	15 (13%)	9 (24%)	6 (8%)			
		Behavioral disorders	13 (11%)	1 (3%)	12 (15%)			
		Psychotic disorders	7 (6%)	3 (8%)	4 (5%)			
		Eating disorders	3 (3%)	0 (0%)	3 (4%)			
	Clinical care units of subjects with current psychiatric diagnosis[b,e]	Outpatient	69 (60%)	31 (83%)	38 (48%)	13.458	**0.001****	−0.262
		Inpatient	35 (30%)	5 (14%)	30 (38%)			
		Partial program	12 (10%)	1 (3%)	11 (14%)			
	Psychopharmacological treatment of subjects with current psychiatric diagnosis[b,e]	No (*n*, %)	28 (24%)	9 (24%)	19 (24%)	0.001	0.974	<0.001
		Yes (*n*, %)	88 (76%)	28 (76%)	60 (76%)			
Oral contraceptive use[b,f]	No (*n*, %)		102 (94%)	47 (98%)	55 (92%)	1.985	0.159	0.056
	Yes (*n*, %)		6 (6%)	1 (2%)	5 (8%)			
Corticosteroid medication[b]	No (*n*, %)		184 (98%)	90 (97%)	94 (100%)	3.082	0.079	−0.032
	Yes (*n*, %)		3 (2%)	3 (3%)	0 (0%)			

(*Continued*)

Table 1. (*Continued.*)

Variable		Total sample ($n = 187$)	Youth without CM ($n = 93$, 50%)	Youth with CM ($n = 94$, 50%)	t/χ^2	p	d/κ
Last year global family environmental (GFES) (M, S.D.)[a,g]		78.24 (15.03)	84.53 (9.65)	71.94 (16.76)	6.104	**<0.001*** **	0.920
Illegal drug use[b]	Never	164 (88%)	90 (97%)	74 (79%)	15.242	**0.002** **	0.124
	Less than once a month	10 (5%)	1 (1%)	9 (10%)			
	Once a month or more	7 (4%)	2 (2%)	5 (5%)			
	Daily use	6 (3%)	0 (0%)	6 (6%)			
BMI (M, S.D.)[a,h]		21.45 (5.17)	19.66 (3.75)	23.23 (5.77)	−4.799	**<0.001*** **	0.733
WHR (M, S.D.)[a,h]		0.84 (0.09)	0.84 (0.09)	0.84 (0.09)	0.059	0.953	−0.011

ADHD, attention-deficit/hyperactivity disorder; BMI, body mass index; CGAS, Children's Global Assessment Scale, rating from 1 to 100 with higher ratings indicating better functioning in a wide range of activities; CM, childhood maltreatment (CM group refers to subjects with a confirmed or suspected history of CM); GFES, The Global Family Environment Scale, ranging from 1 to 90, with higher scores indicating a better family environment; SES, socioeconomic status, raw scores range from 8 to 66, with higher scores reflecting higher SES; WHR, waist-to-hip ratio.

[a]Student's *t* test.

[b]χ^2 test.

[c]Other ethnicities included Latin American (66%), Maghrebin (16%), sub-Saharan (9%), and others (9%).

[d]This analysis was conducted with 183 subjects.

[e]This analysis was only conducted with the 116 subjects with a current psychiatric diagnosis.

[f]This analysis was only conducted with the 108 female subjects.

[g]This analysis was conducted with 176 subjects.

[h]This analysis was conducted within 171 subjects.

p values: $*p < 0.05$, $**p < 0.01$, and $***p < 0.001$. *d* = Cohen's effect size.

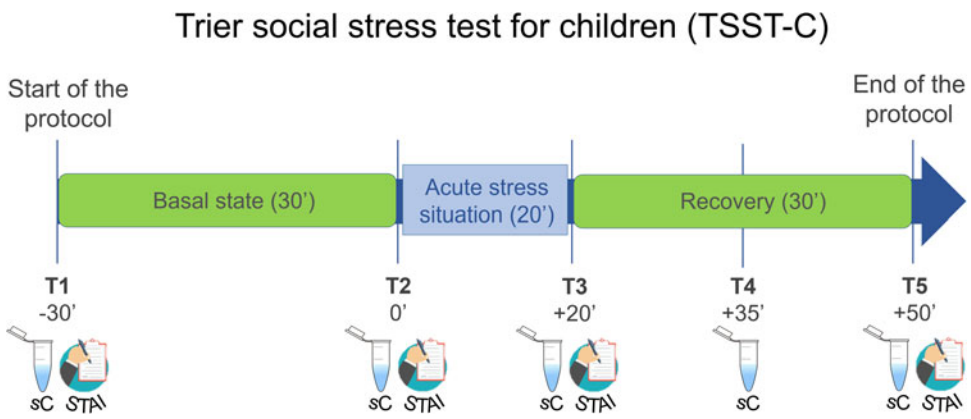


Fig. 1. Summary of the Trier Social Stress Test for children (TSST-C) protocol. sC, salivary cortisol sample; STAI, State/Trait Anxiety Inventory – State.

(GFES) was used to measure the quality of the family environment (Rey et al., 1997). Additionally, ethnicity, BMI and waist-to-hip ratio were recorded.

Both participants and their parents directly recounted the youth's medical history. Psychopathology was assessed using the Spanish version of the Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime Version DSM-5 (K-SADS-PL-5) (de la Peña et al., 2018). Information was completed whenever possible using medical records. Final diagnoses were established by consensus, and based on DSM-5 criteria (APA: American Psychiatric Association, 2013), primary psychiatric diagnoses were later classified into dimensions to better characterize the sample (see Table 1). The global level of functioning was measured by the Children's Global Assessment Scale (CGAS) (Shaffer et al., 1983). The use of psychiatric medication was dichotomized as absence/presence, since there were no differences in cortisol levels according to the different drugs (data available upon request). Current illegal drug use was classified into four frequency groups: never, less than once a month, once a month or more, and daily use (Forti et al., 2019).

Childhood maltreatment assessment

All participants and their parents/legal guardians were interviewed separately, face to face, by one trained psychologist or psychiatrist. They were assessed by means of an exhaustive interview focused on the identification of signs of child vulnerability, adverse experiences, and family interactions, based on the criteria of the instrument 'Tool for assessing the severity of situations in which children are vulnerable' (TASSCV), which has been validated by professionals working in child and adolescent care units (see online Supplementary material) (CARM, 2012). Additionally, adolescents older than 12 were assessed for history of CM via the short version of the Childhood Trauma Questionnaire (CTQ-SF) (Bernstein et al., 2003) and the Childhood Experience of Care and Abuse Questionnaire (CECA-Q2) (Kaess et al., 2011). Children under 12 years answered an adapted hetero-administered *ad hoc* questionnaire (see online Supplementary material). Afterwards, the clinicians completed a table summarizing the different forms of CM effected by caregivers or other adults (not by peers), being TASSCV the main measure of CM used in the primary analyses, while the other measures (CTQ-SF, CECA-Q2, *ad hoc* questionnaire, and reports from social services or teachers) were used as an additional source of information for the clinicians. The exhaustive participants' evaluation during the recruitment process allowed for clinicians to enrich their praxis. In addition, after the interviews of this study, a referral system of urgent appointment was implemented for those subjects who requested it, activating the usual protocols that guarantee the children's protection rights. Following the TASSCV criteria, each CM type was coded as either: (i) absent, (ii) suspected (if significant signs of neglect or abuse emerged during the evaluation), or (iii) confirmed (with clear evidence from social services or family). Severity and frequency of different types of CM were rated on a four-point Likert scale according to TASSCV criteria. CM severity was coded according to the characteristics of the experience suffered as low (1), moderate (2), severe (3), or very severe (4); while frequency was coded as whether CM had occurred once (1), sometimes (2), often (3), or frequently (4). Five types of CM were considered in the following analysis: physical neglect, emotional neglect, physical abuse, emotional abuse, and sexual abuse.

HPA-axis functioning

Four saliva samples were collected during a normal day with the aim to assess HPA-axis diurnal functioning (basal condition), specifically, on waking up (B1), 30 min after waking (B2), before lunch (B3), and before bedtime (B4). On a different day, in order to explore HPA-axis reactivity during acute psychosocial stress, the Trier Social Stress Test for children (TSST-C), a validated protocol that reliably induces HPA-axis activation, was applied (Buske-Kirschbaum et al., 1997). Briefly, upon arrival at the lab, the participants waited in a quiet room for 30 min before entering the examination room, where a panel of judges awaited. During the 20 min of the stress situation, the participants had to perform a speaking and an arithmetic task following instructions from the judges while being videotaped. After the stress task, the participants returned to the first room for 30 min (see online Supplementary material for a more detailed description of the procedure). Five saliva samples were collected during this procedure: 30 min before the stressor (T1), immediately before the stressor (T2), immediately after the stressor (T3), 15 min after the stressor (T4), and 30 min after the stressor (T5) (see Fig. 1). All participants were scheduled at 16:00 h to control for diurnal cortisol variability. Previously, further instructions were given to the participants to avoid factors that have been reported to influence cortisol levels (details in the online Supplementary material). Details about collection time of each salivary cortisol sample are available in Table 2.

Table 2. Cortisol values and anxiety perception according to the presence of CM, CM severity and CM frequency

		Dichotomous CM (mean, S.D.)		Severity of CM (mean, S.D.)		Frequency of CM (mean, S.D.)				
		Youth without CM ($n = 93$)	Youth with CM ($n = 94$)	Youth with low CM ($n = 20$)	Youth with moderate/severe CM ($n = 74$)	Youth once/sometimes exposed to CM ($n = 22$)	Youth often-frequently exposed to CM ($n = 72$)	F (p) dichotomous CM[a]	F (p) severity of CM[a]	F (p) frequency of CM [a]
Diurnal salivary cortisol (μm log-transformed)	B1	−0.66 (0.32)	−0.66 (0.25)	−0.63 (0.24)	−0.67 (0.25)	−0.67 (0.20)	−0.66 (0.26)	1.467 (0.225) B4*	1.214 (0.300) B4*	1.085 (0.375) B4*
	B2	−0.51 (0.31)	−0.52 (0.31)	−0.44 (0.23)	−0.54 (0.33)	−0.40 (0.19)	−0.56 (0.34)			
	B3	−1.09 (0.29)	−1.03 (0.34)	−0.93 (0.34)	−1.05 (0.33)	−0.95 (0.34)	−1.05 (0.34)			
	B4	−1.56 (0.59)	−1.38 (0.45)	−1.46 (0.35)	−1.36 (0.47)	−1.39 (0.38)	−1.38 (0.48)			
	AUCg	−927.77 (262.45)	−831.64 (202.25)	−799.16 (221.60)	−839.42 (198.39)	−765.10 (194.54)	−851.22 (201.84)	**12.244 (0.001**)▲**	**6.349 (0.002**)▲**	**6.068 (0.003**)▲**
	AUCi	−374.70 (326.25)	−291.13 (246.56)	−297.62 (261.08)	−289.58 (244.88)	−234.17 (229.26)	−307.89 (250.57)	3.040 (0.083)	1.716 (0.184)	1.276 (0.282)
Salivary cortisol during TSST-C (μm log-transformed)	T1	−0.97 (0.31)	−0.97 (0.26)	−0.99 (0.30)	−0.96 (0.25)	−0.97 (0.26)	−0.97 (0.26)	**4.530 (0.002**) T3*, T4**, T5***	**2.773 (0.006**) T3*, T4**, T5***	**2.665 (0.008**) T3*, T4**, T5***
	T2	−1.02 (0.26)	−1.01 (0.27)	−1.01 (0.24)	−1.00 (0.28)	−1.01 (0.23)	−1.00 (0.29)			
	T3	−0.89 (0.31)	−0.98 (0.27)	−0.93 (0.25)	−0.99 (0.29)	−0.95 (0.26)	−0.99 (0.29)			
	T4	−0.89 (0.35)	−1.03 (0.32)	−0.99 (0.33)	−1.04 (0.32)	−1.01 (0.30)	−1.03 (0.32)			
	T5	−0.98 (0.35)	−1.07 (0.31)	−1.09 (0.28)	−1.07 (0.32)	−1.07 (0.26)	−1.07 (0.32)			
	AUCg	−75.22 (21.74)	−78.67 (18.75)	−80.52 (22.87)	−78.26 (17.84)	−80.90 (18.94)	−78.02 (18.77)	0.091 (0.763)	0.057 (0.945)	0.074 (0.929)
	AUCi	0.56 (15.55)	−2.79 (15.02)	24 (17.24)	−3.47 (145.3)	−2.19 (16.51)	−2.97 (14.69)	**4.779 (0.030*)**	**3.921 (0.022*)**	**3.194 (0.044*)**
Anxiety trait: STAI-Trait (PC)		36.98 (28.40)	65.39 (32.74)	60.06 (31.50)	66.69 (33.12)	56.10 (34.14)	68.16 (32.04)	**9.129 (0.003**)▲**	**5.109 (0.007**)**	**4.102 (0.019*)**
Perceived anxiety during TSST-C: STAI-State (PC)	T1	25.68 (27.90)	45.34 (33.88)	46.59 (33.13)	45.05 (34.25)	32.05 (28.59)	49.27 (34.50)	1.742 (0.160)	1.670 (0.131)	1.240 (0.287)
	T2	25.20 (27.40)	40.40 (33.04)	32.07 (27.83)	42.07 (33.92)	30.05 (29.99)	43.64 (33.50)			
	T3	43.68 (32.53)	66.58 (32.18)	56.76 (36.70)	68.80 (30.90)	61.62 (32.16)	68.04 (32.27)			
	T5	21.12 (27.42)	42.49 (35.08)	29.41 (34.09)	45.50 (34.84)	27.14 (30.21)	47.10 (35.33)			

AUCg, area under the curve with respect to ground (indicating the total cortisol output); AUCi, area under the curve with respect to increase (reflecting cortisol changes over time); CM, childhood maltreatment (CM group refers to the subjects with a confirmed or suspected history of CM based on TASSCV criteria); STAI-State (PC), percentile scores of state anxiety inventory scale (for adolescents 16–17 years old) and state anxiety inventory for children scale (for participants under 15); STAI-Trait (PC), percentile scores of anxiety trait inventory scale (for adolescents 16–17 years old) and anxiety trait inventory for children scale (for participants under 15); TSST-C, Trier Social Stress Test for children.

Diurnal salivary cortisol was measured at: B1, immediately after awakening; B2, 30 min after waking; B3, before lunch; B4, before bedtime. Mean time for saliva sample collection: 08:52 ± 1:27 (6:00–12:00) (B1); 09:24 ± 1:26 (6:30–12:59) (B2); 14:19 ± 0:53 (12:15–16:40) (B3); and 22:37 ± 01:16 [20:00–2:50(+1day)] (B4). Saliva samples for cortisol measurement during TSST-C were collected at: T1, 30 min before stressor; T2, immediately before stressor; T3, immediately after stressor; T4, 15 min after stressor; T5, 30 min after stressor. Mean time for saliva sample collection during the TSST-C procedure: 16:04 ± 0:11 (15:13–17:15) (T1); 16:33 ± 0:12 (15:42–17:45) (T2); 16:53 ± 0:13 (15:59–18:00) (T3); 17:08 ± 0:13 (16:08-18:16) (T4); and 17:23 ± 0:13 (16:30–18:30) (T5).

Dichotomous CM refers to the analysis comparing youth without CM with youth exposed to any type of CM. Severity of CM refers to the analysis comparing youth without CM, youth exposed to low CM, and youth exposed to moderate/severe CM. Frequency of CM refers to the analysis comparing youth without CM, youth exposed to CM once/sometimes, and youth exposed to CM often/frequently.

[a]Mixed-effects model (for single measurements) and ANOVA (for AUCg and AUCi). The analyses include the following covariates: clinical status, sex, pubertal stage, psychopharmacological treatment, illegal drugs use, oral contraceptive use, corticosteroid medication, ethnicity, SES, and BMI [additionally adjusting by the time of the first cortisol sample collection (B1) for diurnal analysis]. Values in superscript $^{(B4,\ T3,\ T4,\ T5)}$ indicate the samples with a significant difference in the simple effects test in the context of mixed-effect model.

p values: $^{*}p < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.001$. $^{▲}p \leqslant 0.006$ [as the Bonferroni-corrected level of significance for multiple testing (0.05/9 = 0.006)].

Saliva samples were collected using Salivette® tubes (Sarstedt, Inc., Newton, NC, USA) for diurnal cortisol assessment and with Saliva Bio Oral Swabs (SOS) (Salimetrics, LLC, State College, PA, USA) for TSST-C cortisol reactivity. The subjects were asked to chew a swab for 1 min and then transfer it directly from their mouth to the tube. They were instructed to store their saliva samples for diurnal cortisol assessment in a freezer until they could be delivered to the research center, where samples were stored at −20 °C. The saliva samples collected during the TSST-C were directly stored at the research center. Details of salivary cortisol determination procedures are explained in the online Supplementary material.

Anxiety trait and anxiety perception during acute stress

The subscale trait of the State-Trait Anxiety Inventory (STAI) was used to evaluate general proneness to anxious behavior (STAI-Trait for children, for subjects 15 years old and under; STAI-Trait, for adolescents 16–17 years old) (Spielberger, 1973). During the TSST-C, the perceived emotional arousal was assessed via the STAI-State for children scale (for children 15 and under) and the STAI-State subscale (for adolescents 16–17 years old) (Spielberger, 1973). Participants answered the STAI-State questionnaire: 30 min before the stressor (T1), immediately before the stressor (T2), immediately after the stressor (T3), and 30 min after the stressor (T5) (see Fig. 1).

Statistical analysis

All statistical analyses were performed using SPSS 26 for Windows (IBM, Chicago, Illinois, USA). Descriptive statistics were analyzed by Student's t test for continuous variables and a χ^2 test for categorical variables. Cortisol data were log-transformed to reduce skewness. The presence of any type of suspected or confirmed history of CM was included in downstream analysis as a dichotomic variable. The effects of both (i) CM severity (classified as: absent, low, or moderate/severe) and (ii) the frequency of CM (classified as: never, once/sometimes, or often/frequently) were also tested through independent analyses. Sensitivity analysis was conducted to explore the effects of CM when considering only subjects with a confirmed history of CM (with clear evidence from social service reports or family), aggregating those with suspected history of CM together with those without CM (see online Supplementary material).

To examine the effect of CM in diurnal cortisol slopes and changes in cortisol and anxiety perception across the TSST-C, mixed-effects models with a random effect of intercept and a random slope of time, to account for within-subject correlations, were used. Interaction with time was considered the main effect of interest of the model. Time factor had four categories (timepoints) for diurnal cortisol and anxiety perception during TSST-C, and five categories for cortisol during TSST-C. In addition, simple effects tests were performed to evaluate the specific time point interaction between groups. Additionally, the overall cortisol secretion during a normal day and throughout the experimental protocol was summarized applying: (i) the area under the curve with respect to ground (AUCg) to explore the total hormonal output, and (ii) the area under the curve with respect to increase (AUCi) to reflect hormonal changes over time (Pruessner, Kirschbaum, Meinlschmidt, & Hellhammer, 2003). Differences in AUCg, AUCi, and STAI-Trait scores between CM groups were tested by ANOVA. All the analyses were adjusted for the following covariates, as previously described to influence cortisol output during the TSST (Allen, Kennedy, Cryan, Dinan, & Clarke, 2014; De Punder, Heim, & Entringer, 2019; Lê-scherban et al., 2018; Marceau & Abel, 2018): clinical status, sex, pubertal stage, psychopharmacological treatment, illegal drugs use, oral contraceptive use, corticosteroid medication, ethnicity, SES, and BMI. In the diurnal cortisol analyses, the time of first cortisol sample (B1) collection was also included as a covariate. Specifically, in the ANOVA analysis, in order to study the direct effect of clinical status, sex, and pubertal stage on cortisol and anxiety, as well as their potential interactions with CM, these variables were included as inter-subject factors. To correct for the testing of three different CM variables (presence/absence of CM, CM severity, and CM frequency) and three different cortisol summary measures (mixed model, AUCg, and AUCi), in Table 2, a Bonferroni correction was applied by dividing the original α level ($p < 0.05$) by 9 (3×3), and obtained a new significance level of $p < 0.006$. Spearman's non-parametric correlation was calculated separately in participants without CM and those with a history of CM, to explore the relationship between anxiety perception and salivary cortisol during basal conditions and during the TSST-C.

Results

Attrition and descriptive analysis

Nine subjects had no information available on diurnal cortisol levels, so they were not included in the diurnal cortisol analysis. Three participants had no information available on cortisol and anxiety perception during the TSST-C, so they were not included in the corresponding analysis. Sixteen subjects were excluded from the analysis due to missing information on covariates such as BMI or SES. All the excluded participants due to missing BMI or SES values were diagnosed with a current psychiatric disorder. There were no significant differences in either sociodemographic factors or cortisol values when comparing the participants excluded and subjects with psychiatric diagnostic included in the analysis; however, the excluded participants exhibited significantly higher CGAS than those included ($t = 2.360$, $p = 0.020$).

A brief summary of the sociodemographic and anthropometric variables, by CM history, is provided in Table 1. Significant group differences according to CM exposure were observed with regard to age, ethnicity, SES, illegal drug use, CGAS, GFES, BMI, current psychiatric disorder, and type of clinical care unit. Mean cortisol values by CM group measures at each diurnal and TSST-C timepoint, AUCg and AUCi values, and STAI-Trait and STAI-State scores are summarized in Table 1.

Childhood maltreatment and diurnal salivary cortisol

As expected, cortisol levels fluctuated significantly throughout the day, following a circadian rhythm ($F = 218.307$, $p < 0.001$). No global interaction between time and CM was detected ($F = 1.467$, $p = 0.225$), reflecting a similar cortisol diurnal trajectory in both groups (see Table 2), also evidenced by AUCi levels, $F_{(1,160)} = 3.040$, $p = 0.083$, $\eta_p^2 = 0.021$. However, the simple effects analysis in the context of mixed-effect model revealed a significant time point-specific interaction at B4 (before bedtime) between CM groups ($F = 4.678$, $p = 0.032$). Although cortisol levels consistently decreased from lunchtime to bedtime in both groups, this was less pronounced in the CM group, leading to a higher total hormonal output over the whole day, as evidenced

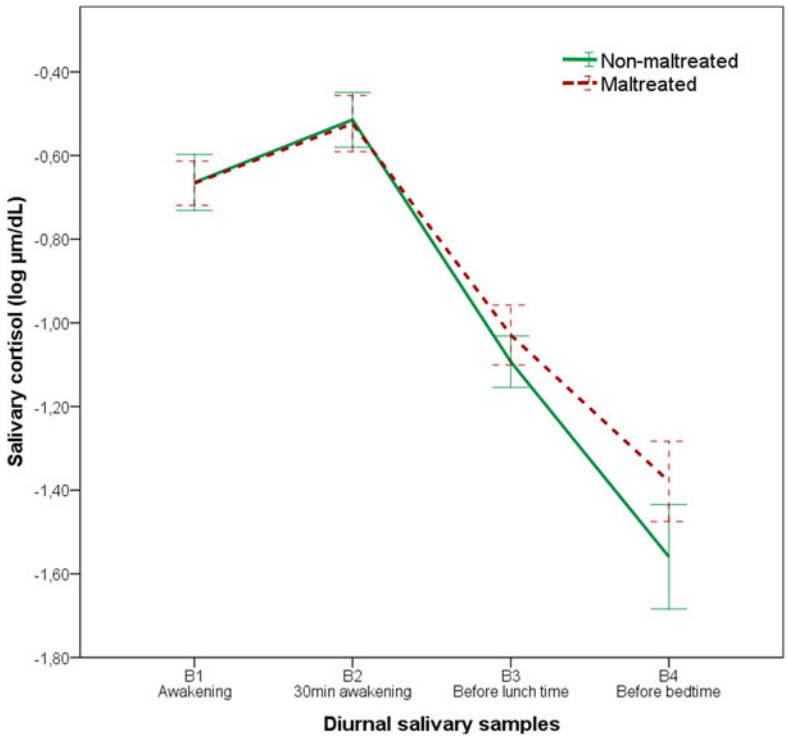


Fig. 2. Diurnal salivary cortisol in participants with and without CM. Exposure to CM significantly increased AUCg levels, indicating a higher total diurnal cortisol output. Specifically, youth exposed to CM showed increased cortisol levels before bedtime (B4). The analysis was adjusted for sex, pubertal stage, clinical status, time of the first cortisol sample collection (B1), psychopharmacological treatment, illegal drugs use, ethnicity, corticosteroid medication, oral contraceptive use, BMI, and socioeconomic status.

by a higher AUCg, $F_{(1,160)} = 12.244$, $p = 0.001$, $\eta_p^2 = 0.079$ (see Table 2 and Fig. 2). No significant interactions have been reported between CM and clinical status, pubertal stage, or sex. The effect of clinical status, pubertal stage, and sex on diurnal cortisol levels is reported in the online Supplementary material. Similar results were observed in the diurnal cortisol response when considering only subjects with confirmed CM (see online Supplementary material).

Neither the frequency nor the severity of CM was associated with diurnal cortisol slope during the day, $F_{\text{severity}} = 1.214$, $p = 0.300$; $F_{\text{frequency}} = 1.085$, $p = 0.372$, reflecting a similar cortisol diurnal trajectory between groups, also evidenced by AUCi, $F_{\text{severity}(2,160)} = 1.716$, $p = 0.184$, $\eta_p^2 = 0.024$; $F_{\text{frequency}(2,160)} = 1.276$, $p = 0.282$, $\eta_p^2 = 0.018$. However, the simple effect analysis revealed a significant interaction at B4 (before bedtime); participants exposed to moderate/severe CM experiences or often/frequently exposed to CM showed higher cortisol levels before bedtime when compared with subjects without CM ($p_{\text{severity}} = 0.020$; $p_{\text{frequency}} = 0.048$). The AUCg levels suggested a dose–response relationship between CM severity/frequency and total cortisol output during the day, $F_{\text{severity}(2,160)} = 6.349$, $p = 0.002$, $\eta_p^2 = 0.084$; $F_{\text{frequency}(2,160)} = 6.068$, $p = 0.003$, $\eta_p^2 = 0.081$. As expected, these results were even more significant when dichotomizing the sample according to the severity/frequency of CM as either: (1) no/low exposure or (2) moderate/severe exposure (see online Supplementary material).

Childhood maltreatment and salivary cortisol response during acute psychosocial stress (TSST-C)

Cortisol levels during the TSST-C significantly differed as a function of time ($F = 8.953$, $p < 0.001$), indicating the validity of this procedure to stimulate cortisol secretion in our cohort. A significant interaction between CM and time was identified ($F = 4.530$, $p = 0.002$), indicating a different trajectory of cortisol levels during the protocol between groups of CM. Specifically, the simple effects analysis in the context of mixed-effect model revealed a significant time point-specific interaction when comparing cortisol levels at T3 (immediately after the stressful situation) ($F = 4.993$; $p = 0.027$), at T4 (15 min after the stressful situation finished) ($F = 10.404$, $p = 0.001$), and at T5 (30 min after the stressful situation finished) ($F = 4.561$, $p = 0.034$). While in individuals without CM the cortisol levels increased after acute stress, there were no changes in cortisol concentration in subjects with CM (see Fig. 3*a* and Table 2). In line with this, participants with CM showed lower levels of AUCi than those without CM, $F_{(1,165)} = 4.779$, $p = 0.030$, $\eta_p^2 = 0.031$, reflecting fewer hormonal changes over time. In contrast, CM was not associated with a global difference in cortisol levels throughout the entire TSST-C procedure ($F = 3.015$, $p = 0.084$), as also indicated by AUCg, $F_{(1,165)} = 0.091$, $p = 0.763$, $\eta_p^2 = 0.001$. Similar results were observed in cortisol response during TSST-C when considering only subjects with a confirmed history of CM (see online Supplementary material). Sex, pubertal stage, and clinical status did not interact with CM, and none of these variables explained a different response pattern during the TSST-C. However, significant differences were observed in the overall cortisol levels according to pubertal stage and clinical status. Adolescents showed higher levels of cortisol (AUCg) when compared with children, and subjects with a current psychiatric diagnosis reported lower levels of cortisol (AUCg) when compared with healthy participants (further details in the online Supplementary material).

When the severity and frequency of CM were analyzed, significant interactions were again identified between CM and time ($F_{\text{severity}} = 2.773$, $p = 0.006$; $F_{\text{frequency}} = 2.665$, $p = 0.008$). Specifically, the simple effects analysis revealed a significant time point-specific interaction when comparing cortisol levels at T3 (immediately after the stressful situation) ($p_{\text{severity}} = 0.012$;

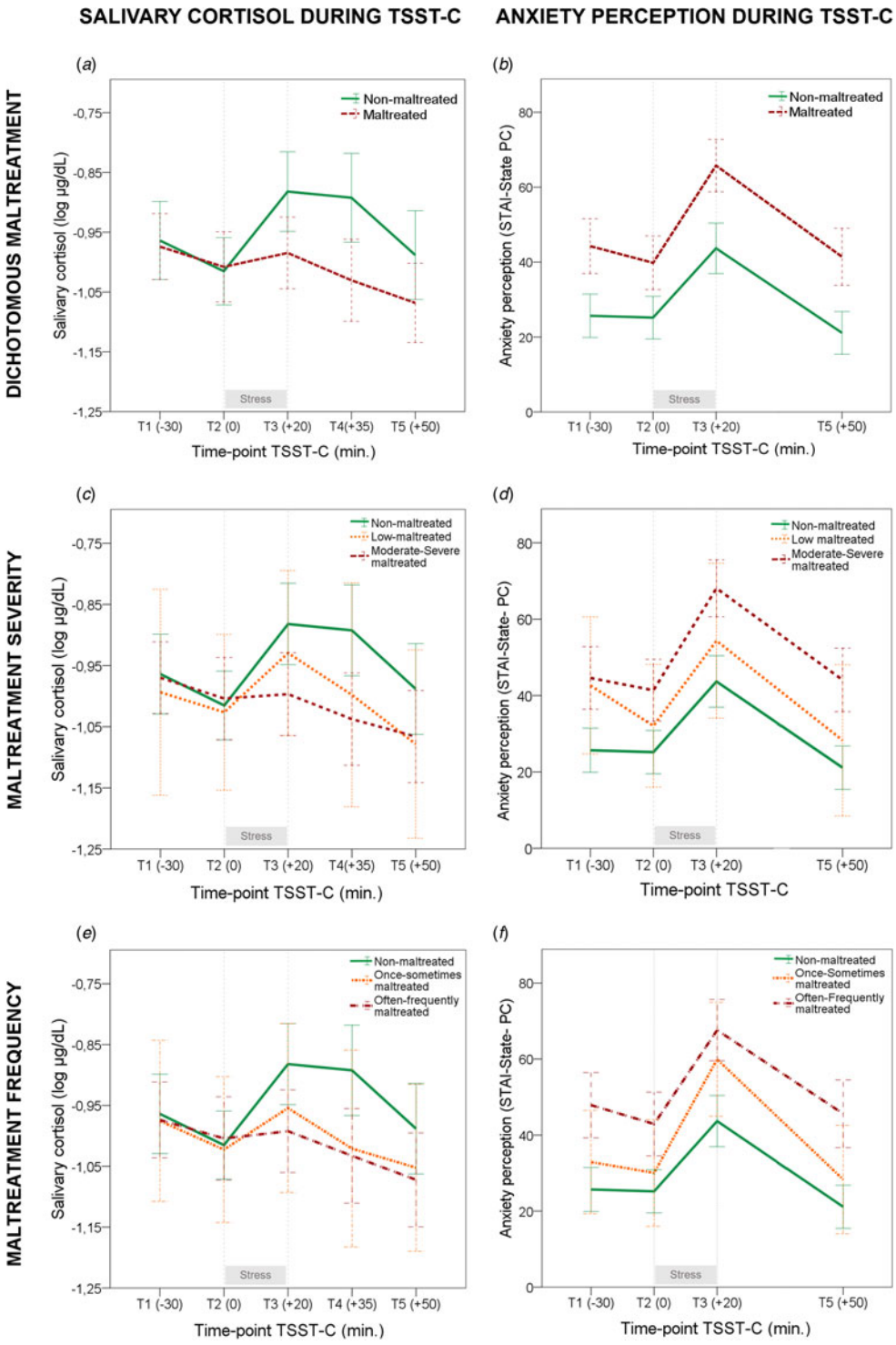


Fig. 3. Salivary cortisol response and anxiety perception during the Trier Social Stress Test for children (TSST-C) according to CM. (*a*) Subjects without CM had increased cortisol levels after exposure to acute psychosocial stress, while in those with a history of CM the cortisol levels remained stable. (*b*) Anxiety perception increased by the same magnitude in both participants with and those without a history of CM, after exposure to psychosocial stress. However, subjects with CM showed higher overall levels of anxiety during the protocol. (*c*) Participants without CM or low exposure to CM had a similar pattern of HPA-axis response during the TSST-C, increasing cortisol levels after acute stress. However, those exposed to moderate/severe CM showed a blunted cortisol response when faced with acute psychosocial stress, indicating hyporeactivity of the HPA-axis. (*d*) Anxiety perception increased by the same magnitude in all subjects, after exposure to psychosocial stress. However, youth with CM, both with low and moderate/severe exposure, had higher overall levels of anxiety during the protocol when compared with non-maltreated participants. (*e*) Subjects without CM and those who suffered CM once/sometimes had a similar pattern of HPA-axis response during the TSST-C. However, those exposed to CM often/frequently showed lower levels of cortisol after exposure to acute psychosocial stress, indicating hyporeactivity in the HPA-axis during acute psychosocial stress. (*f*) Anxiety perception increased by the same magnitude in all the subjects after exposure to psychosocial stress. However, youth with CM, both those who suffered CM once/sometimes and those who suffered CM often/frequently, had higher overall levels of anxiety. The analysis was adjusted for sex, pubertal stage, psychopathological diagnosis, psychopharmacological treatment, illegal drugs use, ethnicity, corticosteroid medication, oral contraceptive use, BMI, and socioeconomic status.

$p_{frequency} = 0.026$), at T4 (15 min after the stressful situation finished) ($p_{severity} = 0.001$; $p_{frequency} = 0.001$), and at T5 (30 min after the stressful situation finished) ($p_{severity} = 0.033$; $p_{frequency} = 0.023$). While subjects without CM showed an increase in cortisol levels after the stressor, those exposed to moderate/severe or often/frequent CM were characterized by a blunted response, suggesting a dose–response relationship between CM severity/frequency and cortisol fluctuation during the TSST-C (see Fig. 3*c* and *e*). In this vein, participants exposed to moderate/severe and often/frequent CM displayed significantly lower values of AUCi than those without CM or exposed to low severity/frequency of CM, $F_{severity(2,165)} = 3.921$, $p = 0.022$, $\eta_p^2 = 0.052$; $F_{frequency(2,165)} = 3.194$, $p = 0.044$, $\eta_p^2 = 0.042$ (see Table 2). As expected, these results were even more significant when a new dichotomization was performed for severity/frequency of CM as either: (1) none or low and (2) moderate or severe exposure (for details see online Supplementary material). No significant differences in overall cortisol levels during the protocol were observed between severity/frequency groups of CM ($F_{severity} = 1.736$, $p = 0.179$; $F_{frequency} = 1.839$, $p = 0.162$), also evidenced by AUCg, $F_{severity(2,\ 165)} = 0.057$, $p = 0.945$, $\eta_p^2 = 0.001$; $F_{frequency(2,\ 165)} = 0.074$, $p = 0.929$, $\eta_p^2 = 0.001$.

Childhood maltreatment, anxiety trait, and anxiety perception during acute psychosocial stress (TSST-C)

Participants with CM exhibited significantly higher levels of anxiety trait than those without CM, $F_{(1,160)} = 9.129$, $p = 0.003$, $\eta_p^2 = 0.060$. The severity and frequency of CM were also associated with anxiety trait, $F_{severity(2,160)} = 5.109$, $p = 0.007$, $\eta_p^2 = 0.062$; $F_{frequency(2,160)} = 4.102$, $p = 0.019$, $\eta_p^2 = 0.056$, with the lowest anxiety trait levels exhibited by subjects none exposed to CM (see Table 2). No significant correlation between anxiety trait and overall diurnal cortisol levels was found (see online Supplementary material).

As seen in Fig. 3*b*, the TSST-C consistently increased perceived anxiety after acute stress in all the subjects ($F = 34.544$, $p < 0.001$). However, there were no interactions between time and CM ($F = 1.742$, $p = 0.160$), reflecting similar trajectories of perceived anxiety during the acute psychosocial stress in both subjects with and those without CM. Furthermore, those with CM showed higher overall perceived anxiety during the entire procedure than subjects without CM ($F = 23.836$, $p < 0.001$). Moreover, in youth without CM, anxiety perception during the TSST-C was negatively correlated with cortisol levels, but not in youth exposed to CM (see online Supplementary material). Subjects exposed to both low and high severity/frequency of CM showed higher overall levels of anxiety during the whole protocol than subjects without CM, $F_{severity} = 11.112$, $p < 0.001$; $F_{frequency} = 12.142$, $p < 0.001$ (see Fig. 3*c* and *d*). However, there were no differences between groups in the magnitude of the increase of perceived anxiety after the acute stressor, $F_{severity} = 1.670$, $p = 0.131$; $F_{frequency} = 1.240$, $p = 0.287$, $\eta_p^2 = 0.022$, with all groups exhibiting the same trajectory (see Table 2). Similar results were obtained when considering only subjects with a confirmed history of CM (for details see online Supplementary material).

Discussion

The present study elucidated how the proximal CM in children and adolescents impacts on HPA-axis functioning and on anxiety perception. In summary, youth exposed to CM, regardless of the presence of a current psychopathology, showed (i) a basal disruption of the HPA-axis circadian rhythm with increased daily cortisol levels, (ii) reduced HPA-axis reactivity during an acute psychosocial stress, and (iii) increased anxiety perception as a trait and during the whole psychosocial stress episode. Interestingly, all the subjects exposed to CM experienced heightened anxiety but only those exposed to more severe or frequent CM exhibited significant HPA-axis dysregulation. To the best of our knowledge, this is the first study to date to report the impact of CM severity measured as the gravity of the experiences suffered, rather than as the accumulation of different types of CM (e.g. pinch with momentary redness considered as low physical abuse, *v.* physical aggression that needs medical intervention considered as very severe).

Our results suggest that subjects who have suffered CM have higher overall diurnal cortisol levels. Specifically, the participants with CM were characterized by a blunted decline of cortisol levels from lunchtime to bedtime, compared with those without CM. This alteration of the circadian cortisol rhythm is consistent with the presence of hypercortisolism, as evidenced by higher AUCg scores in the group exposed to CM, especially those exposed to more severe and frequent CM. This may indicate a desynchrony trend in this intrinsic biological process, which has been described as a risk factor for rising mental health symptoms. Our findings are accordant with other studies focused on CM, which have reported both a blunted decline in HPA-axis activity throughout the day (Bernard, Zwerling, & Dozier, 2015) and higher overall cortisol output (Cicchetti & Rogosch, 2001). Our results could help to elucidate the co-occurrence of hypercortisolism and a flattened diurnal cortisol response, as high diurnal cortisol levels may be explained by an atypical diurnal decline. Similar findings have been reported in adults exposed to childhood adversities, suggesting the persistence of a less pronounced diurnal cortisol slope (Kuras et al., 2017). This HPA-axis dysregulation has important implications for other biological functions, as immune system (e.g. compromising the release of pro and anti-inflammatory substances) ultimately contributes to the increased risk of chronic disease later in life.

Although a recent meta-analysis (Bernard et al., 2017) reported no overall effect of CM on the diurnal cortisol slope, the authors also discussed the impact of many confounders. For example, age may influence the association between CM and cortisol rhythms; whereas cortisol levels could be elevated soon after the onset of a stressor (hypercortisolism), they could decrease over time, reflecting a pattern of hypocortisolism in adulthood (Miller, Chen, & Zhou, 2007). Although we did not observe this interaction between CM and pubertal stage, diurnal cortisol levels showed to be higher in adolescents when compared to children. Furthermore, our findings suggest that CM is associated with biological alterations also in youth without psychiatric disorders. In this regard, different approaches suggest that resilient subjects, who were exposed to CM but are asymptomatic, may present a particular neurobiological adaptive response, as brain connectivity changes to compensate for the alterations caused by abuse (Ohashi et al., 2019).

Secondly, regarding the HPA-axis response to acute psychosocial stress, consistent with the extant literature (Bunea et al., 2017), children and adolescents exposed to CM exhibited a blunted cortisol response during the TSST-C, compared with those without CM. While previous literature supports that the blunted cortisol response is better observed in adult populations (while arguing that smaller effects are seen in children and adolescents due to HPA-axis hyperactivation following immediate trauma), an early hypoactivation is already observed in our sample, as has been reported previously (MacMillan et al., 2009).

Although subjects exposed to CM remained hyporeactive under acute stress, in terms of HPA-axis activity, they experienced a significant increase in perceived anxiety, equivalent to that experienced by those not exposed to CM. This reveals a clear dissociation between anxiety perception and the physiological response to stressful situations in young people with CM, which might impair their ability to manage appropriately and cope with everyday emotionally negative situations (Liu et al., 2012). Notably, emotion regulation deficits have been suggested as a key pathway linking CM with psychopathology (Dvir, Ford, Hill, & Frazier, 2014; Hart et al., 2018). Further studies are required to explore which biomarkers other than cortisol might be linked with heightened anxiety in subjects exposed to CM (Quidé et al., 2019). Our results further suggest that, although participants with a current psychopathology tended to have lower cortisol levels in general, the HPA-axis alterations in subjects exposed to CM were present in both subjects with and without a current psychopathology. Contrary to some previous findings, in our sample neither pubertal stage (Gunnar, Wewerka, Frenn, Long, & Griggs, 2009) nor sex (Trickett et al., 2014) interacted with CM to predict HPA-axis reactivity during the TSST-C.

Furthermore, besides the impact of CM on HPA-axis activity and increased levels of anxiety (trait and state), our findings also showed that the severity and frequency of CM play a key role, thereby supporting a dose–response relationship (Anda et al., 2006). Thus, in line with Trickett et al. (2014), subjects exposed to more severe or more frequent forms of CM manifested the most subdued HPA-axis responses under basal conditions and in response to psychosocial stress; notably, Trickett et al. considered severity as the accumulation of different types of CM, rather than according to the specific characteristics of the experiences suffered. These findings warn of the deleterious impact that milder forms of CM may have once they become chronic. This is important as children who experience mild CM are often not detected or receive less clinical and social care (Humphreys, 2020). Furthermore, it seems that these children start showing higher levels of perceived anxiety before there is a marked biological dysregulation, offering a window of opportunity for early detection and intervention. Hence, the use of accurate child screening instruments at subclinical stages should be generalized, since most children are only identified once they already have severe psychiatric symptomatology (Bailhache, Leroy, Pillet, & Salmi, 2013). Moreover, since dysfunction in neurobiological systems negatively impacts treatment outcomes, youth with CM may also require specific treatment adapted to their condition (Tyrka, Burgers, Philip, Price, & Carpenter, 2013).

The methodology used in the present study includes a wide range of CM experiences reported from different sources, since there is often a substantial gap between subjects identified in informant-based studies and self-report assessments (Baldwin, Reuben, Newbury, & Danese, 2019). Thus, our findings suggest that participants with a suspected history of CM identified by clinicians show the same HPA-axis dysfunctions as subjects with a confirmed history of CM. Likewise, given that CM studies may lack sensitivity when the experiences are not qualitatively assessed (via the severity and frequency of exposure), key information may be lost and findings distorted. This highlights the need for specific training of clinicians in child psychiatric and pediatric services, so CM assessment can be routinely implemented, despite the time and effort required to perform such complex assessments (Zeanah & Edm, 2018).

Although prior evidence suggests that exposure to CM during middle childhood has the greatest effects on emotional dysregulation (Dunn, Nishimi, Gomez, Powers, & Bradley, 2018), it is difficult to pinpoint the exact developmental period when HPA-axis functioning is disrupted. Future research should incorporate more detailed information about the timing and proximity of CM to delineate vulnerable periods (Andersen & Teicher, 2008). It would be interesting to study the clinical course of the children to identify possible risk and protective factors for the future onset of psychopathology. A more dimensional approach focused on symptom dimensions might reveal varying patterns of adrenocortical regulation (Cicchetti & Rogosch, 2001). It is important to note that CM is not a phenomenon that can be studied in isolation, since both its causes and consequences are systematic and there are many factors that must be taken into account in order to fully understand it.

The blunted reactivity observed in our study supports plausible habituation, i.e. chronic exposure to stress may be linked with an adaptive desensitization to new stressors over time (Murali & Chen, 2005). These latent neurobiological alterations could drive an increased vulnerability to psychopathology during childhood and adolescence (Busso et al., 2017), which may persist, leading to the onset of a wide range of psychiatric conditions in adulthood (Kudielka & Wüst, 2010). Other factors with the potential to moderate the consequences of CM should also be taken into account, such as the type of CM suffered, the relationship with the abuser, social support received, and coexistence of other types of trauma such as bullying (Arseneault, 2018), domestic violence (Osofsky, 2018), or recent stressful life events (March-Llanes, Marqués-Feixa, Mezquita, Fañanás, & Moya-Higueras, 2017).

One of the limitations of the current study is the methodology used for assessing the presence and characteristics of CM exposure. Widely used questionnaires such as the CTQ cannot be administered to children younger than 12 years; indeed, there is no validated questionnaire to assess the presence of CM in the 7–17 years range. The main reason behind this is that younger children have a limited understanding of their own exposure, since they are still cognitively immature. Thus, any assessment of CM in this vulnerable population needs to be adjusted to maximize the reliable information that can be captured from the different informants (not only the child) and, at the same time, to minimize the trauma that the interview itself can represent to a victimized child. Thus, use of TASSCV allows the proper assessment of children and adolescents exposed from milder to severe forms of CM, which would have otherwise not been identified. Unfortunately, use of TASSCV requires a longer time for a proper assessment together with the gathering of information from multiple informants, which might make it more challenging to use than simply relying on short self-administered questionnaires such as the CTQ or considering only the most severe children already detected by social services. Since most of the sample was recruited in psychiatric units, there is an unusually high proportion of ADHD cases in the non-CM group; thus, our findings might not be generalizable to other populations. At the same time, the majority of CM-exposed subjects suffered from some sort of psychiatric condition, while most participants non-exposed to CM had no psychopathological history. Further research including a higher proportion of subjects exposed to CM with no psychiatric symptomatology (i.e. resilient) is required to disentangle the role of CM in the development of HPA-axis disturbances and whether the later precede the onset of psychiatric disorders.

Conclusions

CM affects multiple domains of life such as intimate relationships, violence and criminal offending, employment, drug abuse, and physical and mental health (Hughes et al., 2017). It is a serious global health problem with staggering long-term economic costs (Thielen et al., 2016). This study is intended to raise awareness of the biological and clinical repercussions of CM during or proximally to exposure, encouraging clinicians to ask patients about CM history and to respond accordingly, seeking therapeutic alternatives to manage acute stress better. Children exposed to CM and attended in child protection units, child psychiatric, or pediatric units are still at a sensitive period of neurological, cognitive, social, and emotional development, during which high-quality interventions can make an important difference and shift the balance between risk and protective factors (Chinitz, Guzman, Amstutz, Kohchi, & Alkon, 2017). Thus, family psychotherapeutic interventions have the potential to normalize HPA-axis function if implemented promptly (Gunnar, DePasquale, Reid, Donzella, & Miller, 2019).

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S003329172100249X

Acknowledgements. We are indebted to all the participants and their families for taking part in a study with such deep emotional involvement. We also thank all the nurses and lab technicians who made this research possible, especially Anna Valldeperas and José Luís Monteserín.Thank you Sergi Valero for your statistical support.

Financial support. Supported by the Spanish Ministry of Economy and Competitiveness, *Instituto de Salud Carlos III* through the University of Barcelona multicenter project (PI15/00097)-PI L. Fañanas, *Hospital Universitario Araba* (PI15/00793)-PI I. Zorrilla, *Hospital Gregorio Marañón* (PI15/00723)-PI M. Rapado and *Hospital Clinic* (PI15/00685)-PI S. Romero, co-financed by the European Regional Development Fund project, 'A way of making Europe'. We thank the Network Centre for Biomedical Research in Mental Health (CIBERSAM). This study was facilitated by a pre-doctoral research grant from the Catalonian authorities to Laia Marques-Feixa (AGAUR-FI_B100023-2018). Supported by a NARSAD Distinguished Investigator Grant awarded to Professor Lourdes Fañanas (26887) and by the *Comissionat per a Universitats i Recerca del DIUE*, of the *Generalitat de Catalunya* regional authorities (2017SGR1577). Dr Rapado-Castro was supported by a Ramon y Cajal Research Fellowship (RYC-2017-23144), Spanish Ministry of Science, Innovation and Universities; an NARSAD independent investigator grant (24628) from the Brain & Behaviour Research Foundation; *Fundación Familia Alonso* and *Fundación Alicia Koplowitz*.

Conflict of interest. In the last 24 months, Hilario Blasco-Fontecilla received lecture fees from AB-Biotics, Praxis Pharmaceuticals, and Shire. The remaining authors do not have any conflict of interest regarding the publication of this manuscript.

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

EPI-Young Stress GROUP. María Martín[9], Eulalia Anglada[12], Pilar Santamarina[2,3,4], Patricia Rubio[6], Iría Méndez[2,3,4], Dolores Moreno[2,6], María Ramos[2,6], Jorge Vidal[2,6], Juanjo Carballo[2,6], Elena Font[2,3,4], Lydia Gayubo[11], Laura Colino[11], María Rodrigo-Yanguas[11], Maddi Laborde[8], Jaume March-Llanes[5].

References

Allen, A. P., Kennedy, P. J., Cryan, J. F., Dinan, T. G., & Clarke, G. (2014). Biological and psychological markers of stress in humans: Focus on the Trier Social Stress Test. *Neuroscience and Biobehavioral Reviews*, *38*, 94–124. https://doi.org/10.1016/j.neubiorev.2013.11.005.

Anda, R. F., Felitti, V. J., Bremner, J. D., Walker, J. D., Whitfield, C., Perry, B. D., … Giles, W. H. (2006). The enduring effects of abuse and related adverse experiences in childhood: A convergence of evidence from neurobiology and epidemiology. *European Archives of Psychiatry and Clinical Neuroscience*, *256*(3), 174–186. https://doi.org/10.1007/s00406-005-0624-4.

Andersen, S. L., & Teicher, M. H. (2008). Stress, sensitive periods and maturational events in adolescent depression. *Trends in Neuroscience*, *31*(4), 183–191. https://doi.org/10.1016/j.tins.2008.01.004.

APA: American Psychiatric Association. (2013). *DSM-5: Diagnostic and statistical manual of mental disorders* (5th ed.). Washington, DC: American Psychiatric Publishing.

Arseneault, L. (2018). Annual Research Review: The persistent and pervasive impact of being bullied in childhood and adolescence: Implications for policy and practice. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *59*(4), 405–421. https://doi.org/10.1111/jcpp.12841.

Bailhache, M., Leroy, V., Pillet, P., & Salmi, L.-R. (2013). Is early detection of abused children possible?: A systematic review of the diagnostic accuracy of the identification of abused children. *BMC Pediatrics*, *13*(1), 1–11. https://doi.org/10.1186/1471-2431-13-202.

Baldwin, J. R., Reuben, A., Newbury, J. B., & Danese, A. (2019). Agreement between prospective and retrospective measures of childhood maltreatment: A systematic review and meta-analysis. *JAMA Psychiatry*, *76*(6), 584–593. https://doi.org/10.1001/jamapsychiatry.2019.0097.

Bernard, K., Frost, A., Bennett, C. B., & Lindhiem, O. (2017). Maltreatment and diurnal cortisol regulation: A meta-analysis. *Psychoneuroendocrinology*, *78*, 57–67. https://doi.org/10.1016/j.psyneuen.2017.01.005.

Bernard, K., Zwerling, J., & Dozier, M. (2015). Effects of early adversity on young children' s diurnal cortisol rhythms and externalizing behavior. *Developmental Psychobiology*, *57*(8), 935–947. https://doi.org/10.1002/dev.21324.

Bernstein, D. P., Stein, J. A., Newcomb, M. D., Walker, E., Pogge, D., Ahluvalia, T., … Zule, W. (2003). Development and validation of a brief screening version of the Childhood Trauma Questionnaire. *Child Abuse and Neglect*, *27*(2), 169–190. https://doi.org/10.1016/S0145-2134(02)00541-0.

Brown, G. W., Harris, T. O., & Craig, T. K. J. (2019). Exploration of the influence of insecure attachment and parental maltreatment on the incidence and course of adult clinical depression. *Psychological Medicine*, *49*, 1025–1032. https://doi.org/10.1017/S0033291718001721.

Bunea, I. M., Szentágotai-t, A., & Miu, A. C. (2017). Early-life adversity and cortisol response to social stress: A meta-analysis. *Translational Psychiatry*, *7*(12), 1–8. https://doi.org/10.1038/s41398-017-0032-3.

Buske-Kirschbaum, A., Jobst, S., Wustmans, A., Kirschbaum, C., Rauh, W., & Hellhammer, D. (1997). Attenuated free cortisol response to psychosocial stress in children with atopic dermatitis. *Psychosomatic Medicine*, *59*(4), 419–426. https://doi.org/10.1097/00006842-199707000-00012.

Busso, D. S., Mclaughlin, K. A., Brueck, S., Peverill, M., Gold, A. L., & Sheridan, M. A. (2017). Child abuse, neural structure, and adolescent psychopathology: A longitudinal study. *Journal of the American Academy of Child & Adolescent Psychiatry*, *56*(4), 321–328.e1. https://doi.org/10.1016/j.jaac.2017.01.013.

CARM (2012). Instrumento para la valoración de la gravedad de las situaciones de desprotección infantil (Tool for assessing the severity of situations in which children are vulnerable- TASSCV). *Servicios Sociales de Atención Primaria y Especializados de La Región de Murcia*. https://www.carm.es/web/pagina?IDCONTENIDO=9415&IDTIPO=246&RASTRO=c886$m5855.

Chinitz, S., Guzman, H., Amstutz, E., Kohchi, J., & Alkon, M. (2017). Improving outcomes for babies and toddlers in child welfare: A model for infant mental health intervention and collaboration. *Child Abuse and Neglect*, *70*(May), 190–198. https://doi.org/10.1016/j.chiabu.2017.05.015.

Cicchetti, D., & Rogosch, F. A. (2001). The impact of child maltreatment and psychopathology on neuroendocrine functioning. *Development and Psychopathology*, *13*(4), 783–804.

de la Peña, F. R., Villavicencio, L. R., Palacio, J. D., Félix, F. J., Larraguibel, M., Viola, L., … Ulloa, R. E. (2018). Validity and reliability of the kiddie schedule for affective disorders and schizophrenia present and lifetime version DSM-5 (K-SADS-PL-5) Spanish version. *BMC Psychiatry*, *18*(1), 1–7. https://doi.org/10.1186/s12888-018-1773-0.

DePasquale, C. E., Donzella, B., & Gunnar, M. R. (2019). Pubertal recalibration of cortisol reactivity following early life stress: A cross-sectional analysis. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, *60*(5), 566–575. https://doi.org/10.1111/jcpp.12992.

De Punder, K., Heim, C., & Entringer, S. (2019). Psychoneuroendocrinology association between chronotype and body mass index : The role of C-reactive protein and the cortisol response to stress. *Psychoneuroendocrinology*, *109* (February), 104388. https://doi.org/10.1016/j.psyneuen.2019.104388.

Dunn, E. C., Nishimi, K., Gomez, S. H., Powers, A., & Bradley, B. (2018). Developmental timing of trauma exposure and emotion dysregulation in adulthood: Are there sensitive periods when trauma is most harmful? *Journal of Affective Disorders*, *227*(October 2017), 869–877. https://doi.org/10.1016/j.jad.2017.10.045.

Dvir, Y., Ford, J. D., Hill, M., & Frazier, J. A. (2014). Childhood maltreatment, emotional dysregulation, and psychiatric comorbidities. *Harvard Review of Psychiatry*, *22*(3), 149–161. https://doi.org/10.1097/HRP.0000000000000014.

Fogelman, N., & Canli, T. (2018). Early life stress and cortisol: A meta-analysis. *Hormones and Behavior*, *98*(December 2017), 63–76. https://doi.org/10.1016/j.yhbeh.2017.12.014.

Forti, M. Di, Quattrone, D., Freeman, T. P., Tripoli, G., Gayer-anderson, C., Quigley, H.. (2019). The contribution of cannabis use to variation in the incidence of psychotic disorder across Europe (EU-GEI): A multicentre case-control study. *The Lancet Psychiatry*, *6*(5), 427–436. https://doi.org/10.1016/S2215-0366(19)30048-3.

Gunnar, M. R., DePasquale, C. E., Reid, B. M., Donzella, B., & Miller, B. S. (2019). Pubertal stress recalibration reverses the effects of early life stress in postinstitutionalized children. *Proceedings of the National Academy of Sciences*, *116*(48), 23984– 23988. https://doi.org/10.1073/pnas.1909699116.

Gunnar, M. R., Wewerka, S., Frenn, K., Long, J., & Griggs, C. (2009). Developmental changes in hypothalamus–pituitary–adrenal activity over the transition to adolescence: Normative changes and associations with puberty. *Development and Psychopathology*, *21*(1), 69–85. https://doi.org/10.1017/S0954579409000054.Developmental.

Hart, H., Lim, L., Mehta, M. A., Simmons, A., Mirza, K. A. H., & Rubia, K. (2018). Altered fear processing in adolescents with a history of severe childhood maltreatment: An fMRI study. *Psychological Medicine*, *48*(7), 1092–1101. https://doi.org/10.1017/S0033291716003585.

Hollingshead, A. B. (1975). *Four factor index of social status*. New Haven, CT: Yale University Department of Psychology.

Hughes, K., Bellis, M. A., Hardcastle, K. A., Sethi, D., Butchart, A., Mikton, C., … Dunne, M. P. (2017). The effect of multiple adverse childhood experiences on health: A systematic review and meta-analysis. *The Lancet Public Health*, *2*(8), e356–e366. https://doi.org/10.1016/S2468-2667(17)30118-4.

Humphreys, K. L. (2020). Child maltreatment recurrence points to urgent need to improve systems for identification and prevention. *Journal of the American Academy of Child & Adolescent Psychiatry*. https://doi.org/10.1016/j.jaac.2020.07.005.

Hunter, A. L., Minnis, H., & Wilson, P. (2011). Altered stress responses in children exposed to early adversity: A systematic review of salivary cortisol studies. *Stress (Amsterdam, The Netherlands)*, *14*(6), 614–626. https://doi.org/10.3109/10253890.2011.577848.

Kaess, M., Parzer, P., Mattern, M., Resch, F., Bifulco, A., & Brunner, R. (2011). Childhood Experiences of Care and Abuse (CECA) – validation of the German version of the questionnaire and interview, and results of an investigation of correlations between adverse childhood experiences and suicidal behaviour. *Zeitschrift fur Kinder- und Jugendpsychiatrie und Psychotherapie*, *39* (4), 243–252. https://doi.org/10.1024/1422-4917/a000115.

King, L. S., Colich, N. L., LeMoult, J., Humphreys, K. L., Ordaz, S. J., Price, A. N., & Gotlib, I. H. (2017). The impact of the severity of early life stress on diurnal cortisol: The role of puberty. *Psychoneuroendocrinology*, *77*, 68–74. https://doi.org/10.1016/j.psyneuen.2016.11.024.

Koss, K. J., & Gunnar, M. R. (2018). Annual Research Review : Early adversity, the hypothalamic – pituitary – adrenocortical axis, and child psychopathology. *Journal of Child Psychology and Psychiatry*, *59*(4), 327–346. https://doi.org/10.1111/jcpp.12784.

Kudielka, B. M., & Wüst, S.. (2010). Human models in acute and chronic stress: Assessing determinants of individual hypothalamus–pituitary–adrenal axis activity and reactivity. *Stress*, *13*(1), 1–14. https://doi.org/10.3109/10253890902874913.

Kuras, Y. I., Assaf, N., Thoma, M. V., Gianferante, D., Hanlin, L., Chen, X., … Rohleder, N. (2017). *Blunted Diurnal Cortisol Activity in Healthy Adults with Childhood Adversity*, *11*(November), 1–8. https://doi.org/10.3389/fnhum.2017.00574.

Lê-scherban, F., Brenner, A. B., Hicken, M. T., Needhamm, B. L., Seeman, T., Sloan, R. P., … Roux, A. V. D. (2018). Child and adult socioeconomic status and the cortisol response to acute stress: Evidence from the Multi-Ethnic Study of Atherosclerosis. *Psychosomatic Medicine*, *80*(2), 184–192. https://doi.org/10.1097/PSY.0000000000000543.

Lippard, E. T. C., & Nemeroff, C. B.. (2020). The devastating clinical consequences of child abuse and neglect: Increased disease vulnerability and poor treatment response in mood disorders. *American Journal of Psychiatry*, *177* (1), 20–36. https://doi.org/10.1176/appi.ajp.2019.19010020.

Liu, J., Chaplin, T. M., Wang, F., Sinha, R., Mayes, L. C., & Blumberg, H. P. (2012). Stress reactivity and corticolimbic response to emotional faces in adolescents. *JAAC*, *51*(3), 304–312. https://doi.org/10.1016/j.jaac.2011.12.014.

MacMillan, H. L., Georgiades, K., Duku, E. K., Shea, A., Steiner, M., Niec, A., … Schmidt, L. A. (2009). Cortisol response to stress in female youths exposed to childhood maltreatment: Results of the youth mood project. *Biological Psychiatry*, *66*(1), 62–68. https://doi.org/10.1016/j.biopsych.2008.12.014.

Marceau, K., & Abel, E. (2018). Mechanisms of cortisol – substance use development associations: Hypothesis generation through gene enrichment analysis. *Neuroscience and Biobehavioral Reviews*, *92*, 128–139. https://doi.org/10.1016/j.neubiorev.2018.05.020.

March-Llanes, J., Marqués-Feixa, L., Mezquita, L., Fañanás, L., & Moya-Higueras, J. (2017). Stressful life events during adolescence and risk for externalizing and internalizing psychopathology: A meta-analysis. *European Child and Adolescent Psychiatry*, *26*(12), 1409–1422. https://doi.org/10.1007/s00787-017-0996-9.

Miller, G. E., Chen, E., & Zhou, E. S. (2007). If it goes up, must it come down? Chronic stress and the hypothalamic-pituitary-adrenocortical axis in humans. *Psychological Bulletin*, *133*, 25–45. https://doi.org/10.1037/0033-2909.133.1.25.

Morris, N. M., & Udry, J. R. (1980). Validation of a self-administered instrument to assess stage of adolescent development. *Journal of Youth and Adolescence*, *9*(3), 271–280. https://doi.org/10.1007/BF02088471.

Murali, R., & Chen, E. (2005). Exposure to violence and cardiovascular and neuroendocrine measures in adolescents. *Annals of Behavioral Medicine*, *30*(2), 155–163.

Ohashi, K., Anderson, C. M., Bolger, E. A., Khan, A., McGreenery, C. E., & Teicher, M. H. (2019). Susceptibility or resilience to maltreatment can be explained by specific differences in brain network architecture. *Biological Psychiatry*, *85*(8), 690–702. https://doi.org/10.1016/j.biopsych.2018.10.016.

Osofsky, J. D. (2018). Commentary: Understanding the impact of domestic violence on children, recognizing strengths, and promoting resilience: Reflections on Harold and Sellers (2018). *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *59*(4), 403–404. https://doi.org/10.1111/jcpp.12902.

Ouellet-Morin, I., Robitaille, M. P., Langevin, S., Cantave, C., Brendgen, M., & Lupien, S. J. (2019). Enduring effect of childhood maltreatment on cortisol and heart rate responses to stress: The moderating role of severity of experiences. *Development and Psychopathology*, *31*(2), 497–508. https://doi.org/10.1017/S0954579418000123.

Provençal, N., Arloth, J., Cattaneo, A., Anacker, C., & Cattane, N. (2019). Glucocorticoid exposure during hippocampal neurogenesis primes future stress response by inducing changes in DNA methylation. *Proceedings of the National Academy of Sciences*, *117*(38), 23280–23285. https://doi.org/10.1073/pnas.1820842116.

Pruessner, J. C., Kirschbaum, C., Meinlschmidt, G., & Hellhammer, D. H. (2003). Two formulas for computation of the area under the curve represent measures of total hormone concentration versus time-dependent change. *Psychoneuroendocrinology*, *28*(4), 916–931. https://doi.org/10.1016/j.psyneuen.2003.10.002.

Quidé, Y., Bortolasci, C. C., Spolding, B., Kidnapillai, S., Watkeys, O. J., Cohen-Woods, S., … Green, M. J. (2019). Association between childhood trauma exposure and pro-inflammatory cytokines in schizophrenia and

bipolar-I disorder. *Psychological Medicine*, *49*(16), 2736–2744. https://doi.org/10.1017/S0033291718003690.

Rey, J. M., Singh, M., Hung, S., Dossetor, D. R., Newman, L., Plapp, J. M., & Bird, K. D. (1997). A global scale to measure the quality of the family environment. *Archives of General Psychiatry*, *54*(9), 817–822. https://doi.org/10.1001/archpsyc.1997.01830210061006.

Shaffer, D., Gould, M. S., Brasic, J., Ambrosini, P., Fisher, P., Bird, H., & Aluwahlia, S. (1983). A Children's Global Assessment Scale (CGAS). *Archives of General Psychiatry*, *40*(11), 1228–1231. https://doi.org/10.1001/archpsyc.1983.01790100074010.

Spielberger, C. D. (1973). *Inventario de Ansiedad Estado – Rasgo para niños, STAIC*. Palo alto, CA: Consulting Psychologists Press.

Tarullo, A. R., & Gunnar, M. R. (2006). Child maltreatment and the developing HPA axis. *Hormones and Behavior*, *50*(4), 632–639. https://doi.org/10.1016/j.yhbeh.2006.06.010.

Thielen, F. W., ten Have, M., de Graaf, R., Cuijpers, P., Beekman, A., Evers, S., & Smit, F. (2016). Long-term economic consequences of child maltreatment: A population-based study. *European Child and Adolescent Psychiatry*, *25*(12), 1297–1305. https://doi.org/10.1007/s00787-016-0850-5.

Trickett, P. K., Gordis, E., Peckins, M. K., & Susman, E. J. (2014). Stress reactivity in maltreated and comparison male and female young adolescents. *Child Maltreatment*, *19*(1), 27–37. https://doi.org/10.1177/1077559513520466.

Turner, A. I., Smyth, N., Hall, S. J., Torres, S. J., Hussein, M., Jayasinghe, S. U., … Clow, A. J. (2020). Psychological stress reactivity and future health and disease outcomes: A systematic review of prospective evidence. *Psychoneuroendocrinology*, *114* (January), 104599. https://doi.org/10.1016/j.psyneuen.2020.104599.

Tyrka, A. R., Burgers, D. E., Philip, N. S., Price, L. H., & Carpenter, L. L. (2013). The neurobiological correlates of childhood adversity and implications for treatment. *Acta Psychiatrica Scandinavica*, *128*(6), 434–447. https://doi.org/10.1111/acps.12143.

Vachon, D. D., Krueger, R. F., Rogosch, F. A., & Cicchetti, D. (2015). Assessment of the harmful psychiatric and behavioral effects of different forms of child maltreatment. *JAMA Psychiatry*, *72*(11), 1135–1142. https://doi.org/10.1001/jamapsychiatry.2015.1792.

Zeanah, C. H., & Edm, K. L. H. (2018). Child abuse and neglect. *Journal of the American Academy of Child & Adolescent Psychiatry*, *57*(9), 637–644. https://doi.org/10.1016/j.jaac.2018.06.007.

UNIVERSITAT DE BARCELONA

Dr. Lourdes Fañanás Saura
Unitat de Zoologia i Antropologia Biològica
Dept. Biologia Evolutiva, Ecologia i Ciències Ambientals
Facultat de Biologia, Universitat de Barcelona

Informe del director sobre la contribución del doctorando al artículo.

La Prof. Lourdes Fañanás Saura, profesora del Departamento de Biología Evolutiva, Ecologia y Ciencias Ambientales de la Facultad de Biología (Universitat de Barcelona) y directora de la presente tesis doctoral de Laia Marques Feixa, por la presente certifica que ninguno de los coautores del articulo *"Childhood maltreatment disrupts HPA-axis activity under basal and stress conditions in a dose–response relationship in children and adolescents",* ha utilizado esta publicacion para una tesis doctoral, y que la participación del solicitante en este artículo incluyó las siguientes tareas:

- Participación en la concepción y diseño del estudio.
- Reclutamiento y evaluación de los sujetos incluidos.
- Coordinación del proyecto.
- Procesamiento de los datos.
- Análisis estadísticos e interpretación de los datos.
- Redacción del manuscrito.
- Revisión crítica del artículo por contenido intelectual.

Signado por Prof. Lourdes Fañanás

Barcelona, abril 2022

3.6. Secretory immunoglobulin A (s-IgA) reactivity to acute psychosocial stress in children and adolescents: the influence of pubertal development and history of maltreatment

Laia Marques-Feixa, Águeda Castro-Quintas, Helena Palma-Gudiel, Soledad Romero, Astrid Morer, Marta Rapado-Castro, María Martín, Iñaki Zorrilla, Hilario Blasco-Fontecilla, Maite Ramírez, María Mayoral, Íria Méndez, Nerea San Martín-González, María Rodrigo-Yanguas, José Luís Monteserín-García, Lourdes Fañanás y EPI-Young Stress GROUP

Brain Behavior and immunity (2022), July (103) 122-129.

DOI: 10.1016/j.bbi.2022.04.010

Brain, Behavior, and Immunity 103 (2022) 122–129

Contents lists available at ScienceDirect

Brain Behavior and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

Secretory immunoglobulin A (s-IgA) reactivity to acute psychosocial stress in children and adolescents: The influence of pubertal development and history of maltreatment

Laia Marques-Feixa [a,b,1], Águeda Castro-Quintas [a,b,1], Helena Palma-Gudiel [b,c], Soledad Romero [b,d,e], Astrid Morer [b,d,e], Marta Rapado-Castro [b,f,g], María Martín [h], Iñaki Zorrilla [b,i], Hilario Blasco-Fontecilla [b,j], Maite Ramírez [k], María Mayoral [b,f], Iría Mendez [d], Nerea San Martín-Gonzalez [a], María Rodrigo-Yanguas [j], José Luis Monteserín-García [a,b], Lourdes Fañanás [a,b,*], EPI-Young Stress GROUP

[a] Department of Evolutionary Biology, Ecology and Environmental Sciences, Faculty of Biology, University of Barcelona, Biomedicine Institute of the University of Barcelona (IBUB), Barcelona, Spain
[b] Network Centre for Biomedical Research in Mental Health (CIBERSAM), Spain
[c] College of Public Health and Health Professions, Department of Epidemiology, University of Florida, USA
[d] Department of Child and Adolescent Psychiatry and Psychology, 2017SGR88, Institute of Neuroscience, Hospital Clínic de Barcelona, Barcelona, Spain
[e] Institut d'Investigacions Biomediques August Pi i Sunyer (IDIBAPS), Barcelona, Spain
[f] Department of Child and Adolescent Psychiatry, Institute of Psychiatry and Mental Health, Hospital General Universitario Gregorio Marañón, School of Medicine, Universidad Complutense, IiSGM, Madrid, Spain
[g] Melbourne Neuropsychiatry Centre, Department of Psychiatry, The University of Melbourne & Melbourne Health, Victoria, Australia
[h] Hospital Benito Menni, Adolescent Crisis Unit, Sant Boi de Llobregat, Spain
[i] Hospital Santiago Apostol, Department of Psychiatry, Vitoria-Gasteiz, Spain
[j] Department of Psychiatry, Puerta de Hierro University Hospital-Majadahonda, Autonoma University, ITA Mental Health, Madrid, Spain
[k] Day Hospital for Adolescents Barrualde-Galdakao, Child and Adolescent Mental Health, Galdakao, Spain

ARTICLE INFO

Keywords:
secretory Immunoglobulin A (s-IgA)
Acute stress
Children
Adolescents
Childhood maltreatment
Developmental stage
TSST-C

ABSTRACT

Background: Mucosal secretory immunoglobulin A (s-IgA) is an antibody protein-complex that plays a crucial role in immune first defense against infection. Although different immune biomarkers have been associated with stress-related psychopathology, s-IgA remains poorly studied, especially in youth.
Objectives: The present study investigated how s-IgA behaves in front of acute psychosocial stress in children and adolescents, including possible variability associated with developmental stage and history of childhood maltreatment (CM).
Methods: 94 children and adolescents from 7 to 17 years (54 with a current psychiatric diagnostic and 40 healthy controls) drawn from a larger Spanish study were explored (EPI-Young Stress Project). To assess biological reactivity, participants provided five saliva samples during an acute laboratory-based psychosocial stressor, the Trier Social Stress Test for Children (TSST-C). Samples were assayed for s-IgA, as well as for cortisol. Pubertal development was ascertained by Tanner stage and CM following TASSCV criteria.
Results: We observed s-IgA fluctuations throughout the stressor, indicating the validity of TSST-C to stimulate s-IgA secretion ($F(4,199) = 6.200$, $p < .001$). Although s-IgA trajectories followed a reactivity and recovery pattern in adolescents, children exhibited no s-IgA response when faced with stress ($F(4,197) = 3.406$, $p = .010$). An interaction was found between s-IgA and CM ($F(4,203) = 2.643$, $p = .035$). Interestingly, an interaction between developmental stage, CM history and s-IgA reactivity was identified ($F(12,343) = 2.036$, $p = .017$); while children non-exposed to maltreatment exhibited no s-IgA changes to acute stress, children with a history of CM showed a similar response to adolescents, increasing their s-IgA levels after the psychosocial stressor.

* Corresponding authors at: Faculty of Biology, University of Barcelona, Av Diagonal 643, 2n A, Barcelona, Spain.
E-mail address: lfananas@ub.edu (L. Fañanás).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.bbi.2022.04.010
Received 23 December 2021; Received in revised form 31 March 2022; Accepted 10 April 2022
Available online 12 April 2022

Conclusion: Acute psychosocial stress stimulates s-IgA secretion, but only after puberty. However, children with a history of maltreatment exhibited a response resembling that of adolescents, suggesting an early maturation of the immune system. Further studies are needed to clarify the validity of s-IgA as an acute stress biomarker, including additional measures during stress exposure.

1. Introduction

Exposure to stress leads to activation of various biological processes that are aimed at mounting an effective response to a threatening situation and to later restore homeostasis once the stressor has ended. Physiological changes involved in stress response are fundamentally orchestrated by the sympathetic nervous system (SNS) and the hypothalamic–pituitaryadrenal (HPA) axis. Each of these systems involves a quick adaptive response, within minutes or hours, which is known as "fight or flight response". This response prepares the system to detect danger as well as to provide the energy required to survive (Sapolsky et al., 2000; Segerstrom and Miller, 2004). Among others, the SNS activates the immune system, characterized by the activation of inflammatory processes, which could accelerate wound repair and help prevent infections from taking hold (Godoy et al., 2018).

In controlled settings, several studies have documented an increase in certain inflammatory biomarkers such as cytokines following laboratory-induced psychological stress (Steptoe et al., 2007). Although blood sampling is the gold standard to determine levels of inflammatory biomarkers, there is an increasing interest in the ability to assess biological markers of stress reactivity in saliva, a less invasive, cheaper and safer biospecimen that enables sample collection many times per day (Szabo et al., 2020). Salivary levels of pro-inflammatory cytokines such as interleukin (IL)-6, tumor necrosis factor (TNF)-α, and IL-1β have already been found to increase in response to acute stress (Slavish et al., 2015). In this context, secretory Immunoglobulin A (s-IgA), the predominant immunoglobulin in mucosa, has emerged as a promising psychological biomarker of stress exposure due to its key role as a fast first-line immune defense that also provides oral protection from pathogens (Nurkka et al., 2003; Staley et al., 2018).

S-IgA secretion is under strong neuroendocrine control. Several studies support that, in adult populations, s-IgA increased after acute stress exposure (Campisi et al., 2012; Trueba et al., 2012). Specifically, Benham (2007) observed that s-IgA reached a significant increase 6 min after an acute psychological stressor and decreased during the first minutes of the recovery period, while cortisol was still increasing. This rapid response could be explained by an activation of the sympathetic nerves that innervate salivary glands, which enhances s-IgA output. However, very little research on s-IgA has explored antibody release during earlier stages of life such as childhood and adolescence (Castro-Quintas et al., 2022), when s-IgA levels have not yet reached those of adulthood (Sonesson et al., 2011). Additionally, the crosstalk between the neuroendocrine and the immune systems (e.g. cortisol reactivity) is still developing and under the influence of the psychosocial environment during this period (Gunnar et al., 2009).

The most common laboratory-induced psychosocial acute stress protocols may include mental arithmetic tasks, public speaking or cognitive interference tasks. In the case of children and adolescents, the Trier Social Stress Test for Children (TSST-C) is the protocol for inducing stress most recognized and widely used, and it has been shown to reliably trigger the activation of different biological systems (Allen et al., 2017; Wu et al., 2019). However, only one study in the literature explored s-IgA reactivity during TSST-C in children and adolescents. This study supported that youths (from 7 to 17 years old) displayed s-IgA reactivity to and recovery from acute stress (Laurent et al., 2015).

Moreover, when a stress stimulus is prolonged in time, a dysregulation of biological systems may occur leading to brain alterations and physiological disruptions that negatively impact health. This exposure can be particularly harmful during early stages of life leading to more profound and long-lasting effects on the regulation of stress response systems further influencing the vulnerability to develop mental disorders (Oh et al., 2018). Also, individuals experiencing chronic stressors have less effective immune functioning, experiencing nonspecific inflammation, having higher susceptibility to adverse health outcomes, such as vascular disease, autoimmune disorders, and premature mortality (Miller et al., 2011; Wan et al., 2022).

There are several potential pathways leading to a pro-inflammatory state after the exposure to stressors during young age, such as childhood maltreatment (CM) (Danese et al., 2017). Hunter et al., (2011) described an increase of cortisol reactivity in infants (0–5 years) exposed to adverse experiences. Conversely, chronic stressors dysregulate the acute stress response, leading, for example, to a blunted cortisol response. However, less is known about s-IgA alteration after adverse experiences.

This study intends to characterize the variability in s-IgA responses to psychosocial stressors from childhood to adolescence and aims to explore the influence of developmental stage and history of CM on s-IgA response to stress. We hypothesize that adolescents will show higher s-IgA levels than children throughout TSST-C and that participants exposed to CM will show a blunted response to TSST-C compared to non-exposed to CM, following a similar pattern to their cortisol response during TSST-C. We also hypothesize that s-IgA increase and recovery pattern will both be faster than cortisol's.

2. Materials and Methods

2.1. Sample and procedure

Participants were 94 youths aged 7–17 (54 had been diagnosed with a current psychiatric disorder and 40 were healthy controls). Participants in this study were a subset of a larger study cohort (*EPI_young_stress project*) recruited from April 2016 to March 2020 (Marques-Feixa et al., 2021). Participants were eligible for the subset analysis based on availability of data on primary predictors and outcomes of interest. Youths with a current psychiatric diagnosis were recruited from six child and adolescent mental health units in Spain. Healthy controls were recruited at the University of Barcelona or in the psychiatric units via advertisements, primary healthcare centres, schools and other community facilities. Exclusion criteria for all participants included diagnosis of an autism spectrum disorder, an eating disorder with Body Mass Index (BMI) < 18, intellectual disability (IQ < 70), current drug dependence, not being fluent in Spanish, extreme premature birth (<1500 g), head injury with loss of consciousness, and severe neurological or other pathological conditions (such as epilepsy, cancer or autoimmune diseases). The Ethical Review Board of each hospital and university involved in the project approved this study.

Families were explicitly informed of the voluntary nature of the study, their rights, and the procedures, risks and potential benefits involved. Written consent was required from parents/legal guardians. The children provided written assent after the nature of the procedure had been fully explained. Participants and their parents or legal guardians were interviewed separately, face to face, by a trained psychologist or psychiatrist to obtain sociodemographic and medical data, and to explore the CM history. A second appointment on a later date was scheduled at 4 PM to perform the Trier Social Stress Test for Children (TSST-C) at each corresponding research centre. Further details about the nature of the study have been described elsewhere (Marques-Feixa et al., 2021).

2.1.1. Trier social stress Test for children (TSST-C)

The TSST-C is the acute psychosocial stress protocol most widely used in children and adolescents, and it has been shown to reliably trigger the activation of different biological systems (Buske-Kirschbaum et al., 1997). To avoid circadian rhythm variability in biomarkers, participants were scheduled at 4:00 pm (Kudielka et al., 2004). Briefly, upon arrival at the research center each participant rested for 30 min in a quiet room accompanied by a familiar researcher. After this resting period, the participant entered an experimental room where a panel of two unfamiliar judges (a woman and a man) wearing lab coats awaited sitting behind a table. The judges were instructed to maintain a neutral stance throughout the TSST-C and to avoid giving any kind of positive feedback to the participants. The judges explained the nature of the tasks to the participant, highlighting that they would be videotaped to analyze their performance afterwards, and that they were expected to be the best. During the first task (speech task), the participants had 5 min to think of an end of a story explained by experts and 5 min for freely telling their end for the story in front of a microphone. The second task (arithmetic task) consisted of a five-minute long serial subtraction (2 from 421 in children from 7 to 12 years old, and 3 from 758 in adolescents from 13 to 17 years old). Whenever a participant made a mistake, a judge asked them to start over. Participants spent around 20 min in the experimental room. After the stress tasks, participants returned to the quiet room with the familiar researcher for an additional 30-minute recovery period. The entire procedure lasts 80 min (further details can be found in the Supplementary Material of Marques-Feixa et al. (2021)).

Five saliva samples were collected during this procedure: 30 min before the stressor (T1), immediately before the stressor (T2), immediately after the stressor (T3), 15 min after the stressor (T4), and 30 min after the stressor (T5) (see Fig. 1). All the participants were given a series of instructions to avoid factors that have been reported to influence biomarkers levels. Specifically, they were told to refrain from eating or drinking (with the exception of water) for two hours before the TSST-C; to refrain from intense physical activity for 24 h, and not to take benzodiazepines that day; to refrain from smoking for 1 h before; not to consume alcohol or caffeine in the 24 h preceding the TSST-C (Kudielka et al., 2009). The day of the protocol participants were asked about their current health status.

2.2. Measures

2.2.1. Developmental stage and current psychopathology

Pubertal development was ascertained by Tanner stage questionnaire (Morris and Udry, 1980), which was used to classify the participants as either children (Tanner stages 1–3) or adolescents (Tanner stages 4–5). Psychopathology was ascertained using the Spanish version of the Schedule for Affective Disorders and Schizophrenia for School-Age Children: Present and Lifetime Version DSM-5 (K-SADS-PL-5) (APA: American Psychiatric Association, 2013; De la Peña et al., 2018). Diagnoses dimensions are depicted in Table 1.

Table 1
Sociodemographic and anthropometric data of participants (n = 94).

Variables		Value
Age - mean (Sd) [range]		13.8 (2.4) [7–17]
Sex – n (%)	Female	56 (60%)
	Male	38 (40%)
Pubertal stage – n (%)	Child (Tanner stage 1–3)	47 (50%
	Adolescent (Tanner stage 4–5)	47 (50%)
Cultural origin– n (%)	European	78 (83%)
	Others [a]	16 (17%)
Socioeconomic status (SES)- mean (Sd) [range] [b]		40.4 (17.9) [8–66]
Current psychiatric diagnosis status – n (%)	Subjects without current psychiatric diagnosis	40 (43%)
	Subjects with current psychiatric diagnosis [c]	54 (57%)
History of childhood maltreatment (CM) – n (%)	Without history of CM	44 (47%)
	With history of CM	50 (53%)
Current infection – n (%)	No	78 (83%)
	Ambiguous	9 (10%)
	Sick or cold	7 (7%)
Body mass index (BMI) [d] mean (Sd) [range]		21.1 (4.3) [12–34]
BMI-for-age percentile [e] – n %	Underweight	4 (4.6%)
	Healthy weight	59 (67.8%)
	Overweight	10 (11.5%)
	Obesity	14 (16.1%)

[a] Other cultures included Latin American (69%), Maghrebin (19%), and others (12%).
[b] Socioeconomic status (SES) was assessed based on the Hollingshead Four-Factor Index (Hollingshead, 1975), ranging from 8 to 66, with higher scores reflecting higher SES. This analysis was conducted with 92 subjects.
[c] Diagnoses dimensions of the primary psychiatric disorder: Attention-deficit/hyperactivity disorder (27%), Affective disorders (24%), Trauma and stress-related disorders (19%), Anxiety disorders (13%), Behavioral disorders (9%), Psychotic disorders (6%) and Eating disorders (2%).
[d] This analysis was conducted with 87 subjects.
[e] BMI-for-age percentile was calculated based on clinical growth charts for children and teens aged between 2 and 19 years. For calculating it, we considered the precise months of age. Following clinical growth chart criteria participants were classified considering their percentile as: <5th, underweight; ≥5th to 84th, healthy weight; ≥85th to 94th, overweight, and ≥ 95th, obese. This analysis was conducted with 87 subjects.

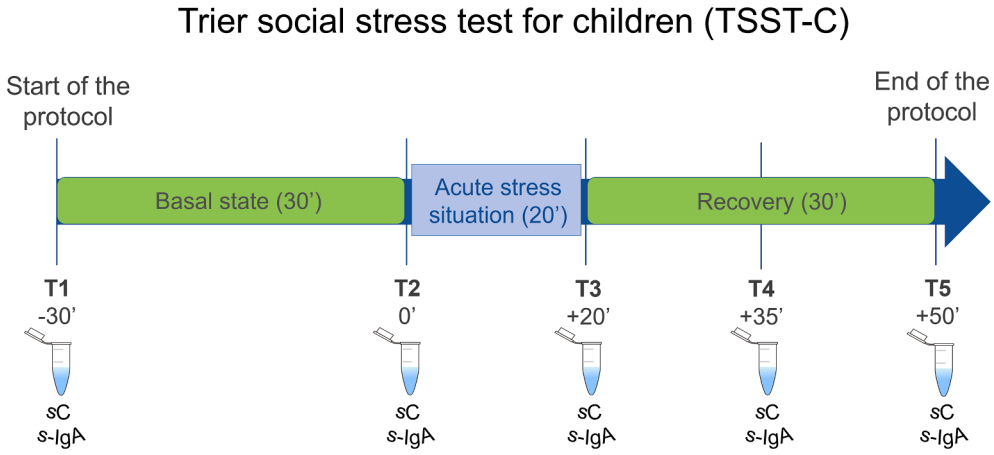


Fig. 1. Summary of the Trier Social Stress Test for Children (TSST-C) protocol.

2.2.2. Childhood maltreatment (CM)

The participants and their parents/legal guardians were evaluated by trained psychologists by means of an exhaustive interview following the criteria of the instrument "Tool for assessing the severity of situations in which children are vulnerable" (TASSCV) (CARM, 2012) (available online in Spanish). Previously, reports from social services or teachers were reviewed, where applicable. In addition, the information was ascertained through questionnaires answered by participants. Adolescents who were older than 12 were administered the self-report versions of the Childhood Trauma Questionnaire short version (CTQ-SF) (Bernstein et al., 2003) and the Childhood Experience of Care and Abuse Questionnaire (CECA-Q2) (Kaess et al., 2011), while participants aged 7–11 answered an adapted *ad-hoc* hetero-administered questionnaire (for details see Supplementary Material of Marques-Feixa et al., (2021)). The CTQ and CECA-Q2 were used as complementary information to determine presence and type of CM.

In summary, CM history was coded by clinicians according to the TASSCV criteria. Every subtype of CM included in the present study (emotional neglect, physical neglect, emotional abuse, physical abuse and sexual abuse) was coded as either: i) non-existent (no indicators of risk for a vulnerable situation), ii) suspect (when there was no conclusive evidence, but there were clear signs of risk that arouse suspicion), or iii) confirmed (clear evidence of it). Confirmed and suspected histories of CM were combined into the same category for downstream analysis.

2.2.3. s-IgA And cortisol determination

Saliva samples were collected by cotton oral swabs (Salimetrics) and were immediately stored at −20 °C for a maximum of 3 months. Before s-IgA and cortisol determination, the tubes were thawed and centrifuged, following the manufacturer's instructions, to remove debris from the saliva. Salivary s-IgA and cortisol concentration were determined using a high sensitivity enzyme-linked immunosorbent assay (ELISA) (commercial kit Salimetrics, LLC, State College, PA). Samples were tested in duplicate and the mean was calculated (μg/dL). The lower limit of sensitivity of s-IgA was 0.025μg/dL and of cortisol was 0.007μg/dL. Cortisol concentrations at any timepoint with a coefficient of variation (%CV) higher than 30% were determined in duplicate for a second time. Whenever this happened, the final cortisol value used for downstream analysis was the mean of the two measurements obtained in the duplicate (i.e., initial measurements were disregarded due to high variability). Two samples out of 470 (0.4%) still had CV > 30% after performing duplicates. Regarding s-IgA, only 10 samples had CV > 15%, of which only 2 had CV > 30%. No s-IgA duplicates were performed. For more details in sample %CV, please see Supplementary Table S3.

2.3. Data analysis

Analyses were conducted using SPSS 26.0. Salivary concentration of both s-IgA and cortisol were log10 transformed to fulfill the requirements for normal distribution in statistical analyses.

To determine the effect of developmental stage and CM in s-IgA fluctuation during TSST-C, mixed-effects models with a random effect of intercept and a random slope of time, were employed (Model 1). Time factor had five categories (time-points) and the interaction with time was considered the main effect of interest of the model. In addition, simple effects tests were performed to evaluate the specific timepoint interaction between groups. In a second step, a post-hoc analysis (Model 2) was conducted to test differential effect of CM history according to the developmental stage, entering a new factor that combines the developmental stage and the history of CM: (1) non-maltreated children, (2) children exposed to CM, (3) non-maltreated adolescents, and (4) adolescents exposed to CM. Considering that cortisol strongly influences s-IgA levels (Guzmán-Mejía et al., 2021; Stojanović et al., 2021); cortisol measures were included in the mixed model as covariates to adjust for cortisol levels at each corresponding time-point during TSST-C. Thus, to account for the possible confounding influence of cortisol variability, sex, current psychopathological status, and current infection (none, ambiguous or definitely sick-cold), these covariates were included in both statistical models. There were not missing data in any of the variables of interest. We have also included results of s-IgA fluctuations without cortisol correction, detailed in Supplementary material.

To determine the effect of developmental stage and CM in cortisol fluctuation during TSST-C, the same analyses were conducted (Model 3 and Model 4). The s-IgA was not considered as covariate since s-IgA secretion is limited to mucosal tissues and cortisol production occurs in the adrenal gland, so we did not consider that s-IgA influenced cortisol. These two analysis are detailed in Supplementary material, as cortisol fluctuations during TSST-C are described in detailed in a previous study (Marques-Feixa et al., 2021). All tests were two-tailed with significance defined as p-value < 0.05.

3. Results

Sociodemographic and anthropometric data of participants are presented in Table 1.

As depicted in Fig. 2, the s-IgA levels fluctuated significantly during the TSST-C ($F(4,199) = 6.200, p \leq 0.001$), indicating the validity of this acute psychosocial stressor to stimulate s-IgA secretion in the present sample (Model 1). Developmental stage was significantly associated with overall s-IgA levels ($F(1,82) = 6.710, p = .011$), reflecting higher s-IgA concentrations throughout the entire TSST-C procedure in adolescents when compared to children (similarly to higher overall cortisol levels observed in adolescents, detailed in Supplementary material). Furthermore, a significant interaction between developmental stage and time was identified ($F(4,197) = 3.406, p = .010$), indicating different trajectories of s-IgA levels between children and adolescents (not observed in cortisol fluctuations, see Supplementary material). Specifically, the simple effects analysis of s-IgA revealed a timepoint-specific interaction at T2 (immediately before the stressful situation) ($F = 8.545, p = .004$), T3 (immediately after the stressful situation) ($F = 12.429; p = .001$), T4 (15 min after the stressful situation finished) ($F = 4.89, p = .029$) and at T5 (30 min after the stressful situation finished) ($F = 4.647, p = .033$). In adolescents, s-IgA levels started to increase immediately before the acute stress, and continued rising immediately after the end of the stress task to finally return to basal s-IgA levels during the recovery period, while children showed no s-IgA changes throughout the protocol. Regarding s-IgA fluctuation through TSST-C, children did not show significant differences. However, adolescents showed a significant increase between T1- T2 (p = .033) and T1-T3 (p < .001), although not significant differences were observed between T2-T3. Between T3-T4 (during the 15 min after the end of the stressor) s-IgA decreased (p < .001) (see Fig. 2 and Table 2).

Additionally, a significant interaction between time and maltreatment was observed ($F(4,203) = 2.643, p = .035$). However, simple effects test did not reveal any significant timepoint-specific interaction. Thus, a second approach (Model 2) was performed to explore simultaneously developmental stage and maltreatment history. A different s-IgA trajectory across the TSST-C was observed between groups ($F(12,343) = 2.096, p = .017$) (see Tab. 2 and Fig. 3). Specifically, in T2 (immediately before stressor) children (both exposed and non-exposed to maltreatment) showed lower s-IgA levels when compared with adolescents without maltreatment ($p = .021$, $p = .004$, respectively). However, after the acute stressor only children non-exposed to maltreatment showed lower s-IgA levels compared with all other groups [children exposed to maltreatment, adolescents exposed to maltreatment and adolescents non-exposed to maltreatment, respectively (T3 ($p = .039$, $p = .001$, $p < .001$) and T4 ($p = 0.50$, $p = .012$, $p = .013$))]. In addition, in T5 non-maltreated adolescents showed higher s-IgA levels when compared with non-maltreated children ($p = .014$). Furthermore, regarding s-IgA fluctuation throughout TSST-C, children non-exposed to CM did not show significant differences, while children exposed to CM had a non-significant increase of s-IgA between T2 and T3 (p = .070).

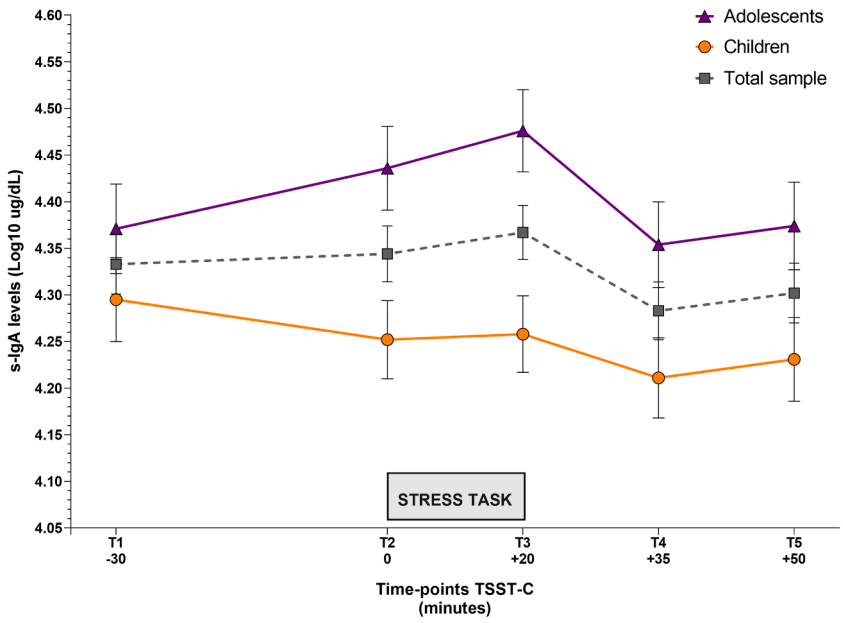


Fig. 2. s-IgA fluctuations during TSST-C in whole sample and according to developmental stage (Model 1). Error bars SE.

Table 2
Mixed-model analysis for s-IgA levels (Model 1 and Model 2).

		Developmental stage				Developmental stage according to CM history					
		Children (n = 47) (Mean, SD)	Adolescents (n = 47) (Mean, SD)	*F* (*p*) [a]	*F* (*p*) [b]	Non-maltreated children (n = 25) (Mean, SD)	Children exposed to CM (n = 22) (Mean, SD)	Non-maltreated adolescents (n = 19) (Mean, SD)	Adolescents exposed to CM (n = 28) (Mean, SD)	*F* (*p*) [a]	*F* (*p*) [b]
s-IgA levels during TSST-C (μg/dL log-transformed)	T1	4.30 (0.045)	4.37 (0.048)	3.406 ** (0.010)	1.274 (0.261)	4.30 (0.062)	4.30 (0.066)	4.36 (0.071)	4.37 (0.066)	2.096* (0.017)	0.361 (0.789)
	T2	4.25 (0.042)	4.44 (0.045)		8.545** (0.004)	4.23 (0.057)	4.27 (0.061)	4.49 (0.065)	4.39 (0.061)		3.292* (0.023)
	T3	4.26 (0.041)	4.48 (0.044)		12.429*** (0.001)	4.18 (0.056)	4.35 (0.061)	4.51 (0.065)	4.46 (0.061)		5.905*** (0.001)
	T4	4.21 (0.043)	4.35 (0.046)		4.899* (0.029)	4.13 (0.060)	4.30 (0.065)	4.36 (0.069)	4.36 (0.064)		3.022* (0.032)
	T5	4.23 (0.045)	4.37 (0.047)		4.647* (0.033)	4.17 (0.062)	4.29 (0.067)	4.41 (0.071)	4.35 (0.065)		2.275 (0.082)

CM: childhood maltreatment.
[a] Mixed-model.
[b] Simple effects tests in the context of mixed-model.
p values: *p ≤ 0.05, **p ≤ 0.01, and ***p ≤ 0.001.

Adolescents non-exposed to CM showed an increase before the stress, between T1-T2 (p =.021), after the TSST-C, specifically between T1-T3 (p =.006) but not between T2-T3 and a decrease between T3-T4 (p =.003). Similarly, adolescents non-exposed to CM showed and increase between T1-T3 (p =.045), a tendency to increase between T2-T3 (0.064) and a decrease between T3-T4 (p =.015), although they did not show an increase before the stressor, between T1-T2. With the exception of cortisol measures throughout TSST-C, none of the covariates (sex, current psychopathology and current infection) were significant in either Model 1 or Model 2 (for more information, see Supplementary material). Similar results were obtained in the analyses non—adjusted for cortisol levels (see Supplementary material).

4. Discussion

The present study indicates that s-IgA measurement constitutes a feasible biomarker to explore peripheral immunological reactivity to stress in young populations. In particular, we observed that, although children and adolescents showed similar s-IgA basal levels, their s-IgA stress reactivity seemed to differ. Adolescents showed an increase after the stressor and a rapid recovery, while children did not show an s-IgA response. Nevertheless, we observed that children exposed to CM exhibited an s-IgA pattern more similar to that of adolescents. To the best of our knowledge, this is the second paper to assess s-IgA response to stress in children and teens and the first one to do so in a young population exposed to CM. Therefore, evidence of s-IgA functioning in young populations is scarce and warrants further inquiry (Castro-Quintas et al., 2022).

Our findings are consistent with the only existing study exploring acute stress response in children and adolescents (Laurent et al., 2015). However, this previous research did not directly compare s-IgA reactivity between children and adolescents. In this regard, our study reveals that there is no s-IgA response to psychosocial stress before puberty. Differences observed could be due to the stressor task not being powerful enough for children to activate their s-IgA secretion. However, a perceived anxiety test administered in this sample during the TSST-C

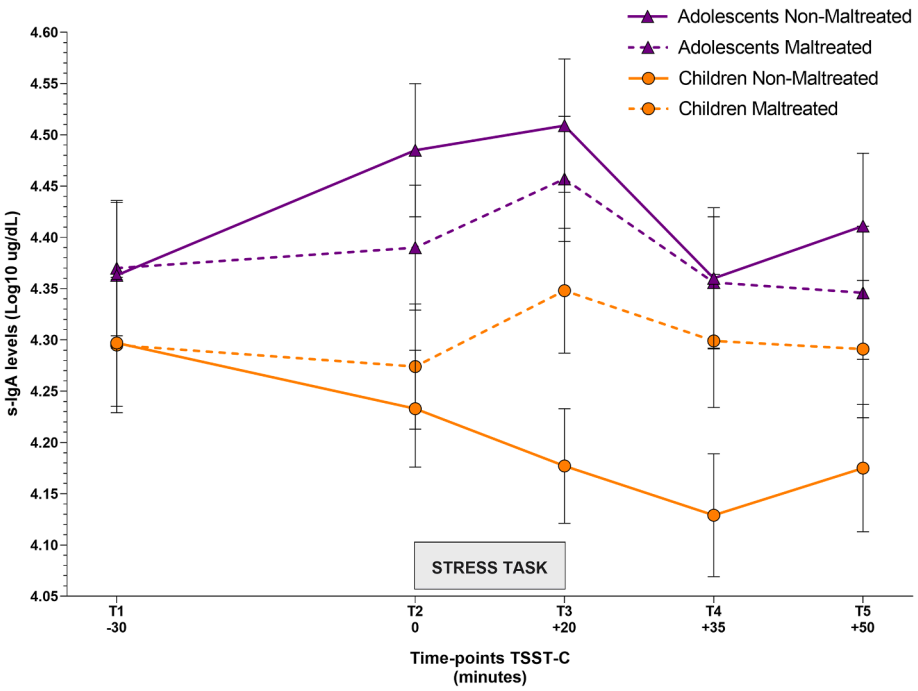


Fig. 3. s-IgA trajectories according to the developmental stage, and the history of CM (Model 2): (1) non-maltreated children, (2) children exposed to CM, (3) non-maltreated adolescents, and (4) adolescents exposed to CM. Error bars SE.

procedure, revealed that participants rated the session as equally stressful independent of developmental stage (Marques-Feixa et al., 2021). Accordingly, literature supports that puberty is one of the most sensitive periods of life with regard to immune system reprogramming by stress (Csaba, 2020), since children are born with an undeveloped and adaptable immune system, which matures and acquires memory as they grow (Simon et al., 2015). However, little is known about when this system becomes responsive to psychosocial cues. Our results here suggest that children's immune system may not respond to acute stress, in comparison to adolescents, although their self-perceived stress or their HPA axis may (Marques-Feixa et al., 2021). Interestingly, the functioning of biological systems are known to be mediated by both intrinsic and environmental factors (Seltzer et al., 2010). Accordingly, Ulmer-Yaniv et al., (2018) supports that during early infancy, children's immune system regulation relies on maternal health and interaction rather than on other environmental signals. Additionally, it has been proposed that biological response to stress may be associated to general cognitive functioning and the development of social cognition (Van Den Bos et al., 2016). It would be of great interest to understand how the brain, depending on the developmental stage, detects psychosocial stress signals and activates different biological systems to respond accordingly.

In this regard, history of CM seems to alter s-IgA response during the TSST-C. Danese et al. (2017) observed that CM is a threatening situation that can be linked to danger and may co-occur with physical abuse, which can facilitate pathogen infection that, in turn, can induce inflammation and damage. Specifically, we observed that children exposed to CM showed a heightened immunological stress response with a pattern equivalent to that exhibited by adolescents. Although the ability to deal with threatening situations is a hallmark of adolescence, CM could make children more aware of potentially dangerous situations leading to an early activation of their stress response. Thus, the apparent advancement of s-IgA reactivity to psychosocial stress observed in children exposed to CM is consistent with accelerated biological aging in this group, as revealed by the epigenetic clock, telomere length and advanced pubertal timing (Chen et al., 2021; Colich et al., 2020). This is in line with human development theories that argue that early adverse environments may accelerate the onset of puberty to increase the opportunity for reproduction prior to possible mortality (Belsky, 2012); e.g., girls who are victims of sexual abuse have been described to experience a precocious puberty (Noll et al., 2017). However, in our study no differences in s-IgA response according to CM history were observed in the adolescent group. This is in contrast with previous studies reporting heightened inflammation in subjects exposed to early adversity and might reflect unique features of s-IgA as opposed to other immune markers such as C-reactive protein or interleukins.

Additionally, our findings suggest that HPA axis and the immune system follow independent maturation processes, since the HPA axis response to TSST-C in the same sample follows a similar pattern in children and adolescents (Marques-Feixa et al., 2021) contrary to our findings on s-IgA reactivity. Adolescents have higher s-IgA and cortisol levels when compared to children, suggesting an influence of pubertal hormones in overall immunoendocrinological levels. However, while cortisol response throughout TSST-C is fundamentally modified by CM, s-IgA response to the acute stressor is modified by developmental stage. Adolescents non-exposed to CM showed both cortisol and s-IgA responses. Both children and adolescents exposed to CM exhibited s-IgA response in front of stress, but no change in cortisol levels. Children non-exposed to CM did show a response for cortisol but they did not show a response for s-IgA. Further research is needed to clarify whether these changes are unique to maturation or may be indicative of early evidence of reprogramming due to stress.

Our findings also suggest that s-IgA increases in a short period after an acute psychosocial stress, highlighting its possible use as a non-invasive immune biomarker in youths. Specifically, we observed an s-IgA increase 20 min after the psychosocial stress was initiated followed by a fast return to basal levels 35 min after the beginning of the stressor. These results contrast with those found in our previous work on this sample, in which cortisol levels remained high after 35 min (Marques-Feixa et al., 2021). This is in line with a previous study based on undergraduate students exposed to the TSST, which reported that cortisol remained high 30 min after completing the stress task, but s-IgA levels had fully recovered by then (Campisi et al., 2012). This might indicate that the s-IgA response is released prior to cortisol and that it follows a faster fashion as reflected by its rapid increase and return to basal levels.

Thus, s-IgA and cortisol might be independent biomarkers providing complementary information that, when studied together, offer a comprehensive view of the stress response in humans. In future studies, it may be interesting to evaluate both cortisol and s-IgA simultaneously.

Some limitations should be noted. First, it would be interesting to increase the number of samples collected during the stressor in order to better understand the pattern of s-IgA response, since Benham (2007) described a peak of s-IgA levels 6 min after stress onset in young adults. Moreover, the only study based in youths found a peak of s-IgA levels 10 min after the stressor start (Laurent et al., 2015). Unfortunately, these intermediate measures were not collected in our study, which could have allowed us to better define s-IgA dynamics. Second, the methodology used to assess CM exposure (TASSCV) requires extensive interviews with multiple informants, and a longer time for administration when compared with the most used questionnaires in the field, which might not always be possible for clinicians in a daily setting. Of note, younger children have a limited understanding of their own exposure due to their cognitive immaturity. Additionally, widely used questionnaires, such as the CTQ or CECA-Q2, can not be administered to children younger than 12 years; indeed, there is no validated questionnaires to assess the presence of CM in the 7 to 17 years range. Thus, use of the TASSCV allowed the proper assessment of different types of CM exposure in the whole age range included in our study, which would have otherwise not been possible to explore. Third, the majority of participants with a history of CM also had a current psychiatric disorder, while most participants non-exposed to CM had no psychopathological history. Further research including a higher proportion of resilient youth (exposed to CM with no psychiatric disorders) would help disentangle the effect of both variables in the biomarkers analyzed. Fourth, although the TSST-C difficulty adaptation was determined by age, the analysis were conducted based on puberty development.

The inclusion of additional SNS biomarkers, such as alpha amylase, and epigenetic measures, such as DNA methylation, could provide a more comprehensive understanding of the complex crosstalk between the neuroendocrine and the immune systems (Martins et al., 2021). Furthermore, the study of other systemic inflammation biomarkers, such as CRP or interleukins, could help to elucidate the biological mechanisms that are responsible for linking higher inflammation to CM (Coelho et al., 2014; Entringer et al., 2020). Moreover, other stress biomarkers, such as cortisol, have been described to follow a non-linear pattern of stress reactivity through development (Gunnar et al., 2009). Thus, further studies should explore s-IgA reactivity patterns across all five Tanner stages to disentangle immune maturation across pubertal transition. Since it has been suggested that youth with more externalizing behaviors were characterized by attenuated and less dynamic s-IgA responses (Laurent et al., 2015), it could be interesting to include different diagnosis as a potential mediator of this relationship in future studies (Cicchetti et al., 2015).

Finally, it might be interesting to explore how the age of exposure to CM, its proximity or its chronicity can influence the resulting s-IgA reactivity to psychosocial stress to determine the most critical developmental periods (Slopen et al., 2013). Similarly, the nature of the adversity (e.g. neglect vs abuse; or physical vs emotional) has a differential impact in the biological deregulation observed (Baumeister et al., 2016; Sumner et al., 2019). Further studies are needed to explore whether social support or secure attachment could buffer the effects of CM on immune dysregulation. However, maternal secure attachment and social support could buffer the impact of CM in early stages of life (Sung et al., 2016).

5. Conclusions

The present study found evidence of an increased s-IgA reactivity to stress only after puberty onset, supporting that the immune system gradually matures from birth to late life (Simon et al., 2015). However, children previously exposed to CM may exhibit an advance of this response, activating their immune system when faced with psychosocial stressors at earlier stages of development. This phenomenon would be in line with widespread theories defending that individuals exposed to a wide range of pernicious exposures (from either psychosocial or chemical nature) experience what is known as accelerated biological aging. Further studies are required to elucidate the role of CM and developmental stage in immune system regulation in young participants.

6. Funding sources

Supported by the Spanish Ministry of Economy and Competitiveness, *Instituto de Salud Carlos III* through the University of Barcelona multicenter project (PI15/00097)-PI L. Fañanas, *Hospital Universitario Araba* (PI15/00793)-PI I. Zorrilla, *Hospital Gregorio Marañón* (PI15/00723)-PI M. Rapado and *Hospital Clinic* (PI15/00685)-PI S. Romero, co-financed by the European Regional Development Funds from the European Commission, "A way of making Europe". We thank the Network Centre for Biomedical Research in Mental Health (CIBERSAM). This study was facilitated by a pre-doctoral research grant from the Catalonian authorities to Laia Marques-Feixa (AGAUR- FI_B100023-2018) and Agueda Castro-Quintas (AGAUR-FI_B 00233–2020). Supported by the *Comissionat per a Universitats i Recerca del DIUE*, of the *Generalitat de Catalunya* regional authorities (2017SGR1577). Dr. Rapado-Castro was supported by a Ramon y Cajal Research Fellowship (RYC-2017–23144) and by a NARSAD independent investigator grant (no. 24628) from the Brain and Behaviour Research Foundation.

Acknowledgments

We are indebted to all the participants and their families for taking part in a study with such deep emotional involvement. We also thank the nurses and lab technicians who made this research possible. Thank you in particular to Anna Valldeperas and Sergi Valero for your support.

Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2022.04.010.

References

Allen, A.P., Kennedy, P.J., Dockray, S., Cryan, J.F., Dinan, T.G., Clarke, G., 2017. The trier social stress test: principles and practice. Neurobiol. Stress 6, 113–126. https://doi.org/10.1016/j.ynstr.2016.11.001.

APA: American Psychiatric Association, 2013. DSM-5: Diagnostic and statistical manual of mental disorders (5th ed.)., 5th ed. Washington, DC.

Baumeister, D., Akhtar, R., Ciufolini, S., Pariante, C.M., Mondelli, V., 2016. Childhood trauma and adulthood inflammation: a meta-analysis of peripheral C-reactive protein, interleukin-6 and tumour necrosis factor-α. Mol. Psychiatry 21, 642–649. https://doi.org/10.1038/mp.2015.67.

Belsky, J., 2012. The development of human reproductive strategies: progress and prospects. Curr. Dir. Psychol. Sci. 21, 310–316.

Benham, G., 2007. The shape of stress: The use of frequent sampling to measure temporal variation in S-IgA levels during acute stress. Stress Heal. J. Int. Soc. Investig. Stress 23, 295–301. https://doi.org/10.1002/smi.1150.

Bernstein, D.P., Stein, J.A., Newcomb, M.D., Walker, E., Pogge, D., Ahluvalia, T., Stokes, J., Handelsman, L., Medrano, M., Desmond, D., Zule, W., 2003. Development and validation of a brief screening version of the Childhood Trauma Questionnaire. Child Abus. Negl. 27, 169–190. https://doi.org/10.1016/S0145-2134(02)00541-0.

Buske-Kirschbaum, A., Jobst, S., Wustmans, A., Kirschbaum, C., Rauh, W., Hellhammer, D., 1997. Attenuated free cortisol response to psychosocial stress in children with atopic dermatitis. Psychosom. Med. 59, 419–426. https://doi.org/10.1097/00006842-199707000-00012.

Campisi, J., Bravo, Y., Cole, J., Gobeil, K., 2012. Acute psychosocial stress differentially influences salivary endocrine and immune measures in undergraduate students. Physiol. Behav. 107, 317–321. https://doi.org/10.1016/j.physbeh.2012.09.003.

CARM, 2012. Instrumento para la valoración de la gravedad de las situaciones de desprotección infantil (Tool for assessing the severity of situations in which children are vulnerable- TASSCV) [WWW Document]. Serv. Soc. Atención Primaria y Espec. la Región Muricia. URL https://www.carm.es/web/pagina?IDCONTENIDO=9415&IDTIPO=246&RASTRO=c886$m5855 (accessed 2.2.16).

Castro-Quintas, Á., Palma-Gudiel, H., Caso, J.R., Leza, J.C., Fañanás, L., 2022. Salivary secretory immunoglobulin A as a putative biomarker of psychosocial stress exposure during the first stages of life: A systematic review. Review submitted by our group.

Chen, M.A., LeRoy, A.S., Majd, M., Chen, J.Y., Brown, R.L., Christian, L.M., Fagundes, C. P., 2021. Immune and epigenetic pathways linking childhood adversity and health across the lifespan. Front. Psychol. 12, 788351 https://doi.org/10.3389/fpsyg.2021.788351.

Cicchetti, D., Handley, E.D., Rogosch, F.A., 2015. Child maltreatment, inflammation, and internalizing symptoms: investigating the roles of C-reactive protein, gene variation, and neuroendocrine regulation. Dev. Psychopathol. 27, 553–566. https://doi.org/10.1017/s0954579415000152.

Coelho, R., Viola, T.W., Walss-Bass, C., Brietzke, E., Grassi-Oliveira, R., 2014. Childhood maltreatment and inflammatory markers: a systematic review. Acta Psychiatr. Scand. 129, 180–192. https://doi.org/10.1111/acps.12217.

Colich, N.L., Rosen, M.L., Williams, E.S., McLaughlin, K.A., 2020. Biological aging in childhood and adolescence following experiences of threat and deprivation: a systematic review and meta-analysis. Psychol. Bull. 146, 721–764. https://doi.org/10.1037/bul0000270.

Csaba, G., 2020. Reprogramming of the immune system by stress and faulty hormonal imprinting. Clin. Ther. 42, 983–992. https://doi.org/10.1016/j.clinthera.2020.03.003.

Danese, A., Lewis, J.S., 2017. Psychoneuroimmunology of early-life stress: the hidden wounds of childhood trauma? Neuropsychopharmacology 42, 99–114. https://doi.org/10.1038/npp.2016.198.

De la Peña, F.R., Villavicencio, L.R., Palacio, J.D., Félix, F.J., Larraguibel, M., Viola, L., Ortiz, S., Rosetti, M., Abadi, A., Montiel, C., Mayer, P.A., Fernández, S., Jaimes, A., Feria, M., Sosa, L., Rodríguez, A., Zavaleta, P., Uribe, D., Galicia, F., Botero, D., Estrada, S., Berber, A.F., Pi-Davanzo, M., Aldunate, C., Gómez, G., Campodónico, I., Tripicchio, P., Gath, I., Hernández, M., Palacios, L., Ulloa, R.E., 2018. Validity and reliability of the kiddie schedule for affective disorders and schizophrenia present and lifetime version DSM-5 (K-SADS-PL-5) Spanish version. BMC Psychiatry 18, 193. https://doi.org/10.1186/s12888-018-1773-0.

Entringer, S., de Punder, K., Overfeld, J., Karaboycheva, G., Dittrich, K., Buss, C., Winter, S.M., Binder, E.B., Heim, C., 2020. Immediate and longitudinal effects of maltreatment on systemic inflammation in young children. Dev. Psychopathol. 32, 1725–1731. https://doi.org/10.1017/S0954579420001686.

Godoy, L.D., Rossignoli, M.T., Delfino-Pereira, P., Garcia-Cairasco, N., Umeoka, E., 2018. A comprehensive overview on stress neurobiology: basic concepts and clinical implications. Front. Behav. Neurosci 12, 127. https://doi.org/10.3389/fnbeh.2018.00127.

Gunnar, M.R., Wewerka, S., Frenn, K., Long, J., Griggs, C., 2009. Developmental changes in hypothalamus–pituitary–adrenal activity over the transition to adolescence: normative changes and associations with puberty. Dev. Psychopathol. 21, 69–85. https://doi.org/10.1017/S0954579409000054.Developmental.

Guzmán-Mejía, F., Godínez-Victoria, M., Vega-Bautista, A., Pacheco-Yépez, J., Drago-Serrano, M.E., 2021. Intestinal homeostasis under stress siege. Int. J. Mol. Sci. 22 https://doi.org/10.3390/ijms22105095.

Hunter, A.L., Minnis, H., Wilson, P., 2011. Altered stress responses in children exposed to early adversity: a systematic review of salivary cortisol studies. Stress 14, 614–626. https://doi.org/10.3109/10253890.2011.577848.

Kaess, M., Parzer, P., Mattern, M., Resch, F., Bifulco, A., Brunner, R., 2011. Childhood Experiences of Care and Abuse (CECA) - validation of the German version of the questionnaire and interview, and results of an investigation of correlations between adverse childhood experiences and suicidal behaviour]. Z. Kinder. Jugendpsychiatr. Psychother. 39, 243–252. https://doi.org/10.1024/1422-4917/a000115.

Kudielka, B.M., Buske-Kirschbaum, A., Hellhammer, D.H., Kirschbaum, C., 2004. HPA axis responses to laboratory psychosocial stress in healthy elderly adults, younger adults, and children: impact of age and gender. Psychoneuroendocrinology 29, 83–98. https://doi.org/10.1016/S0306-4530(02)00146-4.

Kudielka, B.M., Hellhammer, D.H., Wüst, S., 2009. Why do we respond so differently? Reviewing determinants of human salivary cortisol responses to challenge. Psychoneuroendocrinology 34, 2–18. https://doi.org/10.1016/j.psyneuen.2008.10.004.

Laurent, H.K., Stroud, L.R., Brush, B., D'Angelo, C., Granger, D.A., 2015. Secretory IgA reactivity to social threat in youth: relations with HPA, ANS, and behavior. Psychoneuroendocrinology 59, 81–90. https://doi.org/10.1016/j.psyneuen.2015.04.021.

Marques-Feixa, L., Palma-Gudiel, H., Romero, S., Moya-Higueras, J., Rapado-Castro, M., Castro-Quintas, Á., Zorrilla, I., José Muñoz, M., Ramírez, M., Mayoral, M., Mas, A., José Lobato, M., Blasco-Fontecilla, H., Fañanás, L., 2021. Childhood maltreatment disrupts HPA-axis activity under basal and stress conditions in a dose-response relationship in children and adolescents. Psychol. Med. 16, 1–14. https://doi.org/10.1017/S003329172100249X.

Martins, J., Czamara, D., Sauer, S., Rex-Haffner, M., Dittrich, K., Dörr, P., de Punder, K., Overfeld, J., Knop, A., Dammering, F., Entringer, S., Winter, S.M., Buss, C., Heim, C., Binder, E.B., 2021. Childhood adversity correlates with stable changes in DNA methylation trajectories in children and converges with epigenetic signatures of prenatal stress. Neurobiol. Stress 15, 100336. https://doi.org/10.1016/j.ynstr.2021.100336.

Miller, G.E., Chen, E., Parker, K.J., 2011. Psychological stress in childhood and susceptibility to the chronic diseases of aging: moving toward a model of behavioral and biological mechanisms. Psychol. Bull. 137, 959–997. https://doi.org/10.1037/a0024768.

Morris, N.M., Udry, J.R., 1980. Validation of a self-administered instrument to assess stage of adolescent development. J. Youth Adolesc. 9, 271–280. https://doi.org/10.1007/BF02088471.

Noll, J.G., Trickett, P.K., Long, J.D., Negriff, S., Susman, E.J., Shalev, I., Li, J.C., Putnam, F.W., 2017. Childhood sexual abuse and early timing of puberty. J. Adolesc. Heal. Off. Publ. Soc. Adolesc. Med. 60, 65–71. https://doi.org/10.1016/j.jadohealth.2016.09.008.

Nurkka, A., Obiero, J., Käyhty, H., Scott, J.A.G., 2003. Effects of sample collection and storage methods on antipneumococcal immunoglobulin A in saliva. Clin. Diagn. Lab. Immunol. 10, 357–361. https://doi.org/10.1128/cdli.10.3.357-361.2003.

Oh, D.L., Jerman, P., Silvério Marques, S., Koita, K., Purewal Boparai, S.K., Burke Harris, N., Bucci, M., 2018. Systematic review of pediatric health outcomes associated with childhood adversity. BMC Pediatr. 18, 83. https://doi.org/10.1186/s12887-018-1037-7.

Sapolsky, R.M., Romero, L.M., Munck, A.U., 2000. How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. Endocr. Rev. 21, 55–89. https://doi.org/10.1210/edrv.21.1.0389.

Segerstrom, S.C., Miller, G.E., 2004. Psychological stress and the human immune system: a meta-analytic study of 30 years of inquiry. Psychol. Bull. 130, 601–630. https://doi.org/10.1037/0033-2909.130.4.601.

Seltzer, L.J., Ziegler, T.E., Pollak, S.D., 2010. Social vocalizations can release oxytocin in humans. Proc. Biol. Sci. 277, 2661–2666. https://doi.org/10.1098/rspb.2010.0567.

Simon, A.K., Hollander, G.A., McMichael, A., 2015. Evolution of the immune system in humans from infancy to old age. Proc. Biol. Sci. 282, 20143085. https://doi.org/10.1098/rspb.2014.3085.

Slavish, D.C., Graham-Engeland, J.E., Smyth, J.M., Engeland, C.G., 2015. Salivary markers of inflammation in response to acute stress. Brain. Behav. Immun. 44, 253–269. https://doi.org/10.1016/j.bbi.2014.08.008.

Slopen, N., Kubzansky, L.D., McLaughlin, K.A., Koenen, K.C., 2013. Childhood adversity and inflammatory processes in youth: a prospective study. Psychoneuroendocrinology 38, 188–200. https://doi.org/10.1016/j.psyneuen.2012.05.013.

Sonesson, M., Hamberg, K., Wallengren, M.-L.-L., Matsson, L., Ericson, D., 2011. Salivary IgA in minor-gland saliva of children, adolescents, and young adults. Eur. J. Oral Sci. 119, 15–20. https://doi.org/10.1111/j.1600-0722.2010.00794.x.

Staley, M., Conners, M.G., Hall, K., Miller, L.J., 2018. Linking stress and immunity: immunoglobulin A as a non-invasive physiological biomarker in animal welfare studies. Horm. Behav. 102, 55–68. https://doi.org/10.1016/j.yhbeh.2018.04.011.

Steptoe, A., Hamer, M., Chida, Y., 2007. The effects of acute psychological stress on circulating inflammatory factors in humans: a review and meta-analysis. Brain. Behav. Immun. 21, 901–912. https://doi.org/10.1016/j.bbi.2007.03.011.

Stojanović, N.M., Randjelović, P.J., Pavlović, D., Stojiljković, N.I., Jovanović, I., Sokolović, D., Radulović, N.S., 2021. An impact of psychological stress on the interplay between salivary oxidative stress and the classic psychological stress-related parameters. Oxid. Med. Cell. Longev. 2021, 6635310. https://doi.org/10.1155/2021/6635310.

Sumner, J.A., Colich, N.L., Uddin, M., Armstrong, D., McLaughlin, K.A., 2019. Early experiences of threat, but not deprivation, are associated with accelerated biological aging in children and adolescents. Biol. Psychiatry 85, 268–278. https://doi.org/10.1016/j.biopsych.2018.09.008.

Sung, S., Simpson, J.A., Griskevicius, V., Kuo, S.-I.-C., Schlomer, G.L., Belsky, J., 2016. Secure infant-mother attachment buffers the effect of early-life stress on age of menarche. Psychol. Sci. 27, 667–674. https://doi.org/10.1177/0956797616631958.

Szabo, Y.Z., Slavish, D.C., Graham-Engeland, J.E., 2020. The effect of acute stress on salivary markers of inflammation: a systematic review and meta-analysis. Brain. Behav. Immun. 88, 887–900. https://doi.org/10.1016/j.bbi.2020.04.078.

Trueba, A.F., Mizrachi, D., Auchus, R.J., Vogel, P.D., Ritz, T., 2012. Effects of psychosocial stress on the pattern of salivary protein release. Physiol. Behav. 105, 841–849. https://doi.org/10.1016/j.physbeh.2011.10.014.

Ulmer-Yaniv, A., Djalovski, A., Priel, A., Zagoory-Sharon, O., Feldman, R., 2018. Maternal depression alters stress and immune biomarkers in mother and child. Depress. Anxiety 35, 1145–1157. https://doi.org/10.1002/da.22818.

Van Den Bos, E., Van Duijvenvoorde, A.C.K., Michiel Westenberg, P., 2016. Effects of adolescent sociocognitive development on the cortisol response to social evaluation. Dev. Psychol. 52, 1151–1163. https://doi.org/10.1037/dev0000133.

Wan, A., Bernstein, C.N., Graff, L.A., Patten, S.B., Sareen, J., Fisk, J.D., Bolton, J.M., Hitchon, C., Marriott, J.J., Marrie, R.A., 2022. Childhood maltreatment and psychiatric comorbidity in immune-mediated inflammatory disorders. Psychosom. Med. 84, 10–19. https://doi.org/10.1097/psy.0000000000001025.

Wu, J., Phillip, T.M., Doretto, V., van Noordt, S., Chaplin, T.M., Hommer, R.E., Mayes, L. C., Crowley, M.J., 2019. An inactive control of the 'Trier Social Stress Test' for Youth 10–17 years: neuroendocrine, cardiac, and subjective responses. Psychoneuroendocrinology 104, 152–164. https://doi.org/10.1016/j.psyneuen.2019.02.027.

UNIVERSITAT DE BARCELONA

Dr. Lourdes Fañanás Saura
Unitat de Zoologia i Antropologia Biològica
Dept. Biologia Evolutiva, Ecologia i Ciències Ambientals
Facultat de Biologia, Universitat de Barcelona

Informe del director sobre la contribución del doctorando al artículo.

La Prof. Lourdes Fañanás Saura, profesora del Departamento de Biología Evolutiva, Ecologia y Ciencias Ambientales de la Facultad de Biología (Universitat de Barcelona) y directora de la presente tesis doctoral de Laia Marques Feixa, por la presente certifica que ninguno de los coautores del articulo *"Secretory immunoglobulin A (s-IgA) reactivity to acute psychosocial stress in children and adolescents: the influence of pubertal development and history of maltreatment",* ha utilizado esta publicacion para una tesis doctoral, y que la participación del solicitante en este artículo en el que comparte coautoría con Agueda Castro-Quintas, incluyó las siguientes tareas:

- Participación en la concepción y diseño del estudio.
- Reclutamiento y evaluación de los sujetos incluidos.
- Coordinación del proyecto.
- Procesamiento de los datos.
- Análisis estadísticos e interpretación de los datos.
- Redacción del manuscrito.
- Revisión crítica del artículo por contenido intelectual.

Signado por Prof. Lourdes Fañanás

Barcelona, abril 2022

4. Resumen global de los resultados

Las hipótesis específicas planteadas en un inicio se han podido testar en los seis artículos realizados y resumidos a continuación.

Sección I: En cuanto a la evaluación de los acontecimientos vitales estresantes recientes en población adolescente y su relación con la sintomatología internalizante y externalizante, hemos podido concluir que:

1. El metaanálisis demuestra que vivir acontecimientos vitales estresantes recientes de forma agregada puede tener un fuerte impacto en la sintomatología internalizante y externalizante expresada por los adolescentes. Los estudios longitudinales confirman que tanto los estresores aumentan el riesgo de psicopatología (hipótesis de sensibilidad al estrés) como que la psicopatología, en sí misma, aumenta el riesgo de exposición a situaciones de estrés (hipótesis de generación del estrés), produciéndose un círculo vicioso entre estrés y psicopatología. Hay pocos estudios que reporten la naturaleza o tipo de estresores, por lo que concluir qué acontecimientos pueden ser los más dañinos en la salud mental de los adolescentes es todavía una incógnita por resolver.
2. El instrumento *Life Events Inventory for Adolescents* (LEIA) ha sido validado en la población general adolescente, demostrando altos estándares de calidad psicométrica para su uso en el ámbito clínico y de la investigación. El LEIA permite valorar 75 acontecimientos vitales estresantes vividos en el último año y su respectiva afectación. La suma de los acontecimientos vividos (puntuación cuantitativa) se asocia más a la sintomatología externalizante, mientras que la que valora la afectación (puntuación subjetiva) se asocia más a la sintomatología internalizante. El LEIA es el primer instrumento en considerar la naturaleza distinta de los estresores (menores-mayores, dependientes-independientes o interpersonales- no interpersonales). Los acontecimientos considerados como menores no tienen relevancia en la salud mental del menor, pero sí los eventos mayores, que se asocian a un aumento de la sintomatología internalizante, externalizante y a un bajo bienestar. Asimismo, los acontecimientos dependientes (ej. expulsión, peleas) se asocian más con la sintomatología externalizante. El acoso escolar y los eventos independientes-no interpersonales (ej. problemas económicos en la familia) se asocian a síntomas internalizantes. Por último, los estresores independientes interpersonales (ej. enfermedad o muerte de un familiar) parecen no afectar a la sintomatología expresada por los adolescentes.

Sección II: En referencia a las consecuencias clínicas asociadas a las experiencias adversas tempranas (estresores próximos y maltrato), se ha podido observar que:

3. Los diferentes tipos de maltrato coexisten y podrían evaluarse en un contínuum según su severidad, frecuencia y agregación. El maltrato infantil aumenta rasgos típicos del TLP (desregulación emocional, ira intensa e impulsividad) en niños/as

y adolescentes. Tanto estos rasgos como la propia historia de maltrato aumentan el riesgo de exposición a más acontecimientos vitales estresantes, sugiriendo la existencia de una revictimización. La desregulación emocional y los estresores recientes son los constructos que más se asocian a las conductas suicidas presentadas en la población infantojuvenil (autolesiones, ideación suicida, intentos autolíticos, etc.).

4. Los niños/as y adolescentes con historia de maltrato muestran más sintomatología psiquiátrica internalizante y externalizante, presentando un peor ajuste premórbido y funcionamiento global. Los pacientes con historia de maltrato infantil muestran mayor comorbilidad psiquiátrica, polifarmacia, y un inicio más temprano del abuso de sustancias ilegales. Nuestros hallazgos refuerzan el nuevo diagnóstico propuesto por la CIE-11: el TEPT-C. Los participantes con historia de maltrato, independientemente del diagnóstico psiquiátrico actual, muestran más sintomatología de TEPT-C (estrés postraumático, desregulación emocional, autoconcepto negativo y problemas en las relaciones interpersonales). Además, los diferentes tipos de maltrato tienen un impacto diferencial en esta sintomatología dependiendo de la etapa del desarrollo en la que tuvieron lugar, sugiriendo ventanas ontogénicas de vulnerabilidad.

Sección III: En lo que se refiere a las alteraciones neurobiológicas en niños/as y adolescentes expuestos a maltrato, se ha demostrado que:

5. Los niños/as y adolescentes que han sufrido maltrato muestran disfunciones en el eje HHA; i) tanto en el ritmo circadiano, con mayores concentraciones de cortisol diurno (especialmente por la noche) como ii) frente a estrés psicosocial agudo (TSST-C), mostrando un aplanamiento en su reactividad. Asimismo, se observa una relación dosis-efecto: los participantes que han sufrido experiencias de maltrato moderadas-severas o han sido expuestos a menudo-frecuentemente a maltrato muestran mayores disfunciones en el eje HHA. Sin embargo, los participantes con historia de maltrato reportan una elevada percepción de estrés-ansiedad, evidenciando una clara disociación entre su percepción subjetiva y su respuesta biológica frente estrés. Estas asociaciones se observaron independientemente de si actualmente tenían o no un diagnóstico psiquiátrico.
6. El estrés psicosocial agudo estimula la secreción de la Inmonoglobulina A secretora (s-IgA), un biomarcador del sistema inmune. Mientras que los adolescentes aumentan los niveles de s-IgA frente a estrés y disminuyen sus concentraciones al acabar el estímulo, los niños/as prepuberales no presentan variaciones. No obstante, aquellos niños/as con historia de maltrato muestran una respuesta similar a los adolescentes, incrementando los niveles de s-IgA después del estresor psicosocial. Esto podría apuntar a una maduración temprana del sistema inmune en sujetos con experiencias de maltrato.

5. Discusión

El objetivo principal de esta tesis ha sido explorar el impacto de las experiencias adversas durante la infancia en la salud mental de los niños/as y adolescentes. También estudiar cómo el trauma complejo puede dañar importantes mecanismos neuroendocrinos implicados en la respuesta al estrés, afectando a la regulación emocional, la conducta, las habilidades sociales y otras funciones cognitivas esenciales para el desarrollo óptimo de la persona (McCrory et al., 2011; Nemeroff, 2016).

En el inicio de esta tesis nos preguntamos si durante una etapa clave del desarrollo, como es la adolescencia, se podía establecer una clara relación entre la agregación de acontecimientos vitales estresantes recientes y un aumento de la sintomatología internalizante y/o externalizante. También nos planteamos si los jóvenes con psicopatología mostraban un mayor riesgo de exposición a situaciones estresantes, en comparación con los adolescentes sin sintomatología internalizante o externalizante. Para ello, se revisó extensa y sistemáticamente la literatura científica.

De acuerdo con la revisión y el metaanálisis realizado, se ha podido concluir que está profusamente demostrada la asociación entre los acontecimientos vitales estresantes recientes y la presencia de sintomatología internalizante y externalizante en población adolescente (March-Llanes et al., 2017). De hecho, los estudios longitudinales revisados respaldan que esta relación se observa en ambas direcciones (Harkness et al., 2015). Es decir, por un lado, se confirma la hipótesis de sensibilidad al estrés, que apoya que la agregación de eventos estresantes es un claro factor de riesgo para la aparición de síntomas internalizantes y externalizantes (Cohen et al., 2013; Hankin and Abela, 2005). Por otro lado, se corrobora la direccionalidad inversa, es decir, los adolescentes que muestran sintomatología psiquiátrica, tanto internalizante como externalizante, tienen un mayor riesgo de estar expuestos a más situaciones adversas en su día a día, confirmándose la hipótesis de generación de estrés (Hammen, 2005; Rudolph et al., 2000). Por tanto, nos encontramos frente un círculo vicioso entre estas dos variables de riesgo, los acontecimientos estresantes y la psicopatología, que se retroalimentan y afectan al desarrollo y al bienestar del adolescente.

Es importante recordar que el impacto de los eventos vitales estresantes sobre la psicopatología aumenta cuando se viven de manera agregada. Es decir, tanto los adolescentes sanos como con psicopatología previa, si se exponen en un período corto de tiempo a un gran número de eventos vitales estresantes, tendrán una mayor probabilidad de desarrollar diferentes trastornos psiquiátricos, incluyendo: trastornos afectivos (Fernandez-Castelao and Kröner-Herwig, 2013), abuso de sustancias o

adicciones (Charles et al., 2015), hiperactividad y problemas de conducta (Flouri and Kallis, 2011), o comportamientos suicidas (Serafini et al., 2015). Por tanto, podemos afirmar que la agregación de eventos estresantes es un factor de riesgo general y transdiagnóstico durante la adolescencia (March-Llanes et al., 2017), del mismo modo que otros autores lo asocian con los trastornos mentales de aparición más tardía en la vida adulta (Skarbø et al., 2004).

Es interesante recordar que, además de las implicaciones clínicamente relevantes, la literatura científica ha demostrado que esta agregación de estresores también puede tener un impacto neurobiológico. Por ejemplo, Swartz y colaboradores (2015) demostraron que los adolescentes que habían experimentado más eventos negativos durante los últimos doce meses tenían una alteración a largo plazo en la reactividad de la amígdala, lo que producía a su vez un mayor riesgo de depresión. Más adelante se discutirán algunas de las alteraciones neurobiológicas asociadas al maltrato infantil descritas en esta tesis.

El metaanálisis realizado también demuestra que la direccionalidad de la asociación entre estresores y psicopatología se podría comprender separando los eventos vitales en dos categorías: "dependientes" e "independientes" (Wichers et al., 2012). Es decir, los eventos de vida que dependen directamente de la conducta del adolescente (repetir curso, pelearse, fugarse de casa, etc.) estarían más asociados con la psicopatología a través de las correlaciones gen-ambiente y se relacionarían más con la hipótesis de generación del estrés (Kendler and Baker, 2007). En otras palabras, la exposición a eventos estresantes “dependientes” estaría, en gran parte, influenciada por el efecto de los genes sobre los rasgos temperamentales del adolescente, como por ejemplo una mayor impulsividad (McAdams et al., 2013). En cambio, los eventos de vida que son independientes de la conducta del adolescente (la muerte de un ser querido, ingreso en prisión de un familiar, cambio de trabajo de los padres, etc.) se asociarían más con la hipótesis de sensibilidad al estrés y los mecanismos de interacción gen-ambiente (Young-Wolff et al., 2012). En este sentido, algunos autores afirman que los eventos estresantes “independientes” predicen sobre todo la sintomatología depresiva, pero no tanto de otro tipo (Kendler et al., 2003). Sin embargo, nuestro metaanálisis no ha podido confirmar esta asociación, ya que la mayoría de los estudios no diferencian la naturaleza de los eventos sufridos y habitualmente se incluyen en un único constructo, por lo que no se han podido extraer conclusiones firmes al respecto.

En síntesis, este trabajo puso de manifiesto la necesidad de desarrollar instrumentos validados mucho más completos y adaptados para poder estudiar los estresores vividos por los adolescentes en la sociedad del siglo XXI. A su vez, se reafirmó la falta de investigación más específica que permita profundizar en la relación entre la naturaleza de los acontecimientos estresantes vividos y la psicopatología asociada.

En ese marco, en la presente tesis se validó el LEIA, un nuevo instrumento para valorar en la población general adolescente (12-17 años) los acontecimientos vitales estresantes vividos en el último año (Moya-Higueras et al., 2020). El LEIA se ha diseñado siguiendo las recomendaciones metodológicas de los expertos en la materia (Dohrenwend, 2006) y ha sido validado con altos estándares de calidad psicométrica. Incluye 75 acontecimientos vitales estresantes y es el primer instrumento en España en considerar el impacto diferencial de los acontecimientos "menores-mayores", "dependientes-independientes" o "interpersonales-no interpersonales".

Antes de entrar en el efecto específico de los estresores, cabe mencionar que este estudio, al igual que el metaanálisis realizado, indica que los acontecimientos vitales estresantes se asocian tanto con sintomatología internalizante y externalizante, como con un nivel de bienestar bajo y menor sensación de felicidad. Sin embargo, este trabajo sugiere que las chicas puntúan más en sintomatología internalizante y, en cambio, los chicos en sintomatología externalizante (agresividad y comportamiento antisocial). Tradicionalmente, se habían asociado más las conductas externalizantes al sexo masculino, señalando como una posible explicación un aumento en los niveles de testosterona, una hormona descrita como ligada al comportamiento impulsivo y agresivo. Sin embargo, las investigaciones en los últimos años señalan que los niveles de testosterona no predicen en sí mismos las conductas agresivas que tiene una persona y, de hecho, esta hormona se asocia más a comportamientos prosociales que a la agresividad (Jordan-Young and Karkazis, 2019). Por tanto, es necesaria una visión mucho más amplia que la del debate hormonal sexual ligado a la agresividad y considerar también otros factores de riesgo. Por ejemplo, el temperamento, los roles socioculturales y las experiencias previas de violencia podrían ser elementos importantes que determinan la manera de expresar el malestar y la forma de sobrevivir al contexto ambiental.

Por otra parte, los datos aportados defienden que los acontecimientos estresantes considerados como "menores" o menos importantes (nacimiento de un hermano o cambios de trabajo de los padres, etc.), no se asocian con la psicopatología presentada por el adolescente, como ya habían apuntado otros investigadores (Vrshek-Schallhorn

et al., 2015). Este aspecto puede ser relevante a la hora de intervenir con menores, ya que conocer los eventos de riesgo que merece la pena priorizar durante el tratamiento puede evitar perderse entre otros acontecimientos vitales menos relevantes para la salud del adolescente.

Adicionalmente, se han observado asociaciones muy similares entre estresores y psicopatología, tanto si se considera la "puntuación cuantitativa" como la "puntuación objetiva" que otorga el LEIA. Es decir, no hay apenas diferencias entre hacer un recuento simple del número de estresores vividos (puntuación cuantitativa) y reajustar la afectación de cada estresor según parámetros objetivos (puntuación objetiva), como ya describieron hace años algunos autores (Zimmerman, 1983). Por consiguiente, usar la puntuación cuantitativa simple sería suficiente. Sin embargo, en nuestro estudio sí que se observan diferencias en la psicopatología asociada a los estresores si se utiliza la "puntuación subjetiva", que pondera todos los acontecimientos vividos según la afectación particular de cada persona. A menudo, en el ámbito científico y clínico la pregunta más reportada ha sido qué aproximación (la objetiva o la subjetiva) es mejor usar a la hora de prever un peor pronóstico clínico (Dohrenwend, 2006). Sin emabargo atentiendo a nuestros resultados, la pregunta debería ser cuál de las dos puntuaciones usar en función del tipo de psicopatología que se quiera predecir, ya que cada tipo de aproximación es útil para predecir un tipo de sintomatología diferente, internalizante o externalizante.

De acuerdo con nuestro estudio, la puntuación cuantitativa se asocia más a la sintomatología externalizante (agresividad), mientras que la puntuación subjetiva se asocia más a la sintomatología internalizante (ansiedad y somatización). Esto podría deberse a que los adolescentes con sintomatología más externalizante (tendencia a comportarse de manera más agresiva, impulsiva, con alteraciones de la conducta, etc.) pueden ser personas con tendencia a minimizar sus emociones. Por tanto, tener en cuenta simplemente si les ha ocurrido o no el evento, daría más información que preguntarles cómo les ha afectado. En cambio, en adolescentes que tienen tendencia a expresar su malestar de forma internalizante, con tristeza, ansiedad o somatización, será más relevante tener en cuenta la afectación que describen ante los hechos que les ha tocado vivir. Esto iría en la línea de las teorías cognitivas de los trastornos emocionales como la depresión (Alloy et al., 1999).

Otro de los hallazgos importantes de este trabajo ha sido la asociación entre los distintos tipos de acontecimientos estresantes y la sintomatología expresada por el

adolescente. Por ejemplo, los mayores predictores de la sintomatología externalizante serían los acontecimientos "dependientes" (que dependen directamente de la conducta de la persona) pero "no interpersonales" (que no involucran a otras personas directamente) como sería repetir curso. No obstante, en chicas, la sintomatología externalizante también se ha asociado con aquellos eventos "dependientes" pero "interpersonales", como pelearse o distanciarse con un amigo/a. Por el contrario, los eventos más predictores de la sintomatología internalizante y de insatisfacción con la vida serían los "independientes, no interpersonales" (como tener problemas económicos en la familia); aunque los acontecimientos "dependientes e interpersonales" (pelearse con alguien o distanciamiento con un amigo/a), también se han asociado con el espectro internalizante.

Finalmente, cabe señalar que, de acuerdo con nuestros resultados, los acontecimientos estresantes de naturaleza "independiente e interpersonal", como el divorcio de los padres, la enfermedad grave o la muerte de un familiar, no se asocian por sí solos a ninguna sintomatología, aunque suelen ser los eventos más explorados en las investigaciones. Por tanto, nuestro estudio invita a un cambio de paradigma que considere realmente otros estresores que puedan emerger de estos eventos clásicamente evaluados como, por ejemplo, un incremento de los problemas económicos familiares, peleas entre los padres o de los padres con el menor, siendo estos últimos los que realmente afectarían a la salud mental del adolescente. Por último, cabe mencionar que los acontecimientos que podrían vincularse a experiencias de acoso escolar (p. ej. los compañeros excluyen o insultan) o a vivencias de violencia verbal entre los padres, sí que se asocian a sintomatología internalizante (depresión, ansiedad y somatización). Esto es acorde a los resultados presentados por Kontak y colaboradores (2019) en su estudio longitudinal basado en población infantojuvenil canadiense.

Por tanto, desde el punto de vista clínico, en adolescentes con síntomas internalizantes (ansiedad, apatía, somatización, depresión) se debería ser especialmente cuidadoso y explorar las experiencias de acoso escolar, problemas económicos en casa o peleas entre los padres (entre otras). Mientras que en adolescentes con síntomas externalizantes (alteraciones de la conducta, agresividad, impulsividad), los acontecimientos más importantes a valorar serían los dependientes de su conducta (expulsión, peleas, problemas de drogas, etc.). En estos últimos, sin embargo, existe una limitación considerable y es que, a menudo, los ítems que conforman el constructo externalizante son muy similares a los acontecimientos estresantes en sí (Grant et al., 2004). Por tanto, deberían valorarse también otros factores de riesgo que puedan explicar

el inicio de estas conductas que son, a la vez, una forma de expresar el sufrimiento y un nuevo estresor por sí mismo.

En este sentido, se debe de considerar que el apoyo y las estrategias personales de las que dispone el adolescente, como el estilo de afrontamiento frente estas situaciones de estrés (*coping* en inglés), serán aspectos clave para decantar finalmente la balanza a sufrir sintomatología psiquiátrica o no (Meng et al., 2011). Por ejemplo, entendemos por estilos adaptativos aquellos estilos de afrontamiento que permiten resolver los problemas de forma asertiva. En cambio, los estilos desadaptativos serían aquellos que directamente no permiten resolver el problema o permiten afrontarlo, pero solo de manera temporal o a corto plazo (p. ej. consumo de drogas, aislamiento, huida, agresividad, rumiación, autolesiones, etc.). Es evidente que tener estilos de afrontamiento desadaptativos frente situaciones estresantes incrementa el riesgo de exposición a más situaciones adversas (Miron and Orcutt, 2014). A su vez, estos estilos retroalimentan la probabilidad de manifestar más síntomas psiquiátricos (ansiedad, adicción a sustancias, trastornos de la personalidad, depresión, etc.)(van den Heuvel et al., 2020). Por consiguiente, tanto en la práctica clínica como en investigación, será importante tener en cuenta los recursos internos de los que dispone el adolescente, para poder estimar el riesgo psicopatológico o de revictimización frente adversidades (Herman, 2004).

En esta línea, el tercer artículo presentado en esta tesis ha pretendido clarificar los factores de riesgo o posibles desencadenantes asociados a las autolesiones u otros comportamientos suicidas llevados a cabo por los niños/as o adolescentes (Marques-Feixa, et al., 2021a). En ambos casos, estas conductas podrían reflejar un déficit en el repertorio de recursos internos disponibles y en las estrategias de afrontamiento de los adolescentes.

Las conductas suicidas o autolesiones sin intención de morir son un fenómeno muy preocupante actualmente, que comporta un gran sufrimiento tanto para la persona como para los familiares y que cada vez tiene lugar en población más joven (Steinhoff et al., 2021). Dentro del conjunto de comportamientos suicidas, existen conductas con características muy diferentes entre ellas; sin embargo, todas ellas se relacionan y, en su forma más extrema, pueden llevar a la muerte por suicidio (Hamza et al., 2012). Según la OMS, en los últimos 45 años las muertes por suicidio a nivel mundial se han incrementado un 60% y, desgraciadamente, la franja de edad que ha incrementado más ha sido la población adolescente (World Health Organization, 2005), convirtiéndose en

la segunda causa principal de muerte entre los jóvenes de 15 a 29 años (Paniagua, 2021; World Health Organization, 2014).

Con el fin de estudiar este grave problema de la sociedad actual, nuestro trabajo incluyó un conjunto de variables para identificar su contribución directa e indirecta en las conductas suicidas observadas. Los factores incluidos en el modelo fueron la historia de maltrato (considerando tanto la agregación de distintos subtipos como su severidad y frecuencia), los eventos vitales estresantes próximos, así como distintos rasgos de la personalidad asociados clásicamente al trastorno límite de la personalidad (TLP): la desregulación emocional, la ira intensa y la impulsividad.

Es interesante recordar que este trabajo ha adoptado una visión continua en base a todos estos constructos, alejándose de la clásica aproximación categórica o dicotómica. De esta forma, se han considerado en un contínuum de severidad las experiencias de maltrato, los rasgos de la personalidad desadaptativos, la acumulación de estresores próximos y los diferentes comportamientos suicidas. Esta aproximación iría en la línea de los autores que defienden que el uso de un factor general de psicopatología (p. ej. el concepto de *Factor p* propuesto por Caspi et al. (2020)) puede resultar más útil a la hora de aproximarnos y estudiar la realidad clínica que separar entre diferentes entidades diagnósticas. Además, en el ámbito infantojuvenil todavía es más difícil discernir entre lo sano y lo patológico, ya que los diferentes constructos están en pleno desarrollo. Así, esta aproximación puede ayudar a reflejar mucho mejor la realidad de nuestra muestra de niños/as y adolescentes, que incluye tanto a menores que no cumplen criterios diagnósticos de un trastorno mental, como niños/as y adolescentes con diferentes diagnósticos mentales de menor y mayor funcionalidad.

Los hallazgos de este trabajo demuestran, en primer lugar, que la historia de maltrato sufrida por los niños/as y adolescentes se asocia con una mayor exposición a eventos vitales estresantes en el último año, apoyando, una vez más, la existencia de revictimización (Hosser et al., 2007). Además, se observa cómo el maltrato aumenta los rasgos de personalidad desadaptativos asociados al TLP (Krause-Utz et al., 2019). A su vez, estos rasgos (la desregulación emocional, la ira intensa y la impulsividad) aumentan la probabilidad de que los menores se expongan a más situaciones estresantes, apoyando de nuevo la hipótesis de generación de estrés. En última instancia, se demuestra que esta mayor agregación de acontecimientos estresantes en los últimos doce meses sería el principal factor predictor de los comportamientos suicidas observados en niños/as o adolescentes, confirmándose la hipótesis de sensibilidad al estrés. Todo este entramado

de variables podría explicarse de acuerdo con la teoría del apego descrita por Bowlby (1969); aquellos menores expuestos a trauma complejo a menudo tienen un apego inseguro (asociado a carencias en el afecto, la confianza y la seguridad) que afecta tanto a su forma de ser como a la forma de responder frente a nuevos estresores.

Por otro lado, en nuestro trabajo, la desregulación emocional también ha resultado ser, por sí misma, un factor determinante en los comportamientos suicidas observados en menores. Otros autores ya han puesto de manifiesto como los menores expuestos a una tensión emocional negativa en el hogar, tanto dirigida directamente a ellos como a otros, muestran una intensa emotividad negativa difícil de controlar (Caspi et al., 2004; Maughan and Cicchetti, 2002). En línea con el modelo de Autotrauma (Briere and Scott, 2013), los adolescentes con trauma complejo pueden sentirse emocionalmente abrumados cuando la angustia excede su capacidad relativa para manejar el malestar. En consecuencia, frente nuevas adversidades, los niños/as o adolescentes con historia de maltrato pueden recurrir a conductas de evitación, como por ejemplo las autolesiones u otras conductas suicidas. Esta forma de responder puede resultarles útil al momento, pero a largo plazo les bloquea emocional y cognitivamente y les suele comportar más estrés añadido. Por tanto, es esencial que en la intervención con esta población infantojuvenil se priorice la regulación de las emociones, más que otros aspectos como la impulsividad o la ira intensa. Además, hay que tener en cuenta que en los últimos años la desregulación emocional se ha establecido como un factor de riesgo transdiagnóstico y predictor de una peor evolución clínica en todos los trastornos mentales (Paulus et al., 2021). Por tanto, es importante ayudar a las familias y a los adultos a cargo de niños/as para que se fomenten las estrategias de manejo emocional desde las primeras etapas de la vida. Los niños/as y adolescentes que actúen con el piloto automático, y desde el cerebro más emocional, es más probable que muestren alteraciones conductuales, de la integración de la realidad y dificultades en la regulación del afecto, siendo finalmente un grupo de elevado riesgo para presentar trastornos mentales (McKay et al., 2021). Cabe mencionar que estos rasgos desadaptativos son elementos clave en el cuadro clínico que conforma el TLP y, en línea con la teoría biopsicosocial de Linehan (1993), las personas con este diagnóstico son pacientes que requieren un tratamiento especializado e integral, en parte dirigido a reducir las conductas suicidas que presentan.

Sin embargo, en nuestra muestra de estudio no se ha detectado una relación directa entre el maltrato y las conductas suicidas, siendo los rasgos de la personalidad desadaptativos y la agregación de estresores próximos los que hacen desencadenar, finalmente, las conductas suicidas. Esta circunstancia brinda una oportunidad de

intervención focalizada en estas variables intermedias y concuerda con la extensa literatura existente, según la cual, la desregulación emocional es un importante factor mediador entre el maltrato infantil y las conductas autolesivas (Titelius et al., 2018) y otros problemas de salud mental (Jennissen et al., 2016). Además, algunos estudios ya han apuntado que los eventos vitales estresantes, al ser conductas más fácilmente evaluables y próximas, son reportados más fácilmente y parecen predecir mejor, que la historia de maltrato en sí, todo tipo de conductas o malestar asociado (Baglivio et al., 2020). Por tanto, aunque no se encuentre una relación directa entre maltrato y comportamiento suicida, en muchos casos el trauma relacional es el telón de fondo, a menudo inconsciente para la persona, que afecta a la salud mental y a las conductas desadaptativas actuales.

No hay que perder de vista que, además de las variables estudiadas en este trabajo, existen otros factores ambientales y genéticos, tanto protectores como de riesgo, que pueden jugar un papel muy importante en este marco conceptual (Bozzatello et al., 2021). Sin embargo, un estudio reciente sugiere que el componente genético de los rasgos de personalidad es poco probable que tenga un fuerte impacto causal en el comportamiento suicida que tienen los pacientes con enfermedades mentales severas (Kalman et al., 2022).

Por último, es preciso señalar que el 75% de las personas con TLP han experimentado abuso emocional, físico o sexual en la infancia (Wagner et al., especialmente los que muestran conductas suicidas (Paris, 2019). Estas condiciones, junto con las disfunciones que muestran en su forma de ser, estar y relacionarse con el mundo, han hecho que este diagnóstico se haya vinculado mucho al cuadro clínico que recoge la nueva entidad diagnostica del TEPT-C. De hecho, las nuevas dimensiones añadidas en el TEPT-C (más allá de los síntomas clásicos del TEPT) son características que se asemejan a las que presentan las personas con TLP: problemas graves y persistentes en la regulación del afecto, creencias sobre uno mismo de incapacidad y poca valía (sentimientos de vergüenza, culpa o fracaso), así como dificultades para mantener las relaciones y sentirse cerca de los demás. Sin embargo, algunos autores concluyen que, aunque comparten similitudes, son constructos diferentes que deben evaluarse por separado (Ford and Courtois, 2021).

En este contexto, y conociendo el problema diagnóstico asociado a los niños/as y adolescentes con historias de maltrato infantil (Herman, 1992; van der Kolk, 2005), el cuarto artículo de esta tesis ha pretendido explorar, de manera completa, la

sintomatología asociada al trauma complejo, sus afectaciones en la funcionalidad global del menor, así como verificar si coexiste con la sintomatología del nuevo diagnóstico de TEPT-C propuesto por la CIE-11 (Marques-Feixa et al., 2022a). Asimismo, se ha explorado si los diferentes tipos de maltrato y la edad de exposición a ellos impacta de manera diferencial en la sintomatología de TEPT-C.

Nuestro estudio demuestra que una gran parte de la sintomatología que expresan los menores atendidos en centros de salud mental podría ser explicada directamente por la historia de maltrato (12-15%). Esto constata que tenemos sobre la mesa un claro factor ambiental que, por definición, puede ser modificado; por tanto, si se le dedicaran más recursos y fuera realmente una prioridad social y política, estaríamos reduciendo un gran número de problemas de salud mental. Hay que recordar que nuestro estudio tiene una visión transdiagnóstica, es decir, incluye niños/as y adolescentes con diagnósticos psiquiátricos muy dispares: trastornos de la conducta, ansioso-depresivos, psicóticos, alimentarios, déficit de atención e hiperactividad y adaptativos, entre otros. Esta condición pone de manifiesto que, si solo se abordan los síntomas clínicos concretos de cada trastorno, sin abordar la posible historia de trauma o su sintomatología asociada, el tratamiento puede quedar incompleto y no resultar eficaz (Karatzias et al., 2019; Lanktree and Briere, 2008; Sachser et al., 2017). De hecho, la práctica clínica demuestra que a menudo, en pacientes con historia de trauma complejo, cuando mejora un tipo de sintomatología, si no se ha abordado de manera integral la problemática, aparece con el tiempo otra de diferente (van der Kolk, 2020).

En esta línea, nuestro estudio demuestra que el maltrato infantil incrementa el número de diagnósticos psiquiátricos que recibe un niño/a o adolescente a lo largo del desarrollo, llegándose a describir hasta siete etiquetas diagnósticas diferentes en estos menores. Posiblemente, esto se deba a las distintas formas que va adoptando el sufrimiento interno del niño/a o adolescente a lo largo del tiempo. Sin embargo, hay que ser cautelosos, ya que elevados cambios en el diagnóstico van a comportar también abordajes terapéuticos diferentes, tanto psicológicos como farmacológicos. Este aumento de diagnósticos puede conducir también a una sensación de fracaso terapéutico y comportar una mayor generación de estrés o revictimización del menor. Asimismo, nuestro estudio confirma que los niños/as o adolescentes con maltrato muestran una mayor comorbilidad psiquiátrica actual, seguramente relacionada con la dificultad de los clínicos para encajar la amplia e inespecífica sintomatología que manifiestan estos menores en las entidades diagnósticas que propone el DSM-5.

Curiosamente, el estudio señala que, aunque la historia de maltrato no va a determinar si el menor va a ser tratado con psicofármacos o no, los niños/as y adolescentes con historia de trauma complejo reciben más polimedicación, llegando a tomar hasta cuatro familias distintas de fármacos simultáneamente. Esto puede deberse al empeño de muchos psiquiatras de intentar encontrar remedio y disipar la compleja sintomatología que presentan estos niños/as mediante psicofármacos. En cambio, algunos países como Suecia, con políticas más generosas en el bienestar de las familias y la infancia, encabezan las tasas más bajas de niños/as y adolescentes con historia de maltrato con prescripción de psicofármacos (Gilbert et al., 2012). Contrariamente, España encabeza el ranking mundial de mayor consumo lícito de ansiolíticos, hipnóticos y sedantes en adultos, junto con Bélgica y Portugal (Brauer et al., 2021), pero también en niños/as y adolescentes (Steinhausen, 2015). Además, su consumo va en aumento tanto en población infantil como en adultos y, especialmente, en las mujeres con problemas de ansiedad (Carrasco-Garrido et al., 2016; Steinhausen, 2015). Con este marco de referencia, será interesante revisar si después de entrar en vigor la nueva especialidad de Psiquiatría infantil en España surgirá un nuevo paradigma o manera de intervenir con estos niños/as y adolescentes, ya que está ampliamente demostrado que necesitan otro abordaje terapéutico diferente al de los adultos (Lakhan and Hagger-Johnson, 2007).

Por otro lado, y en concordancia con la literatura que describe que años antes de la aparición de un trastorno mental grave, como la psicosis, ya existe un peor ajuste premórbido (Chang et al., 2020), nuestro estudio demuestra que los participantes con maltrato tienen un peor ajuste premórbido desde edades muy tempranas, en preescolar (0-6 años), durante la primaria (6-12 años) y la adolescencia (13-17 años). Por tanto, estos niños/as ya muestran señales en etapas bien tempranas y sería importante que los profesionales aprendieran a reconocerlas para intervenir precozmente, antes de que sea demasiado tarde. A su vez, se describe que estos niños/as y adolescentes con maltrato tienen un peor funcionamiento global en la actualidad, tanto si tienen o no diagnósticos psiquiátricos. Por añadidura, parecen ser especialmente vulnerables los niños/as de familias con bajo nivel socioeconómico, seguramente porque disponen de un menor acceso a recursos externos para compensar algunas de estas afectaciones (espacios seguros para actividades extraescolares que motiven al menor, viviendas más tranquilas o de mayor calidad, repasos escolares, etc.). Explorar y potenciar los factores protectores asociados a la resiliencia en esta población es de gran importancia (Gartland et al., 2019).

Todos estos hallazgos que conforman la primera parte del cuarto artículo de esta tesis irían en la línea de los estudios previos en adultos, que demuestran como las

personas con historia de maltrato constituyen un subtipo de pacientes clínicamente distinto, presentando sintomatología más severa, de inicio más temprano, con más comorbilidad y con una peor adherencia y respuesta al tratamiento psicológico y farmacológico (Lippard and Nemeroff, 2020; Nanni et al., 2012). Además, nuestros resultados son similares para el grupo control, poniendo de manifiesto que los niños/as o adolescentes con historia de maltrato que no cumplen criterios diagnósticos muestran también un incremento de sintomatología internalizante y externalizante, pudiendo detectar malestar subclínico en estos chicos/as (De Rose et al., 2016).

Por otro lado, y en referencia al segundo objetivo de este estudio, se ha podido constatar que los niños/as y adolescentes con historia de maltrato muestran más sintomatología de TEPT-C, explorada a partir de los cuatro subdominios que la conforman: la sintomatología de estrés postraumático, la desregulación emocional, el bajo autoconcepto y las dificultades en las relaciones interpersonales. Además, el estudio demuestra que el procesamiento del trauma será diferente según la etapa del desarrollo en la que haya tenido lugar cada tipo de maltrato. La excpeción es la negligencia emocional, que ha resultado ser demoledora durante todo el desarrollo y para todos los subdominios del TEPT-C (Marques-Feixa et al., 2022a).

En referencia al primer subdominio del TEPT-C, la sintomatología de estrés postraumático simple, nuestro estudio demuestra que se asocia a todos los tipos de maltrato. Esto refleja la dificultad que tienen los niños/as y adolescentes expuestos a cualquier tipo de trauma para procesar algunos *inputs* sensoriales que les activan la respuesta de amenaza intensamente (lucha, huida o congelación). Además, pone de manifiesto que la negligencia (física y emocional) y el maltrato emocional también se asocian al estrés postraumático, y no solamente el abuso físico o sexual, como se ha explorado comúnmente a lo largo de la historia (Pate, 2021).

Específicamente, en cuanto a las etapas del desarrollo de máxima vulnerabilidad para sufrir estrés postraumático, se ha visto que la negligencia y el maltrato físico son especialmente perjudiciales cuando ocurren en los primeros cinco años de vida, periodo en el que el cerebro necesita de los cuidados más básicos para crecer y madurar óptimamente. Es interesante recordar que en estas etapas tempranas tiene lugar la maduración del sistema límbico, que va a permitir el desarrollo y control de las emociones complejas y va a establecer las primeras asociaciones entre los estímulos sensoriales recibidos y las respuestas conocidas como "piloto automático". De hecho, los sucesos que ocurran previamente a la maduración de las áreas corticales superiores

se almacenarán de forma primaria como un conjunto de percepciones y aprendizajes inconscientes, sin la capacidad de poder integrar, reflexionar y representar escenarios futuros (van der Kolk, 2020). Por tanto, no es de extrañar que la negligencia y el maltrato físico en estas etapas tempranas se relacionen con niños/as o adolescentes que van a mostrar respuestas asociadas al estrés postraumático: hiperreactividad intensa, activación de memorias emocionales y/o dificultades para integrar y procesar la información. En cambio, el maltrato psicológico es especialmente nefasto cuando ocurre entre los 6 y 12 años, una etapa del desarrollo que coincide con la maduración del córtex prefrontal y el desarrollo de funciones como la empatía, la comprensión del lenguaje y la integración de conceptos. Tiene sentido, por tanto, que recibir insultos, desprecio, manipulación o rechazo durante esta etapa sea más dañino para el menor y se asocie a la sintomatología de estrés postraumático. Por último, el abuso sexual afecta de manera integral a muchas áreas del desarrollo de la persona y nuestro estudio indica que es especialmente dañino cuando ocurre a partir de la segunda infancia y durante la adolescencia (6-17 años), etapas cruciales para el desarrollo sexoafectivo. Sin embargo, no parece ser tan dañino si ocurre en los primeros seis años de vida, aunque son escasos los sujetos con abuso sexual en esta franja de edad en nuestra muestra y serían necesarios más estudios al respecto.

Por otro lado, en referencia a los otros tres dominios que componen el TEPT-C (desregulación emocional, autoconcepto y relaciones interpersonales), parece que la etapa de exposición al trauma no tendría tanta relevancia como el hecho en sí de sufrirlo. Este resultado tiene sentido, sabiendo que todas ellas son dimensiones muy inherentes al ser humano. Esto concuerda con otros estudios que reportan que el trauma complejo en la niñez impide el desarrollo de habilidades básicas de la personalidad (Gold, 2004; Herman, 1992) e irían en la línea de la teoría de Autotrauma descrita por Briere (2002), que describe que el trauma complejo deteriora el desarrollo de tres capacidades primarias: la regulación del afecto, la propia identidad y las relaciones interpersonales.

Por lo que se refiere a la desregulación emocional, se ha observado que son la negligencia emocional y el maltrato emocional y físico los que ejercen un fuerte impacto. Seguramente, los niños/as expuestos a estos traumas relacionales no desarrollaron un apego seguro con sus principales cuidadores, por lo que no pudieron establecer la capacidad de autorregulación emocional en situaciones de estrés que sí consiguen los niños/as con apego seguro (Ainsworth et al., 1978). Además, nuestro estudio apoya que estos tipos de maltrato afectan negativamente a la regulación emocional a lo largo de todo el desarrollo, contrariamente a algunos estudios que consideran la segunda infancia como una etapa especialmente sensible (Dunn et al., 2019). Como ya se ha descrito

previamente en esta tesis doctoral, la desregulación emocional vinculada al maltrato se ha establecido como un factor de riesgo para un sinfín de condiciones psiquiátricas (Dvir et al., 2014) incluyendo los comportamientos suicidas (Marques-Feixa et al., 2021a), por lo que proteger a los niños/as de estos traumas y promover su óptima regulación emocional es una prioridad.

Es importante mencionar que, en nuestro estudio, no se ha detectado que la negligencia física o el abuso sexual tengan un impacto claro en la regulación emocional de los niños/as y adolescentes, como sí apuntan algunos autores (Kim et al., 2021). Así, según nuestro estudio, las carencias alimentarias, físicas o de vivienda, por ejemplo, no serían tan relevantes para un menor a la hora de establecer la capacidad de regular sus estados emocionales. Por otro lado, en un inicio nos sorprendió que el abuso sexual tampoco se relacionara con la desregulación emocional, dado que en la práctica clínica y en la literatura ha sido ampliamente reportada esta asociación (Walker et al., 2021). Sin embargo, a diferencia de los otros tipos de maltrato, es más habitual que el abuso sexual pueda ocurrir fuera del núcleo familiar de convivencia, por lo que se podría hipotetizar que estos niños/as y adolescentes, si disponen de afecto y apoyo emocional en su seno familiar, podrían mantener intacta la capacidad de regular sus emociones (aunque otras áreas como el estrés postraumático o las que veremos a continuación sí que se verían alteradas). Lo mismo podría ocurrir cuando el agresor forma parte del núcleo familiar, pero existe otro progenitor que actúa en consecuencia protegiendo al menor de edad rápidamente. De hecho, el trabajo reciente de Ensink et al. (2021) refiere que las adolescentes que han sufrido abuso sexual, si tienen un apego seguro con sus principales cuidadores, tienen una menor sintomatología traumática asociada. Sin embargo, serían necesarios más estudios para explorar este impacto diferencial en función de la relación con el agresor y la respuesta recibida por parte de la familia después de la revelación del abuso.

En cuanto al autoconcepto negativo, vemos que todos los tipos de maltrato ejercen un fuerte impacto. El trauma complejo durante la infancia sitúa al menor en una situación muy ambivalente hacia sus cuidadores, en la que conviven los sentimientos de sufrimiento, pero también de lealtad y respeto hacia su familia. Este juego perverso puede llevar al niño/a a experimentar un sinfín de sentimientos contradictorios difíciles de procesar y que serán demoledores para la formación de su identidad. Estos niños/as pueden llegar a sentirse merecedores de este maltrato, responsabilizarse de lo que les sucede y perder su marco de referencia, dudando de sus creencias y valores y dejando en un segundo plano su sufrimiento, sus necesidades y su valía. Por tanto, no es de extrañar

que estos niños/as crezcan formando un concepto negativo acerca de sí mismos. En cuanto a las etapas del desarrollo de más vulnerabilidad, una vez más, parece que la negligencia física impacta sobre todo cuando ocurre en los primeros cinco años de vida, mientras que el maltrato emocional cuando ocurre en la segunda infancia (6-12 años).

Por último, este artículo demuestra que todos los tipos de maltrato afectan a las habilidades que va a tener un menor a la hora de establecer relaciones interpersonales sanas. El maltrato físico parece que es especialmente dañino cuando ocurre en la primera infancia (0-5 años), mientras que el maltrato emocional y abuso sexual lo son cuando ocurren en la segunda infancia (6-12 años). Esto podría deberse a que el cerebro primario de un niño/a, al sufrir abuso físico inesperado en las primeras etapas de la vida (0-5 años), aprendió que debía protegerse de las personas porque podían dañarle en cualquier momento, especialmente de aquellas más próximas y que merecían su confianza, como sus cuidadores. Así, es lógico que estos niños/as o adolescentes puedan mostrarse más desconfiados, estar más a la defensiva y tener dificultades a la hora de establecer relaciones interpersonales o íntimas. Por otro lado, en la segunda infancia (6-12 años), cuando la comprensión del lenguaje es mucho más amplia y el niño/a aprende la mayor parte de las habilidades sociales para interactuar con el mundo, es lógico pensar que si es insultado, menospreciado o abusado sexualmente va a mostrar dificultades para confiar y establecer relaciones óptimas interpersonales.

Finalmente, este cuarto artículo respalda la relación dosis-efecto que existe entre la historia de maltrato sufrida (multisubtipos, severidad y cronicidad) y la mayor gravedad en la psicopatología expresada (Warmingham et al., 2019). Este fenómeno demuestra lo importante que resulta intervenir tempranamente con el niño/a o la familia y evitar que estas experiencias de maltrato se cronifiquen o se agraven. Hay estudios longitudinales esperanzadores que demuestran que, si las experiencias de maltrato finalizan durante la segunda infancia, se reduce el riesgo de psicopatología tanto a corto como largo plazo (Jung et al., 2021). Nuestro artículo también otorga evidencia para apoyar que todas las formas de maltrato tienen efectos generalizados en la salud de la persona (Vachon et al., 2015), aunque hasta día de hoy la literatura científica haya sido dominada por los estudios sobre abuso sexual (Hovdestad et al., 2015). La inclusión de este nuevo diagnóstico psiquiátrico, ya respaldado por numerosos estudios científicos (Brewin et al., 2017), puede suponer un punto de inflexión para el tratamiento psicoterapéutico de muchos pacientes con historia de trauma complejo (Bohus and Priebe, 2018; Lanktree and Briere, 2008; Myers et al., 2002).

Hay que considerar que todas estas afectaciones sistémicas asociadas al maltrato (De Bellis and Zisk, 2014) también se han asociado a múltiples alteraciones funcionales y morfológicas en el cerebro (Heim et al., 2010; Nemeroff, 2016; Teicher et al., 2016). En este contexto, los dos últimos artículos que conforman esta tesis exploran, en la misma muestra de niños/as y adolescentes, las posibles alteraciones neurofisiológicas vinculadas al maltrato, estudiando algunos de los principales mecanismos biológicos de regulación del estrés: el eje HHA y el sistema inmune.

El primer trabajo analiza la función del eje HHA en condiciones basales y frente un estresor agudo de tipo psicosocial (el TSST-C) y su posible asociación con la historia de maltrato (Marques-Feixa et al., 2021b). Respecto a la función basal responsable del mantenimiento del ritmo circadiano, se demuestra que aquellos niños/as y adolescentes con experiencias de maltrato (con o sin psicopatología actual) muestran niveles más altos de cortisol a lo largo del día, especialmente por la noche. Niveles altos de cortisol son neurotóxicos y podrían dañar otros sistemas biológicos. Además, la hipercortisolemia por la noche podría alterar los ritmos de sueño-vigilia y hacer que estos niños/as y adolescentes estén más activos a la hora de acostarse, con un estado de hipervigilancia que les dificulte relajarse y conciliar el sueño. De hecho, algunos estudios han vinculado altos niveles de cortisol al medio día o por la noche con trastornos ansiosos en población infantil (Dieleman et al., 2015). A diferencia de nuestro estudio, algunos autores reportan que los niños/as expuestos a maltrato muestran mayores niveles de cortisol por la mañana (Cicchetti and Rogosch, 2001). No obstante, sigue habiendo estudios contradictorios en la literatura, en parte debidos a la gran heterogeneidad en la metodología usada durante la recogida de muestras biológicas y en la valoración de la historia de maltrato (Bernard et al., 2017).

Por otro lado, nuestro artículo demuestra que, mientras que los niños/as y adolescentes sin trauma complejo aumentan sus niveles de cortisol después de una situación de estrés psicosocial (TSST-C), los que reportan historia de maltrato muestran un eje HHA hipoactivo, es decir, no aumentan sus niveles de cortisol como se esperaría frente a estrés agudo. Lo más paradójico es que estos niños/as con experiencias de maltrato muestran altos niveles de ansiedad, habiendo una clara disociación entre su percepción de estrés y su respuesta biológica. Esto tiene una gran relevancia, ya que, si uno de los mecanismos más importantes para activar el cerebro y otros sistemas biológicos no funciona óptimamente frente al estrés, nos encontremos con personas a las que les suponga mucho más esfuerzo gestionar emocional y conductualmente las situaciones de estrés cotidiano. En consecuencia, estas personas podrían recurrir más

fácilmente a estrategias desadaptativas de autorregulación con el fin de reducir el malestar invasivo que experimentan, como consumir sustancias, autolesionarse o realizar intentos autolíticos (Bae et al., 2015), aumentando a largo plazo los problemas interpersonales en el entorno familiar, social y laboral y su riesgo para desarrollar un trastorno mental.

Cabe mencionar que estas alteraciones en el eje HHA se han detectado independientemente de la presencia de un trastorno mental en curso actual, demostrando que las disfunciones podrían estar latentes antes incluso de que el menor tenga problemas de salud mental (Carr et al., 2013; Mccrory, Gerin and Viding, 2017; Teicher and Samson, 2013). Asimismo, estas alteraciones podrían situar al menor ante una mayor vulnerabilidad para sufrir trastornos mentales. En este sentido, es importante señalar que las alteraciones en el eje HHA se han vinculado tanto con sintomatología internalizante y externalizante durante la infancia (Conradt et al., 2014) como con diferentes diagnósticos psiquiátricos en la edad adulta (Kudielka et al., 2004; Zorn et al., 2017).

Hay que destacar, igualmente, que nuestros resultados irían en la línea de la revisión sistemática de Bunea, Szentágotai-t y Miu (2017) que reporta un patrón de respuesta atenuado durante el TSST en personas expuestas a adversidades tempranas (sobre todo adultos), reflejando que existe una desensibilización del sistema tras la exposición al maltrato. Sin embargo, algunos estudios basados en niños/as que han sufrido maltrato proximal reportan un patrón de hipercortisolismo frente situaciones de estrés (Heim et al., 2000; Hunter et al, 2011). Las diferencias entre estudios podrían explicarse también por la gravedad, la frecuencia, el sexo o la etapa del desarrollo de la exposición al maltrato (King et al., 2017; Ouellet-Morin et al., 2019; Trickett et al., 2014). A este respecto, un estudio apoya que aquellos menores que han presenciado conflictos interparentales puntuales, o solo en los últimos meses, muestran un patrón de hiperreactividad del eje HHA frente al TSST, mientras que, si han presenciado conflictos parentales continuados muestran un eje HHA atenuado.

Nuestro estudio también ha explorado el impacto de la severidad y la frecuencia del maltrato, demostrando que existe una relación dosis-efecto asociada a las alteraciones del eje HHA, tanto en su funcionamiento basal diurno como frente a estrés. Es decir, en niños/as con experiencias de malos tratos que aparentemente son más leves, si se sostienen en el tiempo y se cronifican, el eje HHA también se puede desregular. Asimismo, mientras que los niños/as y adolescentes que reportan experiencias de maltrato graves tienen disfunciones en el eje HHA, los que han vivido experiencias más leves o puntales muestran un funcionamiento del eje HHA a medio camino entre la

reactividad óptima y la desregulación. En vista de que estos niños/as sí que muestran mayores niveles de ansiedad, este estudio anima a los profesionales a detectar tempranamente este sufrimiento y poder intervenir proximalmente antes de que estos sistemas biológicos se desregulen por completo.

En este sentido, existen datos esperanzadores que resaltan la posibilidad de recuperar la reactividad del eje HHA, incluso varios años más tarde, si existe una mejora en el ambiente de crianza. Un equipo que investigó a niños/a adoptados antes de los 5 años procedentes de centros negligentes, describió que inicialmente mostraban un eje HHA alterado. Sin embargo, en etapas pre y postpuberales, después de muchos años en un nuevo contexto ambiental positivo con la familia adoptiva, estos niños/as mostraban el eje HHA recalibrado, similar al grupo de no adoptados criados en sus familias biológicas (DePasquale et al., 2019). Estos resultados apuntarían a una posible recuperación de la funcionalidad del eje HHA si el ambiente mejora antes de la pubertad. Desafortunadamente, también existen muchos estudios que apoyan que, si el ambiente no mejora muy tempranamente, estos cambios podrían ser irreversibles y mantenerse durante la edad adulta (McCrory et al., 2011).

Sin embargo, no hay que olvidar que el cerebro es plástico y las variables ambientales influirán en la consolidación y desaparición de sinapsis durante toda la vida. De hecho, varios estudios de neuroimagen y conectividad cerebral reportan que aquellas personas resilientes con historia de maltrato infantil tienen una arquitectura cerebral distinta al de las personas con historia de maltrato y psicopatología, pero a su vez también distinta a las personas sin maltrato (Ohashi et al., 2019). Estos resultados dejanconstancia de que, aunque el maltrato pueda desregular la primera vía de respuesta al estrés, si el entorno mejora el cerebro puede crear nuevas conexiones para afrontar estas situaciones.

Finalmente, y en referencia al sexto artículo de esta tesis, hay que recordar la estrecha relación existente entre la exposición a estrés, el funcionamiento del eje HHA y la respuesta del sistema inmunológico (Koss and Gunnar, 2018). De hecho, los glucocorticoides actúan como antiinflamatorios y, por tanto, cuando se desarrolla resistencia al cortisol, la respuesta inflamatoria también se descontrola. Por este motivo, las personas que experimentan factores estresantes crónicos tienen un funcionamiento inmunitario menos efectivo y una mayor susceptibilidad a sufrir enfermedades (Miller et al., 2002). También se ha observado que aquellos adultos que padecieron maltrato de niños/as, muestran un mayor riesgo de enfermedad con potencial origen inflamatorio (Felitti et al., 1998). De hecho, una revisión sistemática llevada a cabo este año refiere

que el maltrato infantil conlleva a una inflamación sistémica en la adultez, mostrando los sujetos expuestos a maltrato infantil elevadas concentraciones de la proteína C reactiva (CRP), un biomarcador inflamatorio importante (Kerr et al., 2021).

A pesar de las evidencias reportadas en población adulta, las alteraciones inmunológicas han sido escasamente investigadas en niños/as y adolescentes con experiencias de maltrato más proximales. En nuestro sexto estudio se optó por estudiar la s-IgA, una proteína que desempeña un papel fundamental en la primera línea de defensa inmunitaria y que ha emergido como un prometedor biomarcador (Marques-Feixa, Castro-Quintas, et al., 2022). A pesar de su interés, la s-IgA está infraestudiada y solo existe un artículo que haya explorado su funcionamiento frente estrés psicosocial agudo en población infantojuvenil (Laurent et al., 2015).

En esta línea, nuestros hallazgos demuestran que, aunque los niños/as y adolescentes muestran niveles basales similares de s-IgA, su reactividad frente al estrés agudo difiere según el desarrollo puberal. Mientras que los adolescentes muestran un aumento de s-IgA frente al estresor y una recuperación rápida, los niños/as no modifican sus niveles de s-IgA. Cabe mencionar que los adolescentes tienen niveles más altos de s-IgA y cortisol en general, en comparación con los niños/as. Esto sugiere una influencia de las hormonas puberales en los niveles inmunoendocrinológicos generales. Sin embargo, mientras que la respuesta del cortisol a lo largo de TSST-C se modifica fundamentalmente por el maltrato, la respuesta de s-IgA al estresor agudo se modifica por la etapa de desarrollo. Nuestros hallazgos serían, en parte, consistentes con el único estudio disponible en la literatura que ha explorado la reactividad de la s-IgA frente a estrés agudo en población infantojuvenil (Laurent et al., 2015); sin embargo, estos investigadores no estudiaron las posibles diferencias entre los niños/as y los adolescentes, ni tampoco la relevancia del maltrato en las fluctuaciones de la s-IgA.

La literatura sustenta que la infancia es uno de los períodos de la vida más sensibles para la reprogramación del sistema inmunitario (Csaba, 2020), ya que los bebés nacen con un sistema inmunitario poco desarrollado que madura y adquiere memoria con el paso de los años (Simon et al., 2015). Durante las primeras etapas de la infancia, la regulación del sistema inmunitario podría depender fundamentalmente de la salud del niño/a y de la interacción con la madre, más que de otras señales ambientales (Ulmer-Yaniv et al., 2018). Por ejemplo, los estudios en modelos animales sugieren que el cuidado materno ejerce una influencia crítica en el desarrollo de la respuesta al estrés mediada por el eje HHA (Meaney and Szyf, 2005).

Según lo comentado, la maduración de la respuesta inmunoendocrina a estrés puede verse alterada por la exposición a experiencias adversas en las primeras etapas de la vida (Entringer, 2021). Nuestro estudio demuestra que los niños/as prepúberes expuestos a trauma complejo tienen una respuesta de la s-IgA frente al estrés similar a los adolescentes, sugiriendo un adelantamiento de la maduración del sistema inmune cuando existen experiencias de maltrato. Por tanto, podemos hipotetizar que el maltrato infantil actuaría sobre el organismo de los niños/as obligando a los sistemas de respuesta al estrés a lidiar más tempranamente con situaciones potencialmente peligrosas, sin esperar la protección de los adultos (Danese and Lewis, 2017). Este adelantamiento de la reactividad de la s-IgA en niños/as expuestos a maltrato sería consistente con el envejecimiento biológico acelerado en sujetos expuestos a estrés, como revela el reloj epigenético o la longitud de los telómeros (Chen et al., 2021; Colich et al., 2020). Esto concuerda con las teorías del desarrollo humano que argumentan que los entornos adversos pueden acelerar el inicio de la pubertad para aumentar la oportunidad de reproducción antes de una posible mortalidad (Belsky, 2012); como se ha descrito, por ejemplo, en niñas víctimas de abuso sexual que experimentan una pubertad precoz (Noll et al., 2017). Sin embargo, este adelanto madurativo puede ser perjudicial para la salud mental del menor, ya que el adelantamiento puberal se ha asociado, por ejemplo, con un mayor riesgo para desarrollar cuadros ansioso-depresivos durante la adolescencia (Barendse et al., 2022). Por otro lado, no hay que olvidar que estos sistemas biológicos son sensibles a la percepción de apoyo social por parte de la persona y, cuanto mayor es el nivel de integración social, mejor es la regulación de estos sistemas fisiológicos y la salud del sujeto (Ditzen, 2022).

En definitiva, las experiencias adversas en la infancia afectan de manera global al organismo y se asocian a diversas alteraciones biológicas con consecuencias duraderas para la salud mental y física de la persona, aumentando el riesgo de enfermedades psiquiátricas, cardiovasculares, metabólicas, respiratorias, gastrointestinales o inmunitarias, entre otras (Norman et al., 2012). Todas estas alteraciones hacen que, por ejemplo, aquellas personas que han sufrido seis o más experiencias adversas durante su infancia tengan una esperanza de vida de hasta 20 años menor (Brown et al., 2009).

Tal y como proponen distintos autores, los procesos por los cuales el estrés temprano impacta sobre la salud de la persona podrían ser explicados por mecanismos epigenéticos, es decir, un conjunto de mecanismos complejos que actúan coordinadamente y permiten la regulación de la expresión de los genes (Palma-Gudiel and Fananas, 2017; Szyf, 2014). Aunque la teoría de sensibilización al estrés apoya que

los sistemas pueden desregularse al cabo de mucho tiempo de exposición al maltrato, la presente tesis demuestra que esta desregulación se observa ya en población infantojuvenil expuesta a trauma complejo. De acuerdo con Uher y Zwicker (2017) estos mecanismos neurobiológicos alterados son multifactoriales, regidos por una interacción gen-ambiente, y actuarán de manera genérica y transversal en el origen de la mayoría de los trastornos mentales. Comprender los mecanismos neurobiológicos implicados en la transición entre los estados mentales de riesgo a cuadros clínicos severos será esencial para desarrollar una prevención efectiva y un tratamiento adecuado.

Limitaciones

La principal limitación de los estudios acerca del maltrato infantil radica en la gran complejidad que supone su identificación y la dificultad para clasificarlo en dominios específicos. Esta simplificación metodológica implica la eliminación de una gran cantidad de información sobre el sujeto y su experiencia particular de la vivencia del maltrato. Estos aspectos, sin embargo, pueden ser de gran relevancia para el clínico y el investigador. Por ejemplo, el tipo de relación con el perpetrador, el estilo de afrontamiento de la persona, el apoyo recibido por otros familiares, etc., pueden explicar las diferentes consecuencias de un evento muy similar en dos personas y jugar un papel fundamental en la psicopatología expresada (Morgan and Fisher, 2007; Read et al., 2007). Por ejemplo, aunque algunos autores consideran que la negligencia y el abuso pueden tener un impacto diferencial en las alteraciones del cerebro (Kim-Spoon et al., 2021; Teicher et al., 2018), resulta difícil discernir entre estos dos subtipos de maltrato ya que, como se ha visto en esta tesis, la negligencia emocional suele subyacer al resto de tipos de maltrato, por lo que estudiar el impacto del abuso de forma aislada es muy complicado.

Por otro lado, es necesaria una investigación adicional que incluya una mayor proporción de jóvenes resilientes, es decir, sujetos jóvenes expuestos a maltrato infantil, pero sin trastornos psiquiátricos asociados. El estudio de estos grupos ayudaría a desentrañar el efecto de estas dos condiciones en las distintas variables exploradas.

Asimismo, los patrones divergentes entre sujetos respecto al desarrollo de patología mental podrían explicarse por factores genéticos y mecanismos de interacción gen-ambiente (GxE) que no han sido explorados en la presente tesis doctoral. Cabe mencionar que se prevé realizar este abordaje en los próximos meses a partir de análisis de *polygenic risk score*. También se pretende incluir otros biomarcadores, como la alfa

amilasa, la CRP, la dehidroepiandrosterona (DHEA) y la oxitocina, entre otros. Estos abordajes podrían proporcionar una comprensión más completa de la compleja relación entre los diferentes sistemas biológicos estudiados (Martins et al., 2021; Bertsch and Herpertz, 2018; Smigielski et al., 2021). En esta línea, varios estudios apoyan la utilidad de la "carga alostática" para medir de forma global y sistémica la desregulación en distintos sistemas biológicos frente a estrés crónico (McEwen, 2017; Widom et al., 2015).

Por último, dado que la presente tesis se ha basado en estudios transversales, no se puede asumir una clara direccionalidad entre las experiencias adversas y la psicopatología o las alteraciones neurobiológicas observadas (McDonald et al., 2017). Dado que los estudios longitudinales permiten esclarecer estas asociaciones e inferir causalidad, sería interesante poder realizar un seguimiento de los niños/as de nuestro proyecto y detectar periodos críticos del desarrollo en los que ha actuado la experiencia de maltrato modificando el sistema biológico de regulación del estrés (Miller et al., 2007), así como detectar otros factores de riesgo y protección.

Reflexiones finales

No quisiera finalizar esta tesis sin recordar que las consecuencias del maltrato no son solamente para el individuo que las sufre, sino que afectan también a su entorno más cercano y a la sociedad, generando un coste muy elevado en el gasto de servicios públicos y comunitarios a largo plazo (Thielen et al., 2016). De hecho, haber vivido maltrato infantil aumenta un 47% la probabilidad de realizar conductas delictivas y tener más reincidencia (Fang et al., 2015).

Merece la pena recordar que las personas que ejercen malos tratos a menudo han crecido en sistemas sociales y/o familiares también violentos (Yehuda and Lehrner, 2018). Esto es importante para reflexionar sobre el fenómeno transgeneracional del maltrato y pone de relevancia la necesidad de generar un cambio asistencial con programas centrados en el cuidado de las familias y la prevención de la violencia (Hock et al., 2020). De hecho, parece sorprendente que no se reconozcan estas conductas como un factor de riesgo al mismo nivel que tantos otros identificados por los estudios epidemiológicos en el ámbito de la salud. Es lógico pensar que el reconocimiento del maltrato infantil como un claro factor de riesgo para la salud física y mental debería incitar a las autoridades a promover políticas públicas más enfocadas a las familias durante la crianza. Destinar los recursos humanos y económicos en estas edades trempranas, en lugar de paliar las consecuencias del daño causado por el maltrato años más tarde, permitiría tanto reducir el número de infancias rotas como mejorar el bienestar social.

Si algo parece claro es que las familias son el marco imprescindible e idóneo para cubrir las necesidades de protección, afecto y estimulación que tenemos los seres humanos, especialmente durante las primeras etapas de la vida. No es tan importante la estructura o la configuración de una familia, sino la dinámica relacional que se da. Los aspectos clave para un óptimo desarrollo están relacionados con hogares en los que se aporten dosis de afecto y comunicación, sean sensibles a las necesidades presentes y futuras y se pueda garantizar una vida estable con normas razonables que se respeten, al tiempo que se mantengan relaciones armónicas, fluidas y de apoyo mutuo (Gonzalez-Rodriguez et al., 2010).

6. Conclusiones

Los resultados de los trabajos presentados en esta tesis proporcionan nuevas evidencias sobre las consecuencias psicológicas y neurobiológicas del maltrato infantil y los acontecimientos vitales estresantes recientes en la población infantojuvenil. En resumen, las conclusiones principales son:

1. La agregación de acontecimientos vitales estresantes se asocia con una mayor sintomatología internalizante y externalizante en adolescentes. Se confirma tanto la hipótesis de sensibilidad al estrés (los estresores incrementan el riesgo de sintomatología), como de generación del estrés (la psicopatología aumenta el riesgo de exposición a situaciones de estrés), generándose un círculo vicioso entre estas dos variables.
2. Se ha validado el instrumento *Life Events Inventory for Adolescents* (LEIA) con el fin de valorar en adolescentes los acontecimientos vitales estresantes en el último año, con altos estándares de calidad psicométrica. La naturaleza de los estresores y la forma de valorarlo afecta a la sintomatología internalizante o externalizante asociada.
3. El trauma complejo en niños/as o adolescentes se asocia con rasgos típicos del trastorno límite de la personalidad (desregulación emocional, ira intensa e impulsividad). Estos rasgos y la propia historia de maltrato aumentan el riesgo de exposición a más acontecimientos vitales estresantes. Los estresores próximos y la desregulación emocional serían los constructos que más se asocian a las conductas suicidas que presentan los niños/as y adolescentes.
4. Los niños/as y adolescentes con historia de maltrato muestran sintomatología de todo tipo y presentan un peor curso clínico y funcionamiento global. Existen evidencias para apoyar el nuevo diagnóstico de Trastorno por Estrés Postraumático Complejo (TEPT-C) en niños/as y adolescentes expuestos a maltrato. La edad de exposición a cada subtipo de maltrato influye de forma distinta en los dominios descritos por el TEPT-C (estrés postraumático, desregulación emocional, autoconcepto negativo y problemas en las relaciones interpersonales).
5. Aquellos niños/as o adolescentes que han sufrido maltrato muestran alteraciones en el funcionamiento del eje HHA, mostrando mayores concentraciones de cortisol diurno (especialmente por la noche) y una hiporeactividad frente situaciones de estrés psicosocial agudo (TSST-C). Existe además una relación dosis-efecto entre la severidad y frecuencia del maltrato sufrido y las alteraciones del eje HHA.
6. El estrés psicosocial agudo estimula la secreción de la Inmonoglobulina A secretora (s-IgA), pero solo después de la pubertad. Sin embargo, los niños/as con historia de maltrato muestran una respuesta similar a los adolescentes, sugiriendo una maduración adelantada del sistema inmune en niños/as víctimas de trauma complejo.

7. Referencias

Achenbach, Thomas M., Stephanie H. McConaughy, and Catherine T. Howell. 1987. "Child/Adolescent Behavioral and Emotional Problems: Implications of Cross-Informant Correlations for Situational Specificity." *Psychological Bulletin* 101(2):213–32.

Ainsworth, Mary D. Salter, Mary C. Blehar, Everett Waters, and Sally Wall. 1978. *Patterns of Attachment: A Psychological Study of the Strange Situation*. Oxford, England: Lawrence Erlbaum.

Ainsworth, Mary D. Salter, Mary C. Blehar, Everett Waters, and Sally N. Wall. 2015. *Patterns of Attachment: A Psychological Study of the Strange Situation*. New York: Psychology Press.

Allen, A. P., P. J. Kennedy, S. Dockray, J. F. Cryan, T. G. Dinan, and G. Clarke. 2017. "The Trier Social Stress Test: Principles and Practice." *Neurobiology of Stress* 6:113–26.

Allen, Brian, Robert J. Cramer, Paige B. Harris, and A. Katrina. 2013. "Archives of Suicide Research Borderline Personality Symptomatology as a Mediator of the Link Between Child Maltreatment and Adult Suicide Potential." (April 2015):37–41.

Alloy, Lauren B., Lyn Y. Abramson, and Erika L. Francis. 1999. "Do Negative Cognitive Styles Confer Vulnerability to Depression?" *Current Directions in Psychological Science* 8(4):128–32.

Anda, Robert F., Vincent J. Felitti, J. Douglas Bremner, John D. Walker, Charles Whitfield, Bruce D. Perry, Shanta R. Dube, and Wayne H. Giles. 2006. "The Enduring Effects of Abuse and Related Adverse Experiences in Childhood: A Convergence of Evidence from Neurobiology and Epidemiology." *European Archives of Psychiatry and Clinical Neuroscience* 256(3):174–86.

Angelakis, Ioannis, Emma Louise Gillespie, and Maria Panagioti. 2019. "Childhood Maltreatment and Adult Suicidality: A Comprehensive Systematic Review with Meta-Analysis." *Psychological Medicine* 49(7):1057–78.

APA: American Psychiatric Association. 2013. *DSM-5: Diagnostic and Statistical Manual of Mental Disorders (5th Ed.)*. 5th ed. edited by American Psychiatric Publishing. Washington, DC.

Arseneault, Louise. 2018. "Annual Research Review: The Persistent and Pervasive Impact of Being Bullied in Childhood and Adolescence: Implications for Policy and Practice." *Journal of Child Psychology and Psychiatry, and Allied Disciplines* 59(4):405–21.

Arseneault, Louise, D. Ph, Mary Cannon, D. Ph, Helen L. Fisher, D. Ph, Guilherme Polanczyk, D. Ph, Terrie E. Moffi, D. Ph, Avshalom Caspi, and D. Ph. 2011. "Childhood Trauma and Children ' s Emerging Psychotic Symptoms : A Genetically Sensitive Longitudinal Cohort Study." (January):65–72.

Atzil, Shir, Wei Gao, Isaac Fradkin, and Lisa Feldman Barrett. 2018. "Growing a Social Brain." *Nature Human Behaviour* 2(9):624–36.

Bach, Bo and Michael B. First. 2018. "Application of the ICD-11 Classification of Personality Disorders." *BMC Psychiatry* 18(1):351.

Bae, Yoon Ju, Stephanie Stadelmann, Annette Maria Klein, Sonia Jaeger, Andreas Hiemisch, Wieland Kiess, Uta Ceglarek, Alexander Gaudl, Michael Schaab, Kai von Klitzing, Joachim Thiery, Juergen Kratzsch, and Mirko Döhnert. 2015. "The Hyporeactivity of Salivary Cortisol at Stress Test (TSST-C) in Children with Internalizing or Externalizing Disorders Is Contrastively Associated with α-Amylase." *Journal of Psychiatric Research* 71:78–88.

Baglivio, Michael T., Kevin T. Wolff, Matt DeLisi, and Katherine Jackowski. 2020. "The Role of Adverse Childhood Experiences (ACEs) and Psychopathic Features on Juvenile Offending Criminal Careers to Age 18." *Youth Violence and Juvenile Justice* 18(4):337–64.

Bai, Dan, Benjamin Hon Kei Yip, Gayle C. Windham, Andre Sourander, Richard Francis, Rinat Yoffe, Emma Glasson, Behrang Mahjani, Auli Suominen, Helen Leonard, Mika Gissler, Joseph D. Buxbaum, Kingsley Wong, Diana Schendel, Arad Kodesh, Michaeline Breshnahan, Stephen Z. Levine, Erik T. Parner, Stefan N. Hansen, Christina Hultman, Abraham Reichenberg, and Sven Sandin. 2019. "Association of Genetic and Environmental Factors With Autism in a 5-Country Cohort." *JAMA Psychiatry* 76(10):1035–43.

Barendse, Marjolein E. A., Michelle L. Byrne, John C. Flournoy, Elizabeth A. McNeilly, Victoria Guazzelli Williamson, Ann-Marie Y. Barrett, Samantha J. Chavez, Elizabeth A. Shirtcliff, Nicholas B. Allen, and Jennifer H. Pfeifer. 2022. "Multimethod Assessment of Pubertal Timing and Associations with Internalizing Psychopathology in Early Adolescent Girls." *Journal of Psychopathology and Clinical Science* 131(1):14–25.

Barnett, D., J. T. Manly, and D. Cicchetti. 1993. "Defining Child Maltreatment: The Interface between Policy and Research." *Advances in Applied Developmental Psychology, Volume 8* (1993):7-73.

De Bellis, Michael D. and Abigail Zisk. 2014. "The Biological Effects of Childhood Trauma." *Child and Adolescent Psychiatric Clinics of North America* 23(2):185–222.

Belsky, Jay. 2012. "The Development of Human Reproductive Strategies: Progress and Prospects." *Current Directions in Psychological Science* 21(5):310–16.

Bernard, Kristin, Allison Frost, Charles B. Bennett, and Oliver Lindhiem. 2017. "Maltreatment and Diurnal Cortisol Regulation: A Meta-Analysis." *Psychoneuroendocrinology* 78:57–67.

Bernstein, David P., Taruna Ahluvalia, David Pogge, and Leonard Handelsman. 1997. "Validity of the Childhood Trauma Questionnaire in an Adolescent Psychiatric Population." *Journal of the American Academy of Child and Adolescent Psychiatry* 36(3):340–48.

Bernstein, David P., Judith A. Stein, Michael D. Newcomb, Edward Walker, David Pogge, Taruna Ahluvalia, John Stokes, Leonard Handelsman, Martha Medrano, David Desmond, and William Zule. 2003. "Development and Validation of a Brief Screening Version of the Childhood Trauma Questionnaire." *Child Abuse and Neglect* 27(2):169–90.

Bertsch, Katja and Sabine C. Herpertz. 2018. "Oxytocin and Borderline Personality Disorder." *Current Topics in Behavioral Neurosciences* 35:499–514.

Bohus, Martin and Kathlen Priebe. 2018. "DBT–PTSD: A Treatment Programme for Complex PTSD after Childhood Abuse."

Bowlby, J. 1969. *Attachment and Loss*. Vol. 1. New York: Basic Books.

Bozzatello, Paola, Paola Rocca, Lorenzo Baldassarri, Marco Bosia, and Silvio Bellino. 2021. "The Role of Trauma in Early Onset Borderline Personality Disorder: A Biopsychosocial Perspective ." *Frontiers in Psychiatry* 12.

Brandtzaeg, Per. 2007. "Do Salivary Antibodies Reliably Reflect Both Mucosal and Systemic Immunity?" *Annals of the New York Academy of Sciences* 1098:288–311.

Brauer, Ruth, Basmah Alfageh, Joseph E. Blais, Esther W. Chan, Celine S. L. Chui, Joseph F. Hayes, Kenneth K. C. Man, Wallis C. Y. Lau, Vincent K. C. Yan, Maedeh Y. Beykloo, Zixuan Wang, Li Wei, and Ian C. K. Wong. 2021. "Psychotropic Medicine Consumption in 65 Countries and Regions, 2008–19: A Longitudinal Study." *The Lancet Psychiatry* 8(12):1071–82.

Bremner, J. Douglas. 2004. "Early Trauma Inventory Self Report-Short Form (ETISR-SF)." 1.

Bremner, J. Douglas, Roger Bolus, and Emeran A. Mayer. 2007. "Psychometric Properties of the Early Trauma Inventory-Self Report." *The Journal of Nervous and Mental Disease* 195(3):211–18.

Bretherton, I., D. Oppenheim, H. Buchsbaum, R. N. Emde, and MacArthur Narrative Group. 2003. *Revealing the Inner Worlds of Young Children: The MacArthur Story Stem Battery and Parent–Child Narratives*. New York.

Brewin, Chris R., Marylène Cloitre, Philip Hyland, Mark Shevlin, Andreas Maercker, Richard A. Bryant, Asma Humayun, Lynne M. Jones, Ashraf Kagee, Cécile Rousseau, Daya Somasundaram, Yuriko Suzuki, Simon Wessely, Mark van Ommeren, and Geoffrey M. Reed. 2017. "A Review of Current Evidence Regarding the ICD-11 Proposals for Diagnosing PTSD and Complex PTSD." *Clinical Psychology Review* 58:1–15.

Briere, John. 2002. "Treating Adult Survivors of Severe Childhood Abuse and Neglect: Further Development of an Integrative Model." Pp. 175–203 in *The APSAC handbook on child maltreatment, 2nd ed.* Thousand Oaks, CA, US: Sage Publications, Inc.

Briere, John N. and Catherine Scott. 2013. *Principles of Trauma Therapy: A Guide to Symptoms, Evaluation, and Treatment, 2nd Ed., Revised and Expanded*. Thousand Oaks, CA, US: Sage Publications, Inc.

Brown, David W., Robert F. Anda, Henning Tiemeier, Vincent J. Felitti, Valerie J. Edwards, Janet B. Croft, and Wayne H. Giles. 2009. "Adverse Childhood Experiences and the Risk of Premature Mortality." *American Journal of Preventive Medicine* 37(5):389–96.

Brown, Emily, Michelle M. Garrison, Hao Bao, Pingping Qu, Carole Jenny, and Ali Rowhani-rahbar. 2019. "Assessment of Rates of Child Maltreatment in States With Medicaid Expansion vs States Without Medicaid Expansion." 2(6).

Brown, George W., Tirril O. Harris, and Thomas K. J. Craig. 2019. "Exploration of the Influence of Insecure Attachment and Parental Maltreatment on the Incidence and Course of Adult Clinical Depression." *Psychological Medicine* 49:1025–32.

Brumariu, Laura E. and Kathryn A. Kerns. 2010. "Parent-Child Attachment and Internalizing Symptoms in Childhood and Adolescence: A Review of Empirical Findings and Future Directions." *Development and Psychopathology* 22(1):177–203.

Bunea, Ioana Maria, Aurora Szentágotai-t, and Andrei C. Miu. 2017. "Early-Life Adversity and Cortisol Response to Social Stress : A Meta-Analysis."

Buske-Kirschbaum, A., Jobst, S., Wustmans, A., Kirschbaum, C., Rauh,W., & Hellhammer, D., Angelika Buske-Kirschbaum, Silke Jobst, Andrea Wustmans, Clemens Kirschbaum, Wolfgang Rauh, and Dirk Hellhammer. 1997. "Attenuated Free Cortisol Response to Psychosocial Stress in Children with Atopic Dermatitis." *Psychosomatic Medicine* 59(4):419–26.

Campisi, Jay, Yesika Bravo, Jennifer Cole, and Kyle Gobeil. 2012. "Acute Psychosocial Stress Differentially Influences Salivary Endocrine and Immune Measures in Undergraduate Students." *Physiology & Behavior*

107(3):317–21.
Carr, Clara Passmann, Camilla Maria Severi Martins, Ana Maria Stingel, Vera Braga Lemgruber, and Mario Francisco Juruena. 2013. "The Role of Early Life Stress in Adult Psychiatric Disorders: A Systematic Review According to Childhood Trauma Subtypes." *Journal of Nervous and Mental Disease* 201(12):1007–20.
Carrasco-Garrido, Pilar, Valentín Hernández-Barrera, Isabel Jiménez-Trujillo, Jesús Esteban-Hernández, Alejandro Álvaro-Meca, Ana López-De Andrés, José Luis Delbarrio-Fernández, and Rodrigo Jiménez-García. 2016. "Time Trend in Psychotropic Medication Use in Spain: A Nationwide Population-Based Study." *International Journal of Environmental Research and Public Health* 13(12).
Caspi, Avshalom, Renate M. Houts, Daniel W. Belsky, Sidra J. Goldman-mellor, Honalee Harrington, Madeline H. Meier, Sandhya Ramrakha, Idan Shalev, Richie Poulton, and Terrie E. Moffitt. 2020. "The p Factor : One General Psychopathology Factor in the Structure of Psychiatric Disorders ?"
Caspi, Avshalom, Terrie E. Moffitt, Julia Morgan, Michael Rutter, Alan Taylor, Louise Arseneault, Lucy Tully, Catherine Jacobs, Julia Kim-Cohen, and Monica Polo-Tomas. 2004. "Maternal Expressed Emotion Predicts Children's Antisocial Behavior Problems: Using Monozygotic-Twin Differences to Identify Environmental Effects on Behavioral Development." *Developmental Psychology* 40(2):149–61.
Cassidy, Jude, Jason D. Jones, and Phillip R. Shaver. 2013. "Contributions of Attachment Theory and Research: A Framework for Future Research, Translation, and Policy." *Development and Psychopathology* 25(4pt2):1415–34.
Chang, W. C., C.. Wong, P.. Or, A. Chu, C. Hui, S. Chan, E. Lee, Y. Suen, and E. Chen. 2020. "Inter-Relationships among Psychopathology, Premorbid Adjustment, Cognition and Psychosocial Functioning in First-Episode Psychosis: A Network Analysis Approach." *Psychological Medicine* 50(12):2019–27.
Charles, Nora E., Stacy R. Ryan, Ashley Acheson, Charles W. Mathias, Yuanyuan Liang, and Donald M. Dougherty. 2015. "Childhood Stress Exposure among Preadolescents with and without Family Histories of Substance Use Disorders." *Psychology of Addictive Behaviors : Journal of the Society of Psychologists in Addictive Behaviors* 29(1):192–200.
Chen, Michelle A., Angie S. LeRoy, Marzieh Majd, Jonathan Y. Chen, Ryan L. Brown, Lisa M. Christian, and Christopher P. Fagundes. 2021. "Immune and Epigenetic Pathways Linking Childhood Adversity and Health Across the Lifespan." *Frontiers in Psychology* 12:788351.
Cicchetti, D. and F. A. Rogosch. 2001. "Diverse Patterns of Neuroendocrine Activity in Maltreated Children." *Development and Psychopathology* 13(3):677–93.
Cicchetti, Dante and Fred A. Rogosch. 2002. "A Developmental Psychopathology Perspective on Adolescence." *Journal of Consulting and Clinical Psychology* 70(1):6–20.
Clark, Helen, Awa Marie Coll-Seck, Anshu Banerjee, Stefan Peterson, Sarah L. Dalglish, Shanthi Ameratunga, et al.,.. and Anthony Costello. 2020. "A Future for the World's Children? A WHO–UNICEF–Lancet Commission." *The Lancet* 395(10224):605–58.
Cohen, Joseph R., Benjamin L. Hankin, Brandon E. Gibb, Constance Hammen, Nicholas A. Hazel, Denise Ma, Shuqiao Yao, Xiong Zhao Zhu, and John R. Z. Abela. 2013. "Negative Attachment Cognitions and Emotional Distress in Mainland Chinese Adolescents: A Prospective Multiwave Test of Vulnerability-Stress and Stress Generation Models." *Journal of Clinical Child and Adolescent Psychology : The Official Journal for the Society of Clinical Child and Adolescent Psychology, American Psychological Association, Division 53* 42(4):531–44.
Colich, Natalie L., Maya L. Rosen, Eileen S. Williams, and Katie A. McLaughlin. 2020. "Biological Aging in Childhood and Adolescence Following Experiences of Threat and Deprivation: A Systematic Review and Meta-Analysis." *Psychological Bulletin* 146(9):721–64.
Conradt, Elisabeth, Beau Abar, Barry M. Lester, Linda L. Lagasse, Henrietta Bada, Charles R. Bauer, Toni M. Whitaker, and Jane A. Hammond. 2014. "Cortisol Reactivity to Social Stress as a Mediator of Early Adversity on Risk and Adaptive Outcomes." 85(6):2279–98.
Cousien, Anthony, Eric Acquaviva, Solen Kernéis, Yazdan Yazdanpanah, and Richard Delorme. 2021. "Temporal Trends in Suicide Attempts among Children in the Decade before and during the COVID-19 Pandemic in Paris, France." *JAMA Network Open* 4(10).
Csaba, György. 2020. "Reprogramming of the Immune System by Stress and Faulty Hormonal Imprinting." *Clinical Therapeutics* 42(6):983–92.
Danese, Andrea and Stephanie J. Lewis. 2017. "Psychoneuroimmunology of Early-Life Stress: The Hidden Wounds of Childhood Trauma." *Neuropsychopharmacology Reviews* 42:99–114.
DePasquale, Carrie E., Bonny Donzella, and Megan R. Gunnar. 2019. "Pubertal Recalibration of Cortisol

Reactivity Following Early Life Stress: A Cross-Sectional Analysis." *Journal of Child Psychology and Psychiatry and Allied Disciplines* 60(5):566–75.

Dieleman, Gwendolyn C., Anja C. Huizink, Joke H. M. Tulen, Elisabeth M. W. J. Utens, Hanneke E. Creemers, Jan van der Ende, and Frank C. Verhulst. 2015. "Alterations in HPA-Axis and Autonomic Nervous System Functioning in Childhood Anxiety Disorders Point to a Chronic Stress Hypothesis." *Psychoneuroendocrinology* 51:135–50.

Dillon, Gina, Rafat Hussain, Deborah Loxton, and Saifur Rahman. 2013. "Mental and Physical Health and Intimate Partner Violence against Women: A Review of the Literature." *International Journal of Family Medicine* 2013:313909.

Ditzen, Beate. 2022. "When Intimate Relationships Improve Immune Functioning: More than a Gut Feeling." *Brain, Behavior, and Immunity* 103:10–11.

Dohrenwend, Bruce P. 2006. "Inventorying Stressful Life Events as Risk Factors for Psychopathology: Toward Resolution of the Problem of Intracategory Variability." *Psychological Bulletin* 132(3):477–95.

Dunn, Erin C., Kristen Nishimi, Stephanie H. Gomez, Abigail Powers, and Bekh Bradley. 2018. "Developmental Timing of Trauma Exposure and Emotion Dysregulation in Adulthood: Are There Sensitive Periods When Trauma Is Most Harmful?" *Journal of Affective Disorders* 227(October 2017):869–77.

Dunn, Erin C., Thomas W. Soare, Yiwen Zhu, Andrew J. Simpkin, Matthew J. Suderman, Torsten Klengel, Andrew D. A. C. Smith, Kerry J. Ressler, and Caroline L. Relton. 2019. "Archival Report Sensitive Periods for the Effect of Childhood Adversity on DNA Methylation : Results From a Prospective , Longitudinal Study." *Biological Psychiatry* 85(10):838–49.

Dvir, Yael, Julian D. Ford, Michael Hill, and Jean A. Frazier. 2014. "Childhood Maltreatment, Emotional Dysregulation, and Psychiatric Comorbidities." *Harvard Review of Psychiatry* 22(3):149–61.

Ensink, Karin, Peter Fonagy, Lina Normandin, Abby Rozenberg, Christina Marquez, Natacha Godbout, and Jessica L. Borelli. 2021. "Post-Traumatic Stress Disorder in Sexually Abused Children: Secure Attachment as a Protective Factor ." *Frontiers in Psychology* 12.

Entringer, Sonja. 2021. "Childhood Abuse Accelerates Inflammaging." *Brain, Behavior, and Immunity* 94(February):25–26.

Erikson, Erik. 1968. *Identity: Youth and Crisis*. New York: W. W. Norton & Company.

Fang, Xiangming, Deborah A. Fry, Kai Ji, David Finkelhor, Jingqi Chen, Patricia Lannen, and Michael P. Dunne. 2015. "The Burden of Child Maltreatment in China: A Systematic Review." *Bulletin of the World Health Organization* 93(3):176-185C.

Fearon, R. Pasco, Marian J. Bakermans-Kranenburg, Marinus H. van Ijzendoorn, Anne-Marie Lapsley, and Glenn I. Roisman. 2010. "The Significance of Insecure Attachment and Disorganization in the Development of Children's Externalizing Behavior: A Meta-Analytic Study." *Child Development* 81(2):435–56.

Felitti, Vincent J., Robert F. Anda, Dale Nordenberg, David F. Williamson, Alison M. Spitz, Valerie Edwards, Mary P. Koss, and James S. Marks. 1998. "Household Dysfunction to Many of the Leading Causes of Death in Adults The Adverse Childhood Experiences (ACE) Study." *American Journal of Preventive Medicine* 14(4):245–58.

Fernandez Castelao, Carolin and Birgit Kröner-Herwig. 2013. "Different Trajectories of Depressive Symptoms in Children and Adolescents: Predictors and Differences in Girls and Boys." *Journal of Youth and Adolescence* 42(8):1169–82.

Finkelhor, David, Sherry L. Hamby, Richard Ormrod, and Heather Turner. 2005. "The Juvenile Victimization Questionnaire: Reliability, Validity, and National Norms." *Child Abuse and Neglect* 29(4):383–412.

Flouri, Eirini and Constantinos Kallis. 2011. "Adverse Life Events and Mental Health in Middle Adolescence." *Journal of Adolescence* 34(2):371–77.

Fogelman, Nia and Turhan Canli. 2018. "Early Life Stress and Cortisol: A Meta-Analysis." *Hormones and Behavior* 98(December 2017):63–76.

Folkman, S. 2013. *Stress: Appraisal and Coping*. Springer. Berlin.

Ford, Julian D. and Christine A. Courtois. 2021. "Complex PTSD and Borderline Personality Disorder." *Borderline Personality Disorder and Emotion Dysregulation* 8(1):1–21.

Fossati, Andrea, Kim L. Gratz, Cesare Maffei, and Serena Borroni. 2014. "Impulsivity Dimensions, Emotion Dysregulation, and Borderline Personality Disorder Features among Italian Nonclinical Adolescents." *Borderline Personality Disorder and Emotion Dysregulation* 1:5.

Fryers, Tom and Traolach Brugha. 2013. "Childhood Determinants of Adult Psychiatric Disorder." *Clinical Practice & Epidemiology in Mental Health* 9(1):1–50.

García, N. and V. Noguerol. 2007. *Infancia Maltratada: Manual de Intervención*. edited by Instituto de Orientación

Psicológica Asociados.
Gartland, Deirdre, Elisha Riggs, Sumaiya Muyeen, Rebecca Giallo, Tracie O. Afifi, Harriet Macmillan, Helen Herrman, Eleanor Bulford, and Stephanie J. Brown. 2019. "What Factors Are Associated with Resilient Outcomes in Children Exposed to Social Adversity ? A Systematic Review." 1–14.
Van Geel, Mitch, Paul Vedder, and Jenny Tanilon. 2014. "Relationship between Peer Victimization, Cyberbullying, and Suicide in Children and Adolescents Ameta-Analysis." *JAMA Pediatrics* 168(5):435–42.
Giedd, Jay N., Jonathan Blumenthal, Neal O. Jeffries, F. X. Castellanos, Hong Liu, Alex Zijdenbos, Tomáš Paus, Alan C. Evans, and Judith L. Rapoport. 1999. "Brain Development during Childhood and Adolescence: A Longitudinal MRI Study." *Nature Neuroscience* 2(10):861–63.
Gilbert, Ruth, John Fluke, Melissa O'Donnell, Arturo Gonzalez-Izquierdo, Marni Brownell, Pauline Gulliver, Staffan Janson, and Peter Sidebotham. 2012. "Child Maltreatment: Variation in Trends and Policies in Six Developed Countries." *The Lancet* 379(9817):758–72.
Giourou, Evangelia, Maria Skokou, Stuart P. Andrew, Konstantina Alexopoulou, Philippos Gourzis, and Eleni Jelastopulu. 2018. "Complex Posttraumatic Stress Disorder: The Need to Consolidate a Distinct Clinical Syndrome or to Reevaluate Features of Psychiatric Disorders Following Interpersonal Trauma?" *World Journal of Psychiatry* 8(1):12–19.
Godoy, L. D., M. T. Rossignoli, P. Delfino-Pereira, N. Garcia-Cairasco, and Ehl Umeoka. 2018. "A Comprehensive Overview on Stress Neurobiology: Basic Concepts and Clinical Implications." *Front. Behav. Neurosci* 12:127.
Gold, Steven N. 2004. "The Relevance of Trauma to General Clinical Practice." *Psychotherapy: Theory, Research, Practice, Training* 41(4):363–73.
Gonzalez Rodriguez, María del Mar, Francisca López Gaviño, and Ana Belén Gómez. 2010. "Familias Homoparentales." Pp. 110–20 in *Desarrollo psicológico en las nuevas estructuras familiares*, edited by E. Arranz Freijo and A. Oliva Delgado. Pirámide.
Grant, Kathryn E., Bruce E. Compas, Audrey E. Thurm, Susan D. McMahon, and Polly Y. Gipson. 2004. "Stressors and Child and Adolescent Psychopathology: Measurement Issues and Prospective Effects." *Journal of Clinical Child and Adolescent Psychology : The Official Journal for the Society of Clinical Child and Adolescent Psychology, American Psychological Association, Division 53* 33(2):412–25.
Groeschel, S., B. Vollmer, M. D. King, and A. Connelly. 2010. "Developmental Changes in Cerebral Grey and White Matter Volume from Infancy to Adulthood." *International Journal of Developmental Neuroscience* 28(6):481–89.
Groh, Ashley M., Angela J. Narayan, Marian J. Bakermans-Kranenburg, Glenn I. Roisman, Brian E. Vaughn, R. M. Pasc. Fearon, and Marinus H. van IJzendoorn. 2017. "Attachment and Temperament in the Early Life Course: A Meta-Analytic Review." *Child Development* 88(3):770–95.
Gross, James J. 1998. "The Emerging Field of Emotion Regulation: An Integrative Review." *Review of General Psychology* 2(3):271–99.
Gunnar, Megan R., Nicole M. Talge, and Adriana Herrera. 2009. "Stressor Paradigms in Developmental Studies: What Does and Does Not Work to Produce Mean Increases in Salivary Cortisol." *Psychoneuroendocrinology* 34(7):953–67.
Haller, Moira and Laurie Chassin. 2012. "A Test of Adolescent Internalizing and Externalizing Symptoms as Prospective Predictors of Type of Trauma Exposure and Posttraumatic Stress Disorder." *Journal of Traumatic Stress* 25(6):691–99.
Hammen, Constance. 2005. "Stress and Depression." *Annual Review of Clinical Psychology* 1:293–319.
Hamza, Chloe A., Shannon L. Stewart, and Teena Willoughby. 2012. "Examining the Link between Nonsuicidal Self-Injury and Suicidal Behavior: A Review of the Literature and an Integrated Model." *Clinical Psychology Review* 32(6):482–95.
Hankin, Benjamin L. and John R. Z. Abela. 2005. *Development of Psychopathology: A Vulnerability-Stress Perspective.* edited by B. L. Hankin and J. R. Z. Abela. Thousand Oaks, CA, US: Sage Publications, Inc.
Harkness, Kate L., Elizabeth P. Hayden, and Nestor L. Lopez-Duran. 2015. "Stress Sensitivity and Stress Sensitization in Psychopathology: An Introduction to the Special Section." *Journal of Abnormal Psychology* 124(1):1–3.
Harkness, Kate L. and Scott M. Monroe. 2016. "The Assessment and Measurement of Adult Life Stress: Basic Premises, Operational Principles, and Design Requirements." *Journal of Abnormal Psychology* 125(5):727–45.
Heim, C., D. J. Newport, S. Heit, Y. P. Graham, M. Wilcox, R. Bonsall, A. H. Miller, and C. B. Nemeroff. 2000. "Pituitary-Adrenal and Autonomic Responses to Stress in Women after Sexual and Physical

Abuse in Childhood." *JAMA* 284(5):592–97.
Heim, Christine, Margaret Shugart, W. Edward Craighead, and Charles B. Nemeroff. 2010. "Neurobiological and Psychiatric Consequences of Child Abuse and Neglect." *Developmental Psychobiology* 52(7):671–90.
Herman, J. 2004. *Trauma y Recuperación: Cómo Superar Las Consecuencias de La Violencia*. Ilustrada. edited by Espasa. Espasa.
Herman, Judith L. 1992. "Complex PTSD: A Syndrome in Survivors of Prolonged and Repeated Trauma." *Journal of Traumatic Stress* 5(3):377–91.
Herr, R. M., A. Barrech, N. Riedel, H. Gündel, P. Angerer, and J. Li. 2018. "Long-Term Effectiveness of Stress Management at Work: Effects of the Changes in Perceived Stress Reactivity on Mental Health and Sleep Problems Seven Years Later." *International Journal of Environmental Research and Public Health* 15(2).
van den Heuvel, Marieke W. H., Yvonne A. J. Stikkelbroek, Denise H. M. Bodden, and Anneloes L. van Baar. 2020. "Coping with Stressful Life Events: Cognitive Emotion Regulation Profiles and Depressive Symptoms in Adolescents." *Development and Psychopathology* 32(3):985–95.
Hillman, Saul, Jill Hodges, Miriam Steele, Antonella Cirasola, Kay Asquith, and Jeanne Kaniuk. 2020. "Assessing Changes in the Internal Worlds of Early- and Late-Adopted Children Using the Story Stem Assessment Profile (SSAP)." *Adoption & Fostering* 44(4):377–96.
Hock, Rebecca S., Arielle G. Rabinowitz, Cyralene P. Bryce, Garrett M. Fitzmaurice, Paul T. Costa Jr, and Janina R. Galler. 2020. "Intergenerational Effects of Childhood Maltreatment and Malnutrition on Personality Maladaptivity in a Barbadian Longitudinal Cohort." *Psychiatry Research* 290:113016.
Hodges, Jill, M. Steele, S. Hillman, and K. Henderson. 2007. "The Standardisation and Validation of the Story Stem Assessment Profile (SSAP): A Clinical Narrative-Based Assessment for Children." *Unpublished Manuscript*.
Hosser, Daniela, Stefan Raddatz, and Michael Windzio. 2007. "Child Maltreatment, Revictimization, and Violent Behavior." *Violence and Victims* 22(3):318–33.
Hovdestad, Wendy, Aimée Campeau, Dawn Potter, and Lil Tonmyr. 2015. "A Systematic Review of Childhood Maltreatment Assessments in Population-Representative Surveys since 1990." *PLoS ONE* 10(5):1–26.
Hunter, Ann Louise, Helen Minnis, and Philip Wilson. 2011. "Altered Stress Responses in Children Exposed to Early Adversity: A Systematic Review of Salivary Cortisol Studies." *Stress* 14(6):614–26.
Izard, Carroll E., Christina A. Fantauzzo, Janine M. Castle, O. Maurice Haynes, Maria F. Rayias, and Priscilla H. Putnam. 1995. "The Ontogeny and Significance of Infants' Facial Expressions in the First 9 Months of Life." *Developmental Psychology* 31(6):997–1013.
Jennissen, Simone, Julia Holl, Hannah Mai, Sebastian Wolff, and Sven Barnow. 2016. "Emotion Dysregulation Mediates the Relationship between Child Maltreatment and Psychopathology: A Structural Equation Model." *Child Abuse and Neglect* 62:51–62.
Joana-Santiveri, A., L. Marques-Feixa, M. Ignacio-Ibañez, G. Ortet, J. March-Llanes, L. Fañanás, and J. Moya-Higueras. 2018. "Estudio de La Calidad Psicométrica de Los Instrumentos de Acontecimientos Vitales Estresantes Usados En La Investigación de Población Española En Relación Con Los Trastornos Mentales." P. 162 in *Libro de resúmenes. Ansiedad y estrés. XII Congreso Internacional de la Sociedad Española para el estudio de la ansiedad y el estrés*, edited by A. Cano-vindel, I. Iruarrizaga-Díez, and M. V. Mestre Escrivá. Valencia: SEAS.
Jordan-Young, Rebecca and Katrina Karkazis. 2019. *Testosterone*. Cambridge (Massachusetts): Hardvard University Press.
Jung, Eunji, Joung-Sook Ahn, Jaehyun Han, and Min-Hyuk Kim. 2021. "Trajectories of Psychopathology According to Continuation or Discontinuation of Child Abuse: A Longitudinal Observational Study." *International Journal of Environmental Research and Public Health* 18(17):8968.
Kaess, Michael, Romuald Brunner, and Andrew Chanen. 2014. "Borderline Personality Disorder in Adolescence." 134:782–93.
Kaess, Michael, Peter Parzer, Margarete Mattern, Franz Resch, Antonia Bifulco, and Romuald Brunner. 2011. "Childhood Experiences of Care and Abuse (CECA) - validation of the German version of the questionnaire and interview, and results of an investigation of correlations between adverse childhood experiences and suicidal behaviour]." *Zeitschrift fur Kinder- und Jugendpsychiatrie und Psychotherapie* 39(4):243–52.
Kalman, Janos L., Tomoya Yoshida, Till F. M. Andlauer, Eva C. Schulte, Kristina Adorjan, Martin Alda, Raffaela Ardau, et al… Thomas G. Schulze, and Sergi Papiol. 2022. "Investigating the Phenotypic and Genetic Associations between Personality Traits and Suicidal Behavior across Major Mental Health Diagnoses." *European Archives of Psychiatry and Clinical Neuroscience*.

Karatzias, Thanos, Philip Murphy, Marylene Cloitre, Jonathan Bisson, Neil Roberts, Mark Shevlin, Philip Hyland, Andreas Maercker, Menachem Ben-Ezra, Peter Coventry, Susan Mason-Roberts, Aoife Bradley, and Paul Hutton. 2019. "Psychological Interventions for ICD-11 Complex PTSD Symptoms: Systematic Review and Meta-Analysis." *Psychological Medicine* 49(11):1761–75.

Kendler, Kenneth S. and Jessica H. Baker. 2007. "Genetic Influences on Measures of the Environment: A Systematic Review." *Psychological Medicine* 37(5):615–26.

Kendler KS, Hettema JM, Butera F, Gardner CO, and Prescott CA. 2003. "LIfe Event Dimensions of Loss, Humiliation, Entrapment, and Danger in the Prediction of Onsets of Major Depression and Generalized Anxiety." *Archives of General Psychiatry* 60(8):789–96.

Kerr, Daniel M., James McDonald, and Helen Minnis. 2021. "The Association of Child Maltreatment and Systemic Inflammation in Adulthood: A Systematic Review." *PLoS ONE* 16(4 April).

Kessler, R. C. 1997. "The Effects of Stressful Life Events on Depression." *Annual Review of Psychology* 48:191–214.

Kessler, R. C., S. Avenevoli, E. J. Costello, K. Georgiades, J. G. Green, M. J. Gruber, J. P. He, D. Koretz, K. A. McLaughlin, M. Petukhova, N. A. Sampson, A. M. Zaslavsky, and K. R. Merikangas. 2012. "Prevalence, Persistence, and Sociodemographic Correlates of DSM-IV Disorders in the National Comorbidity Survey Replication Adolescent Supplement." *Archives of General Psychiatry* 69(4):372–80.

Kessler, R. C., K. A. McLaughlin, J. G. Green, M. J. Gruber, N. A. Sampson, A. M. Zaslavsky, S. Aguilar-Gaxiola, A. O. Alhamzawi, et al.,… M. C. Viana, and D. R. Williams. 2010. "Childhood Adversities and Adult Psychopathology in the WHO World Mental Health Surveys." *British Journal of Psychiatry* 197(5):378–85.

Kim-Spoon, Jungmeen, Toria Herd, Alexis Brieant, Kristin Peviani, Kirby Deater-Deckard, Nina Lauharatanahirun, Jacob Lee, and Brooks King-Casas. 2021. "Maltreatment and Brain Development: The Effects of Abuse and Neglect on Longitudinal Trajectories of Neural Activation during Risk Processing and Cognitive Control." *Developmental Cognitive Neuroscience* 48:100939.

Kim, Stephanie Gyuri, David G. Weissman, Margaret A. Sheridan, and Katie A. McLaughlin. 2021. "Child Abuse and Automatic Emotion Regulation in Children and Adolescents." *Development and Psychopathology* 1–11.

King, Lucy S., Natalie L. Colich, Joelle LeMoult, Kathryn L. Humphreys, Sarah J. Ordaz, Alexandria N. Price, and Ian H. Gotlib. 2017. "The Impact of the Severity of Early Life Stress on Diurnal Cortisol: The Role of Puberty." *Psychoneuroendocrinology* 77:68–74.

van der Kolk, Bessel A. 2005. "Developmental Trauma Disorder: Toward a Rational Diagnosis for Children with Complex Trauma Histories." *Psychiatric Annals* 35(5):401–8.

van der Kolk, Bessel A. 2020. *El Cuerpo Lleva La Cuenta: Cerebro, Mente y Cuerpo En La Superación Del Trauma*. Eleftheria.

Kontak, Julia C. H., Sara F. L. Kirk, Lynne Robinson, Arto Ohinmaa, and Paul J. Veugelers. 2019. "The Relationship between Bullying Behaviours in Childhood and Physician-Diagnosed Internalizing Disorders." *Canadian Journal of Public Health* 110(4):497–505.

Koss, Kalsea J. and Megan R. Gunnar. 2018. "Annual Research Review : Early Adversity , the Hypothalamic – Pituitary – Adrenocortical Axis , and Child Psychopathology." *Journal of Child Psychology and Psychiatry* 59: 4:327–46.

Krause-Utz, Annegret, Ezgi Erol, Athina V. Brousianou, Sylvia Cackowski, Christian Paret, Gabriele Ende, and Bernet Elzinga. 2019. "Self-Reported Impulsivity in Women with Borderline Personality Disorder: The Role of Childhood Maltreatment Severity and Emotion Regulation Difficulties." *Borderline Personality Disorder and Emotion Dysregulation* 6(1):1–14.

Krueger, Robert F. and Kristian E. Markon. 2006. "Reinterpreting Comorbidity: A Model-Based Approach to Understanding and Classifying Psychopathology." *Annual Review of Clinical Psychology* 2:111–33.

Kubany, Edward S., Stephen N. Haynes, Mary Beth Leisen, Julie A. Owens, Aaron S. Kaplan, Susan B. Watson, and Katie Burns. 2000. "Development and Preliminary Validation of a Brief Broad-Spectrum Measure of Trauma Exposure: The Traumatic Life Events Questionnaire." *Psychological Assessment* 12(2):210–24.

Kudielka, B. M., A. Buske-Kirschbaum, D. H. Hellhammer, and C. Kirschbaum. 2004. "HPA Axis Responses to Laboratory Psychosocial Stress in Healthy Elderly Adults, Younger Adults, and Children: Impact of Age and Gender." *Psychoneuroendocrinology* 29(1):83–98.

Kudielka, B. M., N. C. Schommer, D. H. Hellhammer, and C. Kirschbaum. 2004. "Acute HPA Axis Responses, Heart Rate, and Mood Changes to Psychosocial Stress (TSST) in Humans at Different Times of Day." *Psychoneuroendocrinology* 29(8):983–92.

Kuhlman, Kate Ryan, Rena L. Repetti, Bridget M. Reynolds, and Theodore F. Robles. 2018. "Interparental

Conflict and Child HPA-Axis Responses to Acute Stress: Insights Using Intensive Repeated Measures." *Journal of Family Psychology : JFP : Journal of the Division of Family Psychology of the American Psychological Association (Division 43)* 32(6):773–82.

Lakhan, Shaheen E. and Gareth E. Hagger-Johnson. 2007. "The Impact of Prescribed Psychotropics on Youth." *Clinical Practice and Epidemiology in Mental Health : CP & EMH* 3:21.

Lanktree, C. and J. Briere. 2008. "Integrative Treatment of Complex Trauma for Children (ITCT-C): A Guide for the Treatment of Multiply-Traumatized Children Aged Eight to Twelve Years." *National Child Traumatic Stress Netork (NCTSN)*.

Laurent, Heidemarie K, Laura R. Stroud, Bridget Brush, Christina D'Angelo, and Douglas A. Granger. 2015. "Secretory IgA Reactivity to Social Threat in Youth: Relations with HPA, ANS, and Behavior." *Psychoneuroendocrinology* 59:81–90.

Laurent, Heidemarie K., Laura R. Stroud, Bridget Brush, Christina D'Angelo, and Douglas A. Granger. 2015. "Secretory IgA Reactivity to Social Threat in Youth: Relations with HPA, ANS, and Behavior." *Psychoneuroendocrinology* 59:81–90.

Lazarus, R. and S. Folkman. 1986. *Estrés y Procesos Cognitivos*. Barcelona: Ediciones Martínez Roca.

Lenroot, Rhoshel K. and Jay N. Giedd. 2006. "Brain Development in Children and Adolescents: Insights from Anatomical Magnetic Resonance Imaging." *Neuroscience & Biobehavioral Reviews* 30(6):718–29.

Levenson, R. W. 2003. "Blood, Sweat, and Fears." *Annals of the New York Academy of Sciences* 1000(1):348–66.

Levy, Kenneth N. 2005. "The Implications of Attachment Theory and Research for Understanding Borderline Personality Disorder." *Development and Psychopathology* 17(4):959–86.

Lewis, Michael, Margaret Wolan Sullivan, Catherine Stanger, and Maya Weiss. 1989. "Self Development and Self-Conscious Emotions." *Child Development* 60(1):146–56.

Linehan, Marsha M. 1993. *Cognitive-Behavioral Treatment of Borderline Personality Disorder*. New York, NY, US: Guilford Press.

Lippard, Elizabeth T. C. and Charles B. Nemeroff. 2020. "The Devastating Clinical Consequences of Child Abuse and Neglect : Increased Disease Vulnerability and Poor Treatment Response in Mood Disorders." (January).

Liu, Richard T. and Ivan Miller. 2014. "Life Events and Suicidal Ideation and Behavior: A Systematic Review." *Clinical Psychology Review* 34(3):181–92.

Livesley, W. John. 2021. "Why Is an Evidence-Based Classification of Personality Disorder so Elusive?" *Personality and Mental Health* 15(1):8–25.

Low, Nancy Cp, Erika Dugas, Erin O'Loughlin, Daniel Rodriguez, Gisele Contreras, Michael Chaiton, and Jennifer O'Loughlin. 2012. "Common Stressful Life Events and Difficulties Are Associated with Mental Health Symptoms and Substance Use in Young Adolescents." *BMC Psychiatry* 12:116.

Maier, S. F. and L. R. Watkins. 1998. "Cytokines for Psychologists: Implications of Bidirectional Immune-to-Brain Communication for Understanding Behavior, Mood, and Cognition." *Psychological Review* 105(1):83–107.

March-Llanes, Jaume, Laia Marqués-Feixa, Laura Mezquita, Lourdes Fañanás, and Jorge Moya-Higueras. 2017. "Stressful Life Events during Adolescence and Risk for Externalizing and Internalizing Psychopathology: A Meta-Analysis." *European Child and Adolescent Psychiatry* 26(12):1409–22.

Mardomingo, M. J. and S. Gonzalez-Garrido. 1990. "Escala de Acontecimientos Vitales Para Adolescentes." *Rev. Psiquiat. Infant. Juv.* 2:123–25.

Mardomingo, M. J., S. Kloppe, and S. Gallego. 1986. "Escala de Acontecimientos Vitales Adaptada a La Población Infantil Española." *Rev. de Psiquiatría Lnfanto-Juvenil*.

Marín, Oscar. 2016. "Developmental Timing and Critical Windows for the Treatment of Psychiatric Disorders." *Nature Medicine* 22(11):1229–38.

Marques-Feixa, Laia, Jorge Moya-Higueras, Soledad Romero, Pilar Santamarina-Pérez, Marta Rapado-Castro, Iñaki Zorrilla, María Martín, Eulalia Anglada, María José Lobato, Maite Ramírez, Nerea Moreno, María Mayoral, María Marín-Vila, Bárbara Arias, Lourdes Fañanás, and Epi-Young Stress. 2021 (a). "Risk of Suicidal Behavior in Children and Adolescents Exposed to Maltreatment: The Mediating Role of Borderline Personality Traits and Recent Stressful Life Events." *J. Clin. Med* 10:5293.

Marques-Feixa, Laia, Helena Palma-Gudiel, Soledad Romero, Jorge Moya-Higueras, Marta Rapado-Castro, Águeda Castro-Quintas, Iñaki Zorrilla, María José Muñoz, Maite Ramírez, María Mayoral, Ariadna Mas, María José Lobato, Hilario Blasco-Fontecilla, Lourdes Fañanás and EPI_young_stress. 2021 (b). "Childhood Maltreatment Disrupts HPA-Axis Activity under Basal and Stress Conditions in a Dose-Response Relationship in Children and Adolescents." *Psychological Medicine* 16:1–14.

Marques-Feixa, Laia, Jorge Moya-Higueras, Soledad Romero, Pilar Santamarina-Pérez, Nerea San Martín-

González, Maria José Muñoz, Eulalia Anglada, Hilario Blasco-fontecilla, Marta Rapado-castro, Iñaki Zorrilla, Maite Ramírez, Lourdes Fañanás, and EPI-young-stress. 2022 (a). "Reinforcing the New Diagnosis of Complex Post-Traumatic Stress Disorder (CPTSD) of ICD-11 in Children and Adolescents Exposed to Relational Trauma: Developmental Stage at Exposure and Its Associated Clinical Outcomes." *Submitted to Psychological Medicine*.

Marques-Feixa, Laia (b), Águeda Castro-Quintas, Helena Palma-Gudiel, Soledad Romero, Astrid Morer, Marta Rapado-Castro, María Martín, Iñaki Zorrilla, Hilario Blasco-Fontecilla, Maite Ramírez, María Mayoral, Iría Mendez, Nerea San Martín-Gonzalez, María Rodrigo-Yanguas, José Luis Monteserín-García, Lourdes Fañanás and EPI_Young_stress. 2022 (b). "Secretory Immunoglobulin A (s-IgA) Reactivity to Acute Psychosocial Stress in Children and Adolescents: The Influence of Pubertal Development and History of Maltreatment." *Brain, Behavior, and Immunity* 103:122–29.

Martins, Jade, Darina Czamara, Susann Sauer, Monika Rex-Haffner, Katja Dittrich, Peggy Dörr, Karin de Punder, Judith Overfeld, Andrea Knop, Felix Dammering, Sonja Entringer, Sibylle M. Winter, Claudia Buss, Christine Heim, and Elisabeth B. Binder. 2021. "Childhood Adversity Correlates with Stable Changes in DNA Methylation Trajectories in Children and Converges with Epigenetic Signatures of Prenatal Stress." *Neurobiology of Stress* 15:100336.

Maughan, Angeline and Dante Cicchetti. 2002. "Impact of Child Maltreatment and Interadult Violence on Children's Emotion Regulation Abilities and Socioemotional Adjustment." *Child Development* 73(5):1525–42.

McAdams, Tom A., Alice M. Gregory, and Thalia C. Eley. 2013. "Genes of Experience: Explaining the Heritability of Putative Environmental Variables through Their Association with Behavioural and Emotional Traits." *Behavior Genetics* 43(4):314–28.

McCrory, Eamon, Stephane A. De Brito, and Essi Viding. 2010. "Research Review: The Neurobiology and Genetics of Maltreatment and Adversity." *Journal of Child Psychology and Psychiatry and Allied Disciplines* 51(10):1079–95.

McCrory, Eamon, Stephane A. De Brito, and Essi Viding. 2011. "The Impact of Childhood Maltreatment: A Review of Neurobiological and Genetic Factors." *Frontiers in Psychiatry* 2(JUL):1–14.

Mccrory, Eamon J., Mattia I. Gerin, and Essi Viding. 2017. "Annual Research Review : Childhood Maltreatment , Latent Vulnerability and the Shift to Preventative Psychiatry – the Contribution of Functional Brain Imaging." 4:338–57.

McDonald, Suzanne, Francis Quinn, Rute Vieira, Nicola O'Brien, Martin White, Derek W. Johnston, and Falko F. Sniehotta. 2017. "The State of the Art and Future Opportunities for Using Longitudinal N-of-1 Methods in Health Behaviour Research: A Systematic Literature Overview." *Health Psychology Review* 11(4):307–23.

McEwen, Bruce S. 2017. "Neurobiological and Systemic Effects of Chronic Stress." *Chronic Stress (Thousand Oaks, Calif.)* 1.

McKay, Michael T., Mary Cannon, Derek Chambers, Ronán M. Conroy, Helen Coughlan, Philip Dodd, Colm Healy, Laurie O'Donnell, and Mary C. Clarke. 2021. "Childhood Trauma and Adult Mental Disorder: A Systematic Review and Meta-Analysis of Longitudinal Cohort Studies." *Acta Psychiatrica Scandinavica* 143(3):189–205.

Meaney, Michael J. and Moshe Szyf. 2005. "Environmental Programming of Stress Responses through DNA Methylation: Life at the Interface between a Dynamic Environment and a Fixed Genome." *Dialogues in Clinical Neuroscience* 7(2):103–23.

Mendelson, Tamar. 2013. "Stress, Emotional." Pp. 1906–8 in *Encyclopedia of Behavioral Medicine*, edited by M. D. Gellman and J. R. Turner. New York, NY: Springer New York.

Meng, Xiu Hong, Fang Biao Tao, Yu Hui Wan, Yan Hu, and Ren Xi Wang. 2011. "Coping as a Mechanism Linking Stressful Life Events and Mental Health Problems in Adolescents." *Biomedical and Environmental Sciences : BES* 24(6):649–55.

Messman-Moore, Terri L. and Prachi H. Bhuptani. 2017. "A Review of the Long-Term Impact of Child Maltreatment on Posttraumatic Stress Disorder and Its Comorbidities: An Emotion Dysregulation Perspective." *Clinical Psychology: Science and Practice* 24(2):154–69.

Miller, A. H. and C. L. Raison. 2016. "The Role of Inflammation in Depression: From Evolutionary Imperative to Modern Treatment Target." *Nature Reviews. Immunology* 16(1):22–34.

Miller, Adam B., Christianne Esposito-Smythers, Julie T. Weismoore, and Keith D. Renshaw. 2013. "The Relation Between Child Maltreatment and Adolescent Suicidal Behavior: A Systematic Review and Critical Examination of the Literature." *Clinical Child and Family Psychology Review* 16(2):146–72.

Miller, Gregory E., Edith Chen, and Eric S. Zhou. 2007. "If It Goes up, Must It Come down? Chronic Stress

and the Hypothalamic-Pituitary-Adrenocortical Axis in Humans." *Psychological Bulletin* 133(1):25–45.

Miller, Gregory E., Sheldon Cohen, and A. Kim Ritchey. 2002. "Chronic Psychological Stress and the Regulation of Pro-Inflammatory Cytokines: A Glucocorticoid-Resistance Model." *Health Psychology : Official Journal of the Division of Health Psychology, American Psychological Association* 21(6):531–41.

Miron, Lynsey R. and Holly K. Orcutt. 2014. "Pathways from Childhood Abuse to Prospective Revictimization: Depression, Sex to Reduce Negative Affect, and Forecasted Sexual Behavior." *Child Abuse & Neglect* 38(11):1848–59.

Moody, Gwenllian, Rebecca Cannings-John, Kerenza Hood, Alison Kemp, and Michael Robling. 2018. "Establishing the International Prevalence of Self-Reported Child Maltreatment: A Systematic Review by Maltreatment Type and Gender." *BMC Public Health* 18(1):1164.

Moore, Sophie E., Rosana E. Norman, Shuichi Suetani, Hannah J. Thomas, Peter D. Sly, and James G. Scott. 2017. "Consequences of Bullying Victimization in Childhood and Adolescence: A Systematic Review and Meta-Analysis." *World Journal of Psychiatry* 7(1):60.

Morgan, Craig and Helen Fisher. 2007. "Environment and Schizophrenia: Environmental Factors in Schizophrenia: Childhood Trauma - A Critical Review." *Schizophrenia Bulletin* 33(1):3–10.

Mortier, P., G. Vilagut, M. Ferrer, I. Alayo, R. Bruffaerts, P. Cristóbal-Narváez, I. Del Cura-González, J. Domènech-Abella, et al.,… Iñaki Zorrilla, and Saioa L. Zurbano. 2021. "Thirty-Day Suicidal Thoughts and Behaviors in the Spanish Adult General Population during the First Wave of the Spain COVID-19 Pandemic." *Epidemiology and Psychiatric Sciences*.

Moya-Higueras, J., A. Cuevas, L. Marques-Feixa, L. Mezquita, M. Mayoral, L. Fañanás, G. Ortet, and M. I. Ibáñez. 2020. "Recent Stressful Life Events (SLE) and Adolescent Mental Health: Initial Validation of the LEIA, a New Checklist for SLE Assessment According to Their Severity, Interpersonal, and Dependent Nature." *Assessment* 27 (8):1777–95.

Myers, JEB, L. Berliner, John Briere, CT Hendrix, T. Reid, and C. Jenny. 2002. *The APSAC Handbook on Child Maltreatment*. Second edi. Sage Publications.

Nanni, Valentina, Rudolf Uher, and Andrea Danese. 2012. "Childhood Maltreatment Predicts Unfavorable Course of Illness and Treatment Outcome in Depression: A Meta-Analysis." *Am J Psychiatry* 169:141–51.

Nemeroff, Charles B. 2016. "Paradise Lost: The Neurobiological and Clinical Consequences of Child Abuse and Neglect." *Neuron* 89(5):892–909.

Nivard, Michel G., Gitta H. Lubke, Conor V Dolan, David M. Evans, Beate St Pourcain, Marcus R. Munafò, and Christel M. Middeldorp. 2017. "Joint Developmental Trajectories of Internalizing and Externalizing Disorders between Childhood and Adolescence." *Development and Psychopathology* 29(3):919–28.

Noll, Jennie G., Penelope K. Trickett, Jeffrey D. Long, Sonya Negriff, Elizabeth J. Susman, Idan Shalev, Jacinda C. Li, and Frank W. Putnam. 2017. "Childhood Sexual Abuse and Early Timing of Puberty." *The Journal of Adolescent Health : Official Publication of the Society for Adolescent Medicine* 60(1):65–71.

Norman, Rosana E., Munkhtsetseg Byambaa, Rumna De, Alexander Butchart, James Scott, and Theo Vos. 2012. "The Long-Term Health Consequences of Child Physical Abuse, Emotional Abuse, and Neglect: A Systematic Review and Meta-Analysis." *PLoS Medicine* 9(11).

Nurkka, A., J. Obiero, H. Käyhty, and J. A. G. Scott. 2003. "Effects of Sample Collection and Storage Methods on Antipneumococcal Immunoglobulin A in Saliva." *Clinical and Diagnostic Laboratory Immunology* 10(3):357–61.

Ohashi, Kyoko, Carl M. Anderson, Elizabeth A. Bolger, Alaptagin Khan, Cynthia E. McGreenery, and Martin H. Teicher. 2019. "Susceptibility or Resilience to Maltreatment Can Be Explained by Specific Differences in Brain Network Architecture." *Biological Psychiatry* 85(8):690–702.

Oliva, Alfredo, Jesús M. Jiménez, Águeda Parra, and Inmaculada Sánchez. 2008. "Acontecimientos Vitales Estresantes, Resiliencia Y Ajuste Adolescente." *Revista de Psicopatología y Psicología Clínica* 13(1):53–62.

van Oort, J., I. Tendolkar, E. J. Hermans, P. C. Mulders, C. F. Beckmann, A. H. Schene, G. Fernández, and P. F. van Eijndhoven. 2017. "How the Brain Connects in Response to Acute Stress: A Review at the Human Brain Systems Level." *Neuroscience and Biobehavioral Reviews* 83:281–97.

Osofsky, Joy D. 2018. "Commentary: Understanding the Impact of Domestic Violence on Children, Recognizing Strengths, and Promoting Resilience: Reflections on Harold and Sellers (2018)." *Journal of Child Psychology and Psychiatry, and Allied Disciplines* 59(4):403–4.

Ouellet-Morin, Isabelle, Marie Pier Robitaille, Stéphanie Langevin, Christina Cantave, Mara Brendgen, and Sonia J. Lupien. 2019. "Enduring Effect of Childhood Maltreatment on Cortisol and Heart Rate Responses to Stress: The Moderating Role of Severity of Experiences." *Development and Psychopathology* 31(2):497–508.

Palma-Gudiel, H., A. Córdova-Palomera, E. Eixarch, M. Deuschle, and Lourdes Fañanás. 2015. "Maternal Psychosocial Stress during Pregnancy Alters the Epigenetic Signature of the Glucocorticoid Receptor Gene Promoter in Their Offspring: A Meta-Analysis." *Epigenetics* 10(10):893–902.

Palma-Gudiel, H. and L. Fananas. 2017. "An Integrative Review of Methylation at the Serotonin Transporter Gene and Its Dialogue with Environmental Risk Factors, Psychopathology and 5-HTTLPR." *Neuroscience and Biobehavioral Reviews* 72:190–209.

Paniagua, Antontio. 2021. "El Suicidio Se Convierte En La Primera Causa de Muerte Entre Los Jóvenes." *Heraldo*.

Paris, Joel. 2019. "Suicidality in Borderline Personality Disorder." *Medicina (Kaunas, Lithuania)* 55(6).

Pate, Kailey M. 2021. "Understanding Post-Traumatic Stress Disorder in Children: A Comprehensive Review." *Inquiries Journal* 13(02).

Paulus, Frank W., Susanne Ohmann, Eva Möhler, Paul Plener, and Christian Popow. 2021. "Emotional Dysregulation in Children and Adolescents With Psychiatric Disorders. A Narrative Review." *Frontiers in Psychiatry* 12.

Pereda, Noemí, David Gallardo-Pujol, and Georgina Guilera. 2018. "Good Practices in the Assessment of Victimization: The Spanish Adaptation of the Juvenile Victimization Questionnaire." *Psychology of Violence* 8(1):76–86.

Polek, Ela, Peter B. Jones, Pasco Fearon, Jeannette Brodbeck, Michael Moutoussis, NSPN Consortium, Ray Dolan, Peter Fonagy, Edward T. Bullmore, and Ian M. Goodyer. 2018. "Personality Dimensions Emerging during Adolescence and Young Adulthood Are Underpinned by a Single Latent Trait Indexing Impairment in Social Functioning." *BMC Psychiatry* 18(1):23.

Read, John, Paul Hammersley, and Thom Rudegeair. 2007. "Why, When and How to Ask about Childhood Abuse." *Advances in Psychiatric Treatment* 13(2):101–10.

Read, John, J. Van Os, A. P. Morrison, and C. A. Ross. 2005. "Childhood Trauma, Psychosis and Schizophrenia: A Literature Review with Theoretical and Clinical Implications." *Acta Psychiatrica Scandinavica* 112(5):330–50.

Roman, Maite, Jill Hodges, Jesus Palacios, Carmen Moreno, and Saul Hillman. 2018. "Evaluación de Las Representaciones Mentales de Apego a Través de Las Historias Incompletas : Aplicación Española de Story Stem Assessment Profile (SSAP) Assessing Mental Representations of Attachment with Story Stems : Spanish Application of Story Stem." *Revista Iberoamericana de Diagnóstico y Evaluación Psicologica (RIDEP)* 1(46):5–19.

De Rose, Paola, Fortunata Salvaguardia, Paola Bergonzini, Flavia Cirillo, Francesco Demaria, Maria Pia Casini, Deny Menghini, and Stefano Vicari. 2016. "Current Psychopathological Symptoms in Children and Adolescents Who Suffered Different Forms of Maltreatment" edited by H. Minnis. *The Scientific World Journal* 2016:8654169.

Ruano-Ravina, A., A. Figueiras, A. Montes-Martínez, and J. M. Barros-Dios. 2003. "Dose–Response Relationship between Tobacco and Lung Cancer: New Findings." *European Journal of Cancer Prevention* 12(4).

Rudolph, KAREN D., CONSTANCE Hammen, DORLI Burge, NANGEL Lindberg, DAVID Herzberg, and SHANNON E. Daley. 2000. "Toward an Interpersonal Life-Stress Model of Depression: The Developmental Context of Stress Generation." *Development and Psychopathology* 12(2):215–34.

Sachser, Cedric, Ferdinand Keller, and Lutz Goldbeck. 2017. "Complex PTSD as Proposed for ICD-11: Validation of a New Disorder in Children and Adolescents and Their Response to Trauma-Focused Cognitive Behavioral Therapy." *Journal of Child Psychology and Psychiatry, and Allied Disciplines* 58(2):160–68.

Santos, Edalmarys and Chad A. Noggle. 2011. "Synaptic Pruning." Pp. 1464–65 in *Encyclopedia of Child Behavior and Development*, edited by S. Goldstein and J. A. Naglieri. Boston, MA: Springer US.

Sapolsky, R. M., L. M. Romero, and A. U. Munck. 2000. "How Do Glucocorticoids Influence Stress Responses? Integrating Permissive, Suppressive, Stimulatory, and Preparative Actions." *Endocrine Reviews* 21(1):55–89.

Schalinski, Inga, Martin H. Teicher, Daniel Nischk, Eva Hinderer, Oliver Müller, and Brigitte Rockstroh. 2016. "Type and Timing of Adverse Childhood Experiences Differentially Affect Severity of PTSD, Dissociative and Depressive Symptoms in Adult Inpatients." *BMC Psychiatry* 16(1):1–15.

Segerstrom, Suzanne C. and Gregory E. Miller. 2004. "Psychological Stress and the Human Immune System: A Meta-Analytic Study of 30 Years of Inquiry." *Psychological Bulletin* 130(4):601–30.

Selye, H. 1964. *From Dream to Discovery. On Being a Scientist.* McGraw-Hi. New York.

Serafini, Gianluca, Caterina Muzio, Giulia Piccinini, Eirini Flouri, Gabriella Ferrigno, Maurizio Pompili, Paolo

Girardi, and Mario Amore. 2015. "Life Adversities and Suicidal Behavior in Young Individuals: A Systematic Review." *European Child & Adolescent Psychiatry* 24(12):1423–46.

Shields, Grant S. and George M. Slavich. 2017. "Lifetime Stress Exposure and Health: A Review of Contemporary Assessment Methods and Biological Mechanisms." *Social and Personality Psychology Compass* 11(8).

Sierau, Susan, Tilman Brand, Jody Todd Manly, Andrea Schlesier-Michel, Annette M. Klein, Anna Andreas, Leonhard Quintero Garzón, Jan Keil, Martin J. Binser, Kai von Klitzing, and Lars O. White. 2016. "A Multisource Approach to Assessing Child Maltreatment From Records, Caregivers, and Children." *Child Maltreatment* 22(1):45–57.

Simon, A. Katharina, Georg A. Hollander, and Andrew McMichael. 2015. "Evolution of the Immune System in Humans from Infancy to Old Age." *Proceedings. Biological Sciences* 282(1821):20143085.

Skarbø, Tove, J. H. Rosenvinge, and A. Holte. 2004. "Adolescent Life Events and Adult Mental Health 5-9 Years after Referral for Acute Psychiatric Outpatient Treatment." *Clinical Psychology & Psychotherapy* 11(6):401–13.

Sloan, Elise, Kate Hall, Richard Moulding, Shayden Bryce, Helen Mildred, and Petra K. Staiger. 2017. "Emotion Regulation as a Transdiagnostic Treatment Construct across Anxiety, Depression, Substance, Eating and Borderline Personality Disorders: A Systematic Review." *Clinical Psychology Review* 57:141–63.

Smigielski, Lukasz, Diana Wotruba, Valerie Treyer, Julian Rössler, Sergi Papiol, Peter Falkai, Edna Grünblatt, Susanne Walitza, and Wulf Rössler. 2021. "The Interplay Between Postsynaptic Striatal D2/3 Receptor Availability, Adversity Exposure and Odd Beliefs: A [11C]-Raclopride PET Study." *Schizophrenia Bulletin* 47(5):1495–1508.

Solmi, Marco, Joaquim Radua, Miriam Olivola, Enrico Croce, Livia Soardo, Gonzalo Salazar de Pablo, Jae Il Shin, James B. Kirkbride, Peter Jones, Jae Han Kim, Jong Yeob Kim, Andrè F. Carvalho, Mary V Seeman, Christoph U. Correll, and Paolo Fusar-Poli. 2021. "Age at Onset of Mental Disorders Worldwide: Large-Scale Meta-Analysis of 192 Epidemiological Studies." *Molecular Psychiatry*.

Soto, Christopher J. and Jennifer L. Tackett. 2016. "Personality Traits in Childhood and Adolescence: Structure, Development, and Outcomes." *Cancer Research* 76(4):358–62.

Staley, Molly, Melinda G. Conners, Katie Hall, and Lance J. Miller. 2018. "Linking Stress and Immunity: Immunoglobulin A as a Non-Invasive Physiological Biomarker in Animal Welfare Studies." *Hormones and Behavior* 102:55–68.

Steinberg, Alan M., Melissa J. Brymer, Soeun Kim, Ernestine C. Briggs, Chandra Ghosh Ippen, Sarah A. Ostrowski, Kevin J. Gully, and Robert S. Pynoos. 2013. "Psychometric Properties of the UCLA PTSD Reaction Index: Part I." *Journal of Traumatic Stress* 26(1):1–9.

Steinhausen, Hans Christoph. 2015. "Recent International Trends in Psychotropic Medication Prescriptions for Children and Adolescents." *European Child and Adolescent Psychiatry* 24(6):635–40.

Steinhoff, Annekatrin, Denis Ribeaud, Stephan Kupferschmid, Nesrin Raible-Destan, Boris B. Quednow, Urs Hepp, Manuel Eisner, and Lilly Shanahan. 2021. "Self-Injury from Early Adolescence to Early Adulthood: Age-Related Course, Recurrence, and Services Use in Males and Females from the Community." *European Child & Adolescent Psychiatry* 30(6):937–51.

Stoltenborgh, Marije, Marian J. Bakermans-Kranenburg, Lenneke Alink, and Marinus H. Van Ijzendoorn. 2015. "The Prevalence of Child Maltreatment across the Globe: Review of a Series of Meta-Analyses." *Child Abuse Review* 24(April 2014):37–50.

Swartz, Johnna R., Douglas E. Williamson, and Ahmad R. Hariri. 2015. "Developmental Change in Amygdala Reactivity during Adolescence: Effects of Family History of Depression and Stressful Life Events." *The American Journal of Psychiatry* 172(3):276–83.

Szyf, Moshe. 2014. "News and Views Lamarck Revisited : Epigenetic Inheritance of Ancestral Odor Fear Conditioning." *Nature Publishing Group* 17(1):2–4.

Tarullo, Amanda R. and Megan R. Gunnar. 2006. "Child Maltreatment and the Developing HPA Axis." *Hormones and Behavior* 50(4):632–39.

Teicher, Martin H., Carl M. Anderson, Kyoko Ohashi, Alaptagin Khan, Cynthia E. Mcgreenery, Elizabeth A. Bolger, Michael L. Rohan, and Gordana D. Vitaliano. 2018. "NeuroImage Differential Effects of Childhood Neglect and Abuse during Sensitive Exposure Periods on Male and Female Hippocampus." *NeuroImage* 169(June 2017):443–52.

Teicher, Martin H. and Angelika Parigger. 2015. "The 'Maltreatment and Abuse Chronology of Exposure' (MACE) Scale for the Retrospective Assessment of Abuse and Neglect during Development." *PLoS ONE* 10(2):1–37.

Teicher, Martin H. and Jacqueline A. Samson. 2013. "Childhood Maltreatment and Psychopathology: A Case

for Ecophenotypic Variants as Clinically and Neurobiologically Distinct Subtypes." *American Journal of Psychiatry* 170(10):1114–33.

Teicher, Martin H. and Jacqueline A. Samson. 2016. "Annual Research Review : Enduring Neurobiological Effects of Childhood Abuse and Neglect." 3:241–66.

Teicher, Martin H., Jacqueline A. Samson, Carl M. Anderson, and Kyoko Ohashi. 2016. "The Effects of Childhood Maltreatment on Brain Structure, Function and Connectivity." *Nature Reviews Neuroscience* 17(10):652–66.

Thielen, Frederick W., Margreet ten Have, Ron de Graaf, Pim Cuijpers, Aartjan Beekman, Silvia Evers, and Filip Smit. 2016. "Long-Term Economic Consequences of Child Maltreatment: A Population-Based Study." *European Child and Adolescent Psychiatry* 25(12):1297–1305.

Tingskull, Sylvia, Carl Göran Svedin, Sara Agnafors, Gunilla Sydsjö, Linda deKeyser, and Doris Nilsson. 2015. "Parent and Child Agreement on Experience of Potential Traumatic Events." *Child Abuse Review* 24(3):170–81.

Titelius, Elise N., Emily Cook, Jayson Spas, Lindsay Orchowski, Katie Kivisto, Kimberly O'Brien, Elisabeth Frazier, Jennifer C. Wolff, Daniel P. Dickstein, Kerri L. Kim, and Karen E. Seymour. 2018. "Emotion Dysregulation Mediates the Relationship Between Child Maltreatment and Non-Suicidal Self-Injury." *Journal of Aggression, Maltreatment and Trauma* 27(3):323–31.

Tolin, David F. and Edna B. Foa. 2006. "Sex Differences in Trauma and Posttraumatic Stress Disorder: A Quantitative Review of 25 Years of Research." *Psychological Bulletin* 132(6):959–92.

Tonhajzerova, I. and M. Mestanik. 2017. "New Perspectives in the Model of Stress Response." *Physiological Research* 66(Suppl 2):S173–85.

Toro, J., M. .. Font, and G. Canalda. 1983. "Hechos Estresores y Trastornos Psiquiátricos En La Infancia y En La Adolescencia: Un Estudio Piloto." *Rev. Depto. Psiquiatría Dacultad Med. Barna* 10:429–43.

Trickett, Penelope K., Elana Gordis, Melissa K. Peckins, and Elizabeth J. Susman. 2014. "Stress Reactivity in Maltreated and Comparison Male and Female Young Adolescents." 19(1):27–37.

Trueba, Ana F., Dario Mizrachi, Richard J. Auchus, Pia D. Vogel, and Thomas Ritz. 2012. "Effects of Psychosocial Stress on the Pattern of Salivary Protein Release." *Physiology & Behavior* 105(3):841–49.

Turner, R. Jay and Blair Wheaton. 1997. "Checklist Measurement of Stressful Life Events." Pp. 29–58 in *Measuring stress: A guide for health and social scientists*. New York, NY, US: Oxford University Press.

Uher, Rudolf and Alyson Zwicker. 2017. "Etiology in Psychiatry: Embracing the Reality of Poly-Gene-Environmental Causation of Mental Illness." *World Psychiatry : Official Journal of the World Psychiatric Association (WPA)* 16(2):121–29.

Ulmer-Yaniv, Adi, Amir Djalovski, Avital Priel, Orna Zagoory-Sharon, and Ruth Feldman. 2018. "Maternal Depression Alters Stress and Immune Biomarkers in Mother and Child." *Depression and Anxiety* 35(12):1145–57.

Vachon, David D., Robert F. Krueger, Fred A. Rogosch, and Dante Cicchetti. 2015. "Assessment of the Harmful Psychiatric and Behavioral Effects of Different Forms of Child Maltreatment." *JAMA Psychiatry* 72(11):1135–42.

Villalonga-Olives, E., J. M. Valderas, J. A. Palacio-Vieira, M. Herdman, L. Rajmil, and J. Alonso. 2008. "The Adaptation into Spanish of the Coddington Life Events Scales (CLES)." *Quality of Life Research* 17(3):447–52.

Vining, R. F., R. A. McGinley, J. J. Maksvytis, and K. Y. Ho. 1983. "Salivary Cortisol: A Better Measure of Adrenal Cortical Function than Serum Cortisol." *Annals of Clinical Biochemistry* 20(6):329–35.

Voltas, Núria, Estefania Aparicio, Victoria Arija, and Josefa Canals. 2015. "Association Study of Monoamine Oxidase-A Gene Promoter Polymorphism (MAOA-UVNTR) with Self-Reported Anxiety and Other Psychopathological Symptoms in a Community Sample of Early Adolescents." *Journal of Anxiety Disorders* 31:65–72.

Vrshek-Schallhorn, Suzanne, Catherine B. Stroud, Susan Mineka, Constance Hammen, Richard E. Zinbarg, Kate Wolitzky-Taylor, and Michelle G. Craske. 2015. "Chronic and Episodic Interpersonal Stress as Statistically Unique Predictors of Depression in Two Samples of Emerging Adults." *Journal of Abnormal Psychology* 124(4):918–32.

Wagner, Amy W., Shireen L. Rizvi, and Melanie S. Harned. 2007. "Applications of Dialectical Behavior Therapy to the Treatment of Complex Trauma-Related Problems: When One Case Formulation Does Not Fit All." *Journal of Traumatic Stress* 20(4):391–400.

Walker, Hannah E., Rachel Wamser-Nanney, and Kathryn H. Howell. 2021. "Child Sexual Abuse and Adult Sexual Assault among Emerging Adults: Exploring the Roles of Posttraumatic Stress Symptoms, Emotion Regulation, and Anger." *Journal of Child Sexual Abuse* 30(4):407–26.

Warmingham, Jennifer M., Elizabeth D. Handley, Fred A. Rogosch, Jody T. Manly, and Dante Cicchetti. 2019a. "Identifying Maltreatment Subgroups with Patterns of Maltreatment Subtype and Chronicity: A Latent Class Analysis Approach." *Child Abuse and Neglect* 87(August):28–39.

Warmingham, Jennifer M., Elizabeth D. Handley, Fred A. Rogosch, Jody T. Manly, and Dante Cicchetti. 2019b. "Identifying Maltreatment Subgroups with Patterns of Maltreatment Subtype and Chronicity: A Latent Class Analysis Approach." *Child Abuse and Neglect* 87:28–39.

Wesarg, Christiane, Alithe L. Van Den Akker, Nicole Y. L. Oei, Machteld Hoeve, and Reinout W. Wiers. 2020. "Identifying Pathways from Early Adversity to Psychopathology: A Review on Dysregulated HPA Axis Functioning and Impaired Self-Regulation in Early Childhood." *European Journal of Developmental Psychology* 17(6):808–27.

WHO. 2003. "European Report on Preventing Child Maltreatment." *Copenhagen: World Health Organization (WHO) Regional Office for Europe*.

Wichers, M, H. H. Maes, N. Jacobs, C. Derom, E. Thiery, and K. S. Kendler. 2012. "Disentangling the Causal Inter-Relationship between Negative Life Events and Depressive Symptoms in Women: A Longitudinal Twin Study." *Psychological Medicine* 42(9):1801–14.

Wichers, M., H. H. Maes, N. Jacobs, C. Derom, E. Thiery, and K. S. Kendler. 2012. "Disentangling the Causal Inter-Relationship between Negative Life Events and Depressive Symptoms in Women: A Longitudinal Twin Study." *Psychological Medicine* 42(9):1801–14.

Widom, Cathy Spatz, Jacqueline Horan, and Linda Brzustowicz. 2015. "Childhood Maltreatment Predicts Allostatic Load in Adulthood." *Child Abuse & Neglect* 47:59–69.

Wildschut, Marleen, Sanne Swart, Willemien Langeland, Jan H. Smit, and Nel Draijer. 2020. "An Emotional Neglect-Personality Disorder Approach: Quantifying a Dimensional Transdiagnostic Model of Trauma-Related and Personality Disorders." *Journal of Personality Disorders* 34(2):250–61.

Winsper, Catherine, Tanya Lereya, Mary Zanarini, and Dieter Wolke. 2012. "Involvement in Bullying and Suicide-Related Behavior at 11 Years: A Prospective Birth Cohort Study." *Journal of the American Academy of Child and Adolescent Psychiatry* 51(3).

Winter, Sibylle M., Katja Dittrich, Peggy Dörr, Judith Overfeld, Imke Moebus, Elena Murray, Gergana Karaboycheva, Christian Zimmermann, Andrea Knop, Manuel Voelkle, Sonja Entringer, Claudia Buss, John-Dylan Haynes, Elisabeth B. Binder, and Christine Heim. 2022. "Immediate Impact of Child Maltreatment on Mental, Developmental, and Physical Health Trajectories." *Journal of Child Psychology and Psychiatry*.

Wolfe, David A., Claire C. Crooks, Debbie Chiodo, and Peter Jaffe. 2009. *Child Maltreatment, Bullying, Gender-Based Harassment, and Adolescent Dating Violence: Making the Connections*. Vol. 33. Wiley Periodicals, Inc.

World Health Organization. 2005. "The International Health Regulations."

World Health Organization. 2014. *World Health Statistics 2014*. Geneva PP - Geneva: WHO

World Health Organization. 2019. "International Statistical Classification of Diseases and Related Health Problems (ICD-11)."

Wu, Jia, Tammi Marie Phillip, Victoria Doretto, Stefon van Noordt, Tara M. Chaplin, Rebecca E. Hommer, Linda C. Mayes, and Michael J. Crowley. 2019. "An Inactive Control of the 'Trier Social Stress Test' for Youth 10–17 Years: Neuroendocrine, Cardiac, and Subjective Responses." *Psychoneuroendocrinology* 104(February):152–64.

Yehuda, Rachel, Charles W. Hoge, Alexander C. Mcfarlane, Eric Vermetten, Ruth A. Lanius, Caroline M. Nievergelt, Stevan E. Hobfoll, Karestan C. Koenen, Thomas C. Neylan, and Steven E. Hyman. 2015. "Post-Traumatic Stress Disorder." *Nature Publishing Group* (October):1–22.

Yehuda, Rachel and Amy Lehrner. 2018. "Intergenerational Transmission of Trauma Effects: Putative Role of Epigenetic Mechanisms." *World Psychiatry* 17(3):243–57.

Young-Wolff, Kelly C., Kenneth S. Kendler, and Carol A. Prescott. 2012. "Interactive Effects of Childhood Maltreatment and Recent Stressful Life Events on Alcohol Consumption in Adulthood." *Journal of Studies on Alcohol and Drugs* 73(4):559–69.

Zimmerman, Mark. 1983. "Weighted versus Unweighted Life Event Scores: Is There a Difference?" *Journal of Human Stress* 9(4):30–35.

Zorn, Jelle V., Remmelt R. Schür, Marco P. Boks, René S. Kahn, Marian Joëls, and Christiaan H. Vinkers. 2017. "Cortisol Stress Reactivity across Psychiatric Disorders: A Systematic Review and Meta-Analysis." *Psychoneuroendocrinology* 77:25–36.

8. Currículum vitae

Laia Marques Feixa
650 244 211
laiamar34@gmail.com

Psicóloga e investigadora predoctoral
Departamento de Biología Evolutiva, Ecología y Ciencias Ambientales, Facultad de Biología
Universidad de Barcelona
Av. Diagonal 643, 2A
08028, Barcelona

EDUCACIÓN FORMAL

2017 – actual. Doctorado en Biomedicina, Neurociencias – Universidad de Barcelona

2014 – 2015 Máster oficial en Neurociencias - Universidad de Barcelona
Proyecto final en el Instituto Catalán de Oncología (ICO): "Eficacia diferencial de dos tratamientos psicológicos grupales y recaída temprana del cáncer de mama: influencia de factores biopsicosociales". Supervisado por el Dr. Cristian Ochoa. Calificación: 10/10
Calificación: 8.90/10

2010 – 2014 Grado en Psicología – Universidad de Lleida
Cuarto curso realizado en la Universidad Adolfo Ibañez, Chile.
Calificación: 8.68/10

FORMACIÓN REGLADA

2020 – 2022 Postgrado de Experto en Intervención Familiar Sistémica acreditada por la FEATAF – 400 horas y 50 de supervisión. Centro de Terapia Familiar Kine. Barcelona.

2022 Formación básica en EMDR Nivel I – 24 horas. Imaya Formación.

2022 Certificación de competencia para evaluar las representaciones mentales de apego y expectativas de roles familiares a niños de 4-9 años mediante las historietas incompletas "Story Stem Assessment Profile (SSAP)" – 26 horas. Anna Freud National Centre for children and families. Londres.

2019 – 2020 Postgrado en Terapia Relacional Sistémica – 60 horas. Centro Internacional de Psicoterapia Hestia. Barcelona.

2016 – 2017 Curso de Formación de Mentores – 24 horas. Comité para la acogida de personas refugiadas de la Generalitat de Catalunya.

2016 Curso en Cómo detectar e intervenir en maltrato y abuso sexual infantil – 60 horas. TEA ediciones y Centro de Psicología Noguerol.

BECAS Y CONTRATOS DE INVESTIGACIÓN

Nombre:	**Contrato como Personal investigador.**
Organización:	Fundació Bosch i Gimpera
Lugar:	Facultad de Biología, Universidad de Barcelona
Periodo:	1 de enero 2021 – actualidad.
Actividad:	Realizar trabajos de carácter científico y técnico para el desarrollo de enseñanza o actividades especificas de formación.
Nombre:	**Contrato como Técnico en investigación.**
Organización:	Universitat de Barcelona (Grupo SGR, IP: Lourdes Fañanás)
Lugar:	Facultad de Biología, Universidad de Barcelona
Periodo:	1 de abril 2020 – 12 de diciembre de 2020.
Actividad:	Analizar datos y realizar investigación científica sobre trauma complejo, neurobiología y salud mental.
Nombre:	**Beca de Actividades formativas FI.**
Organización:	AGAUR, Generalitat de Catalunya
Lugar:	Facultad de Biología, Universidad de Barcelona
Periodo:	1 de septembre 2019 – 30 gener 2020.
Actividad:	Ayuda para realizar actividades formativas en conocimientos transversales y de relevancia R+D durante el doctorado (3.000 euros).
Nombre:	**Beca de Investigador pre-doctoral FI (B100023).**
Organización:	AGAUR, Generalitat de Catalunya
Lugar:	Facultad de Biología, Universidad de Barcelona
Periodo:	1 de abril 2017 – 31 marzo 2020.
Actividad:	Realizar un proyecto de investigación (doctorado) en un centro de investigación de calidad
Nombre:	**Contrato como Psicologa de apoyo a la investigación.**
Organización:	Universitat de Barcelona (Grupo SGR, IP: Lourdes Fañanás)
Lugar:	Facultad de Biología, Universidad de Barcelona y Unidad de Crisis de Adolescentes (UCA), Sant Boi de Llobregat.
Periodo:	1 de octubre 2015 – 31 de marzo de 2017.
Actividad:	Puesta a punto del proyecto de investigación concedido FIS15/00097. Diseño del proyecto y evaluación de los sujetos.

VINCULACIÓN A PROYECTOS CIENTIFICOS

2021-2023	Miembro investigador del proyecto financiado por la fundación Alicia Koplowitz: "Función del eje HHA y modificaciones epigenéticas como predictores del curso clínico en menores con psicopatología expuestos a maltrato infantil e investigada en la transición puberal-adolescente". (Ref: PI047268. 45.000€). IP: Dra. Soledad Romero. Hospital Clinic de Barcelona.

2020-2022 Miembro investigador del proyecto financiado por la fundación española para la Ciencia y la Tecnología (FECYT) "Sintonizando mundos: neurociencia para adolescentes (MenteScopia)". (Ref: FCT-20-16227. 25.000€). IP: Dr. Benedicto Crespo. Universidad de Sevilla.

2017-2019 Miembro investigador del equipo SGR "Genes, ambiente y desarrollo: una visión longitudinal en la comprensión del origen de la enfermedad mental y la diversidad del comportamiento humano". (Ref: 2017SGR1577. 35.014€). IP: Prof. Lourdes Fañanas. Universitat de Barcelona.

2016 – 2020 Miembro investigador del proyecto financiado por el Instituto de Salud Carlos III: "Estudio multicéntrico del maltrato infantil en niños y adolescentes con trastornos psiquiátricos: modificaciones epigenéticas y correlatos con marcadores periféricos de inmunidad innata" (Ref: PI15-20/00097. 135.520€). IP: Prof. Fañanas L. Universidad de Barcelona".

2016 - 2019 Miembro investigador del proyecto financiado por el Instituto de Salud Carlos III: "Maternal prenatal stress and HPA axis sensitization mediated by 11β-HSD2 gene epigenetic signatures and its interplay with childhood psychosocial stress in explaining risk for psychopathology in adolescence." (Ref: 35.000€). IP Prof. Fañanas L. Universidad de Barcelona.

PREMIOS RECIBIDOS

Nombre: **I Concurso de frases para el calendario de la Universidad de Barcelona.**
Organización: Seguretat, Salut i Medi Ambient, Universitat de Barcelona
Lugar y fecha: Barcelona, 14 de noviembre de 2019

Nombre: **Mejor póster científico en el VI Congreso Catalan en salud mental: trastornos de la conducta en niños y adolescentes.**
Título: Analisis de la disfuncionalidad del eje HHA en niños y adolescentes con trastornos mentales expuestos a maltrato infantil.
Organización: Fundación Congrés Català de Salut Mental.
Lugar y fecha: Barcelona, 24 de noviembre de 2017

ESTANCIAS FORMATIVAS

1. Estancia en el Servicio de Psiquiatría del Hospital Universitario Puerta de Hierro Majadahonda. Presentación y formación el contexto del proyecto EPI_young_stress. Responsable: Hilario Blasco. 12- 18 de marzo del 2016.
2. Estancia en el Servicio de Psiquiatría del niño y del adolescente en Hospital Universitario Gregorio Marañón. Formación y seminario sobre el proyecto EPI_young_stress. Responsable: Marta Rapado. 25 -27 de octubre del 2017.

PUBLICACIONES

Artículos publicados en revistas científicas internacionales

1. **Marques-Feixa L**, Moya-Higueras J, Romero S, Santamarina-PérezP, San Martín-Gonzalez N, Muñoz MJ, Anglada E, Blasco-Fontecilla H, Rapado-Castro M, Zorrilla I, Ramirez M, Fañanas L. *Reinforcing the new diagnosis of Complex Post-Traumatic Stress disorder (CPTSD) of ICD-11 in children and adolescents exposed to relational trauma: developmental stage at exposure and its associated clinical outcomes*. Submitted to Psychological Medicine. 2022.
2. Moreno N, - **Marques-Feixa L**, Castro-Quintas A, San Martin-Gonzalez N, Romero S, Fañanás L. *Childhood maltreatment and allostatic load in children and adolescents: a systematic review*. Submitted to Child abuse and neglect. 2022.
3. **Marques-Feixa L**, Castro-Quintas A, Palma-Gudiel H, Romero S, Morer, A, Rapado-Castro M, Martin, M, Zorrilla I, Blasco-Fontecilla, H, Ramirez, M, Mayoral, M, Mendez, I, San Martin-Gonzalez, N, Rodrigo-Yanguas, M, Monteserin-Garcia, JL, Fañanas, L. *Secretory immunoglobulin A (s-IgA) reactivity to acute psychosocial stress in children and adolescents: the influence of pubertal development and history of maltreatment.* Brain, behavior and immunity. 2022, 103:122-129. doi: 10.1016/j.bbi.2022.04.010
4. Ochoa-Arnedo C, Prats C, Travier N, **Marques-Feixa L**, Flix-Valle A, Medina JC, Serra-Blasco M. *Stressful Life Events and Distress in Breast Cancer: a 5-Years Follow-Up.* Journal of Clinical and Health Psychology. 2022, 22. doi: 10.1016/j.ijchp.2022.100303
5. **Marques-Feixa L**, Palma-Gudiel H, Romero S, Moya-Higueras J, Rapado-Castro M, Castro-Quintas Á, Zorrilla I, José Muñoz M, Ramírez M, Mayoral M, Mas A, José Lobato M, Blasco-Fontecilla H, Fañanás L, EPI-Young Stress Group. *Childhood maltreatment disrupts HPA-axis activity under basal and stress conditions in a dose–response relationship in children and adolescents*. Psychological Medicine. 2021, 16:1-14. doi: 10.1017/S003329172100249X.
6. **Marques-Feixa L**, Moya-Higueras J, Romero S, Santamarina-Pérez P, Rapado-Castro M, Zorrilla I, Martín M, Anglada E, Lobato MJ, Ramírez M, Moreno N, Mayoral M, Marín-Vila M, Arias B, Fañanás L, EPI-Young Stress Group. *Risk of suicidal behavior in children and adolescents exposed to maltreatment: the mediating role of borderline personality traits and recent stressful life events*. Journal of Clinical Medicine. 2021, 10(22):5293. doi: 10.3390/jcm10225293.
7. Rosa Ayesa-Arriola, Esther Setién-Suero, **Marques-Feixa L**, Karl Neergaard, Anna Butjosa, Javier Vázquez-Bourgon, Fañanas L, Benedicto Crespo-Facorro. *The synergetic effect of childhood trauma and recent stressful events in psychosis: associated neurocognitive dysfunction.* Acta Psychiatrica Scandinavica. 2019. 1-9 doi: 10.1111/acps.13114.
8. March-Llanes J, **Marques-Feixa L**, Mezquita L, Fañanás L, Moya-Higueras J. *Stressful life events during adolescence and the development of externalizing and internalizing*

psychopathology: a meta-analysis. European Child and Adolescent Psychiatry. 2017, 26:1409–1422. doi: 10.007/s00787-017-0996-9.

9. Moya-Higueras J, Cuevas S, **Marques-Feixa L**, Mezquita L, Mayoral M, Fañanás L, Ortet G, Ibáñez MI, *Stressful life events (SLE) and adolescent mental health: validation of the LEIA, a new checklist for sle assessment according to their severity, interpersonal and dependent nature*. Assessment. 2018. 1-19. doi: 10.1177/1073191118817648.

*Revisora de artículos científicos: revista Psychoneuroendocrinology (IF=4.905)

Articulos publicaciones en revistas nacionales

1. **Marques-Feixa L** & Fañanás L. *Las consecuencias neurobiológicas del maltrato infantil y su impacto en la funcionalidad del eje HHA*. Revista de psicopatología y salud mental del niño y del adolescente, Monográfico 4, Abuso Sexual Infantil. 2020. 1-24. ISSN: 1695-8691.

Comunicaciones en congresos publicadas en libros de resúmenes

1. **Marques-Feixa L**, Castro-Quintas Á, Palma-Gudiel H, Monteserín-García JL, Romero S, Rapado-Castro M, Blasco-Fontecilla H, Zorrilla I, Fañanás L (2021) *Secretory IgA reactivity to acute psychosocial stress in children and adolescents: the influence of childhood maltreatment and psychopathology*. Psychoneuroendocrinology abstracts, 131: S11. Virtual, 10 Septimebre 2021. Oral
2. Castro-Quintas A, Daura-Corral M, Eixarch E, De la fuente-Tomás L, San Martín-González N, Rocavert-Barranco M, Miguel-Valero A, Crispi F, **Marques-Feixa L**, Palma-Gudiel H, García-Portilla M, Fananas L (2021). *Cortisol diurnal changes during pregnancy and subclinical anxious-depressive maternal symptomatology: A follow-up study of the EPI_maternal_project cohort*. Psychoneuroendocrinology abstracts, 131: S2. Virtual, 9 Septimebre 2021. Oral
3. Palma-Gudiel H, **Marques-Feixa L**, Castro-Quintas A, Fananas L (2019). *The impact of puberty in HPA axis deregulation after exposure to childhood maltreatment*. Psychoneuroendocrinology abstracts, 107(S): 47. Symposium 1: How early adversities get under the skin: a behavioral epigenetics perspective across human development. Milan, 31 Agosto 2019. Oral
4. Castro-Quintas A, Daura-Corral M, De la fuente-Tomás L, Palma-Gudiel H, **Marques-Feixa L**, García-Portilla M, Fananas L (2019). *Neuroticism modulates HPA axis reactivity during the first trimester of pregnancy*. Psychoneuroendocrinology abstracts, 107: S27. Milan, 31 Agosto 2019. Póster
5. **Marques-Feixa L**, Veronica Estrada-Plana, Jaume March-Llanes, Moya-Higueras J, Fañanas L. *Cómo evaluar el maltrato infantil en niños y adolescentes.* Libro de resúmenes. Ansiedad y Estrés. XII Congreso Internacional de la Sociedad Española para el Estudio de la Ansiedad y el Estrés. Valencia, 12 septiembre 2018– SEAS. ISBN: 978-84-09-04594-5, página 177. Oral
6. Palma-Gudiel H, Córdova-Palomera A, **Marques-Feixa L**, Cirera-Miquel, F., Fananas L (2016). *Epigenetic signature of glucocorticoid receptor is associated with the familial component of depression: A twin based-study*. 24th European Congress of Psychiatry, 33S (S72-S113). Madrid, 14 Mayo 2016. Póster

PRESENTACIONES EN CONGRESOS

Comunicaciones orales

1. **Marques-Feixa L**, Moya-Higueras J, Romero S, Santamarina-Pérez P, Rapado-Castro M, Zorrilla I, Martín M, Anglada E, Lobato M J, Ramírez M, Moreno N, Mayoral M, Marín-Vila M, Arias B, Fañanás L, Epi-Young Stress Group. *Maltrato infantil, acontecimientos vitales estresantes y riesgo de conductas suicidas y parasuicidas en niños/as y adolescentes.* XXIV Congreso Nacional de Psiquiatría. Valencia, 29 octubre de 2021.
2. **Marques-Feixa L.** *El maltrato infantil desregula el funcionamiento del eje hipotálamo-hipofisario-adrenal (HHA) en niños y adolescentes: el impacto de la severidad, la frecuencia y el tipo de experiencias sufrida*. Simposio "Eventos vitales estresantes y traumáticos como factor transdiagnóstico". V Congreso Nacional de Psicología e International symposium on public health psychology. Virtual, 9-11 julio 2021.
3. **Marques-Feixa L.** *Alteraciones neurobiológicas del maltrato infantil: implicaciones en la regulación emocional y la salud mental.* XVIII Curso Intensivo de Introducción a la Investigación en Neurociencias "Actualización en la evaluación, Intervención e Investigación del maltrato infantil al principio de la vida". Virtual, 29 de junio de 2021.
4. **Marques-Feixa L,** Palma-Gudiel H, Castro-Quintas A, Anglada E, Muñoz MJ, Martin M, Rapado-Castro M, Rubio P, Romero S, Mas A, Mendez I, Santamarina-Perez P, Font E, Mayoral M, Moreno L, Moreno C, Vidal J, Carballo J, Ramos M, Blasco-Fontecilla H, Lobato MJ, Rodrigo M, Gayubo L, Zorrilla I, Laborde M, Ramirez M, Fañanas L. *The effect of maltreatment on the HPA axis dysregulation in children and adolescents with psychopathology: the impact of severity and frequency of experiences.* XXIII Congreso Nacional de Psiquiatría, Virtual, 30 de octubre de 2020.
5. **Marques-Feixa L.** *Consecuencias neurobiológicas del maltrato infantil y el abuso sexual: implicaciones clínicas.* III Simposio de Psicosomática y Psiquiatría. Barcelona, 9 de octubre de 2020.
6. **Marques-Feixa L.** Conferencia inaugural: *Consecuencias neurobiológicas y psicopatológicas del maltrato temprano.* II Jornada sobre Violencia machista y salud mental – GTRDSM. Lleida, 8 noviembre de 2019.
7. **Marques-Feixa L**, Palma-Gudiel H, Castro-Quintas Á, Anglada E, Muñoz MJ, Martín M, Rapado-Castro M, Rubio P, Romero S, Mas A, Mendez I, Santamarina-PérezP, Font E, Mayoral M, Moreno L, Moreno C, Vidal J, Carballo M, Ramos H, Blasco-Fontecilla H, Lobato M, Rodrigo M, Gayubo L, Zorrilla I, Laborde M, Ramírez M, Fañanás L. *The impact of childhood maltreatment on HPA axis responsitivity to Trier Social Stress Test (TSST): Paradoxical findings between exposed children and adolescents.* XXII Congreso Nacional de Psiquiatría. Bilbao, 27 octubre 2019.
8. Palma-Gudiel H, **Marques-Feixa L**, Castro-Quintas A, Fananas L. *The impact of puberty in HPA axis deregulation after exposure to childhood maltreatment*, IL Congress of Psychoneuroendocrinology. Milán, Italy, 29 – 31 de Agosto de 2019.
9. Palma-Gudiel H, **Marques-Feixa L**, Castro-Quintas A, Fananas L. *Proximal Exposure to Severe Childhood Maltreatment and HPA Axis Deregulation in Young Individuals.* 27th European Congress of Psychiatry EPA. Varsovia, Poland, 6-9 de abril de 2019.
10. **Marques-Feixa L**, Palma-Gudiel H, Martin M, Muñoz MJ, Laborde M, Ramírez M, Zorrilla I, Rapado-Castro M, Moreno L, Rubio P, Romero S, Méndez I, Lobato

MJ, Blasco-Fontecilla H, Fañanás L. *Exposición temprana a maltrato infantil y alteración de la respuesta del eje HHA frente una situación de estrés psicosocial en niños y adolescentes con trastorno psiquiátrico: Discordancia entre el estrés percibido y la respuesta neurofisiológica. XXI* Congreso Nacional de Psiquiatría. Granada, 18 de octubre de 2018.

11. **Marques-Feixa L**, Estrada-Plana V, March-Llanes J, Moya-Higueras J, Fañanás L. *¿Cómo evaluar el maltrato infantil en niños y adolescentes?* XII Congreso Internacional de la Sociedad Española para el Estudio de la Ansiedad y el Estrés (SEAS). Valencia, 12 de septiembre 2018.
12. Moya-Higueras J, **Marques-Feixa L**, Mezquita L, Estrada-Plana V, March-Llanes J, Fañanás L. *Meta-análisis sobre la relación de los acontecimientos vitales estresantes y la psicopatología externalizante e internalizante: conclusiones metodológicas*. XII Congreso Internacional de la Sociedad Española para el estudio de la Ansiedad y el Estrés (SEAS). Valencia, 12 de septiembre de 2018.
13. Joana-Santiveri A, **Marques-Feixa L**, Ibañez M, Ortet G, March-Llanes J, Fañanás L, Moya-Higueras J. *Estudio de la calidad psicométrica de los instrumentos de acontecimientos vitales estresantes usados en la investigación de población española en relación con los trastornos mentales*. XII Congreso Internacional de la Sociedad Española para el estudio de la Ansiedad y el Estrés (SEAS). Valencia, 11 de septiembre de 2018.
14. Ibañez, M Cuevas A, **Marques-Feixa L**, Mezquita L, Fañanás L, Ortet G, Moya-Higueras J. *Stressful life events (SLE) an adolescent mental health: validation of the LEIA, a new checklist for SLE assessment according to their severity, interpersonal and dependent nature.* XII Congreso Internacional de la Sociedad Española para el estudio de la Ansiedad y el Estrés (SEAS). Valencia, 11 de septiembre de 2018.
15. **Marques-Feixa L,** Palma-Gudiel H, Martin M, Muñoz MJ, Laborde M, Zorrilla I, Rapado-Castro M, Mayoral M, Romero S, Picado M, Santamaría P, Lobato MJ, Blasco-Fontecilla H, Fañanas L. *Estudio de lasw variaciones del cortisol diurno y de respuesta a estrés psicosocial en niños y adolescentes con trastornos psiquiátricos: influencia del desarrollo puberal, sexo e historia de maltrato.* VI laboratorio de ideas. CIBERSAM, Cádiz, 2 de mayo 2018.
16. **Marques-Feixa L**, *Factores ambientales y riesgo genético de enfermedad mental en menores.* XXVI Actualización Nacional en Psiquiatría: El reto de la recuperación en Psiquiatria. Vitoria-Gasteiz, 3 de marzo 2018.
17. **Marques-Feixa L**. *Evolución clínica de los casos de maltrato infantil hacia patologías en adolescentes*. VIII Jornadas de Unidad de Crisis de Adolescentes. Maltrato en la infancia y la adolescencia. Hospital Benito Menni, Sant Boi de Llobregat. Barcelona, 23 de febrero de 2018.
18. **Marques-Feixa L**. *Maltrato infantil: consecuencias en la salud mental y la complejidad de su estudio.* VI semana de Psicología, Universidad de Lleida. Lleida 15 febrero 2018.
19. **Marques-Feixa L**. Conferencia Inaugural: *Ambiente temprano, factores de riesgo y trastornos del comportamiento en la infancia y la adolescencia.* VI Congreso Catalán de Salud Mental. Trastornos del comportamiento en la infancia y la adolescencia. Nuevos tiempos, nuevas estrategias. Barcelona, 23 de noviembre de 2017.
20. **Marques-Feixa L**, Palma-Gudiel H, Martin M, Muñoz MJ, Laborde M, Zorrilla I, Gerez D, Rapado-Castro M, Picado M, Lobato MJ, Fañanás L. *Análisis de la disfuncionalidad del eje HHA en niños y adolescentes con trastornos mentales expuestos al maltrato infantil.* VI Congreso Catalán de Salud Mental. Trastornos del comportamiento en la

infancia y la adolescencia. Nuevos tiempos, nuevas estrategias. Barcelona, 24 de noviembre de 2017.

21. **Marques-Feixa L**, Palma-Gudiel H, Martin M, Muñoz MJ, Laborde M, Zorrilla I, Gerez D, Rapado D, Picado M, Lobato MJ, Fañanás L. *Estudio de estrés prenatal y experiencias adversas tempranas en trastornos mentales Infantojuveniles.* XX Congreso Nacional de Psiquiatría. Psiquiatría integradora e innovadora. Barcelona, del 16 a 18 de noviembre de 2017.
22. Moya-Higueras J, Joana-santiveri A, Huguet A, **Marqués-feixa L**, Cirera F, Ibáñez I, Ortet G, March J Fañanas L. *Estudio de la calidad psicométrica de los instrumentos -checklist- de sucesos vitales estresantes o traumáticos utilizados en la investigación de la población española afectada por Enfermedad Mental.* VIII Taller Banco de Instrumentos CIBERSAM- Desarrollo técnico y validación de instrumentos. Parc Sanitari Sant Joan de Déu, Sant Boi de Llobregat. Barcelona, 12 y 13 de junio de 2017.
23. **Marques-Feixa L**, Palma-Gudiel H, Martin M, Muñoz MJ, Laborde M, Zorrilla I, Gerez D, Rapado-Castro M, Picado M, Romero S, Lobato MJ, Fañanás L. *Estudio de la respuesta al estrés psicosocial y alteraciones del eje HHA en niños y adolescentes con trastornos mentales expuestos al maltrato infantil. Resultados preliminares del EPI_Young_Stress_Project (FIS PI/00097).* 5ª Edición del Laboratorio de Ideas CIBERSAM. Investigación clínica y biomédica. Santander, 1 y 2 de junio de 2017.
24. Moya-Higueras J, Ribes MI, Gallego S, Mezquita L, Villa H, Fatjó-Vilas M, **Marques-Feixa L**, Fañanás L, Ortet G. *El inventario de Sucesos Vitales en Adolescentes –ISVA-: predicción de la sintomatología internalizante y externalizante en interacción con la personalidad.* VII Jornada de Banco de Instrumentos CIBERSAM- Desarrollo técnico y validación de instrumentos. (Parc Sanitari Sant Joan de Déu, Sant Boi de Llobregat. Barcelona, 14 - 15 junio 2016.
25. Palma-Gudiel H, Córdova-Palomera A, **Marques-Feixa L**, Cirera F, Fañanás L. *Epigenetic Signature of Glucocorticoid Receptor Is Associated with the Familial Component of Depression: A Twin-Based Study.* 24th European Congress of Psychiatry. Sociedad Española de Psiquiatría. Madrid, 12 – 15 de marzo de 2016.

Presentación de pósters

1. Castro-Quintas A, Daura-Corral M, Eixarch E, Crispi F, De la Fuente L, Rocavert-Barranco M, A. Miguel-Valero, **Marques-Feixa L**, Palma-Gudiel H, Garcia-García-Portilla MP, Fañanas L. *The role of subclinical depressive symptomatology during the prenatal period in cortisol rhythm alterations and postpartum depression risk.* 30th European congress of Psychiatry (EPA). Budapest, 10 junio 2022.
2. **Marques-Feixa L**, Romero S, Moya-Higueras J, March-Llanes J, Santamarina-Perez P, Muñoz MJ, Zorrilla I, Rapado-Castro M, Blasco-Fontecilla H, E. Anglada, M. Ramírez, Fañanas L and EPI-Young Stress GROUP. *Reinforcing the new diagnosis of Complex Post-Traumatic Stress disorder (CPTSD) of ICD-11: exploring the clinical outcomes in youth exposed to complex trauma.* 30th European congress of Psychiatry (EPA). Budapest, 10 junio 2022.
3. Palma-Gudiel H**, Marques-Feixa L**, Romero S, Rapado-Castro M, Blasco-Fontecilla H, Zorrilla I, Martin M, Castro-Quintas A, JL. Monteserín-Garcia, E. Font, Ramirez M, D. Moreno, M. Marin-Vila, N. Moreno, E. Binder, Fañanas L. *Children and adolescents exposed to maltreatment already exhibit epigenetic patterns suggestive of*

heightened low-grade inflammation. 30th European congress of Psychiatry (EPA). Budapest, 10 junio 2022.

4. **Marques-Feixa L**, Castro-Quintas A, Palma-Gudiel H, JL. Monteserín-Garcia, Romero S, Rapado-Castro M, Blasco-Fontecilla H, Zorrilla I, Fañanas L. *Secretory sIgA reactivity to acute psychosocial stress in children and adolescents: the influence of childhood maltreatment and psychopathology*. 51th congress of International Society of Psychoneuroendocrinology (ISPNE). Congreso Virtual, 7-9 de septiembre 2021.
5. Castro-Quintas A, Daura-Corral M, Eixarch E, De la Fuente-Tomás L, N. San Martin-González, A. Miguel-Valero, Rocavert-Barranco M, Crispi F, **Marques-Feixa L**, Palma-Gudiel H, García-García-Portilla MP, Fañanas L. *Cortisol diurnal changes during pregnancy and subclinical anxious-depressive maternal symptomatology: A follow-up study of the Epi_Maternal_Project Cohort.* 51th Congress of International Society of Psychoneuroendocrinology, (ISPNE). Congreso Virtual, 7-9 de septiembre 2021.
6. Castro-Quintas Á, Daura-Corral M, de la Fuente-Tomás L, Miguel-Valero A, Rocavert-Barranco M, **Marqués-Feixa L**, Eixarch E, Crispi F, Palma-Gudiel H, García-Portilla MP, Fananas L. *Maternal depressive symptoms and perceived stress modulate cortisol circadian rhythm during pregnancy*. IV Congreso Nacional de jóvenes investigadores en Biomedicina. Virtual, 4-6 de noviembre de 2020.
7. Moya-Higueras J, Darraz Z, **Marques-Feixa L**, March-Llanes J, Fañanás L. *Stressful life events mediate between childhood maltreatment and psychotic-like experiences.* 27th International symposium on Controversies in Psychiatry –Violence and aggression. Virtual, 28 de setiembre de 2020.
8. **Marques-Feixa L,** Palma-Gudiel H, Romero S, Zorrilla I, Blasco-Fontecilla H, Rapado-Castro M, Castro-Quintas Á, Moya-Higueras J, March-Llanes J, Fañanás L. *The enduring effect of childhood maltreatment on HPA axis reactivity during psychological stress in children and adolescents affected and non-affected by mental disorders: the impact of severity and frequency of adverse experiences.* 27th International symposium on Controversies in Psychiatry –Violence and aggression. Virtual, 28 septiembre 2020.
9. Moya-Higueras J, Nogueras-Penabad A, Sala-Galindo P, Fernandez-Ruiz L, **Marques-Feixa L**, March-Llanes J. *Childhood traumatic experiences and pathological personality traits in poly-victimized victims of gender violence.* 27th International symposium on Controversies in Psychiatry –Violence and aggression. Virtual, 28 de septiembre de 2020.
10. Castro-Quintas Á, Daura-Corral M, de la Fuente-Tomás L, Palma-Gudiel H, **Marques-Feixa L,** Garcia-Portilla MP, Fananas L. *Anxious-depressive status during pregnancy modulate HPA axis reactivity during exposure to acute stress*. 6th CORE in mental Health seminar. Barcelona, 14 de noviembre de 2019.
11. Castro-Quintas Á, Daura-Corral M, de la Fuente-Tomás L, Palma-Gudiel H, **Marques-Feixa L**, Garcia-García-Portilla MP., Fananas L. *Neuroticism modulates HPA axis reactivity during the first trimester of pregnancy.* 49th Congress of Psychoneuroendocrinology. Milán, 29-31 de agosto 2019.
12. Castro-Quintas Á, Daura-Corral M, de la Fuente-Tomás L, Palma-Gudiel H, **Marques-Feixa L**, Soler J, Garcia-García-Portilla MP, Fananas L. *La ansiedad y el neuroticismo modulan la reactividad del eje HPA durante el embarazo.* VII Laboratorio de Ideas, CIBERSAM. Oviedo, 13 y 14 de junio de 2019.

13. **Marques-Feixa L**, Palma-Gudiel H, Castro-Quintas A, Martin M, Rapado-Castro M, Mayoral M, Zorrilla I, Ramirez M, Romero S, Mendez I, Blasco-Fontecilla H, Lobato MJ, Fañanas L. *Children and adolescents affected by psychiatric disorders exhibited lower HPA axis reactivity: the influence of sex and pubertal stage.* 27th European Congress of Psychiatry (EPA). Varsovia, Polonia, del 6 al 9 de abril 2019.
14. **Marques-Feixa L**, Palma-Gudiel H, Á., Muñoz MJ, Martin M, Rapado-Castro M, P. Rubio, Romero S, A. Mas, Mendez I, Santamarina-Perez P, E. Font, Mayoral M, L. Moreno, C. Moreno, J. Vidal, J. Carballo, M. Ramos, Blasco-Fontecilla H, Lobato MJ, M. Rodrigo, L. Gayubo, Zorrilla I, M. Laborde, Ramirez M, Fañanas L. *Differential HPA axis response to stress according to pubertal stage in children and adolescents exposed to maltreatment.* VII laboratorio de ideas, CIBERSAM. Cádiz, 2 de mayo 2018.
15. **Marques-Feixa L**, Palma-Gudiel H, Martin M, Muñoz MJ, Laborde M, Iñaki Zorrilla, Gerez D, Rapado-Castro M, Picado M, Lobato MJ, Fañanas L. *Analysis of the dysfunctionality of the HHA axis in children and adolescents with mental disorders exposed to child maltreatment*. VI Congreso Catalán de Salud Mental. Trastornos del comportamiento en la infancia y la adolescencia. Nuevos tiempos, nuevas estrategias. Barcelona, 24 de noviembre de 2017.

ACTIVIDAD DOCENTE UNIVERSITARIA

Docencia en grados o másters oficiales

1. *Infancia y factores ambientales psicosociales de vulnerabilidad para el trastorno mental*. Clase en la asignatura "Bases fisiopatològiques de les malalties neurològiques i psiquiàtriques" en el Máster en Neurociencias de la Universidad de Barcelona. 2 horas. Curso 2021-2022.

2. *Avaluació i conseqüències del maltractament infantil.* Seminario online en el máster oficial en Psicología general sanitaria. Universidad de Lleida. 2 horas. 22 de abril. Curso 2020-2021.

3. *Factores ambientales psicosociales de riesgo para la enfermedad mental: el impacto del estrés y el maltrato infantil.* Clase en la asignatura "Bases fisiopatològiques de les malalties neurològiques i psiquiàtriques" en el Máster en Neurociencias de la Universidad de Barcelona. 2 horas. 6 de noviembre. Curso 2020-2021.

4. *Evaluación y consecuencias del maltrato infantil.* Seminario online en el máster oficial en Psicología general sanitaria. Universidad de Lleida. 29 de abril. Curso 2019-2020.

5. *Factores ambientales psicosociales de riesgo para la enfermedad mental: el impacto del estrés y el maltrato infantil.* Clase en la asignatura "Bases fisiopatològiques de les malalties neurològiques i psiquiàtriques" en el Máster en Neurociencias de la Universidad de Barcelona. 2 horas. 11 de noviembre. Curso 2019-2020.

6. Profesora docente de la asignatura "Biologia I: Introducció a la Biomedicina" del Grau de Ciències Biomèdiques. Universidad de Barcelona. 16 horas. Curso 2019-2020.

7. *Experiencias adversas en la niñez como factor de riesgo de trastornos mentales en la niñez y la adultez*. Clase en la asignatura "Bases fisiopatològiques de les malalties neurològiques i psiquiàtriques" en el Máster en Neurociencias de la Universidad de Barcelona. 2 horas. Curso 2018-2019.
8. Profesora docente de la asignatura "Biologia I: Introducció a la Biomedicina" del Grau de Ciències Biomèdiques. Universidad de Barcelona. 16 horas. Curso 2018-2019
9. *Predisposició genética i trastorns mentals*. Seminario en el máster oficial en Psicología general sanitaria. Universidad de Lleida. 27 febrero. Curso 2017-2018.
10. *Maltrato en la infancia y riesgo para la enfermedad mental infantojuvenil*. Clase en la asignatura "Bases fisiopatològiques de les malalties neurològiques i psiquiàtriques" en el Máster en Neurociencias de la Universidad de Barcelona. 2 horas. Noviembre. Curso 2017-2018
11. *Maltractament i estrés infantil*. Seminario en el máster oficial en Psicología general sanitaria. Universidad de Lleida. 2 horas. Mayo. Curso 2016- 2017.

Dirección de trabajos de final de máster (TFM)

1. Título: *Childhood maltreatment and allostatic load in children and adolescents*.
   Máster: Máster de Iniciación en Investigación en Salud Mental.
   Alumna: Nerea Moreno Gamazo
   Co-dirección: Laia Marques y Lourdes Fañanás.
   Curso: 2021-2022

ACTIVIDAD DOCENTE EN ENTIDADES DEL ÁMBITO DE LA SALUD

1. *Les conseqüències del maltractament infantil en la neurobiología del cervell*. Cicle de conferències sobre Violències caps als infants i adolescents (DGAIA). Generalitat de Catalunya, consellera de Drets Socials. 3 horas. Barcelona, 10 de abril de 2022.
2. *La neurobiología del maltrato infantil*. Seminario intensivo Asociación EMDR. 4 horas. Virtual, 19 febrero de 2022.
3. *Conseqüències neurobiològiques i psicopatològiques del maltractament primerenc*. Programa de Formació per a referents en Violència Masclista dels centres de salut mental i adicccions. Parc Sanitari Sant Joan de Déu i CatSalut Generalitat de Catalunya 2 horas, Barcelona, 16 de noviembre de 2021.

DIVULGACIÓN CIENTIFICA DIRIGIDA A POBLACIÓN GENERAL O ASOCIACIONES DE AFECTADOS O FAMILIARES

Cursos y charlas

1. *Salut mental,* Fundació La marató de TV3, sessions divulgatives a centres escolars i civics. 9 horas. Barcelona, desembre 2021.
2. *Què és la salut mental?* Conferencia en el festival MENTALFEST Instituto Dominiques de l'Ensenyament. 2 horas. Barcelona, 18 de junio de 2019.
3. *Eines diagnostiques pels trastorns mentals*. Impartición de un taller en el centre cultural La casa Elizalde en el curso "Els trastorns mentals: una mirada des de la neurociència". 2 horas. Barcelona, 24 de mayo de 2018.
4. *Maltractament infantil: conseqüències sobre la salut mental i la complexitat del seu estudi.* Setmana de la Psicología. Universidad de Lleida. 4 horas. 15-16 febrero 2018.
5. *Organizadora del programa Mente Maravillosa del festival Internacional Pint of Science.* Desde el año 2016 hasta la actualdiad. 36 horas. Barcelona.

Publicación de artículos en periódicos

1. *El maltrato y las malas experiencias en la infancia pueden aumentar el riesgo de ideas y conductas suicidas en menores.* Periodico 20 minutos. 14 de enero de 2022. https://www.20minutos.es/noticia/4831673/0/maltrato-y-experiencias-adversas-en-la-infancia-pueden-aumentar-el-riesgo-de-ideas-y-conductas-suicidas-en-menores/
2. *El maltrato infantil altera la actividad del eje HHA en etapas tempranas del desarrollo*. Cibersam ISCIII. 15 septiembre de 2021. https://www.cibersam.es/noticias/el-maltrato-infantil-altera-la-actividad-del-eje-hha-en-etapas-tempranas-del-desarrollo
3. *El maltrato infantil aumenta los factores de riesgo asociados al comportamiento suicida juvenil.* Universidad de Barcelona. 16 septiembre de 2021. https://www.ub.edu/web/ub/es/menu_eines/noticies/2021/12/023.html
4. *¿Cómo afecta el maltrato, incluso leve, al cerebro de los niños?* Periodico el País. 10 de septiembre de 2021. https://elpais.com/mamas-papas/2021-09-10/como-afecta-el-maltrato-incluso-leve-al-cerebro-de-los-ninos.html
5. *El maltractament infantil augmenta el risc de comportament suïcida juvenil. Un estudi amb la UdL reclama més finançament per a l'atenció de la salut mental.* Universidad de Lleida. 16 septiembre de 2021. https://www.udl.cat/ca/serveis/oficina/Noticies/El-maltractament-infantil-augmenta-el-risc-de-comportament-suicida-juvenil/
6. *El maltractament infantil pot derivar en trastorn mental.* Periodico Segre. 16 de febrero de 2018.

ASISTENCIA A OTROS CONGRESOS O SEMINARIOS

1. Congreso Virtual Hispano-Americano Trauma, resiliencia y plenitud. 19-23 de octubre 2021.
2. Seminario de Dr. Carlos Pitillas: "Dinámicas interpersonales del trauma temprano a lo largo del desarrollo: supervivencia, transformaciones, repetición". Grup Assemblea Psicoanalitica (GAP). Barcelona, 16 de octubre de 2021.
3. XVIII Curso Intensivo de Introducción a la Investigación en Neurociencias. Actualización en la Evaluación, Intervención e Investigación del maltrato infantil al principio de la vida. Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM). Facultat de Biologia (UB). 9 horas. Virtual, 28 y 29 de junio de 2021.
4. Seminario de Dr. Jorge Barudy y Dr. Luigi Cancrini: "Diálogo sobre la infancia", Centro Internacional de psicoterapia Hestia. 6 horas. Barcelona 16 de abril de 2021.
5. Seminario de Carlos Lamas: "De la teoría del apego al modelo relacional sistémico". Centro Internacional de psicoterapia Hestia. 4 horas. Barcelona, 12 de marzo de 2021.
6. IV Curso de Psicofarmacología y Neurociencia (SEPB). Virtual, 18 junio de 2020.
7. Jornada "Reflexiones sistémicas en tiempos de pandemia". Societat catalana de Teràpia Familiar (SCTF) y Academia de ciencias mediques i de la salut. 2,5 horas. Virtual, 12 de junio de 2020.
8. Formación "Com afrontar la discriminació LGBTI+". Departament de Treball, Afers Socials i Families. Generalitat de Catalunya. 2 horas. 8 de junio de 2020.
9. Seminario de Stefano Cirillo: "Tratamiento para los trastornos de la personalidad". Centro Internacional de Psicoterapia Hestia. 6 horas. Barcelona, 15 y 22 de mayo de 2020.
10. Supervisiones clínicas con Stefano Cirillo. Centro Internacional de Psicoterapia Hestia. 2 horas. Barcelona, 21 de mayo de 2020.
11. Seminario de Alfredo Canevaro "Terapia individual sistémica y la técnica de la mochila". Centro Internacional de Psicoterapia Hestia. Barcelona, 20 de febrero de 2020.
12. VII Laboratorio de ideas para jóvenes investigadores: Inteligencia artificial en ciencias de la vida. Moderadora. CIBERSAM. Oviedo, 13 y 14 de junio de 2019.
13. XVII Curso Intensivo de Introducción a la Investigación en Neurociencias. Neuroendocrinología del trastorno mental infantojuvenil. Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM). Facultat de Biologia (UB). 6 horas. Barcelona, 10 de mayo de 2019.
14. XIV Congreso Internacional de la Infancia Maltratada: no hablar, no ver, no oir, demos visibilidad al maltrato infantil. Federación de Asociaciones para la prevención del maltrato infantil (FAPMI). Barcelona, 22-24 de diciembre de 2018.

15. IV Seminario Internacional sobre Explotación sexual Infantil y adolescente. Federación de Asociaciones para la prevención del maltrato infantil (FAPMI). Barcelona, 21 de diciembre de 2018.
16. XIII Jornadas Científicas Fundación Alicia Koplowitz. Salud mental en la adolescencia (13-17 años): Desarrollo saludable, riesgos y oportunidades. 12 horas. Madrid, 25 y 26 de octubre de 2018.
17. XVI Curso Intensivo de introducción a la Investigación básica en Neurociéncias. Estrés oxidativo e inflamación en enfermedad mental ¿Causa o consecuencia? Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM). Facultat de Biologia (UB). 6 horas. Barcelona, 27 de abril de 2018.
18. XII Jornadas científicas de la Fundación Alicia Koplowitz: Desarrollo y salud mental en la niñez: Prevención y atención temprana en Psiquiatría infantil. 12 horas. Madrid, 26 y 27 octubre 2017.
19. XV Curso Intensivo de introducción a la Investigación básica en Neurociéncias. The early origin of mental health. Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM). Facultat de Biologia (UB). 6 horas. Barcelona, 28 de junio de 2017.
20. II International symposium CIBERSAM. The early origin of mental health: Exploring maternal stress, lack of maternal care and exposure to childhood maltreatment as risk factors for mental disorders emerging during early stages in life. Facultad de Biología, Universidad de Barcelona. Barcelona, 28 de junio de 2017.
21. Actualización en psicosis de inicio en la infancia y adolescencia. CIBERSAM. Hospital Univeristari Clínic de Barcelona. 9 horas. Barcelona, 21 de abril de 2017.
22. Curso en Proactividad-Inicitativa: La competencia de pasar a la acción. Universidad de Barcelona. 12 horas. Barcelona, 30 y 31 de marzo de 2017.
23. XIV Curso Intensivo de introducción a la Investigación básica en Neurociéncias: Cannabis y Enfermedad Mental. Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM). Facultat de Biologia (UB). 6,5 horas. Barcelona, 27 de enero de 2017.
24. V Foro Internacional en Esquizofrenia. Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM). 12 horas. Madrid, 24 y 25 de noviembre de 2016.
25. IX Workshop de actualización en salud mental y drogodependencias: Infancia y adolescencia, oportunidades en la prevención de la cronicidad den la enfermededad mental. Consorci Sanitari de l'Anoia. 6 horas. Igualada, 18 de november 2016.
26. XI Jornadas científicas de la Fundación Alicia Koplowitz: Etapa perinatal y primera infancia: Prevención y atención temprana en Psiquiatría infantil. 12 horas. Madrid, 26 y 28 octubre 2016.
27. VII Workshop del banco de instrumentos de salud mental y discapacidad. Parc Sanitari Sant Joan de Déu. Sant Boi de Llobregat, 14 y 15 de junio de 2016.
28. XIII Curso Intensivo de introducción a la Investigación básica en Neurociéncias: The early origin of adult mental health. Centro de Investigación Biomédica en Red

de Salud Mental (CIBERSAM). Facultat de Biologia (UB). 6,5 horas. Barcelona, 2 y 3 de junio del 2016.

29. XII Curso Intensivo de Introducción a la Investigación bàsica en Neurociéncias: Sintomas, genes y cerebro, nuevos paradigmes en la investigación de la enfermedad mental grave. Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM). Facultat de Biologia (UB). 6,5 horas. Barcelona, 22 de abril del 2016.
30. 24th European Congress of Psychiatry (EPA). Madrid, 12-15 marzo 2016.
31. Programa de Formación para jóvenes investigadores UB. Modulo 2: Técnicas para la mejora de la investigación. 12 horas. Institut de Desenvolupament Profesional e Instituto Ciencias de la Educación (IDP-ICE). 23 -25 febrero de 2016.
32. Curs d'estadística aplicat a ciències biològiques. Organizado por la representación de los estudiantes de doctorado del Departamento de Biología Animal y celebrado en la Facultat de Biologia (UB). Barcelona, del 25 al 27 de enero de 2016.
33. Jornada de actualización en cáncer de mama: de la prevención al largo superviviente. Asociación Española contra el cáncer (AECC). 5 horas. Hospitalet de Llobregat, 16 de octubre de 2015.
34. XVIII Congreso Nacional de Psiquiatría. Sociedad Española de Psiquiatría, Santiago de Compostela, 24 – 26 de septiembre de 2015.
35. Seminario en Intervención psicológica en crisis y catástrofes. Raul Martinez Mir. Universidad de Lleida. 10 horas. Lleida, 24 julio 2014.
36. Congreso Inteligenica emocional en las organizaciones. Universitat de Lleida. 16 horas. Lleida, abril de 2012.

IDIOMAS

Català (lengua materna) – nivel C1

Español (lengua materna)

English – nivel B2.2

Ilustraciones de la portada por Laura Girona (@lgir23art)