Universitat de Lleida

Neuropsicologia i factors neurobiològics en el trastorn bipolar

Ester Mora i Claramunt

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Universitat de Lleida

TESI DOCTORAL

Neuropsicologia i factors neurobiològics en el trastorn bipolar

Ester Mora i Claramunt

Memòria presentada per optar al grau de Doctora per la Universitat de Lleida
Programa de Doctorat en Salut

Director/a
Maria Mur Laín
Eduard Vieta Pascual

Tutor/a
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Lleida 2017

La nit em deprimeix, el dia m'anima.

Somio mirant com surt i es pon la lluna

Busco les ulleres de sol

Portada: Dibuix realitzat per una persona amb trastorn bipolar que va participar en aquest projecte de recerca.

Aquest treball pretén ser la tercera tesi doctoral fruit d'una línia de recerca iniciada per la Dra. Mur l'any 2002 sobre Trastorn Bipolar consolidada a l'Hospital Universitari Santa Maria de Lleida, dins del grup de recerca de "Fonaments Biològics dels Trastorns Mentals" de l'Institut de Recerca Biomèdica de Lleida (IRB Lleida).

La Dra. Mur, una de les directores d'aquesta tesi doctoral, va presentar el seu projecte de tesi sobre neuropsicologia en el trastorn bipolar l'any 2008. El projecte de recerca va créixer i es va finançar amb una Beca de recerca de l'Institut Carlos III, Beca FIS, "Paper dels marcadors neurobiològics en la disfunció cognitiva i psicosocial en el trastorn bipolar", Nº PI 11/01956. Recentment, es va llegir la segona tesi l'any 2015 sobre reserva cognitiva en el trastorn bipolar. El projecte de tesi actual és el resultat de 8 anys de treball en els quals s'ha fet un seguiment longitudinal de la mostra inicial, s'ha augmentat la mostra pacients eutímics, s'han incorporat pacients maníacs i també s'han ampliat les proves inicials.

Durant aquest temps he pogut aprendre de diferents professionals de reconegut prestigi en el camp de la recerca en Psiquiatria. En primer lloc, he rebut la col•laboració del Professor Eduard Vieta, cap de servei de Psiquiatria de l'Hospital Clínic de Barcelona, qui a més ha sigut un dels directors d'aquesta tesi. En segon lloc, he treballat conjuntament amb la Dra. Maria J. Portella, cap del Grup de Recerca en Trastorns Psiquiàtrics de l'Institut d'Investigació Biomèdica de l'Hospital de Santa Creu i Sant Pau de Barcelona. I per últim, gràcies a la rotació externa del final de la residència vaig tenir l'oportunitat de realitzar una col•laboració a nivell internacional, concretament a la Unitat de recerca sobre els primers episodis maníacs en el centre "Orygen Youth Health Research Centre" a Melbourne (Austràlia) amb el Professor Michael Berk.

D'aquest treball se n'han publicat dos articles i un tercer que està acceptat en revistes internacionals:

- Mora E, Portella MJ, Forcada I, Vieta E, Mur M. Persistence of cognitive impairment and its negative impact on psychosocial functioning in lithium-treated, euthymic bipolar patients: a 6-year follow-up study. *Psychol Med. 2013 Jun;43(6):1187-96. (I.F.:5.491)*
- Mora E, Portella MJ, Forcada I, Vieta E, Mur M. A preliminary longitudinal study on the cognitive and functional outcome of bipolar excellent lithium responders. *Comprehensive Psychiatry. 2016 Jul 30;Volume 71, Pages 25-32. (I.F.:2.252)*

- Mora E, Portella MJ, Martinez-Alonso M, Teres M, Forcada I, Vieta E, Mur M. The impact of obesity on cognitive functioning in euthymic bipolar patients: a cross-sectional and longitudinal study. *Journal of Clinical Psychiatry 2017 (in press). (I.F.:5.408)*

També s'ha escrit un quart article, pendent de ser enviat per publicar:

- Mora E, Portella MJ, Piñol-Ripoll G, López R, Cuadras D, Forcada I, Teres M, Vieta E, Mur M. Neurotrophins, inflammation and oxidative damage as mediators of cognitive functioning in bipolar disorder.

A més, els resultats obtinguts també s'han presentat com a pòsters en congressos nacionals i internacionals:

- Mora E, Forcada I, Vidal N, Portella MJ, Pifarre J, Mur M, Vieta E. Psychosocial functioning and neuropsychology in bipolar disorder. The 15th Biennial Winter Workshop in Psychoses. Barcelona, 15-18 de novembre 2009.
- Mora E, Forcada I, Vidal N, Portella MJ, Pifarre J, Mur M, Vieta E. Neuropsychological and psychosocial impairment in euthymic bipolar patients. *The 23rd European College of Neuropsychopharmacology (ECNP).* Amsterdam, 28 d'agost-3 de setembre del 2010.
- Mora E, Forcada I, Vidal N, Portella MJ, Pifarre J, Mur M, Vieta E. Funcionalidad psicosocial y rendimiento cognitivo en pacientes bipolares eutímicos tratados con litio. *XIV Congreso Nacional de Psiquiatría.* Barcelona, 18-23 d'octubre del 2010.
- Forcada I, Mur M, Mora E, Vieta E, Bartrés-Faz D, Portella MJ. The influence of cognitive reserve on psychosocial and neuropsychological functioning in bipolar disorder. *American Psychiatric Association 167th Annual Meeting,* New York, 3-7 de maig 2014.

Revisions sobre temes relacionats amb aquesta tesi han format part de conferències, jornades i també capítols de llibres:

- Mur M, Mora E, Piñol G. Trastornos del ánimo y de la conducta en el anciano. En: Pifarré J, Piñol G, Torres G (Eds). Interrelación entre las enfermedades mentales y la patologia orgànica. Edición Lozano Faisano s. l., Barcelona, 2011: pp31-50.
- Mur M, Rotger S, Forcada I, Mora E. Impulsividad en el trastorno bipolar. En: Celma J, Abella F (Eds). La impulsividad, aplicaciones clínicas. Ediciones San Juan de Dios-Campus Docent. Barcelona, 2013: pp45-62.

Els resultats d'aquesta tesi han obtingut els següents premis:

- Premi Gestió de Serveis Sanitaris (GSS) de l'any 2009 en la categoria de titulats superiors: Mora E, Forcada I, Mur M, Vidal N i Andreu M. "Funcionalitat psicosocial i neuropsicologia en el trastorn bipolar". Convocat per GSS i el Departament de Formació continuada i lliurat l'octubre de 2010.
- 1r Premi d'investigació sanitària GSS Hospital Santa Maria en la X edició l'any 2014. Mora E, Forcada I i Mur M. "La persistència del dèficit cognitiu i el seu impacte negatiu sobre la funcionalitat psicosocial en pacients bipolars eutímics tractats amb liti: un estudi longitudinal a 6 anys".

A l'Àlex i a l'Ares,
als meus grans tresors

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Per escriure una tesi calen grans dosis d'entusiasme, il·lusió, confiança, motivació i perseverança. Amb les següents paraules vull agrair a totes aquelles persones que m'han ajudat, durant aquest llarg recorregut d'aquest projecte, encomanant-me aquests valors.

En primer lloc vull agrair als directors d'aquesta tesi, a la Dra. Maria Mur, al Dr. Eduard Vieta i a la Dra. Maria J. Portella, haver-me guiat, supervisat i encoratjat durant aquest temps.
A la Dra. Maria Mur per engrescar-me en la recerca del trastorn bipolar durant la residència. Per confiar en mi des del primer moment, per ajudar-me en tot, per sempre estar disposada a trobar un forat a l'agenda per rebre'm al seu despatx. Per ser la meva assessora, confident, guia i mestra incansable. Per ser un exemple d'organització i constància. Perquè és una de les persones més empàtiques que conec. Per mi representa una referent clínica i també personal.
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per facilitar la cerca de pacients a CSM. També vull agrair als pacients i als controls sans la seva col·laboració en l'estudi. La seva participació és imprescindible per l'avanç científic.

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1. RESUMS

RESUM

Objectiu: L'objectiu d'aquesta tesi és examinar com determinats factors neurobiològics influeixen en la disfunció cognitiva dels pacients amb trastorn bipolar eutímics. S'estudiarà a nivell longitudinal l'evolució de la cognició en la mostra i també en el subgrup de pacients excel·lents responedors a liti (ERL). S'avaluarà el rol de l'obesitat en l'evolució de la cognició. S'ampliarà la mostra afegint pacients maníacs per també estudiar el paper de les neurotrofines i de marcadors inflamatoris i d'estrès oxidatiu en les variables clíniques i en la disfunció cognitiva.

Mètode: Aquesta tesi està formada per 4 articles. El primer article és un estudi longitudinal d'una mostra de pacients amb trastorn bipolar eutímics aparellada amb controls sans (n=54) on s'analitzen variables clíniques, cognitives i funcionals en un període de seguiment de 6 anys. El segon article també és un estudi longitudinal a 6 anys de la cognició en el qual s'estudia una submostra d'excel·lents responedors a liti (n=20). En el tercer article s'estudia l'impacte de l'índex de massa corporal (IMC) sobre la cognició a nivell transversal i longitudinal (n=121). El quart article és un estudi transversal en el qual s'inclouen a la mostra anterior pacients en fase maníaca (n total=133) i s'analitzen variables clíniques i cognitives amb els nivells de biomarcadors perifèrics.

Resultats: El dèficit cognitiu en pacients amb trastorn bipolar eutímics i també en els excel·lents responedors a liti es manté estable després de 6 anys comparat amb els controls sans i es relaciona amb una pitjor funcionalitat psicosocial. La interacció de presentar trastorn bipolar i obesitat o sobrepès prediu un pitjor funcionament cognitiu a curt i a llarg termini. Els nivells més baixos de neurotrofines prediuen també un pitjor funcionament cognitiu en les funcions executives i en la memòria verbal.

Conclusions: Aquests resultats permeten comprendre més la naturalesa de la disfunció neurocognitiva en el trastorn bipolar. La persistència de la disfunció cognitiva es relaciona amb una pitjor funcionalitat psicosocial. Tot i ser ERL, aquests individus també presenten dèficit cognitiu i funcional a llarg termini. Factors neurobiològics com l'obesitat i les neurotrofines modulen la cognició. El propòsit d'estudiar els diferents factors que intervenen en la disfunció cognitiva i funcional en el trastorn bipolar és clau per desenvolupar programes de prevenció i/o d'intervenció que permetin millorar la recuperació funcional d'aquests pacients.

RESUMEN:

Objetivo: El objetivo de esta tesis es examinar cómo determinados factores influyen en la disfunción cognitiva de los pacientes con trastorno bipolar eutímicos. Se estudiará a nivel longitudinal la evolución de la cognición en la muestra y también en el subgrupo de pacientes excelentes respondedores a litio (ERL). Se evaluará el rol de la obesidad en la evolución de la cognición. Se ampliará la muestra añadiendo pacientes maníacos para también estudiar el papel de las neurotrofinas y de marcadores inflamatorios y de estrés oxidativo en las variables clínicas y en la disfunción cognitiva.

Método: Esta tesis está formada por 4 artículos. El primer artículo es un estudio longitudinal de una muestra de pacientes con trastorno bipolar eutímicos apareados con controles sanos (n=54) donde se analizan variables clínicas, cognitivas y funcionales en un periodo de seguimiento de 6 años. El segundo artículo también es un estudio longitudinal a 6 años de la cognición en el cual se estudia una submuestra de excelentes respondedores a litio (n=20). En el tercer artículo se estudia el impacto del índice de masa corporal (IMC) sobre la cognición a nivel transversal y longitudinal (n=121). El cuarto artículo es un estudio transversal en el cual se incluyen a la muestra anterior pacientes en fase maníaca (n total=133) y se analizan variables clínicas y cognitivas con los niveles de biomarcadores periféricos.

Resultados: El déficit cognitivo en pacientes con trastorno bipolar eutímicos y también en los excelentes respondedores de litio se mantiene estable después de 6 años comparado con los controles sanos y se relaciona con una peor funcionalidad psicosocial. La interacción de presentar trastorno bipolar y obesidad o sobrepeso predice un peor funcionamiento cognitivo a corto y a largo plazo. Los niveles más bajos de neurotrofinas predicen también un peor funcionamiento cognitivo en las funciones ejecutivas y en la memoria verbal.

Conclusiones: Estos resultados permiten comprender más la naturaleza de la disfunción neurocognitiva en el trastorno bipolar. La persistencia de la disfunción cognitiva se relaciona con una peor funcionalidad psicosocial. A pesar de ser ERL, estos individuos también presentan déficit cognitivo y funcional a largo plazo. Factores neurobiológicos como la obesidad y las neurotrofinas modulan la cognición. El propósito de estudiar los diferentes factores que intervienen en la disfunción cognitiva y funcional en el trastorno bipolar es clave para desarrollar programas de prevención y/o de intervención que permitan mejorar la recuperación funcional de estos pacientes.

ABSTRACT

Objective: The aim of this thesis is to examine how some factors influence cognitive dysfunction in euthymic patients with bipolar disorder. Cognition functioning was assessed twice over a 6-year period of follow-up in the sample and also in the subgroup of excellent lithium responders (ELR). The role of obesity on the evolution of cognition was evaluated. The role of neurotrophins and inflammatory and oxidative stress markers in clinical and cognitive outcome was examined.

Method: This thesis is composed of 4 papers. The first paper was a long-term study, carried out with a sample of euthymic bipolar patients and healthy matched controls (n = 54). Clinical, cognitive and functional variables were analyzed in a 6-year period of follow-up. The second paper, was also a long-term study carried out with a subsample of excellent lithium responders (n= 20). In the third paper, the impact of body mass index (BMI) on cognition cross-sectionally and longitudinally was evaluated (n=121). The fourth paper was a cross-sectional study, in which a group of patients in a manic phase was included to the previous sample (n=133) and clinical outcome and cognitive variables were analysed and peripheral biomarkers.

Results: Cognitive deficits in euthymic bipolar patients and in ELR remained stable throughout the follow-up compared to healthy controls and it was associated with poorer psychosocial functioning. The interaction of presenting bipolar disorder and obesity or overweight predicted worse cognitive functioning in a short and and long-term outcome. Lower levels of neurotrophins also predicted worse cognitive functioning in executive functioning and verbal memory.

Conclusions: These results allow a better understanding of the nature of neurocognitive dysfunction in bipolar disorder. The persistence of cognitive dysfunction is associated with poorer psychosocial functioning. Even being euthymic ERL, these individuals also present cognitive and functional decline at long term. Neurobiological factors such as obesity and neurotrophins modulate cognition. Studying the different factors involved in cognitive and functional decline in bipolar disorder is the key-factor to the develop new prevention and / or intervention programs to achieve functional recovery.

2. INTRODUCCIÓ

2.1 Introducció al trastorn bipolar

Definició

Epidemiologia

Etiologia

Diagnòstic i Classificació

Curs i pronòstic

2.1 Introducció al trastorn bipolar

Definició

El trastorn bipolar és una malaltia psiquiàtrica crònica i recurrent que consisteix en un trastorn episòdic de l'estat d'ànim, caracteritzat típicament per l'oscil·lació i la recurrència de fases (hipo)maníaques i depressives, que alteren la capacitat per mantenir el funcionament habitual diari (APA 2000; Huxley & Baldessarini 2007; Grande et al. 2016). Aquestes fases s'alternen amb períodes d'absència de signes i símptomes que es consideren períodes de remissió complerta quan són superiors a 2 mesos (APA 2013). Són els anomenats estats d'eutímia en les quals hi poden existir també símptomes subclínics residuals (Robinson & Ferrier 2006b; Berk et al. 2008; De Dios et al. 2010).

La prevalença del trastorn bipolar és variable en funció de la literatura revisada. Segons un estudi recent afecta a un 2.4% de la població (Merikangas et al. 2011). Tot i que la seva prevalença és menor que la dels trastorns depressius o d'ansietat, el trastorn bipolar provoca un major i més marcat deteriorament funcional en els pacients i una major reducció de la seva qualitat de vida (Miller et al. 2014). De fet, el trastorn bipolar constitueix la dotzena causa de discapacitat a nivell mundial en tots els grups d'edat (WHO 2008), provocant un important deteriorament de la funcionalitat psicosocial dels pacients que implica un pitjor rendiment laboral i ocupacional, així com una pitjor integració social.

A més, representa un greu problema de salut pública, i també s'hi relacionen, entre altres aspectes, una elevada morbiditat i mortalitat (Kessing et al. 2015). La taxa de mortalitat calculada és dos o tres vegades superior a la de la població general i és especialment preocupant l'elevada taxa de suïcidi (Angst et al. 2002; Crump et al. 2013). L'esperança de vida pot reduir-se entre 9 i 20 anys comparat amb la població general (Crump et al. 2013). El trastorn bipolar és responsable de la pèrdua d'anys de vida ajustats per discapacitat (anys de vida perduts + anys viscuts amb discapacitat) que representa un 7% dels trastorns de salut mental i ús de substàncies a nivell mundial (Whiteford et al. 2013); més que totes les formes de càncer o més que trastorns neurològics com l'epilèpsia i la malaltia d'Alzheimer (Merikangas et al. 2011).

Aquestes dades evidenciades les darreres dècades indiquen que la recuperació funcional del pacient és menys freqüent dels que es considerava. A diferència del que postulaven els autors clàssics com Kraepelin quan l'any 1899 distingia la demència precoç (posteriorment anomenada esquizofrènia) de la malaltia maniacodepressiva (Kraepelin 1921) (denominada l'any 1956 per Leonhard (Leonhard 1957) com a trastorn bipolar) perquè en aquesta última

s'havia descrit un curs i pronòstic més benigne, amb recuperació funcional completa entre els episodis i absència de deteriorament cognitiu.

Epidemiologia

El trastorn bipolar ha sigut identificat a totes les races i cultures i les seves característiques es repeteixen en diversos contexts geogràfics, amb variacions patoplàstiques en funció de la cultura i la personalitat individual. Les diferències de prevalença entre estudis reflecteixen probablement diferències en la metodologia i la sensibilitat dels instruments utilitzats pel diagnòstic. En un recent estudi (Merikangas et al. 2011) en el qual va analitzar 61.392 individus d'onze països, principalment Amèrica, Europa i Àsia, es va trobar una prevalença de trastorn bipolar de 2.4% (0.6% de trastorn bipolar tipus I i 0.4% en el tipus II). Dels onze països analitzats en aquest estudi, EEUU van presentar la major prevalença de trastorn bipolar en un 4.4%, mentre que l'Índia presentà la més baixa amb un 0.1%.

En general pot afirmar-se que entre el 3 i 6% de la població desenvolupa alguna forma de bipolaritat, incloent formes més lleus, com la hipomania lleu o breu o la ciclotímica (Angst 1998; Weissman et al. 1996). La major dificultat dels estudis d'incidència (número de nous casos en una població durant un període de temps) del trastorn bipolar és deguda a les dificultats diagnòstiques dels primers episodis afectius. Actualment hi ha manca d'instruments validats per detectar individus en risc de desenvolupar trastorn bipolar (Ratheesh et al. 2015). Al voltant del 50% dels casos de trastorn bipolar s'inicien amb episodis depressius (Judd et al. 2005), essent diagnosticats erròniament de Trastorn Depressiu Major i en alguns casos (35%) poden estar simptomàtics més de 10 anys fins a ser diagnosticats correctament (Hirschfeld et al. 2003). Per aquest motiu, les xifres d'incidència de trastorn bipolar solen descriure primers episodis de mania (Sherazi et al. 2006). Els estudis publicats mostren variacions de la incidència entre 1.7 i 6.2 per 100.000 habitants per any. Els últims estudis semblen indicar que la incidència està augmentant (Kennedy et al. 2005; Scully et al. 2002) i podria ser per tres motius:

-Increment real per raons genotípiques (fenomen d'anticipació genètica)

-Increment real de casos per raons fenotípiques (inducció d'hipomania o mania en pacients prèviament unipolars per generalització de l'ús d'antidepressius).

-Increment degut a canvis en els sistemes diagnòstics, amb importació de casos anteriorment classificats en d'altres categories.

L'edat d'inici del trastorn en estimacions retrospectives s'ha situat des de finals de l'adolescència fins als vint anys d'edat (Merikangas et al. 2007). El trastorn bipolar és lleugerament més freqüent en el sexe femení, augmentant la proporció de dones a mesura que predomina la depressió sobre la mania, de forma que el trastorn bipolar tipus II hi ha pràcticament dos dones per cada home; a diferència del tipus I que es distribueix igual entre homes i dones (Benazzi 2006). Les dones debuten amb major freqüència amb episodis depressiu (Robb 1999), presenten en general major nombre de recaigudes depressives (Roy-Byrne et al. 1984) i major refractarietat de les depressions. També presenten major tendència a la ciclació ràpida i a la mania disfòrica (Burt & Rasgon 2004).

Etiologia

L'etiopatogènia del trastorn bipolar és multifactorial, en la que s'integren factors genètics, neuroquímics, hormonals, neuroanatòmics, conductuals, psicològics i socials, en un model biopsicosocial de vulnerabilitat-estrès.

El substrat correspondria als factors genètics que expliquen solament una part del risc de patir la malaltia. Sobre aquest substrat hi actuarien factors ambientals d'índole biològica (lesions cerebrals, fàrmacs, canvis hormonals), psicològica (esdeveniments estressants, suport social) i inclús canvis estacionals.

Les bases neurobiològiques de la malaltia encara no estan establertes. Nombrosos estudis indiquen que factors neurobiològics com neurotrofines, citocines inflamatòries i marcadors d'estrès oxidatiu estan implicats en la patogènesi del trastorn bipolar, intervenen en la resposta al tractament psicofarmacològic (Post 2007; Kozisek et al. 2008; Berk et al. 2011); i també es troben alterats en els diferents estadis de la malaltia (Marcia Kauer-Sant'Anna et al. 2009). Aquests biomarcadors implicats en el trastorn bipolar continuen sent desconeguts i podrien explicar els mecanismes fisiopatològics de la neuroprogressió del trastorn bipolar.

Diagnòstic i classificació

El diagnòstic del trastorn bipolar es continua basant en criteris purament clínics i es fonamenta amb la presència actual o passada d'un episodi maníac o hipomaníac. Actualment es disposa de dos manuals de diagnòstics que són la "International Classification of Disease of the World Health Organization" (ICD-10; WHO 1992) i el "Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association 5th Edition, (DSM-V; APA 2013). Aquest últim es va editar durant l'any 2013, prèviament existia la quarta edició revisada (DSM-IV-

TR; APA 2000) que és la que es va utilitzar en aquesta tesi doctoral pel diagnòstic de trastorn bipolar en els pacients.

Les diferències entre les dos edicions del DSM-IV i V no han suposat diferències a l'hora d'establir el diagnòstic del trastorn. Únicament, cal destacar que en l'edició més recent (DSM-V), el trastorn bipolar constitueix una categoria independent i separada dels trastorns depressius (Vieta & Valentí 2013).

El DSM-IV-TR descriu la següent classificació, en funció del tipus d'episodi(s) que ha patit una persona al llarg de la seva vida:

-Trastorn Bipolar I: La seva característica essencial és un curs clínica caracteritzat per la presència d'un o més episodis maníacs.

-Trastorn Bipolar II: el seu curs clínic es caracteritza per l'aparició d'un o més episodis depressius majors acompanyats d'almenys un episodi hipomaníac. No es poden presentar episodis maníacs i podria semblar un trastorn bipolar més lleu. No obstant, el trastorn bipolar tipus II té un curs més crònic, es presenta habitualment associat a un o més trastorns mentals, essent els trastorns d'ansietat els més freqüents (APA 2013). La taxa de risc de suïcidi és més elevada (Vieta 2008) i els pacients passen més temps deprimits (Suppes & Dennehy 2002).

-Trastorn ciclotímic: el seu diagnòstic es basa en una alteració de l'estat d'ànim crònica i amb fluctuacions que inclou nombrosos símptomes hipomaníacs i nombrosos períodes de símptomes depressius.

-Trastorn bipolar no especificat: aquesta categoria s'utilitza quan el pacient presenta símptomes típics de trastorn bipolar però no compleix criteris per cap trastorn bipolar específic.

En ambdós casos, tant el DSM-IV-TR com el ICD-10 es basen en criteris categorials que faciliten tant a clínics com a investigadors que hi hagi una major fiabilitat diagnòstica i una millor valoració interevaluador.

Curs i pronòstic

El trastorn bipolar és una malaltia crònica i recurrent. En estudis longitudinals s'ha descrit una taxa de recurrència de 0.4 per any (Angst et al. 2003; Judd et al. 2003) i que els pacients estan simptomàtics quasi la meitat de la seva vida (Kupka et al. 2007). El risc de recurrència és una mica més alt en el trastorn bipolar tipus II i aquest risc es manté all llarg de la vida fins als 70 anys d'edat. Si bé, a més anys d'estabilitat clínica, el risc de recaiguda disminueix (Goldberg & Harrow 2004).

En diversos estudis s'ha detectat que els pacients amb trastorn bipolar, tot i aconseguir una recuperació clínica, no obtenen recuperació funcional. Es detecta que la majoria de pacients (97%) adquireixen la recuperació sindròmica entre els 6 i els 24 mesos després de l'alta hospitalària, mentre, només un 37% adquireix una recuperació funcional en el mateix període de temps (Zarate et al. 2000; Tohen et al. 2000; Strejilevich & Martino 2013).

Les manifestacions clíniques del trastorn bipolar són altament heterogènies. La seva creixen complexitat sovint està causada per l'elevada comorbiditat amb d'altres trastorns psiquiàtrics, els quals han esdevingut la regla més que l'excepció (Merikangas et al. 2007). La majoria de pacients (95%) que van respondre l'enquesta nacional de comorbiditat d'E.E.U.U. (Kessler et al. 1999) complien criteris de 3 o més trastorns psiquiàtrics al llarg de la vida. Els més comuns són els trastorns d'ansietat (Simon et al. 2004), el trastorn per l'ús d'alcohol i d'altres substàncies i el trastorn per dèficit d'atenció i hiperactivitat entre d'altres (McIntyre et al. 2004).

Finalment, i en la mateix línia, també s'ha descrit comorbiditat amb malalties mèdiques no psiquiàtriques. Autors com Kessing i col·laboradors postulen la hipòtesi que el trastorn bipolar és un trastorn de la neuroprogressió en el qual hi ha un envelliment accelerat amb l'aparició precoç de malalties mèdiques no psiquiàtriques (Kessing et al. 2015). Estudis recents han detectat un risc augmentat, entre els pacients amb trastorn bipolar, de presentar hipertensió arterial, obesitat, tabaquisme, malaltia pulmonar crònica obstructiva, diabetis tipus 2 i d'altres afectacions endocrines i migranya (McIntyre et al. 2004; Kupfer 2005; Strejilevich et al. 2015) amb un conseqüent augment de la mortalitat i reducció de l'esperança de vida degut a la mort causes naturals (malalties cardiovasculars, respiratòries i endocrines entre d'altres) en major grau que les mort per suïcidi o accidentals (Roshanaei-Moghaddam & Katon 2009; Kessing et al. 2015).

2.2 Neuropsicologia i funcionament psicosocial en el trastorn bipolar

Disfunció cognitiva en l'eutímia

Funcionament psicosocial

Estudis previs longitudinals

2.2 Neuropsicologia i funcionament psicosocial en el trastorn bipolar:

La ment i el comportament humà es defineixen a través de dos conceptes que estan interrelacionats: la cognició i l'emoció. L'estat cognitiu pot alterar el processament emocional i els canvis d'estat d'ànim afecten el funcionament cognitiu (Millan et al. 2012). Tot i aquesta associació, els dèficits cognitius no són solament una conseqüència de la pertorbació de l'ànim doncs els substrats neurobiològics subjacents són diferents.

Hi ha molts factors a part del diagnòstic i el tractament farmacològic que influencien la cognició, com per exemple els anys d'educació, l'edat, l'estat hormonal, la progressió de la malaltia i la comorbiditat tant psiquiàtrica com no psiquiàtrica. Per tant la disfunció cognitiva és un constructe complex que sobresurt dels límits tradicionals dels diagnòstics psiquiàtrics i que opera a través de múltiples dimensions i escales temporals que van des de cascades cel·lulars fins a circuïts cerebrals, i finalment la societat en la que viu un individu (Millan et al. 2012).

Disfunció cognitiva en l'eutímia

Com ja s'ha explicat anteriorment, inicialment es pensava que en el cas del trastorn bipolar no existia una disfunció cognitiva tal i com succeeix amb l'esquizofrènia (Berrios 1996). Si bé aquesta afirmació ha estat qüestionada, i durant les darreres dues dècades, s'ha produït un interès creixent per l'estudi de la funció cognitiva en el trastorn bipolar (Martínez-Arán et al. 2004). Tot i que el trastorn bipolar s'hagi associat a millor evolució cognitiva i pronòstic que l'esquizofrènia (Lewandowski et al. 2011); s'ha evidenciat que existeix afectació neurocognitiva de menor intensitat i prevalença que en l'esquizofrènia. En un meta-anàlisi (Bora et al. 2010) es va detectar que un 80% de pacients amb esquizofrènia complien criteris de dèficit cognitiu amb 1 desviació estàndard per sota la normalitat (Keefe & Fenton 2007); mentre que en el trastorn bipolar ho complien un 40%. La disfunció neurocognitiva en el trastorn bipolar afecta principalment determinades àrees com són la memòria verbal, l'atenció i velocitat de processament i la funció executiva (Robinson et al. 2006a; Torres et al. 2007; Mann-Wrobel et al. 2011; Bourne et al. 2013). Aquestes alteracions són presents, no solament als episodis aguts de la malaltia, sinó també en els períodes interepisòdics en els que el pacient roman sense símptomes, anomenats estats d'eutímia.

El perfil neuropsicològic en el trastorn bipolar encara no està ben definit degut a un nombre de variables no controlades en estudis previs, que dificulten obtenir una mostra homogènia, com

l'edat, el nivell d'educació, la història de la malaltia, la cronicitat, el nombre d'episodis previs(Robinson & Ferrier 2006a; López-Jaramillo et al. 2010; Post et al. 2012; Cardoso et al. 2015), els símptomes subclínics i els efectes de la medicació entre d'altres (Mann-Wrobel et al. 2011). En la mateixa línia, en estudis recents s'ha descrit que existeix una associació evident entre factors endocrins, metabòlics i cardiovasculars que poden modular l'evolució de la cognició (Strejilevich et al. 2015).

Atès que el trastorn bipolar és una malaltia crònica i recurrent, els estudis a llarg termini són imprescindibles per poder determinar el curs de la cognició i l'adaptació psicosocial en aquests pacients. La importància d'avaluar la funció cognitiva d'aquests pacients radica en l'impacte que poden arribar a tenir aquestes alteracions cognitives en el funcionament general del pacient. S'ha evidenciat que un pitjor rendiment cognitiu constitueix un potent predictor de pitjor funcionament psicosocial tant en estudis transversals (Dickerson et al. 2004; Martino et al. 2008; Fulford et al. 2014) com en longitudinals (Tabarés-Seisdedos et al. 2008; Martino et al. 2009; Bonnín et al. 2010).

Funcionament Psicosocial

El concepte de funcionament psicosocial és un constructe complex que implica diverses interaccions i activitats en el context personal, ocupacional i recreatiu (Zarate et al. 2000; Tohen et al. 2000). Tradicionalment han estat pocs els estudis previs que hagin avaluat funcionalitat en el trastorn bipolar, atès que no existia una escala consensuada que mesurés aquest concepte en pacients amb aquest trastorn (Martinez-Aran et al. 2007; Malhi et al. 2007). Està ben constatat que els pacients afectats de trastorn bipolar pateixen un dèficit funcional quan estan en una fase de mania, depressiva o mixta (Jansen et al. 2012). De fet, els criteris diagnòstics del DSM-IV presenten el dèficit funcional com a "conditio sine qua non" per establir la presència d'un episodi depressiu, maníac o mixt. Tot i així, estudis recents observen dèficit funcional també en els períodes d'eutímia. Paral·lelament, diferents investigadors han quantificat la taxa de recuperació funcional en el trastorn bipolar només entre el 27-40% (Tohen et al. 2000; Strakowski et al. 2000; Strejilevich et al. 2013).

Les escales utilitzades per mesurar la funcionalitat psicosocial han estat diverses i molt variades en els estudis previs (MacQueen et al. 2000). L'escala GAF (Global Assessment of Functioning Scale) ha estat una de les més utilitzades, però serveix per mesurar símptomes a més d'ajustament psicosocial i solament és una estimació global sense detallar diferents dominis necessaris per una funcionalitat òptima (Vieta et al. 2007).

Actualment es disposa de la validació de l'escala FAST (Rosa et al. 2007), que permet avaluar la funcionalitat psicosocial de forma específica en el trastorn bipolar. Es va dissenyar inicialment per avaluar funcionalitat en trastorn bipolar, però s'ha validat també per altres trastorns mentals (González-Ortega et al. 2016; Pascual et al. 2015; Rotger et al. 2014). És un instrument objectiu, de fàcil aplicació en un període curt de temps (3-6 min), dissenyat per a quantificar els canvis aconseguits amb diferents tractaments tenint en compte l'empitjorament o la millora dels símptomes maníacs o depressius. Consta de 24 ítems distribuïts en 6 àrees de funcionament: autonomia, funcionament laboral, funcionament cognitiu, finances, relacions interpersonals i oci. A més la informació aportada per familiars i/o cuidadors així com el context sociocultural del pacient també han de ser considerats per a obtenir la puntuació final de l'escala.

Durant les últimes dues dècades s'ha produït un canvi substancial en la manera de conceptualitzar els problemes associats al trastorn bipolar. Durant la dècada de 1980, els investigadors es van centrar en la millora dels tractaments psicofarmacològics per la fase aguda, concretament els símptomes maníacs. No obstant, s'ha fet evident que els problemes més importants en el tractament del trastorn bipolar no són la malaltia aguda ni la mania –que són molt perjudicials però poden controlar-se amb relativa rapidesa- sinó els símptomes depressius crònics (Post et al. 2003), el fracàs de la recuperació de la funcionalitat tot i la millora dels símptomes (Goldberg et al. 1995) i la prevenció d'episodis posteriors d'aquest trastorn altament recidivant (Sachs & Rush 2003).

En estudis recents, s'ha atribuït l'etiologia del pobre pronòstic funcional a diferents factors: la gravetat del trastorn, els símptomes afectius residuals/subclínics interepisòdics, els símptomes psicòtics, els efectes secundaris de la medicació, un baix nivell premòrbid funcional, un baix nivell educacional, l'ús de substàncies, un suport social dèbil i sobretot també la disfunció cognitiva (Sanchez-Moreno et al. 2009; Depp et al. 2012) que afecta de manera predominant a les funcions executives (Jaeger & Vieta 2007; Mur et al. 2009).

La recuperació funcional durant els últims anys s'ha convertit en un tema preocupant per la càrrega social i econòmica que representa per a la societat (Kessler et al. 2006). A la literatura trobem dos articles que han avaluat programes de rehabilitació cognitiva i recuperació funcional específics pel trastorn bipolar (Deckersbach et al. 2010; Torrent et al. 2013) amb resultats favorables. Tot i que la disfunció cognitiva persisteix, els pacients són capaços de desenvolupar més habilitats per fer front a les dificultats de la vida diària, després d'haver rebut una formació específica (Torrent et al. 2013).

Estudis previs longitudinals

Fins dates més recents, la gran majoria d'estudis sobre neurocognició i el seu impacte funcional en pacients bipolar eutímics eren transversals. A la literatura actual, hi existeix una manca real d'estudis longitudinals; cosa que, impedeix determinar l'evolució de la cognició (Balanzá-Martínez et al. 2005; Burdick et al. 2006; Mur et al. 2008; Tabarés-Seisdedos et al. 2008) i del funcionament psicosocial (Bonnín et al. 2010; Burdick et al. 2010; Martino et al. 2009) en pacients bipolars eutímics. Donat que el trastorn bipolar és una malaltia crònica i recurrent és imprescindible continuar estudiant l'evolució del rendiment cognitiu i el pronòstic funcional d'aquests individus de manera longitudinal. I així, poder clarificar la naturalesa i l'especificitat dels dèficits cognitiu i com aquests canvien al llarg del temps (Robinson & Ferrier 2006a). A més, el seguiment cognitiu d'aquests pacients esdevé crucial per poder dissenyar les intervencions psicosocials i les estratègies psicofarmacològiques més adequades per aquests pacients (Gildengers et al. 2009).

Actualment, existeix un debat sobre la hipòtesi de la naturalesa progressiva dels dèficits cognitius en el trastorn bipolar, doncs l'evidència disponible sobre els estudis longitudinals mostra resultats contradictoris (Samamé et al. 2014; Cardoso et al. 2015). Per una banda, alguns estudis longitudinals han demostrat que hi ha una persistència de dèficits neuropsicològics, no un deteriorament; i aquests s'han relacionat amb un pobre funcionament psicosocial en pacients amb trastorn bipolar eutímics (Martino et al. 2009; Bonnín et al. 2010). En la mateixa línia, també hi han estudis a llarg termini que no han trobat relació entre les variables de curs clínic com la duració de la malaltia ni la severitat dels símptomes amb la disfunció cognitiva (Normala et al. 2010; Depp et al. 2007; Gildengers et al. 2012).

D'altra banda la teoria de la neuroprogressió indica que el curs del trastorn bipolar implica recaigudes, augment de la severitat dels símptomes i de les comorbiditats mèdiques no psiquiàtriques (Kapczinski et al. 2009). D'aquesta manera la repetició d'episodis afectius pot conduir a un deteriorament cognitiu progressiu (Post et al. 2012); probablement degut a que els pacients que han tingut un debut precoç de la malaltia o més número d'episodis també disposen de menys reserva cognitiva (Stern 2009; Gildengers et al. 2013; Forcada et al. 2015).

2.3 Neurobiologia del trastorn bipolar

Excel·lents responedors a Liti: Representen un endofenotip concret?

El rol de l'obesitat: Quines són les implicacions cognitives i funcionals?

El paper de les neurotrofines i dels marcadors inflamatoris i d'estrès oxidatiu

2.3 Neurobiologia del trastorn bipolar:

Malgrat el recent augment de publicacions en aquest camp, encara es desconeixen les bases neurobiològiques del trastorn bipolar, i la seva possible relació amb la disfunció neurocognitiva que es constata durant la progressió de la malaltia. Existeix una tendència creixent a estudiar les malalties mentals com a malalties sistèmiques i es considera que processos inflamatoris, factors endocrins, metabòlics i cardiovasculars intervenen directament en l'evolució de la cognició (Strejilevich et al. 2015). D'altra banda, també s'estan cercant endofenotips per homogeneïtzar subgrups i minimitzar els factors de confusió i així aprofundir en l'estudi de la naturalesa, l'especificitat, la predisposició genètica i els mecanismes subjacents de la cognició en el trastorn bipolar (Gottesman & Gould 2003; Bora et al. 2009).
És per aquest motiu que en aquesta tesi ens centrarem en l'estudi de tres factors neurobiològics:

a) El subgrup de pacients anomenats: "excel•lents responedors a liti" (ERL).

b) El rol de l'obesitat, com a estat pro-inflamatori, en el trastorn bipolar.

c) Els biomarcadors perifèrics implicats en neurodegeneració: neurotofines, citocines inflamatòries i marcadors d'estrès oxidatiu.

a) Excel·lents responedors a liti: Representen un endofenotip concret?

Des de que John Cade, un metge psiquiatre australià, va descobrir que l'ús de les sals de liti era beneficiós pels pacients amb trastorn bipolar fa més de 60 anys (Cade 1949); el Liti continua essent el tractament estabilitzador de l'ànim de primera línia a les guies clíniques actuals (Yatham et al. 2013). Tot i no ser un fàrmac promogut per la indústria farmacèutica i a diferència de molts altres tractaments psicofarmacològics, el liti, un element de la taula periòdica, ha sobreviscut a nombroses tendències farmacoterapèutiques i segueix sent un element indispensable en l'arsenal psicofarmacològic contemporani (Schulze et al. 2010). Són molts els estudis que avalen la seva eficàcia com a agent antimaníac (Baldessarini & Tondo 2000; Malhi et al. 2009), com a tractament de manteniment i sobretot per la prevenció de recaigudes tant maníaques com depressives (BALANCE investigators and collaborators et al. 2010) i que constaten les seves propietats antisuïcides (Bowden 2000; Baldessarini et al. 2006; Goodwin et al. 2003; Malhi et al. 2013). Aproximadament un 30% presenten una excel•lent resposta amb una remissió complerta dels símptomes en poblacions de pacients descendents de població Europea (Garnham et al. 2007; Rybakowski & Suwalska 2010).

El primer a introduir el terme "excel·lents responedors a liti" fou Paul Grof, un metge psiquiatre canadenc, que l'any 1999 (Grof 1999) va descriure un subgrup de pacients que no tenien recurrències des de que prenien tractament amb liti en monoteràpia i presentaven una restitució "ad integrum", restablint el seu funcionament psicosocial previ.

Diferents estudis han descrit factors predictors de bona resposta al tractament amb liti com l'edat tardana d'aparició del trastorn, els antecedents familiars de trastorn bipolar i presentar bona adherència farmacològica (Kleindienst et al. 2005) suggerint que aquest subgrup de pacients sembla agrupar-se en famílies (Grof et al. 2002; Cruceanu et al. 2009).

Durant els últims anys, trobem a la literatura cada vegada més publicacions que intenten dilucidar els factors clínics i genètics associats a l'eficàcia del tractament amb liti (Rybakowski 2014). L'any 2002, un grup d'investigadors canadencs van crear una escala que permet quantificar de manera retrospectiva la resposta clínica al Liti. La resposta al tractament s'avalua mitjançant l'escala Alda de 11 punts (veure annex 2) que mesura el grau de millora durant el tractament a llarg termini i també mesura la importància dels factors clínics que es considerin rellevants per a determinar si la millora observada es deu al tractament amb liti o no (Grof et al. 2002; Schulze et al. 2010). En estudis previs una puntuació de 7 o superior es va considerar > 90% de reducció de l'activitat de la malaltia (Chen et al. 2014).

D'altra banda, l'impacte del tractament amb liti sobre la cognició encara genera controvèrsia en quant als possibles efectes neuroprotectors vs neurotòxics d'aquest fàrmac (Fountoulakis & Vieta 2008). No obstant, existeix un consens en el qual una excel·lent resposta al tractament amb liti pot ser un dels millors marcadors biològics disponibles en l'actualitat (Malhi et al. 2013).

En aquest sentit, un estudi transversal del nostre grup de pacients bipolars eutímics en tractament amb liti en monoteràpia va constatar que les funcions executives estaven afectades de manera similar en comparació amb els pacients eutímics amb tractaments combinats (incloent el liti) (Mur et al. 2007). A la literatura trobem escasses dades publicades sobre estudis longitudinals sobre pacients amb liti en monoteràpia a llarg termini i el seu impacte sobre el funcionament cognitiu. Per tant, la investigació de les característiques clíniques, el perfil neuropsicològic i els factors neurobiològics d'aquest relativament rar però subgrup sensible al tractament esdevé essencial (Malhi et al. 2013).

b) El rol de l'obesitat: quines són les implicacions cognitives i funcionals?

L'obesitat és la condició del cos en la qual la quantitat de greix acumulat comporta risc per la salut, reduint l'esperança de vida de l'individu (OMS, 2000). Es considera sobrepès quan un individu presenta un índex de massa corporal (IMC) entre 25 i 29.9 kg/m^2 i obesitat quan l'IMC és superior a 30 kg/m^2 (National Heart LaBI 1998).

Es considera que el sobrepès i l'obesitat corresponen a un estat pro-inflamatori crònic de l'organisme creat per les secrecions del teixit adipós com hormones i citocines que poden alterar l'eix hipotàl·lem-pituïtari-adrenal, el sistema serotoninèrgic i/o la neurogènesi (Naderali i cols., 2009). Totes aquestes dades suggereixen que l'obesitat de manera independent pot afectar les funcions cerebrals; tant en individus sans (Cohen 2010) com en trastorns mentals com l'esquizofrènia (Friedman et al. 2010) i també en el trastorn bipolar (Yim et al. 2012; Depp et al. 2014; Lackner et al. 2015).

S'estima una prevalença d'obesitat entre pacients amb trastorn bipolar d'un 60% (McElroy et al. 2002; Fagiolini et al. 2003). A més l'obesitat i altres factors de risc cardiovascular impacten negativament sobre les manifestacions clíniques, el curs i el pronòstic de la malaltia (Depp et al. 2014). L'obesitat i el trastorn bipolar estableixen una relació bidireccional evidenciada per alteracions en l'estructura i funció del sistema nerviós central, a més d'una major risc de recurrència de clínica depressiva, de disfunció cognitiva i de risc de suïcidi (Liu et al. 2013).

Els estudis clínics que han avaluat aquesta qüestió en el trastorn bipolar són escassos i transversals (Yim et al. 2012; Depp et al. 2014; Lackner et al. 2015). Aquests tres estudis troben que la velocitat de processament (Yim et al. 2012), la memòria verbal (Lackner et al. 2015), la resolució de problemes i el manteniment de l'atenció (Depp et al. 2014; Lackner et al. 2015) són les àrees cognitives més afectades en les respectives mostres de pacients amb trastorn bipolar. Actualment no trobem estudis longitudinals que hagin avaluat aquesta associació i es requereixen més estudis per conèixer de manera més sòlida quins són els mecanismes subjacents i les implicacions cognitives i funcionals de l'obesitat en el trastorn bipolar.

c) El paper de les neurotrofines i dels marcadors inflamatoris i d'estrès oxidatiu

Continuant amb la recerca de les bases neurobiològiques del trastorn bipolar, nombrosos estudis s'han centrat a investigar diferents factors neurobiològics com les proves de neuroimatge, els estudis genètics i els biomarcadors perifèrics (Post 2010; Frey et al. 2013). En aquesta tesi ens centrarem en l'estudi d'aquests últims.

Els biomarcadors són característiques biològiques mesurables que s'associen a un procés patogènic o a una resposta al tractament (Atkinson et al. 2001). En molts camps de la medicina s'han descrit biomarcadors que han permès avançar en el diagnòstic i tractament; desafortunadament en el camp de la psiquiatria encara no. Donat que s'està avançant cap a una medicina més personalitzada i amb el disseny individualitzat de les intervencions terapèutiques (Pasco et al. 2010), és necessari identificar biomarcadors psiquiàtrics útils per millorar la pràctica clínica.

Un creixent nombre d'estudis indiquen que mecanismes de neuroprotecció com les neurotrofines (Brain-derived neurotrophic factor (BDNF): factor neurotròfic derivat del cervell) i de neurodegeneració com les citocines inflamatòries (interleuquina-6 (IL-6), interleuquina 10 (IL-10) i factor de necrosi tumoral α (TNF-α)) i els marcadors d'estrès oxidatiu (Thiobarbituric acid reactive substances (TBARS): substàncies reactives a l'àcid tiobarbitúric) estan implicats en la patogènesi del trastorn bipolar (Duman & Monteggia 2006), intervenen en la resposta al tractament psicofarmacològic (Post 2007; Kozisek et al. 2008; Berk et al. 2007) i també es troben alterats en els diferents estadis de la malaltia (Kauer-Sant'Anna et al. 2009).

En la mateixa línia estudis clínics i també de ciències mèdiques bàsiques suggereixen que la repetició d'episodis afectius altera l'homeòstasi entre els mecanismes neuroprotectors i de neurodegeneració conduint a la mort neuronal (Berk et al. 2011; Fries et al. 2012). Aquest cicle d'esdeveniments constitueix un fenomen de neuroprogressió i s'ha relacionat amb un augment de la vulnerabilitat individual a l'estrès psicosocial, a l'atròfia cerebral i últimament també a la disfunció cognitiva (Berk et al. 2010; Kapczinski et al. 2008).

A continuació es detallaran els mecanismes d'acció i la seva relació amb el trastorn bipolar de cadascun dels biomarcadors:

i. El **BDNF** constitueix un grup de proteïnes encarregades de la supervivència neuronal i el funcionament sinàptic (Huang et al. 2012). Fou aïllat per primera vegada (Barde et al. 1982) l'any 1952 en el descobriment del factor de creixement nerviós (Levi-Montalcini et al. 1954). L'any 1997, Dumann, Heniger i Nestler (Duman et al. 1997) varen formular la hipòtesi neurotròfica caracteritzant el trastorn depressiu major com a una conseqüència d'una neurogènesi aberrant en les regions del cervell que regulen l'emoció i la memòria i que s'associava a una expressió de BDNF més baixa.

Aquesta neurotrofina es presenta en altes concentracions en l'escorça cerebral i en l'hipocamp (Post 2007), però també en la sang perifèrica, on essencialment s'emmagatzema en plaquetes, i existeix una forta associació entre els nivells de BDNF en sang i en el cervell (Martinowich & Lu 2008). Inicialment, es varen dur a terme estudis clínics de nivells de BDNF perifèrics amb trastorn depressiu (Karege et al. 2002) i també amb esquizofrènia (Toyooka et al. 2002). Posteriorment, s'ha demostrat la seva relació amb variables clíniques, atès que els nivells cerebrals de BDNF disminueixen durant els episodis maníacs (Laske et al. 2005) i depressius, correlacionant negativament amb la gravetat dels símptomes i augmenten després del tractament agut d'una descompensació (Palomino et al. 2006). No obstant això, existeixen discrepàncies en els resultats de BDNF durant la eutímia, on alguns estudis afirmen que tornen a aconseguir els nivells normals, sense arribar a presentar diferències significatives amb els controls (Tramontina et al. 2007) i uns altres afirmen una reducció del BDNF en els pacients amb trastorn depressiu o bipolar eutímics independentment del tractament (Monteleone et al. 2008). També s'ha descrit que els nivells de BDNF correlacionarien negativament amb els anys de durada del trastorn bipolar, constituint un potencial marcador de l'evolució de la malaltia (Kauer-Sant'Anna et al. 2009).

El BDNF està altament expressat en estructures cerebrals que regulen funcions cognitives complexes (Duman & Monteggia 2006; Post 2007). En un principi es va estudiar el BDNF amb l'objectiu d'entendre la fisiopatologia dels trastorns de l'estat d'ànim; no obstant, durant el últims anys, s'ha postulat el BDNF com a un biomarcador potencial en el camp de la medicina personalitzada en psiquiatria (Frey et al. 2013).

Alguns estudis suggereixen que el sistema BDNF podria estar implicat en el dèficit neurocognitiu observat en certs trastorn neuropsiquiàtrics, com a esclerosi múltiple (Caggiula et al. 2005); malaltia d'Alzheimer (Laske et al. 2006); demència de cossos de Lewy (Imamura et al. 2005) i trastorns de l'humor (Shaltiel et al. 2007). Tot i així, encara hi ha evidència controvertida sobre la seva relació amb la disfunció cognitiva demostrada en la progressió del trastorn bipolar (Dias et al. 2009; Lee et al. 2016; Cao et al. 2016).

ii. D'altra banda, existeix evidència sobre la implicació de la respostes immunitàries i inflamatòries en el trastorn bipolar (Brietzke & Kapczinski 2008). Les citocines són petites proteïnes solubles segregades per cèl·lules que actuen com a mediadors

intercel·lulars i que produeixen creixement, diferenciació i/o activació en elles mateixes o en altres cèl·lules; així com l'activació de receptors específics de membrana (Czéh & Lucassen 2007). En el trastorn bipolar trobem un augment perifèric d'agents proinflamatoris com les interleuquines (IL-6, IL-2R, IL-1β), el TNF-α i la proteïna C reactiva (PCR; C reactive protein: CRP); en contraposició dels agents antiinflamatoris, com per exemple la IL-10 que està disminuïda (Kapczinski et al. 2011). Aquest increment perifèric de la inflamació es tradueix en un procés de neuroinflamació; en el qual les citocines travessen la barrera hematoencefàlica i arriben al cervell on indueixen processos inflamatoris com un augment de monòcits i macròfags, una alteració de la neurogènesi i una reducció de la gliogènesi (veure Figura 1) (Bauer et al. 2014). Aquestes troballes també s'han correlacionat/constatat en estudis de neuroimatge on el pacients amb trastorn bipolar presenten pèrdua significativa del volum de substància gris i de la integritat de la substància blanca (Frey et al. 2008).

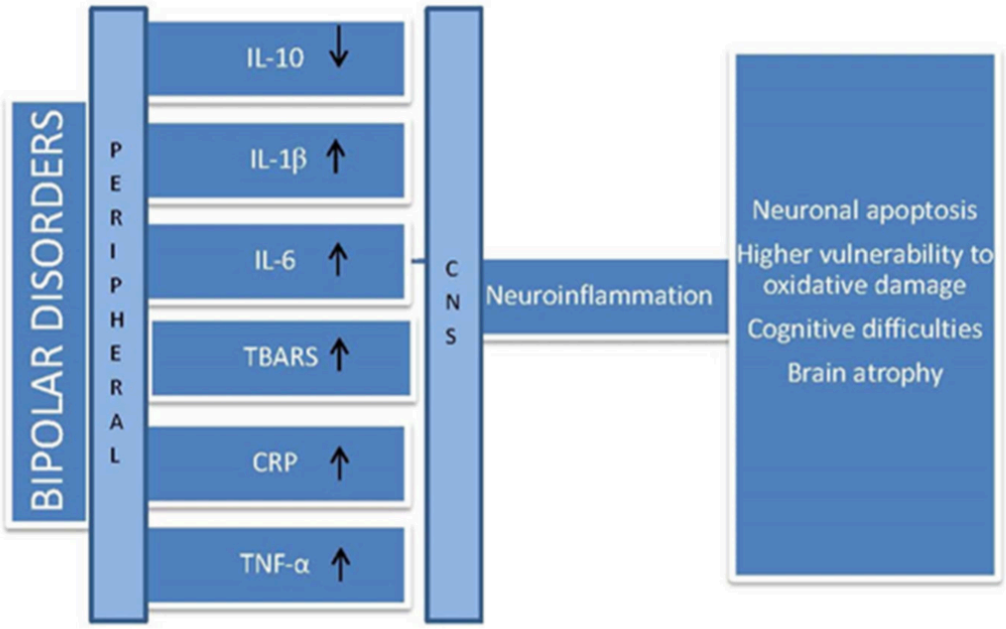

Figura 1. Agents inflamatoris que arriben al Sistema Nerviós Central a través de la barrera hematoencefàlica i activen l'alliberació d'agents inflamatoris, monòcits i macròfags al cervell. L'exposició a substàncies proinflamatòries està associada al dany neuronal i a la disfunció cerebral (extret de Bauer et al., 2014)

Estudis recents descriuen un augment de citocines proinflamatòries (TNF-α i IL-6) durant els episodis de mania i de depressió (Kim et al. 2007). Aquest augment també s'ha detectat en els períodes de eutímia tant en etapes primerenques com en etapes tardanes de la malaltia comparat amb controls sans; a diferència de la citocina antiinflamatòria IL-10 que només augmentava en edats primerenques (Kauer-Sant'Anna et al. 2009). També s'han relacionat alteracions inflamatòries amb la severitat del trastorn (Barbosa et al. 2013), les altes taxes de comorbiditat (Leboyer et al. 2012) i l'efecte dels fàrmacs (Nery et al. 2008). Concretament, diversos estudis suggereixen que el mecanisme d'acció dels estabilitzadors de l'ànim indueix una inhibició de la ciclooxigensa 2 (COX-2) i una reducció de les citocines inflamatòries. En concret, s'ha descrit una disminució de IL-10 en pacients bipolars eutímics en tractament amb liti (Boufidou et al. 2004) comparat amb controls.

Paral·lelament, a la literatura trobem que l'augment de citocines proinflamatòries van ser associats amb una alteració en l'aprenentatge espaial en estudis preclínics (Larson & Dunn 2001). En la mateixa línia, un augment de TNF-α es va associar amb un deteriorament cognitiu en d'altres trastorns com la malaltia d'Alzheimer (Tobinick et al. 2006) o en pacients amb VIH (Seilhean et al. 1997). Malgrat la possibilitat que les citocines siguin mediadores de la disfunció cognitiva, trobem pocs estudis que avaluïn aquesta relació en el trastorn bipolar (Brietzke & Kapczinski 2008; Bauer et al. 2014).

iii. Finalment, estudis recents han descrit una forta associació entre l'estrès o dany oxidatiu i el trastorn bipolar (Andreazza et al. 2008; Berk et al. 2011; Kapczinski et al. 2011). L'estrès oxidatiu està causat per un desequilibri entre la producció d'espècies reactives de l'oxigen i la capacitat per reparar el dany provocat. Succeeix quan espècies reactives d'oxigen interaccionen amb lípids, proteïnes i àcids nucleics i és un mecanisme de dany cel·lular implicat en malalties neoplàsiques, estats inflamatoris i també en la neurodegeneració (Opara 2006). El sistema nerviós central és molt vulnerable al dany oxidatiu, degut al seu alt consum d'oxigen que genera de radicals lliures i també per la seva baixa capacitat antioxidant (Olmez & Ozyurt 2012). L'augment de l'estrès oxidatiu té efectes negatius en la transmissió de senyal i la plasticitat i resiliència cel·lular (Khairova et al. 2012).

Com a paràmetres de dany oxidatiu es poden utilitzar els nivells de peroxidació lipídica (thiobarbituric acid reactive substances (TBARS)) descrit per Wills (Wills 1966).

Estudis recents descriuen un augment de TBARS en pacients amb trastorn bipolar en episodis maníacs i depressius comparat amb pacients eutímics i amb controls (Andreazza et al. 2008; Kapczinski et al. 2011). Aquests autors suggereixen que l'estrès oxidatiu també podria estar relacionat amb la persistència de la disfunció cognitiva dels pacients amb trastorn bipolar.

Durant l'última dècada, s'han proposat diferents mecanismes fisiopatològics per comprendre la interacció d'aquests biomarcadors amb la simptomatologia afectiva del trastorn bipolar (Rosenblat et al. 2015); si bé, són pocs els estudis que hagin investigat la relació de la neuroplasticitat, la inflamació i l'estrès oxidatiu amb la cognició en aquest trastorn (Stewart et al. 2009; Barbosa et al. 2014; Khandaker et al. 2014; Rosenblat et al. 2015).

2.4 Justificació de l'estudi

2.4 Justificació de l'estudi

Com ja s'ha explicat prèviament, el trastorn bipolar és una malaltia crònica i invalidant, que pot causar un funcionament psicosocial deficient a les persones afectades i la disfunció cognitiva n'és un factor clau (Green 2006; Tse et al. 2014).

Durant els últims anys s'ha constatat que aquesta disfunció cognitiva dels pacients amb trastorn bipolar no es limita solament a les fases maníaques o depressives, sinó que persisteix també en els períodes de remissió clínica (Robinson et al. 2006a). En concret, els estudis suggereixen que la disfunció executiva i la memòria verbal esdevindrien el dèficits principals (Kolur et al. 2006; Mur et al. 2007; Robinson et al. 2006a; Torres et al. 2007; Bourne et al. 2013). Malgrat l'augment de publicacions en aquest tema, el perfil de rendiment cognitiu del trastorn bipolar, la seva etiologia i la seva relació amb la progressió de la malaltia i el pronòstic funcional segueix sense estar establerta.

La disminució en el rendiment cognitiu d'aquests pacients representa un problema clínic d'alta magnitud. Malauradament, són pocs els estudis longitudinals que analitzin l'evolució de la disfunció neurocognitiva al llarg del temps. A la literatura no trobem estudis longitudinals que hagin avaluat l'impacte de l'obesitat sobre la cognició ni tampoc l'evolució cognitiva en el subgrup de pacients excel·lents responedors de liti. Per tant, és necessari estudiar quines són les variables clíniques, neurobiològiques i psicosocials implicades en la persistència del dèficit cognitiu en el trastorn bipolar a llarg termini.

Els factors neurobiològics, i la seva relació amb variables clíniques, també han estat objecte d'estudi darrerament en el trastorn bipolar. Entre ells destaquen les neurotrofines, les citocines inflamatòries i els marcadors d'estrès oxidatiu com a principals factors implicats en la fisiopatologia del trastorn (Kapczinski et al. 2011). Tot i la possibilitat que els biomarcadors siguin mediadors de la disfunció cognitiva, trobem pocs estudis i amb resultats contradictoris entre ells que avaluïn aquesta relació (Brietzke & Kapczinski 2008; Rosenblat et al. 2015). La detecció de marcadors perifèrics com a mediadors d'algun tipus de disregulació cel·lular o toxicitat podria ser rellevant per entendre la fisiopatologia de la malaltia i podrien constituir un marcador del grau de la disfunció cognitiva.

Per tant, l'objectiu del nostre treball és estudiar la disfunció neurocognitiva en el trastorn bipolar donat que representa un dels majors obstacles per la recuperació funcional d'aquestes persones (Senturk et al. 2007). Per aquest motiu s'ha dissenyat un primer estudi amb una mostra de pacients bipolars i una altra de controls sans; en la qual s'ha realitzat una avaluació

longitudinal a 6 anys de la cognició amb una bateria neuropsicològica complerta, l'estat clínic i la funcionalitat psicosocial. Paral·lelament, s'han dissenyat un segon i tercer estudis per avaluar el subgrup de pacients excel·lents responedors a liti i també el rol de l'obesitat sobre la cognició a nivell transversal i longitudinal. Per últim, s'ha augmentat la mostra afegint pacients maníacs i així també poder estudiar el paper de les neurotrofines i els marcadors inflamatoris i d'estrès oxidatiu en les variables clíniques i en la cognició.

És de cabdal importància conèixer quins d'aquests factors intervenen, i de quina manera, en el funcionament cognitiu dels pacients amb trastorn bipolar. Aquests resultats podrien revelar potencials mecanismes de neurodegeneració i explicar el dèficit cognitiu. D'aquesta manera es podrien dissenyar estratègies de prevenció i intervencions específiques no només per tractar els símptomes sinó també per revertir els canvis biològics associats a la malaltia (Pfaffenseller et al. 2013) com el dèficit cognitiu i la seva repercussió funcional, per contribuir a que les persones afectades tinguin millor qualitat de vida (Leboyer & Kupfer 2010).

3. OBJECTIUS I HIPÒTESIS

3.1 Objectius

Objectiu principal:

1) Establir la contribució dels factors neurobiològics en la disfunció cognitiva en una mostra de pacients bipolars eutímics comparat amb una mostra de controls sans a nivell transversal i longitudinal a 6 anys.

Objectius secundaris:

2) Avaluar el perfil de rendiment cognitiu en una avaluació transversal basal i longitudinal a 6 anys en una mostra de pacients bipolars eutímics comparat amb una mostra de controls sans.

3) Avaluar el perfil de rendiment cognitiu transversal i longitudinal a 6 anys d'una submostra de pacients bipolars eutímics "excel·lents responedors a liti" comparat amb una mostra de controls sans.

4) Estudiar la implicació de l'índex de massa corporal sobre la disfunció cognitiva a nivell transversal i longitudinal a 6 anys.

5) Descriure les característiques clíniques i funcionals que s'associïn al dèficit cognitiu al llarg del temps.

6) Determinar la relació entre els biomarcadors perifèrics (neurotrofines i marcadors inflamatoris i d'estrès oxidatiu) i les diferents variables clíniques i neuropsicològiques en pacients bipolars i controls sans.

3.2 Hipòtesis

Aquest treball defensa les següents hipòtesis:

1) La disfunció cognitiva en pacients bipolars eutímics romandrà estable als 6 anys i s'associarà a una pitjor funcionalitat psicosocial.

2) El subgrup de pacients "excel·lents responedors a liti" també presentaran disfunció cognitiva en el seguiment longitudinal comparat amb controls sans.

3) L'obesitat explicarà part de la disfunció cognitiva dels pacients bipolars eutímics a nivell transversal i també longitudinal.

4) Els biomarcadors mostraran relació no únicament amb la fase del trastorn, sinó també amb la disfunció cognitiva.

4. METODOLOGIA

Aquesta tesi està formada per quatre articles, un primer publicat al *Psychological Medicine*, un segon també publicat a la revista *Comprehensive Psychiatry* i un tercer article acceptat al *Journal of Clinical Psychiatry*. El quart article està pendent de ser enviat per la seva possible acceptació a una revista internacional.

En aquest apartat es realitza una descripció general del disseny dels articles, de les mostres i de les seves característiques, així com les variables clíniques, cognitives i neurobiològiques avaluades a cadascun d'ells. De la mateixa manera també es farà una breu explicació de la metodologia estadística emprada. Tota aquesta informació consta de manera més detallada a cada article, que s'adjunten a posteriori.

4.1 Disseny dels articles

Els tres primers articles són estudis on s'avalua cognitivament una mostra de pacients bipolars i de controls sans aparellats, en el moment basal i passats 6 anys. S'analitza la relació de la cognició amb les variables clíniques i funcionals (article 1); també amb factors neurobiològics com ésser "excel·lent responedor a liti" (article 2) i amb l'índex de massa corporal (article 3) en una mostra de pacients bipolars eutímics aparellats amb controls sans. En aquest tercer també s'amplia la mostra i s'afegeixen resultats a nivell transversal sobre l'impacte de l'obesitat en la cognició.

L'article 4 és un estudi transversal en el qual també s'incorporen pacients maníacs i s'avalua l'associació de les neurotrofines i dels marcadors inflamatoris i d'estrès oxidatiu amb les variables de curs clínic i la disfunció cognitiva.

4.2 Subjectes a estudi

4.2.1 Per respondre la hipòtesi 1:

Es va reclutar una mostra de 28 pacients amb trastorn bipolar eutímics, a través del Programa de la Clínica de Liti de l'Hospital Universitari Santa Maria de Lleida. A la taula 1 es mostren els criteris d'inclusió i exclusió de la mostra.

Aquesta mostra de pacients es va aparellar per edat, sexe i anys d'educació amb una mostra de 26 controls sans que varen ser reclutats amb anuncis. Els controls no havien de tenir història actual ni prèvia de malaltia mental, determinant-se amb "l'Entrevista Clínica Estructurada pels trastorns de l'Eix I del DSM-IV, SCID-I" (First et al. 1999). No tenien familiars de primer grau amb diagnòstic de trastorn bipolar ni trastorn psicòtic. Es varen utilitzar els mateixos criteris d'exclusió que s'havia utilitzat per a la mostra de pacients.

La mostra inicial consistia en 90 individus (44 pacients bipolars eutímics i 46 controls sans) tal i com es va publicar prèviament (Mur et al. 2007). Després d'un interval de 6 anys es va contactar amb tots ells i un total de 28 pacients eutímics i 26 controls sans aparellats per edat, sexe i anys d'educació (n=54) van acceptar a ser revaluats. L'estudi fou aprovat pel Comitè Ètic del nostre centre i es va obtenir el consentiment informat de tots els participants. De la mostra inicial, 16 no complien criteris d'inclusió: 6 degut a la seva situació clínica actual (mèdica i/o psiquiàtrica) i 10 perquè varen rebutjar tornar a participar a l'estudi.

Taula 1. Criteris d'inclusió i exclusió de la mostra

Criteris d'inclusió	Criteris d'exclusió
Pacients procedents del Centre de Salut Mental de Lleida, i que compleixin criteris DSM-IV-TR per trastorn bipolar tipus I o II	Pacients que no hagin estat estabilitzats durant un període mínim de tres mesos
Edat compresa entre 18 i 65 anys	Pacient amb antecedent de patologia no psiquiàtrica greu.
En fase d'eutimia definida per una puntuació a la HAM-D ≤8 i a la YMRS≤6 durant els darrers 3 mesos.	Tractament amb teràpia electroconvulsiva l'any anterior
El pacient ha de lliurar el seu consentiment informat per escrit, seguint els criteris del Comitè d'Ètica i d'Investigació del nostre centre	Abús o dependència de substàncies durant el moment de l'estudi o durant l'any abans de la inclusió

4.2.2 Per respondre la hipòtesi 2:

Es varen seleccionar el subgrup de pacients excel·lents responedors a liti (n=10) de la mostra de pacients que havien acceptat a fer el seguiment longitudinal i es van aparellar amb deu controls sans per edat, sexe i anys d'educació (n total=20).

Donat que els excel·lents responedors a liti comprenen un terç dels pacients tractats amb liti (Rybakowski et al. 2001), es va determinar la mida de la mostra per detectar diferències en els tests neuropsicològics entre pacients amb trastorn bipolar i controls sans. La mida de la mostra necessària per detectar diferències significatives estandarditzades (Cohen's d=1.05) amb una potència estadística de 0.8 i un interval de confiança de 95% (Whitley & Ball 2002) fou de 20 participants.

La resposta al tractament amb liti es va avaluar amb l'escala Alda d'onze punts (veure annex 2) que mesura el grau de millora durant el tractament a llarg-termini i considera els factors clínics rellevants per determinar si la millora observada és deguda al tractament amb liti o no (Grof et al. 2002; Schulze et al. 2010) En estudis previs la puntuació de 7 o superior s'ha considerat a un augment superior al 90% de la reducció de l'activitat de la malaltia (Chen et al. 2014; Squassina et al. 2011).

4.2.3 Per respondre la hipòtesi 3:

L'article per estudiar l'impacte de l'obesitat sobre la cognició a curt i llarg-termini constava de dos parts: l'estudi longitudinal amb 28 pacients i 26 controls (n=54) i també es va ampliar la mostra per realitzar l'estudi transversal on es va augmentar la mostra a 52 pacients amb trastorn bipolar i 69 controls sans (n=121). Es van seguir els mateixos criteris d'inclusió i exclusió que hem explicat prèviament pel primer article.

Pacients i controls es varen categoritzar en dos grups en funció del seu índex de massa corporal (IMC): pes normal i sobrepès o obesitat basat en els criteris establerts d'IMC (pes normal, IMC entre 18.5-24.9 kg/m^2; sobrepès, IMC entre 25.0-29.9 kg/m^2; i obesitat, IMC > 30 kg/m^2).

4.2.4 Per respondre la hipòtesi 4:

Per estudiar el relació dels biomarcadors amb les variables clíniques i cognitives es van incorporar un grup de 32 pacients maníacs provinents de la Unitat d'Hospitalització d'Aguts del mateix centre, a la mostra de 52 eutímics i 49 controls sans (n=133).

Els criteris d'exclusió i inclusió del grup de maníacs eren els mateixos que els dels pacients eutímics; excepte pel criteri d'estabilitat clínica, havien de tenir una puntuació igual o superior a 14 a l'escala de mania, YMRS (Tohen et al. 2009).

4.3 Variables a estudi

4.3.1 Per respondre la hipòtesis 1:

4.3.1.a Variables sociodemogràfiques, clíniques i psicomètriques:

A la següent taula (veure taula 2) es recullen totes les que es varen estudiar de la mostra de pacients i controls(Young et al. 1978; Hamilton M 1960; Dean et al. 2004; Guy 1976).

Taula 2. Variables sociodemogràfiques, psicomètriques, clíniques i farmacològiques

1.Variables demogràfiques	• Data de naixement • Sexe • Nivell educacional • Situació laboral • Al·lèrgies a fàrmacs • Antecedents mèdics • Tractaments habituals
2.Variables psicomètriques	• Criteris DSM-IV-TR per trastorn bipolar tipus I o II • YMRS: Escala de Mania de Young (1978) • HAMD: Escala d'Avaluació de la Depressió de Hamilton (1960) • EEAG/GAF: Escala d'avaluació d'activitat global (Dean et al. 2004) • ICG: Impressió Clínica Global (Guy, 1976)
3.Variables de curs previ	• Edat d' inici del trastorn • Anys d'evolució del trastorn • Tipus d'episodi inicial • Nombre d'episodis maníacs previs • Número d'hospitalitzacions • Intents autolítics previs • Temps transcorregut des de l'últim episodi • Patró estacional
4.Variables farmacològiques	• Dosi de liti i temps de duració d'aquest tractament • Nivells de litèmia obtinguts en els últims 3 meses. • Analítica completa incloent hemograma, hemostàsia, bioquímica amb perfil renal i hormones tiroïdals. • Anàlisi de tòxics en orina. • Tractaments concomitants en el moment actual i durant l'evolució dels últims 3 mesos.

4.3.1.b Variables neuropsicològiques:

Es va avaluar la funció cognitiva mitjançant una bateria neuropsicològica d'unes dos hores d'administració per subjecte. No existeix una bateria unificada per a avaluar els trastorns cognitius en el trastorn bipolar, i per aquest motiu, s'escullen aquelles proves més freqüentment documentades en la literatura prèvia i que permeten avaluar el perfil cognitiu de manera més global (Savitz et al. 2005; Robinson et al. 2006a); i que el nostre grup ja havia publicat en estudis previs (Mur et al. 2007; Mur et al. 2008).

- Subtest Vocabulari i Subtest Cubs de la Wechsler Adult Intelligence Scale (WAIS-III; (Wechsler 2001)) per avaluar el **quocient intel·lectual premòrbid** (QI) (Lezak et al. 2004). El subtest Cubs també s'utilitza per avaluar capacitat viso-constructiva i estratègies de execució.
- Subtest Dígits de la Wechsler Adult Intelligence Scale (WAIS-III), que avaluen la **atenció** (dígits directes) i la **memòria de treball** (dígits inversos).
- Wisconsin Card Sorting Test (WCST), per mesurar **funció executiva** i conducta perseverant (Heaton 1981).

- Stroop Colour and Word Test, per l'avaluació de **l'atenció selectiva** i la capacitat d' inhibició (Golden 1978).
- Test de Fluidesa Verbal FAS/Categories, per avaluar **funció executiva** (Benton A. & Hamsher K 1976).
- Trail Making Test (TMT), per l'avaluació de la **velocitat de processament** (TMT-A) i la flexibilitat cognitiva (TMT-B) (Reitan 1958).
- Continuos Performance Test (CPT-II), per avaluar **l'atenció sostinguda**, velocitat de processament i conducta perseverativa (Conners 2000).
- Test del Aprenentatge Verbal de California (CVLT), per l'avaluació de la capacitat de aprenentatge verbal i de **memòria verbal** (Delis 1987).
- Test la figura de Rey–Osterrieth (ROCF), per avaluar la **memòria visual** (Meyers & Meyers 1995).

4.3.1.c Variables de funcionalitat psicosocial

Per últim, es va avaluar la funcionalitat psicosocial mitjançant l'escala FAST (Rosa et al. 2007) (veure annex 1). Com ja hem esmentat és un instrument que s'administra en un curt període de temps (3-6 minuts). Consta de 24 ítems distribuïts en 6 àrees de funcionament: autonomia, funcionament laboral, funcionament cognitiu, finances, relacions interpersonals i oci. La puntuació total va de 0 a 72 en els quals obtindrem pitjor funcionalitat a major puntuació i a l'inrevés. Aquest estudi s'ha centrat especialment en l'àrea de funcionalitat cognitiva que comprèn una puntuació de 0 a 15.

4.3.2 Per respondre la hipòtesi 2

Es varen recollir les mateixes variables demogràfiques, clíniques, farmacològiques, funcionals i cognitives que en el primer article, tal i com s'ha explicat en l'apartat 4.3.1.

Es va utilitzar l'escala Alda (veure annex 2) per mesurar la resposta al tractament amb liti, tal i com s'ha explicat prèviament en l'apartat 4.2.2.

4.3.3 Per respondre la hipòtesi 3

Es varen recollir les mateixes variables demogràfiques, clíniques, farmacològiques i cognitives que en el primer article, tal i com s'ha explicat en l'apartat 4.3.1.

Es va calcular l'IMC de tots els participants i es va categoritzar la mostra en dos subgrups en funció de l'IMC, tal i com s'ha explicat en l'apartat 4.2.3.

4.3.4 Per respondre la hipòtesi 4

Es varen recollir les mateixes variables demogràfiques, clíniques, farmacològiques i cognitives que en el primer article, tal i com s'ha explicat en l'apartat 4.3.1.

Cal esmentar que l'extracció de l'analítica en el grup de maníacs es realitzava al moment de l'ingrés mentre que l'avaluació neuropsicològica es duia a terme quan els símptomes maníacs havien remés parcialment, previ a l'alta hospitalària, per tal de garantir la mínima col·laboració dels pacients a l'hora de fer les proves.

4.3.4.a Mesures bioquímiques

A cada participant, se li va extreure deu mil·lilitres de sang per punció venosa en un tub sense anticoagulant entre les 8 i 9h per evitar variacions degudes al ritme circadià. Es va separar el sèrum mitjançant centrifugació durant 2 hores a 3500 g durant 15 minuts a temperatura ambient. Totes les mostres es varen emmagatzemar a - 80 ° C al Biobanc de l'IRBLleida (B.0000682) i PLATAFORMA biobancs PT13 / 0010/0014 fins que es van analitzar. Posteriorment, es varen determinar els nivells de biomarcadors i totes les mostres es van analitzar per duplicat. Els biomarcadors relacionats amb les neurotrofines, la inflamació i l'estrès oxidatiu van ser:

- Els nivells de factor neurotròfic derivat del cervell (Brain-derived neurotrophic factor (BDNF)) en sèrum es van mesurar mitjançant un kit comercial d'ELISA segons les instruccions del fabricant (Chemicon, Temecula, CA, EUA), com es descriu prèviament en un altre treball (Kauer-Sant'Anna et al. 2009). Totes les mostres es van mesurar per duplicat. Les dades es van expressar en ng/ml. Els coeficients de variació intra i interplaca van ser <12%.
- Les citocines inflamatòries en sèrum (Interleuquina-6 (IL-6), interleuquina 10 (IL-10) i factor de necrosi tumoral alfa (TNF-α)) es varen mesurar seguint els procediments subministrats pel fabricant utilitzant kits ELISA altament sensibles per TNF-α, IL-6 i IL-10 (Quantikine, R&D Systems, Minneapolis , Minn., EUA). Totes les mostres es van mesurar per duplicat. Les dades es van expressar en ng/ml. Els coeficients de variació intra i interplaca van ser <10%.
-L'estrès oxidatiu es va mesurar mitjançant els nivells de peroxidació lipídica utilitzant el mètode de les substàncies reactives a l'àcid tiobarbitúric (TBARS) descrit per Wills (Wills 1966). Totes les mostres es van analitzar per duplicat i les dades es van expressar en nmol/mL.

4.4 Anàlisi estadística

S'utilitza el paquet informàtic SPSS per Windows, les versions 15.0 i 22.0 (SPSS Inc.USA) i també el programari estadístic R (versió 3.2.2) (R Core Team 2015) per al processament de dades.

4.4.1 Per respondre les hipòtesis 1 i 2

Les variables sociodemogràfiques, clíniques i psicosocials es varen comparar entre grups mitjançant la prova *t* de Student a nivell basal (T1) i al cap de 6 anys (T2); també es va emprar la prova t de Student per dades aparellades per avaluar les diferències al llarg del temps. Les variables no quantitatives es van analitzar mitjançant proves no paramètriques (χ^2).

Les mesures neuropsicològiques que seguien una distribució normal (test de Kolmogorov-Smirnoff) es varen transformar en valors z i es van agrupar en dominis cognitius (funcions executives, inhibició, atenció, velocitat de processament, memòria verbal i visual) per evitar informació redundant dels tests neuropsicològics per separat. Totes les dades s'analitzaren amb anàlisis de variància i covariància multivariant (MANOVA i MANCOVA respectivament) de mesures repetides, controlant pel QI premòrbid i per símptomes subclínics (YMRS i HAMD) per establir les diferències entre grups.

Per establir la relació entre el rendiment cognitiu al cap de 6 anys amb les variables clíniques i funcionals, es van calcular les diferències entre les variables cognitives que mostraven diferències significatives al llarg del temps en el grup de pacients bipolars eutímics. D'aquesta manera es varen crear noves variables que representaven l'evolució al llarg del temps i van anomenar variables delta cognitives. Posteriorment, es van realitzar correlacions parcials entre aquestes variables delta cognitives i les variables clíniques i funcionals controlant per simptomatologia subclínica (HAMD).

4.4.2 Per respondre la hipòtesi 3

Les variables sociodemogràfiques, clíniques i psicosocials es varen comparar entre grups mitjançant la prova *t* de Student per les variables contínues i amb la prova Khi quadrat (χ^2) per les variables categòriques i així fer l'anàlisi estadística descriptiva.

Per l'anàlisi transversal, les dades neuropsicològiques es van analitzar amb una anàlisis de variància multivariant de dos factors (MANOVA; pacients vs controls sans i el subgrup d'IMC (factor-IMC: sobrepès o obesitat vs per normal)). Aquelles variables que van mostrar

diferències significatives es van transformar en valors z i es van resumir en un valor *composite score* per obtenir un índex cognitiu global.

Per demostrar les hipòtesis del tercer article, es va realitzar un model de regressió on l'índex cognitiu global era la variable dependent per predir l'impacte de l'IMC sobre la cognició comparant els dos grups. Com a factors predictors es varen introduir variables subclíniques (YMRS i HAMD), demogràfiques (edat, sexe, anys d'educació i QI premòrbid) i funcionals (GAF). Per poder determinar el pes estadístic específic del subgrup d'IMC i el trastorn bipolar, es va crear un factor d'interacció (group X factor-IMC) que també es va incloure al model.

Les variables clíniques (edat d'inici del trastorn, número d'hospitalitzacions, anys d'estabilitat clínica, duració de la malaltia i antecedents d'haver patit símptomes psicòtics) també es van incloure en un altre model de regressió que es va realitzar amb la mostra de pacients bipolars eutímics.

Per l'estudi longitudinal, el rendiment neuropsicològic als 6 anys es va analitzar també mitjançant una MANOVA de dos factors (pacients vs controls sans i el factor-IMC). Aquelles variables que van mostrar diferències estadísticament significatives en l'efecte de grup X factor-IMC es van transformar en valors z i es van resumir en un valor *composite score* per obtenir un índex cognitiu global als 6 anys i a nivell basal. Es van calcular les diferències entre els índexs per mesurar els canvis cognitius al llarg del temps. Posteriorment, es va realitzar un model de regressió per predir l'impacte de l'IMC basal sobre els canvis cognitius al llarg del temps.

Per determinar si els canvis de pes al llarg del temps s'associaven amb el rendiment cognitiu als 6 anys, es va realitzar un model de regressió basat en l'equació d'estimació generalitzada (GEE). Es varen introduir les mateixes variables com a factors predictors i també el temps com a variable inter-subjecte.

4.4.3 Per respondre la hipòtesi 4

Les variables sociodemogràfiques, clíniques i psicosocials es varen comparar entre grups mitjançant anàlisis de la variància (ANOVAs) per les variables contínues i amb la prova Khi quadrat (χ^2) per les variables categòriques i així fer l'anàlisi estadística descriptiva. Les variables que no tenien una distribució normal es van convertir en logaritmes. Per contrarestar el problema de les múltiples comparacions es va aplicar la correcció de Bonferroni a les variables que mostraven diferències significatives entre els grups a les ANOVAs.

Les variables neuropsicològiques es van comparar entre els tres grups utilitzant una anàlisi multivariant de la variància (MANOVA). També es varen realitzar anàlisis post-hoc per establir diferències entre els grups de pacients eutímics, maníacs i controls sans. Els nivells de biomarcadors també es van analitzar amb una MANOVA i amb anàlisis post-hoc.

Es varen dur a terme correlacions paramètriques i no paramètriques per explorar les associacions entre variables clíniques, demogràfiques i els nivells de biomarcadors; per així incloure-les en anàlisis posteriors.

Per demostrar les hipòtesis del quart article, es van realitzar models de regressió per estudiar l'impacte de diferents variables (demogràfiques i nivells de biomarcadors) sobre el funcionament cognitiu. Prèviament, les tasques neuropsicològiques s'havien convertit en valors z i s'havien agrupat en dominis cognitius, tal i com s'ha explicat en l'apartat 4.4.1; i aquests eren les variables dependents dels models. Com a factors predictors es varen introduir variables significatives o rellevants com l'edat, el QI premòrbid, l'índex de massa corporal, la condició de grup i els nivells de biomarcadors. Per cada model de regressió es van tenir en conte els diagnòstics de col·linealitat (Tolerància < 0.1 i FIV > 10 indicaven altes correlacions factors i estimacions dolentes dels coeficients).

Per tal de conèixer el paper dels factors clínics i els biomarcadors sobre el funcionament cognitiu, inicialment es varen realitzar correlacions de Pearson entre aquestes variables. Posteriorment, es van dur a terme models de regressió amb la mostra de pacients (bipolars i maníacs), afegint els factors independents que s'acaben d'esmentar juntament amb les variables clíniques (temps d'evolució de la malaltia, nombre d'episodis maníacs, depressius i nombre d'hospitalitzacions).

5. RESULTATS

5.1 Resum dels resultats

A continuació s'exposen els resultats més importants de cadascun dels articles presentats:

5.1.1 Article 1:

Mora E, Portella MJ, Forcada I, Vieta E, Mur M. Persistence of cognitive impairment and its negative impact on psychosocial functioning in lithium-treated, euthymic bipolar patients: a 6-year follow-up study. *Psychol Med. 2013 Jun;43(6):1187-96*

En aquest primer article, i a partir del que s'havia revisat a la literatura, ens preguntàvem com era l'evolució de la disfunció cognitiva al llarg del temps en el trastorn bipolar i quina era la seva repercussió sobre la funcionalitat psicosocial. A la literatura trobàvem escassos estudis longitudinals i el nostre estudi tenia un disseny metodològic únic, donat que era el primera que avaluava els mateixos controls sans en dos ocasions. En un estudi previ del nostre grup (Mur et al. 2008), en el qual es va realitzar un estudi longitudinal als dos anys, el dèficit cognitiu presentat pels pacients bipolars eutímics es mantenia estable. Augmentant el període de seguiment a 6 anys esperàvem corroborar aquests resultats amb un període de seguiment més llarg. A més, en aquest nou article, afegint la valoració funcional amb l'escala FAST preteníem poder definir quines variables clíniques i cognitives s'associaven a la funcionalitat psicosocial. En l'anàlisi descriptiva, pacients i controls sans estaven aparellats per edat, gènere i anys d'educació; diferien però en el QI premòrbid. També es van trobar diferències significatives en les escales psicomètriques, en concret en l'escala clínica de Mania (YMRS) en l'avaluació basal, i en l'escala de depressió (HAMD) al cap de 6 anys.

Per respondre a la pregunta de com era l'evolució de la cognició es varen realitzar anàlisis de MANCOVA de mesures repetides, controlant pel QI premòrbid, i no es van detectar interaccions significatives entre el temps i el grup (pacients vs controls sans); a excepció del domini de memòria verbal. D'altra banda hi havien efectes principals de grup en el domini executiu (TMT-B i dígits invers), en inhibició (inhibició de Stroop), en velocitat de processament (TMT-A i velocitat del CPT-II), i finalment en memòria verbal (memòria a curt i a llarg termini). Donat que d'altres autors (Martínez-Arán et al. 2004; Kurtz & Gerraty 2009) han constatat l'impacte dels símptomes residuals subclínics sobre la cognició, es va refer la MANCOVA afegint la puntuació de la YMRS i la HAMD com a covariants i es van obtenir els mateixos resultats; a excepció de la velocitat del CPT-II.

Finalment, per respondre com era la relació del dèficit cognitiu al llarg del temps amb les variables clíniques i funcionals es van realitzar correlacions. De totes les variables clíniques, el temps d'evolució de la malaltia era l'única variable que es correlacionava amb una pitjor puntuació en la velocitat del CPT II. Des del punt de vista funcional, es va trobar una forta associació entre l'empitjorament cognitiu en funcions executives, velocitat de processament i memòria verbal dels pacients al llarg del temps i la puntuació total de l'escala FAST, així com també en l'àrea de funcionament cognitiu i ocupacional.

5.2.2 Article 2:

Mora E, Portella MJ, Forcada I, Vieta E, Mur M. A preliminary longitudinal study on the cognitive and functional outcome of bipolar excellent lithium responders. *Comprehensive Psychiatry. 2016 Jul 30;Volume 71, Pages 25-32.*

En aquest segon article ens plantejàvem investigar si els excel·lents responedors a liti (ELR) també presentaven dèficit cognitiu i quina evolució tenia al llarg del temps. I també ens qüestionàvem si tenia repercussions funcionals. Per aquest motiu es va seleccionar aquesta submostra i es va seguir el mateix procediment estadístic que en el primer article.

En l'anàlisi descriptiva es va constatar que els pacients eutímics ELR estaven aparellats per edat, sexe, any d'educació i també QI premòrbid. En aquest estudi no hi havien diferències significatives entres les puntuacions de les escales clíniques de mania (YMRS) i depressió (HAMD) al nivell basal ni tampoc passats 6 anys.

A partir d'aquests resultats, es va optar per fer una MANOVA de mesures repetides, per constatar el comportament de la cognició al llarg del temps. No es varen detectar interaccions significatives entre el temps i el grup (pacients vs controls sans); a excepció del domini d'atenció. D'altra banda hi havien efectes principals de grup en el domini executiu (TMT-B), en inhibició (inhibició de Stroop), en velocitat de processament (TMT-A i velocitat del CPT-II), i finalment en memòria verbal (memòria a curt termini). També es varen realitzar anàlisis de MANCOVA de mesures repetides, afegint el QI premòrbid i les puntuacions d'escales clíniques i els resultats eren els mateixos; a excepció de la memòria a curt termini del CVLT que no arribava al llindar significatiu.

Per acabar, es va estudiar l'associació entre la disfunció cognitiva al llarg del temps i les variables clíniques i funcionals. En aquest article, els anys de duració de la malaltia eren l'única variable clínica que es correlacionava amb l'empitjorament cognitiu. Des del punt de vista funcional, es va trobar una forta associació entre l'empitjorament cognitiu en funcions

executives, velocitat de processament i memòria verbal dels pacients al llarg del temps i la puntuació total de l'escala FAST, així com també en l'àrea de funcionament ocupacional.

5.2.3 Article 3

Mora E, Portella MJ, Martinez-Alonso M, Teres M, Forcada I, Vieta E, Mur M. The impact of obesity on cognitive functioning in euthymic bipolar patients: a cross-sectional and longitudinal study. *Journal of Clinical Psychiatry 2017 (in press).*

En aquest article ens preguntàvem quin era l'impacte de l'obesitat sobre la cognició a curt i a llarg termini; donat que existeix evidència recent que considera l'obesitat com un fenotip neurotòxic i inflamatori que té repercussions clíniques i cognitives sobre els trastorns de l'estat d'ànim. Per aquest motiu es van dissenyar dos parts: es va augmentar la mostra per un estudi transversal i vam incloure les dades del seguiment longitudinal.

Inicialment, es va fer l'anàlisi descriptiva de la mostra de pacients bipolars eutímics aparellats per edat i sexe amb els controls sans per l'estudi transversal. Es van detectar diferències estadísticament significatives en els anys d'educació, el QI premòrbid i les escales clíniques de mania (YMRS) i depressió (HAMD). Cada grup es va categoritzar segons el seu índex de massa corporal (factor-IMC: pes normal vs sobrepès o obesitat). En el grup de pacients hi havien diferències entre l'edat i anys d'educació en els subgrup d'IMC; mentre que no hi havien diferències en el QI premòrbid ni en les escales de mania (YMRS) i depressió (HAMD). En els controls sans hi havien diferències en l'edat dels subgrups d'IMC; però no n'hi havia en la resta de variables demogràfiques ni subclíniques.

Per analitzar la cognició, es van agrupar les tasques neuropsicològiques que mostraven diferències significatives en la MANOVA de dos factors (grup X factor-IMC) i es va obtenir un índex cognitiu global. Posteriorment, es va realitzar un model de regressió lineal per predir l'impacte de l'IMC sobre la cognició. La interacció del grup amb el factor-IMC (tenir trastorn bipolar juntament amb el sobrepès o l'obesitat) era factor predictor de l'índex cognitiu global juntament amb l'edat i el QI premòrbid. Cal esmentar que ni el grup ni el factor-IMC esdevenien factors predictors significatius quan s'introduïen per separat dins del model.

Ens vam preguntar quina era la implicació de les variables clíniques en la relació de l'obesitat i la cognició. Per aquest motiu, es va fer un model de regressió només per pacients en el qual es va observar que l'edat d'inici del trastorn i la duració de la malaltia eren les úniques variables clíniques que juntament amb el factor-IMC explicaven l'índex cognitiu global.

Per respondre la qüestió de l'obesitat i la cognició a llarg termini, es varen crear 2 índexs cognitius globals: un basal i l'altre als 6 anys de seguiment; seguint el mateix procediment amb la MANOVA de dos factors, tal i com s'ha descrit prèviament. Posteriorment, es varen calcular les diferències entre els dos índexs. I també es va fer un model de regressió on la interacció de grup amb el factor-IMC i l'IMC basal eren factors predictors dels canvis cognitius experimentats en el període de 6 anys.

5.1.4 Article 4

Mora E, Portella MJ, Piñol-Ripoll G, López R, Cuadras D, Forcada I, Teres M, Vieta E, Mur M. Neurotrophins, inflammation and oxidative damage as mediators of cognitive functioning in bipolar disorder.

En aquest article volíem aprofundir més en l'estudi de la disfunció cognitiva i les bases neurobiològiques del trastorn bipolar. L'objectiu era conèixer el paper de les neurotrofines i dels marcadors inflamatoris i d'estrès oxidatiu sobre les variables clíniques i la cognició. Per poder avaluar aquesta qüestió es va incorporar un grup de maníacs a l'estudi que es va comparar amb la mostra de pacients eutímics i controls sans.

Inicialment, es va fer l'anàlisi descriptiva de les dades demogràfiques i de les característiques clíniques de tota la mostra. Hi havien diferències estadísticament significatives entres els grups en quant a l'edat, els anys d'educació, el QI premòrbid, l'IMC i les escales clíniques de mania (YMRS) i depressió (HAMD).

Estudiant la relació entre les variables clíniques i els biomarcadors, es va observar que els nivells de neurotrofines (BDNF) estaven disminuïts en maníacs i eutímics comparat amb controls sans. Els marcadors inflamatoris i d'estrès oxidatiu mostraven un patró en el sentit oposat, tal i com s'esperava. En la mateixa línia, les escales de mania (YMRS) i depressió (HAMD) es correlacionaven negativament amb els nivells de BDNF i positivament amb els nivells del marcador inflamatori IL-6. De totes les variables clíniques, la duració de la malaltia era l'única que es correlacionava amb el mateix marcador inflamatori, IL-6.

El funcionament cognitiu entre els grups es va analitzar a través d'una MANOVA on la memòria verbal era l'únic domini que mostrava diferències significatives entre eutímics i maníacs.

Ens vam plantejar quina era la relació entre cognició i biomarcadors i es van fer models de regressió per cada domini cognitiu. De tots els biomarcadors, el BDNF era l'únic que era factor predictor del funcionament cognitiu, concretament en les funcions executives i en la memòria

verbal, juntament, amb l'edat i el QI premòrbid. En el cas de la memòria verbal, l'IMC també era factor predictor de pitjor puntuació.

També ens vam plantejar quin paper hi jugaven les variables clíniques, les quals es varen introduir en un model de regressió que avaluava la mostra de pacients eutímics i maníacs. L'única variable clínica que mostrava alguna relació amb els dominis era el nombre d'hospitalitzacions que predeia el domini d'atenció. Novament, el BDNF era l'únic biomarcador predictor del funcionament cognitiu, concretament, en la memòria verbal, també juntament amb l'IMC, l'edat i el QI premòrbid.

ARTICLE 1

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ORIGINAL ARTICLE

Persistence of cognitive impairment and its negative impact on psychosocial functioning in lithium-treated, euthymic bipolar patients: a 6-year follow-up study

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Background. Previous cross-sectional studies report that cognitive impairment is associated with poor psychosocial functioning in euthymic bipolar patients. There is a lack of long-term studies to determine the course of cognitive impairment and its impact on functional outcome.

Method. A total of 54 subjects were assessed at baseline and 6 years later; 28 had DSM-IV TR bipolar I or II disorder (recruited, at baseline, from a Lithium Clinic Program) and 26 were healthy matched controls. They were all assessed with a cognitive battery tapping into the main cognitive domains (executive function, attention, processing speed, verbal memory and visual memory) twice over a 6-year follow-up period. All patients were euthymic (Hamilton Rating Scale for Depression score lower than 8 and Young mania rating scale score lower than 6) for at least 3 months before both evaluations. At the end of follow-up, psychosocial functioning was also evaluated by means of the Functioning Assessment Short Test.

Results. Repeated-measures multivariate analysis of covariance showed that there were main effects of group in the executive domain, in the inhibition domain, in the processing speed domain, and in the verbal memory domain ($p<0.04$). Among the clinical factors, only longer illness duration was significantly related to slow processing ($p=0.01$), whereas strong relationships were observed between impoverished cognition along time and poorer psychosocial functioning ($p<0.05$).

Conclusions. Executive functioning, inhibition, processing speed and verbal memory were impaired in euthymic bipolar out-patients. Although cognitive deficits remained stable on average throughout the follow-up, they had enduring negative effects on psychosocial adaptation of patients.

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Key words: Bipolar disorder, cognition, follow-up study, lithium treatment, psychosocial functioning.

Introduction

A considerable amount of evidence has confirmed that neuropsychological functioning is impaired in individuals with bipolar disorder, not only during acute episodes but also during periods of remission of affective symptoms, namely euthymic states (Torres *et al*. 2007). Despite current evidence, the neuropsychological profile during euthymia has not yet been well established and substantial heterogeneity has been reported (Mann-Wrobel *et al*. 2011). Emerging data suggest that patients with bipolar disorder exhibit cognitive impairment in attention, verbal memory and executive functioning during remission (Martínez-Arán *et al*. 2004*b*; Mur *et al*. 2007; Torres *et al*. 2007; Mann-Wrobel *et al*. 2011). Several studies reveal that it is important to examine cognitive performance in euthymic bipolar disorder patients since there is a strong association between neuropsychological impairment and poor psychosocial functioning outcome (Wingo *et al*. 2009).

Most of the previous studies on neurocognition and its functional impact in euthymic patients are cross-sectional. Since bipolar disorder is a chronic and recurrent disease it is necessary to proceed examining longitudinally the cognitive and functional course of these individuals in order to clarify the particular nature and specificity of the reported deficits and how these can change over time (Robinson & Ferrier, 2006). There is an actual lack of longitudinal studies in the current literature foreclosing the possibility to

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determine the evolution of cognition (Balanzá-Martínez *et al.* 2005; Burdick *et al.* 2006; Mur *et al.* 2008; Tabarés-Seisdedos *et al.* 2008) and psychosocial functioning (Martino *et al.* 2009; Bonnín *et al.* 2010; Burdick *et al.* 2010) in euthymic bipolar patients. Furthermore, the cognitive follow-up of these patients becomes crucial for providing tools to administer the most suitable pharmacological and psychosocial treatment strategies (Gildengers *et al.* 2009).

The aim of the present study is to investigate the longitudinal neuropsychological profile of euthymic bipolar out-patients compared with healthy matched controls in a 6-year period of follow-up and to examine the psychosocial disabilities as related to cognitive deficits. An important methodological feature of this study, as compared with the very few previous studies that looked at this issue, is that healthy control subjects were also assessed at baseline and 6 years later, controlling for the effects of time and ageing. We hypothesized that the cognitive deficits would remain stable regardless of the clinical course of the illness, and this impairment would be related to the psychosocial adaptation at the end of the follow-up.

Method

Subjects

A total of 28 euthymic bipolar patients and 26 healthy matched controls were admitted into the study and were evaluated at baseline and 6 years later with a clinical interview, biochemical tests and a neuropsychological battery. On average, the endpoint (T2) occurred 6.1 years after baseline (T1) (range 8.2–4.9 years) and was conducted by the same neuropsychologist. The Local Ethics Committee approved the study, and written informed consent was obtained from all participants (patients and healthy controls).

The patient sample was obtained from the Lithium Clinic Program at Hospital Santa Maria, Lleida, in 2003. Inclusion criteria included being on lithium treatment at T1, aged between 18 and 65 years, fulfilling Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR) criteria for bipolar disorder, and being in remission for at least 3 months (Mur *et al.* 2007). Following previous studies (Robinson *et al.* 2006), patients were characterized as euthymic if they had a total 17-item Hamilton Rating Scale for Depression (HAMD; Hamilton, 1960) score below 8 and a total Young Mania Rating Scale (YMRS; Young *et al.* 1978) score below 6 for at least 3 months at the time of assessment. Exclusion criteria were the following: significant physical or neurological illness, substance abuse or dependence in the last 12 months, electroconvulsive therapy in the preceding year. At the endpoint, patients had to fulfil the same inclusion and exclusion criteria, except for medication that was allowed to be changed during the 6 years, if clinically needed. Therefore, at follow-up, all subjects were retested if they had been euthymic for at least 3 months, as confirmed by the criteria as at baseline.

A total of 26 healthy controls from the same geographic area, matched in terms of gender, age and years of education were recruited via advertisements and from non-medical hospital staff. Controls had no current or past psychiatric history, as determined by the Structured Clinical Interview for DSM-IV Axis I Disorders. They had no first-degree relatives with bipolar or psychotic diagnoses. Controls were subject to the same exclusion criteria and were assessed with the same full study protocol as the patients. They were also evaluated twice (at baseline and 6 years later).

Demographic, clinical and pharmacological data

Demographic variables for euthymic bipolar patients and healthy controls were age, gender, years of education and family history of mental illness. Clinical variables were obtained from the sample of bipolar patients, including: age at illness onset, number of prior manic episodes and hospitalizations, period of stabilization (years), history of psychotic symptoms, seasonal pattern, suicide attempts and bipolar subtype (I or II). Biochemical tests were performed on all patients, including for thyroid function, serum lithium levels and urine drug testing.

With respect to pharmacological variables, at baseline, T1, 14 patients were receiving lithium as monotherapy and the other 14 were on combination treatment (lithium plus antidepressants and/or antipsychotics). Lithium dosages at T1 were 820–1380 mg/day (serum lithium levels 0.46–0.86 mmol/l; treatment duration 1–10 years). At the study endpoint, T2, two patients were drug-free, 10 were receiving lithium monotherapy, 11 were on combination treatment (lithium dosage 916–1388 mg/day; serum lithium levels 0.51–0.71 mmol/l; treatment duration 5–15 years); and five were receiving other psychopharmacological treatments (two were receiving other mood stabilizers, one was on a combination of antidepressant and antipsychotic, another one was receiving another mood stabilizer plus antidepressant and the other was on another mood stabilizer plus antipsychotic).

Neuropsychological assessment

To provide a more general pattern of cognitive performance, this battery included neuropsychological

tests that tapped into broad cognitive categories as documented in previous literature (Mur *et al.* 2007). The estimated mean intelligence quotient (IQ) of the subjects was obtained from the weighted scores of the Vocabulary and Block Design subtests of the Wechsler Adult Intelligence Scale (WAIS-III; Wechsler, 2001), because these two scores are the most highly correlated with total IQ. The instruments administered were:

(i) Vocabulary, Block Design and Digits Subtests from WAIS-III (Wechsler, 2001);
(ii) Wisconsin Card Sorting Test (WCST; Heaton, 1981);
(iii) Stroop Colour and Word Test (Spreen & Strauss, 1998);
(iv) Verbal fluency task of the Controlled Oral Word Association Test/Categories (FAS; Spreen & Strauss, 1998);
(v) Trail Making Test (TMT), part A (TMT-A) and part B (TMT-B) (Reitan, 1958);
(vi) Conners' Continuous Performance Test II (CPT-II; Conners, 2000);
(vii) California Verbal Learning Test (CVLT; Delis *et al.* 1987);
(viii) Rey Complex Figure Test (RCFT; Meyers & Meyers, 1995).

Psychosocial functioning

At baseline, to obtain information about global activity, patients and controls were assessed with the Global Assessment of Functioning scale. Moreover, occupational functioning was specifically assessed and defined as follows: active (subjects with a full- or part-time job, students and housewives), inactive (unemployed subjects and those with temporary sick leave) and retired (permanent sick leave or retired subjects). At the endpoint, another scale was also administered in order to evaluate psychosocial functioning more accurately. The Functioning Assessment Short Test (FAST; Rosa *et al.* 2007) is more appropriate since it takes into consideration different domains and it is more specific for assessing different levels of functioning in bipolar disorder. Its 24 items of the scale are divided into six specific areas of functioning: autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships and leisure time. Therefore, subscores can be obtained from these areas as well as a total score.

Statistical procedures

Data analyses were carried out with the statistical package SPSS for Windows, version 15.0 (SPSS Inc., USA). Differences between groups in demographic, psychosocial and clinical variables were assessed with a univariate analysis of variance, by examining a single factor of group (out-patients *versus* healthy controls) at T1 and at T2; and paired two-sample *t* tests were used to assess time differences for such variables. Non-quantitative variables were examined by means of non-parametric tests.

Neuropsychological tasks were sorted by cognitive domains: executive functions, attention, processing speed, verbal memory and visual memory (Mur *et al.* 2008). Performance on neuropsychological tasks was compared across the two groups by means of separate multivariate repeated-measures analyses of covariance (MANCOVA) for each cognitive domain. Estimated pre-morbid IQ, YMRS and HAMD scores were included as covariates since they showed significant differences between groups at T2, as shown in Table 2. The cognitive variables that did not meet the criterion of normality were excluded from the multivariate analyses: CVLT recognition, number of perseverative errors at CPT-II and number of categories of WCST. No other analyses were carried out with these latter variables as the cognitive domains were already sufficiently explored with other neuropsychological tests.

In order to establish correlations between cognitive changes in neuropsychological performance after 6 years in bipolar patients with clinical and functional variables, the difference between scores at T2 and T1 was calculated for those variables that showed significant differences between groups. Therefore new variables that reflected performance decrement or increment across time were obtained (ΔDigit backward, ΔTMT-B, ΔTMT-A, ΔCVLT immediate recall, ΔCVLT delayed recall, ΔStroop Inhibition and ΔHit Reaction Time in CPT-II). Then, associations between cognitive changes and clinical and functional variables were analysed with partial correlations by controlling for low-level depressive symptoms (HAMD) as shown in Table 3.

Results

Demographic, clinical and functional results

Demographic, clinical and pharmacological variables of the euthymic bipolar patients and healthy controls are displayed in Table 1 for the two time points (T1 and T2). Both groups of participants were matched in terms of age and gender. At T1, estimated pre-morbid IQ showed differences between the groups ($F_{1,52}=10.06$, $p=0.003$) although it was not clinically relevant as all scores were situated within the range of 100 ± 15, not exceeding the limits of normality. In terms of work status, the groups displayed significant differences [$\chi^2=8.4$, degrees of freedom (df) = 1,

Table 1. *Demographic, clinical and pharmacological variables at T1 and T2*

	Bipolar patients ($n=28$)		Healthy controls ($n=26$)	
Variable	T1	T2	T1	T2
Mean age, years (S.D.)	41.71 (12.4)	46.71 (13)	41.38 (12.1)	47.81 (12.2)
Mean years of education (S.D.)	10.1 (2.5)	10.1 (2.5)	12.2 (3.3)	12.5 (3.2)
Mean estimated pre-morbid IQ (S.D.)	97.8 (11.8)	102.2 (12.3)	107.3 (10.2)	111.1 (9.7)
Mean YMRS score (S.D.)	1.64 (1.9)	1 (1.3)	0.62 (0.9)	0.5 (1)
Mean HAMD score (S.D.)	1.46 (1.7)	2.11 (2.2)	1.23 (1.1)	0.62 (1.2)
Mean GAF score (S.D.)	72.32 (10.1)	72.86 (9.7)	92.4 (3.9)	
Mean age at onset, years (S.D.)	22.39 (9.4)	22.39 (9.4)		
Mean number of hospitalizations (S.D.)	3.04 (2.4)	3.64 (2.9)		
Mean total number of manic episodes (S.D.)	2.54 (2.1)	3.14 (2.9)		
Mean years of stabilization (S.D.)	3.18 (3.2)	7.11 (5.2)		
Mean duration of illness, years (S.D.)	18.43 (13.5)	24.29 (13.5)		
Mean years of lithium treatment (S.D.)	5.33 (4.4)	10 (4.9)		
Mean serum lithium levels, mmol/l (S.D.)	0.66 (0.2)	0.71 (0.2)/21		
Mean lithium dosage, mg/d (S.D.)	1100 (280)	1152 (236)/21		
Gender, number of males (%)	14 (50)		12 (46.2)	
Current work status, *n* (%)				
Active	14 (50)	13 (46.4)	23 (88.5)	22 (84.6)
Inactive	4 (14.3)	2 (7.2)	1 (3.8)	0
Retired/disabled	10 (35.7)	13 (46.4)	2 (7.7)	4 (15.4)
Positive family history of mental illness, *n* (%)	21 (75)	21 (75)	6 (23.1)	6 (23.1)
Lifetime history of psychotic symptoms, *n* (%)	22 (78.6)	22 (78.6)		
Lifetime history of seasonal pattern, *n* (%)	17 (60.7)	17 (60.7)		
Personal history of suicide attempts, *n* (%)	14 (50)	16 (57.1)		
Diagnosis, *n* (%)				
Bipolar I disorder	19 (67.9)	19 (67.9)		
Bipolar II disorder	9 (32.1)	9 (32.1)		
Type of current medication, *n* (%)				
Lithium monotherapy	14 (50)	10 (35.7)		
Lithium + combination	14 (50)	11 (39.3)		
Others		5 (17.9)		
None		2 (7.1)		

T1, Baseline; T2, 6-year endpoint; S.D., standard deviation; IQ, intelligence quotient; YMRS, Young Mania Rating Scale; HAMD, Hamilton Rating Scale for Depression; GAF, Global Assessment of Functioning.

$p=0.004$]; the bipolar patients were less active and more retired than the healthy controls. With regard to subclinical symptomatology, YMRS score also differed between the two groups ($F_{1,52}=6.24$, $p=0.016$), but HAMD score did not differ ($F_{1,52}=0.36$, $p>0.05$). At T2, 6 years later, the bipolar euthymic patients and healthy controls also differed in estimated IQ ($F_{1,52}=8.52$, $p=0.005$) and work status ($\chi^2=7.4$, df = 1, $p=0.006$). On this occasion, they differed in HAMD score ($F_{1,52}=9.24$, $p=0.004$), but not in YMRS score ($F_{1,52}=2.49$, $p>0.05$). None of the participants showed any evidence of clinical abnormality as checked with biochemical tests.

The group of bipolar patients exhibited significant worsening along the 6-year follow-up in their work status ($\chi^2=11.3$, df = 1, $p=0.001$) and in subsyndromal depressive symptoms, measured by HAMD score ($t=0.45$, $p=0.016$). At the endpoint, illness duration was of 24 years and patients had been stable for 7 years on average. However, during the study period 12 out of 28 patients (42.9%) suffered relapses: six patients (21.4%) suffered one or two episodes and the rest (21.4%) suffered more than two episodes. These episodes were clinically characterized as follows: 16 were depressive, seven mixed, 10 manic and two hypomanic.

Neuropsychological performance

All neuropsychological variables included in each cognitive domain are listed in Table 2. As can be observed, after controlling for estimated pre-morbid

Table 2. *Neuropsychological results at T1 and T2 for all participants*

	Bipolar patients		Healthy controls		Statistical analysis			
Test	T1	T2	T1	T2	F	df	p^a	p^b
Executive test					1.96[c]	3,42	N.S.	N.S.
TMT part B	82.96 (27.7)	102.7 (50.1)	55.9 (22.1)	55.7 (20.0)	7.1[d]	1,44	0.006	0.008
FAS	38.1 (12.2)	37.0 (12.8)	44.1 (9.4)	43.7 (10.1)	0.8[d]	1,44	N.S.	N.S.
WAIS-III digit span backward	5.1 (1.7)	4.9 (1.8)	6.5 (1.9)	6.6 (1.6)	7.0[d]	1,44	0.008	0.012
Inhibition					0.46[c]	2,46	N.S.	N.S.
Stroop inhibition	35.93 (10.9)	33.93 (12.4)	44.32 (6.2)	43.18 (8.2)	7.82[d]	1,47	0.004	0.011
No. of perseverative errors WCST	26.68 (21.1)	21.71 (14.5)	18.27 (12.7)	11.73 (11.1)	2.05[d]	1,47	N.S.	N.S.
Attention					2.6[c]	3,45	N.S.	N.S.
Stroop interference	−0.70 (6.6)	1.11 (7.7)	0.82 (4.7)	3.9 (7.8)	0.95[d]	1,47	N.S.	N.S.
WAIS-III digit span forward	7.5 (1.9)	7.5 (1.8)	8.9 (2)	8.6 (2.1)	2.80[d]	1,47	N.S.	N.S.
CPT-II detectability, d′	0.97 (0.5)	0.87 (0.4)	0.87 (0.5)	1.1 (0.4)	0.08[d]	1,47	N.S.	N.S.
Processing speed					0.27[c]	2,46	N.S.	N.S.
TMT part A, ms	45.89 (21.5)	47.75 (22.23)	29.73 (16.5)	28.23 (10.5)	6.54[d]	1,47	0.009	0.030
CPT-II hit reaction time, ms	474.2 (75.6)	492.8 (112)	423.6 (68.1)	425.4 (66.3)	6.52[d]	1,47	0.022	N.S. 0.079
Verbal memory					4.53[c]	4,44	0.024	0.049
CVLT first trial	6.75 (1.8)	6.11 (2)	6.55 (1.3)	7.59 (1.9)	0.88[d]	1,47	N.S.	N.S.
CVLT total words	51.5 (10)	49.36 (12.1)	54.86 (5.8)	57.68 (7.3)	3.59[d]	1,47	N.S. 0.052	N.S.
CVLT immediate recall	10.68 (2.7)	10.64 (3.1)	11.5 (2.2)	13.45 (1.6)	5.26[d]	1,47	0.008	0.013
CVLT delayed recall	11.07 (2.5)	11.21 (3.1)	12.32 (2.1)	14.09 (1.5)	6.57[d]	1,47	0.009	0.028
Visual memory					1.39[c]	2,44	N.S.	N.S.
RCFT immediate recall	19.33 (6.6)	19.6 (6)	23.34 (4.7)	23.41 (4.6)	4.19[d]	1,45	N.S.	N.S.
RCFT delayed recall	18.38 (6.1)	20.71 (6.2)	22.7 (5.2)	23.3 (5.4)	1.88[d]	1,45	N.S.	N.S.

Data are given as mean (standard deviation).

T1, Baseline; T2, 6-year endpoint; df, degrees of freedom; N.S., not significant; TMT, Trail Making Test; FAS, verbal fluency task of the Controlled Oral Word Association Test; WAIS-III, Wechsler Adult Intelligence Scale-III; WCST, Wisconsin Card Sorting Test; CPT-II, Continuous Performance Test II; CVLT, California Verbal Learning Test; RCFT, Rey Complex Figure Test; MANCOVA, multivariate repeated-measures analyses of covariance; IQ, intelligence quotient; HAMD, Hamilton Rating Scale for Depression; YMRS, Young Mania Rating Scale.

[a] Probability of repeated-measures MANCOVA controlling for IQ.

[b] Probability of repeated-measures MANCOVA controlling for IQ, HAMD and YMRS.

[c] Repeated-measures MANCOVA multivariate effects for each cognitive domain (group × time interactions).

[d] Repeated-measures MANCOVA main effects of group (test of between-subjects effects).

IQ, the repeated-measures MANCOVA showed no significant interactions of time (T1 *versus* T2) by group (patients *versus* healthy controls) except in the verbal memory domain. By contrast, there were main effects of group in the executive domain (TMT-B and digit span backward), in the inhibition domain (Stroop inhibition), in the processing speed domain (TMT-A and hit reaction time of CPT-II), and finally in the verbal memory domain (immediate and delayed recall). Since previous studies (Clark *et al.* 2002; Martínez-Arán *et al.* 2004*a*; Savitz *et al.* 2005; Kurtz & Gerraty, 2009) have already established the impact of residual mood symptoms, a repeated-measures MANCOVA was also performed, controlling for pre-morbid IQ and by YMRS and HAMD score. Even including these covariates, the results showed again the same effects, except for the interaction in the hit reaction time of CPT-II (although it depicted a similar trend), which did not reach the significance threshold. Significant group effects are presented in Fig. 1. Given that five patients were not on lithium treatment at T2, data were reanalysed excluding those individuals and the results were statistically similar to the whole sample results (data not shown) which might indicate that even when the medication regimen is less homogeneous, cognitive performance is statistically equivalent.

Association results

Relationships between cognitive impairment across time and clinical and functional variables in bipolar

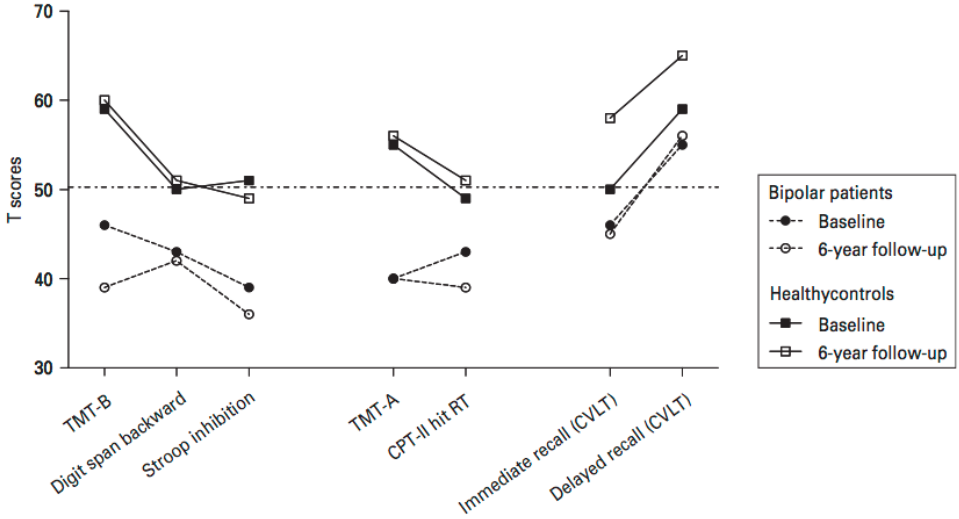

Fig. 1. Neuropsychological performance of the two groups (patients and healthy controls) at two time points (baseline and 6-year endpoint) for those tests that showed group effects in the multivariate repeated-measures analyses. Raw scores were transformed into *t* scores from normative data for adult subjects. Transformation makes the comparison among tests more easily understandable. TMT, Trail Making Test; CPT-II, Continuous Performance Test II; RT, reaction time; CVLT, California Verbal Learning Test.

patients can be seen in Table 3. Clinical characteristics at the endpoint were not related to a worsening in neuropsychological results, with the exception of duration of illness that showed a significant correlation with hit reaction time of CPT-II ($p=0.01$). In respect of FAST total score, partial correlations displayed strong relationships between poorer psychosocial functioning and a worsening of cognition. Interestingly, some of the neuropsychological tests (TMT-B, hit reaction time of CPT-II, immediate and delayed recall of CLVT and Stroop inhibition) that were more impaired at T2 also correlated with worse cognitive and occupational areas and total score of the FAST.

Discussion

The present findings show that the cognitive functioning of euthymic bipolar patients remains, on average, steadily affected in 6 years of follow-up. Interestingly, psychosocial impairment was more evident in those patients showing a neuropsychological decline. The cognitive domains found to be affected in the present study (executive functioning, inhibition, processing speed and verbal memory) are in congruence with the reported data in recent meta-analyses (Robinson *et al.* 2006; Torres *et al.* 2007; Mur *et al.* 2008; Arts *et al.* 2008; Bora *et al.* 2009; Kurtz & Gerraty, 2009). Furthermore, our results indicate that these particular cognitive domains are linked with psychosocial functioning.

As has already been mentioned, there are very few data regarding follow-up studies on neurocognition in bipolar disorder (Robinson & Ferrier, 2006; Mann-Wrobel *et al.* 2011). Our investigation had a unique design because the cognitive performance was assessed at two time points in a 6-year period of follow-up in euthymic bipolar patients and in the same healthy controls. Indeed, only five longitudinal studies on bipolar disorder and neurocognition have been published so far. Among these previous studies, four of them detected persistent cognitive impairment along time (Engelsmann *et al.* 1988; Balanzá-Martínez *et al.* 2005; Mur *et al.* 2008; Tabarés-Seisdedos *et al.* 2008), whereas one of them (Burdick *et al.* 2006) reported that executive and memory functioning suffered more variations over time.

In the present study, extending the re-examination until 6 years has demonstrated that cognitive dysfunction persists even during longer periods of clinical remission. What is more relevant, however, is that the changes in cognitive performance in 6 years affect directly the psychosocial adaptation of these patients as observed in the correlations with the FAST (Rosa *et al.* 2007). In particular, the areas that appear to be associated with the neuropsychological changes were the cognitive and occupational areas of the FAST. This latter area deserves a comment, since patients with

Table 3. *Association of neuropsychological delta scores (follow-up minus baseline) between clinical and psychosocial functioning variables in bipolar patients*

	Executive function		Processing speed		Verbal memory		
	ΔForward span	ΔTMT-B	ΔTMT-A	ΔCPT-II RT	ΔImmediate memory	ΔDelayed memory	Inhibition: ΔStroop inhibition
Clinical variables							
Age at onset, years	0.19	0.25	0.04	0.16	0.17	0.22	−0.05
Duration of the illness, years	−0.09	−0.33	0.33	−0.48*	−0.27	−0.26	−0.001
Time of stability, years	0.31	0.36	0.18	0.24	−0.02	0.17	0.35
Psychosocial functioning variables							
FAST overall score	−0.09	−0.67**	−0.06	−0.50**	−0.26	−0.47*	−0.32
Cognitive area of FAST	−0.16	−0.60**	0.02	−0.22	−0.41*	−0.63**	−0.43*
Occupational area of FAST	−0.08	−0.57**	−0.12	−0.46*	−0.18	−0.34	−0.29

Data are given as partial correlations controlling for affective low-level symptomatology (HAMD score).
TMT, Trail Making Test; CPT-II, Continuous Performance Test II; RT, reaction time; FAST, Functioning Assessment Short Test; HAMD, Hamilton Rating Scale for Depression.
* $p<0.05$, ** $p<0.01$.

bipolar disorder tend to have high rates of unemployment (Dean *et al.* 2004; Mur *et al.* 2009), and it may reflect the impact of the disorder on the psychosocial adaptation of patients. In this regard, previous studies have reported that unemployment would be particularly impaired in those with processing speed deficits (Mur *et al.* 2008) or with attention deficits (O'Shea *et al.* 2010).

Previous longitudinal studies evaluating clinical and neurocognitive predictors of functional outcome by means of the FAST (Martino *et al.* 2009; Bonnín *et al.* 2010) or other scales (Burdick *et al.* 2010) have demonstrated the strong relationship of neuropsychological performance and the daily functioning of patients. The cognitive variables that appeared to be related with poor functional outcome were processing speed (Burdick *et al.* 2010), verbal memory and executive functions (Bonnín *et al.* 2010), and verbal memory and attention (Martino *et al.* 2009). However, the neuropsychological performance of patients in these studies was obtained only once, and was used as a predictor of psychosocial adaptation, so the actual impact of cognitive changes on functioning could not be evaluated. This present study suggests that patients with changes in some cognitive domains (executive function, inhibition domain, processing speed and verbal memory) also exhibited poorer psychosocial functioning.

The linkage between clinical variables of severity and cognitive impairment has been evaluated in several studies in terms of age at illness onset (Bora *et al.* 2009), age (Arts *et al.* 2008; Gildengers *et al.* 2009), number of episodes (Robinson & Ferrier, 2006), years of stabilization and psychotic symptoms (Bora *et al.* 2007; Mann-Wrobel *et al.* 2011). In our study the only relevant clinical variable related to cognitive impairment was illness duration, where the longer the duration of illness the slower the processing speed. In the same line as other studies, analysing the moderator effect of aspects of illness progression is imprecise and not well defined.

The presumable impact of psychopharmacological treatment on cognitive dysfunction was not directly assessed because it was not the primary aim of the study. Medication can be a confounder (Robinson *et al.* 2006) and can have a negative impact on cognitive performance; effects on psychomotor speed have been described (Bora *et al.* 2009). Nonetheless, cognitive deficits are still evident in euthymic medication-free patients (Goswami *et al.* 2006) and our sample was not excessively medicated (two or fewer drug classes for most of them), which possibly may have reduced the effect on cognition (Donaldson *et al.* 2003; Martínez-Arán *et al.* 2005). Moreover, a previous study (López-Jaramillo *et al.* 2010) reported minimal effects of lithium on cognitive performance.

In spite of the growing number of studies about neurocognition in bipolar disorder, the neurobiological underpinnings of bipolar disorder remain unknown (Berk *et al.* 2011). The present study helps to elucidate the evolution of cognitive dysfunction in a sample of patients with bipolar disorder. The reported stability of cognitive impairment in the mid–late stages of the illness may contrast with recent evidence which supports the notion of neuroprogressive changes over time (Moorhead *et al.* 2007; Kauer-Sant'Anna *et al.* 2009; Berk *et al.* 2011). Our results are not completely inconsistent with this hypothesis because at the same time that the cognitive deficit persists across time in our sample, the findings also point out that a longer duration of illness is related to progressive changes associated with the illness itself. Future studies focused on cognition in unaffected first-degree relatives, drug-naive patients, early and late stage in bipolar disorder or on measurement of neurobiological biomarkers could answer the question of whether cognitive impairment is a part of neurodevelopmental abnormalities and clarify the pathophysiology and the links between cognitive dysfunction and disease progression (Dias *et al.* 2009; Kapczinski *et al.* 2011).

Some limitations warrant acknowledgement in the current study. First, the sample size is relatively small and there is a need of replication with larger samples; even though this is an extended follow-up of a sample published elsewhere (Mur *et al.* 2008), it is worth mentioning that the drop-out rate at 6 years later was only 15%. An additional weakness of this extended follow-up is that some of the key demographics were not matched any more (e.g. estimated pre-morbid IQ which was included as a covariate). Second, this considerably homogeneous sample with low rates of recurrence might not be representative of the majority of bipolar patients, being biased to patients with better outcomes (Maj *et al.* 1998; Goodwin & Vieta, 2005). However, the good clinical outcome of our sample has allowed us to demonstrate the continuity of neuropsychological deficits across a long period of time. Finally, our sample included both bipolar I and II patients; the sample size did not allow enough statistical power to conduct separate analyses for the two groups, but previous studies have reported similar rates of cognitive dysfunction and disability in both subtypes (Rosa *et al.* 2010; Solé *et al.* 2011, 2012).

In conclusion, cognitive performance is impaired in euthymic bipolar patients and this deficit remains stable on average over time. In spite of this, there was individual variability where some patients displayed a greater neuropsychological decline, which was associated with a poorer psychosocial adaptation at the end of the follow-up. This finding endorses the fact that longitudinal studies are needed to shed more light on the relative progression of cognitive impairment in subjects with bipolar disorder (Mann-Wrobel *et al.* 2011). The results of the follow-up studies provide clues about the disease process involved as they may contribute to the development of psychosocial and neuropsychological programmes for improving the currently low functional recovery rates in treated bipolar disorder patients (Gildengers *et al.* 2009; Martínez-Arán *et al.* 2011).

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Declaration of Interest

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ARTICLE 2

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A preliminary longitudinal study on the cognitive and functional outcome of bipolar excellent lithium responders

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Abstract

Background: Neurocognitive dysfunction in bipolar disorder represents a possible marker of underlying pathophysiology, but to date, most studies are cross-sectional and heterogeneous with regard to pharmacological treatments. In the present study we investigated the 6-year cognitive and functional outcome of a sample of euthymic excellent lithium responders (ELR).
Method: A total sample of twenty subjects was assessed at baseline and 6 years later: ten diagnosed of bipolar disorder according to DSM-IV criteria and ten healthy matched controls. The sample size was enough to find statistical differences between groups, with a statistical power of 0.8. Bipolar patients were on lithium treatment during all this follow-up period and fulfilled ELR criteria as measured by the Alda scale. A neuropsychological test battery tapping into the main cognitive domains was used at baseline and at after 6-year of follow-up. Functional outcome was evaluated by means of the Functioning Assessment Short Test at study endpoint.
Results: Repeated measures multivariate analyses of variance showed that bipolar patients were cognitively impaired in the executive functioning, inhibition, processing speed and verbal memory domains ($p < 0.03$) compared to controls and such deficits were stable over time. Longer duration of illness and lower psychosocial outcome were significantly related to cognitive impairment ($p < 0.05$).
Conclusions: Cognitive dysfunction was present even in euthymic ELR. These deficits remain stable over the long term, and are basically associated with greater symptoms and poorer psychosocial adjustment.
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1. Introduction

A growing body of evidence indicates that bipolar disorder (BD) is associated with cognitive deficits that worsen during manic or depressive episodes, persisting even during long-term periods of clinical remission [1]. This relation is still not well defined due to a number of uncontrolled variables such as age, level of education, illness history, chronicity, number of previous episodes, sub-threshold symptoms and, particularly, the effects of medication [2]. In the same line, there is a clear relationship with endocrinal, metabolic and cardiovascular issues which can modulate cognitive evolution [3]. Given that bipolar disorder is a chronic and recurrent disease, there is a strong need of long-term studies to ascertain the course of cognition and psychosocial adaptation in these patients [4].

To date, the available evidence from longitudinal studies is not in accordance with the hypothesis of a progressive nature of cognitive deficits in bipolar disorder [5]. Few longitudinal studies have demonstrated that there is a persistence of neuropsychological deficits, not a deterioration; and it has been related with psychosocial faulty adaptation in patients with remitted bipolar disorder [6,7]. A previous study from our group showed that cognitive deficits and poor psychosocial adjustment remained stable during a 6-year follow-up [8].

Following current treatment guidelines, the use of lithium as a long-term therapy is considered the first-line option for bipolar disorder [9]. Whether lithium impacts on cognition or not is still a matter of controversy about the neuroprotective vs. neurotoxic effects of this drug [10]. However, there is a consensus that an excellent lithium response may be one of the best biomarkers available [11]. In this regard, a cross-sectional

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study of euthymic bipolar patients on lithium monotherapy showed that executive functioning, but not processing speed, was similarly affected as compared to euthymic patients with combined treatments (including lithium) [12]. However, scarce longitudinal data are published on the long-term lithium monotherapy and its impact on cognitive functioning. Therefore, the investigation of the clinical features, the neuropsychological profile and the neurobiological factors of this relatively rare but treatment-sensitive subgroup becomes essential [11].

1.1. Aims of the study

The aim of this prospective, 6-year long-term study is to investigate the progression of cognitive performance and psychosocial functioning in a sample of excellent lithium responders compared with healthy-matched control subjects, and their relation with clinical variables.

2. Method

2.1. Subjects

Given that excellent lithium responders (ELR) comprise only one third of lithium-treated patients [13], we determined the sample size using differences in neuropsychological tests between BD patients and healthy controls. The total sample size required to detect a significant standardized difference (Cohen's d = 1.05) with a statistical power of 0.8 and a level of confidence of 95% [14] was of 20 participants. Ten euthymic bipolar patients on lithium monotherapy and ten healthy matched controls were evaluated at baseline and 6 years later with a clinical interview, biochemical tests and a neuropsychological battery.

The source sample consisted of 90 individuals: 44 patients attending an outpatient lithium clinic and 46 healthy matched controls, as reported elsewhere [12]. At 6-year interval, a total of 28 euthymic bipolar patients and 26 healthy matched controls agreed to be reassessed [8]. From these individuals, patients with lithium monotherapy at endpoint (i.e. excellent lithium responders; N = 10) were selected. Then, a matched sample of healthy controls was also selected from the sample of 26 (N = 10). These participants were selected to be perfectly matched in terms of age, gender and years of education, but never in terms of their neuropsychological performance. From the original sample, at endpoint, up to 16 euthymic patients could not participate in the reassessment because they did not fulfill the inclusion criteria: six of them due to their medical or psychiatric conditions; and the rest of them who refused to participate were taking polipharmacy and would have not met the criteria for being ELR. The local ethics committee approved the study and written informed consent was obtained from all participants.

Inclusion criteria included fulfilling Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR) criteria for bipolar disorder, being aged between 18 and 65 years and being in remission for at least 3 months [12]. Following previous studies [4], patients were characterized as euthymic if they had a total 17-item Hamilton Rating Scale for Depression (HAMD [15]); score below 8 and a total Young Mania Rating Scale (YMRS [16]); score below 6 for at least 3 months at the time of assessment. Exclusion criteria were the following: significant physical or neurological illness, substance abuse or dependence in the last 12 months and electroconvulsive therapy in the preceding year. At endpoint all patients could not receive any co-treatment with any mood-stabilizing medication other than lithium and had to fulfill the same inclusion and exclusion criteria.

Treatment response was assessed using the 11-point Alda scale that measures the extent of improvement during long-term treatment and weighs clinical factors considered relevant for determining whether or not the observed improvement is due to lithium treatment [17,18]. In previous studies a score of 7 or higher was considered >90% reduction of illness activity [19–21].

2.2. Demographic, clinical and pharmacological data

Demographic variables included age, gender, years of education and current work status. Clinical variables referred to depressive and manic symptoms, and other disease characteristics. Biochemical tests were performed on all patients, including for thyroid function, serum lithium levels and urine drug testing.

During all this follow-up period all patients had been attending lithium outpatient clinic and were on lithium treatment continuously; except for one female patient to whom lithium treatment had to be withdrawn during her pregnancy period. With respect to pharmacological treatment, at baseline all patients were on lithium monotherapy, except for two who were on combination treatment; specifically, one was with an antidepressant and another one was taking a low dose of an atypical antipsychotic. Both of them were on lithium monotherapy one year after baseline; following their psychiatrist prescription. Any other medications were needed during all this follow-up period. At endpoint, all patients were on lithium monotherapy. Lithium dosages at T1 were 834–1406 mg/day (serum lithium levels 0.52–0.86 mmol/l; treatment duration 1–11 years). At the study endpoint, T2, all patients were receiving lithium monotherapy (lithium dosage 800–1440 mg/day; serum lithium levels 0.39–0.99 mmol/l; treatment duration 6–17 years) (see Table 1).

2.3. Neuropsychological assessment

To characterize the cognitive functioning, a selected battery that included neuropsychological tasks covering the most impaired cognitive domains in bipolar disorder, i.e. executive and memory functioning [12,22–24] was administered to all participants (see Table 2 and Fig. 1). The estimated mean intelligence quotient (IQ) of the subjects was

Table 1
Demographic, clinical and pharmacological variables at baseline (T1) and at 6-year endpoint (T2).

	Bipolar patients (n = 10)		Healthy controls (n = 10)		Between groups at T1	Between groups at T2	Time differences Group patients
Variable	T1	T2	T1	T2	F/p	F/p	t/p
Mean age (S.D.)	45,6 (10.9)	50 (12.3)	42,30 (13)	48,80 (12.7)	0,73/NS	0.0/NS	0.91/<0.001
Mean years of education (S.D.)	10,3 (2.6)	10,3 (2.6)	11,8 (3.6)	12,2 (3.3)	0.38/NS	0.05/NS	0
Mean estimated pre-morbid IQ (S.D.)	101,5 (11.5)	110 (11)	106,5 (14.6)	110 (12.2)	1.15/NS	2.03/NS	0.3/NS
Mean YMRS Score (S.D.)	1.5 (2)	0.9 (1.6)	0.5 (0.9)	0.3 (0.9)	2.2/NS	1.05/NS	−0.2/NS
Mean HAMD Score (S.D.)	0.4 (0.5)	1.1 (1.1)	0.8 (0.6)	0.5 (0.7)	2.4/NS	2.1/NS	−0.27/NS
Mean GAF Score (S.D.)	78 (11.1)	77.5 (9.2)					−0.05/NS
Mean age of onset (S.D.)	24.4 (8.3)	24.4 (8.3)					0
Mean number of hospitalizations (S.D.)	2.2 (2.4)	2.2 (2.5)					0.74/0.015
Mean total number of manic episodes (S.D.)	2.2 (1.6)	3 (2.8)					0.98/<0.001
Mean total number of depressive episodes (S.D.)	1.6 (1)	1.6 (1)					0
Mean years of stabilization (S.D.)	5.2 (3.7)	10.7 (4.7)					0.96/<0.001
Mean duration of illness (S.D.)	19.4 (15.7)	25.6 (15.3)					0.97/<0.001
Mean years of lithium treatment (S.D.)	6.6 (4.8)	11.8 (5.2)					0.98/<0.001
Mean serum lithium levels, mmol/l (S.D.)	0.69 (0.2)	0.69 (0.3)					0.53/NS
Mean lithium dosage, mg/l (S.D.)	1120 (286)	1120 (320.3)					0.77/0.009
Mean Alda scale score (S.D.)		8 (1)					
Mean of cholesterol mmol/L (S.D.)	189.2 (24.3)	185.9 (27.2)					0.61/NS
Mean of fasting glucose mmol/L (S.D.)	101.9 (17.8)	106.6 (15.5)					0.56/NS
					χ^2/p	χ^2/p	χ^2/p
Gender, number of males (%)/females (%)	6 (60)/4 (40)		6 (60)/4 (40)		0/NS		
Current work status, N (%)					1.2/NS	2.3/NS	5.8/0.016
Active	7 (70)	6 (60)	9 (90)	9 (90)			
Inactive	0	0	0	0			
Retired/Disabled	3 (30)	4 (40)	1 (10)	1 (10)			
Positive family history of mental illness, N (%)	7 (70)	7 (70)	1 (10)	1 (10)	7.1/0.008		
Lifetime history of psychotic symptoms, N (%)	6 (60)	6 (60)					
Lifetime history of seasonal pattern, N (%)	6 (60)	6 (60)					
Personal history of suicide attempts, N (%)	5 (50)	6 (60)					
Diagnosis, N (%)							
Bipolar I disorder	8 (80)	8 (80)					
Bipolar II disorder	2 (20)	2 (20)					
Type of current medication, N (%)							
Lithium	8 (80)	10 (100)					
Lithium + other treatment	2 (20)	0 (0)					

T1, baseline; T2, 6-year endpoint; S.D., standard deviation; IQ intelligence quotient; YMRS, Young Mania Rating Scale; HAMD, Hamilton Rating Scale for Depression; GAF, Global Assessment of Functioning.

obtained from the weighted scores of the vocabulary and block design subtests of the Wechsler Adult Intelligence Scale (WAIS-III) [25], because these two scores are the most highly correlated with total IQ.

2.4. Psychosocial functioning

At endpoint, the Functioning Assessment Short Test (FAST) [26] scale was also administered in order to evaluate the psychosocial functioning more accurately. Its 24 items are divided among 6 specific areas of functioning: autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships and leisure time.

2.5. Statistical procedures

Data analyses were carried out with the statistical package SPSS for Windows, version 15.0 (SPSS Inc., USA). Differences between groups in demographic, psychosocial and clinical variables were assessed with univariate analyses of variance, by examining a single factor of group (out-patients versus healthy controls) at T1 and at T2; and paired two-sample t tests were used to assess time differences for such variables. Non-quantitative variables were examined by means of non-parametric tests.

Following the principles provided by Lezak et al. [27], neuropsychological tasks were sorted by cognitive domains [24] so as to reduce the number of analyses:

Table 2
Neuropsychological results at T1 and T2 for all participants.

	Bipolar patients		Healthy controls		Statistical analysis			Within-group effect size[c]	
Test	T1	T2	T1	T2	F	df	p Value	Bipolar patients	Healthy controls
Executive test					0.35[a]	3.15	NS		
TMT part B	78.7 (17)	81.3 (25.3)	55.56 (24.1)	52.11 (14.9)	8.74[b]	1.17	0.009	−0.12 (-0.99 - 0.76)	0.17 (-0.72 - 1.04)
FAS	37.4 (11.4)	37.6 (10.2)	40 (7.3)	40.89 (8.9)	0.48[b]	1.17	NS		
WAIS-III digit span backward	4.8 (1.8)	4.8 (2.4)	5.44 (1.8)	6.33 (1.7)	2.39[b]	1.17	NS		
Inhibition					1.14[a]	2.17	NS		
Stroop Inhibition	31.2 (6.4)	35.8 (9.8)	42.7 (6.7)	41.7 (6)	10.05[b]	1.18	0.005	−0.56 (-1.42 - 0.36)	0.16 (-0.73 - 1.03)
No. of perseverative errors WCST	27.5 (20.7)	18.5 (18.3)	21.9 (14.2)	15.1 (13.4)	0.46[b]	1.18	NS		
Attention					7.35[a]	3.16	0.003		
WAIS-III digit span forward	7.1 (1.8)	7.7 (1.7)	8.6 (1.9)	7.8 (1.8)	1.44[b]	1.18	NS		
CPT-II detectability (d')	0.98 (0.2)	0.82 (0.5)	0.64 (0.3)	1.26 (0.4)	0.12[b,*]	1.18	NS		
Processing speed					0.54[a]	2.17	NS		
TMT part A	42.7 (13.4)	41.9 (12.1)	30.5 (21.3)	27.8 (6.7)	6.31[b]	1.18	0.022	0.06 (-0.82 - 0.94)	0.17 (-0.71 - 1.04)
CPT-II hit reaction time	484.06 (36.5)	484.78 (81.7)	401.16 (48.6)	426.64 (52.9)	10.13[b]	1.18	0.005	−0.01 (-0.89 - 0.87)	−0.50 (-1.37 - 0.41)
Verbal memory					0.5[a]	5.14	NS		
CVLT first trial	7.4 (1.6)	6.3 (1.6)	6.9 (1)	7.2 (1.9)	0.16[b]	1.18	NS	−0.14 (-1.01 - 0.75)	−0.63 (-1.50 - 0.29)
CVLT total words	53.8 (9.3)	51 (10.5)	57 (6.7)	57.6 (7.1)	2.14[b]	1.18	NS		
CVLT immediate recall	10.3 (2.4)	10.7 (3.4)	12.2 (2.3)	13.5 (1.8)	6.02[b]	1.18	0.025		
CVLT delayed recall	10.8 (2.6)	11.7 (2.9)	12.5 (2)	14 (1.9)	4.03[b]	1.18	NS		
CVLT recognition	14 (1.2)	15 (0.9)	15 (1.1)	15.6 (0.7)	0.8[b]	1.18	NS		
Visual memory					2.22[a]	2.16	NS		
RCFT immediate recall	18.3 (3.2)	20.7 (3.8)	23.05 (4.4)	22.1 (5.4)	3.15[b]	1.17	NS		
RCFT delayed recall	18.44 (4.7)	21 (4.9)	22.5 (4.6)	21 (6.6)	0.82[b]	1.17	NS		

Data are given as mean (standard deviation).
T1, Baseline; T2, 6-year endpoint; df, degrees of freedom; NS, not significant; TMT, Trial Making Test; FAS, verbal fluency task of the Controlled Oral Word Association Test; WAIS-III, Wechsler Adult Intelligence Scale-III; WCST, Wisconsin Card Sorting Test; CPT-II, Continuous Performance Test II; CVLT, California Verbal Learning Test; RCFT, Rey Complex Figure Test.
[a] Repeated-measures MANOVA multivariate effects for each cognitive domain (group × time interactions).
[b] Repeated-measures MANOVA main effects of group (test of between-subjects effects).
[c] Calculated for T1 and T2 in each group (values in parenthesis refer to 95% CI).
* Group × time univariate significant interaction (p = 0.0001).

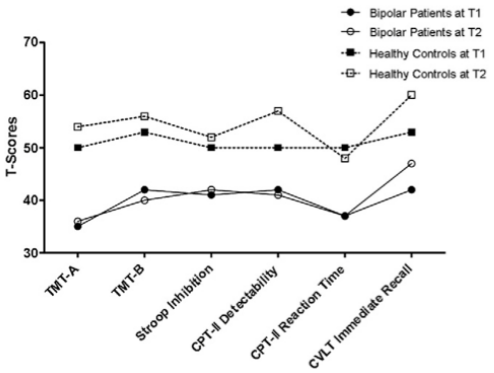

Fig. 1. Neuropsychological performance of the two groups (patients and healthy controls) at two time points (baseline and 6-year endpoint for those tests that showed group effects in the multivariate repeated-measures analyses. Raw scores were transformed into T scores from validated normative data for adult subjects. Transformation makes the comparison among tests more easily understandable. Abbreviations: CPT-II = Continuous Performance Test II, CVLT = California Verbal Test, TMT = Trail Making Test.

1. executive functions: the Trail Making Test part B (TMT-B) [28], the Verbal fluency task of the Controlled Oral Word Association Test (FAS) [29], the number of categories from the Wisconsin Card Sorting Test (WCST) [30], and the Digit Span backward from the WAIS-III [25], in which continuous monitoring and quick addition or deletion of contents are assessed.
2. inhibition: the Stroop Inhibition from the Stroop Color and Word Test [29], the number of perseverative errors at the Conners' Continuous Performance Test II (CPT-II) [31], and the number of perseverative errors from the Wisconsin Card Sorting Test (WCST). This cognitive domain was separated from the executive functioning to account for a different aspect of the executive functioning, i.e. to test individuals' capacity to supersede responses that are prepotent in a given situation [32].
3. attention: the Stroop interference from the Stroop Color and Word Test, the Digit span forward from the WAIS-III [25] and the detectability from the CPT-II [31];
4. processing speed: the Trail Making Test part A (TMT-A) [28] and the hit reaction time of CPT-II [31];
5. verbal memory: the first trial, total words, immediate recall, delayed recall and recognition from California Verbal Learning Test (CVLT) [33];

Table 3
Association of neuropsychological delta scores (follow-up minus baseline) between clinical and psychosocial functioning variables in bipolar patients.

	Executive function		Processing speed		Verbal memory		Inhibition
	ΔBackward Span	*ΔTMT-B*	*ΔTMT-A*	*ΔCPT_RT*	*ΔImmediate Memory*	*ΔDelayed Memory*	*ΔStroop Inhibition*
Clinical variables							
Age at onset (years)	0.3	0.57	0.06	0.6	0.12	0.31	−0.36
Duration of the illness (years)	−0.5	−0.75*	0.15	−0.68*	−0.61	−0.68*	−0.12
Time of stability (years)	0.18	0.18	−0.00	0.08	−0.32	− 0.17	0.09
Psychosocial functioning variables							
FAST overall score	−0.28	−0.72*	−0.3	−0.66*	−0.4	−0.74*	−0.05
Cognitive area of FAST	−0.21	−0.6	−0.3	−0.29	−0.25	−0.52	−0.06
Occupational area of FAST	−0.35	−0.70*	−0.55	−0.65*	−0.44	−0.63	−0.15

CPT, Continuous Performance Test; GAF, global assessment of functioning; RT, reaction time; TMT, Trail Making Test; FAST, Functioning Assessment Short Test.
* Significant correlations at $p < 0.05$.

6. and visual memory: immediate and delayed recall from Rey Complex Figure Test (RCFT) [34].

Performance on neuropsychological tasks was compared across the two groups by means of separate multivariate repeated-measures analyses of variance (MANOVAs) for each cognitive domain (see Table 2). Additional multivariate repeated-measures analyses of covariance were performed controlling for pre-morbid IQ, and for residual mood symptoms, as previous studies have reported that these variables may impact on cognition [22,35,36]. Cognitive variables that did not meet criteria for normal distribution were excluded: Stroop interference, number of perseverative errors at CPT-II and number of categories of WCST.

In order to establish changes in neuropsychological performance at 6-year follow-up, differences between scores at T2 and T1 were calculated for those variables that showed significant differences between groups, again to avoid multiple comparisons in a small sample. Therefore new variables that reflected performance decrement or increment across time were obtained (ΔDigit-backward, ΔTMT-B, ΔTMT-A, ΔCVLT immediate recall, ΔCVLT delayed recall and ΔStroop Inhibition). Relations between cognitive impairment and clinical and functional variables were analyzed with non-parametric correlations as shown in Table 3.

3. Results

3.1. Demographic, clinical and functional results

Demographic, clinical and pharmacological variables of euthymic bipolar patients and healthy controls are displayed in Table 1, separated by the two time points (T1 and T2). Both groups were well-matched in age, gender, years of education and estimated premorbid IQ, all scores being within the range of 100 ± 15, not exceeding the limits of normality. With regard to subclinical symptomatology, there were no significant differences on either YMRS score or HAMD between two groups at two time points. None of the participants showed any evidence of clinical abnormality as checked with biochemical tests. None of the participants presented diabetes mellitus; neither high blood pressure neither any cardiovascular disease. There were no statistical differences between groups neither in the mean of cholesterol nor in the mean of fasting glucose during the follow-up period (see Table 1).

During the study period, only two out of ten patients suffered relapses, still meeting ELRs criteria because the mean score in the Alda Scale was 8 at endpoint.

3.2. Neuropsychological performance

All neuropsychological variables included in each cognitive domain are listed in Table 2. The repeated-measures MANOVA showed no significant interactions of time (T1 versus T2) by group (patients versus healthy controls) except in the attention domain. In this domain, there was a significant time by group effect in the CPT-II detectability ($F(1,18) = 23.81$, $p = 0.0001$). By contrast, there were main effects of group in the executive domain (TMT-B), in the inhibition domain (Stroop inhibition), in the processing speed domain (TMT-A and CPT hit reaction time) and finally in the verbal memory domain (immediate recall). Even controlling for estimated pre-morbid IQ, the repeated-measures MANCOVA showed the same results (data not shown). The repeated-measures MANCOVA performed with pre-morbid IQ and with YMRS and HAMD scores showed again the same effects, except for the CVLT immediate recall which did not reach the significance threshold.

3.3. Association results

Relationships between cognitive impairment across time and clinical and functional variables in bipolar patients were analyzed as shown in Table 3. Clinical characteristics at study endpoint were not related to a worsening in neuropsychological results, with the exception of duration of illness that showed a significant correlation with delayed recall of CVLT ($rho = -0.68$, $p = 0.03$), TMT-B ($rho = -0.75$, $p = 0.01$) and hit reaction time of CPT ($rho = -0.68$, $p = 0.03$). With respect to FAST total score, correlations displayed

relationships between poorer psychosocial functioning and a worsening of cognition in the same neuropsychological tests (rho > 0.66, $p < 0.03$). Interestingly TMT-B and hit reaction time of CPT performance, which were more impaired at T2, also correlated with worse occupational functioning (rho = −0.7 and rho = −0.65, respectively, $p < 0.05$).

4. Discussion

The pattern of cognitive functioning across the course of illness is a poorly understood and important topic in research on bipolar disorders. Excellent lithium responders are relatively rare but provide an excellent opportunity to study cognitive effects and outcome over time. The present study shows that euthymic bipolar patients, even being ELR on lithium monotherapy, are impaired in many of the cognitive domains studied here, and such permanent deficits are related to chronicity and stationary psychosocial impairment. The apparent inconsistency that cognitive deficits remain stable during the follow-up period but chronicity is associated to poor cognitive performance may be explained by the fact that cognitive dysfunction is already detectable by the time of initial diagnosis or after the first episode [37,38] or at a pre-clinical stage and remain stable over the course of the illness [5]; before the current treatment had been established. Similar findings have been reported in unipolar depression [39]. Moreover lithium treatment may play a role as a protective factor [11,40] and may have contributed to the stability and lack of progression of cognitive impairment [41]. However, the significant group × time interaction for attention indicated that there was a differential change in longitudinal cognitive performance between patients and controls, which may suggest meaningful differences in cognitive trajectories between patients and controls for some of the tests. These results would be contrary to the hypothesis that there is no difference in longitudinal cognitive function.

Our results are partly consistent with the few previous longitudinal studies on the cognitive effects of lithium in bipolar samples [24,42–44]. Recently, in a 2-year naturalistic study [44], lithium was associated with better psychomotor speed. Post-hoc analysis also revealed that lithium treatment positively predicts improvements in verbal learning, and negatively predicts deterioration in verbal memory. In the 2-year follow-up study from our group [24], the lithium monotherapy group was cognitively impaired (executive dysfunction, attention, processing speed and visual memory) and such deficits were also maintained over time. However, the current sample displayed less neuropsychological tests impaired (except for attention differences), which may be explained by the low power of the current study. Alternatively, these differences may be explained by selecting ELR provides a great opportunity to study a more homogenous clinical sample with a better cognitive outcome; corresponding to the bipolar "core phenotype" [45]. Besides none of the patients sample presented any endocrinal or cardiovascular issue which could have modulated cognitive evolution [3].

In the present study, selecting ELR provides further evidence about the stability of neuropsychological impairment over time, and it confirms its association with poor psychosocial functioning.

The present study does not pretend to assess the presumable impact of psychopharmacological treatment on cognition but rather to assess cognitive and functional outcome in a particularly interesting group of patients in whom the influence of recurrences and pharmacotherapy can be easily controlled for. Previous works have described the deleterious effects of lithium: in verbal memory [46–49], in visual memory [50] and in psychomotor performance [48,49]. It is worth mentioning that in the findings from Pfennig et al., [50] there may exists a selection bias; given that there is no random assignation of patients in treatment groups (lithium vs non lithium group). In this regard, cognitive results may not be attributable to the treatment but to the sample characteristics in itself. Conversely, there is also evidence of improved cognition in lithium-treated patients [51,52]. One important aspect that has recently come to light is that lithium possibly preserves cognitive functioning [11], but only in the presence of pathology.

Bipolar disorder is associated with significant impairment in work [53], family and social life even in periods of clinical remission [7]. Subsyndromal symptoms, clinical variables and neurocognitive impairment appear to increase the risk of low functioning and disability [54,55]. From all clinical variables examined in our sample, chronicity was the only one related to neurocognitive impairment in some domains; as it was reported in previous works [50,53]. Interestingly, patients with dysfunction in those cognitive domains also exhibited lower psychosocial and occupational functioning.

There are some methodological limitations to mention. The present findings are based on a subset of ELR patients, so it cannot be ensured that the sample is representative of all patients with ELR, as some individuals who were not included may have been good lithium responders. The small sample size may be a limitation, although some differences could actually be detected and the hypotheses demonstrated; it could be insufficient power to detect and effect. The study is, however, still underpowered to detect changes along time, yielding to difficulties in interpreting the negative longitudinal findings. Some methodological strengths such as the good matching between groups and the re-evaluation of the healthy control subjects in the same time-lag are worth mentioning as well. This may have helped to overcome the practice effect artifact and normal effects of aging [5].

5. Conclusions

In conclusion, cognitive performance is impaired in executive functioning, attention, processing speed and verbal memory domains of ELR bipolar patients compared to

healthy controls. Apparently, some cognitive domains do not significantly change over the long term. These results may be suggestive that such deficits would take place in the early stages of the illness without being worsened by long-lasting lithium treatment. Poor cognitive performance is associated to chronicity and poor psychosocial and occupational adjustment. The results also indirectly support the hypothesis that most of the deficits take place in the early stages of the illness and do not worsen over time under the effects of lithium.

Even after a long period of euthymia and being an ELR on monotherapy, a cognitive and psychosocial functioning recovery cannot be achieved. These deficits may prove to be the greatest barrier to patient rehabilitation [46]. Even though some deficits may persist, patients exhibit greater ability and more strategies to cope with those deficits in daily life after having received a specific training [56]. It is time to implement new psychosocial interventions [57] and neuropsychological tools that may help these individuals to recover in all senses [58,59].

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Conflict of interest

E.V. has received research grants and served as consultant, advisor or speaker for the following companies: Almirall, AstraZeneca, Bristol-Myers Squibb, Elan, Eli Lilly, Forest Research Institute, Geodon Richter, Glaxo-Smith-Kline, Janssen-Cilag, Jazz, Lundbeck, Merck, Novartis, Organon, Otsuka, Pfizer Inc., Roche, Sanofi-Aventis, Servier, Solvay, Schering-Plow, Shire, Sunovion, Takeda, United Biosource Corporation, and Wyeth. E.V. has received research funding from the Spanish Ministry of Science and Innovation, the Stanley Medical Research Institute and the 7th Framework Programme of the European Union. MJP has received honoraria from Lundbeck and Glaxo-Smith-Kline for research and educational activities. The rest of the authors have no conflicts of interest to declare.

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ARTICLE 3

The impact of obesity on cognitive functioning in euthymic bipolar patients: a cross-sectional and longitudinal study

Running title: Obesity and cognition in bipolar disorder

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Authors EM and MM designed the study and wrote the protocol. MJP and EV contributed to the final design of the study. Authors EM, IF and MT collected data. EM managed the literature searches. Authors EM, MMA, MM and MJP undertook the statistical analyses and the interpretation of data. EM and MM wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

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ABSTRACT

Objective: To determine the influence of Body Mass Index (BMI) on cognition in euthymic bipolar patients and healthy matched controls in a post-hoc study of 2 cross-sectional and longitudinal exploratory studies.

Method: A total sample of 121 individuals was examined, which included 52 euthymic bipolar disorder (BD) I or II patients (DSM-IV-TR criteria) and 69 healthy controls (HC) matched by age and gender, categorized in two subgroups in terms of body mass index (BMI-factor): normal weight (BMI: 18.5-24.9 kg/m^2) vs. overweight-obesity (overweight, BMI of 25.0–29.9kg/m^2; and obese, BMI > 30 kg/m^2). Demographic, clinical, cognitive and psychosocial functioning data were collected from 2003 until 2011. Cognitive domains studied were: executive function, attention, processing speed, verbal memory and visual memory. Fifty-four subjects (28 BD and 26 HC) were re-evaluated after 6 years of follow-up.

Results: Obesity and BD showed a significant effect on cognition in cross-sectional and long-term MANOVA analyses ($F=2.54$; $df=7, 111$; $p=0.018$ and $F=2.25$; $df= 19, 23$; $p=0.033$, respectively). In cross-sectional linear regression model, global cognitive functioning was predicted by the interaction BMI-factor X group ($\beta=-0.44$, $SE=0.14$, $p=0.002$), current age ($\beta=-0.44$, $p<0.0001$) and premorbid IQ ($\beta=0.28$, $p=0.0002$), which explained a 56% of variance ($F=29.6$; $df=5, 115$; $p<0.0001$). Change on cognitive functioning over time was predicted by the interaction BMI-factor X group ($\beta=-0.8$, $SE=0.34$, $p=0.022$) and cognition at baseline ($\beta=-0.46$, $SE=0.15$, $p=0.004$), which explained a 27.65% of variance ($F=2.548$; $df=6,40$; $p=0.0349$). GEE showed that group × BMI (Wald $\chi^2=5.37$; $df=1$; $p=0.02$), age (Wald $\chi^2=22.08$; $df=1$; $p<0.0001$) and premorbid IQ (Wald $\chi^2=25.65$; $df=1$; $p<0.0001$) were the significant predictors.

Conclusions: Obesity was significantly associated with cognitive impairment in euthymic bipolar patients and it also appeared to affect cognition at long-term.

INTRODUCTION

Obesity can be conceptualized as a neurotoxic phenotype among individuals with neuropsychiatric disorders evidenced by: alterations in the structure and function of neural circuits and disseminated networks, diminishing cognitive performance, and adverse effects on illness trajectory[1]. Moreover, strong evidence also indicates that individuals with bipolar disorder exhibit cognitive deficits in attention, verbal memory and executive functioning during long-term periods of clinical remission [2–4]. However, there are still few studies that focus on both obesity and cognitive impairment and their interaction in bipolar disorder (BD).

Available data further suggest that being overweight is associated with cognitive deficits and numerous pathophysiological changes such as cardiovascular problems[5], impaired insulin regulation[6,7], systemic inflammation[8,9], abnormal leptin levels in the brain[10,11] and oxidative stress markers[12]. A growing number of literature now links obesity to poor adult cognitive functioning in healthy individuals[13–21] and in patients with psychiatric disorders such as schizophrenia[22–24] and bipolar disorder[25–27].

It is well known that bipolar disorder is associated with roughly twice the risk of obesity compared to non-clinical controls and the prevalence of obesity is approximately 60%[28]. Obesity, type II diabetes and insulin resistance (IR) have been found to be associated with a more advanced stage of BD with greater burden of disease, poorer functioning and greater disability [29]. In addition, poor treatment response, more previous depressive and manic episodes, higher baseline depression scores, and prolonged acute treatment were found in overweight and obese patients compared to normal-weight individuals with BD[30]. Obesity and bipolar disorder establish a bidirectional relationship evidenced by alterations in the structure and function of the central nervous system, in addition to greater depressive recurrence risk, cognitive dysfunction and risk of suicidality[31,32].

It is proposed that the co-occurrence between bipolar disorder and obesity may exert a toxic effect on the structures and connections within the brain which are associated with specific cognitive impairments[31]. A previous study has shown reductions in cortical white matter structures in obese bipolar patients[33]. It is known that clinical factors and pathophysiological mechanisms may contribute to obesity condition[26], but it may also be true that difficult-to-treat bipolar patients may be more prone to obesity, as a result of increased depressive and anxious morbidity, sedentary lifestyle, and medication side-effects[34]. Currently, there is growing interest in studying the obesity consequences in terms of cognition. To date, bipolar disorder is scarcely studied and only in cross-sectional designs[27] and there is a lack of long-term studies assessing this issue.

The effect of obesity on cognitive impairment in bipolar patients remains without a clear answer. The aim of the present study is to investigate the role of obesity in the progression of cognition in euthymic bipolar outpatients compared with healthy matched controls in a cross-sectional and longitudinal study. We hypothesize that obesity will impact on neuropsychological performance. Furthermore, we hypothesize that euthymic bipolar patients with higher body mass index at baseline will display worse cognitive outcome at endpoint.

METHOD

Subjects

The results from the current article are post-hoc analyses from previous publications[35,36]. For the cross-sectional study, a total of 121 subjects: 52 euthymic bipolar patients and 69 healthy matched controls were admitted into the study and were evaluated with a clinical interview, biochemical tests and a neuropsychological battery. Patients were recruited from the Outpatient Lithium Clinic at Hospital Santa Maria, Lleida, from 2003 until 2011. Inclusion criteria included fulfilling Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR) criteria for bipolar disorder, being aged between 18 and 65 years and

being in remission for at least 3 months[37]. Following previous studies[38], patients were characterized as euthymic if they had a total 17-item Hamilton Rating Scale for Depression[39] (HAMD) score below 8 and a total Young Mania Rating Scale[40] (YMRS) score below 6 for at least 3 months at the time of assessment. Exclusion criteria were the following: significant physical or neurological illness, substance abuse or dependence in the last 12 months and electroconvulsive therapy in the preceding year. Sixty-nine healthy controls, comparable in terms of gender, age and years of education were recruited with advertisements and from nonmedical hospital staff. Controls had no current or past psychiatric history, as determined by the Structured Clinical Interview for DMS-IV Axis I Disorders[41]. They had no first-degree relatives with bipolar or psychosis diagnoses. Control subjects underwent the same exclusion criteria as the patients and were assessed at the same full clinical and demographics interview by a trained psychiatrist. The Local Ethics Committee approved the study and written informed consent was obtained from all participants.

After six years of follow-up, the final sample was comprised by 54 subjects (28 euthymic individuals with bipolar disorder and 26 healthy matched controls), which was primarily used to investigate the longitudinal neuropsychological profile of euthymic bipolar out-patients compared with healthy matched controls in a 6-year period of follow-up[36]. On this occasion, participants were assessed again with the previous full study protocol (a clinical interview and a neuropsychological evaluation).

Demographic, clinical and pharmacological data

Demographic variables included age, gender, years of education and current work status. Psychiatric variables were obtained from the sample of bipolar patients, including: age at illness onset, number of prior manic episodes and hospitalizations, period of stabilization (years), history of psychotic symptoms, seasonal pattern, suicide attempts and bipolar subtype (I o II) during the psychiatric interview. Other physical and medical issues (e.g. cardiovascular, neurological, gastrointestinal, hematological, renal, hepatic, respiratory or endocrine illnesses)

and concurrent psychiatric and non-psychiatric medications were recorded in the same interview. Biochemical tests were performed in all patients, including for thyroid function, lipid profile, serum lithium levels and urine drug testing.

With respect to pharmacological variables, 17 patients were on lithium monotherapy, 32 on combination treatment (plus antidepressant or antipsychotic) and 3 with another mood stabilizers (i.e., valproate; see Table 1).

Body Mass Index (BMI)

BMI was calculated for each participant. Patients and healthy controls were categorized into two groups (BMI-factor): normal weight and overweight or obese based on the established criteria of BMI (normal weight, BMI of 18.5–24.9 kg/m^2; overweight, BMI of 25.0–29.9kg/m^2; and obese, BMI > 30 kg/m^2)[42].

Neuropsychological Assessment

To characterize the cognitive functioning, a selected battery that included neuropsychological tasks covering the most impaired cognitive domains in bipolar disorder, i.e. executive and memory functioning[37,43,44], was administered to all participants. The estimated mean intelligence quotient (IQ) of the subjects was obtained from the weighted scores of the Vocabulary and Block Design subtests of the Wechsler Adult Intelligence Scale (WAIS-III)[45],because these two scores are highly correlated with total IQ.

The instruments administered were:

i) Vocabulary, Block Design and Digits Subtests from WAIS-III[45];

ii) Wisconsin Card Sorting Test (WCST)[46], to assess executive function and perseverative behavior;

iii) Stroop Color and Word Test[47], to evaluate selective attention and inhibition capacity;

iv) FAS verbal fluency task of the Controlled oral Word Association Test/Categories[48], to assess executive function;

v) Trail making Test (TMT), to evaluate processing speed parts A (TMT-A) and cognitive flexibility parts B (TMT-B)[49];

vi) Conners' continuous Performance Test II (CPT-II)[50], to evaluate sustained attention, processing speed, and perseverative behavior;

vii) The California Verbal Learning Test (CVLT)[51], to evaluate verbal learning, recall, and recognition;

viii) Rey-Osterrieth Complex figure (RCFT)[52]; to evaluate visual memory.

Psychosocial functioning

To obtain information about the global activity, patients were assessed with the Global Assessment of Functioning (GAF) Scale[53]. Moreover, occupational functioning was specifically assessed and defined as follows: active (subjects with a full- or partial-time job, student and housewives), inactive (unemployed subjects and those with temporary sick leave) and retired (permanent sick leave or retired subjects) as reported elsewhere[37].

Statistical Procedures

Data analyses were carried out with the statistical package SPSS for Windows, version 22.0 (SPSS Inc., USA) and R statistical software (version 3.2.2)[54]. Demographics, clinical and psychosocial characteristics of groups were compared with t-tests for continuous variables and Chi-square for tests for categorical variables as descriptive statistics analyses.

For the cross-sectional analyses, neuropsychological data were analyzed in a 2-way multivariate analysis of variance (MANOVA; patients vs. controls and overweight or obese vs. normal weight). Those cognitive variables that showed a significant group X BMI-factor effect were z-transformed and then summed up into a composite score so as to obtain a global cognitive

index[35]. On measures of reaction time (where low scores indicate good performance), z-scores were reversed before forming the index.

Afterwards, a multivariate linear regression model was performed, in which the global cognitive index was the dependent factor to predict the impact of BMI on cognition comparing both groups (bipolar individuals and healthy controls). Subclinical (YMRS score and HAMD score), demographical (age, gender, years of education and estimated premorbid IQ) and functional (GAF) variables and BMI were included in the model using backward stepwise method in the whole sample, with the exception of significant interaction terms that were included together with the main effects. In order to determine the specific statistical weight of BMI subgroups and bipolar disorder, an interaction factor was created (group X BMI-factor), which was included in the regression model.

Clinical (age at onset, number of hospitalizations, years of stabilization, duration of illness and lifetime history of psychotic symptoms) variables were also included in another model using the backward stepwise method for the sample of bipolar individuals.

For the longitudinal analyses, the neuropsychological performance at endpoint was analyzed in a 2-way MANOVA with two between-subject factors (overweight or obesity vs. normal weight at baseline and bipolar individuals vs. healthy controls). Those cognitive variables that showed a significant effect of group X BMI-factor were z-transformed and then summed up into a composite score so as to obtain a long-term cognitive index at endpoint. A baseline cognitive index based on the follow-up sample was created using the same neuropsychological variables used for the endpoint cognitive index. Difference between both indexes was used to measure cognitive change over time. Afterwards, a general linear regression model was performed using the same backward stepwise method mentioned above to predict the impact of BMI at baseline on cognitive changes after a 6-year period of follow-up.

In order to determine whether changes in weight over time were associated with cognitive performance at follow-up a linear regression model, based on generalized estimating equations

(GEE) analysis, was fitted including the same predictors (group and gender as factors; and BMI, age, years of education, premorbid IQ, YMRS and HDRS as covariates) and time as the within-subject variable.

RESULTS

Baseline results

Demographic, clinical and pharmacological results

A total of 121 subjects were enrolled into the study. The demographic and clinical characteristics for the euthymic bipolar group and control group are shown in Table 1. Patients and healthy controls were comparable in age and gender. There were statistical differences between groups in terms of years of education, HAMD and YMRS. A total of 52 euthymic individuals with bipolar disorder were included in the analysis and they were categorized in two groups: 15 of them had a normal BMI and 37 patients presented overweight or obesity (18 and 17 respectively). There were statistical differences between BMI subgroups in age ($p<0.0001$) and in years of education ($p=0.013$). But there were not differences between BMI subgroups in IQ, HAMD and YMRS. There were no differences in the mean of cholesterol levels. As it was expected, there were statistical differences in the mean of triglycerides levels ($F=11.89$; $df=1, 50$; $p=0.001$) and fasting glucose ($F=5.41$; $df=1, 50$; $p=0.024$) between normal weight and overweight/obese patients groups. Table 1 displays mean scores, standard deviation and statistical results. From the 69 healthy controls that participated into the current study, two groups of BMI were obtained: 33 individuals presented normal weight and 35 exhibit overweight or obesity (24 and 8, respectively). There was a statistical difference between groups in terms of age (see Table 1), but there were not differences between groups in years of education, IQ, HAMD and YMRS. In terms of medical issues, participants with higher BMI presented more cardiovascular and endocrinal problems in both groups ($\chi^2=6.9$, $df=6$, $p=0.33$).

Neuropsychological performance

All neuropsychological variables and univariate effects at baseline are listed in Table 2. MANOVA showed a significant association between bipolar disorder individuals and BMI-factor ($F=2.54$; $df=7, 111$; $p=0.018$). In order to study the impact of obesity on cognitive functioning, a global cognitive index was created using the neuropsychological tests scores that displayed group X BMI-factor significant interactions in the two-way MANOVA: FAS, Stroop inhibition subscore, TMT-A, TMT-B, WCST number of categories, perseverative errors and detectability of CPT.

Impact of BMI, demographic and clinical variables on cognitive functioning

The regression linear model with cross-sectional data, including demographic, subclinical and functional variables to predict the global cognitive index, showed that the interaction factor (group by BMI-factor) was significantly associated to cognitive functioning ($\beta=-0.44$, Standard Error (S.E.)$=0.14$, $p=0.002$), as well as current age ($\beta=-0.44$, $p<0.0001$) and premorbid IQ ($\beta=0.28$, $p=0.0002$). The model explained a 56% of variance ($F=29.6$; $df=5, 115$; $p<0.0001$) (see Figure 1). Noteworthy, group and BMI scores were not significant factors when entered separately in the model.

A similar model was run for the bipolar individuals group including clinical variables. The model showed a significant association with age at onset ($\beta=-0.39$, $p=0.004$), duration of illness ($\beta=-0.34$, $p=0.017$) and BMI-factor ($\beta=-0.42$, S.E.$=0.16$, $p=0.009$), and it explained 40% of variance ($F=10.71$; $df=3, 48$; $p<0.00009$).

Longitudinal results

Long-term effects of overweight on cognitive functioning.

The dropout rate after 6 years was 55.4%; however, there were no differences at baseline between dropouts and those patients who were followed-up in terms of BMI, illness severity or

other relevant clinical variables (data not shown). Within the whole sample of 54 retested individuals, there were 7 (5 healthy controls and 2 euthymic bipolar patients) who refused to perform the neuropsychological evaluation again and were considered missing values. There were no significant effects of time × group nor group in BMI (F=0.90; df= 1, 52; p=0.77; and F=1.65; df=1, 53; P=0.2, respectively).

The results of two-way MANOVA showed again a significant main effect of group X BMI-factor at baseline (n=54; F=2.25; df= 19, 23; p=0.033). The cognitive variables that displayed significant differences in the two-way MANOVA analysis comparing patients and controls and BMI-factor were: FAS (F=10.47; df=1, 43; p=0.002); TMT-B (F=4.38; df=1, 43; p=0.042); and WCST number of categories (F=7.53; df=1, 43; p=0.009). These variables were used to create the baseline and endpoint cognitive indexes. Thus a new long-term cognitive index was created to capture the cognitive change over time calculating the difference between these two indexes. The regression linear model showed that cognitive changes were predicted by the interaction factor between group and BMI-factor (β=-0.8, S.E.=0.33, p=0.022), and baseline cognitive index (β=-0.46; S.E.=0.15, p=0.004), and explained a 27.65% of variance (F=2.548; df=6,40; p=0.0349; see Figure 2). The linear model based on GEE showed that group × BMI (Wald χ^2=5.37; df=1; p=0.02), age (Wald χ^2=22.08; df=1; p<0.0001) and premorbid IQ (Wald χ^2=25.65; df=1; p<0.0001) were the significant predictors of the cognitive changes along time. The rest of predictors or interactions were not significant.

DISCUSSION

The results of the current study show that bipolar individuals with overweight or obesity exhibit worse cognitive functioning compared to healthy controls and they still display worse cognitive performance than normal weight bipolar individuals after a 6-year follow-up period. These findings are consistent with the few available cross-sectional studies[25–27], but by adding the long-term results and using a global cognitive index, the present study may contribute to expand knowledge on how overweight or obesity affect cognition over a follow-up period, particularly

in bipolar patients. This represents a highly relevant finding as there are no studies that have considered the role of obesity on the longitudinal trajectory of cognitive deficits in BD.

This study shows that a global cognitive index composed by executive functioning, inhibition, processing speed and attention is impaired in bipolar patients with overweight or obesity. Previous works have already found that higher BMI is associated with worse cognitive performance cross-sectionally, but each study shows different cognitive domains to be affected and they used different cognitive tests and different comparison groups. In particular, Lackner and colleagues found that overweight patients with BD exhibit lower performance in the TMT-A/B as well as in the free recall performance of the CVLT compared to normal-weight patients with BD and controls[27]. In another recent study[26], comparing outpatients with either bipolar disorder or schizophrenia, obesity was associated with worse global cognitive ability only in bipolar disorder, as well as with poorer performance on individual tests of processing speed, sustained attention, verbal memory and reasoning/problem-solving. Previously, Yim et al.,[25] found that BMI was negatively correlated with attention and psychomotor processing speed as measured by the Digit Symbol Substitution Test in bipolar disorder patients. Furthermore, overweight or obese bipolar individuals had significantly lower score on the Verbal Fluency Test when compared to normal weight subjects with bipolar disorder. None of them show long-term effect of obesity on cognitive outcome, while in our study obesity affects cognition after 6-year follow-up, suggesting that overweight might be a neurotoxic factor of BD.

Indeed, the relationship between obesity and mental illness is bidirectional and surrounded by many confounding factors. Possible factors contributing obesity in bipolar disorder include lifestyle, medication exposure, neuroendocrine and neurotransmitter dysfunctions, genetic predisposition, immune dysfunction[55], and co-morbid conditions such as binge-eating disorder[56,57]. A severe course of illness[34] and symptoms such as disorganization and depression are themselves associated with overeating and subsequent weight gain[21]. Moreover, greater cognitive impairment may result in placement in treatment facilities that might alter access to health-promoting diets and lifestyle activities[58]. Selective impairments in cognitive functioning

can be predicting factors for obesity or play an according mediating role[27]. Our data were unable to determine whether obesity occurred prior to the onset of bipolar disorder or as a consequence of multi-episode/chronic illness and treatment. In any case, overweight or obese bipolar individuals displayed cognitive worsening after a 6 year-follow-up period, while normal weight bipolar individuals did not. Therefore, our findings may shed some new light to the neuroprogression model in bipolar disorder[59]. In our study, some clinical variables (such as age at onset and duration of illness) together with overweight or obesity contribute to worse cognitive functioning in short- and long-term outcomes.

The linkage between obesity and mood disorders may be due to a pathophysiological nexus that includes abnormalities in hypothalamus-pituitary-adrenal axis function[60], immune[55], inflammatory and metabolic systems[59], insulin resistance[29], disruption of brain circuitry[61], all of which are potential mediators of cognitive function[62]. More studies on inflammatory biomarkers (proinflammatory cytokines, anti-inflammatory agents including TNF-α inhibitors)[55,63] and peripheral markers of oxidative stress[64,65] may shed more light to this field.

Some limitations warrant acknowledgement in the current study. First, the sample size of the long-term study is relatively small, even though 6-year follow-up is quite a long time and more than the half of the bipolar disorder sample could be reevaluated. Second, another anthropometric data such as waist circumference, hip circumference, waist-to-hip-ratio, waist-to-height-ratio, and subcutaneous fat measurement should have been included. Third, BD individuals did not receive the same medication, even though most of them were on lithium treatment (94.2%), which might have influenced BMI and cognition similarly, although it cannot be disentangled whether obesity is a consequence of the illness or of the medication. In any case, the interaction of BMI and group was significant in all regression models, indicating that both conditions impact on cognitive performance. Fourth, glycemic control, cholesterol and triglycerides levels from healthy control group were not available. Hence, it was not possible to study the role of metabolic dysfunction in the relation between obesity and cognition. However, it is important to mention that more endocrinal and cardiovascular issues were registered in

participants with higher BMI regardless of whether they were patients or healthy controls. So the synergistic effect of bipolar disorder and obesity might be a better explanation of the cognitive dysfunction in euthymic bipolar individuals.

Conclusions

The prevalence of obesity is higher in bipolar disorder individuals than in healthy controls in the current sample. The presence of obesity explains worse cognitive performance mainly in executive functioning over non-obese bipolar subjects, and it is maintained over time. Hence, overweight bipolar disorder constitutes a neurotoxic phenotype, which may impact adversely on cognitive outcome. Better understanding of the mechanisms and management of obesity may aid in efforts to preserve cognitive[26] and general health[66] in bipolar disorder. Early intervention programs aimed at preventing neuroprogression[67] may benefit from including healthy habits modules focused on diet and preserving normal weight, as a way to prevent cognitive and functional decline.

CLINICAL POINTS:

1.- The impact of obesity on cognitive impairment has been addressed in this study. Some questions remain to be answered.

2.- Overweight or obesity together with some clinical variables (such as age at onset and duration of illness) contribute to worse cognitive functioning in a short and long-term outcome in bipolar patients.

3.- Preventing obesity in bipolar individuals may help to prevent cognitive decline.

FIGURES AND TABLES

Table 1. Demographic, clinical and pharmacological variables

Table 1. Demographic, Clinical and Pharmacological Variables

	Bipolar patients N=52			Healthy controls N=69			Between Bipolar patients groups		Between healthy control groups		Between patie and controls	
Variable	Normal weight BMI=18-24.9 kg/m² N=15	Overweight BMI >25 kg/m² N=37	All bipolar patients	Normal BMI=18-24.9 kg/m² N=34	Overweight BMI > 25 kg/m² N=35	All healthy controls	F	p	F	p	F	p
Age, mean (SD), y	35.2 (10.4)	48.19 (11.2)	44.44 (12.4)	39.06 (12)	49.6 (11.1)	44.41 (12.6)	14.9/	<0.0001	14.4/	<0.0001		<0.0001/0.9
Years of education, mean (SD)	12.2 (2.7)	10.11 (2.7)	10.71 (2.8)	13.29 (3.1)	12.14 (3.2)	12.71 (3.2)	6.6/	0.013	2.3/	0.1	13.1/	<0.000
Estimated premorbid IQ, mean (SD)	104.2 (11.9)	98.78 (11)	100.3 (11.5)	111 (11.5)	112.9 (9.4)	112 (10.4)	2.4/	0.1	0.5/	0.5	33.8/	<0.000
YMRS Score, mean (SD)	1.4 (1.8)	2.19 (2.4)	1.67 (0.3)	0.65 (1)	0.8 (1.1)	0.72 (1)	0.4/	0.5	0.4/	0.5	12.3/	0.001
HAMD Score, mean (SD)	1.8 (1.7)	1.78 (2)	2.08 (2.2)	1.06 (1.3)	1.57 (1.5)	1.32 (1.4)	0.3/	0.6	2.3/	0.1	5.4/	0.022
GAF Score, mean (SD)	78 (8.6)	70.57(9.4)	72.71 (9.7)	85.2 (5.1)	84.69 (5.1)	84.91 (5)	6.9/	0.011	0.1/	0.8	32.2/	<0.000
BMI, mean (SD)	22.82 (1.6)	31 (3.9)	28.65 (5)	22.47 (1.5)	29.07 (4.6)	25.82 (4.8)	62.3/	<0.0001	64.3/	<0.0001	10/	0.002
Age of onset, mean (SD), y	22.67 (9)	25.24 (10.7)	24.5 (10.3)				0.7/	0.4				
N° of hospitalizations, mean (SD)	1.4 (1.2)	3.37 (2.8)	2.42 (2.4)				4/	0.050				
Total n° of manic episodes, mean (SD)	1.6 (0.9)	2.84 (2.7)	2.33 (2.3)				2.2/	0.1				
Years of stabilization, mean (SD)	1.92 (2)	4.48 (5.6)	3.74 (4.9)				3/	0.1				
Duration of illness, mean (SD), y	12.47 (9.1)	22.65 (12.5)	19.71 (12.4)				8.2/	0.006				
Years of lithium treatment, mean (SD)	2.72 (2.3)	7.93 (7.2)	6.45 (6.6)				7/	0.011				
Serum lithium levels, mean (SD), mmol/l	0.58 (0.2)	0.70 (0.2)	0.67 (0.2)				4.5/	0.039				
Lithium dosage, mean (SD), mg/d	1014 (199)	1148 (316)	1110 (292)				2.2/	0.1				
Mean of Cholesterol, mean (SD), mg/dl	186.5 (42.2)	193.38 (36)	191.49 (37.5)				0.3/	0.6				
Mean of Triglycerides, mean (SD), mg/dl	91.33(36.9)	172.5 (87.5)	148.18 (84.4)				11.9/	0.001				
Mean of fasting Glucose, mean (SD), ,mg/dl	87.6 (8.9)	110 (36.7)	103.54 (32.8)				5.4/	0.024				
							χ^2	p	χ^2	p	χ^2	p
Gender, (number of males, %)	8 (53.3)	18	26 (50)	12	20	32 (47.8)	0.92/	0.8	3.3/	0.1	0.2/	0.7
Current work status, N (%)							10.9/	0.001	6/	0.014	13.9/	<0.000
Active	10	12	22 (42.3)	31	26	57 (82.6)						
Inactive	5	5	10 (19.2)	2	2	4 (5.8)						
Retired/disabled	0	20	20 (38.5)	1	7	8 (11.6)						
Positive family history of mental illness, N(%)	13	28	41 (78.8)	13	13	26 (37.7)	0.8/	0.4	0.01/	0.9	20.2/	<0.000
Lifetime history of psychotic symptoms, N (%)	12	29	41 (78.8)				0.02/	0.9				
Lifetime history of seasonal pattern, N (%)	8	21	29 (55.8)				0.05/	0.8				
Personal history of suicide attempts, N (%)	6	12	18 (34.6)				0.3/	0.6				
Suicidal Thoughts, N (%)	11	30	41 (78.8)				0.4/	0.5				
Diagnosis, N (%)							0.2/	0.7				
Bipolar I disorder	11	25	36 (69.2)									
Bipolar II disorder	4	12	16 (30.8)									
Type of current medication, N (%)							2.6/	0.6				
Lithium monotherapy	8	9	17 (32.7)									
Lithium + combination	6	26	32 (61.5)									
Other mood stabilizers	1	2	3 (5.8)									
Concomitant treatment, N (%)							1.2/	0.3				
Antidepressants	4	14	18 (34.6)									
Antipsychotics	5	16	21 (40.4)									
Benzodiazepines as hypnotic	0	3	3 (5.8)									
BMI subgroup, N (%)	15 (28.8)	37 (71.2)		34 (49.3)	35 (50.7)						5.1/	0.024

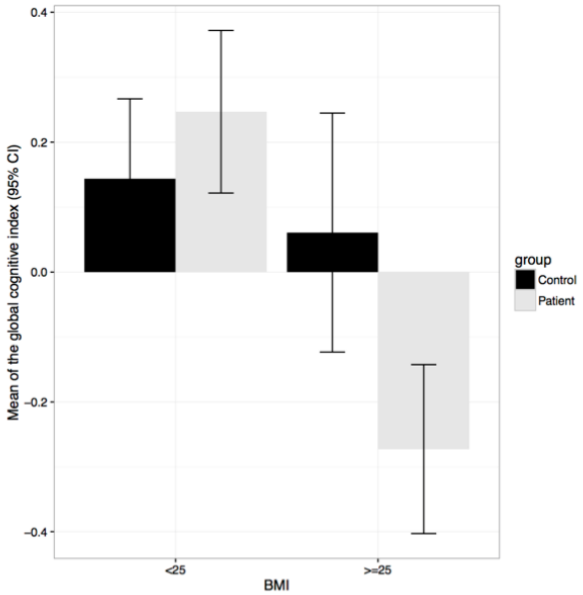
Table 2. Neuropsychological Results in all individuals

Table 2. Neuropsychological Results in all individuals

	Bipolar patients N=52			Healthy controls N=69			Bipolar patients (overweight vs normal weight)		Healthy controls (overweight vs normal weight)		Between patients and controls		Interaction	
Test	Normal weight BMI=18-24.9 kg/m² N=15	Overweight BMI >25 kg/m² N=37	All bipolar patients	Normal BMI=18-24.9 kg/m² N=34	Overweight BMI > 25 kg/m² N=35	All healthy controls	F	p	F	p	F	p	F	p
TMT part B	74.13 (31.6)	124.97 (73.9)	110.31 (68.4)	61.26 (26.2)	65.4 (24.1)	63.36 (25.1)	6.5	0.014	0.5	0.5	27.7	<0.0001	6.5	0.012
FAS	40.93 (11.7)	32.35 (10.5)	34.83 (11.4)	44.38 (9.7)	44.71 (10.1)	44.55 (9.8)	6.7	0.013	0.02	0.9	25.2	<0.0001	5	0.027
Digit span backward	5.6 (1.7)	5.03 (1.9)	5.19 (1.9)	6.56 (2)	6.03 (1.8)	6.29 (1.9)	1	0.3	1.3	0.3	9.9	0.002	0.02	0.9
No. of categories WCST	4.73 (1.3)	2.57 (1.8)	3.19 (1.9)	4.82 (1.8)	4.06 (2)	4.43 (1.9)	17.1	<0.0001	2.8	0.1	12.1	0.001	4.4	0.037
Stroop Inhibition	43.73 (10.2)	32.95 (9.9)	36.06 (11)	46.65 (9)	45.69 (8.4)	46.16 (8.7)	12.5	0.001	0.2	0.6	31.8	<0.0001	7.4	0.008
No. Persev. errors WCST	14.33 (14.2)	20.95 (18.3)	19.04 (17.3)	12.82 (9)	14.71 (11.6)	13.78 (10.4)	1.6	0.2	0.6	0.4	4.3	0.04	0.7	0.4
No. Persev. errors CPT	0.33 (0.7)	2.19 (2.8)	1.65 (2.5)	0.12 (0.4)	0.2 (0.4)	0.16 (0.4)	6.3	0.015	0.7	0.4	23.25	<0.0001	7.9	0.006
Stroop interference	3.53 (6.6)	1.06 (11.6)	1.77 (10.4)	2.99 (6.2)	2.59 (7.1)	2.78 (6.6)	0.6	0.4	0.06	0.8	0.42	0.5	0.4	0.5
Digit span forward	8.2 (2)	8.03 (2.3)	8.08 (2.2)	8.82 (2)	8.94 (1.5)	8.88 (1.7)	0.1	0.8	0.08	0.8	5.15	0.025	0.2	0.7
CPT detectability, d'	0.97 (0.4)	0.67 (0.5)	0.76 (0.5)	0.89 (0.4)	0.97 (0.4)	0.93 (0.4)	4.3	0.043	0.6	0.4	4.3	0.04	4.3	0.04
TMT part A	33.8 (11.1)	60.81 (32.2)	53.02 (30.3)	30.47 (13.2)	34.74 (14.3)	32.64 (13.8)	10	0.003	1.6	0.2	24.5	<0.0001	7.5	0.007
CPT-II hit RT, ms	438.16 (76)	475.84 (80.4)	464.97 (80.3)	400.3 (47.8)	455.81 (67.3)	428.45 (64.5)	2.4	0.1	15.5	<0.0001	7.7	0.006	0.3	0.6
CVLT first trial	6.93 (2)	5.95 (2.2)	6.23 (2)	6.71 (1.9)	6.77 (1.7)	6.74 (1.8)	2.7	0.1	0.02	0.9	2.2	0.1	2	0.2
CVLT total words	54.93 (8.1)	46.76 (11.6)	49.12 (11.3)	57.47 (8.2)	55.14 (7.8)	56.29 (8)	6.2	0.016	1.5	0.2	16.7	<0.0001	2.4	0.1
CVLT immediate recall	11.4 (3.2)	9.68 (3.5)	10.17 (3.5)	12.62 (2.6)	12.46 (2.7)	12.54 (2.6)	2.7	0.1	0.06	0.8	17.9	<0.0001	1.6	0.2
CVLT delayed recall	12.27 (2.8)	10.57 (3.6)	11.06 (3.5)	13.32 (2.4)	13.37 (2.3)	13.35 (2.3)	2.6	0.1	0.007	0.9	18.9	<0.0001	2.3	0.1
CVLT recognition	14.73 (1.5)	14.11(1.9)	14.29 (1.8)	15.35 (1.1)	15.26 (1.3)	15.3 (1.2)	1.3	0.3	0.1	0.7	13.9	<0.0001	0.8	0.4
RFCT immediate recall	20.67 (6)	17.16 (6.6)	18.17 (6.7)	24.15 (5.1)	24.4 (5.2)	24.27 (5.1)	3	0.1	0.04	0.8	31.9	<0.0001	2.7	0.1
RFCT delayed recall	20.57 (6)	16.84 (7.1)	17.91 (7)	23.82 (5.8)	24.04 (5.6)	23.93 (5.7)	3.2	0.1	0.02	0.8	27.5	<0.0001	2.4	0.1

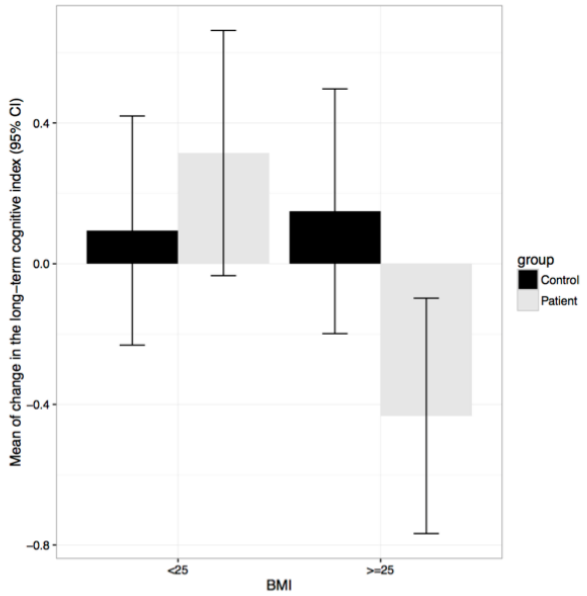
Results are shown as mean (SD). * = p<0.0001. Abbreviations: TMT: Trail Making Test; FAS: verbal fluency task if the controlled oral word association test; No: number; WCST, Wisconsin Card Sorting Test; Persev: perseverative; CPT-II: Continuous Performance Test II; RT: reaction time; CVLT California Verbal Learning Test; RFCT: Rey Complex Figure Test.

Figure 1. Prediction of global cognitive index by body mass index (BMI-factor) (BMI<25 and BMI >=25) and groups of participants (healthy controls and bipolar individuals) [a]



a. This figure shows the significant interaction effect between group and BMI-factor on the global cognitive index (Likelihood ratio test for the interaction with p=0.0088), adjusted by age and premorbid intelligence quotient (IQ)

Figure 2. Prediction of long-term cognitive index changes by body mass index (BMI-factor) (BMI<25 and BMI>=25) and groups of participants (healthy controls and bipolar individuals) [a]



a. This figure shows the significant interaction effect between group and BMI-factor measured at baseline, on the change in the long- term cognitive index (Likelihood ratio test for the interaction with p=0.01726), adjusted by age, premorbid intelligence quotient (IQ) and long-term cognitive index, all of them at baseline.

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ARTICLE 4

Neurotrophins, inflammation and oxidative damage as mediators of cognitive functioning in bipolar disorder

Running title: Biomarkers and cognition in bipolar disorder

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KEY WORDS: bipolar disorder, cognition, euthymia, biomarkers, Brain-derived neurotrophic factor.

ABSTRACT:

Background: Neurotrophins such as brain-derived neurotrophic factor (BDNF), inflammation and oxidative damage may contribute to the pathophysiology of bipolar disorder (BD) in terms of illness activity. To date, there is a lack of studies linking the cognitive impairment observed in BD with these neurobiological mechanisms. The study aimed to investigate the role of biomarkers in clinical and cognitive outcomes in a sample of bipolar individuals.

Methods: We measured BDNF, cytokines and oxidative stress markers in a sample of 133 individuals: 52 euthymic bipolar patients, 32 manic patients and 49 healthy controls. They were all assessed with a cognitive battery taping into the main cognitive domains (executive functioning, inhibition, attention, processing speed, verbal and visual memory). Sociodemographic and clinical data were collected. Multiple lineal regression models were built to study the impact of biomarkers on cognitive functioning.

Results: BDNF levels were decreased in euthymic ($p=0.039$) and manic ($p<0.001$) individuals. Conversely, inflammatory (interleukin 6 (IL-6)) ($p=0.019$) and oxidative stress ($p=0.003$) markers were increased in bipolar individuals compared to controls. BDNF predicted executive functioning ($\beta=0.01$, $p=0.02$) and verbal memory ($\beta=0.013$, $p=0.005$), together with other demographic variables. In particular, verbal memory was modulated by other conditions such obesity ($\beta=-0.04$, $p=0.005$). Neither inflammatory and oxidative stress biomarkers nor other relevant clinical variables showed any association with cognitive outcome.

Conclusions: From all the biomarkers analysed, BDNF was the only one which predicted cognitive dysfunction in bipolar disorder individuals. This study emphasizes the role of BDNF not only across mood phases but also in cognitive functioning.

INTRODUCTION

Bipolar disorder (BD) is a highly prevalent mood disorder affecting 1-3% of population (Merikangas et al. 2011). It has a long-term outcome much less favourable than previously thought, with incomplete recovery between episodes, cognitive impairment, and functional decline (Merikangas et al. 2011; Mora et al. 2012; Bourne et al. 2013; Samamé et al. 2014; Cardoso et al. 2015; Grande et al. 2016). Cognitive dysfunction is the key feature of functional impairment throughout periods of mania, depression and euthymia in BD (Green 2006; Tse et al. 2014).

The neurobiological underpinnings of cognitive dysfunction remain unknown in psychiatric disorders (Millan et al. 2012). Cognition is affected by a range of neurochemical mechanisms and cardiovascular parameters (Bauer et al. 2014). There is evidence that endocrine (such as obesity, insulin resistance and type II diabetes), metabolic and cardiovascular issues which are more common in BD (Kupfer 2005; Soreca et al. 2009; McIntyre et al. 2010; Calkin & Alda 2015), can negatively modulate cognitive progression (Strejilevich et al. 2015; Mora et al. 2017). In addition, clinical and preclinical evidence suggests that multiple mood episodes disrupt the homeostasis between neuroprotective mechanisms, such as brain-derived neurotrophic factor (BDNF) and inflammatory mechanisms or oxidative processes, and lead to neuronal death (Berk et al. 2011; Fries et al. 2012). This cycle of events is defined as "neuroprogression" and has been linked to an increase of individual's vulnerability to psychological stress, brain atrophy and ultimately, cognitive impairment (Kapczinski et al. 2008; Berk et al. 2010).

In the last decade, several pathophysiological mechanisms have been proposed and investigated to understand the interaction between these biological markers and mood symptomatology in BD (Pfaffenseller et al. 2013; Rosa et al. 2014; Rosenblat et al. 2015); however, significantly less investigation has been conducted to elucidate the effect of

inflammation, oxidative stress and neuroplasticity on cognition in BD (Barbosa et al. 2014; Khandaker et al. 2014; Rosenblat & McIntyre 2016; Stewart et al. 2009).

Peripheral biomarkers have been incorporated in the routine diagnosis, treatment and prognosis of psychiatric patients, but not to the same extent as in other medical specialties (Kapur et al. 2012; McGorry et al. 2014). The development of biomarkers, reflecting the underlying pathophysiological process, is a necessary step in the development of a more personalized and stratified practice of psychiatry, and specifically in BD (McGorry et al. 2014; Murck et al. 2015).

The aim of the current study is to investigative the role of biomarkers (neurotrophins and inflammation and oxidative stress markers) in clinical outcome and cognitive impairment in BD. We hypothesized that (1) bipolar individuals (euthymic and manic) compared to healthy controls would display different pattern of BDNF, inflammatory-cytokine and oxidative stress markers; and (2) cognitive performance would be associated with biomarkers levels regardless mood state.

METHOD

Participants

A total of 133 individuals were admitted into the study: 49 healthy controls, 52 euthymic bipolar and 32 manic bipolar individuals. All of them were evaluated with a clinical interview by a psychiatrist, and neuropsychological and biochemical tests.

Euthymic bipolar patients were recruited from the Outpatient Lithium Clinic at Hospital Universitari Santa Maria, Lleida, from 2003 until 2011. All of them met Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR) criteria for BD and they were aged between 18 and 65 years old. Euthymia state was determined when bipolar individuals obtained a total 17-item Hamilton Rating Scale for Depression (HAMD) (Hamilton M 1960) score below 8 and a total Young Mania Rating Scale (YMRS) (Young et

al. 1978) score below 6 for at least 3 months prior to the assessment (Mur et al. 2007). Significant non-psychiatric illness, substance abuse or dependence or electroconvulsive therapy during the preceding year were exclusion criteria.

Manic bipolar patients were recruited from the Inpatient Psychiatric Unit, at Hospital Universitari Santa Maria, Lleida, during manic phase from 2012 until 2014. Inclusion and exclusion criteria were the same as for euthymic patients, except for the criteria of clinical stability: manic patients were included if they had a total score of 14 or above in the YMRS (Tohen et al. 2009). The sample of manic patients was composed by patients who did not participated in previous studies by our group, with the exception of one male who had participated in the study as a euthymic patient and five years later participated as manic. Blood extraction was performed at the beginning of the hospitalization in the acute phase of the disorder. Cognitive assessment was performed in days before discharge when major manic symptoms were partially remitted.

Forty-nine healthy controls were enrolled with advertisements and from nonmedical hospital staff. Controls had no current or past psychiatric history, as determined by the Structured Clinical Interview for DMS-IV Axis I Disorders (First et al. 1999). If they had a history of any Axis I disorder in the first-degree relatives, they were excluded. Healthy subjects underwent the same exclusion criteria as the patients and were assessed at the same full clinical and demographics interview by a trained psychiatrist. The Local Ethics Committee approved the study and written informed consent was obtained from all participants.

Demographic, Clinical and Pharmacological data

Demographic variables included age, gender, years of education and current work status. Body mass index (BMI) was also calculated for each participant. The stablished criteria for BMI were: normal weight, BMI of 18.5–24.9 kg/m^2; overweight, BMI of 25.0–29.9kg/m^2; and obese, BMI > 30 kg/m^2 (National Heart LaBI NI of D and D and KD (National Heart LaBI

1998). Psychiatric variables were obtained from the sample of bipolar patients, including: age at illness onset, number of prior manic episodes and hospitalizations, period of stabilization (years), history of psychotic symptoms, seasonal pattern, suicide attempts and bipolar subtype (I o II) during the psychiatric interview. Other physical and medical issues (e.g. cardiovascular, neurological, gastrointestinal, haematological, renal, hepatic, respiratory or endocrine illnesses) and concurrent psychiatric and non-psychiatric medications were recorded in the same interview. Biochemical tests were performed in all patients, including for thyroid function, lipid profile, serum lithium levels and urine drug testing.

Neuropsychological Assessment

To characterize the cognitive functioning, a selected battery that included neuropsychological tasks covering the most impaired cognitive domains in BD, i.e. executive and memory functioning (Mur et al. 2007; Martinez-Aran et al. 2008; Mora et al. 2012) was administered to all participants. The estimated mean intelligence quotient (IQ) of the subjects was obtained from the weighted scores of the Vocabulary and Block Design subtests of the Wechsler Adult Intelligence Scale (WAIS-III) (Wechsler 2001), because these two scores are highly correlated with total IQ.

The instruments administered were:

i) Vocabulary, Block Design and Digits Subtests from WAIS-III (Wechsler 2001);

ii) Wisconsin Card Sorting Test (WCST) (Heaton 1981), to assess executive function and perseverative behaviour;

iii) Stroop Color and Word Test (Golden 1978), to evaluate selective attention and inhibition capacity;

iv) FAS verbal fluency task of the Controlled oral Word Association Test/Categories (Benton A. & Hamsher K 1976), to assess executive function;

v) Trail making Test (TMT), to evaluate processing speed parts A (TMT-A) and cognitive flexibility parts B (TMT-B) (Reitan 1958);

vi) Conners' continuous Performance Test II (CPT-II) (Conners 2000), to evaluate sustained attention, processing speed, and perseverative behavior;

vii) The California Verbal Learning Test (CVLT) (Delis 1987), to evaluate verbal learning, recall, and recognition;

viii) Rey-Osterrieth Complex figure (RCFT) (Meyers & Meyers 1995); to evaluate visual memory.

Biochemical Measures

In each participant, the blood was collected between 8:00 and 9:00 to avoid variations due to the circadian rhythm. Ten millilitres of blood were withdrawn from all participants by venepuncture into a free-anticoagulant vacuum tube. Serum was separated within 2 hours by centrifugation at 3500 *g* during 15 minutes at room temperature. All samples were stored at –80ºC until assayed in the IRBLleida Biobanc (B.0000682) and PLATAFORMA BIOBANCOS PT13/0010/0014. Afterwards, biomarkers were determined and all samples were assayed in duplicates. The biomarkers related to neurotrophins, inflammation and oxidative stress examined were:

-Brain-derived neurotrophic factor (BDNF) serum levels were measured with sandwich-ELISA, using a commercial kit according to the manufacturer's instructions (Chemicon, Temecula, CA, USA), as previously described (Kauer-Sant'Anna et al. 2009). All samples were assayed in duplicates. Data were expressed as ng/ml. Intra- and inter-assay coefficients of variation were <12%.

-Serum pro-inflammatory cytokines, such as interleukin 6 (IL-6) and tumor necrosis α (TNF-α) and an anti-inflammatory cytokine, interleukin 10 (IL-10) were measured according to the procedures supplied by the manufacturer using highly sensitive sandwich-ELISA kits for TNF-

α, IL-6 and IL-10 (Quantikine, R&D Systems, Minneapolis, Minn., USA). All samples were assayed in duplicates. Data were expressed as ng/ml. Intra- and inter-assay coefficients of variation were <10%.

-Oxidative damage was measured by the levels of lipid peroxidation using the thiobarbituric acid reactive substances (TBARS) method described by Wills (Wills 1966). All samples were assayed in duplicates and data were expressed as nmol/mL.

Statistical Procedure

Data analyses were carried out with the statistical package SPSS for Windows, version 22.0 (SPSS Inc., USA) and R statistical software (version 3.2.2) (R Core Team 2015). Demographics, clinical, pharmacological characteristics of groups were compared with analysis of variance (ANOVAs) for continuous variables and Chi-square (or exact's F) for categorical variables as descriptive statistics analyses. All variables were assessed for normality and those variables that were not normally distributed were log-transformed. To counteract the problem of multiple comparisons the Bonferroni correction was performed in variables which displayed statistical differences between the three groups in the ANOVAs. Performance on neuropsychological tasks was compared among three groups using a multivariate analysis of variance (MANOVA), and post-hoc analyses were then performed to establish pairwise differences. Neurobiological variables were also analysed with a MANOVA, and post-hoc analyses. Parametric and non-parametric correlations were carried out to explore associations between clinical, demographical and neurobiological variables to be included in further analyses. Multiple lineal regression models were built to study the impact of different variables (demographics and neurobiological markers) on cognitive functioning. For this purpose, neuropsychological tasks were z-transformed and grouped by cognitive domains (i.e., executive function, processing speed, inhibition, attention, and verbal and visual memories) based on our previous works (Mur et al. 2008). A composite score was created for

each cognitive domain, which included all the tests encompassed within each domain. On measures of reaction time (were low scores indicate good performance), z-scores were reversed before forming the composite score. Then, each cognitive composite score was used as a dependent variable in the regression models. Multi-collinearity was checked for each model using tolerance and variance inflation factor (VIF) criteria. Significant or relevant demographic variables, such as current age, premorbid IQ, body mass index and neurobiological variables and were included as predictive factors. The obtained results will be explained using standardized coefficient (β) and p values.

In order to elucidate the role of clinical factors and biomarkers on cognitive functioning, Pearson's correlations were firstly performed between these variables. Further regression models were carried out in the sample of patients (euthymic and manic individuals) including the independent factors mentioned above together with duration of illness, number of manic and depressive episodes and number of hospitalizations.

RESULTS

Demographical and Clinical Characteristics of the Sample

Demographics, clinical features and biomarkers levels of the 133 participants are depicted in Table 1. Euthymic bipolar patients and healthy controls were comparable in age and gender. There were statistical differences between groups in terms of years of education, IQ, BMI, HAMD and YMRS.

With respect to pharmacological variables, most of euthymic bipolar patients (81%) were on lithium treatment (15 patients were on lithium monotherapy and 27 on combination treatment -plus antidepressant or antipsychotic-). From the manic bipolar patients group, half of them (16 individuals) were on lithium combination treatment and the other half (16 individuals) with another mood stabilizers plus antipsychotics (i.e., valproate; see Table 1).

In terms of medical issues, there was a history of cardiovascular and endocrine issues in all groups without statistical differences (χ^2=11.8, df=16, p=0.76). Particularly, they had high blood pressure (9 healthy controls, 4 euthymic and 2 manic bipolar individuals), history of diabetes mellitus type 2 (4 healthy controls, 3 euthymic and 1 manic bipolar individuals), and subclinical (4 euthymic bipolar individuals) and clinical (2 manic) hypothyroidism. Regarding body mass index (BMI), euthymic bipolar individuals presented more overweight than manic individuals and healthy controls (F=4.8; p=0.01)

Neuropsychological Performance

All neuropsychological variables included in each cognitive domain and univariate effects are listed in Table 2. As it was expected, in the post-hoc analyses, euthymic and manic individuals performed worse compared to healthy control group (p<0.0001) in executive functioning, inhibition, processing speed, verbal and visual memory (see Figure 1). The only domain that displayed statistical differences between euthymic and manic groups was verbal memory (p<0.0001).

Analyses with Biomarkers and Association with Demographic, Clinical and Pharmacological variables

BDNF levels in both groups of bipolar patients (euthymic and manic individuals; p=0.039 and p<0.0001 respectively) were significantly lower compared to healthy controls. Conversely, the pro-inflammatory cytokine interleukin 6 (IL-6) levels were significantly higher in the group of manic patients compared to healthy controls (p=0.019), and the anti-inflammatory interleukin 10 (IL-10) levels were higher in both groups of patients compared to healthy controls (both comparisons with statistical significance; p<0.0001). Levels of TBARS were higher in euthymic bipolar group compared to healthy controls (p=0.003); but there were not statistical differences between manic patients group and the other groups, neither euthymic patients nor healthy controls.

Correlations between biomarkers and demographic variables showed that there was an association between IL-6 and BMI ($r=0.515$; $p<0.0001$) and with current age ($r=0.313$; $p<0.0001$) in all participants. Premorbid IQ displayed a significant relationship with IL-10 ($r=-0.268$; $p=0.002$) and with levels of oxidative damage (TBARS; $r=-0.247$; $p=0.005$).

BDNF showed a negative correlation with HDRS ($r=-0.251$, $p=0.004$) and YMRS ($r=-0.284$, $p=0.001$) in all participants. Conversely, as it was expected, IL-6 displayed a positive association with the same scales (HDRS: $r=0.176$, $p=0.045$; and YMRS: $r=0.192$, $p=0.029$). IL-10 did not show any association with these scales. When analysing patients alone (euthymic and manic), correlations between clinical variables and biomarkers showed that only IL-6 was associated with duration of illness ($r=0.245$; $p=0.025$). Regarding pharmacological treatment, most of bipolar euthymic patients and half of manic patients were on lithium treatment. There was not any significant correlation between lithium variables and BDNF levels.

Bipolar type I and type II euthymic individuals did not display any statistical differences in biomarkers levels (data no shown).

Impact of Biomarkers and Demographic Variables and BMI on Cognitive Functioning

Six regression models were performed, one for each neuropsychological domain, to explore the impact of biomarkers and other demographic variables on cognitive functioning. BDNF ($\beta=0.01$, $p=0.02$) was the only biomarker that explained executive functioning together with other variables: being manic ($\beta=-0.4$, $p=0.012$), current age ($\beta=-0.023$, $p<0.0001$) and premorbid IQ ($\beta=0.03$, $p<0.0001$), and explained a 56% of variance ($F=16.5$; $df=9,115$; $p<0.0001$) (see Figure 2).

Again BDNF ($\beta=0.013$, $p=0.005$) together with BMI ($\beta=-0.4$, $p=0.005$) and other variables [being euthymic ($\beta=-0.345$, $p=0.019$), being manic ($\beta=-1.07$, $p<0.0001$), current age ($\beta=-0.015$, $p=0.002$) and premorbid IQ ($\beta=0.018$, $p<0.0001$)] predicted worse performance in

verbal memory, and explained a 58% of variance (F=17.2; df=9.115; p<0.0001) (see Figure 2). The rest of the biomarkers did not predict any other cognitive domain.

Impact of Biomarkers and Clinical Variables on Cognitive Functioning in Bipolar Patients

Again 6 regression models were performed only analysing euthymic and manic bipolar individuals. Current age and premorbid IQ were predictor factors in all models (p<0.05). Being manic bipolar individual predicted worse performance on executive functioning (β=–0.33, p=0.029), verbal memory (β=–0.864, p<0.0001) and visual memory (β=–0.459, p=0.039).

From the clinical variables, the number of manic episodes (β=-0.066, p=0.011) was the only clinical variable that predicted worse performance on attention domain, together with current age (β=–0.025, p=0.001) and premorbid IQ (β=0.014, p=0.015), and explained a 32 % of variance (F=2.7 ; df=12, 70; p=0.004). The rest of clinical variables did not predict none of the other domains.

Verbal memory was predicted by BDNF (β=0.023, p=0.001), BMI (β=-0.05, p=0.017), together with being manic (β=–0.864, p<0.0001), current age (β=–0.018, p=0.023) and premorbid IQ (β=0.022, p=0.001), and explained a 54 % of variance (F=7; df=12, 70; p<0.0001).

DISCUSSION

The most remarkable finding of this study was the influence of neurotrophins on illness phases and cognitive dysfunction in bipolar patients, affecting particularly executive functioning and verbal memory. This represents valuable information as few studies had explored the role of biomarkers on cognitive symptoms in BD, and results had been contradictories.

Linking biomarkers and cognition, BDNF was the only one which influence positively cognitive performance, particularly in executive functioning and verbal memory. Interestingly, this latter domain (verbal memory) was modulated negatively by other conditions such as

obesity. Our results are partly consistent with the few previous studies that focus on biomarkers and cognitive outcome in BD (Dias et al. 2009; Lee et al. 2016; Cao et al. 2016). In terms of executive functioning, recently Lee and colleagues (Lee et al. 2016) reported that changes in plasma BDNF levels significantly correlated with changes in executive functioning (WCST scores) in BD type I with a specific BDNF genotype (Val66Met). There are three studies that have assessed verbal memory and biomarkers. Dias and colleagues (Dias et al., 2009) found a significant positive association between serum BDNF levels and a test of verbal fluency (Controlled Oral Word Association Test; COWAT) in both euthymic BD patients and controls. Recently, Cao and colleagues (Cao et al. 2016) have described BD patients carrying the met allele of the BDNF gene were found to have reduced memory performance on multiple CVLT scores and smaller hippocampus volumes compared to controls. In the same line, TNF-α, was found to be negatively correlated with accuracy on the delayed memory component on the Rey Auditory Verbal Learning Test (RAVLT) (Doganavsargil-Baysal et al. 2013) in euthymic type I individuals. Remarkably, the presence of verbal memory impairment across mood phases may indicate that these deficits are trait markers of bipolar illness (Gualtieri & Johnson 2006). Furthermore, current evidence indicates that the BD phenotype is heterogeneous and there may be different illness trajectories that could be at least in part explained by distinct underlying pathophysiological underpinnings (Berk et al. 2011; Birmaher et al. 2014). The current study provides evidence that other conditions such as obesity, which is considered a neurotoxic phenotype (McIntyre et al. 2013), can play a role on defining verbal memory as a trait marker. In a recent study from our group, we found that cognitive dysfunction was explained by the interaction of bipolar disorder and obesity at a time-point and at long-term (Mora et al. 2017). Duration of illness was the only clinical variable related with an inflammatory marker (IL-6) in the current study. In the same line, another study found that IL-6 levels showed significant differences between early and late stages of BD (Grande et al. 2014). A recent meta-analysis

(Fernandes et al. 2015), by contrast, reported that duration of illness in euthymia was not associated with BDNF levels, suggesting that it may not be a useful marker of illness stage but it could be a marker of illness activity instead. Furthermore, it has been reported that BDNF levels did not differ between bipolar patients, unaffected first-degree relatives and healthy controls. Thus, BDNF levels may not reflect high genetic risk for BD, acting as state markers rather than trait markers of the disease (Nery et al. 2016). The correlation of BDNF levels with mood symptomatology scales and mood phases may corroborate this hypothesis.

In our study, lithium variables were not significantly associated with BDNF levels which may indicate that lithium did not influence the relationship between neurotrofins and cognition. In this paper the impact of psychopharmacological treatment on the association between biomarkers and cognitive dysfunction was not directly assessed because it was not methodologically designed for this purpose. Focusing on lithium, it has been reported in the current literature that excellent lithium responders (ELR) had higher plasma BDNF levels and performed better on all neuropsychological tests than the remaining lithium patients (Rybakowski & Suwalska 2010) but worse than healthy controls at long-term (Mora et al. 2016). Further analysis with biomarkers selecting individuals taking lithium are warranted to understand the effects of lithium on cognition.

In our study, neither inflammatory neither oxidative stress markers influenced cognitive performance. Our results differ from previous studies (Bauer et al. 2014; Doganavsargil-Baysal et al. 2013). Although negative results could be attributed to sample size, it is important to report negative results (i.e. statistically non significant) since the literature on peripheral biomarkers for BD may be prone to publication bias and may have limited epidemiological credibility (Carvalho et al. 2016). Noteworthy, many other factors, related with mood symptoms, which may result in inflammation and oxidative stress have not been controlled for, such as undiagnosed inflammatory medical comorbidities, history of early childhood adversity,

dysfunctional gut-microbiota, dietary patterns, and low-grade idiopathic systemic inflammation (Bercik 2011; Brietzke et al. 2012; Salagre et al. 2017; Fagundes et al. 2013; Post et al. 2013; Jacka et al. 2017).

The reported discrepancies could arguably be attributed to some methodological limitations of the current study that warrant acknowledgement: the variety of techniques to measure biomarkers and demographic and clinical characteristics of the sample, such as sample size, age and gender-related brain characteristics (Blumberg et al. 2003), BD subtype (Strasser et al. 2005) and medication history (Yucel et al. 2007). In our sample euthymic bipolar disorder individuals might represent mid-late stage of the illness with low rates of recurrence which might not be representative of the majority of bipolar patients, being biased to patients with better outcomes (Goodwin & Vieta 2005). But including manic patients groups to the sample has allowed us to demonstrate the cognitive consequences of neurotrophins in different mood phases. Besides our sample was comparable in terms of gender and there were not statistical differences between groups BD type I and type II in terms of biomarkers levels.

Future investigations using larger samples, drug-naïve patients, selecting homogenous treatment response like excellent lithium responders, and longitudinal design incorporating repeated measures of these markers (Frey et al. 2013) are needed to reveal the specific connections between BD, biomarkers and neurocognitive performance. Moreover, in terms of oxidative stress markers, it would be very interesting to study other biomarkers like for example plasma glutathione levels, which are a measure of whole organism oxidative status (Jones 2006). These have been recently related to the onset and development of bipolar disorder and might account for both cognitive impairment and physical co-morbidities (Rosa et al. 2014). Furthermore, in terms of neuroplasticity, genotyping of BDNF might be more informative about the relation between neurotrophins and cognition since recent evidence reported BDNF val66met polymorphism, which modulate BDNF secretion, as a potential

vulnerability factor for cognitive impairment in BD (Rybakowski et al. 2006; Bauer et al. 2014; Lee et al. 2016) with its neuroimaging correlate (Cao et al. 2016). In the same line, BDNF Val66Met genotype has been described as a potential risk factor for obesity and insulin resistance measures in patients with BD receiving antipsychotics as well (Bonaccorso et al. 2015). Given the complexity of mental illnesses aetiology -which involves multiple interacting genetic, environmental and biological factors-, the study of child and adolescent offspring of bipolar parents who are at risk of developing mood disorders, may shed light on the understanding of the neurobiological underpinnings of BD (Mansur et al. 2016).

In conclusion, our findings support the hypothesis that BDNF is a biomarker for clinical and cognitive functioning in BD, specifically in executive functioning and verbal memory. Other variables such mood phase and obesity may be underneath the link between neurotrophins and cognition. Additional work is needed to understand how pro-inflammatory and oxidative damage processes affect brain function and induce cognitive impairment (Bauer et al. 2014). Monitoring biomarkers levels at the time of assessment in clinical psychiatry could help to tailor specific and individualized treatment interventions not only to treat mood symptoms but also to revert biological changes associated with the illness (Pfaffenseller et al. 2013) such as cognitive and functional decline.

FIGURES AND TABLES

Table 1. Demographical, clinical and neurobiological variables for euthymic bipolar and manic patients and healthy controls

Variables	Healthy Controls (n=49)	Euthymic Bipolar Patients (n=52)	Manic patients (n=32)	F or χ^2/p	Bonferroni post-Hoc
Age, y	48.3 (12.1)	47.52 (11.9)	41.25 (12.9)	3.6/0.029	HC>Ma
Gender, (number of males, %)	21 (42.9)	26 (50)	18 (56.3)	1.43/NS	
Mean estimated premorbid IQ	115.3 (9.9)	102.6 (11.6)	97.8 (11.6)	28.6/<0.0001	HC>Eu; HC>Ma
Current work status, N (%)					
Active	40 (81.6)	21 (40.4)	13 (40.6)	28/*	
Inactive	2 (4.1)	7 (13.5)	10 (31.3)		
Retired/Disabled	7 (14.3)	24 (46.2)	9 (28.1)		
Positive family history of mental illness, N (%)	18 (36.7)	39 (75)	15 (46.9)	15.8/*	
Education, y	12.7 (2.9)	10.3 (2.7)	11.75 (3.4)	7.9/0.001	HC>Eu
GAF score	NA	73 (9.5)	31.41 (7.1)	545.8/*	
BMI, kg/m^2	26.5 (5)	29 (4.6)	26.5 (3.8)	0.010	Eu>HC; Eu>Ma
Clinical Variables					
YMRS score	0.6 (1.1)	1.4 (1.7)	31.3 (5.9)	1118.2/*	Ma>Eu; Ma>HC
HAM-D score	0.9 (1.4)	2.4 (2.3)	8.3 (3.7)	100/*	Ma>Eu>HC;
Age of onset, y	NA	24.5 (10.3)	29.3 (10.7)	4.2/0.043	Ma>HC
No. of hospitalizations	NA	2.7 (2.7)	3 (2.6)	0.3/NS	
Duration of illness, y	NA	22.9 (12.4)	11.9 (11.2)	16.8/*	
Total no. of manic episodes	NA	2.6 (2.7)	2.9 (3.7)	0.2/NS	
Years of stabilization	NA	6 (5.9)	3 (3.4)	6.8/0.011	
Lifetime history of psychotic symptoms, N (%)	NA	41 (78.8)	27 (84.4)	0.39/NS	
Lifetime history of seasonal pattern, N (%)	NA	29 (55.8)	18 (56.3)	0.002/NS	
Personal history of suicide attempts, N (%)	NA	20 (38.5)	6 (18.8)	3.6/0.06	
Diagnosis, N (%)					
Bipolar I disorder	NA	34 (65.4)	31 (96.9)	11.1/0.001	
Bipolar II disorder	NA	18 (34.6)	1 (3.1)		
Type of current medication, N (%)					
Lithium monotherapy	NA	15 (28.8)	0	18.8/*	
Lithium + combination	NA	27 (51.9)	16 (50)		
Valproate + combinarion	NA	8 (15.4)	16 (50)		
None	NA	2 (3.8)	0		
Lithium					
Years of treatment, y	NA	9.2 (6.7)	1.2 (1.6)	21.6/*	
Serum lithium levels, mml/dL	NA	0.7 (0.2)	0.65 (0.1)	0.7/NS	
Lithium dosage, mg/day	NA	1128.6 (278.7)	1062.5 (215.6)	0.7/NS	
Biomarkers					
BDNF, ng/ml	45.86 (13.6)	40 (9.9)	35.05 (10.6)	8.6/*	HC>Eu; HC>Ma
logIL-6	0.86 (0.5)	1.09 (0.6)	1.23 (0.7)	4.1/0.018	Ma>HC

logIL-10	-2.24 (0.4)	-1.18 (1.4)	-1.18 (1.4)	12.5/*	Ma>HC; Eu>HC
logTNF	-0.51 (2.4)	-0.04 (2.8)	0.71 (2.8)	2/0.14	
logTBARS	2.51 (0.6)	3.08 (1)	2.79 (0.9)	5.6/0.005	Eu>HC

Values represent mean and standard deviation (SD) unless otherwise specified.
Statistics of between-subject effects from the multivariate analyses of variance. Abbreviations: GAF = Global Assessment of Functioning, YMRS = Young Mania Rating Scale, HAM-D = Hamilton Rating Scale for Depression, CR= Cognitive Reserve, NA = Not applicable, NS = Not significant. HC=Healthy Controls, Eu=Euthymic Patients, Ma=Manic patients. *=<0.0001

Table 2. Neuropsychological Test Results: Comparison of Euthymic Bipolar and Manic Patients and Healthy Controls

Neurocognitive Tests	Healthy Controls (N = 49)[a]	Euthymic Bipolar Patients (N = 52)	Manic Patients (N=32)	F/*p*	Bonferroni Post Hoc
Executive Functioning Domain				<0.0001	HC>Eu; HC>Ma
TMT part B	62.1 (26)	117 (72.2)	117.9 (64.3)	13/<0.0001	HC>Eu; HC>Ma
FAS	43.47 (9.2)	34.25 (11.6)	37.16 (11.9)	8.8/<0.0001	HC>Eu; HC>Ma
WAIS-III digit span backward	6.51 (1.8)	5.06 (2)	4.31 (1.6)	14.8/<0.0001	HC>Eu; HC>Ma
Number of categories WCST	4.16 (2)	3.13 (2)	1.94 (1.5)	12.4/<0.0001	HC>Eu >Ma; HC>M
Inhibition Domain				<0.0001	HC>Eu; HC>Ma
Stroop inhibition	45.87 (9.6)	34.94 (11.9)	30.47 (11.4)	38.5/<0.0001	HC>Eu; HC>Ma
No. of perseverative errors WCST	10.6 (9.5)	16.81 (12.7)	10.87 (6.5)	5.4/0.006	HC>Eu; Ma>Eu
No. of perseverative errors CPT	0.24 (0.6)	2.42 (4.3)	3.35 (3.6)	9.1/<0.0001	HC>Eu; HC>Ma
Attention Domain				0.002	HC>Eu
Stroop interference	4.92 (7.7)	2.63 (10.7)	-0.4 (8.9)	3.1/0.05	HC>Ma
WAIS-III digit span forward	8.76 (1.9)	8.06 (2.1)	8.34 (1.6)	1.6/0.21	NS
CPT-II detectability	1.02 (0.4)	0.72 (0.4)	0.7 (0.5)	7.3/0.001	HC>Eu; HC>Ma
Processing Speed Domain				<0.0001	HC>Eu; HC>Ma
TMT part A	32.4 (12.5)	54 (30.4)	50.19 (19.9)	11.5/<0.0001	HC>Eu; HC>Ma
CPT-II hit reaction time	428.43 (63.3)	479.18 (98.4)	501.65 (103.2)	6.9/0.001	HC>Eu; HC>Ma
Verbal Memory				<0.0001	HC>Eu >Ma; HC>M
CVLT first trial	7.07 (2.1)	5.9 (2)	4.94 (1.6)	11.4/<0.0001	HC>Eu; HC>Ma
CVLT total words	58.93 (7.5)	48.13 (12.1)	40.34 (10.6)	31.9/<0.0001	HC>Eu >Ma; HC>M
CVLT immediate recall	13.93 (2)	10.12 (3.7)	7.06 (3.5)	45.7/<0.0001	HC>Eu >Ma; HC>M
CVLT delayed recall	14.56 (1.6)	11.19 (3.1)	7.28 (3.6)	51.3/<0.0001	HC>Eu >Ma; HC>M
CVLT recognition	15.82 (0.4)	14.62 (1.7)	14.03 (2.6)	11.2/<0.0001	HC>Eu; HC>Ma
Visual Memory				<0.0001	HC>Eu; HC>Ma
RCFT immediate recall	25.22 (4.9)	18.2 (6.5)	16 (7.4)	23.8/<0.0001	HC>Eu; HC>Ma
RCFT delayed recall	25.26 (5.5)	19.26 (7.3)	15.22 (7.9)	20.7/<0.0001	HC>Eu >Ma; HC>M

Values shown as mean (SD).
Statistics of between-subject effects from the multivariate analyses of variance.
Abbreviations: CVLT = California Verbal Learning Test, TMT = Trail Making Test, RCFT=Rey Complex Figure Test, HC=Healthy Controls, Eu=Euthymic Patients, Ma=Manic patients

Figure 1. Neuropsychological performance adjusted by age, premorbid IQ and years of education from all participants

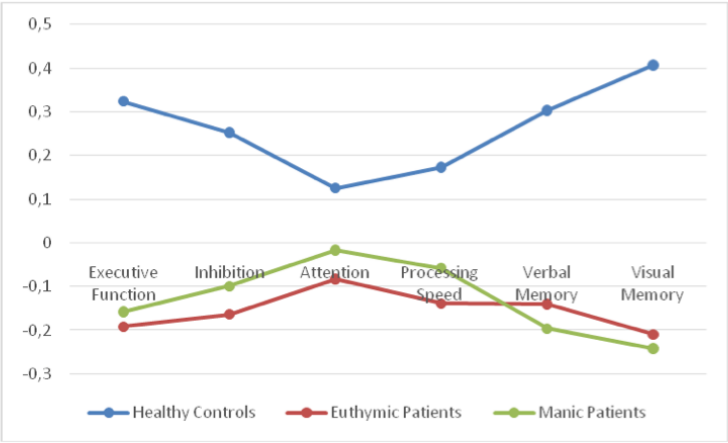
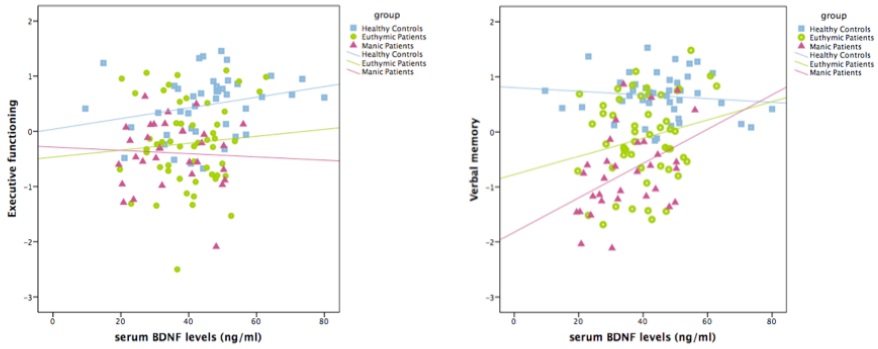


Figure 2. Scatter plots displaying predicted executive functioning (a) and verbal memory (b) by BDNF levels clustered by euthymic and manic bipolar individuals and healthy controls.

a b



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6. DISCUSSIÓ

6.1 Discussió dels resultats

El nostre estudi amplia el coneixement de la disfunció cognitiva en el trastorn bipolar, que representa el major obstacle de la recuperació funcional d'aquests pacients (Green 2006). La principal troballa d'aquesta tesi és que s'ha pogut descriure l'evolució de la disfunció cognitiva en un estadi intermedi de la malaltia i la seva relació amb diferents variables neurobiològiques: la resposta al tractament amb liti, l'obesitat i les neurotrofines.

A la literatura no existeix consens sobre com és perfil cognitiu propi del trastorn bipolar (Strejilevich et al. 2015). Hi ha discussió sobre la teoria de la neuroprogressió en la qual el curs del trastorn bipolar inclou recaigudes, augment de la severitat dels símptomes i de la comorbiditat mèdica (Kapczinski, Dias, Márcia Kauer-Sant'Anna, et al. 2009) i per tant, la repetició dels episodis condueix al deteriorament cognitiu progressiu (Post et al. 2012); mentre que d'altres autors (Martino et al. 2009; Samamé et al. 2014) no donen suport a aquesta teoria i defineixen la disfunció cognitiva com una causa i no com una conseqüència de la progressió de la malaltia. Els estudis longitudinals poden contribuir a resoldre aquesta qüestió.

En el primer article s'ha definit que les àrees afectades de la cognició són les funcions executives, la inhibició, la velocitat de processament i la memòria verbal comparat amb controls sans. Aquests dèficits es van mantenir estables al llarg del temps; a excepció de la memòria verbal, en la qual el controls milloraven al llarg del temps mentre els pacients no; per tant, podrien tenir afectada la capacitat d'aprenentatge. Els estudis longitudinals discrepen sobre les àrees cognitives afectades i sobre les variables que hi intervenen (Bourne et al. 2013; Cardoso et al. 2015; Samamé et al. 2014; Strejilevich et al. 2015). En un recent meta-anàlisis (Samamé et al. 2014) també descriuen que el pacients bipolars eutímics no mostren diferències al llarg del temps comparat amb els controls; si bé, també detecten pocs estudis on s'hagi avaluat extensament a controls sans i a més, un terç dels estudis que revisaven disposaven de mostra amb població d'edat avançada on també es podien atribuir canvis cognitius secundaris a l'envelliment (Gildengers et al. 2013). Cal esmentar que el disseny metodològic dels nostres articles longitudinals (articles 1, 2 i 3) no mostren les limitacions que es descriuen en d'altres, donat que s'avaluen els controls sans en dos ocasions i s'utilitza una bateria neuropsicològica extensa.

La persistència de disfunció cognitiva tant en la mostra general (article 1) com en la submostra d'ELR (article 2) s'ha associat amb la cronicitat i amb una pobra funcionalitat psicosocial al llarg del temps. Aquesta aparent inconsistència entre que els dèficits cognitius romanen

estables però s'associen als anys de duració de la malaltia, es podria explicar pel fet que la disfunció cognitiva ja és present en el moment inicial del diagnòstic o després del primer episodi (Lera-Miguel et al. 2011; Lewandowski et al. 2011), o fins i tot abans del primer episodi, en els estadis pre-clínics, i es mantenen estables al llarg del curs de la malaltia (Samamé et al. 2014). De fet, quan s'estudien familiars de primer grau de persones afectades de trastorn bipolar, aquests també presenten dèficits significatius en les funcions executives, la memòria verbal i l'atenció sostinguda (Bora et al. 2009; Nehra et al. 2014). Aquests resultats indiquen que la disfunció cognitiva podria ser un marcador de malaltia i no una conseqüència del curs del trastorn (Cardoso et al. 2015). Per altra banda, també existeixen diferents estudis que suggereixen que els pacients amb trastorn bipolar podrien tenir les funcions cognitives premòrbides preservades abans de l'inici del trastorn (Cannon et al. 2002; Zammit et al. 2004; Tiihonen et al. 2005; MacCabe et al. 2010; Lewandowski et al. 2011). Fins i tot, alguns troben que el rendiment escolar d'excel·lent durant la secundària augmenta el risc 4 vegades de desenvolupar trastorn bipolar (MacCabe et al. 2010). Aquests resultats indiquen que les bases del neurodesenvolupament del trastorn bipolar difereixen d'altres trastorns com l'esquizofrènia (Zammit et al. 2004).

La relació entre la disfunció cognitiva i les variables clíniques les valorem en tots 4 articles. La discrepància entre els perfils neuropsicològics descrits a la literatura pot ser deguda a múltiples motius. Alguns autors adverteixen que s'ha de ser cautelós a l'hora de confiar en les descripcions subjectives de la malaltia (Cardoso et al. 2015). Per exemple, el nombre d'hospitalitzacions no sempre correspon amb el nombre d'episodis. Els episodis hipomaníacs o depressius menys severs no se solen identificar com a episodis de recaiguda per part dels pacients. Des del punt de vista estadístic, a la literatura trobem que s'han emprat diferents procediments. Alguns estudis han utilitzat les correlacions, mentre d'altres han realitzat tècniques més complexes com els anàlisis de regressió. També a l'hora d'analitzar el rendiment cognitiu, hi ha estudis que analitzen els dominis cognitius com s'han fet al 1r, 2n i 4t articles mentre en el tercer article, s'ha realitzat un índex cognitiu global a partir dels resultats d'una MANOVA de dos factors. Si bé, d'altres estudis empren totes les tasques neuropsicològiques on hi ha més risc d'obtenir error tipus I, amb els nostres procediments estadístics s'ha intentat minimitzar aquest error. Un altre motiu pel qual els resultats dels longitudinals mostren discrepàncies és que en els estudis longitudinals es produeix un biaix de selecció de pacients amb poques recaigudes i amb un millor pronòstic clínic (Goodwin & Vieta 2005), que no és

representativa de la majoria de pacients amb trastorn bipolar, deixant a fora els pacients amb més recaigudes i irregular adherència al tractament.

La medicació està descrita com un factor de confusió en l'avaluació cognitiva (Robinson & Ferrier 2006b). La relació entre cognició i medicació no ha estat l'objectiu dels nostres treballs, donat que és difícil dissenyar estudis amb mostres exactament comparables. Tot i així, la nostra mostra de pacients eutímics no estava excessivament medicada (2 o menys famílies de fàrmacs en la majoria d'ells) que possiblement ha reduït l'efecte del tractament sobre la cognició. Existeix literatura amb resultats ambigus sobre els efecte de la medicació sobre la cognició, sobretot el liti (López-Jaramillo et al. 2010). En el segon article, seleccionant la submostra d'ELR, s'ha pogut descriure el perfil cognitiu que afecta als mateixos dominis que a la mostra general de l'article 1 i també implica una repercussió funcional. No hi ha consens a la literatura sobre si l'ús perllongat de Liti pot tenir un efecte neuroprotector vs neurotòxic (Malhi et al. 2013). De fet, se li han atribuït propietats neurotròfiques i trobem evidència que els excel·lents responedors a liti també presenten nivells més alts de BDNF (Rybakowski & Suwalska 2010). Recentment s'ha descrit que factors cardiovascular, endocrins i metabòlics, com l'obesitat, que també són més freqüents en trastorn bipolar (Kupfer 2005; Soreca et al. 2009; McIntyre et al. 2010; Calkin & Alda 2015), es relacionen amb la funció cognitiva (Strejilevich et al. 2015). El tercer article d'aquesta tesi no era el primer que avaluava aquesta relació entre cognició i obesitat a nivell transversal però sí que ha sigut el primer en estudiar-ho a nivell longitudinal. En concret, els resultats constaten que la interacció de tenir trastorn bipolar i obesitat afecta a la cognició també a llarg termini. La relació de l'obesitat amb els trastorns mentals és bidireccional i està envoltada de molts factors de confusió, com l'estil de vida, l'exposició a medicació, la disfunció neuro-endocrina, la predisposició genètica, la disfunció immunològica i les condicions de comorbiditat com el trastorn per afartaments (McElroy et al. 2011; McIntyre et al. 2008). Paral·lelament, un curs de la malaltia més greu (Kim et al. 2010) i símptomes com la desorganització i la depressió estan associats a un augment de la ingesta i conseqüentment a un augment de pes (McElroy & Keck 2012).

Estudiant les bases fisiopatològiques del trastorn bipolar s'han detectat que determinats biomarcadors, com les neurotrofines, els marcadors inflamatoris i d'estrès oxidatiu, es relacionen amb les fases de la malaltia, però hi ha escassa evidència avaluant la relació d'aquests mecanismes neurobiològics amb la cognició. El quart article ha replicat els resultats sobre els biomarcadors i les fases clíniques de la malaltia. Però, el que és més rellevant, és que s'ha trobat que les neurotrofines modulen la cognició, en concret les funcions executives i a la

memòria verbal. Recents estudis han trobat les mateixes àrees de la cognició relacionades amb les neurotrofines (Dias et al. 2009; Lee et al. 2016; Cao et al. 2016). Cal esmentar que existeixen factors relacionats amb els símptomes afectius i que poden provocar inflamació i estrès oxidatiu, que no es poden controlar; com les comorbiditats mèdiques inflamatòries no diagnosticades, la història d'adversitats en edat primerenques, la disfunció en l'eix microbiota-intestí-cervell, els estils d'alimentació i la inflamació sistèmica idiopàtica de baix grau (Salagre et al. 2017; Brietzke et al. 2012; Fagundes et al. 2013; Post et al. 2013; Jacka et al. 2017).

6.2 Línies futures de recerca

Existeix un interès creixent en psiquiatria de conèixer les bases biològiques dels trastorns mentals, la seva fisiopatologia, i les implicacions que poden tenir en la clínica i en el seu tractament. En el cas del trastorn bipolar, durant les últimes dècades hi ha hagut un interès creixent en com millorar el pronòstic funcional dels nostres pacients, no solament amb els avanços en els tractaments psicofarmacològics sinó també a buscar estratègies rehabilitadores a nivell cognitiu i funcional que millorin la qualitat de vida del pacient.

El nostre treball d'investigació pretén estudiar de quina manera els factors neurobiològics modulen la cognició i quina és la seva repercussió funcionals. Amb l'objectiu de continuar investigant en aquest camp es proposen algunes línies futures de recerca:

- Demostrar les relacions directes i indirectes mitjançant la tècnica de recerca bioinformàtica d'anàlisi de vies (*Pathway analysis)* per explicar com s'interrelacionen els diferents factors neurobiològics, descrits en aquesta tesi, s'associen amb la cognició.
- Investigar la relació entre la reserva cognitiva (Stern 2009) del pacients amb trastorn bipolar i els nivells de neurotrofines i els marcadors inflamatoris i d'estrès oxidatiu. I d'aquesta manera, analitzar si aquesta relació modifica la manifestació clínica de la malaltia (Forcada et al. 2015).
- Continuar investigant l'evolució de la cognició en mostres de pacients amb tractaments farmacològics homogenis com per exemple els excel·lents responedors a liti; i així minimitzar l'efecte de confusió de la medicació sobre la cognició (Robinson et al. 2006a).
- Comparar l'evolució del perfil neuropsicològic dels pacients amb trastorn bipolar amb d'altres poblacions amb diferents trastorns psiquiàtrics en els quals existeix un

solapament clínic com són el trastorn depressiu (Murrough et al. 2011)(Hasselbach et al., 2013) i el trastorn per dèficit d'atenció i hiperactivitat (TDAH) (Torres et al. 2015).

- Dissenyar i aplicar programes de rehabilitació cognitiva i funcional en els pacients amb trastorn bipolar amb diferents estadis de la malaltia (Torrent et al. 2013; Reinares et al. 2014).
- Estudiar individus d'alt risc de presentar trastorn bipolar, concretament, fills de pacients amb trastorn bipolar (Bora et al. 2009); i d'aquesta manera poder definir factors de risc i factors protectors per al desenvolupament de la malaltia; així com el perfil neuropsicològic.
- Dissenyar i aplicar programes d'intervenció amb mòduls sobre alimentació i estils de vida saludable per prevenir l'obesitat en pacients amb trastorn bipolar en les fases inicials del trastorn. I també d'aquesta manera observar com el tipus de dieta pot implicar canvis en la clínica i en la cognició, des del punt de vista de l'eix microbiota-intestí-cervell (Salagre et al. 2017).
- Determinar altres marcadors neurobiològics també relacionades amb la cognició com podrien ser el genotip de BDNF, donat que el polimorfisme de BDNF val66met, el qual regula la secreció de BDNF, s'ha descrit com factor de vulnerabilitat a la disfunció cognitiva (Lee et al. 2016).
- Determinar altres marcadors d'estrès oxidatiu com els nivells de glutatió en plasma, que són una mesura de l'estat oxidatiu de tot l'organisme i recentment s'ha relacionat amb l'edat d'inici del trastorn i podria influir també en la disfunció cognitiva i la comorbiditat de malalties no psiquiàtriques (Rosa et al. 2014).

6.3 Limitacions dels estudis

Els quatre articles del nostre projecte de recerca presenten algunes limitacions que cal esmentar:

- La mostra de pacients bipolars eutímics dels 4 articles representa un grup homogeni de pacients en un estadi mig-tardà de la malaltia, amb una inusual bona adherència al tractament, amb poca medicació, amb un llarg període d'eutímia i amb poques recurrències. Per tant, s'ha pogut esbiaixar la mostra als pacients amb millor evolució clínica; mentre que els pacients amb múltiples recaigudes/episodis no estan representats. Tot i que, per altra banda, el fet que fos una mostra amb millor

pronòstic/evolució clínica, sense pautes de tractament complexes, pot considerar-se també un punt fort (Nivoli et al. 2013), donat que la medicació pot influenciar el rendiment cognitiu. Per tant, haver seleccionat aquest tipus de mostra i també la submostra d'excel·lents responedors a liti, ens ha permès descriure l'especificitat i demostrar la continuïtat dels dèficits cognitius als llarg del temps.

- La mida de la mostra pacients amb trastorn bipolar tipus I i II no permetia realitzar les anàlisis per separat amb suficient potència estadística. De totes maneres, estudis previs demostren taxes similars de disfunció cognitiva i de discapacitat entre ambdós subtipus de trastorn bipolar (Solé et al. 2012). En la mateixa línia, en el quart article i no es troben diferències en quant al nivell de biomarcadors perifèrics en pacients bipolars tipus I i tipus II.
- La mida de la mostra del segon article longitudinal dels excel·lents responedors a liti (ERL) és petita, un terç de la mostra inicial. Tot i que, cal esmentar que es va calcular la mida de la mostra (Cohen's d=1.05) per detectar diferències significatives amb una potència estadística de 0.8 i un interval de confiança de 95%. A més, els ERL representen també un terç dels pacients tractats amb liti (Rybakowski et al. 2001).
- En l'article d'obesitat la taxa d'abandonament als 6 anys és de 55.4%; si bé, no hi havien diferències basals entre els pacients que havien completat l'estudi, des del punt de vista de l'IMC, la severitat de la malaltia i d'altres variables clíniques rellevants.

6.4 Verificació de les hipòtesis

Hipòtesi 1:

La disfunció cognitiva en pacients bipolars eutímics romandrà estable als 6 anys i s'associarà a una pitjor funcionalitat psicosocial.

Aquesta hipòtesi es verifica amb els resultats del primer article. Els pacients bipolars eutímics mostren dèficits cognitius comparats amb el grup control. Concretament, mostren disfunció en les funcions executives, la inhibició, la velocitat de processament i la memòria verbal. Aquests dèficits es van mantenir estables al llarg del temps. A més, el que és més rellevant, és que el canvi al llarg del temps d'aquests mateixos dominis en els pacients amb trastorn bipolar implica directament una pitjor funcionalitat psicosocial, tal i com s'ha observat a través de l'escala FAST; tant en la puntuació total com també en l'àrea cognitiva i ocupacional.

Hipòtesi 2:

El subgrup de pacients "excel·lents responedors a liti" també presentaran disfunció cognitiva en el seguiment longitudinal comparat amb controls sans.

Aquesta hipòtesi es verifica amb els resultats del segon article. En aquest subgrup de pacients, tot i ser excel·lents responedors a liti i rebre un tractament amb liti amb monoteràpia també presentaven diferències en el rendiment cognitiu en la majoria de dominis comparat amb els controls sans. Aquests dèficits també es mantenien estables al llarg del temps; a excepció del domini d'atenció. Aquests resultats poden suggerir que hi han diferències en les trajectòries cognitives d'algunes tasques neuropsicològiques. El més rellevant de tot plegat és que la cronicitat i l'empitjorament cognitiu d'aquests dominis afecta a la funcionalitat psicosocial també en els excel·lents responedors a liti.

Hipòtesi 3:

L'obesitat explicarà part de la disfunció cognitiva dels pacients bipolars eutímics a nivell transversal i també longitudinal.

Aquesta hipòtesi es verifica amb els resultats del tercer i quart article. A nivell transversal, els pacients bipolars eutímics obesos o amb sobreprès presentaven pitjors resultats en el rendiment cognitiu, sobretot en les funcions executives; a diferència dels eutímics amb un pes normal. Aquesta diferència entre individus amb un pes normal i individus obesos o amb sobrepès dins del grup de pacients bipolars eutímics, no s'observava en el grup de controls sans. A més, els resultats del quart article també donen suport a aquesta hipòtesi doncs trobem que l'índex de massa corporal també és un dels factors predictors de funcionament cognitiu en la memòria verbal. A nivell longitudinal, en el tercer article detectem que la interacció de l'índex de massa corporal a nivell basal i el grup també predeia pitjor rendiment cognitiu a a llarg termini, al cap de 6 anys. Per tant, es confirma l'efecte sinèrgic del trastorn bipolar i l'obesitat com a factor predictor de la disfunció cognitiva a curt termini i el que és més rellevant, donat que no s'havia estudiat prèviament, també a nivell longitudinal.

Hipòtesi 4:

Els biomarcadors mostraran relació no únicament amb la fase del trastorn, sinó també amb la disfunció cognitiva.

Aquesta hipòtesi es verifica amb els resultats del quart article. Els nivells de neurotrofines (factor neurotròfic derivat del cervell (BDNF)) estan disminuïts en els pacients amb trastorn bipolar respecte els controls sans. D'altra banda, els marcadors inflamatoris i d'estrès oxidatiu estan augmentats en pacients respecte els controls sans. En la nostra mostra, de tots els biomarcadors analitzats, el BDNF és l'únic que modula el funcionament cognitiu. Ni els marcadors d'inflamació ni els d'estrès oxidatiu prediuen la cognició. Destacar que hem obtingut aquests resultats, tot i sabent que existeixen d'altres factors biològics, socials i ambientals que estan associats amb la inflamació i l'estrès oxidatiu.

7. CONCLUSIONS FINALS

En aquesta tesi s'ha estudiat contribució de diferents factors neurobiològics en la disfunció cognitiva en el trastorn bipolar. Les principals conclusions d'aquesta tesi deriven dels 4 articles que en formen part i es detallen a continuació:

1. **La persistència de la disfunció cognitiva en el trastorn bipolar s'associa a pitjor funcionalitat psicosocial.** Els pacients bipolar eutímics presenten disfunció cognitiva que es manté estable al cap de 6 anys comparat amb controls sans. La persistència de la disfunció cognitiva impacta sobre el funcionament psicosocial dels pacients bipolars eutímics. Els estudis longitudinals són imprescindibles per entendre l'evolució de la malaltia i aquestes dades són crucials per dissenyar intervencions neuropsicològiques i psicosocials per millorar la recuperació funcional d'aquests pacients.

2. **Els excel·lents responedors a liti també presenten disfunció cognitiva en la majoria de dominis cognitius i es manté estable a llarg termini.** Els anys de duració de malaltia i un pobre funcionament psicosocial també estan relacionats amb la persistència d'aquest dèficit. La disfunció cognitiva és el major obstacle per la recuperació funcional d'aquests pacients. També aquest subgrup de pacients es beneficiaria de programes específics per millorar la funcionalitat i la seva qualitat de vida.

3. **El fet de tenir el diagnòstic de trastorn bipolar i presentar sobrepès o obesitat impacta sobre la cognició a nivell transversal i longitudinal.** La presència d'obesitat en el trastorn bipolar explica pitjor rendiment cognitiu comparat amb pacients no obesos. Per tant, l'obesitat constitueix un fenotip neurotòxic, que impacta negativament sobre la cognició. Els programes de prevenció i tractament haurien d'intervenir de forma específica sobre estils d'alimentació i hàbits de vida saludables per preservar el pes normal; com a una manera de prevenir la disfunció cognitiva i també funcional en el trastorn bipolar.

4. **Les neurotrofines no només tenen relació amb la fase de la malaltia sinó també amb la disfunció cognitiva.** Es confirma que el BDNF explica part de la disfunció cognitiva en les funcions executives i la memòria verbal. Mesurar els nivells de biomarcadors dins de les valoracions psiquiàtriques podria ajudar a dissenyar intervencions terapèutiques individuals no només per tractar símptomes clínics però també per revertir els canvis biològics associats a la malaltia.

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9. ANNEX

Annex 1. Functioning Assesment Short Test (FAST)

PRUEBA BREVE DE EVALUACIÓN DEL FUNCIONAMIENTO (FAST)

¿Cuál es el grado de dificultad del paciente en relación con los siguientes aspectos?

Interrogue al paciente respecto a las áreas de funcionamiento que se especifican a continuación, utilizando la siguiente escala: (0): Ninguna, (1): Poca, (2): Bastante o (3): Mucha.

AUTONOMIA				
1. Encargarse de las tareas de la casa	(0)	(1)	(2)	(3)
2. Vivir solo	(0)	(1)	(2)	(3)
3. Hacer la compra	(0)	(1)	(2)	(3)
4. Cuidar de sí mismo (aspecto físico, higiene...)	(0)	(1)	(2)	(3)
FUNCIONAMIENTO LABORAL				
5. Realizar un trabajo remunerado	(0)	(1)	(2)	(3)
6. Acabar las tareas tan rápido como era necesario	(0)	(1)	(2)	(3)
7. Trabajar en lo que estudió	(0)	(1)	(2)	(3)
8. Cobrar de acuerdo con el puesto que ocupa	(0)	(1)	(2)	(3)
9. Alcanzar el rendimiento previsto por la empresa	(0)	(1)	(2)	(3)
FUNCIONAMIENTO COGNITIVO				
10. Concentrarse en la lectura, película	(0)	(1)	(2)	(3)
11. Hacer cálculos mentales	(0)	(1)	(2)	(3)
12. Resolver adecuadamente un problema	(0)	(1)	(2)	(3)
13. Recordar el nombre de gente nueva	(0)	(1)	(2)	(3)
14. Aprender una nueva información	(0)	(1)	(2)	(3)
FINANZAS				
15. Manejar el propio dinero	(0)	(1)	(2)	(3)
16. Hacer compras equilibradas	(0)	(1)	(2)	(3)
RELACIONES INTERPERSONALES				
17. Mantener una amistad	(0)	(1)	(2)	(3)
18. Participar en actividades sociales	(0)	(1)	(2)	(3)
19. Llevarse bien con personas cercanas	(0)	(1)	(2)	(3)
20. Convivencia familiar	(0)	(1)	(2)	(3)
21. Relaciones sexuales satisfactorias	(0)	(1)	(2)	(3)
22. Capaz de defender los propios intereses	(0)	(1)	(2)	(3)
OCIO				
23. Practicar deporte o ejercício	(0)	(1)	(2)	(3)
24. Tener una afición	(0)	(1)	(2)	(3)

Annex 2. Escala Alda

Table 2. Retrospective Criteria of Lithium Response in Research Subjects[a]

Criterion A is used to determine an association between clinical improvement and lithium treatment. Criteria B1–B5 establish whether there is a causal relationship between the improvement and the treatment.

A: Rate the degree of response (activity of the illness while on adequate lithium treatment) on the following 10-point scale:
- 10 Complete response; no recurrences during the course of adequate treatment; full functional recovery at work and at home, no residual symptoms
- 9 Very good response; no recurrences, but there may be minimal residual symptoms that could include transient anxiety, sleep disturbance, dysphoria, irritability; these symptoms have not required intervention
- 8 Very good response; illness activity reduced by more than 90%
- 7 Good response; illness activity reduced by 80%–90%
- 6 Good response; reduction in the activity of illness by 65%–80%
- 5 Moderate response; greater than 50% reduction (50%–65%) in illness activity
- 4 Moderate (35%–50%) improvement, i.e., more than one third reduction of illness activity
- 3 Mild improvement, reduction of illness activity by 20%–35%
- 2 Mild improvement (10%–20%)
- 1 Minimal improvement (0%–10%)
- 0 Nonresponse; the frequency, duration, and severity of episodes are unchanged or increased in the course of prophylactic treatment

B: Rate the degree of confidence about the response—subtract 0, 1, or 2 points for each of the following items:

B1: Number of episodes before lithium treatment
- 0 4 or more
- 1 2 or 3
- 2 1

B2: Frequency of episodes before lithium
- 0 Average to high, including rapid cycling
- 1 Low, spontaneous remissions of 3 or more years on average
- 2 1 episode only; risk of recurrence cannot be established

B3: Duration of lithium treatment
- 0 2 or more years
- 1 1–2 years
- 2 Less than 1 year

B4: Compliance during period(s) of stability
- 0 Excellent; documented by serum lithium levels in the therapeutic range
- 1 Good; more than 80% of serum lithium levels in the therapeutic range
- 2 Poor; repeated periods of more than 1 week off lithium treatment; fewer than 80% of serum lithium levels in the therapeutic range

B5: Use of additional medication during the period of stability
- 0 None except infrequent sleep medication (1 dose per week or less); no other mood stabilizers, antidepressants, or antipsychotics for control of mood disorder
- 1 Low-dose antidepressants or antipsychotics as an "insurance" or prolonged use of sleep medication
- 2 Systematic use of antidepressant or antipsychotic medications or additional mood stabilizers

C: Ascertain diagnosis of a mood disorder

[a]This scale should be applied to the period of treatment closest to optimal, i.e., adequate dosage and least use of medications interfering with the effect of lithium. © Martin Alda, M.D.

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