Universitat Autònoma de Barcelona

POTENCIAL TERAPÈUTIC DE L'AYAHUASCA EN LA DESREGULACIÓ EMOCIONAL I L'AUTOCRÍTICA: IMPLICACIONS EN EL TRASTORN LÍMIT DE LA PERSONALITAT (TLP)

Elisabet Domínguez Clavé

Universitat Autònoma de Barcelona

Departament de Farmacologia de Terapèutica i de Toxicologia

Programa de Doctorat en Farmacologia

Facultat de Medicina

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Tesi Doctoral presentada per:

Elisabet Domínguez Clavé

Per a obtenir el grau de Doctora per la Universitat Autònoma de Barcelona

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Directors:

Dr. Joaquim Soler Ribaudi

Dr. Juan Carlos Pascual Mateos

Tutora:

Dra. Rosa Maria Antonijoan Arbós

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El Dr. **Joaquim Soler Ribaudi** i el Dr. **Juan Carlos Pascual Mateos** (ambdós del Departament de Psiquiatria i Medicina Legal UAB – Servei de Psiquiatria, Hospital de la Santa Creu i Sant Pau), en qualitat de Codirectors i la Dra. **Rosa M. Antonijoan Arbós** (CIM-IIB, Hospital de la Santa Creu i Sant Pau; Departament de Farmacologia de Terapèutica i de Toxicologia, Universitat Autònoma de Barcelona), en qualitat de Tutora.

Certifiquen:

Que han supervisat la present tesi doctoral titulada:

Potencial terapèutic de l'Ayahuasca en la desregulació emocional i l'autocrítica: implicacions en el Trastorn Límit de la Personalitat (TLP)

Realitzada per Elisabet Domínguez Clavé i consideren que és apta per a la seva lectura i defensa pública per optar al grau de Doctora per la Universitat Autònoma de Barcelona.

Per aquest motiu, en queda constància al present document a Barcelona,

13 d'Octubre de 2021.

Directors: Tutora:

Dr. Joaquim Soler Dr. Juan Carlos Pascual Dra Rosa M. Antonijoan

Alumna:

Elisabet Domínguez Clavé

AGRAÏMENTS

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SUMARI

ABREVIACIONS I ACRÒNIMS

ABCT	Teràpia de Compassió basada en els Estils d'Aferrament
ACC	Còrtex cingulat anterior
ACT	Teràpia d'Acceptació i Compromís
B. caapi	*Banisteriopsis caapi*
BDNF	Factor Neurotròfic Derivat del Cervell
CBCT	Entrenament Cognitiu basat en Compassió
CBT	Teràpia Cognitiu Conductual
CCT	Entrenament en el Cultiu de la Compassió
CFT	Teràpia enfocada en Compassió
DE	Desregulació Emocional
DBT	Teràpia Dialèctica Conductual
DERS	*Difficulties in EmotionRegulationScale*
DMN	Xarxa Neuronal per Defecte
DMT	N,N-Dimethiltriptamina
EEG	Electroencefalograma
EPM	Prova de Laberint Elevat
EQ	*ExperiencesQuestionnaire*
NGF	Factor de Creixement Nerviós
FFMQ	*FiveFacets Mindfulness Questionnaire*
FSCSR	*Forms of Self-Criticismand Self-Reassurance*
IMAO	Inhibidors de la monoaminooxidasa
LORETA	Tomografia Electromagnètica de Baixa Resolució
MAO	Monoaminooxidasa
MAO-A	Monoaminooxidasa-A
MBCT	Teràpia Cognitiva basada en Mindfulness
MBI	Intervencions basades en mindfulness
MBSR	Mindfulness basat en reducció de l'estrès
MCT	Entrenament de continuació en Mindfulness
MSI-BPD	*McLean Screening Instrument for BPD*
MSC	Programa d'Autocompassió en Mindfulness
MTL	Lòbul medial temporal

P. viridis	*Psychotria viridis*
OFT	Prova de Camp Obert
PCC	Còrtex cingulat posterior
RE	Regulació Emocional
S1R	Receptor intracel·lular sigma-1
SC-SF	*Self-CompassionScale-Short Form*
SPECT	Tomografia computada per emissió de fotó simple
TE	Entropia de Transferència
TEPT	Trastorn d'Estrès Posttraumàtic
THH	Tetrahidroharmina
TLP	Trastorn Límit de la Personalitat
UDV	*União do Vegetal*

NOTA: En aquesta tesi es mantindrà l'ús dels termes *mindfulness* en anglès (enlloc d'atenció plena), *set* i *setting* (que fan referència a l'estat de l'individu i al seu context, respectivament), amb l'objectiu d'evitar possibles confusions. També es fa distinció de *Mindfulness*, amb la primera lletra en majúscula, quan es tracti de la intervenció o l'entrenament i no de l'habilitat interna.

JUSTIFICACIÓ DE LA TESI

Si bé l'ús dels psicodèlics s'ha anat estenent en les últimes dècades, ens aquests darrers anys la seva ingesta s'ha anat orientant cap a un objectiu més psicoterapèutic. D'aquí que hagin anat sorgint les anomenades teràpies assistides amb psicodèlics, que avui en dia existeixen a Europa, el Canadà i els Estats Units, per tractar la depressió i el trauma principalment, i que segueixen expandint-se arreu del món. També al nostre país s'estan fent assajos amb pacients per a estudiar si es poden implementar en un futur proper.

De la ingesta de psicodèlics s'han reportat al llarg de molts anys efectes beneficiosos. Molts d'aquests efectes s'han anat publicant en forma d'estudis de casos, casos control i fins i tot assajos clínics amb voluntaris i pacients.

En el cas de l'Ayahuasca, diversos estudis *in vitro*, en animals i en humans han reportat beneficis d'aquesta substància sobre diverses condicions psicològiques i també sobre alguns trastorns mentals (depressió, ansietat, dependència i abús de substàncies, etc.). L'eficàcia terapèutica descrita, juntament amb el fet que també s'ha reportat la seva capacitat de facilitar l'exposició segura a records autobiogràfics emocionals (quelcom potencialment efectiu en trauma) i que, per tant, actuaria com un potencial facilitador del processament emocional, fa plantejar que l'Ayahuasca podria ser un potencial agent psicoterapèutic. Alguns estudis de neuroimatge han pogut demostrar l'augment de l'activitat en àrees límbiques i regions lligades a la formació de records (amígdala i hipocamp).

Les teràpies psicològiques de tercera generació i més concretament les intervencions basades en mindfulness (*MBI*), han recuperat l'interès pels processos bàsics comuns a les diferents intervencions i que incideixen en el benestar, com la capacitat de descentrament o l'acceptació i altres capacitats relacionades amb el mindfulness. Per això hem volgut observar els processos subjacents a la presa d'Ayahuasca i comparar els efectes induïts d'aquestes teràpies amb els efectes induïts de l'Ayahuasca. Això permetria poder continuar en la investigació d'aquests processos subjacents que explicarien millor els efectes terapèutics de la substància. Així, en un primer estudi, es va comparar un entrenament en Mindfulness amb la presa d'Ayahuasca per veure l'impacte que podien tenir sobre capacitats relatives al mindfulness com les anteriorment esmentades. És a dir, es va comparar una

intervenció de vuit setmanes de Mindfulness basat en reducció de l'estrès (*Mindfulness-Based Stress Reduction*, *MBSR*) amb una presa setmanal d'Ayahuasca durant quatre setmanes en un entorn comunitari. Es pretenia demostrar que els efectes beneficiosos en capacitats relacionades amb mindfulness que fins ara milloraven amb la pràctica de les *MBI*, com la Teràpia Cognitiva basada en Mindfulness (*Mindfulness-based cognitive therapy*, *MBCT*) i de teràpies de tercera generació com la Teràpia Dialèctica Conductual (*Dialectical behaviour therapy*, *DBT*) i la Teràpia d'Acceptació i Compromís (*Acceptance and commitment therapy*, *ACT*), també podien ser produïts per la presa l'Ayahuasca. És a dir, demostrar si ambdues vies terapèutiques són comparables o fins i tot, si l'Ayahuasca pot arribar a complementar aquest tipus d'intervencions, o si més no, ajudar a potenciar-ne els resultats.

En un segon estudi, i basant-nos en les descripcions d'aspectes comuns entre l'experiència amb aquesta substància i la pràctica del Mindfulness, es pretenia explorar si l'Ayahuasca podria mostrar efectes també sobre la regulació emocional i en especial sobre la regulació emocional en persones amb trets de Trastorn Límit de la Personalitat (TLP) i que per tant, tenen tendència a estar més desregulades emocionalment. Amb aquesta finalitat, es van avaluar una mostra de població comunitària amb auto informes la regulació emocional i capacitats del mindfulness abans i després (24 hores després de la sessió amb Ayahuasca) i es van separar també els participants amb trets de TLP per comparar el pre-post d'ambdós grups. Però què passa si en una mostra comunitària detectem que hi ha persones amb trets objectivables de TLP, mesurables a través d'un instrument de cribatge específic? Sempre hi ha hagut moltes discrepàncies al voltant de l'ús de psicodèlics sobre aquest trastorn (el temor a un possible brot psicòtic, clínica dissociativa o al fet que la persona accedeix a contingut autobiogràfic dolorós han estat alguns dels dissuasius). Aquest és el primer estudi en abordar els efectes de l'Ayahuasca sobre la regulació emocional i el primer en avaluar-ne els efectes sobre una submostra de persones amb trets de TLP.

Per últim, en el tercer estudi, preteníem examinar els possibles efectes induïts de la presa d'Ayahuasca sobre l'autocompassió i l'autocrítica en una mostra comunitaria. La pràctica del mindfulness també ha demostrat augmentar l'autocompassió i s'ha vist que aquesta sembla funcionar com una estratègia de regulació emocional. Alguns estudis sobre teràpia assistida

en psicodèlics han reportat que aquesta capacitat puntua millor després de les sessions, però l'impacte de l'Ayahuasca sobre l'autocompassió i l'autocrítica ha rebut escassa atenció.

La present tesi doctoral intenta aportar informació sobre aquestes qüestions. Els resultats publicats obren la porta a futures línies de investigació respecte a una intervenció terapèutica amb l'Ayahuasca amb patologies psiquiàtriques caracteritzades per la desregulació emocional com el trastorn límit de la personalitat o el trauma.

INTRODUCCIÓ

1. Introducció

1.1 Definició i orígens de l'Ayahuasca

L'Ayahuasca, també coneguda com *yagé*, *caapi*, *natem*, *hoasca*, *daime* i *vegetal* és una infusió al·lucinògena originària de la conca de l'Amazones (Dos Santos et al., 2017; Rivier i Lindgren, 1972). Ayahuasca és un terme *quechua*, l'etimologia del qual és: *aya* – persona, ànima, esperit mort i *waska* – corda trepadora, parra liana, que podria ser entesa com "trepadora d'ànimes" (Dos Santos, 2007). La documentació arqueològica ha demostrat que els seus orígens es remunten al període neolític (una antiguitat de 5.000 anys) (Naranjo, 1986). El *chamán*, que és qui coneix les herbes i les seves propietats, controla l'ús i la distribució de l'Ayahuasca en la seva utilització col·lectiva i també és qui guia l'experiència amb la substància. L'ús d'aquest te en les tribus amazòniques tenia la finalitat d'establir una connexió amb els esperits de la selva, aconseguir poders sobrenaturals i també s'emprava per a curar a les freqüents víctimes de maleficis (Samorini, 2001). Per a ells, les experiències visionaries obtingudes amb l'Ayahuasca representaven una font d'informació d'importància primària per a la interpretació de la realitat (Ott, 1996).

El seu us es va anar estenent per més de 70 grups indígenes diferents, repartits pel Brasil, Colòmbia, el Perú, Veneçuela, Bolívia i l'Equador (Goulart, 1996). La influència de les missions catòliques va introduir en aquestes poblacions un cert grau de sincretisme amb el cristianisme amb les conseqüents implicacions pel què fa al simbolisme i a la interpretació de l'experiència visionaria (Luna, 1986, 1993). Entre algunes poblacions mestisses mes urbanes del Perú, el seu ús està estretament limitat al diagnòstic i la cura de malalties (Samorini, 2001). També s'han establert principalment al Brasil cultes religiosos com el *Santo Daime*, l'*União do Vegetal (UDV*) o *Barquinha*, esglésies cristianes de l'Ayahuasca que gaudeixen de tolerància legal, ja que allà el seu ús està acceptat a nivell jurídic des del 1986 (Barbosa, et al., 2005; Labate, 2011; MacRae, 1992). Aquests cultes s'han anat estenent i alguns han arribat a establir-se a Catalunya (Ott, 1996). Més recentment, s'ha intensificat el turisme enfocat al fenomen de l'Ayahuasca oferint retirs curts i viatges arreu, ja sigui d'autoconeixement o per viure l'experiència xamànica (Holman, 2011; Winkelman, 2005).

Tot i que ha estat tradicionalment lligada a finalitats ritualistes (Frecska et al., 2016), en les últimes dècades, les motivacions per prendre-la són diverses i han fet que la seva utilització s'estengués abastament a tot el món. Les més habituals son l'autoconeixement, la voluntat de millorar les relacions interpersonals i de guanyar noves perspectives vitals especialment lligades a superar problemes mentals (Kavenska i Simonova, 2015; Sessa, 2005). Des que Richard Spruce (1851), el primer botànic europeu que va entrar en contacte amb aquesta beguda, en va descriure el seu ús i propietats, innumerables antropòlegs i etnògrafs han anat descrivint els rituals i material mitològic, com Dobkin de Rios (1972), Reichel-Dolmatoff (1975), Schultesi Hofmann (1980), Naranjo (1983), Luna i Amaringo (1991) i Ott (1994), entre d'altres (Ott, 1996, p. 195; Samorini, 2001, p. 19).

1.2 Química de l'Ayahuasca

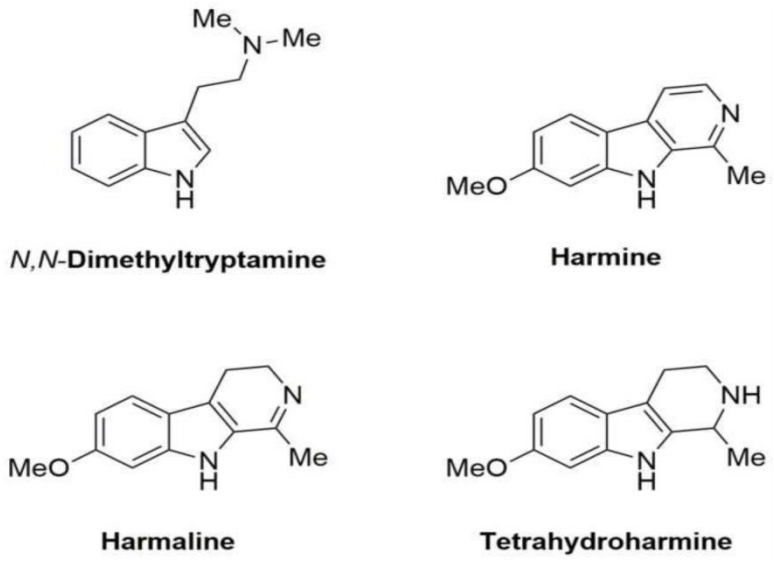
L'Ayahuasca sovint conté diverses plantes que pel seu efecte enteogènic, estimulant o simplement terapèutic s'utilitzen simultàniament o s'inclouen al brou per a potenciar-ne o contrarestar-ne els efectes. Gran part d'aquestes espècies vegetals emprades com additius de l'Ayahuasca estan inclosos a les notes de l'etnobotànic Jonathan Ott (1996, p. 264). La versió d'Ayahuasca més usada a nivell mundial és la resultant d'una mescla de la liana *Banisteriopsis caapi* (Malpighiaceae) amb fulles de l'arbust *Psychotria viridis* (Rubiaceae) infusionades (McKenna et al., 1984). Segons la literatura prèvia existent, aquesta combinació sembla ser raonablement segura, en termes d'impacte fisiològic, quan s'administra a individus sans (Dos Santos et al., 2011, 2012; Riba et al., 2001, 2003; Sánches et al., 2016) i sota certes condicions, beneficiosa (Barbosa et al., 2012).

La *B. caapi* conté alcaloides betacarbolínics, principalment harmina, tetrahidroharmina (THH) i, en menor mesura, harmalina (McKenna et al., 1984; Rivieri Lindgren, 1972). Les fulles de l'arbust *P. viridis* són riques en l'alcaloide al·lucinògen N,N-Dimethiltriptamina (DMT), que és oralment inactiu degut a la seva transformació per l'activitat de la monoaminoxidasa (MAO) al tracte gastrointestinal. Com els alcaloides betacarbolínics exerceixen un efecte específic com inhibidors reversibles de la monoaminooxidasa-A (MAO-A) (Bouso, 2012; Ott, 1999; Wang et al., 2010), prevenen la degradació de la DMT, el que li permet entrar al sistema circulatori general i al sistema nerviós central (Bouso i Riba, 2014; McKenna, et al., 1984), on pot produir efectes psicoactius (Szara, 1956).

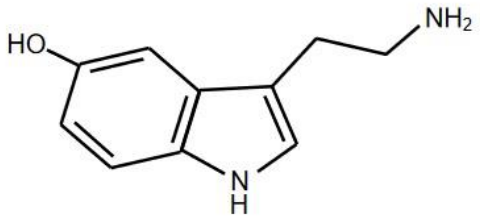
Per altra banda, el principal constituent de la liana *B. caapi* i el principal ingredient de l'Ayahuasca - juntament amb la DMT- és l'alcaloide betacarbolínicharmina. Sempre s'ha considerat que l'indol psicodèlic DMT juga un major paper en la farmacologia de l'Ayahuasca, ja que mostra activitat agonista serotoninèrgica en llocs receptors 5HT2A i 5HT1A (González-Maeso i Sealfon, 2009) induint modificacions curtes però intenses de l'estat natural de consciència (Riba et al., 2002; Strassman et al., 1994). Tanmateix, no està clar si és la seva ingesta o és la mescla amb altres alcaloides betacarbolínics (THH i harmalina) el que produeix efectes psicoactius o al·lucinògens (Dos Santos i Hallak, 2016; Dos Santos et al., 2017). De fet, estudis en humans han mostrat resultats poc concloents, descrivint els efectes sedants de les betacarbolines o fins i tot la manca d'efectes (Dos Santos et al., 2017). Tot i així, un estudi conduit en voluntaris sans (Schenberg et al., 2015) va mostrar que les betacarbolines (incloent l'harmina) estan associades amb alteracions electroencefalogràfiques específiques, suggerint la presència d'efectes centrals/psicoactius. També un altre estudi més recent (Morales-García et al., 2017) mostrava que en concret l'harmina, la THH i l'harmol estimulen la neurogènesi in vitro, com també han demostrat alguns antidepressius clínicament efectius (Dean i Keshavan, 2017; Hill et al., 2015).

Les estructures químiques del DMT i les principals betacarbolines es mostren a la **Taula 1**.

L'estructura química de la serotonina és mostra a la **Taula 2**.



Taula 1. Estructures químiques del DMT i les principals betacarbolines



Taula 2. Estructura química de la serotonina

1.3 Correlats neurobiològics de l'Ayahuasca

Diversos estudis han definit el lòbul mediotemporal (*MTL*), que inclou l'hipocamp, l'amígdala i regions parahipocampals, com la diana neurobiològicade l'experiència induïda amb Ayahuasca (de Araujo et al., 2012; Riba et al., 2004, 2006). Estudis com el de Riba et al. (2006), ja va mostrar que, sota els efectes de l'Ayahuasca, augmentava el flux sanguini en algunes àrees implicades en el control cognitiu, l'emoció i la memòria, com la ínsula, la amígdala i l'hipocamp (Riba et al., 2006).

També s'ha reportat que, durant la fase aguda de l'Ayahuasca, la major part de la Xarxa Neuronal per Defecte (*DMN*) exhibeix una activitat disminuïda i el còrtex cingulat posterior (*CCP*) mostra una connectivitat reduïda (Palhano-Fontes et al., 2015). La hiperactivitat en aquesta regió ha estat associada a psicopatologia (ex. ruminació depressiva) (Dutta et al., 2014) i per contra, una menor activació d'aquesta s'ha relacionat amb més autoconsciència (Vogt i Laureys, 2005). El *CCP* és un nòdul clau de la *DMN* (Raichle et al., 2001). La *DMN* és un conjunt de regions cerebrals connectades funcional i estructuralment que acostumen a desactivar-se durant la realització de tasques que exigeixen atenció externa. Aquesta zona també presenta un elevat flux sanguini cerebral i consum d'oxigen durant l'estat de repòs (Lin et al., 2017).

Un altre estudi (Alonso et al., 2015) va avaluar els canvis induïts per l'Ayahuasca en la interacció dinàmica de les oscil·lacions cerebrals i la direccionalitat de les modificacions induïdes per la substància utilitzant l'entropia de transferència (TE). L'estudi avaluava a deu voluntaris sans amb experiència prèvia en l'ús de drogues psicodèliques. Els autors varen

trobar una densitat reduïda en les àrees posteriors medials (precuneus i cuneus) i en el còrtex cingulat anterior (*CCA*). Les àrees posteriors medials s'ocupen de la integració de les informacions cerebrals internes amb les ambientals (l'autoconsciència) i el *CCA* s'ocupa del control executiu i emocional, en concret de funcions com l'atenció executiva, la detecció i monitoreig de l'error, la presa de decisions, la flexibilitat cognitiva i el control inhibitori. Aquestes funcions es troben alterades en trastorns com o el dèficit d'atenció i hiperactivitat (TDAH) (Guzmán-Ramírez et al., 2018).

L'Ayahuasca també ha mostrat tenir un efecte excitador en les regions corticals implicades en el processament de la informació sensorial visual (alfa-occipital), la memòria-afecte (delta-*MTL*) i la cognició-afecte (theta-còrtex frontolateral i frontomedial) (Valle et al., 2016). L'administració d'Ayahuasca en aquell estudi va donar lloc a augment significatius de les mesures de modificacions afectives, tal com apuntaven estudis anteriors (Dos Santos et al., 2011; Riba et al., 2003, 2006). També trobem reduccions de potència EEG en àrees associades amb el processament afectiu, és a dir, el *MTL* i el lòbul frontal medial (*MFL*)/ *ACC*. La disminució de l'energia i l'augment del flux sanguini en aquestes regions s'havien reportat prèviament utilitzant *LORETA* (Riba et al., 2004) i *SPECT* (Riba et al., 2006), respectivament. Aquestes àrees comprenen el còrtex d'associació unimodal, el còrtex d'associació multimodal i les regions límbiques involucrades en la integració de la informació sensorial multimodal, l'emoció i els processos de memòria. L'amígdala, el *MTL* i l' *ACC* són centres clau de tractament afectiu. L'amígdala s'associa amb la por i l'excitació emocional, mentre que l'*ACC* i les àrees frontals medials veïnes integren l'emoció i la cognició. A partir d'aquest i d'altres estudis s'ha suggerit que els efectes a aquests nivells podrien ser subjacents al potencial terapèutic de l'ayahuasca (Soler et al., 2015).

Els assajos clínics aleatoris amb usuaris de psicodèlics experimentats també suggereixen un paper destacat del receptor 5-HT2A en els efectes neurofisiològics i visionaris d'aquesta substància. Valle et al. (2016), també varen observar efectes psicodèlics significatius i disminucions de potència en el rang de freqüències delta-alfa induïdes per l'Ayahuasca. A més, les disminucions en les oscil·lacions de la banda alfa es varen donar en regions cerebrals posteriors i van correlacionar amb la intensitat de les modificacions visuals. L'antagonista de 5-HT2A utilitzat (ketanserina), en canvi, va bloquejar aquestes disminucions i reduir aquesta correlació (veure Annex A).

1.4 Efectes subjectius de l'experiència amb Ayahuasca

D'aquesta alteració de la consciència induïda per l'Ayahuasca, s'han observat i reportat canvis perceptius, contingut alterat de pensament, intensificació de les emocions, introspecció, un estat d'ànim més positiu i sensació de benestar (Dos Santos et al., 2012; Riba et al., 2003). Tanmateix, d'entre els efectes subjectius que es descriuen de l'experiència amb Ayahuasca, el més comú és una desagradable sensació de cremor a l'estómac, que fàcilment es podria atribuir a l'acidesa de la infusió (Riba et al., 2001). Poc després del seu consum, apareixen vòmits i sovint diarrees intenses i és després d'això que apareixen les visions (Desmarchelier et al., 1996).

Els usuaris també descriuen canvis en la sensibilitat de la pell, punxades, onades de calor i fred i badalls. A això li segueix un desig de tancar els ulls i l'aparició d'imatges visuals als 45-60 minuts que es descriuen com similars als somnis, amb escenes complexes que sovint impliquen llocs i persones que coneixen o el record d'esdeveniments passats. La persona és conscient que les visions són induïdes per la substància i no són al·lucinacions o idees delirants, si no que les pot fer marxar quan obre els ulls i quan adreça l'atenció cap a un altra banda (Riba et al., 2001). Aquests efectes subjectius acostumen a anar i venir, amb períodes alterns de major i menor intensitat. Tot i això, basant-nos en estudis de laboratori, després de la ingesta d'una sola dosi d'Ayahuasca, els efectes psicològics no assoleixen la seva màxima intensitat fins a la hora i mitja o dues hores. La intensitat global disminueix gradualment, tornant a la línia de base entre quatre i sis hores després de la ingesta (Dos Santos et al., 2012; Riba et al., 2003; Strassman et al., 1994).

Pel que fa a la percepció auditiva, aquesta consisteix principalment en sorolls o modificacions de sons externs i de major intensitat en el cas que s'estigui escoltant música. Un altre efecte és que la velocitat del pensament augmenta i es faciliten així noves associacions i reflexions sobre qüestions personals. També els records autobiogràfics emanen, podent desencadenar emocions intenses. Aquesta interacció entre pensaments, records i emocions és molt valorada pels usuaris, doncs consideren la experiència els pot proporcionar noves percepcions sobre les preocupacions personals, i per això solen valorar-la com anàloga a una intervenció psicoterapèutica (Riba et al., 2001).

En relació als efectes no desitjats, també s'han descrit hipertensió i taquicàrdia (Heisei Brooks, 2017), dificultats per dormir la nit posterior a la cerimònia, disminució de la memòria fins a un dia després, i esgotament en els dos dies després de la ingesta (Halpern et al., 2008), preocupació durant la setmana següent (Barbosa et al., 2005). No s'ha descrit casos de clínica dissociativa que no tingués a veure amb patologia psiquiàtrica prèvia i amb possibles interaccions de medicació. En individus amb trastorn per ús de substàncies com els opioides, per exemple, s'ha demostrat un major risc de patir esdeveniments adversos que en la població general (Celentano et al., 2017). També cal considerar l'ús de medicació psiquiàtrica com factor de risc degut a la seva possible interacció amb els components amb activitat IMAO de l'Ayahuasca. Un resultat especialment preocupant de la inhibició dels enzims MAO, sobretot en combinació amb agents serotoninèrgics, es la acumulació de serotonina fins a nivells tòxics, una condició coneguda com "síndrome serotoninèrgic", que, és poc freqüent però pot ser mortal (Volpi-Abadie et al., 2013).

1.5 Potencials usos terapèutics de l' Ayahuasca

Diversos estudis han reportat resultats sobre l'ús terapèutic de l'Ayahuasca i els seus components per al tractament del trastorn d'abús de substàncies (Dos Santos et al., 2018; Hamill et al., 2019; Sessai Johnson, 2015; Tofolii de Araujo, 2016; Winkelman, 2014), de la depressió (Da Silva et al., 2019; Osorio et al., 2015) i de l'ansietat (Dos Santos et al., 2016, 2018; Muttoni et al., 2019) entre altres condicions (veure Annex B).

1.5.1 Dependència i abús de substàncies

Fins al moment no s'ha descrit que l'Ayahuasca comporti problemes de salut o d'addicció a la pròpia substància (Doering-Silveiraet al., 2005; Fabregas et al., 2010; Gable, 2007). En canvi, l'ús d'aquest al·lucinogen en el tractament de l'addicció a altres drogues d'abús es remunta a unes quantes dècades enrere. Ja als anys vuitanta, es descriu un model de teràpia de grup assistit amb Ayahuasca per tractar addiccions a la que els participants podien assistir tantes setmanes com els calgués amb una aportació voluntària (Lemlij, 1978). En usuaris habituals d'Ayahuasca també s'ha descrit tant disminució com remissió del consum d'alcohol, cocaïna i altres drogues addictives (Fabregas et al., 2010; Thomas et al., 2013).

Halpern et al. (2008) van informar d'una remissió del consum/dependència de drogues o alcohol en una mostra comunitària (6,5 anys de mitjana de pertinença). En un altre estudi de sèrie de casos (Thomas et al., 2013), es van reportar reduccions estadísticament significatives en el consum de cocaïna després d'una teràpia assistida amb Ayahuasca en una mostra de membres d'una comunitat de les *Primeras Naciones* del Canadà sense experiència prèvia amb Ayahuasca. Efectes similars sobre el consum de substàncies es van trobar en dos estudis de casos i controls (Fabregas et al., 2010; Grob et al.,1996). Grob et al. (1996) varen informar de la remissió dels trastorns d'alcohol, depressius o d'ansietat i de canvis en el comportament, la actitud cap als altres i la visió de la vida en una mostra de 15 usuaris d' Ayahuasca a llarg termini, en comparació amb 15 controls aparellats sense historia prèvia d'ingesta d'Ayahuasca. Fabregas et al. (2010) varen informar d'una millora en el consum d'alcohol i la remissió en el consum de drogues (excepte el cannabis) en dos grups d'usuaris d'Ayahuasca de la selva i de la ciutat en comparació amb no usuaris d'Ayahuasca. Aquests resultats es varen mantenir en el seguiment a un any. Altres estudis descriptius, com estudis pilot d'observació, informes i entrevistes informals (Bousoi Riba, 2014; Doering-Silveira et al., 2005; Labate et al., 2014), han presentat proves preliminars que suggereixen un possible paper beneficiós de l'Ayahuasca en el tractament dels trastorns per consum de substàncies.

Un estudi en animals Oliveira-Lima et al. (2015), va demostrar que l'Ayahuasca (en la combinació de *B. caapi* i *P. viridis*) no només inhibia els comportaments precoços associats amb l'inici i el desenvolupament de l'addicció a l'etanol, si no que també era eficaç per a revertir la sensibilització conductual associada amb l'administració crònica d'aquest.

1.5.2 Depressió

Tot i que encara es desconeix el potencial complet de l'Ayahuasca, l'evidència acumulada al llarg dels anys indica que pot tenir beneficis potencials per tractar la depressió. Aquesta hipòtesi està fonamentada en dades sobre la capacitat moduladora dels receptors 5-HT2A prefrontals de l'amígdala i l'*ACC*, tal com s'explica en estudis previs (Vollenweideri Kometer, 2010). Nombrosos estudis en animals (Aricioglui Altunbas, 2003; Farzini Mansouri, 2006; Fortunato et al., 2009, 2010; Lima et al., 2007; Pic-Taylor et al., 2015; Réus et al., 2010,2012) i humans (Barbosa et al., 2005; Dos Santos et al., 2007) han investigat aquest potencial efectes de l'Ayahuasca. Estudis recents han avaluat els efectes d'una sola

administració d'Ayahuasca en pacients depressius resistents a tractament. Osório et al. (2015) varen observar una reducció significativa dels símptomes depressius i ansiosos durant la primera setmana. Els autors varen suggerir que l'Ayahuasca sembla tenir l'inici d'acció terapèutica abans que els antidepressius tradicionals, que triguen unes dues setmanes de mitjana en fer efecte. En un altre estudi amb major mostra (n=17) el mateix grup va tenir disminucions significatives en les puntuacions de simptomatologia depressiva, que es van donar als 80 minuts i fins al vint-i-unè dia posterior la presa d'Ayahuasca. (Sanches et al., 2016). L'anàlisi amb *SPECT* va revelar que el fluxe sanguini estava augmentat en les regions implicades en la regulació de l'estat d'ànim i emocional.

Recentment, Palhano-Fontes et al. (2017) va conduir un assaig controlat amb doble cec i placebo en pacients depressius resistents a tractament per comparar una sessió d'una sola dosi d'Ayahuasca o placebo. Els resultats mostren que una sola dosi d'Ayahuasca tenia efectes antidepressius de seguida. La magnitud de l'efecte entre grups va créixer del dia 1 al 7 i l'índex de resposta van ser significativament més gran al grup Ayahuasca el dia 7. La taxa de remissió va mostrar una tendència cap a la significació entre grups (36% v. 7%, p = 0.054). El receptor intracel·lular sigma-1 (S1R), que augmenta el Factor neurotròfic derivat del cervell (*BDNF*) i el factor de creixement nerviós (*NGF*), sembla que estaria implicat en la depressió. La regulació i la expressió del *BDNF* i del *NGF* s'han vist recentment lligades a la patofisiologia i al tractament de la depressió (Otte et al., 2016), dades que suggereixen que la modulació del S1R mediat per DMT jugaria un rol central en els esforços per identificar futures teràpies per tractar la depressió i trastorns relacionats.

1.5.3 Ansietat

Estudis sobre simptomatologia d'ansietat en models animals (Aricioglui Altunbas, 2003) han trobat que el betacarbolínic harmà disminueix les conductes ansioses en la prova de laberint elevat (*elevated plus maze*, *EPM*). Hilberi Chapillon (2005) varen reportar resultats similars amb l'harmalina per a la mateixa prova. Pic-Taylor et al. (2015) va reportar una disminució en activitats exploratòries dels ratolins en la prova de camp obert (*open field test, OFT*) i en l' *EPM* de manera similar a la fluoxetina. Aquests autors també varen observar expressió c-fos augmentada en àrees dels cervell específiques, confirmant que els alcaloides d'Ayahuasca afecten àrees del cervell implicades en el processament emocional.

En humans, Barbosa et al. (2005) varen reportar una disminució en els símptomes relatius a l'ansietat després del primer ritual amb Ayahuasca entre membres d'un grup religiós (Santo Daime) a Brasil. També varen observar canvis conductuals autoreportats, com assertivitat augmentada, vivacitat i alegria. Un estudi cas-control (Dos Santos et al., 2007) va reportar puntuacions més baixes en les escales de pànic i desesperança entre individus que varen prendre Ayahuasca però no va detectar canvis en l'ansietat tret o estat. Els resultats obtinguts fins al moment actual són preliminars, hi ha pocs estudis i amb mostres petites que no permeten afirmar la eficàcia de l'Ayahuasca però sí encoratgen a explorar-ne el potencial ús terapèutic.

1.6 Potencials mecanismes psicològics subjacents als efectes terapèutics de l'Ayahuasca

1.6.1 Capacitats relacionades amb mindfulness

Una de les descripcions més acceptades de la paraula mindfulness és la proposada per John Kabat-Zinn (1990) segons la que el mindfulness es defineix com "parar atenció de manera intencional en el moment present i sense jutjar". Per la perspectiva budista, el mindfulness implica una dimensió cognitiva, actitudinal i afectiva, així com una dimensió social i ètica que es pot obtenir amb la meditació (Grossman et al., 2010). Per al món occidental, el mindfulness és un tret disposicional que tots tenim en major o menor mesura (Baer et al., 2006; Brown i Ryan, 2003) i que es pot entrenar (Baer et al., 2006; Bishop et al., 2004; Kabat-Zinn, 1990).

Segons Bishop et al. (2004), el mindfulness es pot separar en dos components principals: un component atencional, centrat en la capacitat d'observar i prestar atenció a l'experiència, i un component actitudinal, centrat en tenir una actitud oberta, curiosa, d'acceptació i de no jutjar independentment de la valència del contingut de l'experiència. Altres autors com Brown i Ryan (2004) han proposat que el mindfulness és unifactorial, mentre que Baer (2006) va arribar a descriure cinc factors. Aquesta última va elaborar el qüestionari autoinformat més emprat a nivell mundial per avaluar capacitats relacionades amb mindfulness, el *Five Facets Mindfulness Questionnaire* (*FFMQ*; Baer et al., 2006; validació espanyola: Cebolla et al., 2012). Les capacitats que mesura són, per al domini atencional

Observing i *Acting with awareness*, per al domini actitudinal *Non-judging* i *Non-reacting* i una cinquena subescala que no s'acaba d'emmarcar en cap dels dos dominis, *Describing.* Cal tenir en compte que les poblacions psiquiàtriques obtenen una puntuació inferior a les persones sanes en aquestes capacitats (Cardaciotto et al., 2008; Lavender et al., 2011; Tejedor et al., 2014). Fins a l'actualitat, s'han publicat més de quinze escales amb la intenció d'avaluar el constructe (Carmona, 2019).

Pel que fa a l'entrenament en Mindfulness, la Teràpia Dialèctica Conductual (DBT) va ser una de les primeres teràpies en incorporar-lo com a part troncal del seu programa. La finalitat d'aquesta és que l'individu aprengui a participar de l'experiència, a fondre's amb aquesta i a trencar amb la tendència a avaluar la realitat de manera polaritzada i rígida. A partir de la *DBT* han anat sorgint moltes altres teràpies, algunes ja anomenades com la *MBSR* (Kabat-Zinn, 1990), la *MBCT* o la *ACT*. El potencial terapèutic de les *MBI,* està abastament reconegut tant en població general (Irving et al., 2009; Shapiro et al., 2005) com en població clínica (en TLP: Carmona i Farrés et al., 2019; Cristea et al., 2017; en TDAH: Cairncross & Miller, 2020; en ansietat i depressió: Hofmann, et al. 2020), amb resultats que van des de l'increment del benestar a la reducció de la simptomatologia de diferents trastorns (Khoury et al., 2013). A més, aquestes teràpies han mostrat ser cost-efectives per a diversos trastorns (Mavranezouli et al., 2015, Pompoli et al., 2016, Skapinakis et al., 2016).

D'altra banda, alguns estudis han suggerit que no totes les facetes de l'atenció plena són igualment modificades per la pràctica de Mindfulness i que certes facetes com la d'observació o la de no reactivitat semblen ser més sensibles que les altres a la pràctica formal de la meditació (Soler et al., 2014). Tanmateix, els beneficis en aquestes capacitats mostren l'existència d'una associació directa entre la millora de les capacitats de mindfulness i la freqüència i la pràctica de la meditació durant tota la vida (Bergomi et al., 2013; Soler et al., 2014).

El concepte de mindfulness també es relaciona amb el concepte de descentrament o "decentering", el qual fa referència a la capacitat de prendre distància de la pròpia experiència interna, observant els pensaments i les emocions com a fenòmens temporals que no necessàriament reflecteixen la realitat (Fresco et al., 2007). Els enfocaments basats en mindfulness, i en particular la teràpia cognitiva basada en mindfulness per a la depressió

(*MBCT*) semblen millorar el descentrament. No obstant això, la millora d'aquesta capacitat també s'ha reportat com a conseqüència de la Teràpia Cognitiu Conductual (*Cognitive Behavioral Therapy, CBT*; Fresco et al., 2007). Diversos estudis han reportat que millorar la capacitat de descentrament podria millorar directament la depressió (Bieling et al., 2012; Fresco et al., 2007a, b; Gecht et al. 2014; Hargus et al., 2010; Teasdale et al., 2002), el trastorn d'ansietat generalitzada (Hayes-Skeltonet al., 2015; Hoge et al., 2015), l'ansietat social (Hayes-Skeltoni Graham, 2013), els trastorns alimentaris, SUD (Shapiro, et al. 2006) i el trastorn límit de la personalitat (TLP) (Soler et al., 2014). En trastorns relacionats amb la impulsivitat (com l'abús de drogues o el TLP), s'ha suggerit que un augment de la capacitat de descentrament pot disminuir el comportament "estat d'ànim- dependent" mitjançant la interrupció d'hàbits desadaptatius recurrents (Shapiro et al., 2006).

En gran mesura, els potencials beneficis terapèutics de l'Ayahuasca poden atribuir-se a la capacitat de la substància de promoure les capacitats relacionades amb el mindfulness com el descentrament i l'acceptació (Loizaga-Velder, 2013; Shanon, 2003; Soler et al., 2016a), de manera similar al que fa la pràctica del Mindfulness (Carmody i Baer, 2008; Soler et al., 2014, 2018). Alguns estudis indiquen que el descentrament (Franquesa et al., 2018; Soler et al., 2016a) i certes capacitats relacionades amb el mindfulness com el *Non-judging* i *Non-reacting* milloren després de la ingesta d'Ayahuasca (Sampedro et al., 2017; Soler et al., 2016a, 2018).

1.6.2 Regulació emocional

D'acord amb el model biosocial de Linehan (1993), la desregulació emocional (DE) sorgeix de la transacció entre una vulnerabilitat emocional de base biològica amb un ambient invalidant. La vulnerabilitat emocional dificulta que l'ambient respongui de manera apropiada a les demandes de l'individu i això reforça la seva sensibilitat emocional resultant en un patró de DE. Segons aquest model, la vulnerabilitat emocional es caracteritza per: a) una elevada sensibilitat (llindar baix), que apareix ja en les primeres etapes del desenvolupament; b) una alta reactivitat, és a dir, una tendència a experimentar les emocions de manera inusualment forta (Carpenteri Trull, 2013) i c) un retorn lent a la línia emocional base (llarga durada) - la llarga durada es deu principalment a la manca d'estratègies apropiades de regulació emocional (RE)-.

La RE té una relació directa amb el mindfulness disposicional i també nombrosos estudis han demostrat que les *MBI* milloren la RE (Britton et al., 2012; Hölzel et al., 2011). La desregulació emocional és un símptoma central comú a molts trastorns psiquiàtrics com els trastorns afectius, d'ansietat, de personalitat i de consum de substàncies (Barkley, 2010; Bradley et al., 2011; Gross i Thomson, 2007; Leichsenring et al., 2011) i especialment en el trastorn límit de la personalitat (TLP) (Crowell et al., 2009; Fruzzetti, 2002; Linehan, 1993). Les persones que pateixen TLP també tenen nivells baixos i fluctuants de descentrament i mindfulness, els quals semblen millorar després d'aquest tipus d'intervencions (Carmona et al., 2020). Com a conseqüència, la millora d'aquestes capacitats podria facilitar respostes més reflexives i menys impulsades per les emocions (Eisenlohr-Moul et al., 2016), la qual cosa és crucial per millorar la vida quotidiana dels pacients amb TLP i altres amb aquesta condició psicopatològica de desregulació emocional.

Tot i els potencials efectes beneficiosos de l'Ayahuasca sobre la capacitat de regular les emocions, aquesta tesi recull el primer estudi en investigar-ho. En els últims anys, nombrosos estudis han descrit els efectes positius de l'Ayahuasca a diferents trastorns relacionats amb la RE (principalment trastorns afectius i trastorns per ús de substàncies) (Domínguez-Clavé et al., 2016). La RE és un objectiu essencial de diverses intervencions psicoterapèutiques, algunes de les quals se centren exclusivament en aquesta capacitat (*DBT*, Feigenbaum, 2007; *ERT*, Renna et al., 2017). Una teràpia basada en la RE emfatitza el contacte amb les emocions i l'acceptació d'aquestes com a manera fonamental de regular-les (Gratz et al., 2006; Neacsiu et al., 2014; Soler et al., 2009).

1.6.3 Autocompassió i autocrítica

L'autocompassió ha estat definida com una actitud d'amabilitat cap a un mateix davant de la crisi, que permet que hom reconegui les pròpies emocions sense identificar-se amb elles (Neff, 2003a). En altres paraules, és una millor adaptació als esdeveniments vitals negatius i estressants. De manera similar a les capacitats de mindfulness, l'autocompassió implica la promoció d'una actitud de curiositat i no judici cap a les pròpies experiències (MacBeth i Gumley, 2012). De fet, també s'ha descrit que l'autocompassió sembla funcionar com una estratègia de regulació de les emocions ensenyant als individus com fer front al dolor i el sofriment (Hölzel et al., 2011). L'autocompassió està relacionada amb la salut mental i la

resiliència (MacBeth i Gumley, 2012) i pot actuar com un "matalàs" per esmorteir possibles estressants psicològics (Gilbert, 2010a, b). Alguns estudis suggereixen que l'autocompassió prediu condicions psiquiàtriques relacionades amb la preocupació, la ruminació i la supressió emocional (Jazaieri et al., 2014; Leary et al., 2007). L'autocrítica per altra banda, també es considera com un tret transdiagnòstic (Gilbert i Irons, 2005) i especialment marcat en el TLP (Leichsenring, 2011; Southwick et al., 1995), com ho és la DE. De fet, la Teràpia Dialèctica Conductual (*DBT*), que és fins ara la que ha demostrat més solidesa per al tractament d'aquest trastorn (Stoffers et al., 2012), aborda en gran mesura l'autocrítica/autoinvalidesa, així com emocions derivades com la vergonya i la culpa (Linehan et al., 1993).

Actualment existeixen diverses intervencions psicològiques basades específicament en treballar l'autocompassió, com el programa d'Autocompassió en Mindfulness (*Mindful Self-Compassion, MSC*) de Neff i Germer (2013), la Teràpia enfocada en Compassió (*Compassion-Focused Therapy, CFT*) de Gilbert i Procter (2006), l'Entrenament Cognitiu basat en Compassió (*Cognitively-Based Compassion Training, CBCT*) de Mascaro et al. (2013) o l'Entrenament en el Cultiu de la Compassió (*Compassion Cultivation Training, CCT*) de Jazaieri et al. (2013). Alguns estudis han reportat que aquestes indueixen canvis positius moderats en autocompassió i en altres resultats de salut mental (Braehler et al., 2013, Kirby et al., 2017, Navarro-Gil et al., 2018). No obstant això, altres estudis han suggerit que els resultats d'aquestes teràpies tant específiques no semblen ser superiors a altres tractaments psicològics actius pel que fa a la millora de la l'autocompassió (Wilson et al., 2018). En general, s'ha vist que la pràctica de Mindfulness augmenta l'autocompassió (Hofmann et al., 2011; Kuyken et al., 2010; Svendsen et al., 2017) i també que una major capacitat de mindfulness és predictiva de millors nivells d'autocompassió (Bergen-Cico i Cheon, 2014; Shapiro et al., 2007). En un estudi de Feliu-Soler et al. (2017) en pacients amb TLP que havien realitzat prèviament 10 sessions grupals d'entrenament en habilitats de mindfulness en un context de DBT, es comparaven els que posteriorment realitzaven tres sessions d'un programa breu d'entrenament enfocat en compassió i autocompassió (*Loving-kindness and compassion meditation, LKM/CM*) i els que, en canvi, feien tres sessions d'un programa ordinari decontinuïtaten Mindfulness (*Mindfulness continuation training, MCT*). Tots dos grups van obtenir millores similars en les mesures d'autocompassió i autocrítica. Els pacients assignats a la condició *LKM/CM* varen obtenir puntuació més alta en

autoamabilitat (subescala *Self-kindness* de la *Self-Compassion Scale-Short Form* (*SC-SF*; Neff, 2003b; validació espanyola: Garcia-Campayo et al., 2014), un instrument de primera elecció que mesura l'autocompassió).

Tot i que en el context dels psicodèlics l'autocompassió ha rebut poca atenció, diversos estudis sobre psicoteràpia assistida amb psicodèlics han vist que els individus que la rebien puntuen més alt en mesures d'autocompassió i d'acceptació (Bogenschutz et al., 2018; Gasser et al., 2015; Malone et al., 2018). Un estudi que va avaluar l'Ayahuasca amb finalitats terapèutiques en una mostra d'individus amb trastorns alimentaris va trobar que l'autocompassió sembla tenir un paper important en la recuperació (Lafrance et al., 2017). Un estudi obert en voluntaris sans realitzat per Sampedro i col·legues (2017) va trobar que una sola dosi d'Ayahuasca podia millorar significativament l'autocompassió. Un altre estudi (Franquesa et al., 2018) també va trobar que els usuaris regulars de Ayahuasca semblen tenir també una visió més positiva d'ells mateixos.

Els consumidors d'Ayahuasca també descriuen que la substància té un component de compassió, amb capacitat per evocar un sentiment d'amor i bondat cap a un mateix. En aquest context, sembla més fàcil entendre l'Ayahuasca com un agent potencial per que pot ajudar a reprocessar esdeveniments altament emocionals si el procés està "eclipsat" per aquesta compassió. L'Ayahuasca podria ser d'interès clínic com una potencial nova línia de tractament per a tractar esdeveniments traumàtics del passat o fins i tot per al trastorn d'estrès posttraumàtic (TEPT) (Nielson i Megler, 2017).

1.7 Resum introductori

Estudis preliminars suggereixen que un potencial efecte beneficiós de l'Ayahuasca en trastorns com la depressió, l'ansietat i les addiccions. D'altra banda, recentment s'ha suggerit un possible mecanisme psicològic que explicaria aquest efecte terapèutic de l'Ayahuasca sobre els trets de mindfulness, la desregulació emocional i, possiblement l'autocompassió. No obstant això, els resultats descrits fins al moment actual encara no tenen prou evidències per a donar prou estructura a aquestes propostes. Calen més estudis controlats i amb mostres majors per confirmar aquestes hipòtesis. D'aquest plantejament sorgeix la present tesi doctoral.

HIPÒTESIS I OBJECTIUS

2. Hipòtesis i objectius

2.1 Hipòtesis

Hipòtesi 1: L'Ayahuasca facilita el procés psicoterapèutic, permetent una actitud de descentrament, orientada a l'acceptació i sense jutjar de forma similar a una intervenció de vuit setmanes de Mindfulness.

Hipòtesi 2: L'Ayahuasca té la capacitat de millorar la desregulació emocional, així com capacitats de mindfulness com l'acceptació.

Hipòtesi 3: L'Ayahuasca millora significativament la desregulació emocional i algunes capacitats de mindfulness en subjectes amb trets de personalitat límit.

Hipòtesi 4: L'Ayahuasca té la capacitat de millorar significativament aspectes d' autocompassió i autocrítica.

2.2 Objectius

2.2.1 Primaris

- Aprofundir en el coneixement dels mecanismes d'acció psicològics atribuïbles a la Ayahuasca.

- Avaluar el potencial terapèutic de l'Ayahuasca millorant aspectes psicològics relacionats amb el mindfulness, la regulació emocional i l'autocompassió.

2.2.2 Secundaris

- Avaluar l'impacte sobre capacitats relatives al mindfulness com l'acceptació i el descentrament de la presa d' Ayahuasca en comparació amb una intervenció de vuit setmanes de Mindfulness basat en reducció de l'estrès (MBSR).

- Examinar els possibles efectes induïts de la presa d'Ayahuasca sobre la desregulació emocional (DE) en una mostra comunitària i confirmar els efectes sobre capacitats relatives al mindfulness.

- Examinar els possibles efectes induïts de la presa d'Ayahuasca sobre la desregulació emocional (DE) i sobre capacitats relatives al mindfulness en individus amb trets de Trastorn Límit de la Personalitat (TLP).

- Examinar els possibles efectes induïts de la presa d'Ayahuasca sobre l' autocompassió i l'autocrítica en una mostra comunitària.

MÈTODES I RESULTATS

3. Mètodes i resultats

3.1 ARTICLE 1

Soler, J., Elices, M., Dominguez-Clavé, E., Pascual, J. C., Feilding, A., Navarro-Gil, M., Garcia-Campayo, J. i Riba, J. (2021). Corrigendum: Four Weekly Ayahuasca Sessions Lead to Increases in "Acceptance" Capacities: A Comparison Study with a Standard 8-Week Mindfulness Training Program. *Frontiers in pharmacology, 11*, 635111. https://doi.org/10.3389/fphar.2020.635111

Four Weekly Ayahuasca Sessions Lead to Increases in "Acceptance" Capacities: A Comparison Study With a Standard 8-Week Mindfulness Training Program

Joaquim Soler[1,2,3], Matilde Elices[1,2]*, Elisabeth Dominguez-Clavé[1,2,3], Juan C. Pascual[1,2,3], Amanda Feilding[4], Mayte Navarro-Gil[5], Javier García-Campayo[6] and Jordi Riba[2,7]

[1] Department of Psychiatry, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain, [2] Centro de Investigación Biomédica en Red de Salud Mental, Madrid, Spain, [3] Department of Pharmacology, Therapeutics and Toxicology, Universitat Autònoma de Barcelona (UAB), Barcelona, Spain, [4] The Beckley Foundation, Oxford, United Kingdom, [5] Primary Care Prevention and Health Promotion Research Network, University of Zaragoza, Zaragoza, Spain, [6] Miguel Servet Hospital, University of Zaragoza, Zaragoza, Spain, [7] Human Neuropsychopharmacology Group, Sant Pau Institute of Biomedical Research, Barcelona, Spain

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Edited by:
Rick Strassman, University of New Mexico School of Medicine, United States

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Frederick Streeter Barrett, Johns Hopkins University, United States

***Correspondence:**
Matilde Elices
matilde.elices@yahoo.com

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Background: The therapeutic effects of the Amazonian plant tea ayahuasca may relate to its ability to enhance mindfulness capacities. Ayahuasca induces a modified state of awareness through the combined action of its active principles: the psychedelic *N,N*-dimethyltryptamine (DMT) and a series of centrally acting β-carbolines, mainly harmine and tetrahydroharmine. To better understand the therapeutic potential of ayahuasca, here we compared the impact on mindfulness capacities induced by two independent interventions: (a) participation in four ayahuasca sessions without any specific purpose related to improving mindfulness capacities; and (b) participation in a standard mindfulness training course: 8 weeks mindfulness-based stress reduction (MBSR), with the specific goal of improving these skills.

Methods: Participants of two independent groups completed two self-report instruments: The Five Facet Mindfulness Questionnaire (FFMQ) and the Experiences Questionnaire (EQ). The MINDSENS Composite Index was also calculated, including those EQ and FFMQ items that have proven to be the most sensitive to meditation practice. Group A (n = 10) was assessed before and after the last of four closely spaced consecutive ayahuasca sessions. Group B (n = 10) was assessed before and after completion of a standard 8-week MBSR course.

Results: MBSR training led to greater increases in overall mindfulness scores after the 8-week period. MBSR but not ayahuasca led to increases in the MINDSENS Composite Index. However, the ayahuasca sessions induced comparable increases in the Non-Judging subscale of the FFMQ, specifically measuring "acceptance." Improving this capacity allows for a more detached and less judgmental stance toward potentially distressing thoughts and emotions.

Conclusion: The present findings suggest that a small number of ayahuasca sessions can be as effective at improving acceptance as more lengthy and costly interventions. Future studies should address the benefits of combining ayahuasca administration with mindfulness-based interventions. This will allow us to investigate if ayahuasca will improve the outcome of psychotherapeutic interventions.

Keywords: ayahuasca, mindfulness, acceptance, Non-Judging, human

INTRODUCTION

In recent years there has been a renewed interest in the potential use of psychedelics for the treatment of different psychiatric conditions (Sessa, 2005; Mithoefer et al., 2016). One of the substances that have gained attention is ayahuasca; a tea obtained from the mix of *Banisteriopsis caapi* with *Psychotria viridis* (Rubiaceae) or *Diplopterys cabrerana* (Malpighiaceae) (McKenna et al., 1984). The β-carboline alkaloids present in ayahuasca [i.e., harmine, tetrahydroharmine (THH), and harmaline] show monoamine-oxidase (MAO) inhibiting properties (Buckholtz and Boggan, 1977b) and also serotonin reuptake inhibition (THH; Buckholtz and Boggan, 1977a). The leaves of *P. viridis* and *D. cabrerana* contain *N,N*-dimethyltryptamine (DMT), an alkaloid that is also extracted into the ayahuasca brew during the infusion process. DMT is the main psychotropic agent of ayahuasca, and possibly the responsible for the dream-like experience induced by the tea. This modified state of consciousness is characterized by the presence of visual imagery and the recollection of highly emotional autobiographic memories (Riba et al., 2001). On a molecular level, DMT has affinity for 5-HT_{2A} and 5-HT_{1A} binding sites, where it acts as an agonist or partial agonist (Riba et al., 2001; Carbonaro et al., 2015). Although DMT has been regarded as the primary ayahuasca compound acting on the CNS, recent research has shown that the β-carbolines may also have a relevant contribution to the overall effects of ayahuasca in the brain. Specifically, harmine, THH, and the harmine metabolite harmol, stimulate adult neurogenesis *in vitro* (Morales-García et al., 2017). Traditionally, ayahuasca has been consumed for ritual and medical purposes in the Amazon Basin. Today its use has spread worldwide, encouraging research on its potential therapeutic effects (Domínguez-Clavé et al., 2016). Compared to non-users, habitual ayahuasca consumers show lower hopelessness (Santos et al., 2007) and depression levels, and higher scores on certain personality traits like agreeableness and openness (Barbosa et al., 2016). Experimental studies of acute ayahuasca administration to healthy volunteers have found that ayahuasca targets key nodes of the default mode network (Valle et al., 2016; Sampedro et al., 2017) that are associated with higher self-consciousness and pathological ruminations (Vogt and Laureys, 2005). Additionally, data shows increased blood flow in several brain regions implicated in cognitive control, emotion regulation, and memory (Riba et al., 2006; Sanches et al., 2016). Recent clinical studies on its utility as an adjunct to psychological interventions have demonstrated therapeutic benefits in treatment-resistant depression (Osório Fde et al., 2015; Dos Santos et al., 2016; Sanches et al., 2016) and substance abuse (Fábregas et al., 2010; Thomas et al., 2013).

In a previous work by our group (Soler et al., 2016), we argued that the therapeutic effects of ayahuasca might be related to increases in mindfulness-related capacities. Mindfulness entails a focus on the present experience and reaching a state of non-judgmental awareness, enhanced curiosity and openness (Kabat-Zinn, 1990; Bishop et al., 2004; Baer et al., 2006). These qualities can be considered from a dimensional trait perspective, but can also be fostered through meditative practice. In the last three decades there has been a proliferation of mindfulness-based interventions designed to teach individuals how to maximize these skills. Probably the most commonly used intervention is the Mindfulness-Based Stress Reduction (MBSR; Kabat-Zinn, 1990) approach, an 8-week program that has been widely applied to deal with a number of medical and psychiatric conditions. MBSR focuses on the cultivation of mindfulness through formal meditation practices (i.e., body scan, sitting meditation and yoga), and on the integration of mindfulness-principles into everyday activities (Kabat-Zinn, 1990). In our previous study (Soler et al., 2016), we assessed mindfulness-related capacities before and after one dose of ayahuasca, finding that ayahuasca intake led to increases in three core mindfulness facets: decentering, defined as the capacity to observe one's thoughts and inner experiences in a detached manner (Fresco et al., 2007); Non-Judging and Non-Reacting, defined, respectively, as the ability to take non-judgmental and non-reactive stances toward emotions, thoughts and experiences in general (Baer et al., 2006). Moreover, in a subsequent study using magnetic resonance imaging (MRI) we reported that post-acute metabolic and connectivity changes in the brain after a single ayahuasca session were associated with maintained elevations in the non-judgmental attitudes 2 months later (Sampedro et al., 2017).

Together, the above data indicates that traditional mindfulness training techniques are not the only pathway to foster mindfulness capacities. They further suggest that ayahuasca intake may attain analogous results (Soler et al., 2016). However, the specific domains targeted by either approach have not been assessed. Here, we conducted an exploratory-comparison study in order to evaluate the similarities and differences of the two approaches. Specifically, we compared the impact on mindfulness scores of: (a) participation in four consecutive ayahuasca sessions without the specific purpose of improving mindfulness capacities; and (b) participation in a standard mindfulness training course (8 weeks MBSR), with the specific goal of improving these skills. We hypothesized that both interventions would result in significant improvements in mindfulness capacities. However, given the lack of previous research comparing these two interventions

hypotheses in regards to changes in specific-mindfulness facets were not made.

MATERIALS AND METHODS

Participants

A total of 20 individuals (ten per group) were enrolled in the study. Groups were comparable in terms of age [ayahuasca group mean age = 50.00 years (*SD* = 14.71); MBSR group mean age = 42.00 years (*SD* = 11.44; *F* = 1.84, *p* = 0.19)] and sex (seven females in each group). Based on a previous study (Soler et al., 2016) where ayahuasca users demonstrated unusually high baseline scores on decentering, as measured by the Experiences Questionnaire (EQ), we used the single-factor EQ scale to match participants between groups. **Table 1** shows that there were not baseline differences between ayahuasca and MBSR groups in neither FFMQ facets or the EQ.

Individuals interested in participating in more than one ayahuasca session were contacted and received information about the study aims. They were also asked to pass the information to their acquaintances. The participant's principal motivation was to use ayahuasca to increase self-knowledge and introspection. To be included in the study, participants in the ayahuasca group needed to: (1) have abstained from ayahuasca, medications or illicit drugs at least 2 weeks before the initial assessment, (2) have abstained from alcohol, in the 24 h prior to the initial and final assessments; and (3) agree to abstain from taking any drug other than ayahuasca for the entire duration of the study. To increase recruitment success, prior experience with ayahuasca was not an exclusion criterion. No participant in the ayahuasca group reported having any meditation experience.

The mindfulness group consisted of individuals naïve to meditation who were interested in mindfulness and who had enrolled in a MBSR course. The study's aims were explained to them before the beginning of the course. Inclusion criteria for the MBSR group were: (1) no history of ayahuasca consumption; (2) no alcohol intake in the 24 h prior to the initial and final assessments; and (3) agree to abstain from taking any psychoactive drug for the entire duration of the study.

TABLE 1 | Differences in FFMQ and EQ baseline scores between participants in the ayahuasca group and participants in the mindfulness group.

	Ayahuasca (*n* = 10)		MBSR (*n* = 10)			
	M	*SD*	*M*	*SD*	*F*	*p*
FFMQ						
Observing	25.70	8.08	25.10	1.72	0.05	0.82
Describing	29.00	9.36	26.50	2.01	0.68	0.42
Acting with awareness	30.70	6.36	26.90	0.87	3.50	0.80
Non-Judging	30.00	9.32	27.10	0.73	0.96	0.34
Non-Reacting	22.00	8.39	23.40	1.77	0.26	0.61
EQ	38.00	9.62	39.00	3.49	0.09	0.76

MBSR, Mindfulness-Based Stress Reduction; M, Mean; SD, Standard Deviation; FFMQ, Five Facets Mindfulness Questionnaire; EQ, Experiences Questionnaire.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Sant Pau Hospital Ethics Committee. All participants gave their written informed consent prior to participation.

Study Groups

Ayahuasca Group

Participants were recruited from a pool of individuals who had freely decided to participate in ayahuasca sessions in the Barcelona area, in a non-religious setting. Ayahuasca was taken in a dimly light room with participants sitting or lying down on mattresses while recorded music was played. Participants were free to leave the room if they so desired. Experimenters were present before, during, and after each session, sessions lasted between 6 and 8 h. Questionnaires were administered before the first and 24 h after the last of four consecutive sessions held a week apart.

MBSR Group

Participants in this group participated in a standard MBSR program consisting of weekly 2.5 h sessions for eight consecutive weeks. Training was conducted according to the MBSR guidelines (Kabat-Zinn, 1990). During the 8 weeks participants were trained in three types of mindfulness techniques. Through "body scan," participants learn to focus attention sequentially on parts of the body, non-judgmentally noticing any sensation that might be present. The second technique involves practicing mindful hatha yoga postures to develop body awareness through gentle movements and stretching. The third, "sitting meditation" involves using awareness of the sensations associated with breathing as an anchor, while noticing other bodily sensations, sounds or thoughts. In the course of the program participants were also encouraged to conduct informal mindfulness exercises, by carrying out everyday activities (e.g., eating, walking, washing the dishes) with a full awareness of the movements, sensations, cognitions, and feelings that may be involved in each particular task. CD's containing recorded formal meditation practices were given to participants, who were encouraged to practice at home by listening to the CD 45 min each day throughout the duration of the program (Kabat-Zinn, 1990). Between sessions 5 and 6, individuals participated in a "day of silence" during which they were guided through various practices. Participants in the MBSR group filled out the administered questionnaires 24 h prior to the first MBSR session and after the eighth and final MBSR session.

Measures

To assess mindfulness-related capacities the Spanish versions of two instruments were used.

The *Five Facet Mindfulness Questionnaire or FFMQ* (Baer et al., 2006; Cebolla et al., 2012) is a self-reported questionnaire that measures five mindfulness components: (1) Observing: noticing external and internal experiences, e.g., body sensations, thoughts or emotions; (2) Describing: putting words to, or labeling the internal experience; (3) Acting with awareness: focusing on the present activity instead of behaving mechanically; (4) Non-Judging the inner experience: taking a non-evaluative stance toward the present experience, thoughts or emotions; and

(5) Non-Reacting to the inner experience: allowing thoughts and feelings to come, without getting caught up in, or carried away, by them. Sample items for each sub-scale include: Observing "When I take a shower or bath, I stay alert to the sensations of water on my body"; Describing "I'm good at finding words to describe my feelings"; Acting with awareness "I am easily distracted"; Non-Judging "I tell myself I should not be feeling the way I am feeling"; and Non-Reacting "I watch my feelings without getting lost in them." Study participants were asked to rate the degree of agreement with each statement on a 5-point scale that ranges from 1 (*never, or very rarely true*) to 5 (*very often, or always, true*). After reverse scoring specific items, mean ratings are calculated for each of the five facets. Facet scores range from 8 to 40, with the exception of the non-reactivity facet, which ranges from 7 to 35 and higher scores reflect greater mindfulness.

The "Non-Judging" and "Non-Reacting" factors represent the "acceptance" component of the FFMQ, while the other factors are more related to the attentional aspect of mindfulness (Baer et al., 2006).

The *EQ* (Fresco et al., 2007; Soler et al., 2014b) was used as a measure of decentering. The EQ has 11 items and measures a metacognitive ability known as "decentering," i.e., the capacity to observe one's thoughts and emotions in a detached manner, considering them transient events of the mind. Sample items include: "I can observe unpleasant feelings without being drawn into them" or "I can separate myself from my thoughts and feelings." The EQ items are scored in a 5-point scale, ranging from *never* to *all the time*, with higher scores indicating more decentering. EQ scores are obtained by adding the scores of each item and dividing them by the total number of items.

The MINDSENS Composite Index was also calculated (Soler et al., 2014a). This index includes those EQ and FFMQ items that have proven to be the most sensitive to meditation practice (Soler et al., 2014a). The MINDSENS Composite Index is the average of the sum of 9 items of the EQ and 10 items of the FFMQ (corresponding to the observing and non-reacting sub-scales; Soler et al., 2014a).

Data Analysis

Between groups differences at pre-intervention in mindfulness scores (FFMQ and EQ) were explored by means of an ANOVA. FFMQ, EQ, and MINDSENS scores were analyzed by means of multivariate (FFMQ subscale scores) and univariate (EQ and MINDSENS scores) repeated-measures analyses of variance (ANOVAs). FFMQ subscale scores, EQ scores and MINDSENS scores were entered in the respective ANOVAs as the dependent variables. Participant group (ayahuasca vs. mindfulness) was entered as a between-subjects factor and time (pre- and post-assessment) as a within subject's factor. *Post hoc* analyses were conducted using Student's *t*-test. Results were considered significant for p-values < 0.05.

RESULTS

The multivariate-repeated measures ANOVA using FFMQ's scores as the dependent variables showed a significant effect of time × group [$F(5,14) = 5.16$, $p = 0.007$]. Univariate tests showed a significant time × group effect for the following FFMQ facets: Observing [$F(1,19) = 22.60$, $p < 0.001$], Describing [$F(1,19) = 13.61$, $p = 0.00$], Acting with awareness [$F(1,19) = 8.52$, $p = 0.01$], and Non-Reacting [$F(1,19) = 6.50$, $p = 0.02$]. For scores on Non-Judging no significant time × group effect was found [$F(1,19) = 3.43$, $p = 0.08$]. Participants in the mindfulness group showed significant pre–post treatment increases in all mindfulness facets: Observing [$t(9) = -17.14$, $p < 0.001$], Describing [$t(9) = -9.18$, $p < 0.001$], Acting with awareness [$t(9) = -18.46$, $p < 0.001$], Non-judging [$t(9) = -14.95$, $p < 0.001$], and Non-Reacting [$t(9) = -8.15$, $p < 0.001$]. In the ayahuasca group a significant pre–post improvement was found for Non-Judging [$t(9) = -2.67$, $p = 0.02$], while no significant pre–post differences were observed for the remaining FFMQ facets: Observing [$t(9) = -1.10$, $p = 0.29$], Describing [$t(9) = -1.45$, $p = 0.17$], Acting with awareness [$t(9) = -1.86$, $p = 0.09$], and Non-Reacting [$t(9) = -1.23$, $p = 0.25$].

For EQ scores a significant time × group interaction was found [$F(1,18) = 7.87$, $p = 0.01$] and *post hoc* analyses showed significant pre–post differences in the mindfulness group [$t(9) = -9.63$, $p < 0.001$], whereas no significant differences were found for the ayahuasca group [$t(9) = -1.82$, $p = 0.10$].

The ANOVA for the MINDSENS Composite Index also revealed a significant time × group effect [$F(1,18) = 21.13$, $p < 0.001$]. *Post hoc* analyses showed significant differences in the mindfulness group [$t(9) = -17.84$, $p < 0.001$], but not in the ayahuasca group [$t(9) = -1.50$, $p = 0.17$]. **Table 2** and **Figure 1** show pre–post mindfulness scores for each group.

DISCUSSION

The current study aimed to better understand the psychological mechanisms related to ayahuasca's therapeutic effects by studying its impact on mindfulness-related capacities. Extending our previous work (Soler et al., 2016), here we compared the effects of four consecutive ayahuasca sessions with those of a standard mindfulness training. Whereas individuals in the ayahuasca group had decided to take the psychedelic for personal reasons unrelated to the objectives of our study, those receiving standard mindfulness training (i.e., MBSR), had enrolled in the program with the specific purpose of improving their mindfulness capacities. Results showed that mindfulness training had an overall greater impact on mindfulness capacities. However, ayahuasca intake led to spontaneous increases in certain aspects of the "acceptance" domain, as measured by the Non-Judging subscale of the FFMQ. Acceptance is one the psychological spheres cultivated in mindfulness meditation and in mindfulness-based psychotherapy. Increasing acceptance enables the individual to attain a non-evaluative stance toward their experience of "being," their thoughts and their emotions without getting carried away by them, no matter how painful these may be.

Our results concerning the Non-Judging subscale replicate the findings obtained by our group in two prior independent studies that assessed ayahuasca users after a single session

TABLE 2 | Comparison of FFMQ and EQ scores between participants in the ayahuasca group and participants in the mindfulness group.

	Ayahuasca (n = 10)				MBSR (n = 10)					
	Pre		Post		Pre		Post		Group × time	
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*F*	*p*
FFMQ										
Observing	25.70	8.08	27.60	9.38	25.10	1.72	35.70**	1.33	22.60	< 0.001
Describing	29.00	9.36	31.40	6.73	26.50	2.01	36.10**	1.52	13.61	0.00
Acting with awareness	30.70	6.36	34.10	4.81	26.90	0.87	35.80**	1.13	8.52	0.01
Non-Judging	30.00	9.32	34.50*	5.66	27.10	0.73	35.50**	1.43	3.43	0.08
Non-Reacting	22.00	8.39	24.20	6.30	23.40	1.77	30.70**	1.63	6.50	0.02
EQ	38.00	9.62	42.10	5.66	39.00	3.49	50.20**	3.35	7.87	0.01
MINDSENS	3.33	0.91	3.61	0.74	3.31	0.16	4.50**	0.19	21.13	< 0.001

*MBSR, Mindfulness-Based Stress Reduction; M, Mean; SD, Standard Deviation; FFMQ, Five Facets Mindfulness Questionnaire; EQ, Experiences Questionnaire *p < 0.05; **p < 0.001.*

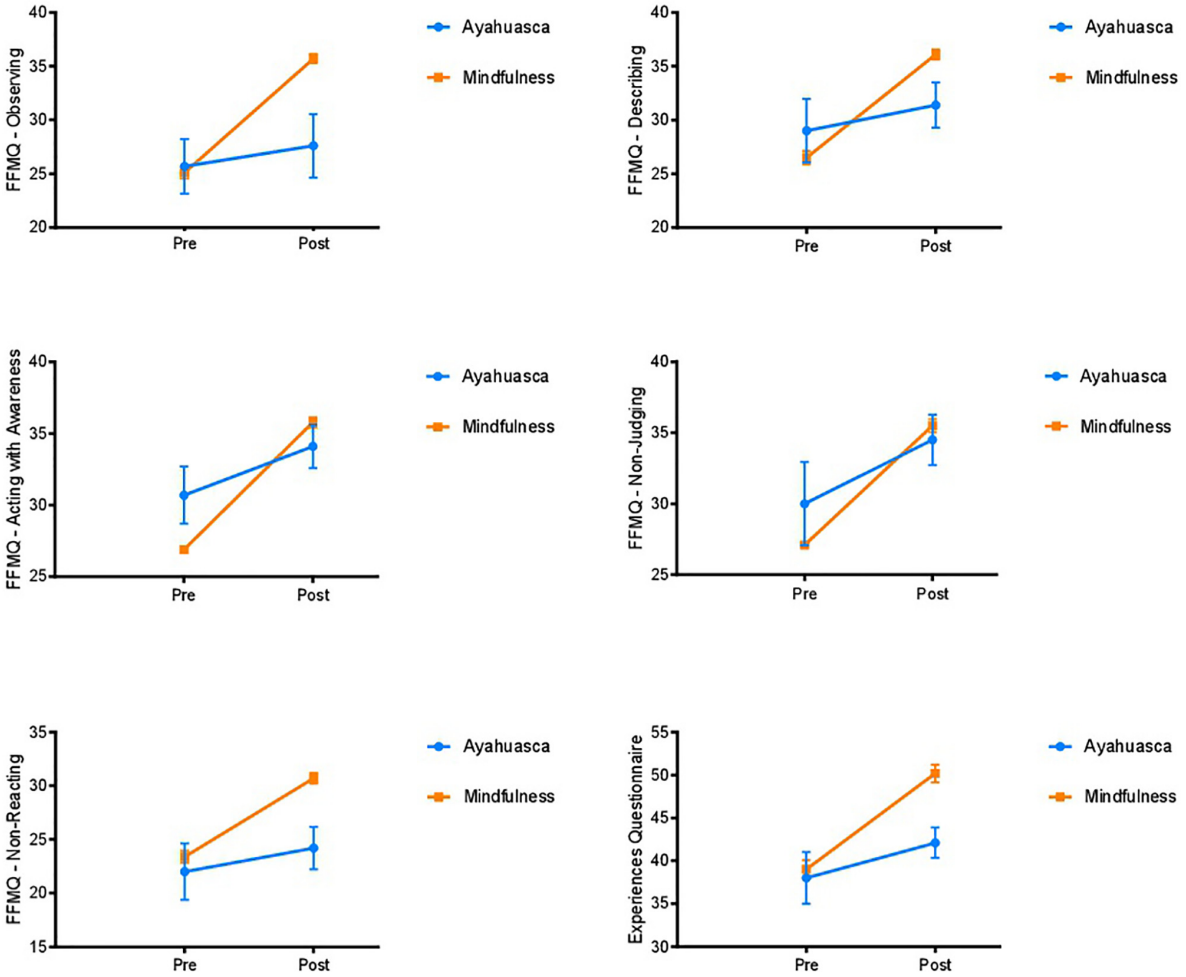

FIGURE 1 | Pre–post changes in FFMQ facets and decentering scores (Experiences Questionnaire) in group A (ayahuasca intake) and group B (mindfulness training). Values are shown as means with standard errors represented by vertical bars.

(Soler et al., 2016; Sampedro et al., 2017). In both cases, ayahuasca increased the scores on the Non-Judging and Non-Reacting subscales of the FFMQ, which focus on the "acceptance" domain of mindfulness abilities. Similar to our present results, these previous studies did not find any effect of ayahuasca on the other three subscales of the FFMQ that assess the "attention"

domain of mindfulness abilities. Interestingly, in the Sampedro et al. (2017) study a follow-up assessment was carried out 2 months after the ayahuasca session and found that Non-Judging was the only subscale that remained elevated (Sampedro et al., 2017). The present findings thus further support for the following ideas: (a) ayahuasca intake leads to psychological modifications that are observable beyond the time frame of the acute inebriation; and (b) a reduction in self-judgmental patterns of thought is a key feature of the post-acute stage.

A novel and relevant finding in the present investigation is that both ayahuasca and MBSR produce improvement in acceptance, although only the latter -MBSR- is a theoretical and practical training program specifically designed to foster mindfulness domains (Gu et al., 2015; Khoury et al., 2015). While individuals in the ayahuasca group may have had a wide variety of reasons to engage in ayahuasca taking, subjects in the comparison group had enrolled in the MBSR course with the explicit purpose of enhancing mindfulness capacities. Importantly, ayahuasca would thus appear to have the potential to increase acceptance *per se*, without this being a manifest and desired outcome of ayahuasca intake. Although studies with larger sample size are needed, the above finding is relevant for a number of reasons, theoretical and clinical. First, reducing automatic judgmental attitudes is particularly hard to achieve. Montero-Marin et al. (2016) found improvements in Observing, Non-Reacting, decentering and non-attachment in individuals who had participated in a 1-month meditation retreat, but failed to find modifications in Non-Judging. In another study, the authors assessed the influence of practice (i.e., frequency of meditation, session duration, lifetime practice) on various mindfulness facets. Results showed that Non-Judging improved with practice significantly less than Non-Reacting, Observing and decentering (Soler et al., 2014a). Second, acceptance has been found to play a fundamental role in psychological health. Non-judgmental awareness is commonly impaired in diverse clinical populations (Coffey et al., 2010). Deficits have been reported for individuals with eating disorders (Lavender et al., 2011), borderline personality disorder (Baer et al., 2004), and cocaine use disorder (Tejedor et al., 2014). Moreover, Brown et al. (2015) have found an association between higher Non-Judging capacities and lower depressive symptoms and anxiety. Kotsou et al. (2018), showed that higher acceptance is a better predictor of lower psychopathology than other variables related to mental health such as emotional competence, emotion regulation or even present-centered awareness. Interestingly, increasing acceptance has been directly linked to the positive outcomes of mindfulness practice (Holzel et al., 2011), and of exposure interventions (Brown et al., 2015). The acute stage of ayahuasca has been assimilated to a controlled exposure to autobiographical material (Domínguez-Clavé et al., 2016). Our results suggest that acute exposure is followed by a subsequent stage of increased acceptance. These combined effects could be of great value in a psychotherapeutic context (Domínguez-Clavé et al., 2016; Mithoefer et al., 2016).

From a neurobiological perspective, our findings can be linked to the selective modulation by ayahuasca of specific brain regions and networks. In a neuroimaging study using MRI, we found associations between Non-Judging increases and post-acute neurometabolic and connectivity changes (Sampedro et al., 2017). Reductions in the levels of the excitatory glutamate–glutamine complex in the posterior cingulate cortex (PCC) correlated with Non-Judging increases 24 h after ayahuasca intake and at follow-up 2 months later. In the same study, increased functional connectivity between the anterior cingulate cortex (ACC) and the PCC and between the ACC and the medial temporal lobe (MTL) also correlated with Non-Judging at the two assessment time points. Thus, desirable effects at the psychological level were linked on the one hand to neurometabolic reductions in the PCC, a region which is key to the sense of self (Vogt and Laureys, 2005) and is abnormally hyperactive in certain psychiatric conditions (Hamilton et al., 2011). On the other hand, enhanced Non-Judging relied also on increased neural network cross-talk and on an increased coupling of activity between the ACC, a key center of self-monitoring and other aspects of executive function (Kelly et al., 2009) and the MTL, a limbic region processing memory and emotion (Dolcos et al., 2004).

Contrary to our previous findings (Soler et al., 2016; Sampedro et al., 2017), scores on the Non-Reacting subscale of the FFMQ and on the EQ questionnaire (decentering) were not significantly modified after ayahuasca. These discrepancies may indicate a less robust effect of ayahuasca on these variables. As a matter of fact, in our previous neuroimaging study we found that post-acute increases in these variables had returned to baseline levels 2 months later, while scores on Non-Judging remained elevated (Sampedro et al., 2017). Another possible explanation could be that Non-Judging is difficult to increase and thus less prone to show ceiling effects or erratic behavior (see limitations paragraph below). The fact that ayahuasca users were only assessed twice, i.e., before and after fourth ayahuasca session may have prevented us from detecting these potential problems. This brings up the question of the potential impact of the pattern of ayahuasca consumption (e.g., frequency, amount, time between intakes) on the modulation of each mindfulness facet and domain. This question warrants further research in order to optimize the number of ayahuasca sessions and the spacing between sessions in future therapeutic studies.

The observational and exploratory nature of our study involved several limitations that need to be mentioned. The main limitation of the present study was the small sample size that limited the statistical power of the study. Assessments were only conducted, respectively, before the first and after the fourth ayahuasca session, and before and at the end of the MBSR course. No assessments were conducted in between. This approach was selected to avoid imposing an excessive burden on the ayahuasca-using participants that might have led to high drop-out levels. The fact that individuals in the ayahuasca group had prior experience with this psychedelic may have led to ceiling effects on the study variables. On the other hand, the higher scores obtained for several variables in the MBSR group may have been biased by the fact that participants in the mindfulness training course had the explicit intention of enhancing their mindfulness capacities. Ideally, future studies

could assign ayahuasca-naïve and meditation-nature participants to either group randomly. In order to shorten the assessment, we did not explore subjective effects of ayahuasca intake nor the specific motivations to attend to ayahuasca sessions. In addition, including a placebo control group for the ayahuasca condition could also have been interesting to assess possible placebo effects. Assessments could be conducted in both groups at several time points along the study period and follow-up data gathered in order to determine the temporal stability of the findings. Additionally, the design of the study did not include alkaloid determinations in the ayahuasca used by the participants. Lastly, and although participants did not report any current psychiatric disorder or medical condition, no formal medical history was obtained.

CONCLUSION

To conclude, the present results suggest that the "acceptance" domain of mindfulness capacities is particularly sensitive to improvement by ayahuasca, and potentially other psychedelics. Together with previous findings (Soler et al., 2016; Sampedro et al., 2017), the current results open the interesting possibility of using ayahuasca as a tool to enhance acceptance in the context of psychotherapy. Our findings indicate that a small number of ayahuasca sessions could be effective at improving acceptance, similarly to more lengthy and costly interventions. The present findings should be interpreted in light of the aforementioned limitations. The small sample size compromised the statistical power of the study, increasing the possibility of false positive and false negatives. Studies with a larger sample size are needed to confirm the findings of this exploratory study. Future studies should address the benefits of combining ayahuasca administration with mindfulness-based interventions, in order to investigate if ayahuasca will improve the outcome of these psychotherapeutic interventions.

AUTHOR CONTRIBUTIONS

JS, JP, and JR conceived the study. ME and ED-C performed the statistical analyses and drafted the first version of the manuscript. JG-C and MN-G performed the mindfulness intervention. AF contributed to the interpretation of the study's findings. All authors contributed to the writing and reviewing of the manuscript.

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3.2 ARTICLE 2

Domínguez-Clavé, E., Soler, J., Pascual, J. C., Elices, M., Franquesa, A., Valle, M., Alvarez, E. i Riba, J. (2019). Ayahuasca improves emotion dysregulation in a community sample and in individuals with borderline-like traits. *Psychopharmacology*, *236*(2), 573–580. https://doi.org/10.1007/s00213-018-5085-3

ORIGINAL INVESTIGATION

Ayahuasca improves emotion dysregulation in a community sample and in individuals with borderline-like traits

Elisabet Domínguez-Clavé[1,2,3] · Joaquim Soler[1,3,4] · Juan C. Pascual[1,3,4] · Matilde Elices[1,3] · Alba Franquesa[1] · Marta Valle[2,3,5] · Enric Alvarez[1,4] · Jordi Riba[3,6,7]

Abstract

Background Research suggests that mindfulness-based interventions may improve mindfulness-related capacities (e.g., decentering, non-judging, and non-reacting) and emotion regulation. Previously, our group reported that ayahuasca could be a potential analogue of mindfulness practice. The main aim of the current study was to examine the effects of ayahuasca on emotional regulation and mindfulness-related capacities. Secondarily, we sought to explore the effects of ayahuasca on individ-uals with borderline personality disorder (BPD) traits.

Method This is an observational study of 45 volunteers who participated in an ayahuasca session. The volunteers com-pleted various self-report instruments designed to measure emotional dysregulation (Difficulties in Emotion Regulation Scale (DERS)) and mindfulness traits (Five Facet Mindfulness Questionnaire (FFMQ)–Short Form and Experiences Questionnaire (EQ)) prior to and 24 h after the ayahuasca session. The volunteers were divided into two subgroups based on their score on the McLean Screening Instrument for BPD (MSI-BPD). Twelve participants were grouped into the BPD-like traits subgroup while the rest of them were included in the non-BPD-like subgroup. We performed within-subjects and between-group analyses.

Results Overall, the participants showed significant improvements on the FFMQ subscales *observing*, *acting with awareness*, *non-judging*, and *non-reacting* and also significantly improved on *decentering* (EQ scale) and on the DERS subscales *emotional non-acceptance*, *emotional interference*, and *lack of control*. The BPD-like subgroup also showed significant improvements on the DERS subscales emotional interference and lack of control but not in mindfulness capacities.

Conclusions These findings suggest a potential therapeutic effect for ayahuasca in emotion regulation and mindfulness capacities (including decentering, acceptance, awareness, and sensitivity to meditation practice). Based on these results, we believe that ayahuasca therapy could be of value in clinical populations, such as individuals with BPD, affected by emotion dysregulation.

Keywords Ayahuasca · Emotional dysregulation · Mindfulness · Borderline personality disorder

✉ Joaquim Soler
jsolerri@santpau.cat

✉ Jordi Riba
jordi.riba@maastrichtuniversity.nl

[1] Servei de Psiquiatria, Hospital de la Santa Creu i Sant Pau Institut de Recerca, Barcelona, Spain

[2] Department of Pharmacology and Therapeutics, Universitat Autònoma de Barcelona (UAB), Barcelona, Spain

[3] Centro de Investigación Biomédica en Red de Salud Mental, CIBERSAM, Barcelona, Spain

[4] Departament de Psiquiatria i Medicina Legal, Universitat Autònoma de Barcelona, Barcelona, Spain

[5] Pharmacokinetic and Pharmacodynamic Modelling and Simulation, Sant Pau Institute of Biomedical Research (IIB-Sant Pau), Barcelona, Spain

[6] Human Neuropsychopharmacology Group, Sant Pau Institute of Biomedical Research (IIB-Sant Pau), Barcelona, Spain

[7] Present address: Department of Neuropsychology and Psychopharmacology, Masstricht University, Maastricht, The Netherlands

Introduction

Ayahuasca is a drug that has long been used for religious purposes in the Amazon basin, where it is also known as *natema*, *hoasca*, *daime*, *yagé*, or *yajé* (Frecska et al. 2016). In the last two decades, its use has spread worldwide among non-indigenous people in the Western world. The increased awareness of ayahuasca has led to a growing body of research into the potential therapeutic effects of the drug (Frood 2015; Tupper 2008). Ayahuasca is usually ingested as a tea, generally by mixing *Banisteriopsis caapi* with *Psychotria viridis* (Rubiaceae) (McKenna et al. 1984). *B. caapi* contains β-carboline alkaloids—mainly harmine and tetrahydroharmine (THH), but to a lesser extent, harmaline (McKenna et al. 1984; Rivier and Lindgren 1972). By contrast, *P. viridis* contains *N*,*N*-dimethyltryptamine (DMT), an orally inactive compound due to degradation by monoamine oxidase (MAO) metabolism in the liver and gastrointestinal tract. β-carboline alkaloids are monoamine oxidase inhibitors (Ott 1999) that prevent DMT degradation, which thus allows the drug to maintain its psychoactive effects.

Acute administration of ayahuasca induces a dream-like but conscious state characterized by introspection, visions, enhanced emotions, and recollection of personal memories (Domínguez-Clavé et al. 2016; Riba et al. 2001). These effects have mainly been associated with DMT and its agonist activity at the 5-HT_{2A} and 5-HT_{1A} receptor sites (González-Maeso and Sealfon 2009) and to interaction with the intracellular sigma-1 receptor (S1R) (Fontanilla et al. 2009), which modulates the activity of other proteins and promotes neural plasticity (Chu and Ruoho 2016; Tsai et al. 2009).

In the last decade, several studies have reported that ayahuasca has positive effects on depression, anxiety, substance abuse, and other mental disorders, as well as on overall well-being (Barbosa et al. 2005; Fabregas et al. 2010; Grob et al. 1996; Halpern et al. 2008; Osorio et al. 2015; Sanches et al. 2016; Santos et al. 2007; Thomas et al. 2013). The potential therapeutic benefits of ayahuasca may be attributable to the drug's capacity to promote mindfulness-related capacities such as decentering and acceptance, and the ability to approach thoughts and sensations in a detached manner. Some reports suggest that ayahuasca may enhance these skills, which can also be trained through mindfulness practice (Loizaga-Velder 2013; Shanon 2003). Studies indicate that decentering (Franquesa et al. 2018; Soler et al. 2016b) and certain mindfulness-related capacities such as non-judging and non-reacting (Sampedro et al. 2017; Soler et al. 2016b, 2018) improve after ayahuasca intake. Similar effects have been obtained after a mindfulness-based intervention (MBI) (Carmody and Baer 2008; Soler et al. 2014a, 2018), findings that suggest that both ayahuasca and MBI may provide similar results (Soler et al. 2016b).

Emotion regulation (ER) has a direct relationship to dispositional mindfulness and studies have shown that MBI improves ER (Britton et al. 2012; Feliu-Soler et al. 2014; Hölzel et al. 2011). ER is a core symptom in many psychiatric disorders (Barkley 2010; Bradley et al. 2011; Gross and Thomson 2007; Leichsenring et al. 2011), particularly in borderline personality disorder (BPD) (Crowell et al. 2009; Fruzzetti 2002; Linehan 1993). People who suffer from BPD also have low and fluctuating levels of decentering and mindfulness, both of which seem to improve after MBI (Carmona et al. submitted). Consequently, improving these capacities might facilitate more reflective and less emotion-driven responses (Eisenlohr-Moul et al. 2016a, b), which is crucial to improving the daily life of patients with BPD and others with this core psychopathological condition.

Despite the potential beneficial effects of ayahuasca on the capacity to regulate emotions, no studies have yet been carried out to investigate this. Considering the important role of ER in this patient population, the main aim of the present study was to examine the effects of ayahuasca on ER and to confirm previous findings regarding the mindfulness-related capacities of ayahuasca. A secondary aim was to explore these potential effects in a subset of individuals with BPD-like traits, characterized by at least some degree of emotion dysregulation (ED) and deficits in mindfulness abilities.

Method

Participants and procedure

All of the individuals were enrolled in the study in the context of ayahuasca experience. Potential volunteers for this study were recruited through three groups or communities of ayahuasca users planning to conduct an ayahuasca ceremony in the near future. Communities were located in the province of Barcelona. Ceremonies in each group included 20–25 people and every session involved the intake of the consecutive ayahuasca doses, with a spacing between doses of around 1 h. There were slight context and ritualistic differences between groups, but the main structure of the ceremonies was quite similar. In all groups, assessment procedures were identical. After the volunteers agreed to participate, they were asked to complete a series of questionnaires (see the "Measures" section below) prior to the ayahuasca sessions to determine how they feel and act without the influence of the drug. Following the ayahuasca sessions, the questionnaires were re-administered to determine whether the participants had experienced any changes in their feelings or behavior in the 24-h period after ayahuasca intake.

Given that ER is the core characteristic of BPD, we administered a BPD screening measure to identify volunteers who exhibited some characteristics of BPD (but not necessarily full

BPD). Thus, we divided the 45 volunteers into two subgroups, one consisting of 12 individuals who scored ≥ 5 on the *McLean Screening Instrument for BPD* (MSI-BPD)—denominated the BPD-like group—and the other comprised by the participants ($n = 33$) who scored < 5 on that scale, denominated the non-BPD group. Importantly, for the current study, we used a cutoff score of 5 (rather than 7) because our aim was to identify individuals with BPD-like traits (not necessarily with BPD), following the example established in other studies (Baer and Sauer 2011; Vega et al. 2017). For comparison purposes, we subdivided the sample into non-BPD and BPD-like groups, based on clinical criteria.

Participation was voluntary and written informed consent was obtained from all participants prior to enrollment. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Sant Pau Hospital Ethics Committee.

Measures

The *Difficulties in Emotion Regulation Scale* (DERS; Gratz and Roemer 2004) was used to explore the various facets of ER. The Spanish version (Hervás and Jódar 2008) contains 28 items divided into 5 subscales, as follows: emotional awareness ("I am attentive to my feelings"); lack of clarity ("I have no idea how I am feeling"); emotional non-acceptance ("When I'm upset, I feel guilty for feeling that way"); emotional interference ("When I'm upset, I have difficulty getting work done"); and lack of control ("When I'm upset, I feel out of control"). The instrument is scored on a graduated Likert scale ranging from 1 ("almost never") to 5 ("almost always"), with higher scores indicating greater difficulty of regulating emotions (except for the emotional awareness subscale). Cronbach's alpha for the Spanish version ranges from 0.73 to 0.93.

The *Five Facet Mindfulness Questionnaire–Short Form* (FFMQ-SF; Baer et al. 2006; Cebolla et al. 2012) was used to explore various facets of mindfulness. This questionnaire contains 24 items measuring five different factors, as follows: (1) *observing*, noticing external and internal experiences such as body sensations, thoughts, or emotions; (2) *describing*, putting words to, or labeling the internal experience; (3) *acting with awareness*, focusing on the present activity instead of behaving mechanically; (4) *non-judging* the inner experience, taking a non-evaluative stance towards the experience; and (5) *non-reacting* to the inner experience, allowing thoughts and feelings to come, without being carried away by them.

Participants were asked to rate each sentence on a 5-point scale ranging from 1 (never or very rarely true) to 5 (very often or always true). The FFMQ has shown adequate psychometric properties: the Cronbach's alpha for the Spanish version ranges from 0.80 to 0.90. The non-judging and non-reacting factors represent the "acceptance" component of the FFMQ, while the other factors are more closely related to the attentional aspect of mindfulness (Baer et al. 2006).

The *Experiences Questionnaire* (EQ; Fresco et al. 2007; Soler et al. 2014b) is used to assess an individual's ability to observe thoughts and emotions as temporary objects of the mind, captured under the concept of "decentering." The 11-item EQ has 11 items and measures a metacognitive ability known as decentering, defined as the capacity to observe one's thoughts and emotions in a detached manner, considering them as transient events of the mind. Sample items include the following: "I can observe unpleasant feelings without being drawn into them" or "I can separate myself from my thoughts and feelings." The EQ items are scored on a 5-point scale, ranging from "never" to "all the time," with higher scores indicating a greater decentering capacity.

The MINDSENS Composite Index was also calculated (Soler et al. 2014a). This index includes the items from the EQ and FFMQ that have proven to be the most sensitive to meditation practice.

The McLean Screening Instrument for Borderline Personality Disorder (MSI-BPD) (Zanarini et al. 2003; Soler et al. 2016a) is a BPD screening scale based on DSM-IV diagnostic criteria. It is a simple and rapid 10-item self-report questionnaire that is scored dichotomously (true–false). It includes an item for the first 8 DSM criteria for BPD and 2 items for the ninth criteria (paranoia/dissociation). The original version has good psychometric properties. The Spanish validation study obtained a good internal consistency (KR-20 = 0.873) and an optimal test–retest reliability (ICC = 0.87). According to most studies (including the original study), the best cutoff value is 7 (Sn = 0.71, Sp = 0.68), both in the original version and in most studies that have used the scale. However, it is worth noting that some studies, conducted in other populations and contexts (André et al. 2015; Chanen et al. 2008; Noblin et al. 2014), have used different cutoff values (≥ 5, 5.5, and > 7).

Data analysis

The sociodemographic data for the two subgroups (non-BPD and BPD-like groups) are given as means and standard deviation (SD). These data were then compared by paired *t* tests (continuous variables) or the chi-square test (categorical variables), as appropriate. Missing values were imputed by using the mean of the valid responses when < 20% of the questions were missing for each scale; this was necessary in < 5% of questions overall and thus should not substantially affect the statistical validity of the analysis. To assess possible changes in ED and mindfulness capacities, we compared the scores on the various instruments before and after administration of ayahuasca using multivariate (FFMQ and DERS subscale scores) and univariate (EQ and MINDSENS scores) analyses of variance (ANOVAs). We carried out two-way repeated measures

ANOVA to assess the effects of time, and time × group interaction, and thus evaluate potential differences between groups (MSI-BPD < 5 vs. MSI-BPD ≥ 5). Partial eta squared (η^2) values were also obtained to measure effect sizes. Results were considered significant for p values < 0.05.

Results

Characteristics of the sample

The sociodemographic characteristics of the overall sample and the BPD-like subgroup are described in Table 1. A total of 45 individuals (27 female and 18 male) with a mean age of 39.89 years old participated in the study. Most of the participants had prior experience with ayahuasca but a third of the sample were ayahuasca-naïve individuals.

The mean age of the 12 individuals in the BPD-like subgroup was significantly older than the mean age of those in the non-BPD subgroup (43.58 vs. 39.89; $p = 0.04$). The BPD-like group had a significantly higher mean score on the MSI-BPD scale than the non-BPD group: 6.27 (SD = 1.34) versus 1.52 (SD = 1.48) ($p < 0.025$). Individuals in the BPD-like subgroup (7 female and 5 male) had more experience with ayahuasca than those in the non-BPD subgroup.

Significant between-group differences in baseline values were obtained for the DERS lack of control subscale ($p = 0.10$). No significant differences were obtained for any of the other subscales.

Effects of ayahuasca on emotion regulation and mindfulness-related capacities

The two-way repeated measures ANOVA did not identify any pre-post differences between the groups, except for the DERS subscale lack of control ($p = 0.024$). Pre-post changes were also assessed in the same analysis and showed a significant evolution in time for the DERS subscales emotional non-acceptance ($p < 0.01$), emotional interference ($p < 0.05$), and lack of control ($p < 0.01$), the main FFMQ subscales ($p < 0.01$): observing, awareness, non-judging, and non-reacting (except describing $p > 0.05$), the EQ ($p < 0.01$), and the MINDSENS index ($p < 0.01$). We ran one-factor ANOVA to assess the evolution of every group separately. Detailed results for the significant pre-post changes on the various scales are described in Table 2. The non-BPD group showed significant pre-post differences in DERS scores for the following subscales: emotional non-acceptance with a large effect size ($\eta^2 = 0.37$), emotional interference with a medium effect size ($\eta^2 = 0.15$), and lack of control with a large effect size ($\eta^2 = 0.24$). However, no significant effects were found for the subscales lack of clarity and emotional awareness. For the FFMQ, significant pre-post differences were found on the subscales observing with a large effect size ($\eta^2 = 0.63$), awareness with a large effect size ($\eta^2 = 0.24$), non-reacting with a large effect size ($\eta^2 = 0.20$), and non-judging with a large effect size ($\eta^2 = 0.28$). However, no significant differences were found for the describing subscale. On the EQ, within-group analyses showed significant pre-post increases with a medium size effect ($\eta^2 = 0.16$). Within-group analyses showed significant pre-post changes in the MINDSENS index, with a large effect size ($\eta^2 = 0.25$). The same analysis was carried out for the BPD-like subgroup. On the DERS, the one-factor ANOVA showed significant pre-post differences on the emotional interference subscale with a small to medium effect size ($\eta^2 = 0.08$) and also for the lack of control subscale, with a medium effect size ($\eta^2 = 0.12$). No significant pre-post differences were found on the subscales emotional non-acceptance, lack of clarity, and emotional awareness. No significant pre-post differences were found either for scores on the FFMQ subscales, the EQ, or the MINDSENS index.

None of the participants reported any adverse psychopathological effects related to the ayahuasca sessions.

Discussion

To our knowledge, this is the first study to assess the potential beneficial effects of ayahuasca on emotion regulation, which has not previously been evaluated in individuals who exhibit BPD-like traits. We found, for the first time, that ER appears to be positively influenced by ayahuasca. Emotional dysregulation is a core symptom underpinning multiple mental disorders, including affective, anxiety, personality, and substance use disorders (Barkley 2010; Bradley et al. 2011; Gross and Thomson 2007; Linehan 1993). In recent years, numerous studies have described the positive effects of ayahuasca in several different ER-related disorders (mainly affective and substance use disorders) (Domínguez-Clave et al. 2016). ER is an essential target of several psychotherapeutic interventions, some of which focus exclusively on ER (DBT, Feigenbaum 2007; ERT, Renna et al. 2017). An ER-directed therapy emphasizes contact with emotions and acceptation of emotions as the fundamental manner of regulating them (Gratz et al. 2006; Neacsiu et al. 2014; Soler et al. 2009). In the present study, ayahuasca resulted in significant pre-post changes among individuals without BPD traits on three of the five DERS subscales (emotional non-acceptance, emotional interference, and lack of control), indicating an overall improvement in ER in these individuals.

In the subgroup of individuals with BPD-like traits, we also observed significant pre-post differences on two of the DERS subscales: emotional interference and lack of control. However, the two-way repeated measures ANOVA revealed a group-dependent effect for the latter subscale. According to Glenn and Klonsky (2009), ED is the most influential factor in

Table 1 Sociodemographic data for the general sample and the MSI-BPD subgroup

	General sample ($n = 45$)	MSI-BPD subgroup ($n = 12$)	p
Age	39.89 (7.478)	43.58 (7.166)	0.04*
Sex (women)	27/45 (60%)	7/12 (58.3%)	n.s.
Education (high school)	21/45 (46.7%)	5/12 (41.7%)	n.s.
Previous use of ayahuasca (yes)	29/43 (67.44%)	8/12 (66.6%)	n.s.
Previous use (mean and range 1 to 500 times)	37.64 (104.50)	52.83 (141.95)	n.s.
Main objective of the current ayahuasca intake (therapeutic)	33/45 (73.3%)	9/12 (75%)	n.s.

Means with standard deviation (SD) or number of cases with percentages (%) per each group are represented
MSI-BPD McLean Screening Instrument for Borderline Personality Disorder, *n.s.* non-significant

BPD symptoms, even surpassing measures of negative emotionality affect. Consequently, improving aspects such as emotional interference seems to diminish the impact of negative emotions on quality of life and normal functioning in these patients. We also found significant differences with non-parametric Wilcoxon test on the emotional non-acceptance subscale, but this finding was not confirmed on the ANOVA, probably due to the small sample size of that subgroup. Previous studies have reported significant associations between low scores on the DERS subscale emotional non-acceptance and an experimental measure of intolerance to discomfort in patients with BPD and self-harm behavior (Hervás and Jódar 2008). ED entails disruptive behaviors that are mainly controlled by private emotion rather than by an external rational goal (Linehan 1993): examples of ED are self-injury, suicide, and drug use. Both emotional interference (difficulty of not allowing emotions to interfere with your objectives) and lack of control (feeling overwhelmed by negative emotions) are necessary components of ED.

Another key finding of the present study was the positive effects of ayahuasca on mindfulness-related capacities and decentering, which appear to be similar to those achieved through mindfulness practice (Soler et al. 2016b). Previous studies (Sampedro et al. 2017; Soler et al. 2016b) have found that a single ayahuasca session has the same effect as mindfulness on FFMQ subscales non-judging and non-reacting as well as on decentering and on the MINDSENS scale. Interestingly, Sampedro et al. (2017) performed a follow-up assessment of the participants 2 months after the ayahuasca session, finding that only the non-judging subscale remained elevated. In a more recent study, Soler et al. (2018) compared the benefits of four ayahuasca sessions to 8 weeks of a

Table 2 Baseline and post-ayahuasca scores for the non-BPD and the BPD-like subgroups

		Non-BPD group				BPD-like group			
		Pre mean (SD)	Post mean (SD)	F	p	Pre mean (SD)	Post mean (SD)	F	p
DERS	Emotional non-acceptance	13.56 (5.10)	11.27 (3.90)	25.50	0.000*	17.17 (71.96)	12.47 (59.36)	3.25	0.079
	Emotional interference	9.73 (3.76)	9.10 (3.28)	8.07	0.007*	11.33 (4.63)	8.24 (3.35)	3.75	0.049*
	Emotional awareness	15.69 (3.05)	16.55 (2.55)	1.81	0.185	16.25 (2.49)	16.80 (2.55)	0.003	0.958
	Lack of clarity	7.39 (2.29)	7.20 (2.05)	3.63	0.063	7.25 (2.92)	6.76 (2.34)	0.86	0.357
	Lack of control	15.48 (5.72)	14.17 (3.62)	14.35	0.000*	21.00 (6.96)	15.46 (6.84)	5.52	0.024*
FFMQ	Observing	14.57 (1.74)	17.34 (2.30)	73.08	0.000*	14.07 (2.59)	16.87 (2.52)	0.002	0.968
	Describing	19.37 (3.26)	19.24 (3.60)	1.65	0.205	18.52 (3.87)	19.58 (4.67)	2.66	0.110
	Awareness	16.76 (3.52)	18.59 (3.60)	13.54	0.001*	16.01 (4.19)	17.99 (4.10)	0.02	0.888
	Non-reacting	17.24 (3.36)	18.45 (3.60)	10.58	0.002*	16.33 (2.06)	18.84 (3.45)	2.45	0.125
	Non-judging	18.32 (3.45)	19.59 (3.48)	16.52	0.000*	16.35 (3.98)	19.20 (4.58)	1.29	0.261
EQ		37.91 (6.18)	41.82 (5.95)	8.32	0.006*	38.34 (6.02)	40.71 (5.94)	0.46	0.500
MINDSENS		3.54 (0.53)	3.87 (0.53)	13.51	0.001*	3.48 (0.49)	3.78 (0.48)	0.015	0.902

Means and standard deviations and ANOVAs of the pre-post scores for the non-BPD-like traits (MSI-BPD < 5) and the BPD-like traits (MSI-BPD ≥ 5) subsamples *FFMQ* Five Facet Mindfulness Questionnaire, *DERS* Difficulties in Emotion Regulation Scale, *EQ* Experiences Questionnaire
MINDSENS Composite Index. No significant group × time interactions were found ($p > 0.05$) for any of the subscales. *$p \leq 0.0$

mindfulness-based stress reduction (MBSR) program. Those authors found that the ayahuasca sessions induced comparable increases to those obtained with MBSR in the non-judging FFMQ subscale. Non-judging and non-reacting are two mindfulness characteristics improved by ayahuasca. Both of these capacities pertain to the "Acceptance" domain. Increasing both facets enables the individual to attain a non-evaluative stance toward their experience without getting carried away by their thoughts and their emotions. In contrast to previous studies, we found that ayahuasca had a significant effect on observing and awareness FFMQ subscales, which assess the "Attention" domain of mindfulness (Baer et al. 2006). By improving both observing and awareness capacities, individuals can become more fully connected with the present moment. Development of these important capacities might thus be targeted not only through mindfulness but also in combination with ayahuasca (Thomas et al. 2013). In our sample, we also found significant improvements in EQ decentering scores. In a recent study comparing ayahuasca users to non-users (Franquesa et al. 2018), the users had higher decentering scores. However, these effects on mindfulness facets were not seen for the BPD-like subgroup in our study but could happen also due to the small size of this subgroup. Significant improvements in the FFMQ subscales non-judging, non-reacting, and observing were found when we applied a non-parametric Wilcoxon paired test. The non-reacting and non-judging subscales could be important for this population, because such capacities seem to facilitate more reflective, less emotion-driven responses (Eisenlohr-Moul et al. 2016a, b).

Individuals with BPD suffer from ED and impulsivity symptoms that may be severe or even disabling. Although no specific pharmacological treatments are indicated to treat BPD, most patients with BPD receive pharmacotherapy and a substantial percentage of these patients use illicit drugs (Martin-Blanco et al. 2017). Given the lack of any specific pharmacological treatment for these patients, ayahuasca could be an interesting option for clinical practice. Several studies (Dos Santos et al. 2011, 2012; Riba et al. 2001, 2003) suggest that ayahuasca appears to be reasonably safe in terms of its physiological and clinical impact. Hence, ayahuasca could be used as a complementary therapy to increase the effect of psychological interventions (e.g., mindfulness or DBT) to improve ER and mindfulness-related capacities. However, more research is needed to examine this possibility.

The main limitation of this study is the design, as it was an exploratory, uncontrolled study performed in healthy volunteers without any formal diagnosis of BPD. However, this design was intentional as we sought to evaluate the effects of ayahuasca in a real-world sample of individuals with some BPD traits. Another limitation is that most individuals had previous experience with the substance. However, a third of the sample were individuals who took ayahuasca for the first time. We believe that results derived from such a combined sample strengthen the general characterization of our outcomes. This approach also reduces the chances that they obey a potential self-selection bias. Another limitation is that we did not administer any instrument to measure the acute effects of ayahuasca. The individuals of our sample kindly agreed to collaborate in this study without any other motivation than to provide help. Their participation was non-remunerative and our assessment was reduced to a minimum in order to not interfere in their experience with the substance. Despite the small size of the BPD-like subgroup, the preclinical outcomes presented here seem promising. Future studies are granted to address the issue of ED on clinical populations using larger samples. It would also be valuable to compare ayahuasca users (long-term vs. naïve users) to determine whether the usage history affects certain capacities. Similarly, it would be of value to assess possible placebo effects.

Conclusions

The results of the present study suggest that ayahuasca may positively influence both emotion regulation and mindfulness capacities. These findings open new horizons for the therapeutic use of this ancestral substance in several mental disorders. Although the use of ayahuasca in BPD remains somewhat controversial, mainly due to the dissociative symptoms commonly associated with this disorder, the beneficial effects demonstrated in the present exploratory study in individuals with BPD-like-traits suggest that further research is merited.

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Compliance with ethical standards

Participation was voluntary and written informed consent was obtained from all participants prior to enrollment. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Sant Pau Hospital Ethics Committee.

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

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3.3 ARTICLE 3

Domínguez-Clavé, E., Soler, J., Elices, M., Franquesa, A., Álvarez, E. i Pascual, J. C. (2021). Ayahuasca may help to improve self-compassion and self-criticism capacities. *Human psychopharmacology, e2807*. Advance online publication. https://doi.org/10.1002/hup.2807

Ayahuasca may help to improve self-compassion and self-criticism capacities

Elisabet Domínguez-Clavé[1,2,3] | **Joaquim Soler**[1,3,4] | **Matilde Elices**[1,3] | **Alba Franquesa**[1] | **Enric Álvarez**[1,3,4] | **Juan C. Pascual**[1,3,4]

[1]Psychiatry Service, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

[2]Department of Pharmacology and Therapeutics, Universitat Autònoma de Barcelona (UAB), Barcelona, Spain

[3]Centre for Biomedical Research in Mental Health, CIBERSAM, Barcelona, Spain

[4]Department of Psychiatry and Forensic Medicine, Universitat Autònoma de Barcelona (UAB), Barcelona, Spain

Correspondence
Joaquim Soler, Psychiatry Service, Hospital de la Santa Creu i Sant Pau, C/ Sant Antoni Maria Claret 167, 08025, Barcelona, Spain.
Email: jsolerri@santpau.cat

Abstract

Objective: Ayahuasca is a psychedelic brew that originated in the Amazon basin. The psychological effects of this drug are becoming better understood due to the growing research interest in identifying new potential therapeutic agents for the treatment of emotion dysregulation and other disorders. Previous studies suggest that ayahuasca enhances mindfulness-related capacities (decentering, non-judging, non-reacting and acceptance) and emotion regulation. The aim of the present exploratory study was to determine the effects of ayahuasca on self-compassion in a community sample.

Methods: We administered validated questionnaires (the Self-Compassion Scale-Short Form and Forms of Self-Criticism and Self-Reassurance) to evaluate pre-post changes in self-compassion and self-criticism/self-reassurance in 45 volunteers (27 women; 60%) before and after (≤24 h) an ayahuasca ceremony. Most participants ($n = 29$; 67.4%) had previously used ayahuasca.

Results: Ayahuasca resulted in significant improvements, with medium to large effect sizes ($\eta^2 = 0.184–0.276$), in measures of self-compassion ($p < 0.05$), self-criticism ($p < 0.01$) and self-reassurance ($p < 0.01$).

Conclusions: The findings of this study suggest that ayahuasca promotes well-being and self-compassion, which could have a therapeutic effect on individuals with negative affect and other psychopathological conditions. Large, controlled studies are needed to confirm these findings.

KEYWORDS
ayahuasca, self-compassion, self-criticism, well-being

1 | INTRODUCTION

Ayahuasca is a traditional psychedelic beverage from the upper Amazon region that has traditionally been used for ritual and therapeutic purposes (dos Santos et al., 2017). In the last 2 decades, ayahuasca use has grown substantially in the Western world (Frecska et al., 2016).

The ayahuasca brew is generally prepared by decocting the stems of the *Banisteriopsis caapi* vine and combining these with the leaves of the *Psychotria viridis* bush. This plant-derived preparation contains *N*,*N*-dimethyltryptamine (DMT), a classical psychedelic with 5-HT2A agonist properties (González-Maeso & Sealfon, 2009). DMT is structurally related to the neurotransmitter serotonin (5-hydroxytryptamine) and induces brief but intense modifications in the ordinary state of awareness (Strassman et al., 1994). The main subjective effects are perceptual changes, altered thought content, intensification of emotions, introspection, positive mood and a sense of well-being (dos Santos et al., 2012; Riba et al., 2003). A growing

body of evidence, including case reports, animal model studies, observational studies, and preliminary clinical data, suggest that ayahuasca and its alkaloids may have anxiolytic, antidepressant, and anti-addictive properties (Domínguez-Clavé et al., 2016). In the last decade, the reported effects of ayahuasca have increasingly attracted the attention of biomedical researchers due to the potential clinical benefits of this drug (Frood, 2015).

To better understand the psychological mechanisms underlying the effects of ayahuasca, several studies have evaluated the impact of this drug on mindfulness-related capacities (e.g., acceptance, non-reactivity and decentering), finding that it appears to increase these capacities (Franquesa et al., 2018; Sampedro et al., 2017; Soler et al., 2016, 2018), similar to the effects observed with mindfulness training (MT) (Chiesa et al., 2014; Germer, 2009; Neff, 2003a; Van Dam et al., 2011). Ayahuasca has also been shown to improve emotion dysregulation (Domínguez-Clavé et al., 2019).

Mindfulness practice has been shown to increase self-compassion (SC) (Kuyken et al., 2010; Svendsen et al., 2017). According to Neff and Dahm (2015), an individual who maintains a state of mindful awareness while suffering is capable of acknowledging the pain without judgment, leading to feelings of self-kindness and common humanity, which actively soothes the self. In a review of mindfulness meditation, Hölzel et al. (2011) explained that SC seems to work as an emotion regulation strategy by teaching individuals how to cope with pain and suffering. SC has also been positively associated with psychological wellbeing (MacBeth & Gumley, 2012) and other studies suggest that SC can predict psychiatric conditions related to worry, rumination and emotional suppression (Jazaieri et al., 2014; Leary et al., 2007).

Interventions that specifically focus on fostering SC have been shown to induce moderate positive changes in measures of SC and other mental health outcomes (Braehler et al., 2013, Kirby et al., 2017, Navarro-Gil et al., 2018). However, other studies have suggested that SC-based therapies do not appear to be superior to other active psychological treatments in terms of improving SC (Wilson et al., 2018). By contrast, other studies have shown that a greater mindfulness capacity is predictive of higher levels of SC (Bergen-Cico & Cheon, 2014, Shapiro et al., 2007).

Although in the context of psychedelics SC has received scant attention, several studies have found that individuals who receive psychedelic-assisted psychotherapy score higher on measures of acceptance and SC (Bogenschutz et al., 2018; Gasser et al., 2015; Malone et al., 2018). One study that evaluated ayahuasca for therapeutic purposes in a sample of individuals with eating disorders found that SC appears to play an important role in recovery (Lafrance et al., 2017). An open-label study in healthy volunteers conducted by Sampedro and colleagues (Sampedro et al., 2017) found that a single dose of ayahuasca could significantly improve SC. Another study (Franquesa et al., 2018) also found that regular ayahuasca users seem to have more positive views of the self than ayahuasca-naive users.

Based on the reports described above, we hypothesized that ayahuasca could improve self-compassion. In the present exploratory study, we investigated the effects of ayahuasca on SC and self-criticism in a community sample.

2 | MATERIALS AND METHOD

2.1 | Participants and procedure

This exploratory study recruited participants through ayahuasca communities in Barcelona, Spain. We contacted people planning to attend an ayahuasca session and asked them to participate in this study. The study aims and procedures were explained in detail and those individuals who agreed to participate ($n = 45$) were asked to sign an informed consent form. The main sociodemographic and clinical data of the participants are shown in Table 1. A more extended version is described in a previous study (Domínguez-Clavé et al., 2019).

The ayahuasca ceremonies in our region generally include from 20 to 25 people and most participants take from two to four consecutive doses of ayahuasca, with approximately 1 h between doses. The context and ritualistic characteristics of the setting include an introductory discussion in which the facilitator or ceremony guide explains the steps involved, and the possible effects of the drug, and also reminds participants of the facilitator's role (to provide assistance or guidance as needed). The aim of this initial presentation is to ensure that the user is relaxed and open to the experience. The ayahuasca session concluded with a group discussion of the experience (which is called "integration") during which participants shared their own subjective experiences.

A series of questionnaires (see below) were administered pre- and post-ceremony. Participants were requested to complete the questionnaires from 2 to 3 h before the ceremony and ≤24 h after the ceremony. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Sant Pau Hospital Ethics Committee.

2.2 | Outcome measures

The Self-Compassion Scale-Short Form (SC-SF) (Neff, 2003b) was used to assess SC. The SC-SF is a 12-item scale that distinguishes three facets of compassion: (1) Common Humanity, which acknowledges that human suffering is inherent to the nature of life ("*I try to see my failings as part of the human condition*") (2) Mindfulness, representing a stance of equanimity, rather than over-identification ("*When something upsets me I try to keep my emotions in balance*") and (3) Self-kindness, which is an alternative to self-criticism and self-blaming ("*When I'm going through a very hard time, I give myself the caring and tenderness I need*"). Responses are given on a 5-point scale ranging from 1 (almost never) to 5 (almost always). SC-SF facet scores were calculated by summing the corresponding scores of the positive and negative factors that compose them (e.g., self-kindness + self-judgment reversed; common humanity + isolation reversed; mindfulness + over-identification reversed) and dividing for the number of factors to reach the mean value of each facet of self-compassion. We used the Spanish version of this scale (Garcia-Campayo et al., 2014), which has shown good reliability, with Cronbach's α values ranging from 0.72 to 0.79.

TABLE 1 Sociodemographic data ($n = 45$)

	Mean (SD) or frequencies (%)
Age, years	39.89 (7.47)
Sex (women)	27/45 (60%)
Education (high school)	21/45 (46.7%)
Previous use of ayahuasca (yes)	29/43[a] (67.4%)
Previous use of ayahuasca (number of intakes)	37.64 (104.50)
Reason for current intake (therapeutic)	33/45 (73.3%)

Note: Means with standard deviation (SD) or number of cases with percentages (%).
Abbreviation: SD, standard deviation.
[a]Two participants did not respond.

TABLE 2 Baseline and post-ayahuasca scores ($n = 45$)

	Pre mean (SD)	Post mean (SD)	F	*p*
Self-Compassion Scale-Short Form (SC-SF)				
Common humanity	6.77 (1.27)	7.37 (1.24)	11.21	0.002**
Mindfulness	6.87 (1.70)	7.70 (1.54)	15.44	0.000**
Self-compassion	6.21 (0.97)	6.51 (0.89)	5.17	0.028*
Total SC-SF	6.62 (1.12)	7.19 (1.00)	16.75	0.000**
Forms of Self-Criticism and Self-Reassurance (FSCSR)				
Self-criticism form	1.31 (0.60)	1.06 (0.62)	8.33	0.006**
Self-reassuring form	3.09 (0.58)	3.36 (0.57)	12.81	0.001**

Note: Means and standard deviations and ANOVAs of the pre-post scores.
Abbreviations: FSCSR, Forms of Self-Criticism and Self-Reassurance; SC-SF, Self-Compassion Scale-Short Form, SD, standard deviation.
*$p < 0.05$, **$p < 0.01$.

To evaluated the participants' tendency to be self-critical or self-reassuring when things go wrong, we administered the Forms of Self-Criticism/Self-Attacking and Self-Reassuring Scale (FSCSR) (Gilbert et al., 2004). This comprises 22 items rated on a 5-point-scale from 0 (not at all like me) to 4 (extremely like me). The scale measures two forms of self-criticism: inadequate self, which focuses on a sense of personal inadequacy ("*I am easily disappointed with myself*") and hated-self, which measures the desire to hurt or persecute the self ("*I call myself names*"), with Cronbach's alphas of 0.90 and 0.86, respectively. In addition, the scale includes one factor to assess the ability to self-reassure ("*I find it easy to forgive myself*"). The validated Spanish translation (Lopez Cavada et al., 2017) shows moderate to high internal consistency for all subscales ($\alpha = 0.71$ to $\alpha = 0.88$).

2.3 | Statistical analyses

The sociodemographic data are given as means with standard deviation (SD). Missing values were imputed by using the mean of the valid responses when <20% of the questions were missing for each scale. This approach was necessary in <5% of questions overall and thus should not substantially affect the statistical validity of the analysis. Changes in self-compassion, self-criticism/self-reassuring evaluation styles and acceptation were assessed by comparing pre- and post-ayahuasca intake scores within participants using repeated measures ANOVA. Results were considered significant for *p* values <0.05. Effect sizes were calculated by computing partial eta-squared.

3 | RESULTS

Repeated measures ANOVA showed significant pre-post differences for the three subscales of the SC-SF: *Common humanity* ($F = 11.21$, $p < 0.01$), with a large size effect ($\eta^2 = 0.203$); *Mindfulness* ($F = -15.44$, $p < 0.01$), with a large size effect ($\eta^2 = 0.260$); and *Self-compassion* ($F = 5.17$, $p < 0.05$), with a medium to large size effect ($\eta^2 = 0.105$). The total SC-SF mean score showed significant differences ($F = 16.75$, $p < 0.01$) with a large size effect ($\eta^2 = 0.276$).

Repeated measures ANOVA also showed significant pre-post changes for the two forms of the *FSCSR* scale: *Self-Criticism* form ($F = 8.33$, $p < 0.01$), with a large size effect ($\eta^2 = 0.184$) and *Self-reassuring* form ($F = 12.81$; $p < 0.01$), with a large size effect ($\eta^2 = 0.257$).

Table 2 provides details on significant changes in the pre- and post-assessments.

4 | DISCUSSION

Several different psychotherapeutic interventions, including "third-wave" therapies, such as mindfulness-based cognitive therapy, dialectical behavioral therapy, and acceptance and commitment therapy, have been shown to successfully improve self-compassion in the long-term (Wilson et al., 2018). Our group previously reported ayahuasca-induced improvements in mindfulness and emotion regulation (Franquesa et al., 2018, Sampedro et al., 2017, Soler et al., 2016, 2018). We also explored and reported positive effects for mindfulness on SC in one study (Sampedro et al., 2017), although SC was not the main study objective, which is why it was assessed by means of an overall score. Given that the impact of ayahuasca on SC and self-criticism has received scant attention, we performed the present study was to specifically examine the effect of ayahuasca on those facets. We found significant pre-post differences in the mean total SC-SF scores and also for the three subscales (Common humanity, Mindfulness and Self-Compassion) of that instrument. Additionally, significant pre-post changes were also observed for the two forms of the FSCSR scale (Self-Reassurance and Self-Criticism).

Studies on the effects of MT programs have shown that MT appears to improve SC (Bergen-Cico & Cheon, 2014; Rimes & Wingrove, 2011; Robins et al., 2012). However, it is still not clear whether the therapeutic effects of ayahuasca intake are related to increased levels of SC, or whether SC mediates mindfulness capacities (or the other way round). However, it seems probable that the processes that occur after ayahuasca intake could enhance SC. The ranges of change observed on the SC-SF are similar to those observed after a psychological intervention in the study by Montero-Marin et al. (2020). Those authors evaluated the effects of two different interventions—Attachment-Based Compassion Therapy (ABCT), targeting increase self compassion, and a Relaxation therapy as a control group—finding a significative mean pre-post changes in all facets of SC scores $\Delta = 2.19$ for self-kindness, $\Delta = 2.26$ for Common humanity and $\Delta = 1.05$ for Mindfulness after 8 weeks of ABCT. In the Relaxation control branch, with the same group setting and duration, no increases were observed in overall SC, on any of the scales five facet mindfulness questionnaire and SCS subscales administered. Given those findings, the one-point increase on the SC-SF scale after a single ayahuasca session (vs. 8 weeks of psychotherapy) is a promising outcome, especially considering that relaxation therapy was unable to achieve a similar increase. This finding suggests that ayahuasca could improve SC more rapidly than other methods. In this regard, ayahuasca could potentially be combined with MT or a specific compassion-based therapy such as ABCT to further enhance these effects on SC.

Users of ayahuasca have reported that the drug has a compassionate component, with the capacity to evoke a feeling of loving and self-kindness. In this context, it seems easier to understand ayahuasca as a potential agent to help reprocess highly emotional events if the process is "overshadowed" by this compassion. More research is needed to deeply examine the role of SC in the ayahuasca experience, its possible influence on well-being, and its potential clinical utility. Ayahuasca could also be of clinical interest as a potential new line of treatment for traumatic past events or even for post-traumatic stress disorder or other psychopathological conditions.

This study has several limitations. First, it is an exploratory study in a community sample with no control group. Recent studies (Olson et al., 2020, Uthaug et al., 2021) have shown how the influence of psychological set and setting must be further considered and controlled. However, self-compassion is a prosocial variable, and it is not easy to change perception of the self, as evidenced by Uthaug et al. (2021) that found an increase in emotional empathy only in the ayahuasca group (but not in the placebo group). Another limitation is that we did not examine the influence of long-term ayahuasca use on the study findings. In this regard, future studies should compare the effects of ayahuasca between regular users and ayahuasca-naïve users. In this study, most of the participants (67%) had prior experience with ayahuasca, which may have had a "ceiling" effects on the study variables. However, as described in our previous larger study (Domínguez-Clavé et al., 2019), we did not observe any differences between ayahuasca-naïve and regular users. A final limitation is that we did not obtain the participants' medical history, instead relying on self-reports regarding the absence of any current psychiatric disorder or medical conditions.

Given that the data from our study and other studies suggest that ayahuasca may improve self-compassion, it seems possible that this drug could have clinical and therapeutic benefits. Moreover, the limited data currently available suggest that ayahuasca could potentially be as effective at improving self-compassion as more lengthy and costly interventions. However, controlled studies are needed to confirm this observation and to assess the potential clinical benefits of ayahuasca combined with mindfulness-based interventions.

Although more data are needed, it seems likely that the therapeutic effect of ayahuasca on SC could be even greater if combined with mindfulness training. This study adds to the growing body of evidence suggesting that ayahuasca can improve well-being.

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CONFLICT OF INTEREST

No conflicts of interest have been declared.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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DISCUSSIÓ GENERAL

4. Discussió general

La present tesi doctoral pretén ser una continuació en l'estudi per comprendre millor els mecanismes psicològics relacionats amb els efectes terapèutics de l'Ayahuasca a través de capacitats relatives al mindfulness però també un punt de partida per explorar els potencials efectes terapèutics de la substància sobre la desregulació emocional, una variable transdiagnòstica molt associada a trastorns com el TLP.

La línia d'investigació orientada a estudiar els efectes de l'Ayahuasca en capacitats relatives al mindfulness es va iniciar amb un treball del nostre equip (Soler et al., 2016a), un estudi exploratori que avaluava els canvis potencials en algunes d'aquestes capacitats entre el pre i post ingesta (24 hores després) emprant alguns dels instruments d'avaluació usats en els estudis continguts en el primer i segon article d'aquesta tesi, l'*FFMQ* i l'*Experiences Questionnaire* (*EQ*; Fresco et al., 2007, validació espanyola: Soler et al., 2014). Els resultats d'aquell estudi indicaven una reducció del judici i de la reactivitat (que en l'*FFMQ* es corresponen a les subescales *Non-judging* i *Non-reacting*), així com un augment significatiu en la capacitat de descentrament (*EQ*); canvis que, altrament, són objectius diana de l'entrenament en Mindfulness.

Al primer article de la tesi, es comparen els efectes de quatre sessions consecutives de la substància amb els d'un entrenament estàndard de Mindfulness de vuit setmanes basat en la reducció de l'estrès, l'*MBSR*. Tot i que els resultats varen mostrar que l'entrenament en Mindfulness tenia un major impacte general en les capacitats de mindfulness, la ingesta d'Ayahuasca també va mostrar un augment enla subescala de l'*FFMQ Non-judging*, especialment significatiu examinant per separat la faceta d'acceptació (o actitudinal) de l'escala. En un altre estudi del nostre equip (Sampedro et al., 2017), també vàrem obtenir millores significatives en aquesta faceta (amb resultats mantinguts als 2 mesos per a la subescala *Non-judging*) i de manera similar tampoc vàrem trobar canvis per a cap de les subescales que conformen la faceta atencional. Des d'una perspectiva neurobiològica, aquell estudi (Sampedro et al., 2017) mostrava associacions entre els augments de *Non-judging* tant al post ingesta com al seguiment i reduccions en els nivells del complex excitatori glutamat-glutamina en el còrtex cingulat posterior (PCC),una regió que es clau per al *self* (Vogt i Laureys, 2005) i que es troba anormalment hiperactiva en certes condicions psiquiàtriques

(Hamilton et al., 2011). L'augment de la connectivitat funcional entre el còrtex cingulat anterior (ACC) i el PCC i entre el ACC i el lòbul temporal medial (MTL) també varen correlacionar amb el *Non-judging*. D'altra banda, les millores en *Non-judging* raurien també en l'augment de la xarxa neuronal cross-talk i en un augment de l'acoblament de l'activitat entre l'ACC, un centre clau d'autocontrol i altres aspectes de la funció executiva (Kelly et al., 2009) i l'MTL, una regió límbica que processa la memòria i l'emoció (Dolcos et al., 2004).En consonància amb això, el component actitudinal del mindfulness – no judici i no reactivitat- (i no tant l'atencional: -observar i actuar amb consciència), semblaria ser el més implicat en la psicopatologia (Coffeyet al., 2010; Lavender et al., 2011; Tejedor et al., 2014). Paral·lelament, s'ha vist que l'augment de l'acceptació (component actitudinal) està directament relacionat amb els resultats positius de la pràctica del Mindfulness (Holzel et al., 2011) ide lateràpia d'exposició (Brown et al., 2015).

Els resultats de l'article 1 obren la possibilitat d'utilitzar l'Ayahuasca com a eina per millorar l'acceptació en el context de la psicoteràpia, ja que segons sembla, amb poques sessions de la substància seria suficient per millorar el *Non-judging* un dels *targets* de la majoria d'*MBI*, que són intervencions més llargues i costoses. El fet quel'Ayahuasca sembla tenir el potencial d'augmentar l'acceptació per se, podria ser de gran valor en un context psicoterapèutic (Domínguez-Clavé et al., 2016; Mithoefer et al., 2016).

Al segon article de la tesi, s' administraven els anteriorment esmentats *FFMQ* i *EQ*, així com la Difficulties in Emotion Regulation Scale (*DERS*; Gratz i Roemer, 2004, adaptació espanyola: Hervás i Jódar, 2008) - construïda per avaluar la desregulació emocional (DE) - a una mostra de 45 voluntaris que anaven a fer una cerimònia d'Ayahuasca. Com que la DE és una característica central del TLP, abans de la sessió se'ls va administrar una escala de cribatge, la *McLean Screening Instrument for BPD* (*MSI-BPD;* Zanarini et al., 2003) que permet identificar la presència d'aquest trastorn de manera preliminar. L'adaptació espanyola de l'escala (veure Annex C) presenta una elevada consistència interna (*KR-20* = 0,873) i una òptima fiabilitat test retest (CCI = 0,87). Sorprenentment, dotze dels voluntaris van presentar una puntuació igual o superior a 5.Tot i que el punt de tall establert en la versió espanyola és de 7 com a la versió original, 5 és una puntuació considerablement alta i que vàrem interpretar en aquest estudi com *BPD-like symptoms*, o el que vindria a ser el mateix, trets TLP. Altres adaptacions, com la de André et al. (2015) o la de Noblin et al. (2014) han

presentat punts de tall de ≥5 i de 5,5 respectivament. L'objectiu principal d'aquest estudi era la d'avaluar els potencials efectes de l'Ayahuasca sobre la DE i refermar els ja vistos anteriorment sobre capacitats de mindfulness. La mostra global va mostrar millores significatives en quatre de les cinc subescales de l'*FFMQ* (*Observing, Acting with awareness, Non-judging* i *Non-reacting*) i també en descentrament (*EQ*). A diferència de l'estudi anterior, aquest també demostra efectes significatius en les subescales de l'*FFMQ Observing* i *Acting with awareness,* que són relatives al domini de l'atenció (Baer et al., 2006). Amb aquesta millora, els individus poden connectar-se més plenament amb el moment present. Els resultats, juntament amb altres reportats per Thomas et al. (2013) indicarien que aquesta faceta es pot potenciar tant a través del Mindfulness com de l'Ayahuasca (Thomas et al., 2013).Pel que fa al descentrament, l'estudi mostra canvis significatius en les puntuacions de l'*EQ*. En un estudi que comparava usuaris versus no usuaris d'Ayahuasca (Franquesa et al., 2018), els primers van obtenir puntuacions de descentrament més altes. Pel que fa l'escala *DERS*, la mostra global va mostrar millores significatives pre-post per a les subescales *Emotional non-acceptance*, *Emotional interference*, i *Lack of control*, que tenen a veure amb no acceptar les pròpies emocions, en veure que aquestes interfereixen les tasques pròpies de la vida quotidiana i en no saber identificar els propis sentiments, respectivament. Com s'ha dit anteriorment, la DE és un símptoma central subjacent a moltes patologies mentals; com els trastorns afectius, d'ansietat, de consum de substàncies i de personalitat (com el TLP) (Barkley, 2010; Bradley et al., 2011; Gross i Thomson, 2007; Linehan, 1993) i s'ha convertit per tant en l'objectiu de moltes intervencions psicoterapèutiques, la més comú és la *DBT* (Feigenbaum, 2007) que emfatitza, tant el contacte i l'acceptació de les emocions, com regulació d'aquestes (Gratz et al. 2006; Neacsiu et al., 2014; Soler et al., 2009). D'aquí podríem també indicar que l'Ayahuasca podria contribuir a reduir la RE, de manera similar a com s'obté amb les teràpies de tercera generació i a les *MBI*.

Pel que fa al grup amb trets TLP, es varen observar millores significatives en les subescales *Observing, Non-judging* i *Non-reacting*. Les subescales *Non-judging* i *Non-reacting* podrien ser importants per a aquesta població, ja que aquestes capacitats semblen facilitar respostes més reflexives i menys emocionals (Eisenlohr-Moul et al., 2016). També es varen observar diferències significatives pre-post en les subescales de la *DERS*: *Emotional interference*, i *Lack of control*. No obstant això, l' ANOVA de mesures repetides va revelar un efecte de

grup dependent per a aquesta última subescala, ja que la mostra ja presentava una manca de control emocional (que té a veure amb sentir-se sobrepassat per les emocions negatives) considerablement alta en el moment basal, amb una puntuació mitja de 21 en comparació amb 15.48 per l'altre grup. Segons Glenn i Klonsky (2009), la DE és el factor més influent en la simptomatologia TLP, fins i tot per sobre de l'afecte negatiu. Conseqüentment, millorar aspectes com la interferència emocional podria disminuir l'impacte de les emocions negatives en la qualitat de vida i el funcionament normal en aquests pacients. També vàrem trobar diferències significatives en la subescala *Emotional non-acceptance*. Estudis previs han reportat associacions significatives entre les puntuacions d'aquesta subescala i una mesura experimental d'intolerància al malestar en pacients amb TLP i comportaments d'autolesió (Hervás i Jódar, 2008). Cal apuntar que la DE implica comportaments disruptius com les autolesions, les temptatives autolítiques o el consum de drogues. Les persones amb TLP pateixen de DE i d'impulsivitat, símptomes que poden ser fins i tot incapacitants. Actualment no hi ha tractaments farmacològics específics per tractar aquest trastorn, per la qual cosa l'Ayahuasca podria suposar una opció que altrament ha demostrat ser segura pel que fa al seu impacte fisiològic i clínic (Dos Santos et al., 2011, 2012; Riba et al. 2001, 2003). També cal tenir en compte, que la majoria dels pacients reben farmacoteràpia (no específica) i un percentatge substancial d'aquests usen drogues il·lícites (Martin-Blanco et al., 2017). Tot i que l'ús de l'Ayahuasca sempre ha estat considerat de risc, especialment pels símptomes dissociatius que sovint s'associen a aquest trastorn, es tracta d'un fet inexplorat, del que no hi ha resultats descrits. Al segon estudi (article 2), no es varen observar efectes secundaris com clínica psicòtica o dissociativa en aquesta submostra amb trets de TLP. Això ens fa replantejar aquest temor, ja podria no basar-se en fets objectius.

Al tercer article de la tesi, també en una mostra comunitària, s'administraven escales d'autocompassió, la *SC-SF* i d'autocrítica, la *Forms of Self-Criticism and Self-Reassurance (FSCSR;* Gilbert et al., 2004; validació espanyola: Navarrete et al., 2021) abans i 24 hores després d'una cerimònia d'Ayahuasca, amb l'objectiu d'avaluar els efectes de la substància sobre aquestes habilitats, atesa la poca atenció que ha rebut l'impacte de l'Ayahuasca en l'autocompassió i l'autocrítica. Els resultats van mostrar diferències significatives pre-post en les puntuacions mitjanes totals de la *SC-SF* i també per a les tres subescales (*Common humanity*, *Mindfulness* and *Self-Compassion*) d'aquest instrument i canvis significatius pre-post en relació a autoreafirmació i autocrítica, les dues facetes de l'escala *FSCSR* (*Self-*

reassurance i *Self-Criticism*). En un estudi amb Ayahuasca anteriorment esmentat (Sampedro et al., 2017) ja es va trobar un augment significatiu en la puntuació global de la *SC-SF*, que a més va correlacionar amb un augment de la connectivitat entre el còrtex cingulat anterior (*ACC*) i el lòbul medial temporal (*MTL*).

Com s'ha comentat anteriorment, alguns programes basats en Mindfulness han demostrat millorar l'autocompassió (Bergen-Cicoet al., 2013; Rimes i Wingrove, 2013; Robins et al., 2012). A l'estudi prèviament esmentat de Feliu-Soler et al. (2017), comparant una intervenció de de continuïtat de Mindfulness amb una altra centrada en compassió, tots dos subgrups varen mostrar millores significatives en autocompassió i autocrítica, tot i que cap dels dos va mostrar diferències significatives per al domini d'autoreafirmació (*Self-reassurance*) de la *FSCSR*. Un altre estudi comparava una Teràpia de Compassió basada en els estils d'aferrament (*ABCT*), també centrada en autocompassió, versus una intervenció de Relaxació (Montero-Marin et al., 2020). Els resultats varen mostrar millores significatives en les puntuacions pre-post per a totes les facetes de l'escala per al primer grup però no per al grup de relaxació.

Els nostres resultats després d'una sola sessió d'ayahuasca poden considerar-se tant prometedors com els de Montero-Marin et al. (2020), ja que suggereixen que l'ayahuasca podria millorar l' autocompassió més ràpidament que altres mètodes (com la relaxació) i que fins i tot es podria combinar amb una intervenció de Mindfulness o amb una teràpia més específica basada en compassió. No obstant això, encara no està clar si els efectes terapèutics de la ingesta d'ayahuasca estan relacionats amb l'augment dels nivells d'autocompassió, o si és l' autocompassió que media en la millora de les capacitats de mindfulness (o a l'inrevés).

Les troballes dels tres articles que componen aquesta tesi, reafirmen la hipòtesi sobre el potencial efecte terapèutic de l'ayahuasca descrit abastament en la literatura i assenyalarien el potencial efecte terapèutic de l'ayahuasca en la desregulació emocional i l'autocrítica, un efecte que altrament podria ser més gran en combinació amb altres teràpies com les *MBI*. Aquest tipus d'intervencions, portades en un context de seguretat a l'àmbit clínic per tractar determinades psicopatologies, podrien ser de gran utilitat i cost-efectives.

CONCLUSIONS

5. Conclusions

i. L'Ayahuasca millora significativament capacitats relatives al mindfulness com l'acceptació (i en concret el *Non-judging*) de manera similar a com ho fa una intervenció de vuit setmanes de Mindfulness basat en reducció de l'estrès (MBSR).

ii. L'Ayahuasca millora capacitats de mindfulness, no només actitudinals (com l'acceptació: el *Non-judging* i el *Non-reacting*), si no també atencionals (com l'*Observing* i l'*Acting with awareness*) i el descentrament en una mostra comunitària.

iii. L'Ayahuasca millora significativament la desregulació emocional en una mostra comunitària mixta d'usuaris i de persones que no han pres mai abans la substància.

iv. L'Ayahuasca millora significativament la desregulació emocional en subjectes amb trets de personalitat límit, per als quals és la principal vulnerabilitat.

v. L'Ayahuasca té la capacitat de millorar significativament aspectes d' autocompassió i autocrítica en una mostra comunitària de manera similar al que s'ha observat en intervencions basades en Mindfulness, tant si són o no intervencions específiques d'autocompassió.

FUTURES LÍNIES D'INVESTIGACIÓ

6. Futures línies d'investigació

Els recents descobriments descrits en aquesta tesi sobre nous mecanismes d'acció i capacitats psicològiques de l'Ayahuasca, com el seu impacte en facetes del mindfulness, la regulació emocional o l'autocompassió, obren nous horitzons pel que fa a potencials noves intervencions terapèutiques per als trastorns mentals i fins i tot a la possible combinació de tractaments com l'Ayahuasca amb intervencions psicològiques basades en Mindfulness. Alguns d'aquests efectes s'han pogut contrastar amb tècniques de neuroimatge i neurofisiològiques i actualment podem dir que la ingesta d'Ayahuasca té afectació en regions del cervell associades a aquestes capacitats. Tanmateix, calen més estudis per investigar si un tractament combinat podria produir millors resultats terapèutics, quina seria la intervenció més adient, per quina població clínica, el tipus de dosatge, el *set* i el *setting*, entre altres aspectes.

Una potencial línia d'investigació, seria la realització d'estudis controlats amb pacients amb desregulació emocional i amb trauma i veure si es pot concloure definitivament que existeix una millora sobre aquestes capacitats. Seria especialment interessant replicar el primer estudi de la tesi per comparar els efectes d'ambdues intervencions amb mostra clínica.

Els resultats de la tesi també suggereixen que l'Ayahuasca podria millorar capacitats relatives al mindfulness i també l'autocompassió. Les dades actualment disponibles a la literatura suggereixen que l'Ayahuasca podria ser potencialment eficaç per millorar aquestes capacitats com altres intervencions més llargues i costoses. Tanmateix, es necessiten estudis controlats per a confirmar aquesta observació i avaluar els potencials beneficis clínics de l'Ayahuasca combinada amb intervencions basades en Mindfulness i també d'intervencions orientades al treball de l'autocompassió. En general, cal continuar investigant sobre els mecanismes d'acció de l'Ayahuasca i de les diferents psicoteràpies per tal de traslladar aquests resultats a la pràctica clínica i millorar l'eficiència de les intervencions.

Pel que fa als futurs estudis comunitaris, aquests haurien de tenir majors mides mostrals per augmentar la potència estadística dels resultats i comparar els efectes induïts de l'Ayahuasca entre consumidors habituals i usuaris que no han pres mai la substància o l'han pres un o dos

cops (*naïve*). Seria necessari confirmar l'estabilitat dels canvis observats després de la presa d'Ayahuasca i la seva relació amb la freqüència de consum de la substància.

Idealment, els estudis haurien de comparar també entre participants naïve i usuaris regulars, tant d'Ayahuasca com de la pràctica meditativa en Mindfulness i també comparar els nivells de consum o de pràctica dels usuaris. L'experiència prèvia pot provocar un efecte sostre en les altres variables de l'estudi. Un altre aspecte suposa plantejar l'impacte potencial del patró de consum d'Ayahuasca (e.g., freqüència, quantitat, temps entre les ingestes) en la modulació de cada faceta i domini relatiu a mindfulness. Aquesta qüestió justifica una major investigació amb la finalitat d'optimitzar el nombre de sessions d'Ayahuasca i l'espaiament entre les sessions en futurs estudis terapèutics.

També seria interessant incloure altres aspectes com els efectes subjectius de la ingesta d'Ayahuasca i les motivacions específiques per assistir a les sessions amb Ayahuasca. A més, incloure un grup control amb placebo per comparar amb la condició d'Ayahuasca.

Les avaluacions podrien incloure dades de seguiment per a determinar l'estabilitat temporal dels resultats. Els dissenys també podrien incloure les quantitats d'alcaloides (tot i que és molt difícil, sobretot quan es tracta d'estudis comunitaris) en el cas de l'ayahuasca utilitzada per als participants.

Per últim, és important poder disposar de historial mèdic i conèixer possibles trastorns psiquiàtrics o patologies orgàniques. Encara que l'ús de l'Ayahuasca en el TLP segueix sent un tema complex, pels motius explicats anteriorment, els efectes beneficiosos demostrats en aquesta tesi en individus amb trets de TLP animen a seguir explorant els potencials beneficis de la substància en aquest trastorn de manera gradual i en un context clínic. L'ús i la investigació de l'Ayahuasca en Salut Mental haurien d'estar emmarcats en contextos clínics i supervisats pels professionals adequats (e.g. farmacòlegs, psicòlegs, psiquiatres, infermers especialistes, etc.) i el major coneixement possible en intervencions amb psicodèlics, concretament, en els efectes del tractament i la integració de la experiència.

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ANNEXOS

8. Annexos

Annex A

Valle, M., Domínguez-Clavé, E., Elices, M., Pascual, J.C, Soler, J., Morales-García, J.A., Pérez-Castillo, A. i Riba, J. (2021). Ayahuasca as a Versatile Therapeutic Agent: From Molecules to Metacognition and Back. A: Labate, B., Cavnar, C. (Eds.), Ayahuasca Healing and Science, Springer Heidelberg, Cham, https://doi.org/10.1007/978-3-030-55688-4_1

Chapter 1
Ayahuasca as a Versatile Therapeutic Agent: From Molecules to Metacognition and Back

Marta Valle, Elisabet Domínguez-Clavé, Matilde Elices, Juan Carlos Pascual, Joaquim Soler, José A. Morales-García, Ana Pérez-Castillo, and Jordi Riba

N,N-Dimethyltryptamine, β-carboline Alkaloids, and the Biochemical Effects of Ayahuasca

One of the most common versions of ayahuasca tea available globally comes from a mix of *Banisteriopsis caapi* (Malpighiaceae) and *Psychotria viridis* (Rubiaceae) (McKenna, Towers & Abbott, 1984). Based on published reports (Dos Santos et al., 2011, 2012; Riba et al., 2001, 2003; Sanches et al., 2016), this combination appears to be reasonably safe, in terms of its physiological impact, when administered to healthy individuals.

B. caapi contains β-carboline alkaloids; mainly harmine, tetrahydroharmine (THH), and to a lesser extent, harmaline (McKenna et al. 1984; Rivier & Lindgren, 1972). *P. viridis* contains N,N-Dimethyltryptamine (DMT), which is orally inactive

M. Valle
Pharmacokinetic and Pharmacodynamic Modelling and Simulation, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain
e-mail: mvallec@santpau.cat

E. Domínguez-Clavé
Department of Pharmacology, Therapeutics and Toxicology, UAB, Birmingham, AL, USA

Borderline Personality Disorder Unit, Psychiatry Service, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain
e-mail: edominguezcl@santpau.cat

M. Elices
Borderline Personality Disorder Unit, Psychiatry Service, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

J. C. Pascual (✉) · J. Soler
Pharmacokinetic and Pharmacodynamic Modelling and Simulation, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

Department of Psychiatry and Forensic Medicine, UAB, Birmingham, AL, USA
e-mail: jpascual@santpau.cat; jsolerri@santpau.cat

due to its transformation by monoamine oxidase (MAO) activity in the gastrointestinal tract. Since β-carboline alkaloids are MAO inhibitors (Ott, 1999; Wang et al., 2010), they prevent DMT degradation, thereby allowing DMT to enter the general circulatory and central nervous systems (Bouso & Riba, 2014; McKenna, et al. 1984), where they can produce psychoactive effects (Szára, 1956).

The indole psychedelic DMT has long been considered to play a major role in the pharmacology of ayahuasca. DMT shows serotoninergic agonist activity at the 5-HT2A and 5-HT1A receptors sites (González-Maeso & Sealfon, 2009) and induces brief but intense modifications of the ordinary state of awareness (Strassman, Qualls, Uhlenhuth & Kellner, 1994; Riba et al., 2002). DMT also interacts with the intracellular sigma-1 receptor (S1R) (Fontanilla et al., 2009), which modulates the activity of other proteins and promotes neural plasticity (Chu & Ruoho, 2016; Tsai et al., 2009).

In mice, DMT blocks sodium channels and induces hypermobility (Fontanilla et al., 2009). DMT is also an agonist at the trace amine associated receptor (TAAR) (Bunzow et al., 2001), which has been reported to have a potential role in schizophrenia, fibromyalgia, affective disorders, addiction, drug abuse, and Parkinson's disease (Berry, Gainetdinov, Hoener & Shahid, 2017). TAAR was initially discovered through a search for novel 5HT receptors (Borowsky et al., 2001). DMT is also a substrate of the vesicle monoamine and serotonin transporters (Cozzi et al., 2009). A recent study (Szabo et al., 2016) found that DMT-mediated S1R mitigates hypoxic stress of in vitro-cultured human cortical neurons, monocyte-derived macrophages, and dendritic cells, and increases their survival. Hence, downregulation of S1R abrogates DMT-mediated effects on cellular survival and hypoxia-inducible factor 1-alpha (HIF-1a) expression in hypoxic in vitro cultures of human primary cells.

J. A. Morales-García
Center for Networked Biomedical Research on Neurodegenerative Diseases (CIBERNED), Madrid, Spain

Department of Cellular Biology, School of Medicine, Universidad Complutense de Madrid, Madrid, Spain
e-mail: jmorales@iib.uam.es

A. Pérez-Castillo
Center for Networked Biomedical Research on Neurodegenerative Diseases (CIBERNED), Madrid, Spain

Instituto de Investigaciones Biomédicas (CSIC-UAM), Madrid, Spain
e-mail: aperez@iib.uam.es

J. Riba (deceased)
Human Neuropsychopharmacology Research Group, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

Department of Neuropsychology and Psychopharmacology, Masstricht University, Maastricht, The Netherlands
e-mail: jordi.riba@maastrichtuniversity.nl

Another proposed mechanism for DMT-mediated S1R modulation is that S1R activation would, in turn, modulate Ca2+ signaling, thereby altering the function of intracellular kinases involved in cellular survival. These results suggest a novel and important role for DMT in human cellular physiology, indicating the potential value of DMT-mediated S1R modulation in future therapies targeted at hypoxia/ischemia-related pathologies.

The main constituent of the *B. caapi* vine and the principal ingredient—together with DMT—of ayahuasca preparation is the β-carboline alkaloid harmine. It is still unclear if orally ingested harmine in ayahuasca or related β-carboline alkaloids (THH and harmaline), produces psychoactive or hallucinogenic effects (Dos Santos & Hallak, 2016; Dos Santos, Bouso & Hallak, 2017). In fact, studies in humans have shown inconclusive results, describing sedative-like effects or even a lack of psychoactive effects instead of hallucinogenic (see Dos Santos, Bouso & Hallak 2017). Interestingly, a study conducted in healthy volunteers showed that the β-carbolines (including harmine) are associated with specific electroencephalographic (EEG) alterations, suggesting central/psychoactive effects (Schenberg et al., 2015).

In rodents, harmine improves memory and learning-related deficits in an object recognition task (short-term memory), the MM test (spatial memory), and a delayed match-to-sample asymmetrical 3-choice water maze task. This has been supported by improvements in several biochemical parameters in the rodent hippocampus and in hippocampal cell cultures. Besides, harmine could also induce neuroprotective effects by inhibiting DYRK1A, a protein implicated in neuronal development and apparently involved in abnormal brain development and memory and learning deficits in Alzheimer's and Parkinson's disease and in Down syndrome (Frost et al., 2011; Göckler et al., 2009). According to a recent in vitro study (Li et al., 2017), both harmaline and harmine could potentially be used to treat Alzheimer's disease, Parkinson's disease, depression, and other central nervous system diseases. However, harmine appears to be a multidrug resistance-associated protein isoform2 (MRP2) substrate (it would upregulate its expression) and would be easier metabolized than harmaline, eventually leading to low oral bioavailability (Li et al., 2017). Other preclinical studies show that β-carbolines have affinity for 5-HT2A/2 C receptors (Glennon et al., 2000).

It is not clear if the antidepressant and antiaddictive properties of ayahuasca are related to the pharmacological properties of harmine or DMT, or to a combination of these (Dos Santos, Osório, Crippa, & Hallak, 2016a; Dos Santos et al., 2016b). Future research should assess the role of other molecular mechanisms, such as S1R agonism, in the perceptual, affective, and cognitive effects of DMT and ayahuasca. Given that certain antidepressants (e.g., fluvoxamine) stimulate the S1R, it is plausible that the antidepressant effects recently reported for ayahuasca (Osório et al., 2015; Palhano-Fontes et al., 2017; Sanches et al., 2016) are mediated, at least in part, by S1R agonism.

Neurobiological Effects of Ayahuasca

Some areas implicated in cognitive control, emotion, and memory, such as the insula, the amygdala, and the hippocampus, have been reported to increase blood flow under the effects of ayahuasca (Riba et al., 2006). Other studies have identified the mediotemporal lobe (MTL), which includes the hippocampus, amygdala, and parahippocampal regions, as a target of ayahuasca-induced experience (de Araujo et al., 2012; Riba, Anderer, Jané, Saletu, & Barbanoj, 2004; Riba et al., 2006). The posterior cingulated cortex (PCC) is a key node of the default mode network (DMN) (Raichle et al., 2001). Hyperactivity in this region has been associated with psychopathology (e.g., rumination in depression) (Dutta et al., 2014). DMN is a set of functionally and structurally connected brain regions that are typically deactivated during the performance of externally oriented attention-demanding tasks. This area also exhibits high cerebral blood flow and oxygen consumption during the resting state (Lin et al., 2017).

During the acute phase of ayahuasca, studies have shown that most of the DMN exhibits decreased activity and the PCC shows reduced connectivity (Palhano-Fontes et al., 2015). The spatial brain distribution of ayahuasca-induced changes in the brain has been assessed with low-resolution electromagnetic tomography (LORETA) and EEG recordings. Riba, et al. (2004) reported a decrease of power density in the alpha-2, delta, and beta-1 frequency bands predominantly over the temporo-parieto-occipital junction, whereas theta power was reduced in the temporomedial cortex and in frontomedial regions after ayahuasca intake. These areas comprise the unimodal association cortex, multimodal association cortex, and limbic regions involved in the integration of multimodal sensory information, emotion, and memory processes (Riba et al., 2004).

Ayahuasca has also showed an excitatory effect on cortical regions involved in the processing of visual sensory information (alpha-occipital), memory-affect (MTL), and cognition-affect (theta-frontolateral and frontomedial cortex) (Valle et al., 2016). Randomized clinical trials with experienced psychedelic users suggest a prominent role for the 5-HT2A receptor in the neurophysiological and visionary effects of this substance. Ayahuasca induced significant psychedelic effects and power decreases in the delta-alpha frequency range; decreases in alpha-band oscillations were in posterior brain regions and correlated with the intensity of the visual modifications. The placebo (ketanserin) used in that study blocked these decreases and reduced this correlation.

Another study of our group (Alonso, Romero, Mananas, & Riba, 2015) assessed ayahuasca-induced changes in the dynamic interaction of brain oscillations and the directionality of drug-induced modifications using transfer entropy (TE). That study consisted of 10 healthy volunteers with previous experience in psychedelic drug use. The authors found a reduced density in the medial posterior (precuneus and cuneus) areas and in the ACC.

Similar findings have been observed using magnetoencephalography (MEG) after psilocybin administration, which modified the interaction dynamics between the higher order frontal regions and the more sensory-selective posterior areas (Muthukumaraswamy et al., 2013). 5-HT2A agonism is considered a key mechanism in modifying ayahuasca-induced brain dynamics (McKenna & Riba, 2015). Modifications in the information transfer imply that the predictability of activity in posterior areas (based on information available at anterior sites) decreases while, conversely, the predictability of activity in anterior areas increases (when information is taken into account at posterior sites). Furthermore, in the study by Alonso et al. (2015), these neurophysiological changes, which were related to a reduced top-down control and increased bottom-up information transfer in the brain, were correlated with DMT plasma concentrations and the perceived intensity of psychedelic effects.

The effects of ayahuasca on long-term ayahuasca users have also been examined. The magnetic resonance imaging (MRI) study of Bouso et al. (2015) found an association with opposite changes in brain structure in the anterior and posterior cingulate cortices. Findings included: (a) a decrease in cortical thickness in the PCC and neighboring areas, and (b) an increase in cortical thickness in the medial frontal lobes, specifically in the ACC.

Studies with radiotracer data—mainly Single Photon Emission Computed Tomography (SPECT)— have also been carried out. In a randomized double-blind clinical trial (Riba et al., 2006) increased blood perfusion in the anterior insula (bilaterally) was reported, with greater intensity in the right hemisphere, and in the anterior cingulate/frontomedial cortex (another region of the DMN) of the right hemisphere. Additional increases were observed in the left amygdala/parahippocampal gyrus. Another study (Sanches et al., 2016) found increased blood perfusion in the left nucleus accumbens, the right insula and the left subgenual area; all areas implicated in the regulation of mood and emotions. There are no reports examining the effects of ayahuasca with Positron Emission Tomography (PET) up to date.

The visual network is an area rich in 5-HT2A receptors (Savli et al., 2012). After ayahuasca intake, users are aware that the visions which disappear when opening their eyes and when attention is directed to external cues, are drug-induced (Riba et al., 2001). The visionary phenomena experienced by participants with eyes closed may be attributable to the suppression of inhibitory alpha in the visual network (Valle et al., 2016). Despite their vividness, these images clearly differ from "true hallucinations" (Riba et al., 2001), a state of awareness characterized by dream-like visions more than a pathological distortion of perception. A previous neuroimaging study found increased activity in the visual cortex under ayahuasca (de Araujo et al., 2012). According to Sampedro et al. (2017), visual areas show increased coupling with the PCC but reduced coupling with the ACC. Those authors suggested that there was a greater interplay between internally generated visual information and spontaneous mind-wandering, and a decrease in cognitive control.

Potential Therapeutic Uses of Ayahuasca

Although the full potential of ayahuasca remains unknown, a growing body of evidence accumulated over the last two decades suggests that it may have potential benefits to treat depression. This hypothesis is supported by data on the modulatory capacity of prefrontal 5-HT2A receptors on the amygdala and ACC reported in previous studies (Vollenweider & Kometer 2010). Numerous studies in animals (Aricioglu & Altunbas 2003; Farzin & Mansouri 2006; Fortunato et al., 2009, 2010a, b; Lima et al., 2007; Pic-Taylor et al., 2015; Réus et al., 2010, 2012) and humans (Barbosa Giglio & Dalgalarrondo, 2005; dos Santos, Landeira-Fernandez, Strassman, Motta & Cruz, 2007) have investigated this potential effect of ayahuasca. Several recent studies have evaluated the effects of a single dose of ayahuasca in psychiatric depressive inpatients. Osório et al. (2015) observed a significant reduction in depressive symptoms and anxiolytic effects in six resistant-to-treatment depressive patients during the first week. Those authors suggested that ayahuasca might have an earlier onset of action than traditional antidepressants that have a mean onset of therapeutic action of 2 weeks. In a subsequent study with a larger sample size (n = 17), that same group found significant decreases in depression scale scores, which occurred as soon as 80 minutes after intake up to day 21 post-intake (Sanches et al., 2016). The SPECT analysis revealed increased blood perfusion in brain regions implicated in the regulation of mood and emotional states, as mentioned before.

Recently, Palhano-Fontes et al. (2017) conducted a double-blind placebo-controlled trial (RCT) in treatment-resistant depressive patients to compare a single dosing session of ayahuasca to placebo, and found that the single dosing session showed rapid antidepressant effects. Between-group effect sizes increased from day 1 to 7, and response rates were significantly higher in the ayahuasca group at day 7. Remission rate showed a trend toward significance between groups (36% v. 7%, $p = 0.054$). As discussed above, S1R, which upregulates brain derived neurotrophic factor (BDNF) and nerve growth factor (NGF), has been implicated in depression. The regulation and expression of BDNF and NGF have been recently linked to the pathophysiology and treatment of depression (Otte et al., 2016), data that suggest that DMT-mediated S1R modulation will likely play a key role in efforts to identify future therapies to treat depression and related disorders.

Studies of anxiety symptoms in animal models (Aricioglu & Altunbas, 2003) have found that harmane (another β-carboline) diminishes anxious behaviors in the elevated plus maze (EPM) test; Hilber and Chapillon (2005) reported mixed results for harmaline in that same EPM anxiety test. Pic-Taylor et al. (2015) reported decreases in locomotor and exploratory activities in the open field and EPM tests (similar to fluoxetine). Those authors also observed increased c-fos expression in specific brain areas, confirming that ayahuasca alkaloids affect areas involved in emotional processing.

In humans, Barbosa, Giglio & Dalgalarrondo (2005) reported a decrease in anxiety associated symptoms after the first-time ritual use of ayahuasca among members

of a religious group (Santo Daime) in Brazil. They also observed self-reported behavioral changes, such as increased assertiveness, vivacity, and joy. A case-control study (dos Santos et al., 2007) reported lower scores on panic- and hopelessness-related scales among individuals who took ayahuasca, but no changes in state or trait anxiety.

In recent years, promising findings about the potential effects of ayahuasca on addiction disorders have been reported. Oliveira-Lima et al. (2015) developed a substance use disorder (SUD) model in animals. Those researchers induced hyper-locomotion using ethanol, leading to locomotor sensitization. The results of that study showed that ayahuasca not only inhibited early behaviors associated with the initiation and development of ethanol addiction, but was also effective for reversing the behavioral sensitization associated with chronic ethanol administration.

In humans, effects of ayahuasca on substance use were reported in two case-control studies (Fabregas et al., 2010; Grob et al., 1996). Grob et al. (1996) reported remission of alcohol use in a sample of 15 long-term ayahuasca users compared to 15 matched controls with no prior history of ayahuasca ingestion. Fabregas et al. (2010) reported a reduction in alcohol use and cessation of drug use (except for cannabis) in two groups of jungle and urban-based ayahuasca users compared to non-ayahuasca users, with outcomes maintained at one-year follow-up. Halpern, Sherwood, Passie, Blackwell & Ruttenber (2008) reported remission of drug or alcohol abuse/dependence in a community sample of ayahuasca users (average length of membership, 6.5 years). In another case series (Thomas, Lucas, Capler, Tupper & Martin, 2013), Thomas and colleagues found statistically significant reductions in cocaine use after an ayahuasca-assisted intervention in a sample of members of a First Nations community in Canada who had no prior experience with ayahuasca. Other descriptive studies (Bouso & Riba, 2014; Doering-Silveira et al., 2005a, b; Labate, dos Santos, Strassman, Anderson & Mizumoto, 2014) have presented preliminary evidence suggesting a potentially beneficial role for ayahuasca in the treatment of SUD.

Given the growing body of evidence on the potential therapeutic use of ayahuasca in depression, anxiety and SUD, there is increasing interest in testing whether ayahuasca can be used to treat a broader range of related disorders. In this context, in a recent review (Domínguez-Clavé et al., 2016), our group postulated that ayahuasca could also be valuable in treating other impulse-related disorders, personality disorders, and even trauma.

Psychological Mechanisms Underlying the Therapeutic Effects of Ayahuasca

In recent years, our group has published research suggesting that a psychological mechanism—an increase in mindfulness-related capabilities (e.g., Soler et al., 2016)—could underlie the potential therapeutic effects of ayahuasca. In our first

study, 25 individuals completed the Five Facets Mindfulness Questionnaire (FFMQ) and the Experiences Questionnaire (EQ) before and 24 h after an ayahuasca session. We found significant reductions in two facets of mindfulness, "nonjudging" and "non-reacting." A decrease in nonjudging indicates a reduced tendency to be evaluative and judgmental; that is, the person is less likely to dichotomize experiences into either "good" or "bad." Improvements in nonreacting indicate decreased reactivity to private experiences such as thoughts and feelings, regardless of whether those are pleasant or unpleasant.

The study also found significant increases in "decentering" as measured by the EQ. Decentering is considered a product of mindfulness practice. This concept has been defined as "the ability to observe one's thoughts and feelings in a detached manner, as temporary events in the mind, as neither necessarily true nor reflections of the self" (Safran & Segal, 1990). Previous reports (Bergomi, Stroehle, Michalak, Funke, & Berking, 2013; Soler et al., 2014) have found that meditation practice is beneficial for all three of the aforementioned facets (i.e., nonjudging, nonreactivity, and decentering).

However, improvement in decentering can be achieved by therapeutic interventions other than mindfulness practice, such as Acceptance and Commitment Therapy (ACT) (Hayes, Strosahl & Wilson, 1999) and Metacognitive-Based Therapy (MBT, Wells, 2009). These therapies focus on decentering, which plays a key role in contributing to their beneficial effects (Moritz et al. 2011; Van der Heiden, Muris & van der Molen, 2012; Wells et al., 2010). Franquesa et al. (2018) compared ayahuasca-naive subjects (n = 41) to experienced users (n = 81), finding that ayahuasca users scored higher on decentering measures than nonusers, even when the most and least experienced users were compared. By improving decentering, individuals gain mastery over their thoughts and emotions, minimizing or even eliminating the tendency to identify with them (Shapiro, Carlson, Astin & Freedman, 2006).

Studies have found that the capacity to "decenter" may be protective against suicidal ideation and that an individual's decentering ability is predictive of the intensity of depressive symptoms at a 6-month follow-up (Bieling et al. 2012; Hargus, Crane, Barnhofer & Williams, 2010). In this regard, the efficacy of cognitive behavior therapy (CBT) in the treatment of depression may rely on increasing this decentering capacity (Teasdale, Segal & Williams, 1995). In the context of these findings, studies have found that improving an individual's decentering capacity could directly improve depression (Bieling et al., 2012; Fresco et al., 2007a, Fresco, Segal, Buis & Kennedy, 2007b; Gecht et al. 2014; Hargus et al., 2010; Teasdale et al., 2002), generalized anxiety disorder (Hayes-Skelton, Calloway, Roemer, & Orsillo, 2015; Hoge et al., 2015), social anxiety (Hayes-Skelton & Graham, 2013), eating disorders, SUD (Shapiro, et al. 2006), and borderline personality disorders (BPD) (Soler et al., 2014). In impulsive-related disorders (such as drug abuse or BPD), an increase in the decentering capacity may diminish mood-dependent behavior by interrupting recurring maladaptive habits (Shapiro et al., 2006).

Regarding mindfulness-related capacities, ayahuasca intake seems to induce a pattern of change similar to that produced by mindfulness practice. In fact, the two

main facets that improve after ayahuasca use—nonjudging and nonreacting to inner experience (Soler et al., 2016)—make up the acceptance-measuring components of the FFMQ (Baer, Smith, Hopkins, Krietemeyer & Toney, 2006).

A recently published neuroimaging study examined the effects of ayahuasca in a sample of healthy volunteers with prior experience using the substance (Sampedro et al., 2017). That study found increases in the nonjudging subscale and found that post-acute neural changes predicted sustained elevations on the nonjudging subscale at 2 months post-intake. An even more recent study (Soler et al., 2018), which compared mindfulness training to ayahuasca, found that ayahuasca induced increases in the nonjudging scale that were comparable to those of mindfulness. Based on these studies, it appears that only a few ayahuasca sessions may be as effective at improving acceptance as costly interventions. Improving this capacity allows a more detached and less judgmental stance towards potentially distressing thoughts and emotions.

In a recent observational study (Domínguez-Clavé et al., 2019), our group examined the effects of ayahuasca in a sample of volunteers participating in an ayahuasca ceremony. Of the 45 participants, 12 exhibited BPD-like traits and were allocated to a subgroup. After comparing both samples (non-BPD-like and BPD-like), we found that the BPD-trait subgroup showed significant pre-post difference in the emotion regulation (ER) subscales of Difficulties in Emotion Regulation Scale (DERS) *Lack of Control* and *Emotional Interference*. The non-BPD traits subgroup showed significant pre-post differences for those same two subscales, as well as for DERS *Emotional Non-acceptance*. The non-BPD subgroup also showed significant effects on most FFMQ subscales (*Observing*, A*cting with Awareness*, *Nonjudging* and *Nonreacting*) and in decentering (EQ).

That study was the first to examine the effects of ayahuasca on ER and the first to use a subsample of individuals with BPD-like traits. Those findings led us to believe that ayahuasca therapy could be of value in clinical populations affected by emotion dysregulation. Moreover, an exploratory study conducted by members of our team in 45 volunteers found that ayahuasca use positively influenced measures of self-compassion and self-criticism assessed 24 h before and after ayahuasca intake.

An improved understanding of this connection between ayahuasca-induced experience and mindfulness techniques could help to better characterize the therapeutic effects of ayahuasca. If ayahuasca enhances ER—or more specifically, acceptance or self-compassion—it could conceivably also exert a therapeutic effect on individuals with mental disorders by targeting ER capacities. Future studies should address the benefits of combining ayahuasca with mindfulness-related practices to provide a more focused approach to better treat specific disorders. The influence of ayahuasca on these psychological mechanisms suggests its potential to also treat trauma-related conditions and other disorders such as BPD (Bohus Dyer, Priebe, Krueger, & Steil, 2011; Bohus et al., 2013; Harner & Burgess, 2011; Harner, Budescu, Gillihan, Riley & Foa, 2015), obsessive-compulsive disorder, and phobias, in a structured, safe, and comfortable setting.

Metabolic and Connectivity Changes and Mindfulness-Related Capacities

The term "after-glow" designates the positive post-acute effects of psychedelic drugs characterized by elevated mood and openness (Pahnke, Kurland, Unger, Savage & Grof, 1970). Sampedro et al. (2017) has investigated the post-acute neurometabolic and connectivity changes induced by ayahuasca. Neuroimaging techniques (1H-magnetic resonance spectroscopy and functional connectivity) revealed post-acute reductions in glutamate+glutamine (Glx), creatine, and N-acetylaspartate+N-acetylaspartylglutamate (NAA-NAAG) in the PCC. Additionally, reductions in Glx correlated with increases in the FFMQ non-judging subscale and were maintained after 2 months. The inverse correlation between Cr and NAA-NAAG and the scores on the Hallucinogen Rating Scale (HRS)-cognition subscale suggested a relationship between the intensity of acute effects and subsequent neurometabolic reductions. Moreover, connectivity between the ACC and PCC and between the ACC and limbic structures in the right MTL increased. The results suggest that cross-talk lingers beyond the acute stage and contributes to the "after-glow" that is reflected in enhanced mindfulness capacities. These findings confirm previous data regarding the capacity of ayahuasca to enhance mindfulness capacities, including increased "decentering" and decreased judgmental and reactive attitudes (Soler et al., 2016).

Interestingly, in a study published in 2014 (Soler et al., 2014), the authors found that ayahuasca can even increase mindfulness and self-compassion capabilities in individuals who already have high baseline capabilities. In that study, ayahuasca users had higher post-acute scores than meditators. Additionally, Sampedro and colleagues' study showed increased DMN-TPN connectivity correlated with reduced judgmental processing, inner reactivity, and increased self-kindness, providing a neurobiological basis for these modifications. These findings also points to a potential biological basis for therapeutic benefits. Conventional mindfulness training also increases this cross-talk between networks (Doll et al., 2015).

The potential of ayahuasca to influence brain dynamics at multiple levels suggests its potential to treat disorders that are highly refractory to other therapeutic interventions. Its combined effect on the psychological and neural spheres may be particularly well-suited to treating addiction disorders, where high impulsivity and self-centeredness coexist with alterations in brain function and structure.

B. Caapi, β-carbolines, and Neurogenesis

Given that β-carbolines, unlike DMT, are present in all ayahuasca brews, Morales-García et al. (2017) recently evaluated these metabolites to investigate the capacity of harmine, THH, harmaline, and harmol to induce neurogenesis in vitro using neural progenitor cells from adult mice. In the adult brain of mammals, neurogenesis—

the process of generating functional neurons from progenitor cells—is limited to specific brain regions such as the subventricular zone (SVZ) of the lateral ventricle and the subgranular zone of the dentate gyrus of the hippocampus (SGZ). Although this system in the adult brain is considered relatively robust, the number of neural stem cells (NSC) progressively decreases with age and in neurodegenerative diseases.

Impaired adult neurogenesis in neurodegenerative diseases, in addition to losing existing neurons, involves brain's endogenous loss of capacity for cell renewal and therefore the impairment and/or loss of putative function of these new neurons. Morales-García and colleagues showed that *B. caapi* alkaloids stimulate the proliferation and migration of progenitor cells and promote differentiation (predominantly) into neurons. These alkaloids increase the number and size of primary neurospheres (neural stem cell-enriched spheres), induce the loss of their undifferentiated state, and promote subsequent cell migration and differentiation into a neuronal phenotype (as indicated by the positive expression of the neuronal markers β-III-tubulin and MAP 2), as well as astrocytes. Taken together, these three effects indicate that β-carbolines have the capacity to regulate the expansion and fate of stem cell populations. The largest effects on migration have been observed for harmaline and THH. Increased migration capacity is relevant in certain conditions such as brain injury, where stem cell niches are far from the damaged area.

Neural stem cells can differentiate into neurons, astrocytes, and oligodendrocytes. In the aforementioned study, the observed increase in Tuj-1 and MAP-2 protein expression indicated differentiation, mainly towards a neuronal phenotype (Fig. 1.1). In the SVZ, both proteins were equally expressed after treatment with each of the four compounds (harmine, THH, harmaline, and harmol). However, in the SGZ, harmine administration did not influence Tuj-1 levels, a marker of immature neurons, but did significantly increase the expression of MAP-2, suggesting that harmine has a larger impact on neuronal maturation. Importantly, the magnitude of the neurogenic effects was similar for the four alkaloids, whose versatility is of interest given that, in pathological conditions, these compounds could optimize the replacement of neurons by simultaneously acting on various processes.

A likely possible explanation for the observed effects of β-carbolines on neurogenesis is the increase in monoamine levels caused by MAO inhibition. However, other studies reported neurogenesis as independent of elevated serotonin levels. A recent study (Song et al., 2016) found that serotonin depletion appears to promote, rather than decrease, hippocampal neurogenesis. Another group of researchers (Dakic et al., 2016) found that harmine—but not the MAO inhibitor pargyline—stimulated the proliferation of human neural progenitor cells in vitro. In that case, the effects of harmine were mediated through inhibition of the DYRK1A kinase rather than through MAO inhibition. These results suggest that β-carbolines regulate stem cell fate via DYRK1A or other alternative mechanisms.

The association between neurogenesis and anti-depressant activity is well-documented. Clinically effective antidepressants have been reported to stimulate this process, regardless of their specific chemical structure and mechanism of action.

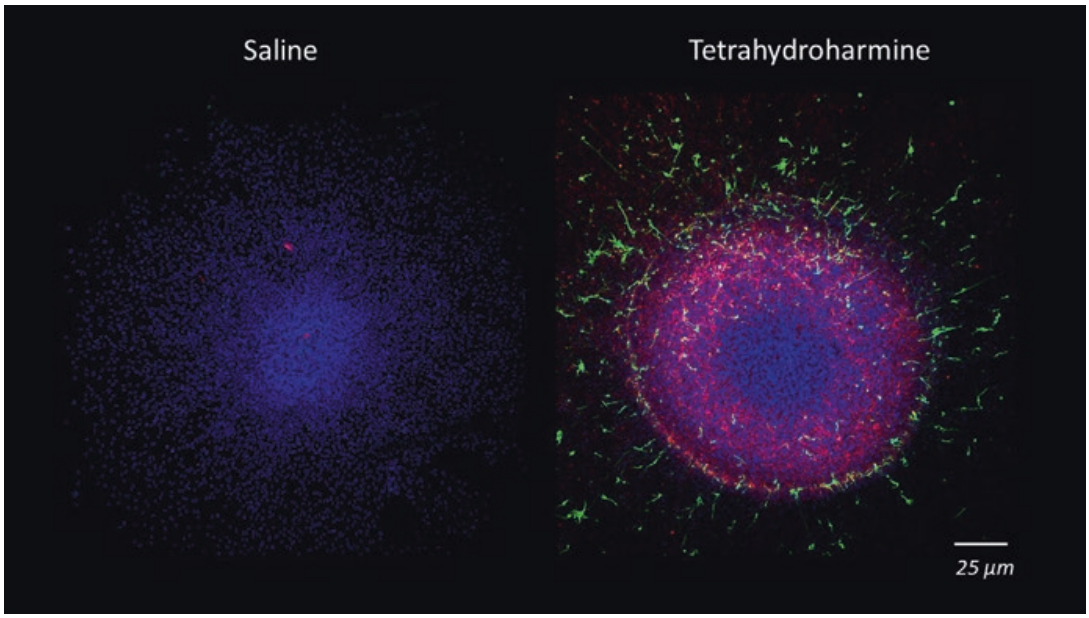

Fig. 1.1 Ayahuasca β-carboline alkaloids induce neurogenesis in vitro, promoting stem cell differentiation towards a neuronal phenotype. Rodent neural stem cells were isolated from one of the most important adult neurogenic niches, the subgranular zone of the hippocampal dentate gyrus, and cultured as free-floating neurospheres in the presence of tetrahydroharmine (THH). After 7 days, neurospheres were adhered on coated coverslips and allowed to differentiate for 3 days in the presence of THH
The figure shows triple confocal immunofluorescence images showing the expression of the neuronal markers β-III-Tubulin (TuJ-1 clone, green, early neurogenesis) and microtubule-associated protein 2 (MAP-2, red, mature neurons) in control (left) and treated (right) neurospheres. DAPI was used for nuclear staining. Scale bar = 25 µm
The left half of the figure shows results after saline (no neurogenesis)
The right half of the figure shows results after THH (evidence of early neurogenesis and presence of mature neurons)

However, it is still unclear if enhanced hippocampal neurogenesis reduces depression-like behavior (Dean & Keshavan, 2017; Hill, Sahay & Hen, 2015).

More research is needed to determine the true magnitude of the therapeutic potential of ayahuasca in mental health and to better identify the mechanisms that mediate the action of *B. caapi* alkaloids.

Conclusions

Recent years have witnessed an explosion in the number of studies on the effects of psychedelics. In this chapter, we have described the latest research on ayahuasca. Highly promising research results showing that (a) DMT can protect neurons from hypoxia; (b) the serotonin-2A receptor mediates the visual effects of ayahuasca; and (c) ayahuasca intake can diminish pathological patterns of thought and behavior,

such as those observed in depression and addiction. Here, we have discussed how these modified patterns result from the enhancement of metacognitive capacities that allow individuals to observe their own thoughts and emotions in a healthier and less judgmental manner.

The recent discoveries described in this chapter about new mechanisms of action and psychological capacities of ayahuasca, such as its impact on facets of mindfulness, decentering, and emotional regulation, open new horizons in terms of potential therapeutic interventions for mental disorders. Given the important effects of ayahuasca on many regions of the brain—as shown by neuroimaging studies and neurophysiologic techniques—the optimal approach may be to combine ayahuasca with psychological interventions, as a combined treatment may yield better treatment outcomes. This chapter has also described the neural correlates underlying these psychological benefits, which have been identified through a combination of state-of-the-art neuroimaging techniques. Finally, at the cellular level, we have described how the β-carbolines present in ayahuasca stimulate the formation of new neurons in the adult mammal brain.

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Annex B

Domínguez-Clavé, E., Soler, J., Elices, M., Pascual, J. C., Álvarez, E., de la Fuente Revenga, M., Friedlander, P., Feilding, A. i Riba, J. (2016). Ayahuasca: Pharmacology, neuroscience and therapeutic potential. *Brain Research bulletin*, *126*(1), 89–101. https://doi.org/10.1016/j.brainresbull.2016.03.002

Review

Ayahuasca: Pharmacology, neuroscience and therapeutic potential

Elisabet Domínguez-Clavé[a,b], Joaquim Soler[a,c,d,e], Matilde Elices[a,b,c,d], Juan C. Pascual[a,b,c,d], Enrique Álvarez[a,b,c,d], Mario de la Fuente Revenga[d,f], Pablo Friedlander[g], Amanda Feilding[g], Jordi Riba[c,d,f,*]

[a] *Department of Psychiatry, Hospital de la Santa Creu i Sant Pau, Sant Antoni Maria Claret, 167, 08025 Barcelona, Spain*
[b] *Department of Psychiatry and Forensic Medicine, School of Medicine, Universitat Autònoma de Barcelona, 08193 Bellaterra (Cerdanyola del Vallès), Spain*
[c] *Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM). Hospital de la Santa Creu i Sant Pau. Sant Antoni Maria Claret, 167, 08025 Barcelona, Spain*
[d] *Institut d'Investigació Biomèdica—Sant Pau (IIB-Sant Pau), Hospital de la Santa Creu i Sant Pau, Sant Antoni Maria Claret, 167, 08025 Barcelona, Spain*
[e] *Department of Clinical and Health Psychology, School of Psychology, Universitat Autònoma de Barcelona, 08193 Bellaterra (Cerdanyola del Vallès), Spain*
[f] *Human Neuropsychopharmacology Research Group, Hospital de la Santa Creu i Sant Pau, Sant Antoni Maria Claret, 167, 08025 Barcelona, Spain*
[g] *The Beckley Foundation, Beckley Park, Oxford OX3 9SY, United Kingdom*

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A B S T R A C T

Ayahuasca is the Quechua name for a tea obtained from the vine *Banisteriopsis caapi,* and used for ritual purposes by the indigenous populations of the Amazon. The use of a variation of the tea that combines *B. caapi* with the leaves of the shrub *Psychotria viridis* has experienced unprecedented expansion worldwide for its psychotropic properties. This preparation contains the psychedelic 5-HT_{2A} receptor agonist *N*,*N*-dimethyltryptamine (DMT) from *P. viridis*, plus β-carboline alkaloids with monoamine-oxidase-inhibiting properties from *B. caapi*. Acute administration induces a transient modified state of consciousness characterized by introspection, visions, enhanced emotions and recollection of personal memories. A growing body of evidence suggests that ayahuasca may be useful to treat substance use disorders, anxiety and depression. Here we review the pharmacology and neuroscience of ayahuasca, and the potential psychological mechanisms underlying its therapeutic potential. We discuss recent findings indicating that ayahuasca intake increases certain mindfulness facets related to acceptance and to the ability to take a detached view of one's own thoughts and emotions. Based on the available evidence, we conclude that ayahuasca shows promise as a therapeutic tool by enhancing self-acceptance and allowing safe exposure to emotional events. We postulate that ayahuasca could be of use in the treatment of impulse-related, personality and substance use disorders and also in the handling of trauma. More research is needed to assess the full potential of ayahuasca in the treatment of these disorders.

1. A brief introduction to the history, plant sources and chemical composition of ayahuasca

1.1. History and botany

Ayahuasca, *yajé*, *Daime* and *Vegetal* are four of the many names used to describe the Amazonian liana *Banisteriopsis caapi* (Malpighiaceae) (Fig. 1), and a wide range of water infusions and decoctions prepared from this vine, alone or in combination with other plants (Ott, 1993; Schultes and Hofmann, 1980). The use of this psychotropic plant tea is experiencing unprecedented expan-sion worldwide, and is the object of increasing biomedical research (Frood, 2015). This preparation is a remarkable member of the indigenous pharmacopoeias of the Americas, which is rich in psy-chotropic plants able to induce visionary states of consciousness. These plants were central to the world view of indigenous cul-tures in the New World and were used in their medicine, religious ceremonies and rites of passage (Schultes and Hofmann, 1987). Such practices gradually disappeared, however, with the expansion of European colonization and Christianity. In the early and mid-twentieth century small pockets of native users continued to use plants such as the mescaline-containing *peyote* cactus (*Lophophora williamsii*), psilocybin-containing mushrooms (*Psilocybe* spp.) and salvinorin-A-containing *Salvia divinorum* (Ott, 1993; Valdes et al., 1983).

Perhaps as a result of the greater isolation of human groups liv-ing in the relatively inaccessible Upper Amazon, ceremonial use of ayahuasca brews continued without external interference until more recent times. Different indigenous groups developed com-plex variations of the basic *B. caapi* infusion, adding as admixtures up to 90 different plants (Ott, 1993). In the 1980s, anthropol-ogist Luis Eduardo Luna recorded over 70 different indigenous names for ayahuasca preparations, underscoring its widespread use by unconnected human groups. In Peru he also witnessed that rather than fading, knowledge of ayahuasca had passed from the Amerindian shamans to mestizo healers known as *vegetalistas*, who used the brew to diagnose and treat patients in the frontier cities of the Amazon (Luna, 1984). In Brazil, ayahuasca use underwent an even more radical cultural transformation, blending with Christian and Afro-Brazilian religious beliefs to give birth to the *Santo Daime*, the *União do Vegetal*, the *Barquinha* and other spiritual movements.(Labate et al., 2009). These new forms of use have contributed to the expansion of ayahuasca use to mainstream South American society and also to many other parts of the world in the last two decades (Tupper, 2008).

1.2. Chemistry of B. caapi *and* P. viridis

One of the most common versions of the ayahuasca tea found on the global scene is that combining *B. caapi* with the leaves of the shrub *Psychotria viridis* (Rubiaceae) (Fig. 2).

In contrast with *peyote*, *Psilocybe* mushrooms and *S. divino-rum*, whose active principles can elicit psychedelic effects on their own, the *B. caapi–P. viridis* combination relies on an inter-esting pharmacological interaction between substances present in each plant. *B. caapi* contains the alkaloids harmine, tetrahy-droharmine (THH), and small amounts of harmaline (McKenna et al., 1984; Rivier and Lindgren, 1972). These compounds share a common tricyclic β -carboline structure. For this reason they are commonly referred to as "beta-carbolines", but also as "har-mala alkaloids", because harmine was originally isolated from the unrelated plant, *Peganum harmala*. These beta-carbolines have var-ious pharmacological properties. In humans, they can reversibly block the activity of subtype A of the monoamine-oxidase (MAO) enzyme (Udenfriend et al., 1958; Buckholtz and Boggan, 1977a; Wang et al., 2010; Herraiz et al., 2010). MAO naturally degrades endogenous neurotransmitters and potentially dangerous exoge-nous amines that could be accidentally consumed in the diet. One of these "potentially dangerous" alien amines is the psychedelic *N,N*-dimethyltryptamine or DMT, present in large amounts in the leaves of *P. viridis* (Rivier and Lindgren, 1972; Schultes and Hofmann, 1980). The chemical structures of DMT and the main beta-carbolines are shown in Fig. 3.

DMT is a rather common alkaloid, present not only in *P. viridis* but also in over fifty other plant species pertaining to various fam-ilies (Ott, 1993). It was first isolated from the roots of *Mimosa tenuiflora* by the Brazilian chemist Oswaldo Gonç alves de Lima in 1946, who was not aware of its chemical identity and named it nigerine (cited in McKenna and Riba, 2015). This alkaloid was later found to be identical to DMT by another group (Pachter et al., 1959). The first unequivocal identification of DMT as a natural com-pound was conducted by Fish and coworkers (Fish et al., 1955). These authors identified DMT in the seeds of the tree *Anadenan-thera peregrina*, which they were studying as the putative source of a psychotropic snuff. The presence of DMT in the seeds caught the attention of Stephen Szára, who conducted the first administra-tion studies in humans and found that DMT had powerful visionary effects (Szara, 1956). Studies by Szára and others showed that 30 mg of DMT administered parenterally induced brief but intense psychedelic effects with visual illusions, changes in thought con-tent and mood, and a series of physiological modifications such as tingling sensations, tremors, mydriasis and elevations of blood

Fig. 1. *Banisteriopsis caapi*. Photo courtesy of Dr. Josep Maria Fericgla.

Fig. 2. *Psychotria viridis*. Photo courtesy of Dr. James C. Callaway.

pressure and pulse rate. Remarkably, the drug was not orally active even in doses as high as 150 mg (Szára, 1957).

1.3. The beta-carboline DMT interaction

After confirming the presence of the orally inactive DMT in *Diplopterys cabrerana* (another ayahuasca admixture plant used predominantly in Colombia), Agurell and coworkers postulated that "The combination in *yajé* of monoamine oxidase inhibiting harman alkaloids with *N,N*-dimethyltryptamine might result in specific pharmacological effects" (Agurell et al., 1968). Thus was born the interaction hypothesis stating that MAO-inhibiting beta-carbolines prevent the gastrointestinal and hepatic degradation of DMT, allowing it to reach the general circulation and the central nervous system (McKenna et al., 1984).

2. General pharmacology of ayahuasca in humans

2.1. Subjective effects

After ayahuasca intake there is usually a half-hour lag time until the first effects are felt (Riba et al., 2001, 2003). It is not uncommon to experience an unpleasant burning sensation in the stomach, which can be readily attributed to the acidity of the brew (Riba et al., 2001). Users also report changes in skin sensitivity, pins and needles, heat and cold waves and yawning. This is followed by a strong desire to close the eyes, and the onset of visual imagery at 45–60 min, although some individuals report they do not experience any visual effects. If present, images are usually compared to those in dreams, with complex scenes at times involving places and people they know or the recollection of past events. Despite their vividness, these images clearly differ from "true hallucinations". Individuals are aware that the visions are drug-induced, usually disappearing when eyes are open and when attention is directed to external cues. Auditory perception rarely involves hearing internally-generated complex phenomena such as voices, but rather modifications of external stimuli, with music being more intensely felt and deeply influencing the experience (Riba et al., 2001).

In addition to visual and auditory effects, ayahuasca increases thought speed and facilitates new associations. The introspective state induced by ayahuasca promotes reflection on personal issues. Memories of personal matters may trigger intense emotions (Riba et al., 2001). This interplay between thoughts, memories and emotions is highly valued by ayahuasca users. They consider that the experience can provide new insights into personal concerns, and it is not uncommon that they characterize the ayahuasca-induced experience as analogous to a psychotherapeutic intervention.

These subjective effects typically come and go in waves with alternating periods of higher and lower intensity. However, in average terms and based on laboratory studies, after the intake of a single ayahuasca dose, psychological effects reach a maximum intensity after one and a half to two hours. The overall intensity then gradually decreases, returning to baseline between four and six hours after intake (Riba et al., 2001, 2003). A series of studies implementing a within-subjects design, and using known doses of ayahuasca and quantitative assessment measures, such as subjective effects questionnaires, shows that ayahuasca effects are dose-dependent, although they may reach a ceiling effect past a certain dose. Despite this dose-dependent pattern seen when data from a pool of individuals are analyzed together, the "qualitative" aspects of the experience may vary greatly for one individual from one intake to the next.

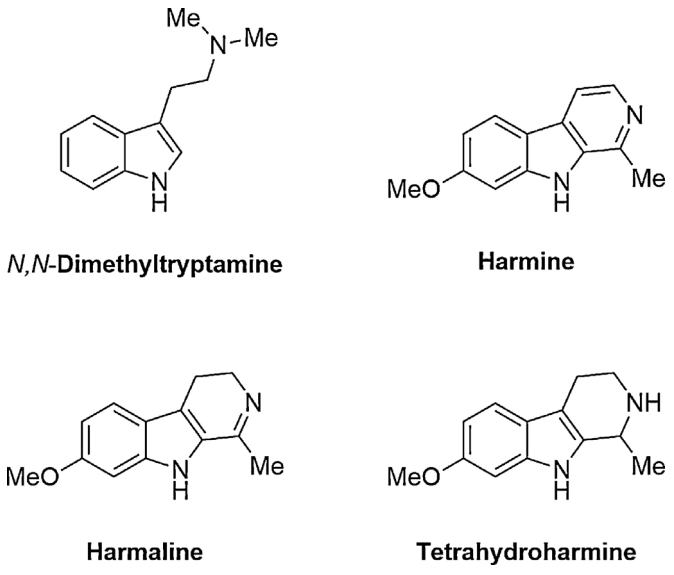

Fig. 3. Chemical structures of the main alkaloids found in *Psychotria viridis* (N,N-dimethyltryptamine) and *Banisteriopsis caapi* (harmine, harmaline and tetrahydroharmine).

2.2. Pharmacokinetics

The rise and fall of subjective effects and other pharmacodynamic variables fits nicely to that of DMT pharmacokinetics. In a study involving both types of measures, we did not find statistically significant differences between the time of the peak intensity of psychological effects (1.5–2 h), measured using visual analogue scales, and the time of the peak DMT plasma concentrations (1.5 h) (Riba et al., 2003). In contrast, the pharmacokinetics of the beta-carbolines is dissociated from the global increase and decrease of subjective effects. Thus, concentrations of harmaline and THH peak later, when the acute visionary effects have resolved. These findings support a major role for DMT in the pharmacology of such a complex alkaloid combination as ayahuasca. Another interesting aspect of ayahuasca pharmacokinetics is that harmine, the main MAO inhibitor present in the tea, appears to be readily metabolized in some individuals who show undetectable levels of this compound in plasma (Riba et al., 2003). Despite the absence of measurable concentrations of harmine in plasma, participants report fully psychoactive effects. This finding suggests that MAO inhibition is mainly peripheral and short-lived, barely enough to allow around 15% of the DMT to reach systemic circulation (Riba, 2003). Thus, partial MAO inhibition by the beta-carbolines would be enough to experience psychoactive effects after ayahuasca intake.

2.3. Physiological effects and tolerability

From a physiological perspective, ayahuasca exerts sympathomimetic effects increasing norepinephrine turnover (Riba et al., 2003) and causing mydriasis (dos Santos et al., 2011). It also increases blood levels of the stress hormones cortisol and prolactin (dos Santos et al., 2011). However, in contrast with the prominent cardiovascular effects reported for pure DMT in studies involving intravenous administration, we observed only moderate increases in systolic (SBP) and diastolic blood pressure (DBP) after ayahuasca, and practically no changes in heart rate. In a first pilot study involving 6 participants, we found a marginally significant increase in SBP at a dose of 1 mg DMT/kg body weight. On average this increase was of 14 mm Hg. Average increases in DBP were of 10 mm Hg and 9 beats per minute in heart rate (Riba et al., 2001). In a subsequent study involving 18 participants and a lower 0.85 mg DMT/kg dose, we obtained inconsistent results. Blood pressure increased but only DBP reached statistical significance. SBP increased an average of 6 mm Hg, DBP an average 10 mm Hg, and heart rate only 4 beats per minute (Riba et al., 2003). This low-to-moderate cardiovascular impact was further supported by a subsequent study in which we administered two consecutive 0.75 mg DMT/kg ayahuasca doses. The second dose led to higher DMT plasma levels than the first, but the increase was linear, showing a mere superposition over the DMT levels remaining from the first dose. This produced linear increases in subjective, neurophysiological and autonomic effects. However, there was a trend to reduced SBP and heart rate, suggesting tolerance for cardiovascular effects (dos Santos et al., 2012).

Based on the above studies, the *B. caapi–P. viridis* version of ayahuasca appears to be reasonably safe in terms of physiological impact when administered to healthy individuals. The most common side effects are nausea and vomiting, especially if more than one dose is taken in a single session (Riba et al., 2001; dos Santos et al., 2012). And even this aspect of the experience is perceived in some contexts as beneficial 'purging'. Several factors may contribute to the low toxicity of ayahuasca, such as selectivity of the beta-carbolines for the MAO-A isoenzyme, the rapid clearance of harmine from the organism, and the availability of MAO-independent biotransformation routes for DMT (Riba et al., 2015). These factors would explain the absence of reports of adverse reactions following the ingestion of foodstuffs containing tyramine after an ayahuasca session. However, as a precautionary measure, combining ayahuasca with other MAO inhibitors and serotonergic drugs such as antidepressants should always be avoided (dos Santos, 2013). Finally, from the perspective of psychological safety, there is the potential risk of anxiety reactions during the experience, as occurs with other psychedelics. Transient dissociative episodes have also been documented during ayahuasca intake. These effects are usually observed at high doses. In a clinical context, verbal support seems to be sufficient to help participants navigate these situations (Riba et al., 2001). More infrequently, longer-lasting psychotic symptoms have been reported in association with ayahuasca use (dos Santos and Strassman, 2011).

3. Neural mechanisms of ayahuasca effects

3.1. DMT and beta-carboline molecular-level and cellular-level interactions

At the receptor level, DMT shows a series of molecular targets. It interacts with serotonergic neurotransmission due to its structural similarity with the endogenous neurotransmitter serotonin (5-hydroxytryptamine; 5-HT) and its affinity for some serotonin receptors. DMT shows agonist activity, at the 5-HT_{2A} and 5-HT_{1A} receptors sites (Gonzalez-Maeso and Sealfon, 2009). The 5-HT_{1A} receptor is mainly pre-synaptic and has been associated with inhibitory activity. It is present in high levels in the raphe nuclei of the brain stem, and its activation reduces serotonergic tone. Although this mechanism may modulate the overall effects of DMT, it is not considered central to the drug's psychedelic effects.

On the other hand, there is a good correlation between the potency of the classical psychedelics, i.e, mescaline, DMT, LSD, psilocybin, etc. and their affinity for the 5-HT_{2A} receptor (Glennon et al., 1984) where they display agonist activity (Gonzalez-Maeso and Sealfon, 2009; Smith et al., 1998). The interaction between psychedelics and the 5-HT_{2A} receptor increases neural firing through excitatory postsynaptic potentials and currents (Klodzinska et al., 2002). Stimulation of the 5-HT_{2A} may have longer-lasting implications besides the more immediate electrophysiological changes. Several studies have shown that psychedelic 5-HT_{2A} agonists stimulate the expression of immediate early genes. These genes encode transcription factors, such as c-fos (Frankel and Cunningham, 2002), egr-1 and egr-2 (Gonzalez-Maeso et al., 2007). They also increase the expression of the brain-derived neurotrophic factor (BDNF) (Gewirtz et al., 2002). These transcription factors are involved in synaptic plasticity (O'Donovan et al., 1999) and have been associated with various aspects of cognition, such as memory (Jones et al., 2001) and attention (DeSteno and Schmauss, 2008).

DMT also interacts with other non-serotonergic molecular targets. Fontanilla and coworkers discovered that it has micromolar affinity for the intracellular sigma-1 receptor (S1R) (Fontanilla et al., 2009). The SR1 is associated with the endoplasmic reticulum, modulating the activity of other proteins and promoting neural plasticity through dendritic spine formation. DMT exerts molecular and behavioral effects in animals through sigma-1 activation. It blocks sodium channels and induces hypermobility in mice. These behavioral effects are absent in sigma-1 knockout mice (Fontanilla et al., 2009). DMT is also an agonist at the trace amine associated receptor (TAAR) (Bunzow et al., 2001) and a substrate of the vesicle monoamine and serotonin transporters (Cozzi et al., 2009). These uptake mechanisms could potentially increase intracellular DMT to pharmacologically significant levels for the sigma-1 receptor.

While the more immediate electrophysiological changes induced by 5-HT_{2A} agonists have been related to the acute effects induced by ayahuasca and other psychedelics, changes in transcription and growth factors may underlie the structural and personality

differences observed in long-term users of ayahuasca (Bouso et al., 2015). Bouso and coworkers found that regular ayahuasca users showed decreased cortical thickness (CT) in the posterior cingulate cortex (PCC), a key structure within the default mode network. Additionally, ayahuasca users scored higher than controls on Self-transcendence, a personality trait that measures the tendency towards religiousness and spirituality. Interestingly, CT values in the PCC were inversely correlated with lifetime use of ayahuasca and with scores on Self-transcendence. The authors postulated that repeated exposure to ayahuasca could underlie the observed structural differences in the PCC, and these, in turn, lead to a shift in attitudes and interests towards less materialistic values and greater open-mindedness. The S1R could also be involved in these differences in life attitudes and views. Considering that certain antidepressants, such as fluvoxamine, stimulate the S1R, it is plausible that the antidepressant effects recently reported for ayahuasca (Osorio et al., 2015; Sanches et al., 2016) are mediated, at least in part, by S1R agonism.

It is worth pointing out that in addition to the effects of DMT on the CNS, the ayahuasca experience may be modulated by the pharmacological effects of the beta-carbolines. Following an ayahuasca dose, THH, harmaline, harmol and harmalol can be measured in plasma (Riba et al., 2003). While the presence of harmine in the organism appears to be short-lived, THH levels in plasma increase dose-dependently and disappear relatively slowly, with an elimination half-life of about 5 h (Riba et al., 2003). Although weaker than harmine, THH inhibits MAO in the nanomolar range (Wang et al., 2010), and it also acts as an inhibitor of the serotonin transporter (Buckholtz and Boggan, 1977b).

3.2. *Neurophysiological and neuroimaging correlates of ayahuasca effects in humans*

Neurophysiological recordings in healthy volunteers have shown that within the time frame of acute inebriation, ayahuasca produces broad-band power decreases in spontaneous brain electrical activity (Riba et al., 2002). The associated intracerebral current source density decreases are particularly pronounced in the delta (1.5–6 Hz), theta (6–8 Hz) and alpha-2 bands (10–12 Hz) and involve two main regions: a) a posterior area including medial and lateral aspects of the parietal, occipital and temporal cortex; and b) the frontomedial cortex including the anterior cingulate (see Fig. 4) (Riba et al., 2004). Decreases in alpha-band oscillations correlate inversely with the intensity of the visual effects and can be blocked by the 5-HT_{2A} receptor antagonist ketanserin (Valle et al., in press). Analogous reductions in alpha oscillations have also been reported for another psychedelic tryptamine, psilocybin (Kometer et al., 2013; Muthukumaraswamy et al., 2013).

Energy decreases in brain oscillations suggest an excitatory effect of ayahuasca on the cerebral cortex (Romei et al., 2008b). The physiologic alpha rhythm inhibits visual areas in the occipital and parietal lobes (Romei et al., 2010, 2008a). Decreases in alpha rhythm are coupled with increased blood flow and metabolism (Buchsbaum et al., 1984; Moosmann et al., 2003). The blood oxygenation level dependent response (BOLD) measured by functional MRI shows a negative correlation with alpha oscillations in the anterior cingulate and in the parieto-occipital cortex (de Munck et al., 2007; Goldman et al., 2002; Laufs et al., 2003). This negative relationship has been extended to the theta band of the EEG (de Munck et al., 2009).

The above neurophysiological measures detect changes mainly in: (a) posterior sensory processing regions; (b) frontal areas involved in emotional processing and cognitive control; and (c) the medial temporal lobe involved in memory processing and affect. In contrast, nuclear medicine studies of serotonergic psychedelics found no changes in blood flow or glucose metabolism in posterior brain regions (Gouzoulis-Mayfrank et al., 1999; Hermle et al., 1992; Vollenweider et al., 1997). In the specific case of ayahuasca, we conducted a neuroimaging study to assess the acute effects of a high 1 mg DMT/kg dose in regional blood flow using single photon emission tomography (SPECT). Contrary to our expectations, we did not see changes in visual or auditory areas. We obtained only a partial overlap with the neurophysiological data. This overlap involved clusters of activation in the medial frontal lobe (see Fig. 4), and in the medial temporal lobe (MTL) around the amygdala, hippocampus and parahippocampal gyrus (Riba et al., 2006).

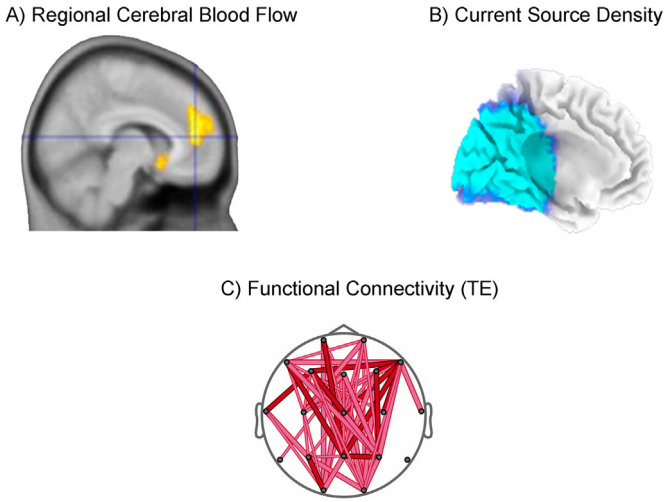

Fig. 4. Neuroimaging and neurophysiological correlates of acute ayahuasca effects in humans. (A) Blood flow increases in frontal brain regions measured using SPECT (Riba et al., 2006); (B) Current source density decreases (EEG alpha band) in posterior brain regions (McKenna and Riba, 2015); (C) Functional connectivity increases measured using Transfer Entropy (TE). With eyes closed, sources in posterior brain regions increase their influence over anterior brain regions (Alonso et al., 2015).

More recently, we were able to reconcile these seemingly contradictory findings from the nuclear medicine and neurophysiological studies (Alonso et al., 2015). Using a measure of directed functional connectivity known as Transfer Entropy, we analyzed the coupling of electrical signals between recording sites. This approach allows inferences regarding the directionality of information flow. Our results showed that ayahuasca modified the flow of information between anterior and posterior recording sites. Frontal sources decreased their influence over central, parietal and occipital sites. At the same time, sources in posterior locations increased their influence over signals measured at anterior locations (see Fig. 4). In this way, the dynamics of the interaction between the higher order frontal regions and the more sensory-selective posterior areas was modified. Analogous findings have been reported using MRI. Araujo and coworkers found a reversal of the functional connectivity between the frontal and parietal cortices (de Araujo et al., 2012). We interpreted our findings on Transfer Entropy as reflecting a modification of the normal hierarchical structure regulating the flow of information in the brain. While feed-back or top-down control is reduced, feed-forward or bottom-up information transfer is increased (Alonso et al., 2015).

Interestingly, in the study on long-term ayahuasca users mentioned in the previous section we found structural brain differences in two main clusters of the brain. Analyzing T1 magnetic resonance images we found a cluster of cortical thickness decrease in the posterior cingulate cortex and neighboring areas (Bouso et al., 2015). This region is a key hub of the so-called Default Mode Network or DMN (Raichle et al., 2001). Hyperactivity of this region has been associated with psychopathology, for instance with ruminations in depression (Dutta et al., 2014). In contrast, we also found in long-term users an increase in cortical thickness in the medial frontal

lobes, specifically in the anterior cingulate cortex. Thus, we found a parallel between the anterior-posterior dynamics observed in the functional connectivity analysis, and the opposite pattern of structural differences between anterior and posterior brain regions.

3.3. A model of ayahuasca effects in the human brain

Based on the extensive data we obtained using the assessment and analysis techniques described above, we recently proposed a model of how ayahuasca and other psychedelics work on the human brain (McKenna and Riba, 2015).

Classical models of brain dynamics have emphasized the bottom-up or feed-forward transfer of information through various stages of increasing processing complexity, from sensory-specific areas up to multimodal association hubs that combine information from different channels into a meaningful whole. However, more recent views postulate that top-down control also plays a significant role in the interpretation of internal and external information. According to this alternative model, the experience of reality would be heavily dependent on previous knowledge and expectations (Friston, 2005; Mesulam, 2008). These constraints would be present at all levels of the hierarchy of feed-forward and feedback loops and the whole system would be under the executive control of the frontal cortex.

We postulate that ayahuasca and psychedelics in general will reduce top-down constraints or expectations and increase excitability in areas involved in sensory, memory and emotional processing. The reduction of the cognitive grip exerted by the frontal cortex combined with increased activation in the mentioned areas will allow weak endogenous activity to become consciously perceptible. This would explain that visions emerge with eyes closed but virtually disappear with eyes open, when they have to compete with strong external stimuli. Increased excitability in multimodal brain areas such as the temporo-parieto-occipital junction and the MTL (Riba et al., 2004, 2006) would explain the rapidly evolving modifications in thought content, the recollections and the novel associations reported by users. The stimulation of areas associated with emotional processing such as the amygdala, the insula and the anterior cingulate cortex, would be responsible for the intensely emotional nature of the experience.

The collapse of top-down constraints (McKenna and Riba, 2015) will give the experience an overall sense of novelty. Ayahuasca users commonly report using ayahuasca to facilitate insight into personal issues or to gain a new perspective into a given matter (Riba et al., 2001). Supporting these claim, we recently found that in the 24 h following an ayahuasca session, certain psychological capacities such as self-acceptance and taking a detached view of one's own thoughts and emotions are increased (Soler et al., 2016). These interesting findings open an avenue for the exploration of the potential therapeutic applications of ayahuasca, and will be discussed in the next section.

4. Potential therapeutic uses of ayahuasca

As described above, acute ayahuasca intake leads to a transient modified state of awareness characterized by introspection, visions, and autobiographic and emotional memories (Riba et al., 2001). Both naïve and regular ayahuasca users have described the experience as positive and valuable, and some individuals have reported health improvements associated with ayahuasca intake (Loizaga-Velder, 2013; Barbosa et al., 2009). Reports of decreased consumption of alcohol, cocaine and other addictive drugs are common in regular ayahuasca users (Fabregas et al., 2010; Thomas et al., 2013). Anecdotal data also suggest an antidepressant effect for ayahuasca (Palhano-Fontes et al., 2014; Schmid, 2014). These testimonies have stimulated research into the potential benefits of ayahuasca in the treatment of substance use disorders and other psychiatric conditions.

The available literature examining the therapeutic potential of ayahuasca can be classified into three main groups. In a first group we find studies on the molecular mechanisms of ayahuasca alkaloids: receptor binding studies and in vitro assays, as well as pharmacological studies in animal models. This group of investigations has examined the mechanisms of action that could explain the psychotropic effects of ayahuasca and the beneficial effects described by users. The second group of studies includes case reports describing beneficial effects in psychiatric symptomatology. Disorders include substance use disorders, anxiety and depression. However, most of these papers provide information from few subjects usually taking ayahuasca in the context of a religious group. This confounding factor has raised doubts as to whether beneficial effects can be attributed exclusively to ayahuasca. The third and more recent group of reports includes case-control studies and open label trials with psychiatric inpatients. These new investigations constitute a step forward in terms of methodological rigor, but designs are still not ideal, as will be discussed below.

4.1. Molecular mechanisms potentially associated with therapeutic effects

As mentioned in previous sections, ayahuasca is a complex mixture of alkaloids. Thus, the molecular mechanisms potentially involved in its therapeutic effects are numerous.

Agonism of DMT at the 5-HT_{2A} receptor sites may already have antidepressant and anxiolytic effects. This has been shown in animals using the selective agonist DOI (Masuda and Sugiyama, 2000; Nic Dhonnchadha et al., 2003). This possibility is supported by the success of recent therapeutic trials that have used various psychedelics which have the common feature of stimulating this receptor (Grob et al., 2011; Gasser et al., 2015). In addition to increased glutamatergic transmission and rapid electrophysiological changes, agonism at this level has been shown to stimulate BDNF release and neurogenesis (Baumeister et al., 2014). These slower secondary events may also play a role in the beneficial effects of 5-HT_{2A} agonists.

The recently uncovered modulatory role of DMT at the orphan receptor sigma-1 receptor (S1R) (Fontanilla et al., 2009) could also be involved in the effects of ayahuasca. As discussed above, the SR1 is a chaperone receptor promoting neural plasticity. Long-term exposure to ayahuasca could potentially lead to neural changes mediated through this mechanism.

The pharmacology of the beta-carbolines can be directly associated with therapeutic effects in depression and anxiety. MAO inhibition is a known therapeutic approach to treat these disorders. All three major beta-carbolines, harmol, harmalol and tetrahydroharmol have MAO-inhibiting properties (Buckholtz and Boggan, 1977a). Additionally, THH is a serotonin reuptake inhibitor (Buckholtz and Boggan, 1977b). Inhibition of the serotonin transporter is the main pharmacological mechanism of many of the antidepressants currently used in clinical practice. Increased monoamine concentrations in the synapse following ayahuasca intake could contribute to the antidepressant and antianxiety properties of B. caapi preparations. Harmine is also known to inhibit DYRK1A (dual specificity tyrosine-(Y)-phosphorylation regulated kinase 1A) in a potent and specific manner (Adayev et al., 2011). This kinase that affects neurite formation and maturation is up-regulated in Down Syndrome as a result of the trisomy (Mazur-Kolecka et al., 2012).

Table 1
Therapeutic effects of Ayahuasca and beta-carbolines: studies in animals.

Publication	Effects	Treatment	Method
Aricioglu and Altunbas (2003)	Decreased dose-dependently immobility time in the forced swimming test. Increased the time spent in open arms in the elevated plus maze test.	Harmane (compared to imipramine)	Elevated plus maze test (anxiety), and forced swimming test (depression)
Hilber and Chapillon (2005)	Changes in emotional reactivity (anxiolytic or anxiogenic depending on dose).	Harmaline	Elevated plus maze test (anxiety)
Farzin and Mansouri (2006)	Antidepressant-like effect in the forced swim test.	Harmane, norharmane and harmine	Forced swimming test (depression)
Lima et al. (2007)	Decreased immobility time in the forced swimming test.	Ayahuasca	Forced swimming test (depression)
Fortunato et al. (2009)	Reduced immobility time, and increased climbing and swimming time at the higher dose. Only harmine increased BDNF protein levels in the hippocampus.	Harmine and imipramine	Forced swimming test and open field test (depression)
Fortunato et al. (2010a)	Reversed anhedonia, increased adrenal gland weight. Normalized ACTH blood levels and BDNF protein levels.	Harmine	CMS Procedure (depression)
Fortunato et al. (2010b)	Decreased immobility time, and increased BDNF levels in hippocampus.	Harmine and imipramine	Forced swimming test (depression)
Reus et al. (2010)	Increased SOD and CAT activities and decreased lipid and protein oxidation.	Harmine and imipramine	Oxidative stress parameters (depression)
Reus et al. (2012)	Modulation of energy metabolism (mitochondrial activity).	Harmine and imipramine	Mitochondrial respiratory chain and creatine kinase activities (depression)
Oliveira-Lima et al. (2015)	Inhibition of early behaviors associated with the initiation and development of ethanol addiction. Reversion of behavioral sensitization associated with chronic ethanol.	Ayahuasca	Ethanol-induced hyperlocomotion and subsequent locomotor sensitization (substance use disorder)
Pic-Taylor et al. (2015)	Increased swimming behavior and lower immobility. Decreased locomotor and exploratory activities in the open field and elevated plus-maze tests. Activation of c-fos expression.	Ayahuasca compared to fluoxetine	Forced swimming test, open field and elevated plus-maze tests (depression and anxiety).

4.2. Studies in animals

There are several studies in animals addressing the potential antidepressant and axiolytic effect of ayahuasca and also its potential effect on substance use disorders (see Table 1).

Aricioglu and Altunbas, (2003) observed that the β-carboline harmane induced an antidepressant effect in the forced swim test. This effect seems to be induced by an inverse-agonist mechanism on the benzodiazepine receptor. Farzin and Mansouri (2006) showed the same antidepressant-like effects for harmane, norharmane and harmine. Similarly, Fortunato et al. (2009) reported antidepressant activity following the acute administration of harmine in the forced swimming and open-field tests. In contrast with the antidepressant imipramine, harmine increased BDNF levels in the hippocampus. In another study by the same group (Fortunato et al., 2010a), the authors assessed harmine in rats exposed to the Chronic Mild Stress (CMS) procedure, an animal model for depression. Interestingly, treatment with harmine reversed anhedonia, reversed hypertrophy of adrenal glands, and normalized blood ACTH and BDNF protein levels. In a later study (Fortunato et al., 2010b), they also demonstrated that chronic treatment with all examined doses of harmine decreased immobility time of rats in the forced swimming test. They also showed increases in swimming and climbing time after harmine. Finally, chronic treatment with harmine, but not imipramine, increased BDNF protein levels in the rat hippocampus. Pic-Taylor et al. (2015) reported antidepressant effects of an ayahuasca infusion (*B. caapi* and *P. viridis* combination) as measured using the forced swimming test. This was evidenced as increased swimming behavior and lower immobility than the controls. Lima et al. (2007) reported decreased immobility time in the forced swimming test. The sample contained various beta-carbolines and DMT. Another study evaluated the positive effects of imipramine and harmine on oxidative stress parameters, thought to be involved in depression. The study reported harmine-induced increases in superoxide dismutase (SOD) and catalase (CAT) activities and decreased lipid and protein oxidation (Reus et al., 2010). The same authors reported increased mitochondrial activity by harmine, and commented that mitochondrial function is impaired in depressive disorders (Reus et al., 2012).

Regarding anxiety symptoms, Aricioglu and Altunbas (2003) reported that harmane attenuated, in a dose-dependent manner, behaviors associated with anxiety in the elevated plus maze test, a common paradigm for the study of anxiety in rodents. Similarly, Hilber and Chapillon (2005) reported mixed results for harmaline in the elevated plus maze anxiety test. Pic-Taylor et al. (2015) reported decreases in locomotor and exploratory activities in the open field and elevated plus-maze tests that were similar to those of fluoxetine. Additionally, increased *c-fos* expression in specific brain areas confirmed an effect of ayahuasca alkaloids on areas involved in emotional processing and that are innervated by serotonergic pathways.

As for studies on substance use disorders, Oliveira-Lima et al. (2015) showed that the ayahuasca brew (*B. caapi* and *P. viridis* combination) not only inhibited early behaviors associated with the initiation and development of ethanol addiction, but was also effective for reversing the behavioral sensitization associated with chronic ethanol administration.

4.3. Studies in humans

Similar to the studies conducted to date in animals, studies in humans have assessed the impact of ayahuasca on: a) substance use disorders (Fabregas et al., 2010; Grob et al., 1996; Halpern et al., 2008; Thomas et al., 2013); and b) depression-anxiety (Barbosa

Table 2
Therapeutic effects of Ayahuasca: studies in humans.

Publication	Samplesize	Effects	Treatment components	Method
Grob et al. (1996)	n = 30	Remission of alcohol use, depressive, or anxiety disorders. Changes in behavior, attitudes toward others, and in outlook on life after joining the group.	Ayahuasca	15 long term ayahuasca-users vs. 15 matched controls with no prior history of ayahuasca ingestion
Barbosa et al. (2005)	n = 28	Reductions in minor psychiatric symptoms (including anxiety and depression) only in the *Santo Daime* subgroup. Behavioral changes, increased assertivity and vivacity/joy (in both groups).	Ayahuasca (first time consumption)	Samples from ayahuasca-using groups (*Santo Daime*, n = 19 and *União do Vegetal*, n = 9) Pre-post intake (2 weeks after)
dos Santos et al. (2007)	n = 9	Lower scores on scales measuring panic and hopelessness. No modification of state- or trait-anxiety.	Ayahuasca and ayahuasca-flavored solution (placebo)	Religious long-term users (double-blind, placebo-controlled procedure)
Halpern et al. (2008)	n = 32	Reported remission of drug or alcohol abuse or dependence after joining the group.	Ayahuasca	Community long term users
Fabregas et al. (2010)	n = 127	Lower scores on the ASI Alcohol Use and Psychiatric Status subscales, cessation of drug use (except cannabis) maintained at the follow-up, and worsening in the Family/Social relationships subscale only in the jungle group.	Ayahuasca	Jungle and urban-based community users vs. controls (non-ayahuasca users)
Thomas et al. (2013)	n = 12	Statistically significant reductions in cocaine use. Improvements in measures of mindfulness, empowerment, hopefulness and quality of life-outlook and quality of life-meaning.	Ayahuasca –assisted therapy (first time consumption)	Individuals with substance use disorders or other behavioral problems Pre-treatment and 6 months after
Osorio et al. (2015)	n = 6	Up to 82% reductions in depressive scores between baseline and 1, 7, and 21 days after AYA administration.	Single dose ayahuasca	Psychiatric inpatients with acute depression. Open-label trial
Sanches et al. (2016)	n = 17	Significant decreases in depression-related scales (HAM-D, MADRS, BPRS) from 80 min to day 21. Increased blood perfusion in the left nucleus accumbens, right insula and left subgenual area.	Single dose ayahuasca (2.2 mL/kg)	Psychiatric inpatients with recurrent depression. Open-label trial

et al., 2005; Sanches et al., 2016; dos Santos et al., 2007; Osorio et al., 2015) (see Table 2).

Halpern et al. (2008) reported a remission of drug or alcohol abuse/dependence in an ayahuasca community sample (6.5 years average of membership). In another case series study (Thomas et al., 2013), the authors found statistically significant reductions in cocaine use after an ayahuasca-assisted therapy in a sample of members of a First Nations community in Canada with no prior experience with ayahuasca. They also reported improvements in mindfulness, empowerment, hopefulness, quality of life-outlook and quality of life-meaning. Similar effects on substance use were found in two case-control studies (Fabregas et al., 2010; Grob et al., 1996). Grob et al. (1996) reported remission of alcohol, depressive, or anxiety disorders and changes in behavior, attitude toward others and outlook on life in a 15 long-term sample of ayahuasca users, compared to 15 matched controls with no prior history of ayahuasca ingestion. Fabregas et al. (2010) reported an improvement in alcohol use and cessation of drug use (except cannabis) in two groups of jungle and urban-based ayahuasca users compared to non ayahuasca users. These findings were maintained at one-year follow-up. Other descriptive studies, such as observational pilot studies, reports and informal interviews (i. e. Bouso and Riba, 2014; Doering-Silveira et al., 2005; Labate et al., 2014), have presented preliminary evidence, suggesting a potential beneficial role for ayahuasca in the treatment of substance use disorders.

As regards anxiety and depression, Barbosa et al. (2005) reported reductions in associated symptomatology after a first consumption of ayahuasca in a sample of Santo Daime members. They also reported behavioral changes, such as increased assertivity, vivacity and joy in members of two groups of ayahuasca users: the *União do Vegetal* and the *Santo Daime*. A case-control study (dos Santos et al., 2007) used psychometric measures of anxiety, panic-like and hopelessness in regular (10 years) ayahuasca users, members of the Santo Daime. While under the acute effects of ayahuasca, participants scored lower on the scales for panic- and hopelessness-related states, but no modification of state- or trait-anxiety was reported following ayahuasca ingestion.

More recently, two open-label trials (Osorio et al., 2015; Sanches et al., 2016) evaluated the effects of a single dose of ayahuasca in psychiatric depressive inpatients. Osorio et al. (2015) observed statistically significant reductions of up to 82% in depressive scores (HAM-D, MADRS, and the Anxious-Depression subscale of the BPRS) between baseline and 1, 7, and 21 days after the administration. Furthermore, ayahuasca administration did not trigger episodes of mania or hypomania as measured by the Young Mania Rating Scale (YMRS). Neither did it lead to increases in the Thinking disorder subscale of the Brief Psychiatric Rating Scale (BPRS). In a subsequent study by the same group (Sanches et al., 2016), the authors reported significant decreases in scores on the same depression scales (HAM-D, MADRS, BPRS- Anxious-Depression), from 80 min after administration to day 21. No effects were observed on the YMRS and Activation BPRS subscale. Nevertheless, they reported increases in dissociative symptoms as measured by the Clinician Administered Dissociative States Scale (CADSS). The study included a SPECT assessment that found increased blood perfusion in the left nucleus accumbens, right insula and left subgenual area, a series of brain regions related to the regulation of mood and emotional states.

5. Potential psychological mechanisms underlying the therapeutic effects of ayahuasca

In addition to the aforementioned reports of beneficial experiences and the improvements in psychiatric symptomatology following ayahuasca intake, a recent work by Soler et al. (2016) suggested the increase of mindfulness-related capabilities as a possible psychological mechanism underlying the therapeutic effects of ayahuasca. The exploratory study assessed twenty-five individu-

als before and 24 h after an ayahuasca session using the Five Facets Mindfulness Questionnaire (FFMQ, Baer et al., 2006; Cebolla et al., 2012) and the Experiences Questionnaire (EQ, Fresco et al., 2007a; Soler et al., 2014). Results showed significant reductions in the FFMQ facets "non-judge" and "non-react to inner experience", both related to self-acceptance. Changes in the first of these two facets indicate decreases in the tendency to be evaluative and judgmental. Changes in the second indicate decreased reactivity in the face of thoughts and feelings regardless of their pleasant or unpleasant nature. Finally, the study also found significant increases in "decentering ability" as measured by the EQ, which will be discussed later.

Analogous benefits in these three psychological domains have been observed in meditators, with a direct association between enhanced mindfulness capacities and the frequency and lifetime practice of meditation (Bergomi et al., 2013; Soler et al., 2014). This association suggests a connection between mindfulness techniques and the ayahuasca-induced experience. In this respect, previous data also show an overall increase in mindfulness scores after ayahuasca administration to substance users (Thomas et al., 2013). These findings are of special interest, if we consider that psychiatric populations score lower than healthy individuals on trait mindfulness (Cardaciotto et al., 2008; Lavender et al., 2011; Tejedor et al., 2014).

Decentering, also called "defusion", is considered a byproduct of mindfulness practice (Gecht et al., 2014; Tanay et al., 2012) and refers to the ability to observe one's own thoughts and feelings in a detached manner. When improving the capacity of decentering the individual gains mastery over their thoughts and emotions, preventing the identification with them (Safran and Segal, 1990; Shapiro et al., 2006). Recent studies also indicate that the capacity to decenter may be protective against suicidal ideation and is predictive of the intensity of depressive symptoms at a 6-month follow-up (Bieling et al., 2012; Hargus et al., 2010). Mindfulness based approaches, and particularly mindfulness-based cognitive therapy for depression (MBCT) seem to improve the capacity of decentering. However, enhancement on this ability has also been reported as consequence of standard Cognitive Behavioral Therapy (CBT) (Fresco et al., 2007b). These studies have reported greater gains in decentering with psychotherapeutic interventions than with antidepressant medications in drug-responders (Fresco et al., 2007a). Benefits were also greater than those induced by antidepressant drugs and placebo in the maintenance phase (Bieling et al., 2012). These results suggest that promoting decentering could be the common mechanism underlying the effectiveness of different psychological treatments for depression.

Impaired decentering has mainly been reported in relation to mood disorders (Bieling et al., 2012; Fresco et al., 2007b; Gecht et al., 2014; Hargus et al., 2010; Teasdale et al., 2002), but also in generalized anxiety disorder (Hayes-Skelton et al., 2015; Hoge et al., 2015), social anxiety (Hayes-Skelton and Graham, 2013), eating disorders, substance use disorders (Shapiro et al., 2006; Soler et al., 2014) and borderline personality disorders (Soler et al., 2014). With regard to impulsive-related disorders (such us drug abuse or borderline personality disorder), an increased capacity to observe thoughts, emotions, and desires more clearly, would diminish mood-dependent behavior by interrupting habitual and automatic maladaptive habits (Shapiro et al., 2006). Similarly, ayahuasca may be useful in the treatment of drug addiction by enhancing the individual's ability to make conscious healthy choices and resist unhealthy urges (Thomas et al., 2013). Liester and Prickett (2012) have proposed that ayahuasca may help treat addiction by acting at various levels from the biochemical and physiological, to the psychological and transcendent (Liester and Prickett, 2012). Moreover, as pointed out by Winkelman (2014, p.13–14), a significant feature of the pharmacological effects of psychedelics in the treatment of addictions is manifested in the so-called "after glow" that goes beyond the acute effects. These after-effects are characterized by positive mood, and increased openness to therapeutic intervention that lasts for several weeks after the intake.

Also, an enhancement of acceptance attitude may promote cessation of maladaptive behavior (abstinence from substance use) and improvements in other areas, such as anxiety sensitivity, and psychological flexibility (Villagra Lanza and Gonzalez Menendez, 2013; Skanavi et al., 2011). Acceptance consists in being willing to notice, feel and connect with what is offered in the present, according to each individual's personal history (Villagra Lanza and Gonzalez Menendez, 2013). In addition to substance use disorders, there is growing empirical evidence of the effectiveness of acceptance-based therapies in the treatment of anxiety disorders and trauma (Roemer and Orsillo, 2007; Skanavi et al., 2011; Vujanovic et al., 2009). These studies emphasize that the effectiveness of these therapies relies on mitigating experiential avoidance, the major cause of chronification. Likewise, ayahuasca intake seems to induce a similar pattern of change. In fact, the two facets improved after ayahuasca use (i.e. "non-judge" and "non-react to inner experience") (Soler et al., 2016), are the acceptance-measuring components of FFMQ (Baer et al., 2006).

Similar to mindfulness interventions and other therapeutic approaches such as prolonged exposure therapy that target traumatic memories (PE; Foa, Hembree, & Rothbaum et al., 2007), ayahuasca appears to facilitate introspection, the processing of unconscious psychological material, and emotional catharsis (Loizaga-Velder, 2013). This introspective state would facilitate the detached view of one's own thoughts and emotions (Shanon, 2003). Levine and Frederick (1997; as cited in Nielson and Megler, 2014) point out that in posttraumatic stress disorder (PTSD) maladaptive patterns cease when subjects are able to slow down and experience all the elements, sensation and feelings that accompany them. If victims allow themselves to acknowledge the thoughts and sensations associated with their traumas, the perceptions will have their natural flow, peak, and then begin to diminish and resolve. This process will allow the nervous system to regain its capacity for self-regulation. According to Luciano et al. (2013), exposure can be conceived of as a strategy intended not only to cause the extinction of conditioned fear responses, but also to disconfirm the avoidance rules associated with the feared situation or event.

Brain imaging studies in humans suggest that ayahuasca significantly activates brain regions, such as the left amygdala and parahippocampal gyrus (Riba et al., 2006), which play a prominent role in emotional processing and the formation of memories. Activation of these areas potentially opens the limbic pathways of the brain to influence the emotional core of trauma in a way similar to affective psychotherapy. Ayahuasca also modulates activity in higher cognitive regions (Riba et al., 2006; de Araujo et al., 2012). Thus, users feel that the visions and emotions that emerge under the effects of ayahuasca are "real," and, if they are real, then one may work therapeutically toward "real" new behaviors in the future (Bouso and Riba, 2014). This process may assign a new context to trauma and help patients understand traumatic memories and move past them (Nielson and Megler, 2014). However, ayahuasca might have the associated risk of re-traumatization by introducing traumatic memories or triggers. Special care should thus be taken to ensure the adequate state of mind of patients and a safe setting to maximize the individual's ability to look at each aspect of the self in order to resolve traumatic symptoms (Nielson and Megler, 2014).

The autobiographical aspects of the ayahuasca experience would be analogous to the "imaginal exposure" procedure, with the additional benefit of a relatively long duration (4–6 h) and vividness of the visual effects. With regard to the visions, it is possible to temporarily interrupt them (escape) by opening the eyes, which allows taking control over the situation, but not avoiding it.

In this respect, avoidance is a key variable in the maintenance of anxiety and PTSD symptoms as stated in several studies and treatment guidelines (i.e. Dunmore et al., 1999; Ehlers, 2000; Eifert and Forsyth, 2005; Foa, 2011; Forsyth et al., 2007; Moran et al., 2013; Steil and Ehlers, 2000; Walser and Westrup, 2007). Escape, on the other hand, may occur during Systematic Desensitization procedure. The goal is actually to expose gradually to the phobic object until it can be tolerated. In that sense, escape is part of a progressive process of change. Some reports on trauma sufferers who have used ayahuasca suggest that the beneficial effect of the drug could rely on the combination of several psychological factors: a) the non-identification with the content of the visions, which they regard as "safe" (i.e. decentering); b) imaginal exposure; and c) acceptance. In this positive context, acceptance can arise. Therefore, ayahuasca may act as an enhancer of acceptance and exposure to thoughts and sensations in a detached context. These psychological mechanisms suggest its potential to treat trauma-related conditions and other disorders like borderline personality disorder (Bohus et al., 2011, 2013; Harner and Burgess, 2011; Harner et al., 2015), obsessive-compulsive disorder (OCD), and phobias, in a structured, safe and comfortable setting.

6. Closing remarks

Ayahuasca has a long history of ceremonial use and its recent worldwide expansion is providing an unprecedented opportunity to study its impact on human health. An increasing number of papers suggest reasonable safety and benefits in mood and psychiatry symptoms in the areas of substance use disorders, anxiety and depression.

Preliminary findings on the potential psychological mechanisms associated with therapeutic benefits indicate similarities with mindfulness-based therapy. Ayahuasca appears to enhance self-acceptance and decentering, crucial aspects associated with psychotherapeutic treatment outcome in several psychiatric disorders. From a neural perspective, neuroimaging studies after an ayahuasca intake have reported activation in areas associated with emotional processing and memory formation. These results suggest that similarly to exposure therapies, ayahuasca allows reviewing emotional events, but with increased vividness and sense of "reality". We postulate that the state induced by ayahuasca could be useful in the treatment of trauma, substance use disorders, impulsive-related disorders, and certain patients suffering from borderline personality disorder.

More research is warranted in clinical populations, using larger samples, matched comparison groups, randomized designs and blinded raters to confirm its efficacy. Finally, it will be necessary for future studies to implement adequate settings and involve clinicians with specific training to ensure the safety of participants.

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Annex C

Soler, J., Domínguez-Clavé, E., García-Rizo, C., Vega, D., Elices, M., Martín-Blanco, A., Feliu-Soler, A., Carmona, C. i Pascual, J.C. (2016b). Validación de la versión espanyola del McLean Screening Instrument for Borderline Personality Disorder. *Revista de Psiquiatría y Salud Mental, 9*(4), 195-202, https://doi.org/10.1016/j.rpsm.2016.03.002

ORIGINAL ARTICLE

Validation of the Spanish version of the McLean Screening Instrument for Borderline Personality Disorder

Joaquim Soler[a,*], Elisabet Domínguez-Clavé[a], Clemente García-Rizo[b], Daniel Vega[c,d], Matilde Elices[a], Ana Martín-Blanco[a], Albert Feliu-Soler[a], Cristina Carmona[a], Juan C. Pascual[a]

[a] *Servei de Psiquiatria, Departament de Psiquiatria i Medicina Legal, Hospital de la Santa Creu i Sant Pau, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Institut d'Investigació Biomèdica-Sant Pau (IIB-Sant Pau), Universitat Autònoma de Barcelona (UAB), Barcelona, Spain*
[b] *Unidad de Esquizofrenia, Instituto Clínic de Neurociencias, Hospital Clínic de Barcelona, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain*
[c] *Departament de Psiquiatria i Salut Mental, Consorci Sanitari de l'Anoia, Igualada, Barcelona, Spain*
[d] *Institut de Neurociències, Departament de Psiquiatria i Medicina Legal, Universitat Autònoma de Barcelona (UAB), Barcelona, Spain*

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KEYWORDS
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Validation;
Screening;
Assessment

Abstract
Introduction: Borderline personality disorder (BPD) is a common and severe mental illness. Early detection is important and reliable screening instruments are required. To date, however, there has been no evidence of any specific BPD screening tool validated for the Spanish-speaking population. The McLean Screening Instrument for Borderline Personality Disorder (MSI-BPD) is a 10-item self-report questionnaire that can detect the presence of BPD in a reliable and quick manner. The aim of the present study is the validation of the MSI-BPD for its use in the Spanish-speaking population.
Method: Psychometric properties of the MSI-BPD Spanish version were examined in a sample of 344 participants (170 outpatients with the possible diagnosis of BPD and 174 healthy controls).
Results: Exploratory factor analysis revealed the existence of a bi-factorial structure. The scale showed a high internal consistency (KR-20 = 0.873) and an optimal test-retest reliability (ICC = 0.87). Using logistic regression analyses and taking the DIB-R as reference, a best cut-off of 7 was determined, obtaining a good sensitivity (0.71) and specificity (0.68). The area under the curve was 0.742 (95% CI 0.660–0.824). The discriminant analysis showed a classification ability of 72.8%.

Conclusions: The Spanish version of the MSI-BPD has good psychometric properties as a measure for the screening of BPD. Its ease and quickness of use make it valuable to detect the presence of BPD in clinical and research settings.

PALABRAS CLAVE
Trastorno límite de la personalidad;
McLean Screening Instrument for Borderline Personality Disorder;
Validación;
Cribado;
Evaluación

Validación de la versión española del *McLean Screening Instrument for Borderline Personality Disorder*

Resumen
Introducción: El trastorno límite de la personalidad (TLP) es un trastorno mental frecuente y grave. Su detección precoz es importante y para ello se requieren instrumentos fiables de cribado. Sin embargo, no existen hasta la fecha instrumentos de *screening* específicos para el TLP validados en población castellanohablante. El *McLean Screening Instrument for Borderline Personality Disorder* (MSI-BPD) es un cuestionario autoinformado de 10 ítems que permite detectar la presencia de TLP de forma fiable y rápida. El objetivo de este estudio es la validación del MSI-BPD para su uso en población de habla española.
Método: Se examinaron las propiedades psicométricas de la versión española del MSI-BPD en una muestra de 344 participantes (170 pacientes con orientación diagnóstica de TLP y 174 controles sanos).
Resultados: El análisis factorial exploratorio mostró la existencia de una estructura bifactorial. La escala presentó una elevada consistencia interna (KR-20 = 0,873) y una óptima fiabilidad test-retest (CCI = 0,87). Mediante un análisis de regresión logística y con la DIB-R como referencia se estableció un punto de corte óptimo de 7, obteniendo una adecuada sensibilidad (0,71) y especificidad (0,68). El área bajo la curva fue de 0,742 (IC 95% 0,660-0,824). El análisis discriminante permitió observar una capacidad clasificatoria de la escala del 72,8%.
Conclusiones: La versión española del MSI-BPD presenta buenas propiedades psicométricas como instrumento de cribado del TLP. Su aplicación en la práctica clínica y en la investigación puede ser de gran utilidad para la detección del TLP por su rapidez y facilidad de uso.

Introduction

Borderline personality disorder (BPD) is a common and serious mental disorder which has a prevalence estimated at from 0.5% to 5.9% of the general population, and 10% of psychiatric outpatients.[1] Subjects diagnosed with BPD give rise to high direct and indirect economic costs, as well as severe social consequences for themselves, their families and the mental health system. This is due to their difficulties in social adaptation, their increased use of healthcare services and their high rate of suicide.[1–4]

BPD is characterised by a persistent pattern of instability in interpersonal relationships, self-image and affectivity, together with marked impulsiveness, especially in self-harming behaviour.[5] The clinical heterogeneity of BPD, frequent comorbidity with other personality disorders and the periodic appearance of axis I disease add to the difficulty of establishing a reliable diagnosis, so that it is often underdiagnosed in many care contexts.[1,4–7] This complexity makes it advisable to use standardised instruments to complement the usual clinical examiniation.[8] Semistructured interviews such as the Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II)[9] and the Revised Diagnostic Interview for Borderlines (DIB-R),[10] both of which have been validated in Spanish, are current the standard instruments for the diagnosis of BPD.[11] Nevertheless, the need for clinicians to have previous experience to conduct these interviews and the long time they require hinder their use in general clinical practice.

Self-conducted instruments may be a good complementary tool, as they offer certain advantages over those conducted by others: as they are short and self-reporting they can easily be introduced in clinical practice. They save time for clinicians, permit better use in different healthcare or research contexts, reduce defensiveness in replies and, due to their greater standardisation, they usually offer superior psychometric properties. Their speed and ease of use make them especially useful as a screening system; however, it has to be pointed out that they must not be used as the sole diagnostic instrument, but should rather be used in an initial phase as a tool to identify those subjects who have to be examined subsequently more exhaustively.[7,12]

The McLean Screening Instrument for Borderline Personality Disorder (MSI-BPD)[7] is the first screening scale for the diagnosis of BPD that is based on the diagnostic criteria of the DSM-IV and DSM-V. It emerged in response to the need for a valid and reliable scale that is easy to administer, making the preliminary identification of BPD possible. Until then the

Personality Diagnostic Questionnaire[13] was the only available screening method, although it was not specific for BPD and gave rise to a high rate of false positives and a low specificity (0.41). The MSI-BPD is a self-reporting questionnaire with 10 items that score as a disjunction (true-false). Its original version had suitable psychometric properties, especially in adolescent and young adult samples.[7] Different studies with community, student and psychiatric populations have confirmed the psychometric reliability of this instrument as a means of screening for BPD.[14–16] Due to this in recent years the scale has been adapted and validated in other languages.[17–19]

Several instruments have now been validated for the diagnosis and evaluation of personality disorders in Spanish-speaking populations. There are interviews and questionnaires for the diagnosis of general personality disorders, such as the SCID-II,[9,20] the International Personality Disorder Examination,[21,22] the Personality Assessment Inventory,[23,24] the Minnesota Multiphase Personality Inventory-2,[25,26] the Millon Clinical Multiaxial Inventory[27,28] and the Personality Diagnostic Questionnaire-4,[29,30] the last of which has a specific scale for BPD. There is also the above-mentioned DIB-R[6,10] semistructured interview which is specific for BPD. Finally, in recent years scales have been validated to evaluate the clinical severity of BPD such as the Borderline Symptom List-23[31,32] and the Clinical Global Impression Scale for Borderline Personality Disorder Patients.[33]

However, to date there have been no specific BPD screening instruments validated for Spanish-speaking population. The aim of this study is therefore to validate the Spanish version of the MSI-BPD for use in research as well as clinically for the Spanish-speaking population.

Methodology

Participants

Depending on the different psychometric characteristics to be evaluated, the necessary sample size is estimated to stand at 150 subjects. Of the different psychometric characteristics to be evaluated, the one that requires the largest number of subjects to be properly studied is the validity of the construct (factorial structure). According to the guide (from 5 to 10 cases per item) proposed by Gorsuch,[34] the sample size selected is the most suitable as it is above the high band of the interval which would delimit the necessary number of patients (50–100). The total sample was 344 subjects; Table 1 shows the main sociodemographic characteristics of the sample.

The clinical group of patients was composed of 170 subjects with an initial diagnostic orientation of BPD, referred to the Hospital de la Santa Creu i Sant Pau and the Igualada Hospital for study and diagnosis. The general profile of the clinical sample was: a great majority of women, with an average age of 32 years old, with no stable partner, secondary education and without a stable job (see Table 1 for more details). The diagnosis of BPD was confirmed for 115 of them and ruled out for 47, who were all diagnosed with another personality disorder. It was not possible to finalise the evaluation of 8 patients as they lost contact with the unit.

Table 1 Sociodemographic characteristics of the patient and healthy control samples.

	Patients (n = 170)	Healthy controls (n = 174)
Age	32.08 (8.75)	24.39 (6.75)
Sex, female	86.5	69
Marital status		
No partner	60.6	88
With a partner or married	39.4	12
Educational level		
Primary	25.3	0.8
Secondary	52.9	88.4
University	21.8	10.8
Working status		
In work	31.8	4.9
Unemployed	42.4	2.4
Temporally out of work	7.6	0
Pensioner	12.9	0
Not working	5.3	92.7

In the table data are shown as averages (standard deviations) or percentages.

The control group of healthy subject was composed of 174 volunteers with no psychiatric history, the majority of whom were students selected to participate in clinical pharmacology studies, together with hospital workers.

For the study all those participants who had a history of neurocognitive, schizophrenic spectrum and other psychotic disorders were excluded, together with those with alcohol or other toxic substances dependency and those with bipolar disorder.

Procedure

The procedure of translation-back translation was followed to adapt the scale. The original scale was translated by a bilingual individual with clinical experience, and it was agreed with the rest of the research team. The first version was translated back into English by an independent translator, and this version was correct by the authors of the original scale, who verified the suitability of the original text (see Appendix 1 with the validation into Spanish of the MSI-BPD).

During the procedure the subjects included in the study with suspicion of BPD were first given the MSI-BPD and subsequently both diagnostic interviews: DIB-R and SCID-II. The Psychiatric Diagnostic Screening Questionnaire (PDSQ)[35] was also administered to rule out psychiatric disease. The healthy controls were only given the MSI-BPD. The whole process was undertaken during a period of approximately from one week to 15 days. 3 cases were excluded from the initial sample due to error in filling out the questionnaire. To study the reliability of the test-retest, a subsample of 30 subjects answered the MSI-BPD for a second time, 2 weeks after it had first been administered.

All of the participants read and signed the informed consent form and took part in the study voluntarily.

Instruments

- MSI-BPD[7]: is a self-reporting questionnaire with 10 items that score as a disjunction (true-false). It includes one item for each one of the first 8 criteria of the DSM-IV and DSM-V for BPD and 2 items for the ninth criterion of paranoia/dissociation. The original version of the scale has a high level of sensitivity (0.81) and specificity (0.85), where 7 is the optimum cut-off score. The test-retest was also reported to achieve a correct level of reliability (Spearman's rho = 0.72, $P < 0.0001$).
- DIB-R[6]: is a semistructured interview composed of 125 items (each one of which scores from 0 to 2 depending on frequency in the last 2 years). The items explore 4 dimensions: cognitive, emotional, impulsive patterns of action and interpersonal relationships. The partial scores in each dimension determine the overall score, which runs from 0 to 10 points, where 6 is the cut-off point compatible with diagnosis of BPD for the Spanish version of the interview.
- SCID-II[20]: is a semistructured clinical interview that makes it possible to evaluate all specific axis II personality disorders of the DSM-IV, as well as the 2 of the appendix and the non-specific ones. It contains 15 items for BPD in yes/no format, corresponding to the 9 criteria of the DSM-IV. Each DSM-IV criterion has a question in the SCID-II, except for the third one (identity alteration), which is included in 4 items, the fifth (recurring suicidal behaviour), with 2 items, and the eighth (inappropriate anger), with 3 questions.
- PDSQ[35]: is a self-administered questionnaire composed of 125 items with a response in the form of a disjunction (yes/no) designed to detect 13 of the most common psychiatric disorders. It questions the subject about the presence of symptoms in the previous 2 week for the first 6 sub-scales: major depression, post-traumatic stress disorder, Bulimia, obsessive-compulsive disorder, anxiety crisis and psychosis; or in the previous 6 months for the other 7 disorders included: Agoraphobia, social phobia, alcohol abuse/dependency, substance abuse/dependence, generalised anxiety disorder, somatisation disorder and hypochondria.

Statistical analysis

All analyses were undertaken using version 18.0 of the SPSS statistical package for Windows. Once the descriptive statistics of the sample had been calculated, the psychometric properties of the MSI-BPD were examined.

Exploratory factorial analysis was undertaken to evaluate the validity of the construct for the MSI-BPD. The internal consistency of the scale was also studied using the Kuder-Richardson (KR-20) coefficient. Test-retest reliability was analysed in a subsample of 30 patients diagnosed BPD using the intraclass correlation coefficient (ICC) between the MSI-BPD scores obtained in 2 consecutive administrations separated by 2 weeks.

Subsequently the levels of specificity and sensitivity were established to study the diagnostic concordance between the MSI-BPD and the DIB-R (using this as the gold standard scale for diagnosis of the disorder) in the clinical sample, taking different cut-off points into account and establishing the optimum cut-off point for the Spanish version of the MSI-BPD. Once the said cut-off point had been established logistic regression analysis was performed to analyse the diagnostic precision of the scale. The area under the COR curve was interpreted according to the ranges of diagnostic precision recommended by Fischer et al.[36]

The converging validity with the sub-scales of the SCID-II was estimated using the χ^2 test with scores in the PDSQ subscales using Spearman correlations. The stepwise procedure was used for discriminatory analysis to examine the capacity of the MSI-BPD to correctly classify positive vs negative BPD cases.

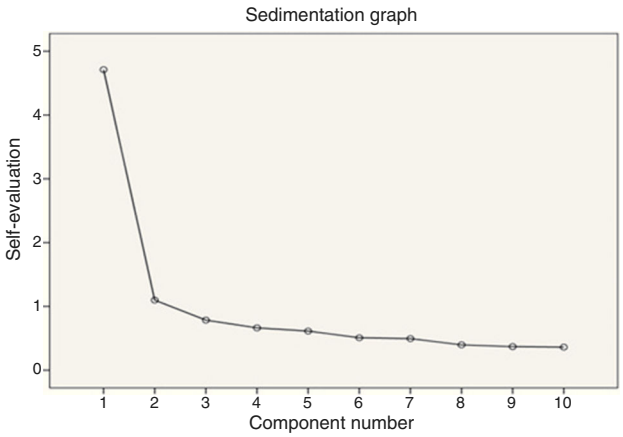

Figure 1 MSI-BPD sedimentation graph.

Results

Construct validity

Exploratory factorial analysis was undertaken with the complete sample. After checking that they fulfilled the application conditions (KMO = 0.90 and Bartlett's significant sphericity test [$\chi^2(45) = 1.301{,}58$, $P < .001$]), the main axes of the scale were factorised with Varimax rotation. The solution indicated the existence of 2 factors observed in the sedimentation graph (Fig. 1). The first factor showed a variance of 33.71%, and the second factor one of 24.37%. All of the items showed commonalities above 50% except for item 2 (46%) and 6 (49%). Respecting the factorial load, all of the items had high loads with the first factor except for item 7. In the matrix of components rotated by Varimax, items 7, 8 and 9 had high loads in the second factor. Analysis of the content of the items of both factors would show the existence of a principle factor characterised by items connected with the ''impulsivity-emotionality'' construct, and a second factor with items on ''cognitive symptoms'' (see Fig. 1). The said bifactor solution explained 58.09% of the total variance of the scale.

Internal consistency

For the total sample the Spanish version of the MSI-BPD showed a good level of internal consistency (KR-20 = 0.873), indicating a high level of overall reliability with total scores

Table 2 Exploratory factorial analysis: explained variance and configuration matrix.

Factors	Self-assessment	Percentage variance
1	3.372	33.716
2	2.438	24.376

Rotated components matrix

	Component	
	1	2
1. Have there been problems in any of your closest personal relationships due to multiple arguments or frequent breaking-offs?	0.778	0.206
2. Have you intentionally tried to harm yourself physically (burning, cutting or hitting yourself)? Have you ever attempted suicide?	0.732	−0.037
3. Have you had at least two of the following problems with impulsiveness; frequent over-eating, disproportionate expenses, alcohol abuse, episodes of verbal aggression?	0.685	0.229
4. Have you felt extremely bad-tempered?	0.681	0.297
5. Have you felt or do you feel angry most of the time? Have you often acted furiously or sarcastically?	0.601	0.359
6. Have you often felt distrust in people?	0.568	0.447
7. Have you often felt yourself to be unreal or that the things around you were not real?	0.535	0.417
8. Have you felt or do you feel chronically empty?	0.026	0.845
9. Have you often felt the feeling that you do not know who you are or that you do not have your own identity?	0.280	0.800
10. Have you made desperate efforts to prevent feeling abandoned or being abandoned, for example by: repeatedly calling someone so that they confirm they are concerned about you, begging them not to leave you, physically grabbing them?	0.499	0.630

that varied from 0 to 10 and an average score of 4.43 (DE = 3.27).

Stability over time

The test-retest reliability of the MSI-BPD was studied in a sub-sample of 30 participants. The scores obtained in two administrations separated by 2 weeks were compared using the ICC between both total scores (ICC = 0.87).

Sensitivity and specificity

In the clinical sample the MSI-BPD displayed a sensitivity of 0.71 and a specificity of 0.68 with the DIB-R, using a cut-off point located at 7 (as was set for the original version of the MSI-BPD).[7] When a cut-off point of 6 was used, a slightly higher sensitivity of 0.84 was found, with a lower specificity of 0.51. The low specificity observed with the cut-off point at 6 justifies the use of the cut-off point at 7 for the Spanish version, the same as for the original one (Table 2).

Logistical regression analysis

Analysis of the COR curves was undertaken by taken the DIB-R as the reference. For the cut-off point at 6, the area under the curve (AUC) was 0.752, $P < .001$ (with an interval of confidence of 0.65–0.85). For the cut-off point at 7 the AUC was 0.742, $P < .001$ (with an interval of confidence of 0.66–0.82) (Fig. 2).

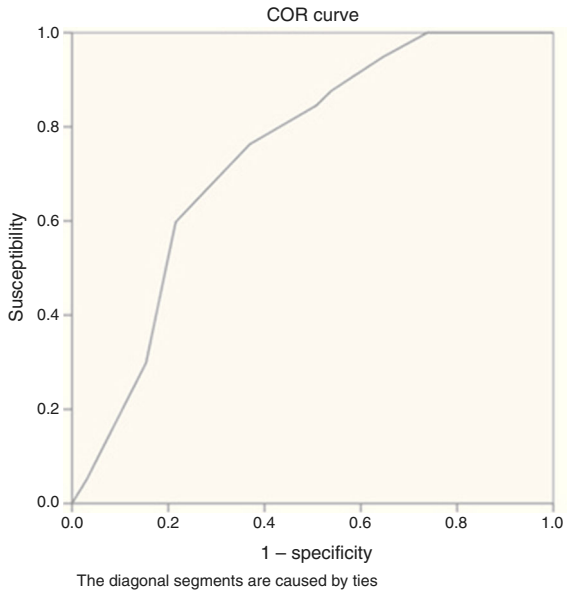

Figure 2 COR for the cut-off point at 7.

Converging validity

For the converging validity analysis the result of the MSI-BPD was compared with the BPD sub-scale of the SCID-II, observing a significant relationship ($\chi^2 = 15.42$, $P < .01$), as well as with the Histrionic and Antisocial sub-scales ($\chi^2 = 4.66$ and $\chi^2 = 6.67$, $P < .05$). The sub-scales for Avoidance, Obsessive, Depressive, Paranoid and Narcissist showed a relationship of

Table 3 Discriminatory analysis of the MSI-BPD: capacity to detect cases of BPD versus non-BPD PD.

Original group member	Predicted group member	
	BPD	Non-BPD PD
BPD (n = 115), n (%)	95 (82.6)	20 (17.4)
Non-BPD PD (n = 47), n (%)	24 (51.1)	23 (48.9)

Classified correctly in 72.8% of the original grouped cases.

independence ($P > .05$), and with the others, the relationship between the variables could not be defined due to very low values in some of the theoretical frequencies.

A Spearman correlation was used to compare the scores of the MSI-BPD with those of the PDSQ (n = 67), obtaining moderate correlations with the sub-scales of Agoraphobia (rho = 0.63), major depression (rho = 0.59), generalised anxiety (rho = 0.53), social phobia (rho = 0.55), Psychosis (rho = 0.59), anxiety crisis (rho = 0.49) and post-traumatic stress disorder (rho = 0.43) (all with $P < .01$); and weaker correlations with the sub-scales of Bulimia (rho = 0.34) and obsessive-compulsive disorder (rho = 0.39) ($P < .01$), and somatisation disorder (rho = 0.31) and Hypochondria (rho = 0.27) ($P < .05$). No significant correlations were observed between the MSI-BPD and the other sub-scales of the PDSQ: alcohol abuse/dependency (rho = 0.20) and substance abuse/dependency (rho = 0.07) ($P > .05$).

Discriminatory analysis

Finally, discriminatory analysis was performed using the stepwise procedure to compare a sub-sample of patients with BPD (n = 115) and another of patients with a non-BPD personality disorder (n = 47). Analysis showed a Wilks' $\lambda = 0.806$, $\chi^2 = 34.20$ ($P < .01$). The discriminatory function counted for 100% of intersubject variability. The canonical correlation was 0.441 and the classification competence of the MSI-BPD was 72.8% (Table 3).

Discussion

Although BPD is the most common personality disorder in the clinical field and the most widely researched at the current time,[1] to date no screening scale had been validated for the Spanish-speaking population. This instrument may be highly useful in clinical practice and research, due to its ease and rapidity of use and because it is self-reporting. In this study the validation of the MSI-BPD in Spanish displays suitable psychometric characteristics.

Analysis of the dimensional structure of the Spanish version of the MSI-BPD showed a bifactorial solution, with a predominant main factor that we term ''impulsiveness-emotionality'' and a second factor labelled ''cognitive symptoms'', which would include items 7, 8 and 9. In spite of the said resolution into 2 factors, a single overall score in the scale should be considered for reasons of consistency with the clinical concept of the disorder. As BPD is a disorder with heterogeneous symptoms and up to 5 areas of dysfunction the appearance of more than one factor is consistent with this, even though it is a single clinical entity.[37] This is why the original version of the MSI-BPD[7] was considered to be about a single factor with a single final score. In a similar way to our study, other validations of the scale have also reported a multifactor structure of the MSI-BPD; thus in a previous study in a Chinese population[14] up to factor different factors were observed (affective deregulation, impulsiveness, chronic void and interpersonal problems), corresponding to the 4 main dimensions in the symptoms of BPD.

The internal consistency (KR-20 = 0.873) and test-retest reliability (ICC = 0.873) of the Spanish version of the MSI-BPD were high, higher than those of the original version. Acceptable values were obtained for sensitivity (0.71) and specificity (0.68), with an optimum cut-off point at 7. This cut-off point was also used in validating the original version of the scale, although with higher diagnostic efficiency, sensitivity = 0.81 and specificity = 0.85. In our case we ruled out a cut-off point at 6 because although we obtained a high level of sensitivity (0.84), specificity fell considerably (0.51). The majority of adaptations have used the same cut-off point as the original scale, except for the ones by André et al.,[38] Noblin et al.[16] and Chanen et al.,[39] whose cut-off points were $\geq$5, 5.5 and >7, respectively, giving slight differences in their results. The AUC observed in our study (0.742) would indicate that the MSI-BPD achieves moderate diagnostic precision. The different results obtained in other studies are largely due to the different populations and contexts in which they were undertaken. Studies such as that by Noblin et al.[16] with hospitalised teenagers, the community study with women by Patel et al.[15] or the one by Kröger et al.,[18] with a heterogeneous population of outpatients, are good examples of this (with an AUC of 0.73, 0.79 and 0.90, respectively).

This study used the DIB-R as the criterion measurement, as this interview is considered to be the most reliable for diagnosis of BPD.[6] The original version as well as the study by Patel et al.[15] used the DIPD-BPD, while in other adaptations the SCID-II was the measurement selected (for example, by Melartin et al.,[17] André et al.[38] and Chanen et al.).[39] This diversity in the choice of gold standard instrument as well as the other points mentioned above may also explain the different results of different validations respecting the validity of the criterion.

In the analysis of convergence between the MSI-BPD and the SCID-II, the correlation with the BPD sub-scale was significant, as could be expected. This was also the case with the Histrionic and Antisocial sub-scales, which could be expected due to the high level of comorbidity described and because they share certain diagnostic criteria, while all 3 are located in Cluster B Personality Disorders.[40]

Positive and significant correlations were observed between the MSI-BPD and different sub-scales of the PDSQ. The said results were expectable given the broad spectrum of symptoms that patients with BPD usually present and the high comorbidity with anxiety and affective disorders.[1] In the same way the study by Noblin et al.[16] also shows concurrencies between the MSI-BPD and axis I psychopathology and suicidal ideas. The validation of the Dutch version of the MSI-BPD[19] also reported a moderate correlation ($r = 0.62$) with the depression scale. Contrary to what could be expected, our study showed no convergence with the MSI-BPD for the PDSQ sub-scale for the consumption of toxic substances. Likewise, nor did Gardner and Qualter[41] observe predictive

validity of the MSI-BPD in connection with substance abuse or eating disorders. Discriminatory analysis between patients with BPD and individuals with other personality disorders showed that the Spanish version of the MSI-BPD seems to be able to correctly classify 72.8% of clinical cases.

It is important to point out the limitations of this study. Firstly, it has to be said that the group of patients was primarily composed of women, and this fact should be taken into account most especially given that the disorder is now thought to be more prevalent in men than was initially thought to be the case.[1,15] Secondly, the fact that the clinical sample of BPD was selected in units that are specifically for BPD at a tertiary level must be taken into account. The severity of the cases selected may be greater than would be the case in the community or in primary care. This may have influenced the observed discriminatory power of the scale, as this discriminatory power would be lower in other environments with less severe cases. Sociodemographic variables may lead to significant differences in connection with the limit symptoms evaluated by the MSI-BPD, with comorbidity and social deterioration, etc., and these should be controlled in future studies. It also has to be pointed out that the size of the sub-sample of 30 subjects used to evaluate the stability of the scale over time was somewhat limited. Another aspect to be considered is the limited sub-sample of patients with a non-BPD personality disorder (n = 47). Future studies should include a larger clinical sample for comparison, to permit better examination of the specificity of the scale.

To conclude, the Spanish version of the MSI-BPD has good psychometric properties and a high level of sensitivity for use as a screening tool for BPD. It may be highly useful in clinical practice for an initial diagnosis in patients with the suspicion of BPD in the Spanish-speaking population. Its rapidity and ease of use make it especially useful as a screening system in different contexts, such as primary care or mental health clinics. Nevertheless, the recommendation should be to use it as an instrument to identify those subjects who should be examined later on more exhaustively. It may also be useful in the field of research to quickly and simply rule out the possibility of a diagnosis of BPD.

Ethical responsibilities

Protection of human and animal subjects. The authors declare that the procedures followed are according to the ethical norms of the responsible human experimentation committee, the World Medical Association and the Helsinki Declaration.

Confidentiality of data. The authors declare that they followed the protocols of their centre of work regarding the publication of patient data.

Right to privacy and informed consent. The authors have obtained the informed consent of the patients and/or subjects referred to in the paper. This document is held by the corresponding author.

Conflict of interests

The authors have no conflict of interests to declare.

Appendix 1. MSI-BDP (McLean Screening Questionnaire)

Name:
Date:
Answer 1 (YES) or 2 (NO) in the following questions:
During this last year:

1. Have there been problems in any of your closest personal relationships due to multiple arguments or frequent breaking-offs? 1 (YES) 2 (NO)
2. Have you intentionally tried to harm yourself physically (burning, cutting or hitting yourself)? Have you ever attempted suicide? 1 (YES) 2 (NO)
3. Have you had at least two of the following problems with impulsiveness; frequent over-eating, disproportionate expenses, alcohol abuse, episodes of verbal aggression? 1 (YES) 2 (NO)
4. Have you felt extremely bad-tempered? 1 (YES) 2 (NO)
5. Have you felt or do you feel angry most of the time? Have you often acted furiously or sarcastically? 1 (YES) 2 (NO)
6. Have you often felt distrust in people? 1 (YES) 2 (NO)
7. Have you often felt yourself to be unreal or that the things around you were not real? 1 (YES) 2 (NO)
8. Have you felt or do you feel chronically empty? 1 (YES) 2 (NO)
9. Have you often felt the feeling that you do not know who you are or that you do not have your own identity? 1 (YES) 2 (NO)
10. Have you made desperate efforts to prevent feeling abandoned or being abandoned, for example by: repeatedly calling someone so that they confirm they are concerned about you, begging them not to leave you, physically grabbing them? 1 (YES) 2 (NO)

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