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CAMBIAR PARA SANAR: UN ESTUDIO EMPÍRICO SOBRE LA ATRIBUCIÓN DE SIGNIFICADO Y LA FLEXIBILIDAD PSICOLÓGICA COMO MECANISMOS DE CAMBIO EN LA TERAPIA ASISTIDA CON PSICODÉLICOS

Óscar Soto Angona

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Tesis Doctoral presentada por:

Óscar Soto Angona

Para obtener el grado de Doctor en Psiquiatría

Programa de doctorado en Psiquiatría.
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Barcelona, 2026

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Tesis Doctoral

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Que esta tesis permita alumbrar nuevos modos hábiles para aliviar el sufrimiento.

AGRADECIMIENTOS

Resulta difícil determinar con precisión cuándo nace la idea de un proyecto y qué hace posible su culminación. Todo producto de la inteligencia humana surge del encuentro entre una persona y su entorno, un encuentro sostenido por una constelación prácticamente infinita de causas y condiciones. Quien firma una obra no es más que el crisol en el que todos estos factores confluyen. Por ello, mi primer y más profundo agradecimiento se dirige a cada circunstancia que ha conspirado para que esta tesis haya podido existir.

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Gracias también a las propias sustancias psicodélicas, maestras y compañeras a lo largo de este viaje, a la ciencia misma, por su capacidad de desvelar la belleza íntima del mundo, y al Dharma, por dar dirección y sentido a todo lo que hago.

Más allá de mis circunstancias materiales e intelectuales, la autoría de esta tesis es inseparable de la extensa red de personas de quienes he recibido inspiración, cuidado y apoyo:

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Y, finalmente, mi gratitud a todas aquellas personas que abrieron camino en circunstancias infinitamente más adversas que las mías. Esta tesis se sostiene sobre el trabajo de miles de individuos que, pese a la estigmatización, la represión, la violencia institucional y la censura, se atrevieron a investigar y a trabajar con sustancias psicodélicas porque confiaban en su enorme potencial. A su vez, ninguno de esos esfuerzos habría sido posible sin la generosidad de los pueblos originarios, que decidieron compartir su conocimiento ancestral por el bien de todos los seres humanos. Es probable que nunca podamos retribuir adecuadamente el legado recibido; sin embargo, en un

panorama cada vez más complejo, en el que actores económicos y políticos podrían instrumentalizar estas sustancias y sus efectos, es nuestra responsabilidad honrar esa herencia luchando por que los psicodélicos se conviertan en terapias seguras, éticas y accesibles para todas las personas que sufren y las necesitan.

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ABREVIATURAS

5-HT – Serotonina

5-HT1A, 5-HT1B, 5-HT2A – Subtipos de receptores serotoninérgicos con efectos diferenciales

5-MeO-DMT – 5-metoxi-N,N-dimetiltriptamina

A-MR – Ayahuasca y reconstrucción de significado (*Ayahuasca and Meaning Reconstruction*)

ACT – Terapia de Aceptación y Compromiso

ADN – Ácido desoxirribonucleico

AMPA – α-amino-3-hidroxi-5-metil-4-isoxazolpropionato

ARNm – Ácido ribonucleico mensajero

CB1 – Receptor de cannabinoides 1

CRF – Factor liberador de corticotropina

D2 – Receptor de dopamina 2

DMN – *Default Mode Network* – Red neuronal por defecto

DMT – N,N-dimetiltriptamina

EAC – Estados alterados de conciencia

EMA – *European Medicines Agency* (Agencia Europea del Medicamento)

FDA – *Food and Drug Administration* (Agencia estadounidense del medicamento)

HPA – Eje hipotalámico-pituitario-adrenal

HPPD – *Hallucinogen Persistent Perceptive Disorder* (Trastorno perceptivo persistente por alucinógenos)

IL-10 – Interleucina 10

IL-6 – Interleucina 6

KOR – Receptor opioide kappa

LSD – Dietilamida de ácido lisérgico (*Lysergic Acid Diethylamide*)

MDMA – 3,4-metilendioximetanfetamina

mTOR – *Mechanistic Target of Rapamycin*

MR – Reconstrucción de significado (*Meaning Reconstruction*)

NMDA – N-metil-D-aspartato

NR3C1 – Gen del receptor de glucocorticoide

NT – Grupo sin tratamiento (*No Treatment*)

REBAS – *Revised Beliefs After Psychedelics* (Creencias revisadas tras los psicodélicos)

REBUS – *Relaxed Beliefs Under Psychedelics* (Creencias relajadas bajo los psicodélicos)

SERT – Transportador de serotonina

TNF-α – Factor de necrosis tumoral alfa

ABSTRACT

Introduction

Psychedelic substances are emerging as promising therapeutic tools for different mental health conditions, including treatment-resistant depression, anxiety, trauma, and addictions. However, their mechanisms of action remain incompletely understood, and their clinical application faces significant methodological and ethical challenges. Evidence suggests that their therapeutic effects cannot be explained only by their pharmacological properties but depend largely on the context in which they are administered and the subjective experience they induce. In this framework, this thesis aims to understand two key psychological processes that mediate these effects: meaning attribution and psychological flexibility.

Objectives

The general objective of this thesis is to evaluate the role of meaning attribution and psychological flexibility as mechanisms of change in the therapeutic effects of psychedelics. It will examine how these mechanisms interact with both context and subjective experience and explore their potential clinical applications.

Methods

The thesis comprises two complementary studies. Study 1 involved the translation, adaptation, and psychometric validation of the APEQ (Acceptance/Avoidance-Promoting Experiences Questionnaire) in an international Spanish-speaking sample (n = 715), assessing the relationship between consumption intentions (context), the subjective psychedelic experience, and retrospective changes in psychological flexibility. Study 2 was a randomized clinical trial comparing three treatment arms: (a) waitlist control, (b) meaning-centered psychotherapy based on a grief reconstruction model, and (c) a combination of this intervention with group ayahuasca sessions in a controlled clinical setting. A total of 84 participants experiencing grief following the loss of a loved one took part.

Results

In Study 1, the Spanish version of the APEQ demonstrated a robust factorial structure, high internal consistency, and good convergent validity. Acceptance-related experiences were significantly associated with therapeutic and growth-oriented intentions, as well as with improvements in psychological flexibility, while avoidance-related experiences had

a negative impact. In Study 2, the combined intervention (ayahuasca + psychotherapy) was significantly more effective than psychotherapy alone and the waitlist in reducing grief symptoms and produced greater increases in post-traumatic growth and psychological well-being.

Conclusions

Psychological flexibility and meaning attribution emerge as key processes influenced by subjective experience and context, offering essential insights to optimize clinical applications, guide the design of effective interventions, and ensure safety. Facilitating these mechanisms, whether through targeted therapeutic strategies or contextual modulation, could enhance the efficacy and safety of psychedelic interventions. However, their potential contribution to adverse effects also warrants further investigation. These findings support the importance of integrating structured therapeutic approaches into psychedelic-assisted clinical practice and provide specific tools for their evaluation and future implementation.

RESUMEN

Introducción

Las sustancias psicodélicas están emergiendo como herramientas terapéuticas prometedoras para diversos trastornos mentales, incluyendo depresión resistente, ansiedad, trauma y adicciones. Sin embargo, sus mecanismos de acción siguen sin estar completamente comprendidos, y su aplicación clínica plantea importantes desafíos metodológicos y éticos. En particular, la evidencia apunta a que sus efectos terapéuticos no pueden explicarse únicamente por sus propiedades farmacológicas, sino que dependen en gran medida del contexto en el que se administran y de la experiencia subjetiva que inducen. En este marco, esta tesis busca comprender dos procesos psicológicos que median dichos efectos: la atribución de significado y la flexibilidad psicológica.

Objetivos

El objetivo general de esta tesis es evaluar el papel de la atribución de significado y la flexibilidad psicológica como mecanismos psicológicos de cambio que median los efectos terapéuticos de las sustancias psicodélicas, considerando su interacción con el contexto y la experiencia subjetiva, y su potencial aplicación clínica.

Métodos

La tesis incluye dos estudios complementarios. El Estudio 1 consistió en la traducción, adaptación y validación psicométrica del cuestionario APEQ (Acceptance/Avoidance-Promoting Experiences Questionnaire) en una muestra internacional de población hispanohablante (n = 715), evaluando la relación entre las intenciones de consumo (contexto), la experiencia subjetiva durante el estado psicodélico, y los cambios retrospectivos sobre la flexibilidad psicológica. El Estudio 2 incluyó un ensayo clínico aleatorizado que comparó tres ramas de tratamiento: (a) lista de espera, (b) psicoterapia centrada en el significado basada en el modelo de reconstrucción del duelo, y (c) combinación de esta intervención con sesiones grupales de ayahuasca en un entorno clínico controlado. Participaron 84 personas en proceso de duelo prolongado tras la pérdida de un ser querido.

Resultados

En el Estudio 1, la versión española del APEQ mostró una estructura factorial robusta, alta fiabilidad interna y validez convergente. Las experiencias relacionadas con la aceptación se asociaron de forma significativa con intenciones terapéuticas y de

crecimiento, así como a mejoras en la flexibilidad psicológica, mientras que las experiencias de evitación tuvieron un impacto negativo. En el Estudio 2, la intervención combinada (ayahuasca + psicoterapia) resultó significativamente más eficaz que la psicoterapia aislada y la lista de espera para reducir la sintomatología de duelo, y mostró mayores incrementos en crecimiento postraumático y bienestar psicológico.

Conclusiones

La flexibilidad psicológica y la atribución de significado emergen como procesos clave, influidos por la experiencia subjetiva y el contexto, lo cual puede ofrecer claves fundamentales para optimizar su uso clínico, guiar el diseño de intervenciones eficaces y garantizar su seguridad. Facilitar la presencia de dichos mecanismos, ya sea mediante intervenciones terapéuticas específicas o a través de abordajes sobre el contexto, podría optimizar la eficacia y seguridad de las intervenciones psicodélicas, si bien es necesario también estudiar su posible contribución sobre los posibles efectos adversos que se han relacionado con el consumo de psicodélicos. Estos hallazgos refuerzan la relevancia de integrar abordajes terapéuticos específicos en la práctica clínica asistida con psicodélicos y proporcionan herramientas concretas para su evaluación e implementación en futuras investigaciones.

INTRODUCCIÓN

1. Sustancias psicodélicas

1.1 Concepto, generalidades y perspectiva histórica

En los últimos años, las sustancias psicodélicas han despertado un renovado interés en el ámbito de la psiquiatría y la psicología clínica, debido a su potencial para facilitar cambios terapéuticos profundos tras una o pocas exposiciones. Estas sustancias se definen por su capacidad de inducir estados alterados de conciencia (EAC) en quienes las consume (Sessa, 2016). Si bien el término "psicodélico" es ampliamente utilizado tanto en contextos científicos como culturales, su definición presenta una notable imprecisión, debido, en gran medida, a la dificultad de operacionalizar qué se entiende por "estado alterado de conciencia".

Charles Tart (Tart, 1975) propuso una definición ampliamente citada, describiendo un EAC como "una modificación cualitativa del modo habitual de experimentar el yo, el entorno o ambos, que implica una ruptura temporal de los patrones ordinarios de organización mental y percepción de la realidad". Desde una perspectiva más reciente y complementaria, Revonsuo y colaboradores (Revonsuo et al., 2009) han sugerido que la cualidad definitoria de un EAC radica en la alteración de la relación entre el mundo y su representación en la conciencia respecto al estado de vigilia normal, destacando también su carácter transitorio. En conjunto, estos enfoques coinciden en concebir los EAC como estados de conciencia que se desvían sustancialmente de la experiencia consciente habitual. Aunque estas definiciones no están exentas de problemas conceptuales derivados de lo que entendemos por "normalidad" en los estados de conciencia, resultan útiles para aproximarse al estudio de los psicodélicos desde una perspectiva experiencial y fenomenológica, ya que apelan a la experiencia compartida de lo que consideramos un estado ordinario de conciencia, y permiten trazar distinciones en base a ella. En el caso de los EACs causados por sustancias psicodélicas, su fenomenología puede variar enormemente en función de la sustancia y el contexto, como detallaremos posteriormente, pero suelen caracterizarse por cambios notables y perceptibles en las percepciones sensoriales, las emociones y la autopercepción (Preller & Vollenweider, 2016).

El término «psicodélico» proviene del griego ψυχή (psykhé, “alma” o “mente”) y δῆλος (dêlos, “manifestar” o “revelar”), y fue acuñado por el psiquiatra Humphry Osmond en 1957, en una correspondencia con el escritor Aldous Huxley, en el marco de sus investigaciones compartidas sobre los efectos subjetivos de la mescalina, bajo el supuesto psicodinámico de que estas sustancias permitían mostrar los procesos inconscientes de la mente (Sessa, 2016). Aunque la palabra es relativamente reciente, el uso de sustancias con propiedades psicodélicas se remonta a tiempos ancestrales. Diversas culturas de todo el mundo han empleado compuestos vegetales psicoactivos en contextos rituales, espirituales y terapéuticos, desde hace milenios. Algunos autores sostienen incluso que estos usos pudieron jugar un papel fundamental en la evolución de la conciencia simbólica y la organización cultural del ser humano (Rodríguez Arce & Winkelman, 2021).

Sin embargo, fue necesario esperar a finales del siglo XIX para que estas sustancias se constituyeran como objeto de estudio por la ciencia empírica occidental. En 1898, el químico alemán Arthur Heffter logró aislar la mescalina del cactus *Lophophora williamsii* (peyote) y documentó sistemáticamente sus efectos subjetivos, marcando así el inicio de la psicofarmacología psicodélica y despertando el tímido interés de otros científicos, que comenzaron a experimentar y estudiar con sus efectos subjetivos. No obstante, el punto de inflexión para la entrada de estas sustancias en el ámbito académico fue el descubrimiento accidental de los efectos psicoactivos de la dietilamida de ácido lisérgico (LSD) por parte del químico suizo Albert Hofmann en 1943, quien había sintetizado y descartado previamente esta molécula mientras investigaba derivados del cornezuelo de centeno con potencial vasoconstrictor para el tratamiento de hemorragias postparto. Hofmann trabajaba en los laboratorios Sandoz, que posteriormente comercializaron el LSD bajo el nombre Delysid. Este compuesto fue objeto de una intensa actividad investigadora entre las décadas de 1950 y 1960, siendo evaluado en más de un centenar de ensayos clínicos por sus posibles aplicaciones en diversos trastornos psiquiátricos. En 1958, Hofmann también aisló la psilocibina a partir de hongos del género *Psilocybe*, incorporándola al arsenal experimental de sustancias psicodélicas en investigación. Durante este periodo, los estudios clínicos con psicodélicos fueron especialmente prominentes en Estados Unidos, donde se llevaron a cabo más de 130 estudios financiados por organismos gubernamentales (Doblin et al., 2019).

En paralelo a su uso clínico, las sustancias psicodélicas comenzaron a ser utilizadas de manera recreativa por colectivos asociados a movimientos contraculturales, generando alarma institucional y cobertura sensacionalista por parte de los medios de comunicación. Además, algunos ensayos realizados en ese periodo fueron criticados por deficiencias metodológicas y éticas. Como consecuencia de esta confluencia de factores científicos, sociales y políticos, y pese a la amplia evidencia sobre su seguridad y eficacia, los principales compuestos psicodélicos fueron incluidos en la Lista I de la Convención de las Naciones Unidas sobre Sustancias Psicotrópicas, una categoría que las define como sustancias peligrosas sin utilidad médica reconocida. Esta reclasificación supuso la interrupción casi total de su uso clínico y su investigación científica. Posteriormente, la 3,4-metilendioximetanfetamina (MDMA), sintetizada en 1912 por Merck y redescubierta para uso psicoterapéutico en la década de 1970, fue también prohibida e incluida en la Lista I en respuesta a la generalización de su uso con finalidad recreativa (López-Arnau et al., 2022).

A pesar de este contexto prohibicionista, algunos grupos lograron superar las barreras legales y retomar la investigación clínica con psicodélicos. Es el caso de Rick Strassman, quien en la década de 1990 llevó a cabo los primeros estudios autorizados en EE. UU. con dimetiltriptamina (DMT), tras obtener la aprobación de la FDA y la DEA (Strassman, 2000). No obstante, la mayoría de las investigaciones quedaron paralizadas hasta finales de los años noventa, salvo excepciones en países con marcos regulatorios más permisivos, como Suiza. En este periodo también se registraron intentos frustrados, como el primer ensayo clínico con MDMA para el tratamiento del trastorno por estrés postraumático en España, que fue interrumpido prematuramente por presiones políticas, a pesar de contar con aprobación ética y clínica (Bouso et al., 2008).

El punto de inflexión que facilitó la reactivación científica contemporánea llegó en 1996, cuando el profesor Roland Griffiths inició un ensayo clínico en la Universidad Johns Hopkins para estudiar los efectos de la psilocibina en pacientes con ansiedad y malestar existencial asociados al final de la vida. Este proyecto, enmarcado en los criterios éticos del uso compasivo, culminó con la publicación de un influyente artículo en 2006, que

demostró la seguridad y eficacia del compuesto, así como la relevancia terapéutica de los estados alterados de conciencia inducidos por la psilocibina. En particular, se destacó la asociación entre la presencia de experiencias místicas y la mejora clínica observada (Griffiths et al., 2006). Este trabajo, realizado con los estándares metodológicos modernos, reactivó el interés internacional por los psicodélicos y motivó una nueva generación de investigaciones, caracterizadas por el uso de técnicas avanzadas como la neuroimagen y por el rigor experimental, que a su vez atrajeron inversión pública y privada. Aquí cabe también mencionar el lugar destacado de la ketamina. Sintetizada en 1962 como anestésico disociativo, su uso se limitó inicialmente al ámbito quirúrgico y de emergencias; su enorme utilidad y su relativamente escaso uso recreativo facilitaron que esta sustancia se mantuviera fuera de la lista I. A partir de la década de 2000, comenzaron a publicarse estudios pioneros que evidenciaban sus efectos antidepresivos rápidos, incluso en pacientes con depresión resistente, lo que supuso un cambio de paradigma respecto a los modelos farmacodinámicos tradicionales (Corriger & Pickering, 2019).

En un contexto de creciente crisis en salud mental, estancamiento en el desarrollo de nuevos tratamientos farmacológicos, y eficacia limitada de las herramientas clínicas disponibles actualmente, la psiquiatría contemporánea ha vuelto su atención hacia el potencial terapéutico de estas sustancias. En 2019, la FDA aprobó el uso de esketamina intranasal como tratamiento adyuvante para la depresión resistente, marcando la primera aprobación regulatoria de una sustancia psicodélica/disociativa para una indicación psiquiátrica específica (Turner, 2020). La esketamina es un fármaco derivado de la ketamina, concretamente el enantiómero S (S-ketamina). Por otro lado, la psicoterapia asistida con MDMA para el tratamiento del trastorno por estrés postraumático y el uso de psilocibina para la depresión resistente constituyen actualmente dos de las indicaciones más estudiadas (Mimms et al., 2025; Mitchell et al., 2021). Paralelamente, y pese a la prohibición y la represión institucional ejercidas sobre su consumo durante décadas, el consumo naturalístico de estas sustancias se ha mantenido entre la población general: se estima que un 13% ha consumido psicodélicos a lo largo de su vida (Simonsson et al., 2021). Esto ha permitido el desarrollo de estudios observacionales en entornos naturalísticos, proporcionando datos relevantes sobre su perfil de seguridad y su impacto

en población sana, que apuntan hacia potenciales efectos protectores sobre la salud mental (Krebs & Johansen, 2013).

En la actualidad, el campo de la investigación con psicodélicos vive un momento de expansión sin precedentes desde su prohibición, con múltiples ensayos clínicos en marcha en distintas fases de desarrollo. La MDMA, la psilocibina y la 5-metoxi-N,N-dimetiltriptamina (5-Meo-DMT) han sido designadas como "terapias innovadoras" (*breakthrough therapies*) por la FDA en Estados Unidos, y las dos primeras sustancias ya han sido aprobadas en Australia para uso clínico en el tratamiento del estrés postraumático y la depresión resistente, respectivamente (Heal et al., 2023). En Europa, diversos ensayos clínicos con distintas sustancias se encuentran actualmente en fases II y III, con vistas a una posible aprobación regulatoria en los próximos años, y la inversión e interés públicos son crecientes, con la reciente concesión de una beca HORIZON para el estudio de la psilocibina dentro de los cuidados paliativos (Proyecto PsyPal). Además, centros académicos de prestigio como Johns Hopkins, Imperial College London o la Universidad de California han creado unidades de investigación dedicadas exclusivamente al estudio de estas sustancias. Si bien su implementación clínica aún está limitada a contextos experimentales, se están desarrollando marcos normativos y formativos para su futura incorporación a la práctica psiquiátrica, y numerosas iniciativas políticas, académicas y populares abogan por un cambio en los marcos regulatorios que facilite su acceso.

1.2 Clasificación farmacológica

Como se ha mencionado previamente, el término "psicodélico" no alude a una estructura química común ni a un mecanismo farmacológico específico, sino que se define por la capacidad de ciertas sustancias de inducir estados alterados de conciencia con potencial terapéutico. Como resultado, su clasificación farmacológica resulta necesariamente heterogénea y, en cierto modo, arbitraria. Diferentes compuestos con estructuras moleculares y mecanismos de acción diversos han sido incluidos bajo esta denominación, debido a la similitud de sus efectos subjetivos y su uso en contextos clínicos o rituales con fines de exploración psicológica, sanación o transformación personal. Sin embargo, todas estas sustancias parecen compartir varios mecanismos de acción neurobiológicos, como se detallará posteriormente, por lo que los diversos efectos farmacológicos pueden

esconder rutas metabólicas con resultados comunes y ayudar a discernir posibles explicaciones para sus efectos subjetivos. Si aplicamos un enfoque estructural y farmacodinámico a las sustancias consideradas como psicodélicas, podemos agruparlas de la siguiente manera:

Psicodélicos clásicos

Los psicodélicos clásicos constituyen el grupo más estudiado y característico dentro del conjunto de sustancias capaces de inducir estados alterados de conciencia. Comparten un mecanismo de acción común centrado en el agonismo del receptor serotoninérgico 5-HT2A, aunque también presentan acciones diferenciales sobre otros receptores que condicionan diferencias específicas entre sustancias, como el agonismo del receptor 5HT1A presente en el 5-MeO-DMT o del receptor D2 presente en el LSD. El receptor 5-HT2A es una proteína acoplada a proteína G, expresada de forma prominente en la corteza prefrontal, el córtex cingulado, la ínsula y otras regiones corticales de alto orden asociadas a la cognición, la percepción y el procesamiento emocional. Los psicodélicos clásicos actúan como agonistas o agonistas parciales de este receptor, provocando una hiperexcitación piramidal cortical y una disrupción en la sincronización de redes neuronales funcionales. Esta desorganización dinámica se ha relacionado con fenómenos característicos de la experiencia psicodélica, como la disolución del ego, la fusión perceptiva o el colapso de estructuras narrativas rígidas del yo (Sharp & Ippolito, 2025). Más allá de sus efectos inmediatos sobre la percepción y la cognición, la activación del receptor 5-HT2A desencadena una serie de cascadas intracelulares que impactan directamente sobre la plasticidad sináptica. En particular, se ha observado que los psicodélicos clásicos aumentan la expresión del BDNF (*Brain-Derived Neurotrophic Factor*), un factor clave en la supervivencia neuronal, la formación de nuevas conexiones sinápticas y la potenciación de la neurogénesis. En modelos animales, se ha observado un aumento de la densidad dendrítica y de la espinogénesis tras la administración de psicodélicos, lo cual respalda la hipótesis de que su acción va más allá de una mera experiencia aguda y puede generar condiciones neurobiológicas propicias para el cambio terapéutico (Calder & Hasler, 2023).

Aunque los psicodélicos clásicos comparten este mecanismo de acción principal, presentan diferencias estructurales, por lo que se pueden dividir a su vez en tres clases (Kelmendi et al., 2022):

- Triptaminas: como la psilocina (metabolito activo de la psilocibina), la N,N-dimetiltriptamina (DMT) y el 5-MeO-DMT (5-metoxi-N,N-dimetiltriptamina). Su estructura química es similar a la serotonina.
- Lisergamidas, o ergolinas semisintéticas, como el LSD, que combina propiedades serotoninérgicas, dopaminérgicas y adrenérgicas. También guardan un parecido estructural con la serotonina.
- Fenetilaminas: como la mescalina, con una estructura más cercana a las anfetaminas

Entactógenos (o empatógenos):

Se trata de un grupo de sustancias con propiedades psicoactivas caracterizadas por la intensificación del vínculo interpersonal, la apertura emocional y la facilitación del procesamiento afectivo, lo cual justifica su inclusión en una clasificación específica, pese formar parte a nivel farmacológico del grupo de las fenetilaminas, al igual que otros psicodélicos clásicos como la mescalina (Baylen & Rosenberg, 2006; Greer & Tolbert, 1986). Su representante más estudiado es la 3,4-metilendioximetanfetamina (MDMA), una fenetilamina sintética que combina propiedades estimulantes y afectivas. Su mecanismo de acción principal consiste en la inversión del transportador de serotonina (SERT), lo que genera una liberación masiva de serotonina (5-HT) en la sinapsis, junto con un aumento de los niveles de dopamina y noradrenalina. Este aumento brusco y masivo de serotonina provocaría un agonismo de diversos receptores serotoninérgicos, en función de su afinidad por este neurotransmisor. Fundamentalmente, los efectos ansiolíticos y antidepresivos observados estarían mediados por los receptores 5-HT1A y 5-HT1B, aunque una activación débil de los receptores 5-HT2A podría contribuir a algunas de las alteraciones subjetivas observadas. Además, la MDMA promueve la liberación de oxitocina, lo que se ha relacionado con los efectos subjetivos de conexión emocional e introspección relacional. Otro aspecto diferencial estriba en su modulación de la reactividad amigdalar, lo que podría facilitar la exposición emocional sin la respuesta defensiva habitual y la facilitación del vínculo terapéutico, aspectos claves en

su prometedor rol como tratamiento para el estrés postraumático (De La Torre et al., 2004; Sessa et al., 2019).

Anestésicos disociativos:

Los anestésicos disociativos constituyen un grupo de sustancias cuyo perfil subjetivo se caracteriza por la interrupción de la integración sensorial, la alteración del sentido del cuerpo y del yo, y un marcado componente disociativo, entendido como la desconexión de la experiencia corporal y emocional (Sumner et al., 2021). Pertenecen a la clase química de las arilciclohexilaminas, y sus ejemplos principales son la ketamina y la fenciclidina (PCP) Su mecanismo de acción principal es el antagonismo del receptor NMDA (N-metil-D-aspartato), un subtipo de receptor glutamatérgico. Al bloquear la transmisión excitatoria mediada por el glutamato en estos receptores, se interrumpe la coherencia de la actividad cortical, generando estados de desorganización funcional que se traducen en experiencias disociativas. Además del efecto sobre el receptor NMDA, estos compuestos modulan indirectamente la actividad de los receptores AMPA (α-amino-3-hidroxi-5-metil-4-isoxazolpropionato), otro subtipo glutamatérgico, mediando un aumento de la liberación de BDNF (factor neurotrófico derivado del cerebro) y la activación de mecanismos de neuroplasticidad dependientes de la proteína mTOR (*mechanistic Target of Rapamycin*). Desde un enfoque neurofuncional, también ejercen su efecto mediante la disrupción de la función de "filtro sensorial" ejercida por el tálamo (Johnston et al., 2023; Sattar et al., 2018).

Psicodélicos atípicos:

Aquí incluye un conjunto heterogéneo de sustancias con mecanismos de acción diversos, que no es posible incluir en otros apartados, capaces también de inducir EAC con propiedades terapéuticas o transformadoras. Por definición, esta clasificación no puede resultar exhaustiva debido al amplísimo catálogo de sustancias psicoactivas que existen en la naturaleza con la capacidad de inducir EACs, pero a continuación se mencionan aquellas sustancias más relevantes y de interés académico:

- Salvinorina A, un agonista selectivo de los receptores opioides kappa (KOR), de acción breve pero extremadamente intensa (Brito-da-Costa et al., 2021).

- Ibogaína, un alcaloide con efectos complejos que incluyen modulación serotoninérgica, dopaminérgica, noradrenérgica y del sistema NMDA, así como potentes efectos antiadictivos y neuroplastógenos, observados en estudios preliminares (Ona et al., 2023).
- Óxido nitroso, un gas inhalado de acción rápida, con efecto disociativo y euforizante, mediado por la inhibición del receptor NMDA y la modulación del sistema opioide endógeno (Emmanouil & Quock, 2007).
- Las plantas del género *Cannabis* (principalmente *Cannabis sativa* y *Cannabis indica*) no se han considerado psicodélicas en sentido estricto pero el cannabis con alto contenido en tetrahidrocannabinol (THC) presenta propiedades psicoactivas que, en determinadas condiciones, pueden inducir experiencias subjetivas similares a las psicodélicas, y que estarían mediadas por el agonismo del receptor CB1 (Wolinsky et al., 2024).

A pesar de esta clasificación, es importante subrayar que la acción sobre un único tipo de receptor o vía neuroquímica no basta para explicar los efectos subjetivos ni los resultados terapéuticos observados con estas sustancias. El modelo farmacológico tradicional resulta insuficiente ante compuestos cuya eficacia depende en gran medida del contexto, la experiencia subjetiva y la integración posterior. Por tanto, esta categorización debe considerarse como un esquema orientativo y provisional, funcional y no taxonómico, que ha de servir para orientar el estudio de estas sustancias y facilitar su comprensión, a la espera de modelos integradores que articulen los niveles farmacológico, psicológico y fenomenológico de manera más coherente y permitan clasificaciones más exhaustivas y sistemáticas. Sin embargo, se recomienda tener en cuenta que estas sustancias pueden presentar mecanismos múltiples y solapamientos interclase.

Tabla 1 Clasificación farmacológica de las principales sustancias psicodélicas

Grupo	Sustancias principales	Mecanismo de acción predominante	Características fenomenológicas y terapéuticas
Psicodélicos clásicos	Psilocibina, LSD, DMT, 5-MeO-DMT, Mescalina	Agonismo 5-HT2A; activación de cascadas intracelulares que incrementan BDNF y mTOR	Alteraciones perceptivas, disolución del ego, experiencias místicas, reorganización de redes funcionales, alta plasticidad
Entactógenos (empatógenos)	MDMA, MDEA	Liberación masiva de 5-HT (inversión de SERT), DA y NA; liberación de oxitocina; disminución de reactividad amigdalar	Apertura emocional, aumento de la empatía, facilitación del vínculo terapéutico y del procesamiento de material traumático
Anestésicos disociativos	Ketamina, PCP	Antagonismo NMDA; potenciación de receptores AMPA; incremento de BDNF; activación de mTOR; disrupción del filtro talámico	Disociación, sensación extracorporal, reducción del dolor emocional, efectos antidepresivos rápidos y plasticidad sináptica
Psicodélicos atípicos	Salvinorina A, Ibogaína, Óxido nitroso, Cannabis (alto THC)	Mecanismos diversos: KOR (salvinorina), múltiples (ibogaína), NMDA y opioides (óxido nitroso), CB1 (THC)	EAC breves, intensos o visionarios; propiedades antiadictivas (ibogaína); experiencias místicas; efectos muy dependientes del contexto

1.3 Mecanismos de acción fisiológicos.

Las sustancias psicodélicas presentan mecanismos de acción multifacéticos que operan a distintos niveles fisiológicos y neurobiológicos, cuya interacción no ha sido aun plenamente dilucidada. En este sentido, el estudio de los mecanismos fisiológicos de los psicodélicos no debe limitarse a una única diana farmacológica, sino que requiere comprender cómo interactúan distintas capas funcionales del organismo, y es importante considerar que es poco probable que un solo mecanismo de acción explique completamente sus efectos, no siendo posible reducir o explicar completamente un mecanismo de orden superior, en base a otro de orden inferior. Esto no es sorprendente,

ya que la mente y el organismo humano son sistemas dinámicos cuyos componentes están conectados íntimamente de manera interrelacionada, por lo que toda separación o demarcación de sus componentes ha de ser entendida con propósitos conceptuales, pero teniendo siempre en cuenta que no existe una diferencia ontológica real (Scheffer et al., 2024) Frente a perspectivas reduccionistas que proponen un enfoque estrictamente ascendente, desde la acción molecular hasta los efectos clínicos, la evidencia actual sugiere que los efectos terapéuticos de los psicodélicos resultan de la interacción sinérgica entre procesos de distinto orden (Acero et al., 2023). Los mecanismos de acción fisiológicos más relevantes descritos hasta la fecha incluyen:

- Disrupción de las redes neuronales y aumento de la entropía

Las redes neuronales son sistemas altamente interconectados de neuronas que cumplen funciones específicas y presentan una distribución jerárquica. Si bien los mecanismos de acción farmacológicos de los distintos psicodélicos varían, todos ellos parecen compartir efectos característicos sobre estas redes, caracterizados por una reducción en la segregación entre redes cerebrales, permitiendo mayor comunicación entre regiones que normalmente están desconectadas. Bajo los efectos de los psicodélicos, las redes cerebrales del cerebro se desintegran y desagregan funcionalmente, es decir, disminuye la actividad de corta distancia dentro de la red y aumenta la actividad de larga distancia entre redes. Esta alteración de la actividad coordinada y jerárquica en todas las redes provoca un aumento de la entropía, es decir, la incertidumbre y el número de estados posibles dentro de un sistema. Además, los sistemas de jerarquía superior pierden su capacidad de regular la información que llega desde niveles inferiores (regulación "top-down"), lo cual facilita que nueva información pueda generar cambios y actualizar estos sistemas de orden más alto (Bharmauria et al., 2024; Kwan et al., 2022).

- Plasticidad neuronal

A nivel celular, las sustancias psicodélicas son potentes compuestos que inducen la neuroplasticidad, es decir, psicoplastógenos. La neuroplasticidad es la capacidad de una neurona para reorganizar sus conexiones y funciones, ejercida a través de cambios en las sinapsis con otras neuronas. Se ha observado que las sustancias psicodélicas pueden aumentar la neuritogénesis, la espinogénesis y la sinaptogénesis, facilitando tanto la

creación de nuevas conexiones entre neuronas, como modulando la eficiencia de las sinapsis preexistentes (Agnorelli et al., 2025). La evidencia preliminar apunta a que las moléculas psicodélicas podrían ejercer estos efectos mediante el agonismo de receptores intracelulares (Vargas et al., 2023). Este fenómeno podría constituir un mecanismo biológico autónomo que prepara el cerebro para integrar nuevos aprendizajes, facilitando procesos de cambio rápidos, profundos y duraderos (Nardou et al., 2023).

- Modulación neuroendocrina

Los psicodélicos modulan de forma significativa el eje hipotalámico-pituitario-adrenal (HPA), promoviendo una liberación aguda de cortisol, prolactina y otras hormonas relacionadas con el estrés y la adaptación emocional. Este efecto se ha documentado para compuestos como la ketamina, el LSD, la psilocibina y el MDMA, y parece estar mediado por la estimulación serotoninérgica de neuronas hipotalámicas productoras de CRF (factor liberador de corticotropina) (Schindler et al., 2018; Van Berckel et al., 1998). Además, compuestos como el MDMA y la psilocibina incrementan los niveles de oxitocina, lo cual podría estar vinculado con su capacidad de facilitar la apertura emocional y la conexión interpersonal (Heifets & Olson, 2023). Esta modulación hormonal puede tener efectos directos sobre la homeostasis emocional, la plasticidad neuroendocrina y los procesos inmunorreguladores (Acero et al., 2023).

- Inmunomodulación

Los psicodélicos clásicos, la MDMA y la ketamina presentan efectos antiinflamatorios e inmunomoduladores, si bien sus mecanismos de acción y contextos de actuación difieren entre sí. Los psicodélicos clásicos (como el LSD, la psilocibina y la DMT) tienden a reducir los niveles de citocinas (como TNF-α, IL-6) y la promoción de citocinas antiinflamatorias (como IL-10), mediante mecanismos mediados por los receptores 5-HT2 y el receptor sigma-1 (Low et al., 2025). Por su parte, la ketamina ha demostrado de manera consistente su capacidad para suprimir citocinas proinflamatorias como la IL-6 y el TNF-α, inhibir la vía de señalización NF-κB, y atenuar las respuestas inflamatorias, lo cual contribuye a sus efectos antiinflamatorios y potencialmente neuroprotectores (Zunszain et al., 2013). La modulación del sistema inmune podría ser particularmente

relevante en trastornos donde la inflamación crónica de bajo grado desempeña un papel patogénico, como la depresión (Barron et al., 2017; Cui et al., 2019; Miller et al., 2018).

- Modulación Glial

Las células gliales son indispensables para la función cerebral saludable. Regulan la formación y transmisión sináptica, a la vez que brindan soporte metabólico a las neuronas, e incluso se está estudiando su rol como sustrato de la consciencia (Butt & Verkhratsky, 2018). Estudios recientes muestran los psicodélicos no solo actúan a nivel neuronal, sino que también modulan la funcionalidad de las células gliales, en especial los astrocitos y la microglía. Se ha documentado un aumento en el tamaño y la complejidad morfológica de los astrocitos tras la administración de ketamina (Stenovec, 2021), si bien sus efectos sobre esta población celular también podrían modular los efectos neurotóxicos observados tras dosis elevadas y repetidas (Choudhury et al., 2021). Los psicodélicos clásicos, a su vez, activan poblaciones celulares heterogéneas en la corteza cerebral, incluidas astrocitos y oligodendrocitos, como se ha evidenciado por el aumento en la expresión de genes de respuesta temprana (cFos) tras la administración de LSD y otros compuestos (Martin & Nichols, 2016). En caso de la ibogaína, se ha documentado un aumento de la expresión del factor neurotrófico derivado de células gliales y es necesaria y suficiente para mediar los efectos antiadictivos (GDNF) (Marton et al., 2019).

- Epigenética

Los procesos epigenéticos, es decir, la regulación de la expresión génica y la traducción de proteínas mediante la metilación del ADN, la modificación de histonas y la degradación o supresión del ARNm, se están considerando como un mecanismo potencial en la mediación de la vulnerabilidad duradera a los trastornos psicológicos y fisiológicos. Por ejemplo, las experiencias traumáticas, sobre todo a edades tempranas, condicionan cambios epigenéticos que podrían justificar una mayor vulnerabilidad al estrés y la aparición de trastornos metabólicos (Grezenko et al., 2023). La evidencia actual sugiere que los psicodélicos pueden influir en estos procesos: por ejemplo, el LSD ha demostrado alterar la metilación de ADN hasta en 635 sitios y modificar la expresión de genes asociados a la plasticidad sináptica y la arquitectura citoesquelética (Inserra et al., 2022). Por otro lado, un estudio piloto reciente encontró que los cambios en la metilación del

gen NR3C1 para el receptor de glucocorticoides, se asociaron con la respuesta al tratamiento con MDMA para el trastorno por estrés postraumático, lo cual también ocurre con otros tratamientos eficaces para este trastorno (Lewis et al., 2023). Estas modificaciones podrían contribuir a explicar la duración prolongada de los efectos terapéuticos observados tras una única dosis, al inducir una reorganización estable en los patrones de expresión génica.

- Microbiota

La interacción bidireccional entre el sistema nervioso central y la microbiota intestinal (eje intestino-cerebro) se reconoce actualmente como un componente clave de la salud mental (Santos et al., 2025) y está siendo objeto de numerosas investigaciones, dado su papel clave para modular funciones neuroendocrinas, inmunitarias y conductuales (Acero et al., 2023). Estudios preclínicos han mostrado que el LSD y la ketamina alteran la diversidad y abundancia de ciertas especies bacterianas intestinales (De La Fuente Revenga et al., 2021; Getachew et al., 2018), lo cual podría actuar como mecanismo modulador sinérgico con los demás mecanismos fisiológicos descritos.

1.4 Fenomenología de las experiencias psicodélicas

Como se ha señalado previamente, los psicodélicos se definen por su capacidad para inducir alteraciones agudas del estado de conciencia, por lo que estudiar las características de sus efectos subjetivos resulta esencial para comprenderlos. El contenido de estas vivencias es de una enorme riqueza y complejidad. A veces, resulta tan alejado del estado ordinario de conciencia que aparecen serias dificultades para su expresión verbal siendo la "inefabilidad" uno de los rasgos fenomenológicos más reiterados. Esta dificultad se ve agravada por el hecho de que, históricamente, la cultura occidental moderna ha marginado o medicalizado los estados no ordinarios de conciencia, fruto de una herencia sociocultural y religiosa que tiende a privilegiar la racionalidad lineal y el estado de vigilia estándar (Yaden & Newberg, 2022). Como consecuencia, existe una escasez de lenguaje compartido para describir estas experiencias en nuestra tradición cultural, a diferencia de otros sistemas simbólicos, como las cosmologías chamánicas o las tradiciones contemplativas orientales, que no solo han reconocido estos estados, sino que los han

cultivado deliberadamente como vías legítimas de conocimiento, transformación y sanación (Eliade, 1974; Huang, 2019).

Con frecuencia se ha recurrido a la sinergia con estas perspectivas espirituales para facilitar la comprensión, integración y uso de los estados alterados de conciencia; si bien esto puede resultar de una utilidad esencial para facilitar procesos terapéuticos y transformativos, puede interferir con el estudio sistemático de estas experiencias, dado que implica la asunción de narrativas y cosmologías diferentes, específicas y apriorísticas sobre su significado y naturaleza. Por otro lado, una de las características más distintivas de la experiencia psicodélica es su elevada dependencia del contexto; esto significa que está modulada por factores como la sustancia específica, la dosis administrada, las características del individuo (historia personal, expectativas, estado emocional) y el contexto físico y relacional en el que se produce la experiencia, lo cual dificulta predecir el contenido de una experiencia psicodélica concreta y plantea desafíos metodológicos importantes para su estudio sistemático.

Para superar estos obstáculos, se ha recurrido a abordajes procedentes de la filosofía, como la fenomenología, que busca describir las experiencias subjetivas de la manera más objetiva y minuciosa posible, y la psicometría, que trata de categorizar dimensiones invariantes de la experiencia, presentes de manera constante entre individuos. Esto ha permitido desarrollar herramientas, como entrevistas semiestructuradas o instrumentos psicométricos, que permiten analizar y categorizar las experiencias subjetivas de manera más rigurosa, e identificar una serie de dimensiones fenomenológicas transversales, que se resumen a continuación (Preller & Vollenweider, 2016):

- Alteraciones perceptivas

Durante los estados psicodélicos agudos, los estímulos sensoriales se experimentan como intensificados, adquiriendo una cualidad vívida, compleja o profundamente significativa, lo que puede incluir una hipersensibilidad a la luz, el sonido o el tacto. Con frecuencia se producen distorsiones marcadas en la percepción del tiempo y el espacio: el tiempo puede percibirse como extremadamente lento, acelerado, cíclico o abolido por completo, mientras que el espacio puede curvarse, contraerse o adoptar cualidades abstractas, fluidas o fractales. En muchos casos se presenta sinestesia, una fusión de modalidades sensoriales en la que los límites entre percepción auditiva, visual o táctil se difuminan,

dando lugar a experiencias como “ver sonidos” o “saborear colores”. Otro fenómeno común es la geometrización visual, consistente en la aparición de patrones caleidoscópicos o fractales en la visualización con los ojos cerrados o incluso abiertos, que evolucionan dinámicamente y tienden a seguir una progresión rítmica. Asimismo, se producen alteraciones en la propiocepción y en el esquema corporal, que pueden oscilar entre sensaciones de expansión, contracción, ligereza, pérdida de límites físicos o levitación. Estas distorsiones del cuerpo propio alcanzan su expresión más característica bajo el efecto de anestésicos disociativos como la ketamina, en los que la experiencia de separación entre la mente y el cuerpo puede ser especialmente intensa, dando lugar a fenómenos de disolución corporal o experiencias extracorpóreas (Kolp et al., 2014).

- Disolución y expansión del ego

La disolución del ego constituye uno de los fenómenos más paradigmáticos y clínicamente relevantes. En su forma positiva, se caracteriza por la disolución de las fronteras del yo, fusión con el entorno, trascendencia del espacio-tiempo y sentimientos de sacralidad o unidad universal. Estas experiencias pueden asimilarse a lo que Freud describió como “Experiencia oceánica”, y también con las experiencias místicas descritas en múltiples corrientes religiosas y espirituales. Parece que su presencia es uno de los predictores transdiagnósticos más robustos de mejoría en personas que reciben un tratamiento basado en sustancias psicodélicas (Barrett & Griffiths, 2017). Esta experiencia, sin embargo, también puede tener una valencia emocional negativa (disolución del ego ansiosa) que puede manifestarse como pérdida de control, paranoia, despersonalización o pánico, típicamente asociada a los llamados “bad trips” (Preller & Vollenweider, 2016).

- Cambios en la cognición

Las funciones cognitivas también se ven profundamente modificadas; se ha descrito un deterioro transitorio en la atención sostenida, la memoria de trabajo y la capacidad de seguimiento de tareas, mientras que otras funciones ejecutivas, como la metacognición, pueden mantenerse o incluso intensificarse de forma no convencional. Por otro lado, es frecuente la aparición de asociaciones inusuales de ideas o conceptos. Esto ha dado lugar a un debate sobre su posible rol en la creatividad, sustentado por las afirmaciones

anecdóticas sobre su papel en ciertos descubrimientos científicos y obras artísticas, sin hallazgos que sustenten claros beneficios (M. Â. Costa, 2023).

- Alteraciones emocionales

Los estados emocionales suelen amplificarse durante la experiencia psicodélica y adquirir una intensidad y profundidad difícilmente comparables con las vivencias emocionales cotidianas. Pueden incluir sentimientos eufóricos, de gratitud profunda, compasión expansiva y amor incondicional, pero también emociones difíciles como la ansiedad, el miedo o la vulnerabilidad extrema. La valencia emocional de una experiencia psicodélica puede variar mucho a lo largo del tiempo; se ha postulado que la resolución de emociones difíciles, con la posterior aparición de emociones agradables, puede ser otro factor terapéutico relevante, asimilable a las catarsis emocionales teorizadas por el psicoanálisis, e incluso se ha desarrollado un instrumento psicométrico orientado a medir este evento (Roseman et al., 2019). En muchos casos, el sujeto experimenta estados de asombro existencial, reverencia o sacralidad ante la propia vida o el mundo, descritos a menudo en términos espirituales o trascendentes, más allá del lenguaje ordinario. Esta dimensión emocional se traduce con frecuencia en incrementos de la empatía, que se traducen en experiencias de conexión profunda con otras personas y seres vivos, con la naturaleza o con una totalidad mayor, especialmente en el caso del MDMA (Kamilar-Britt & Bedi, 2015).

Por otro lado, además de presentar dimensiones específicas, el curso habitual de la experiencia psicodélica también sigue una progresión dinámica que puede dividirse en varias fases sucesivas (Preller & Vollenweider, 2016). En primer lugar, se produce una fase inicial de intensificación sensorial, caracterizada por un aumento de la percepción de estímulos visuales, auditivos y somáticos. A medida que avanza la experiencia, emergen contenidos psicológicos profundos, a menudo de naturaleza emocional o autobiográfica, en lo que puede considerarse una fase psicodinámica o simbólica, donde se facilita el acceso a recuerdos, emociones reprimidas o conflictos existenciales. En las fases más intensas, muchos individuos reportan experiencias de disolución del ego o trascendencia del yo, frecuentemente acompañadas de un sentimiento de unidad, sacralidad o comunión con una totalidad mayor. Finalmente, la experiencia tiende a transitar hacia una fase de

resolución, caracterizada por un tono emocional más calmado y una mayor claridad reflexiva, que permite elaborar e integrar lo vivido. Esta progresión no es rígida ni universal, pero constituye un esquema útil para comprender la dinámica temporal de los estados psicodélicos y su relevancia clínica potencial.

Tanto la clasificación dimensional de la experiencia psicodélica como la descripción de su curso se basan, en gran medida, en el uso de escalas psicométricas autoadministradas. Aunque estas herramientas han permitido avanzar en la comprensión sistemática de los efectos subjetivos de los psicodélicos, presentan limitaciones importantes. Una de las principales críticas es que las medidas actuales podrían no captar adecuadamente toda la riqueza fenomenológica de la experiencia, al estar ancladas en constructos preconcebidos y escalas validadas en poblaciones específicas, a menudo occidentales, educadas y familiarizadas con el lenguaje espiritual o místico (Hovmand et al., 2023). Además, al pedir a los participantes que recuerden y evalúen experiencias pasadas, se introducen sesgos de memoria y expectativas, así como el riesgo de sobreponderar ciertos aspectos que se ajustan al contenido de las preguntas, ignorando otros igualmente significativos, pero no recogidos por el instrumento.

Por otro lado, metodologías cualitativas como la microfenomenología (Petitmengin, 2006) ofrecen una vía más abierta para capturar con precisión la vivencia en su totalidad, permitiendo reconstruir el flujo temporal de la experiencia, identificar elementos nuevos o inesperados, y explorar dimensiones poco accesibles desde escalas estandarizadas. Sin embargo, estas entrevistas en profundidad no permiten fácilmente la cuantificación ni la comparación entre participantes o estudios, y pueden carecer de utilidad clínica directa si no se vinculan con variables terapéuticamente relevantes. En este sentido, se hace evidente la necesidad de instrumentos que integren lo mejor de ambos enfoques: la riqueza descriptiva de los métodos cualitativos y la aplicabilidad clínica y comparativa de las herramientas cuantitativas. Según Yaden et al. (Yaden et al., 2024), la propuesta más prometedora pasa por una nueva generación de medidas psicométricas construidas a partir de marcos teóricos explícitos, validadas empíricamente, y sensibles a la diversidad cultural. Estas medidas deberían captar tanto aspectos positivos como desafiantes de la

experiencia, con el objetivo de avanzar hacia una comprensión más completa, precisa y clínicamente útil de los efectos subjetivos agudos de estas sustancias.

Finalmente, la fenomenología psicodélica representa una oportunidad privilegiada para explorar la conciencia, y establecer relaciones significativas entre hallazgos empíricos y experiencias en primera persona. En este sentido, la investigación reciente ha empezado a adoptar marcos metodológicos más integradores, como la neurofenomenología, que busca correlacionar los cambios en el contenido y la estructura de la experiencia subjetiva con la dinámica neuronal subyacente (Timmermann et al., 2023). Desde este paradigma, utilizar los estados psicodélicos como modelos de investigación se constituye en una herramienta poderosa para perturbar estructuras estables de la experiencia, como el sentido del yo, el dolor, el tiempo o la agencia, y observar los cambios neurales asociados a estas experiencias en tiempo real.

En última instancia, la investigación fenomenológica rigurosa de estos estados amplía el repertorio experiencial disponible para la ciencia y permite refinar nuestra comprensión de los procesos de cambio subjetivo profundo; esto ha permitido elaborar atlas cada vez más detallados de la conciencia, y podría ser la clave para resolver incógnitas fundamentales (Metzinger, 2024). En el contexto terapéutico, esta información no solo es relevante para interpretar los efectos de las sustancias, sino también para diseñar intervenciones más eficaces y personalizadas. Actualmente, existe un debate en marcha sobre la relevancia de la experiencia psicodélica para sus efectos terapéuticos. Si bien la evidencia actual es abrumadora (Yaden & Griffiths, 2021), algunos autores se sustentan en abordajes reduccionistas para proponer que se trata de epifenómenos innecesarios, defendiendo que los mecanismos biológicos subyacentes son suficientes para explicar los cambios positivos observados (Goodwin et al., 2024). Para abordar este debate, resulta fundamental entender la relación entre los diversos niveles explicativos de las sustancias psicodélicas (fenomenológico, neurobiológico y psicológico).

1.5 Mecanismos de acción psicológicos de los psicodélicos

Además de inducir cambios profundos en la fenomenología de la conciencia y en diversos sistemas neurofisiológicos, las sustancias psicodélicas parecen desencadenar procesos

psicológicos significativos que pueden persistir en el tiempo y explicar en gran medida sus beneficios terapéuticos (Weiss et al., 2024). Dado que estos mecanismos también se evalúan utilizando medidas subjetivas, frecuentemente mediante instrumentos psicométricos, resulta complejo estudiarlos de manera separada a las experiencias fenomenológicas puras, y algunos autores han planteado su identidad, defendiendo que estas experiencias tienen un valor terapéutico psicológico per se. Por ejemplo, las experiencias místicas se han propuesto como mecanismo terapéutico fundamental en la terapia asistida con psilocibina (Ko et al., 2022). Sin embargo; en ausencia de datos y abordajes teóricos que expliquen *por qué* estas experiencias son terapéuticas, estos hallazgos no pueden dotarse de un valor más allá de una correlación estadística con cierto poder predictivo. Por eso es fundamental comprender la relación y la diferencia entre mecanismo psicológico y fenomenología: mientras que las experiencias subjetivas inducidas por psicodélicos constituyen vivencias específicas que ocurren durante el estado agudo, los mecanismos psicológicos son procesos generales transversales, responsables de cambios duraderos sobre los patrones de pensamiento y comportamiento de las personas (Koch & Cratsley, 2020). Para entender y utilizar de manera terapéutica ambos aspectos de la acción de las sustancias psicodélicas, es necesario abordarlos por separado y explorar su relación, que puede ser bidireccional: ciertas experiencias podrían activar determinados mecanismos psicológicos, pero también la presencia de los últimos podría facilitar experiencias concretas. Dentro de los mecanismos psicológicos implicados, dos constructos han sido identificados como especialmente relevantes y transdiagnósticos: la flexibilidad psicológica y la atribución de significado. Aunque ambos mecanismos están profundamente entrelazados, ya que una mayor flexibilidad psicológica puede facilitar la resignificación de experiencias vitales y viceversa, resulta útil considerarlos separadamente para clarificar su estudio y comprensión.

- Flexibilidad psicológica

La flexibilidad psicológica se define como la capacidad de permanecer en contacto con la experiencia del momento presente, sin evitar el malestar, y de actuar de manera coherente con los propios valores personales. Este constructo, central en la Terapia de Aceptación y Compromiso (ACT), se operacionaliza mediante seis procesos: aceptación, defusión cognitiva, atención al presente, yo como contexto, clarificación de valores y

acción comprometida. Su relevancia terapéutica ha sido ampliamente demostrada en poblaciones con ansiedad, depresión, trauma y dolor crónico. En términos funcionales, una mayor flexibilidad psicológica permite a los individuos afrontar el malestar y la incertidumbre sin recurrir a estrategias de evitación, favoreciendo la adaptación a circunstancias cambiantes y la regulación emocional efectiva (Kashdan & Rottenberg, 2010; Rolffs et al., 2018).

La evidencia emergente sugiere que los psicodélicos pueden facilitar cambios profundos en la flexibilidad psicológica, lo que en parte explicaría sus efectos terapéuticos, ya que se correlacionan con reducciones en sintomatología depresiva, ansiosa y postraumática, así como con un incremento en el bienestar general (Agin-Liebes et al., 2022; Davis et al., 2020, 2021). Para entender cómo estas sustancias pueden promover la flexibilidad psicológica, el modelo *Learning to Let Go* ("aprender a soltar") (Wolff et al., 2020) propone que las personas que atraviesan una experiencia psicodélica se ven expuestas a experiencias internas intensas e ineludibles. Durante el estado psicodélico, la percepción de pensamientos, emociones y sensaciones se intensifica, lo que obliga a enfrentar este material sin recurrir a la evitación. Si la persona logra adoptar una actitud de apertura en lugar de resistencia, puede aprender que las emociones difíciles no necesitan ser suprimidas o controladas. Este proceso facilita una reestructuración cognitiva, reinterpretando experiencias desde una perspectiva más compasiva o menos autocentrada. Además, la neuroplasticidad aumentada tras la experiencia facilitaría la consolidación de estos aprendizajes, haciendo que la respuesta de aceptación sea más accesible en la vida cotidiana. La relevancia de este modelo estriba en su potencial para establecer conexiones causales entre los distintos niveles explicativos, ya que incorpora elementos relacionados con el sustrato fisiológico, como la neuroplasticidad, y respalda la importancia de ciertas características relacionadas con la experiencia subjetiva. Además, para evaluar la pertinencia de este modelo teórico, y explorar su utilidad para optimizar resultados terapéuticos, se ha desarrollado el *Acceptance/Avoidance-Promoting Experiences Questionnaire (*Cuestionario de experiencias que promueven la evitación o el afrontamiento, *APEQ)* (Wolff et al., 2022)). Este cuestionario, desarrollado originalmente en inglés y alemán, mide la frecuencia e intensidad de experiencias que fomentan la aceptación (*Acceptance-Promoting Experiences*, ACE) y la evitación (*Avoidance-*

Promoting Experiences, AVE) durante la experiencia psicodélica, así como su impacto posterior sobre la flexibilidad psicológica y bienestar. Los estudios iniciales han revelado que la presencia de ACEs se asocia con mejoras en flexibilidad psicológica y bienestar, mientras que la presencia de AVEs se correlaciona con efectos negativos. Estos hallazgos no sólo respaldan el modelo, sino que proporcionan una potencial forma de evaluar la presencia de este mecanismo psicológico durante una experiencia psicodélica.

Finalmente, otros autores plantean que el sentido del yo es fundamental para la flexibilidad psicológica, y proponen que las alteraciones en esta esfera por los psicodélicos podrían explicar las mejoras observadas sobre la flexibilidad psicológica, justificando el rol terapéutico de las experiencias místicas y la disolución del ego y planteando un nuevo nexo causal entre fenomenología y mecanismo psicológico. En esencia, estos cambios fortalecerían la capacidad de adoptar una perspectiva más amplia y menos crítica sobre uno mismo, promoviendo la aceptación emocional y cognitiva (Hayes et al., 2020).

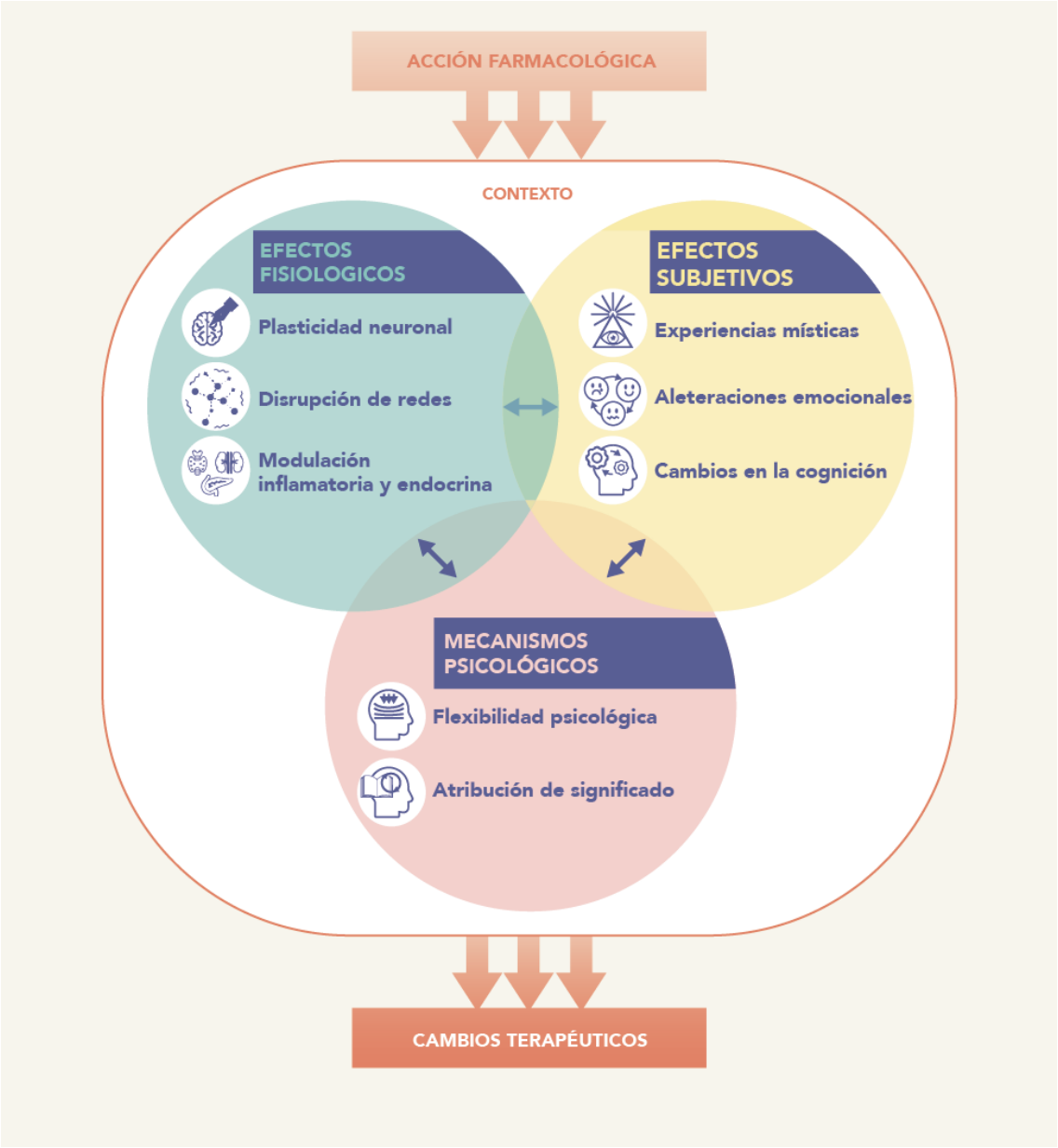
- Atribución de significado

Otro de los rasgos más característicos y consistentes de la experiencia psicodélica es la intensificación del significado que se le atribuye a la realidad percibida, entendiendo significado como la importancia que se le atribuye a los eventos, y su relación simbólica con otros aspectos de la realidad (Hartogsohn, 2018). Esta sensación de significado es un fenómeno reportado de manera recurrente en estudios sobre la experiencia psicodélica, con aproximadamente un 70-80% de los participantes en entornos clínicos o terapéuticos describiendo su experiencia como una de las cinco más significativas de sus vidas, comparable a eventos trascendentales como el matrimonio o la parentalidad, lo cual a su vez parece predecir sus efectos terapéuticos (Roseman et al., 2018). Los motivos por los que este mecanismo psicológico está tan presente durante la experiencia psicodélica no se comprenden completamente, pero podría tener relación con diversos aspectos. Por un lado, parece que la amplificación emocional juega un papel destacado: las emociones son experiencias subjetivas muy complejas, pero todas comparten una valencia positiva o negativa, y sirven para codificar la importancia de los eventos que los causan, y adaptar las conductas y las creencias en relación a ello. Así pues, una experiencia con una

importante carga emocional será codificada como más valiosa a la hora de condicionar nuestra repuesta a ella. Además, la elicitación de memorias e ideas novedosas permite colocar estos eventos mentales a la luz de esta amplificación emocional, de tal modo que experiencias que anteriormente no se consideraban especialmente significativas o contaban con una carga emocional determinada, pueden modificar su repercusión afectiva y ser reconceptualizadas de esta manera dentro de la narrativa personal del individuo. Por otro lado, con frecuencia la experiencia psicodélica es percibida como profundamente real, más incluso que la realidad convencional, lo cual incrementa la importancia atribuida. Este aspecto, denominado frecuentemente "cualidad noética", resulta en la convicción de veracidad de lo percibido sin necesidad de demostrarlo a través del razonamiento. Esta "noesis" escapa al método empírico científico y por tanto ha sido despreciada o descartada por la ciencia académica, y sin embargo resulta fundamental para comprender aspectos centrales de la dimensión humana, como la fe. Esto plantea algunos conflictos que podrían también tener efectos negativos para la persona y que se discutirán posteriormente; sin embargo, también permite explicar en parte este mecanismo de atribución de significado, ya que permite incrementar la importancia atribuida a las experiencias psicodélicas, por encima de las experiencias ordinarias (Wahbeh et al., 2022).

Como resultado de estos posibles elementos subyacentes, los estímulos, pensamientos y recuerdos, tanto pasados como presentes, adquieren una relevancia inusualmente elevada, lo que puede transformar la narrativa personal del individuo y permitir una reinterpretación de su historia vital, y el impacto que ésta tiene sobre su experiencia subjetiva. Pese a que la bibliografía actual soporta este mecanismo como un núcleo fundamental que subyace a los cambios observados en la experiencia psicodélica (Roseby et al., 2025), resulta complejo explorar de manera directa y aislada su presencia, dado que por necesidad su impacto depende del contexto en que se produce (los eventos a los que se atribuye este significado ampliado), y se desconocen los mecanismos neurobiológicos específicos subyacentes. Esto desvela una necesidad no cubierta a la hora de comprender la acción de las sustancias psicodélicas y su impacto sobre la mente, y abre la puerta a explorar su dimensión a un nivel existencial y espiritual, más allá del mero alivio de síntomas (Hearn, 2021).

Ilustración 1- Efectos multinivel de las sustancias psicodélicas



1.6 Teorías unificadoras de los mecanismos de acción

Como se ha expuesto anteriormente, las sustancias psicodélicas inducen efectos sustanciales a nivel fisiológico, subjetivo y psicológico, que a su vez están fuertemente modulados por factores contextuales. Esto genera preguntas fundamentales sobre la conexión entre estos distintos niveles explicativos, reflejando el debate actual en psiquiatría y neurociencia acerca del sustrato de la conciencia, y representando una oportunidad única para explorar la relación entre la experiencia subjetiva y los sistemas

físicos subyacentes, una cuestión fundamental para la ciencia (Yaden et al., 2021). Para abordar esta complejidad se han propuesto teorías integradoras, que buscan ofrecer marcos conceptuales coherentes que articulan los múltiples mecanismos involucrados. Se trata de teorías abiertas que requieren de evidencia científica adicional que permita su calibración y mejoren su poder explicativo, pero resultan extremadamente prometedoras porque mantienen una alta coherencia interna, y plausibilidad biológica. Estas teorías, que se detallan a continuación, no deben considerarse como paradigmas que compitan entre sí; como se observará, comparten axiomas y tienen repercusiones similares. Más bien, resulta recomendable entenderlas como narrativas complementarias que pueden facilitar la comprensión de estas sustancias y establecer nexos causales que puedan ser aprovechados a nivel terapéutico; así, estas teorías buscan comprender la interacción entre los distintos efectos observados tras la administración de una sustancia psicodélica (fisiológicos, subjetivos y psicológicos).

- ***Relaxed Beliefs Under Psychedelics*** **(Creencias relajadas bajo los psicodélicos, REBUS)**

Para comprender esta teoría, resulta fundamental explorar los dos pilares sobre los que se sustenta: por un lado, se plantea que la conciencia fluctúa a lo largo de un continuo entre estados altamente estructurados, como el pensamiento rígido o la rumiación (baja entropía) y estados caóticos o fluidos (alta entropía) (Carhart-Harris et al., 2014). Dicho de otro modo, la entropía cerebral refleja la flexibilidad cognitiva y la diversidad de estados mentales posibles. Por otro lado, la mente funciona como un sistema bayesiano que busca predecir el mundo, con la finalidad de adaptarse a los eventos externos e internos en función a modelos predictivos ("creencias") sobre el mundo que tienen una organización jerárquica, de tal manera que los de nivel superior influyen sobre otros, son más impermeables a nuevos datos recabados por el sensorio, e incluso modulan la percepción y la atención (Bubic, 2010).

En estados normales de vigilia, la actividad cerebral está estructurada de manera jerárquica, con redes como la Red Neuronal por Defecto (DMN) desempeñando un papel clave en la autorreferencialidad, la introspección y la estabilidad del sentido del yo. Este concepto surge de la teoría de la inferencia predictiva, que postula que la mente humana

funciona. Para ello, construye modelos jerárquicos con expectativas previas, o *priors*, que guían la interpretación de la información sensorial y cognitiva. En estados de baja entropía, estos modelos son muy rígidos y dominan la percepción, lo que puede llevar a la perseveración de creencias negativas o autolimitantes, y a ignorar nueva información que no se adecúa al modelo. Los modelos resultantes de estos estados codifican situaciones concretas en contextos específicos con mucha precisión, pero no son capaces de responder a situaciones novedosas y tienen dificultades para actualizarse o integrar información inesperada. Por el contrario, en los estados de alta entropía, los modelos son más flexibles y reactivos a información novedosa, facilitando su adaptación a los cambios, pero generando predicciones más generales, menos precisas, y más vulnerables a datos inesperados (Friston, 2010).

El modelo REBUS postula que los psicodélicos actúan mediante un incremento brusco y marcado en la entropía de la mente, que tiene como consecuencia una relajación de la organización jerárquica de los modelos predictivos cerebrales (priors), facilitando un procesamiento cognitivo y perceptivo más flexible y exploratorio. Este efecto tiene que ver con los mecanismos de acción de los psicodélicos a distintos niveles, no estando claro si es posible reducir alguno de estos niveles a los efectos de otro (Carhart-Harris & Friston, 2019). Desde un punto de vista biológico, el modelo REBUS se puede explicar por el efecto farmacológico a nivel receptorial de los psicodélicos, que induce una activación cortical generalizada que facilita el flujo de información entre distintas áreas cerebrales y redes neuronales, y altera su funcionamiento jerárquico. Esto repercute sobre el balance entre la información ascendente (bottom-up, procedente de la experiencia sensorial inmediata) y la información descendente (top-down, regulada por modelos cognitivos previos), permitiendo que la información sensorial y experiencial fluya con menos restricciones. A nivel subjetivo, estos cambios en la dinámica cerebral se reflejan en alteraciones profundas de la experiencia. La reducción en la rigidez de los modelos predictivos facilita una percepción del mundo menos estructurada, y el procesamiento aberrante de información. Por ejemplo, se producen fenómenos de sinestesia porque los estímulos acústicos son procesados por áreas visuales, o se altera la integración global y los filtros en el acceso de la información, lo que podría explicar fenómenos como la distorsión del tiempo y el espacio, la intensificación de la significación de estímulos

internos y externos, y la emergencia de experiencias místicas o de disolución del ego. También se facilitaría un mayor acceso a contenidos emocionales y memorias profundas. Desde este modelo, el mecanismo de flexibilidad psicológica puede entenderse como una consecuencia directa de la disminución de la rigidez en los modelos de alto nivel. La relajación de creencias previas facilita la revisión y reestructuración de narrativas personales, lo que se traduce en una mayor apertura a nuevas perspectivas y en una reducción de la influencia de patrones cognitivos desadaptativos, promoviendo cambios en la relación del individuo con su historia personal y sus reacciones ante estímulos internos y externos.

Por otro lado, el mecanismo de atribución de significado encuentra su base en la misma relajación de modelos predictivos, pero con implicaciones específicas en la interpretación subjetiva de la experiencia psicodélica. Las experiencias muy significativas tendrán más peso a la hora de actualizar un modelo predictivo, en un proceso asimilable al concepto de aprendizaje por refuerzo.

- Teoría de sistemas dinámicos

La teoría de sistemas dinámicos propone una nueva perspectiva para entender los trastornos mentales, inspirada en el estudio de sistemas complejos que cambian con el tiempo, como el clima o los ecosistemas. Desde la perspectiva de los sistemas dinámicos, los estados mentales se consideran estados con una cierta "resiliencia dinámica", que se puede imaginar como una "cuenca de atracción" dentro de un paisaje dinámico de estados posibles (Scheffer et al., 2024). Cuanto más grande y profunda sea la cuenca de un estado, más difícil será que un evento desplace el estado mental hasta otra posición de equilibrio relativo (por ejemplo, hacia aceptar la ansiedad en lugar de evitarla bebiendo, o utilizar otras estrategias más adaptativas). Esto explica por qué persisten a pesar de los esfuerzos para revertirlos, y también la tendencia a recidivar: el 60% de las personas volverán a presentar depresión mayor a lo largo de su vida tras recuperarse de un primer episodio, cifra que se eleva hasta el 90% tras tres o más episodios (Olaya et al., 2025). Esta "mala resiliencia" se debe a bucles de retroalimentación. Por ejemplo, un estado de ánimo deprimido puede llevar a una disminución de la actividad social y física, lo que a su vez deprime aún más el estado de ánimo; estos comportamientos se potenciarán a lo largo del tiempo mediante mecanismos de potenciación a largo plazo, dificultando cada vez más el

cambio hacia conductas más adaptativas (Frey & Morris, 1997). Sin embargo, los cambios entre estados mentales pueden ocurrir de manera brusca, en los llamados "puntos de inflexión" (*tipping points*). Estos puntos se alcanzan cuando la resiliencia del estado actual disminuye lo suficiente como para que una pequeña perturbación pueda desencadenar una transición a otro estado.

Desde este paradigma, los psicodélicos inducen una disminución de la profundidad de los atractores existentes, lo que permite al sistema explorar configuraciones alternativas de actividad y transitar entre distintos estados con mayor facilidad (Hipólito et al., 2023). Como se podrá intuir, esta teoría complementa REBUS y puede explicarse en sus términos: un incremento en la entropía se podría traducir en un aplanamiento de la "cuenca de atracción" y la transición del estado mental entre distintos estados posibles se puede asimilar con la fenomenología de la experiencia psicodélica y con la disminución de la modulación ejercida por modelos predictivos de jerarquía superior, resultando en una mayor flexibilidad psicológica.

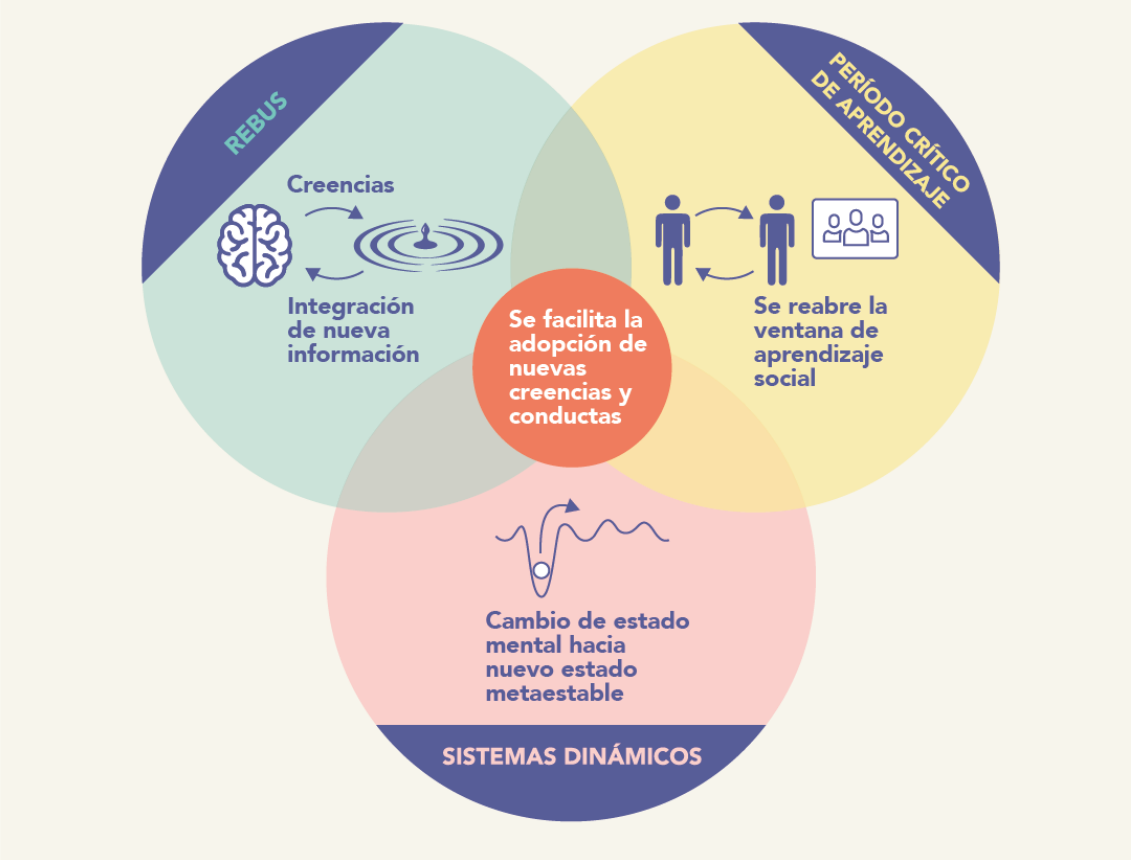
- Período crítico social de aprendizaje

Una aportación reciente y relevante propone que los psicodélicos actúan como inductores de períodos críticos sociales de aprendizaje, mediante la reactivación transitoria de estados de plasticidad neural típicos de períodos críticos del desarrollo temprano, caracterizados por una sensibilidad aumentada para adquirir aprendizajes sociales fundamentales. (Nardou et al., 2023). Desde este marco, los psicodélicos abrirían una ventana temporal en el cerebro adulto durante la cual patrones relacionales profundamente arraigados podrían modificarse significativamente, facilitando procesos similares a los observados durante la infancia y adolescencia temprana. A nivel neurobiológico, esta reapertura estaría mediada por cambios en la plasticidad sináptica y en la regulación de sistemas neuromoduladores como la serotonina y la oxitocina, fundamentales en el aprendizaje social y en el apego interpersonal (Nardou et al., 2019). De nuevo, esta teoría puede relacionarse con las descritas previamente, y permite describir mecanismos moleculares básicos sustentados en la plasticidad neuronal, que podrían subyacer los hallazgos fenomenológicos y psicológicos. Esto ha llevado incluso

a teorizar un mecanismo general, sustentado en la plasticidad, que podría explicar etiológicamente todos los trastornos mentales (Carhart-Harris et al., 2023).

En síntesis, las tres teorías coinciden en que los psicodélicos generan un estado neuropsicológico en el que el cerebro es excepcionalmente sensible al entorno emocional, relacional y cognitivo inmediato. Por tanto, para comprender los efectos terapéuticos o adversos, es necesario explorar también la influencia del contexto específico en el que se produce la experiencia.

Ilustración 2 - Teorías unificadoras de los efectos de las sustancias psicodélicas



1.7. La importancia esencial del contexto

Más allá de las consecuencias implicadas por los marcos teóricos expuestos previamente, toda la evidencia actual, tanto científica como clínica y experiencial, respalda la profunda implicación del contexto a la hora de explicar los efectos de las sustancias psicodélicas

(Carhart-Harris et al., 2018). Esto significa que no dependen exclusivamente de su farmacología, sino de la interacción entre las propiedades neurobiológicas de la sustancia y variables externas que modulan la experiencia subjetiva. La relevancia del contexto es una consecuencia esperable y fácilmente integrable dentro de los mecanismos de cambio y los modelos explicativos detallados previamente, ya que el incremento de la atribución de significado y flexibilidad inducidas se traducen en un estado de mayor sensibilidad al entorno, asimilables a una mayor influencia del procesamiento *bottom-up*, posibilitado por la desjerarquización de los modelos predictivos. Por otro lado, el impacto del contexto sobre los efectos de las sustancias y los tratamientos médicos no es algo restringido a los psicodélicos, ya que parece subyacer al efecto placebo, y estar presente en casi todas las intervenciones médicas (Blasi et al., 2001; Lucassen & Olesen, 2016). Sin embargo, la mayoría de los paradigmas científicos actuales consideran que esta influencia contextual es un factor aislable que debe ser minimizado. En el caso de los psicodélicos esto no parce posible, ya que esta influencia parece estar especialmente presente dados sus mecanismos específicos de acción, lo que plantea importantes consideraciones a tener en cuenta en su investigación y uso clínico: el contexto ha de ser tenido en cuenta como una parte integral a la hora de explicar sus efectos y controlar sus riesgos; la estructura y el acompañamiento pueden orientar la experiencia hacia una resolución adaptativa o por el contrario facilitar la aparición de efectos adversos. La misma desestabilización cognitiva que permite la reevaluación y el cambio puede dar lugar a estados de confusión, angustia o refuerzo de patrones patológicos preexistentes, y de hecho se ha planteado que la psicosis y el estado psicodélico podrían compartir mecanismos neurobiológicos similares (Brouwer & Carhart-Harris, 2020).

Por otro lado, uno de los factores contextuales fundamentales que requieren atención particular es la intersubjetividad y la conexión social. La experiencia psicodélica, tradicionalmente vinculada a ceremonias grupales en contextos indígenas y comunitarios, demuestra que la interacción social juega un papel crucial en el proceso terapéutico, tanto en la intensidad como en la persistencia de sus efectos beneficiosos. De acuerdo con el modelo de la "identidad social", la creación de un sentido compartido de identidad grupal durante estas experiencias puede potenciar significativamente la eficacia terapéutica, facilitando sentimientos de apoyo, pertenencia, confianza y propósito compartido

(Newson et al., 2024). Esta conexión social e intersubjetiva, frecuentemente descrita como "communitas psicodélica", se asocia con incrementos duraderos en el bienestar psicológico y la conexión social, mediada por fenómenos como la sincronía emocional percibida, la auto-revelación (*self-disclosure*) y la percepción de igualdad y unión entre participantes (Kettner et al., 2021). Este fenómeno no es nuevo, ya que ha sido observado en distintas culturas a lo largo de la historia, podría presentarse mediante otros métodos, como la danza y la música, y tendría también una función de cohesión social (Ehrenreich, 2007). La relevancia terapéutica de la intersubjetividad y la identidad social no sólo confirma la necesidad de considerar contextos grupales para maximizar el potencial terapéutico de estas sustancias, sino que también sugiere vías específicas de investigación e intervención clínica orientadas a cultivar explícitamente esta dimensión social como parte integral del tratamiento psicodélico.

Finalmente, la importancia del contexto plantea un importante desafío metodológico para la investigación según los estándares actuales, donde la validez de los ensayos clínicos tradicionalmente depende de la comparación entre una intervención activa y un placebo inerte, buscando aislar el efecto de la intervención de cualquier factor contextual ajeno. En el caso de los psicodélicos, esta distinción se vuelve artificial, y sugiere la necesidad de repensar los paradigmas metodológicos convencionales, integrando modelos que reconozcan el papel del significado y la experiencia subjetiva en los procesos de cambio psicológico. En lugar de tratar de dislocar el contexto de la intervención, se hace necesario explorar estrategias que permitan manipular el contexto para buscar efectos o sinergias específicos. Por ejemplo, el uso de la música parece ser una herramienta fundamental que modula los efectos terapéuticos de las sustancias psicodélicas (Kaelen et al., 2018). Para afrontar este desafío, se plantea evaluar la influencia específica de distintos contextos, reportando de manera sistemática sus características y abordando su posible efecto moderador sobre los resultados clínicos, para lo cual se han elaborado guías clínicas y consensos (Pronovost-Morgan et al., 2025).

2. Implicaciones clínicas para la psiquiatría

Hasta ahora, se han detallado los mecanismos de acción de los psicodélicos desde una perspectiva multinivel, buscando la comprensión de sus efectos sobre la mente humana. Estos mecanismos son novedosos, y su relación con cambios en síntomas y marcadores clínicos permite expandir nuestra comprensión sobre la salud mental o el sustrato de la conciencia. En concreto, su eficacia transdiagnóstica obliga a reconceptualizar nuestras teorías nosológicas actuales, y permite plantear intervenciones novedosas que incorporen aspectos neurobiológicos y psicoterapéuticos. Esto a su vez ha posibilitado el desarrollo (Robinson et al., 2024) de intervenciones terapéuticas, actualmente en fase de desarrollo e investigación, que presentan una eficacia inicial muy prometedora, posiblemente superior a los tratamientos comercializados actualmente. Además, dada la variedad de mecanismos planteados, las sustancias psicodélicas no sólo podrían resultar beneficiosas para el tratamiento de diversos trastornos mentales, sino que se están investigando en otras patologías, como el dolor crónico, las enfermedades autoinmunes y reumatológicas (Aday et al., 2025), o incluso el asma (Flanagan et al., 2020). Sin embargo, nos centraremos en el impacto de estas sustancias sobre los trastornos mentales, siendo estas indicaciones las más estudiadas actualmente, con una amplia evidencia que permitirá explicar los efectos terapéuticos documentados mediante los mecanismos de acción descubiertos, en el contexto de las teorías integradoras y los factores contextuales descritos previamente. Estos mismos mecanismos también implican la posibilidad de eventos adversos característicos, que también se abordarán, dada su relevancia para la seguridad de estos tratamientos.

2.1 Uso terapéutico de los psicodélicos

Como se ha descrito previamente, el interés por el uso terapéutico de sustancias psicodélicas en psiquiatría ha experimentado un notable resurgimiento en los últimos años, dando lugar a lo que diversos autores denominan el "renacimiento psicodélico". Este fenómeno se refleja en numerosos estudios clínicos en curso para diversas indicaciones psiquiátricas, inversiones significativas por parte de instituciones y empresas, y un interés académico sin precedentes. La evidencia científica acumulada hasta la fecha respalda efectos antidepresivos robustos, tanto para la esketamina (Vasiliu,

2023) como para la terapia asistida con psilocibina (Li et al., 2024), además de confirmar la eficacia y seguridad de la terapia asistida con MDMA para el tratamiento del trastorno por estrés postraumático (Yang et al., 2024). Asimismo, existen evidencias sólidas que respaldan el uso de psicodélicos para aliviar la angustia existencial en pacientes en situaciones de final de vida (Marchi et al., 2024), así como en el tratamiento de diversas adicciones, incluyendo tabaquismo, alcoholismo y trastorno por uso de opiáceos (Köck et al., 2022; Meshkat et al., 2025). Estudios preliminares también indican posibles beneficios terapéuticos en condiciones como el trastorno obsesivo-compulsivo (Ehrmann et al., 2021), el trastorno de ansiedad generalizada (Feulner et al., 2023), los trastornos de la conducta alimentaria (Peck et al., 2023), e incluso ciertos síntomas asociados a los trastornos del espectro autista (Danforth et al., 2018). En conjunto, estos estudios han mostrado efectos terapéuticos rápidos y sostenidos, con reducciones clínicas significativas en la sintomatología tras una o dos sesiones administradas en combinación con intervenciones psicoterapéuticas. Estos resultados son especialmente relevantes al compararlos con tratamientos psiquiátricos convencionales, cuya eficacia suele ser más limitada, lenta y a menudo acompañada por efectos adversos que dificultan la adherencia al tratamiento a largo plazo.

A pesar de estos resultados prometedores, el uso clínico de los psicodélicos aún se encuentra en una fase experimental, y existen importantes interrogantes que resolver antes de poder generalizar su aplicación clínica de forma segura, efectiva y escalable. Estas preguntas incluyen determinar la dosis y frecuencia de administración óptimas, definir claramente las características esenciales del acompañamiento terapéutico, y caracterizar con precisión la influencia del contexto sobre los efectos terapéuticos obtenidos. Diversos ensayos clínicos fase III están actualmente en marcha con el objetivo de responder a estas cuestiones (Norring & Spigarelli, 2024). Sin embargo, la naturaleza singular de estas sustancias plantea desafíos metodológicos significativos a la hora de diseñar estudios capaces de generar resultados con alta validez externa respecto a su seguridad y eficacia. Entre estos desafíos se encuentran la dificultad para establecer grupos de control adecuados, la problemática del cegamiento efectivo, la estandarización rigurosa de protocolos terapéuticos, y la identificación precisa de factores individuales que moderan la respuesta al tratamiento. Tales dificultades son especialmente evidentes en los modelos

tradicionales de investigación clínica basados en ensayos aleatorizados con placebo (Van Elk & Fried, 2023).

Adicionalmente, como se ha descrito previamente, el conocimiento actual sobre los mecanismos de acción de los psicodélicos sugiere que su eficacia clínica no puede atribuirse únicamente a sus propiedades farmacológicas, sino que depende crucialmente de la interacción dinámica entre mecanismos neurobiológicos, procesos psicológicos y fenómenos subjetivos, así como del contexto específico en el que se administran. No obstante, tanto la Administración de Alimentos y Medicamentos de EE.UU. (FDA) como la Agencia Europea del Medicamento (EMA) muestran importantes reticencias a la hora de evaluar de esta manera la eficacia de las terapias asistidas con psicodélicos, debido a que sus paradigmas actuales tienden a basarse en enfoques reduccionistas que consideran principalmente los efectos farmacológicos directos. Este desafío quedó evidenciado recientemente cuando la FDA rechazó la aprobación inicial de la terapia con MDMA para estrés postraumático, pese a los notables resultados clínicos obtenidos (Reardon, 2024). En respuesta al clamor académico y público generado por este rechazo, y frente a la creciente necesidad global de nuevos tratamientos efectivos para los trastornos mentales, ambas agencias regulatorias están elaborando guías para orientar el desarrollo adecuado de futuros estudios clínicos que faciliten su aprobación y comercialización (Destoop et al., 2025; Harris, 2023). Paralelamente, algunos estados y países, como Denver, Oregón y California en los Estados Unidos (Siegel et al., 2023), Australia (Hatfield et al., 2024) o Suiza (Liechti, 2017) han decidido anticiparse a estas aprobaciones regulatorias, autorizando el uso médico de sustancias psicodélicas mediante vías legislativas propias con criterios de acceso variables. Otros países, como Ucrania o República Checa, se encuentran inmersos en procesos legislativos que podrían desembocar en la aprobación de estas sustancias para uso médico en los próximos meses o años.

Esta situación demuestra la urgencia de repensar los métodos tradicionales para evaluar la eficacia de las intervenciones terapéuticas en salud mental, desarrollando nuevas estrategias capaces de incorporar la complejidad en sus paradigmas y evaluar los diversos mecanismos terapéuticos en su totalidad. En caso contrario, existe el riesgo de rechazar intervenciones con el potencial de aliviar el sufrimiento de millones de personas, o

aprobar únicamente abordajes restringidos que podrían facilitar la aparición de efectos adversos que no son evaluados correctamente en los estudios tradicionales, como se detallará posteriormente. En escenarios extremos, las agencias regulatorias podrían rechazar el uso médico de estos tratamientos, mientras su despenalización y regulación a nivel político fomentarían un uso naturalístico. Esto podría implicar riesgos para las personas con diagnósticos de salud mental, quienes, ante la falta de opciones adecuadas en los sistemas sanitarios convencionales, podrían recurrir a estos contextos menos seguros, aumentando así el peligro de complicaciones clínicas potencialmente evitables.

Para afrontar estos desafíos, resulta particularmente relevante establecer puentes con la investigación psicoterapéutica, ya que presenta notables similitudes, tanto en la complejidad a la hora de evaluar su eficacia, como en la presencia de mecanismos de acción multinivel que incorporan el contexto, la esfera subjetiva, la neurobiología y la psicología (Cammisuli & Castelnuovo, 2023; Schiepek & Pincus, 2023). El tratamiento con psicodélicos no puede entenderse como una intervención exclusivamente farmacológica: sus efectos dependen intrínsecamente del contexto y del acompañamiento terapéutico, lo cual los sitúa más cerca de un enfoque psicoterapéutico catalizado por fármacos que de un modelo biomédico convencional. Separar los efectos de la sustancia de los del contexto no solo es epistemológicamente inviable, sino éticamente problemático, ya que puede comprometer la seguridad y la eficacia del tratamiento. De hecho, los efectos psicológicos y neurobiológicos de los psicodélicos se caracterizan precisamente por aumentar la susceptibilidad al entorno, facilitando el reaprendizaje emocional y la reorganización de estructuras cognitivas profundas, lo que exige un encuadre relacional y psicoterapéutico cuidadosamente diseñado. Por tanto, es necesario superar el dualismo reduccionista que ha dominado la investigación psiquiátrica durante décadas, e integrar en su lugar marcos explicativos y metodológicos que reconozcan la naturaleza compleja, dinámica y contextual de las intervenciones con psicodélicos (Gründer et al., 2024). En este sentido, el análisis de sus mecanismos de acción y su integración con abordajes psicoterapéuticos constituye una prioridad investigadora y clínica, como se abordará a continuación.

2.2 Psicodélicos y psicoterapia

Actualmente, no existe un consenso definitivo sobre cuál es el modelo psicoterapéutico óptimo para acompañar el uso de psicodélicos, lo que ha llevado al desarrollo de múltiples enfoques, derivados de tradiciones clínicas diversas, como la Terapia de Aceptación y Compromiso (ACT) (Brennan & Belser, 2022), la terapia cognitivo-conductual (Yaden et al., 2022), o manuales estructurados transversales, como el modelo ACE (Accept, Connect, Embody) del Imperial College (Watts & Luoma, 2020). Sin embargo, y a pesar de sus diferencias teóricas, todos estos modelos buscan de manera central favorecer la flexibilidad psicológica. También cabe destacar que existen otros modelos que se utilizan de manera minoritaria, o que históricamente gozaron de gran popularidad en el pasado, como los abordajes psicodinámicos (Passie et al., 2022). En conjunto, como todas las psicoterapias, estas estrategias también comparten factores comunes que podrían favorecerse gracias al uso de psicodélicos, como la relación terapéutica, y que podrían explicar que presenten una eficacia similar (Wolff et al., 2024). Dada la vulnerabilidad y la sugestionabilidad que predominan durante una experiencia psicodélica, se establece por otro lado la necesidad ética de adoptar abordajes no dirigidos que favorezcan la seguridad y la agencia del participante, respetando sus límites y necesidades, y minimizando las devoluciones e indicaciones específicas del terapeuta (McGuire et al., 2024).

Pese a los rasgos comunes descritos, existe sin embargo una notable ausencia de estudios sistemáticos que evalúen la eficacia diferencial de estas combinaciones, o que aborden su implementación desde un paradigma teórico que permita establecer conexiones causales y evaluar la relevancia de los distintos mecanismos terapéuticos. Por este motivo, la forma en que estos mecanismos interactúan con factores contextuales y con intervenciones específicas aún no se comprende con claridad (Cavarra et al., 2022), lo cual dificulta la validación científica de las intervenciones utilizadas actualmente. Un enfoque integrado y basado en la evidencia, que integre los distintos mecanismos de acción de los psicodélicos, permitiría personalizar el tratamiento mediante combinaciones específicas de distintas intervenciones terapéuticas, sustancias psicodélicas y contextos, adaptadas a las características y necesidades de cada paciente, en línea con las recomendaciones de la psiquiatría de precisión, optimizando su eficacia y seguridad. Para lograr este objetivo, es

necesario cerrar esta brecha de conocimiento mediante estudios que aborden intervenciones específicas sustentadas en mecanismos concretos.

En definitiva, y de acuerdo con la evidencia científica actual, utilizar paradigmas psicoterapéuticos parece el camino más sólido para lograr una implementación clínica óptima de los tratamientos basados en sustancias psicodélicas; sin embargo, esta propuesta resulta contraria al paradigma enarbolado actualmente por distintas instituciones reguladoras y promotoras farmacéuticas, que buscan un reduccionismo farmacológico que simplifique y facilite su comercialización (Goodwin et al., 2024). Como síntesis posible ante esta diatriba, algunos autores plantean entender los psicodélicos no como fármacos, sino como catalizadores dentro de un proceso más amplio. Dentro de esta propuesta, no se buscaría probar la eficacia de los psicodélicos para aliviar síntomas mentales, sino su capacidad para generar estados beneficiosos para determinados procesos terapéuticos, de manera similar a cómo los anestésicos se evalúan por su capacidad para generar estados de conciencia determinados, beneficiosos para el éxito de una operación quirúrgica, pero no determinan el éxito de la operación en si (Wolff et al., 2025).

2.3 Efectos adversos de los psicodélicos

Para culminar esta introducción y comprender de manera global las sustancias psicodélicas y su potencial terapéutico, resulta fundamental atender a su perfil de efectos adversos. Las sustancias psicodélicas clásicas han demostrado un perfil de seguridad médica favorable en contextos clínicos controlados: se ha confirmado su buena tolerabilidad general, con efectos secundarios médicos agudos mayoritariamente leves, que incluyen náuseas, vómitos (particularmente con ayahuasca), cefaleas post-sesión (frecuentes con psilocibina), y elevaciones transitorias de la presión arterial (Bouso et al., 2022; Hinkle et al., 2024). En el caso de la ketamina la esketamina, existe un perfil diferencial de efectos adversos caracterizado por la toxicidad vesical, que puede causar cistitis intersticial en usos crónicos o prolongados, y la aparición de fenómenos de tolerancia y dependencia que pueden asociarse a la aparición de un trastorno por uso de sustancias (Schep et al., 2023); pese a ello, es considerada una de las drogas más seguras

que existen, lo cual justifica su amplio uso como anestésico en situaciones de conflicto o en población pediátrica (Kurdi et al., 2014). En el caso del MDMA, cabe considerar su potencial neurotoxicidad (G. Costa & Gołembiowska, 2022), asociado a un incremento del riesgo de hipertermia o de desencadenar un síndrome serotoninérgico, que puede desembocar en complicaciones severas o incluso resultar letal (Green et al., 2004), si bien ninguno de estos efectos se ha documentado en entornos clínicos (Yang et al., 2024). Finalmente, la ibogaína presenta un potencial cardiotóxico que resulta de especial interés dado su potencial en el tratamiento del trastorno por uso de opioides, ya que estas sustancias también presentan un perfil adverso para la función cardíaca (Köck et al., 2022). Dadas las reticencias la hora de investigar y utilizar estas sustancias en las décadas pasadas, debidas en parte a sesgos culturales con escaso fundamento científico, es posible que también sea necesario reevaluar la prevalencia de algunos efectos adversos considerados tradicionalmente, pero con escasa o nula presencia en los ensayos clínicos modernos, como el riesgo de convulsiones y epilepsia. En una revisión reciente acometida por el autor de esta tesis, e incluida como Anexo 1, se documentó que este riesgo se debía fundamentalmente al uso concomitante de otras sustancias, y no fue posible establecer una correlación causal clara; de hecho, algunos estudios observaron un efecto protector.

Estas consideraciones resultan fundamentales cuando se considera el potencial de estas sustancias para ayudar a personas que no han respondido a otros tratamientos, y el peso que el perfil de efectos adversos puede tener a la hora de determinar su acceso. En el caso de la epilepsia, por ejemplo, existe una asociación notable con el trastorno depresivo, y sin embargo se excluye de manera sistemática a las personas con este diagnóstico de todos los ensayos clínicos que involucran sustancias psicodélicas (Soto-Angona et al., 2024). Pese a la aparente robustez de su seguridad médica, cabe mencionar sin embargo que estas sustancias pueden inducir estados mentales intensos y altamente variables que comportan riesgos psicológicos particulares. Entre ellos, se incluyen experiencias desafiantes agudas como ansiedad, miedo, confusión o paranoia (lo que comúnmente se denomina “bad trips”), que, si no son adecuadamente contenidas e integradas, podrían derivar en consecuencias negativas persistentes. Aunque algunos estudios sugieren que este tipo de experiencias pueden tener valor terapéutico si son acompañadas de manera adecuada (Evans et al., 2023), la falta de estrategias sistemáticas para su registro dificulta

su evaluación rigurosa. De hecho, la evidencia actual indica que los efectos adversos psicológicos probablemente están infrarreportados en la literatura científica, debido tanto a la heterogeneidad terminológica (efectos adversos, reacciones adversas, efectos indeseados, etc.) como a la ausencia de métodos estandarizados de evaluación, lo que ha llevado a plantear la incorporación de instrumentos específicos adaptados a las particularidades de las sustancias psicodélicas (Calder & Hasler, 2024).

En contextos no controlados o recreativos, estos riesgos se amplifican, si bien su prevalencia sigue siendo minoritaria (Raison et al., 2022). Se ha descrito la posibilidad de exacerbación o descompensación de trastornos psicóticos en personas vulnerables, así como fenómenos disociativos prolongados o episodios de despersonalización. El trastorno perceptivo persistente por alucinógenos (HPPD), aunque raro, ha sido reconocido clínicamente y puede implicar reexperimentaciones visuales involuntarias ("flashbacks") (Zhou et al., 2025). Asimismo, se han descrito síntomas psicológicos de aparición diferida, como ansiedad, bajo estado de ánimo o dificultades en la regulación emocional, que podrían representar manifestaciones larvadas de una experiencia no resuelta, especialmente si no ha contado con un adecuado acompañamiento psicoterapéutico y que, dada su aparición tardía, podrían ser difíciles de detectar (Bremler et al., 2023). De nuevo, cabe mencionar que podría ser necesario reevaluar la consideración sobre la prevalencia de estos efectos adversos a la luz de la evidencia actual; por ejemplo, parece que el riesgo de síntomas psicóticos podría ser menor de lo esperado, estimándose en el 0.002% en población general usuaria de estas sustancias, y de un 0.6% en población clínica, si bien es cierto que este riesgo parece elevarse al 3.8% en individuos con un diagnóstico previo de esquizofrenia (Sabé et al., 2025).

Desde una perspectiva clínica, es crucial diferenciar entre los efectos adversos propiamente dichos y las experiencias emocionalmente difíciles que, si bien pueden generar malestar agudo, forman parte del proceso terapéutico y pueden estar asociadas a resultados positivos cuando son adecuadamente acompañadas. Estas consideraciones resultan de interés transversal para el conjunto de la investigación psiquiátrica, ya que obligan a reflexionar sobre cuáles son las características que definen un efecto adverso. Por ejemplo, el uso de psicodélicos también se ha asociado a cambios rápidos y drásticos

en las creencias de los usuarios, que en ocasiones dejan de mantener coherencia con las creencias consensuadas en la sociedad sobre la naturaleza de la realidad y la causalidad de determinados fenómenos. Esto ha despertado un encendido debate sobre el impacto de dichos cambios (Borkel et al., 2025), que pone de manifiesto la importancia de incorporar paradigmas filosóficos sustentados en la epistemología, y la necesidad de ampliar la perspectiva a la hora de considerar el espectro completo de los efectos de estas sustancias sobre la mente humana.

JUSTIFICACIÓN

Como se ha defendido en la introducción previa, las sustancias psicodélicas son sustancias psicoactivas que presentan mecanismos de acción sumamente complejos y un notable potencial terapéutico para el tratamiento de diversos trastornos mentales. La mayoría de los estudios actuales se centran en evaluar sus efectos a nivel clínico, examinando cambios a nivel psicométrico en síntomas mentales, o en averiguar el impacto de alguno de estos mecanismos de acción, con frecuencia desde ópticas reduccionistas que no son adecuadas para entender algunos aspectos, como el efecto del entorno. Además, muchos de estos estudios se realizan en población seleccionada, en entornos controlados, por lo que resulta complejo determinar la validez externa; esto tiene especial relevancia dentro del panorama actual, en el que un respaldo mediático creciente está propulsando el consumo de sustancias psicodélicas por parte de la población general, mientras las agencias reguladoras y los investigadores encuentran problemas para determinar su eficacia y seguridad, debido a los sesgos asociados a sus particularidades. En este contexto, la presente tesis doctoral se plantea investigar paradigmas teóricos que permitan desarrollar modelos explicativos con poder predictivo y relevancia clínica. Para ello, se plantea estudiar de manera sistemática el papel de dos mecanismos psicológicos fundamentales para la eficacia terapéutica de las intervenciones asistidas con psicodélicos: la atribución de significado y la flexibilidad psicológica. Estos mecanismos se han escogido por varios motivos: por un lado, la evidencia actual, desarrollada en la introducción previa, apunta a su papel preponderante a la hora de explicar los cambios observados en personas que consumen sustancias psicodélicas. Por otro lado, resultan especialmente valiosos porque se sitúan en la intersección entre la neurobiología, la experiencia subjetiva y el cambio clínico, por lo que comprenderlos en profundidad podría permitir establecer puentes entre distintos niveles explicativos. Finalmente, se trata de mecanismos conocidos y utilizados en distintos abordajes psicoterapéuticos, por lo que explorar cómo las sustancias psicodélicas los afectan podría informar el desarrollo de abordajes terapéuticos específicos que aprovecharan la sinergia con otras intervenciones en las que estos aspectos también están presentes. Para lograr estos objetivos, son necesarios estudios rigurosos que también tengan en cuenta otros factores determinantes, como el contexto, y el desarrollo de instrumentos psicométricos específicos. En este marco, la presente tesis contempla dos estudios complementarios, orientados a estudiar cada uno de estos mecanismos.

El primero se centra en validar y traducir al castellano el cuestionario APEQ (Acceptance/Avoidance-Promoting Experiences Questionnaire), que evalúa experiencias relacionadas con la evitación y el afrontamiento durante una experiencia psicodélica en población hispanohablante. Se trata de un instrumento desarrollado específicamente bajo el paradigma teórico de que estas experiencias se asocian con cambios en la flexibilidad psicológica, y se ven influenciadas por factores contextuales; explorar estos supuestos permitirá observar los nexos entre contexto, experiencia subjetiva y flexibilidad psicológica, y obtener una herramienta psicométrica en castellano que facilite investigaciones futuras sobre estos aspectos. Además, este estudio se centra en población que utiliza psicodélicos de manera naturalística, facilitando recabar información demográfica sobre patrones de uso y posibles efectos positivos y negativos en esta población, algo especialmente relevante dado la tendencia actual, que apunta a incrementos sostenidos y notables en el consumo naturalístico de estas sustancias, que actualmente alcanza máximos históricos (Patrick et al., 2024).

El segundo estudio se enmarca en una intervención clínica estructurada, y adopta un diseño clínico controlado y no aleatorizado para evaluar el efecto de añadir sesiones con ayahuasca a un programa psicoterapéutico basado en la reconstrucción del significado (*Meaning Reconstruction Therapy*), aplicado en personas que habían perdido a un familiar de primer grado en los últimos 12 meses y presentaban síntomas graves de duelo. En este estudio se decidió trabajar con personas que presentaban síntomas graves de duelo en un período anterior al requerido para establecer el diagnóstico formal de duelo prolongado o complicado, habitualmente situado a partir de los 12 meses tras la pérdida. Aunque el duelo constituye un fenómeno humano universal y esperado, la evidencia muestra que la fase inicial del duelo puede conllevar riesgos clínicos significativos, como un aumento del riesgo de suicidio, autolesión y aparición de trastornos psiquiátricos (Guldin et al., 2017), así como con un deterioro de la salud física que incrementa la mortalidad en los primeros seis meses posteriores a la viudez (Aalbaek et al., 2017; Carey et al., 2014). Las personas en esta situación suelen quedar fuera de los abordajes clínicos, al no cumplir con el criterio temporal exigido para recibir el diagnóstico de duelo prolongado. Esto genera una necesidad médica no cubierta, ya que la severidad de los síntomas puede comprometer gravemente la salud mental y física de los dolientes, sin que existan intervenciones específicas adaptadas a esta fase. Evaluar la aceptabilidad, eficacia

y tolerabilidad de un abordaje centrado en este grupo resulta, por tanto, relevante no solo para la prevención de complicaciones a largo plazo, sino también para atender a una población desatendida en un momento de especial vulnerabilidad. Escoger a personas que atraviesan un proceso de duelo como población diana responde también a la evidencia acumulada que sitúa la reconstrucción del significado como uno de los procesos psicológicos más relevantes en la adaptación al duelo, y cuya alteración se asocia con la cronificación del sufrimiento y la aparición de trastornos como el duelo prolongado (Milman et al., 2019; Neimeyer, 2019). La terapia de reconstrucción de significado presenta amplia evidencia como abordaje para mitigar las complicaciones tras una pérdida significativa (Neimeyer, 2016), y permite explorar la atribución de significado de manera indirecta mediante la observación de potenciales sinergias entre una intervención que actúa específicamente sobre este aspecto, y la incorporación de un psicodélico (ayahuasca), lo cual también facilita la exploración de combinaciones específicas (terapia centrada en el significado y psicodélico clásico, en este caso) para abordar indicaciones concretas.

Mientras que el primer estudio se basa en datos retrospectivos obtenidos en contextos naturalísticos, el segundo se realiza en un entorno controlado y evalúa de manera retrospectiva una intervención estructurada. Esta complementariedad metodológica permite estudiar ambos mecanismos desde enfoques convergentes: uno desde la variabilidad natural del consumo y su relación con la experiencia subjetiva y el contexto, y otro desde la manipulación sistemática del encuadre terapéutico y la evaluación prospectiva de los resultados. En conjunto, ambos estudios permiten articular una comprensión más rica e integrada del modo en que los psicodélicos pueden facilitar el cambio psicológico, y ofrecen una base empírica para el diseño de intervenciones más eficaces, seguras y adaptadas a las necesidades específicas de cada paciente.

HIPÓTESIS

Hipótesis general

La presente tesis parte de la hipótesis de que los mecanismos psicológicos de atribución de significado y flexibilidad psicológica constituyen mediadores clave en los efectos terapéuticos sostenidos de las experiencias inducidas por psicodélicos. Se postula que estos mecanismos están modulados tanto por variables contextuales (como la intención previa del usuario o el encuadre terapéutico) como por las características fenomenológicas de la experiencia subjetiva inducida. Para explorar esta hipótesis, se desarrollan dos estudios empíricos complementarios, centrados en cada uno de estos mecanismos.

Hipótesis principales

- En el contexto de usos naturalísticos, se espera que el cambio retrospectivamente reportado en la flexibilidad psicológica tras una experiencia psicodélica esté significativamente asociado a elementos específicos de la experiencia subjetiva (en particular, experiencias que promueven la aceptación o la evitación), así como a factores contextuales como la intención previa al consumo.
- En un entorno clínico controlado, se espera que la administración de ayahuasca potencie los efectos terapéuticos de una intervención psicoterapéutica centrada en la construcción de significado, aumentando su eficacia en la reducción de síntomas de duelo y en la promoción de crecimiento postraumático tras la pérdida de un ser querido.

Hipótesis específicas

- La presencia de experiencias de aceptación o evitación durante una experiencia psicodélica se asociará significativamente con la intención previa al consumo, y ambas variables predecirán cambios en la flexibilidad psicológica.
- La versión española del cuestionario APEQ presentará propiedades psicométricas adecuadas (validez y fiabilidad) para evaluar experiencias relacionadas con la aceptación y la evitación en el contexto de estados alterados de conciencia inducidos por psicodélicos.
- La combinación de una intervención centrada en el significado y la administración de ayahuasca será más eficaz que la intervención psicoterapéutica aislada para reducir los síntomas de duelo en población clínica.

- Esta combinación también favorecerá un mayor crecimiento postraumático en personas en proceso de duelo, en comparación con la psicoterapia aislada o la ausencia de intervención.

OBJETIVOS

Objetivo general

Explorar el papel de la atribución de significado y la flexibilidad psicológica como mecanismos psicológicos de cambio implicados en los efectos terapéuticos de las experiencias inducidas por psicodélicos, considerando su interacción con el contexto de uso y la fenomenología subjetiva, con el fin de informar el desarrollo de intervenciones clínicas eficaces, culturalmente adaptadas y centradas en el paciente.

Objetivos específicos

Estudio 1: Flexibilidad psicológica y experiencia subjetiva en contextos naturalísticos

- Evaluar la validez psicométrica de la versión española del cuestionario APEQ (Acceptance/Avoidance-Promoting Experiences Questionnaire) para medir experiencias que promueven la aceptación o la evitación durante experiencias psicodélicas.
- Analizar la relación entre la intención previa al uso de una sustancia psicodélica y la presencia de experiencias de aceptación o evitación durante la experiencia aguda.
- Examinar el impacto de estas sustancias sobre la flexibilidad psicológica tras una experiencia psicodélica.
- Describir los patrones de uso, características demográficas y motivacionales de la población hispanohablante que utiliza psicodélicos en contextos naturalísticos con fines terapéuticos o ceremoniales, explorando su relevancia clínica y social.

Estudio 2: Atribución de significado y abordaje psicoterapéutico del duelo

- Comparar la eficacia de una intervención psicoterapéutica centrada en la construcción de significado frente a su combinación con la administración de ayahuasca, en la reducción de los síntomas de duelo prolongado.
- Evaluar el impacto de dicha combinación sobre el crecimiento postraumático en personas en proceso de duelo.
- Analizar la viabilidad, seguridad y aceptabilidad de una intervención grupal asistida con ayahuasca en población clínica, en comparación con intervenciones exclusivamente psicoterapéuticas.

RESULTADOS/PUBLICACIONES

ARTÍCULO 1
Accept to Change: Translation and Validation of the Acceptance/Avoidance-Promoting Experiences Questionnaire (APEQ) in an International Survey of Spanish-Speaking Psychedelic Users

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Accept to change: Translation and validation of the Acceptance/Avoidance-Promoting Experiences Questionnaire (APEQ) in an international survey of Spanish-speaking psychedelic users

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ABSTRACT

Introduction: The Acceptance/Avoidance-Promoting Experiences Questionnaire (APEQ) is a theory-based instrument designed to assess acceptance-related (ACE) and avoidance-related experiences (AVE) during psychedelic-induced altered states of consciousness, proposing a model in which these experiences shape psychological flexibility. This study aimed not only to translate and evaluate the psychometric properties of a Spanish version of the APEQ, but also to test its theoretical assumptions and examine contextual and motivational factors modulating therapeutic processes in psychedelic experiences across diverse Spanish-speaking populations.

Material and methods: An international retrospective survey was conducted in a Spanish-speaking cohort (n = 715) reporting a single psychedelic experience in a therapeutic, ritualistic or ceremonial context involving LSD, psilocybin, ayahuasca, mescaline, MDMA, or ketamine. Participants resided in Spain (n = 420), Latin America (n = 274), or other countries (n = 21).

Results: The Spanish APEQ demonstrated good construct, criterion and cross-cultural validity, as well as internal consistency across scales and in diverse Spanish-speaking populations. Indicating context-dependency, ACE scores were positively associated with therapeutic and growth-oriented motives and with increased psychological flexibility, whereas AVE scores were associated with hedonic/escapist motives and decreased flexibility. High rates of comorbid mental health conditions and concurrent substance use were observed, reflecting relevant patterns in naturalistic psychedelic users.

Conclusion: This study supports the validity and reliability of the Spanish APEQ and provides cross-cultural evidence for the context-dependent nature of psychedelic experiences and their psychological consequences. Beyond validation, these findings confirm core theoretical assumptions of the APEQ and suggest that promoting acceptance during psychedelic states may enhance therapeutic outcomes. The observed comorbidities and substance use patterns point to the need for informed risk-reduction strategies in these populations.

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1. Introduction

The term *psychedelic* describes a heterogeneous group of substances that have the capacity to induce altered states of consciousness (ASC. These states are characterized by alterations in sensation, emotion, cognition, and self-perception (Preller & Vollenweider, 2016). For centuries, natural compounds containing psychedelics have been employed for spiritual and therapeutic purposes by traditional and indigenous cultures (Schultes & Hoffman, 1992). Currently, several of these substances are undergoing clinical trials as treatments for a variety of mental disorders, including major depressive disorder and post-traumatic stress disorder (Mitchell et al., 2021; Murnane, 2018). Furthermore, psychedelic substances are used outside of clinical contexts (e.g., for recreational, spiritual, or self-medication purposes), with evidence of benefits (Jungaberle et al., 2018; Raison et al., 2022) and (more rarely) harms (Bouso et al., 2022; Gómez-Sousa et al., 2021; Simonsson et al., 2023).

Despite extensive research, the exact mechanisms by which psychedelic drugs such as psilocybin or ayahuasca produce long-lasting psychological effects remain unclear. Current evidence suggests a complex interplay of mechanisms involving molecular, neurophysiological and psychological pathways (Heifets & Olson, 2023; Jaster & González-Maeso, 2023). There is extensive evidence that the quality of the acute subjective drug effect – the *psychedelic experience* – predicts longer-term psychological changes, including symptom reductions in psychedelic therapy (Aday et al., 2020; Yaden & Griffiths, 2021). The psychedelic experience, in turn, depends strongly on psychological and situational context factors ("set and setting") (Aday et al., 2021; Carhart-Harris et al., 2018a; Wolff et al., 2024). Current clinical practices in the treatment of mental disorders take this into account by always administering psychedelics in the context of psychotherapy (sometimes referred to as "psychological support") (Gründer et al., 2024).

A proposed psychological mechanism of psychedelic therapy involves acceptance-related psychedelic experiences. These experiences, which can occur during the acute drug effect, have been described as a learning process yielding a motivational shift from avoidance to acceptance ("learning to let go") (Wolff et al., 2020). *Acceptance* refers to the ability to acknowledge and tolerate negative emotional experiences in a non-judgmental manner, and has been linked to a number of psychological benefits (Ford et al., 2018). *Experiential avoidance* refers to the converse unwillingness or inability to tolerate negative emotional experiences, including attempts to avoid, suppress, or control these experiences (Mitmansgruber et al., 2009). Psychological change from excessive experiential avoidance towards more acceptance has been linked to increased psychological flexibility and improved mental health after psychedelic use and psychedelic therapy (Watts & Luoma, 2020; Wolff et al., 2020).

The Acceptance/Avoidance-Promoting Experiences Questionnaire (APEQ) (Wolff et al., 2022) is a theory-based psychometric instrument designed to measure experiences related to acceptance and avoidance that occur during psychedelic-induced ASC. The APEQ is self-reported and comprises 32 items, divided into two main scales, Acceptance-Related Experience (ACE) and Avoidance-Related Experience (AVE), and two ancillary scales, Introspection and Interaction. The ACE scale encompasses the subscales Accepting Response, Relief, and Pro-Acceptance Insights, while the AVE scale comprises the subscales Avoidant Response, Distress, and Pro-Avoidance Insights. The ACE and AVE scales were developed as complementary measures of features of a psychedelic experience that cannot occur simultaneously because one private event (i.e., a thought, feeling or bodily sensation) cannot be avoided and accepted at the same time, although both ACEs and AVEs can occur in different moments over the course of an experience. Due to their complementarity, the ACE and AVE scales are not or only slightly negatively correlated (Wolff et al., 2022). Conversely, the three subscales within the ACE and AVE scale, respectively, are assumed to be intertwined and strongly correlated. Items in the APEQ are presented as a visual analogue scale that can be converted to values from 0 to 100. Value 0 means total disagreement with the item, represented by the phrase "No, not at all", whereas value 100 means total agreement with the item, represented by the phrase "Yes, extremely or absolutely".

Another key concept related to the APEQ (and psychedelic-induced experiences in general) is context dependency. It is theorized that psychedelics induce a relaxation of beliefs and a heightened suggestibility (Dupuis, 2021; Zeifman et al., 2025); hence the context in which they are taken would significantly modulate the quality of the resultant experience, which in turn predicts longer-term outcomes (Carhart-Harris et al., 2018b). Consequently, AVE and ACE are influenced by context factors such as use motives or the setting in which the experience occurs. Specifically, approach-motivated uses of psychedelics, such as having a therapeutic intention (e.g., using psychedelics to engage with emotional problems), are associated with higher ACE scores, whereas avoidance-related motives, such as escapist intentions (e.g., using psychedelics to distract oneself from, predict higher AVE scores (Wolff et al., 2022).

Finally, longer-term outcomes related to AVE and ACE are assumed to be not solely related to their additive effects, but also to the interaction between AVE and ACE. This implies that avoidance-related psychedelic experiences do not inevitably lead to a longer-term increase in avoidance, provided that the individual also achieves acceptance during the experience. This shift could even result in a therapeutic outcome comparable to post-traumatic growth (Tedeschi & Calhoun, 1996). In line with this, Wolff et al. (2022) found evidence that changes in experiential avoidance following a psychedelic experience are not only positively associated with ACE and negatively associated with AVE, but also depend on the interaction between ACE and AVE, asAVE was found to have a negative effect on psychological flexibility only in the absence of ACE; however, when ACE were present, no effect was found. This supports the theoretical assumption that challenging, avoidance-promoting experiences can be therapeutic and promote positive outcomes if a shift to acceptance towards them is eventually achieved.

The two ancillary APEQ scales, Introspection and Interaction, were developed to measure complementary attentional and behavioral aspects of psychedelic experiences that are more indirectly related to avoidance and acceptance. For instance, switching from introspection to interaction with the environment may serve as distractions from distressful or challenging situations and could thus be used as an avoidance strategy (Wolff et al., 2020, 2022).

The APEQ so far exists in German and English (Wolff et al., 2022). The German and English versions were developed simultaneously to avoid problems associated with item translation (Tanzer, 2005). As a result, the APEQ is assumed to contain relatively few language- or culture-specific idiosyncrasies and is therefore expected to be easily translatable into third languages. It should be noted that most psychometric instruments to assess psychedelic-induced ASC are only available in English and (to a lesser extent) in German, with limited evidence regarding the validity of these instruments in other languages. Although extensive research has been conducted in populations that speak other languages, such as Spanish or Portuguese, the lack of validated instruments in these languages could potentially limit the external validity of findings. Furthermore, this presents a challenge for researchers studying populations that do not speak English, who are already underrepresented in psychedelic research (Hovmand et al., 2023).

1.1. Objectives

The principal objective of this study was to assess the psychometric properties of a Spanish version of the APEQ. Spanish is the second-most spoken language worldwide, with approximately 500 million native speakers. The large and culturally diverse linguistic area makes Spanish a highly heterogeneous language, which is spoken differently in different parts of the world. This must be acknowledged when

translating a questionnaire into Spanish: the goal here was to achieve a translation that can be used in all parts of the Spanish-speaking world.

Besides replicating the theorized and empirically established factor structure of the APEQ in a Spanish-speaking population, this study aimed to replicate previous results (Wolff et al., 2022): First, the finding that ACE and AVE are associated with context factors (use motives); second, the finding that ACE, AVE, and their interaction are associated with longer-term changes in psychological flexibility. Furthermore, we aimed to establish convergent validity with external scales. The theoretical model underlying the APEQ suggests that mystical experiences (Barrett & Griffiths, 2017) would be positively related to acceptance-related psychedelic experiences, as both involve a sense of openness and acceptance. Conversely, challenging experiences (Barrett et al., 2016), which involve distress, should be positively correlated with AVE scores. Finally, the Psychological Insight Questionnaire (PIQ) (Davis et al., 2021), which measures psychedelic-occasioned insights of a therapeutic quality, was theorized to be correlated with ACE scores. Another objective was to gain insight into possible differences surrounding the naturalistic use of psychedelics between Spanish-speaking population in Spain and Latin America.

2. Material and methods

2.1. Instrument translation

First, the APEQ was translated to Spanish. The translations were carried out by the first author of the present article, fluent in Spanish and English, and the originator of the original APEQ, fluent in Spanish, English and German. Each author performed an independent translation using the English and German original versions of the scale, and then both authors agreed on a final common translation. Then, a team of four experts who are native Spanish speakers, fluent in English and speak or understand German to varying degrees, reviewed this translation, suggested changes, and verified the retro-translation of the Spanish versions. Members of the translation team speak European, Venezuelan, and Guatemalan Spanish, or Spanish as a second language. Together, the team aimed for translations with maximally equivalent meanings across various varieties of the Spanish language by avoiding cultural bias, idioms and other country-specific expressions. Finally, the first and the last author reviewed this second version and agreed on a final version. The resultant Spanish version of the APEQ instrument is publicly available (https://doi.org/10.17605/OSF.IO/JBVDC).

2.2. Survey design

A retrospective online survey was implemented, using Research Electronic Data Capture (REDCap) (Harris et al., 2009, 2019). The survey was accessible through a link and a QR code, as well as from a landing page on the MIND Foundation's website. Between September 2022 and April 2023, the survey link was distributed to different harm reduction associations, retreat centers, internet forums, universities, health care centers, research institutes and other foundations and institutions related to psychedelic use, research, therapy, or teaching, for dissemination among the general Spanish-speaking population. The survey was also posted on different social networks and displayed in newspapers. Participants were asked about a single past psychedelic experience of their choice, and all survey items were framed as related to that specific experience. The complete survey is publicly available (https://doi.org/10.17605/OSF.IO/JBVDC).

2.3. Ethical considerations

No data allowing identification of survey participants were gathered. All data was stored on a secure server physically located at the Vall d'Hebron Research Institute. Access to the survey data was limited to members of the research team, and no data was shared with third parties. Informed consent was obtained from all participants prior to giving them access to the survey. Consent from the Vall d'Hebron Research Institute Ethics Committee was obtained prior to the start of the study (PR(AG)136/2022). Participants were not compensated for their participation. The full survey is available upon request from the corresponding author.

2.4. Participants

Any person that was fluent in Spanish, was older than 18 years, gave informed consent, and indicated having consumed at least once a psychedelic in a therapeutic, ceremonial, or ritualistic setting was eligible to complete the survey. Other settings, such as party settings, were excluded. Only the following substances were included: ayahuasca, lysergic acid diethylamide (LSD) or derivatives, psilocybin or psilocybin containing mushrooms, mescaline or mescaline containing cacti, ketamine, and 3,4-methylenedioxymethamphetamine (MDMA). Short-acting psychedelics such as 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) or smoked dimethyltryptamine (DMT) were excluded, as we considered that the rapid onset, intensity, and shortness of the experience might prevent meaningful avoidance-related or acceptance-related experiences that could be captured with the APEQ.

2.5. Sample size

Regarding sample size, the current consensus recommends a ratio of 10 participants per item to ensure robust factor analysis (Boateng et al., 2018; Nunnally, 1978). A minimum of 300 participants is generally considered sufficient for achieving acceptable pattern comparability, while sample sizes between 500 and 1000 are regarded as very good to excellent, reducing measurement error and enhancing the generalizability of findings (Guadagnoli & Velicer, 1988). Given that the APEQ instrument comprises 32 items, a minimum sample size of 320 participants was deemed appropriate, with a target range of 500 to 1000 respondents to optimize statistical power.

2.6. Study measures

2.6.1. Sociodemographic data

Data about the sociodemographic characteristics of participants were gathered: age, sex, country of residence, and level of education. Participants were also asked about lifetime diagnosis of mental disorders.

2.6.2. Selected psychedelic experience

Participants were asked to select one psychedelic experience to report in the rest of the survey. Both positive and negatively evaluated experiences were eligible. After having chosen an experience to report on, participants were asked to indicate the psychedelic used, the time that passed since the experience, the subjective clarity of their memory of the experience, the perceived strength of the dose, the valence of the acute effects, any concomitant use of other psychoactive substances besides caffeine and nicotine, and global lifetime psychedelic use.

2.6.3. Setting

Participants were asked several questions about specific setting categories (calm and undisturbed; familiar environment; nature or close-to-nature; festival; retreat; ceremonial; therapeutic). They were also asked whether a sitter (i.e., a person who took care of the participant's safety and wellbeing) was present during the reported experience. Participants were also asked to provide an estimate of the total number of people present during the experience.

2.6.4. Use motives

A total of 22 possible motives for psychedelic use were presented. We used the items included in the original development of the APEQ (Wolff

et al., 2022) and added an additional item: "to connect with a community of people". Participants were asked to rate the extent to which each item corresponded to their motives for undergoing the reported experiences at that time on a four-point Likert scale ("not at all"; "somewhat", "moderately", "very much").

2.6.5. Mystical experiences questionnaire (MEQ)

The Mystical Experiences Questionnaire (Barrett & Griffiths, 2017) is a scale designed to assess mystical experiences in the context of psychedelic use. It comprises 30 items and a four-factor structure: (a) mysticality (freedom from the limitations of one's personal self and feelings of unity), (b) positive mood, (c) transcendence of time and space (the sense of being outside of time, beyond past and future), and (d) ineffability (the sense that the experience cannot be described adequately in words). MEQ scores have shown to predict long-term positive therapeutic outcomes in a variety of psychedelic substances used to treat several mental disorders (Ko et al., 2022).

The total score of the Spanish version of the MEQ (Davis et al., 2023) was used in the present study. The measure demonstrated good internal consistency (Cronbach's $\alpha = .96$).

2.6.6. Challenging experiences questionnaire (CEQ)

The Challenging Experience Questionnaire (Barrett et al., 2016) was developed to measure psychologically difficult experiences during the acute effects of psychedelics. The CEQ has 26 items on seven subscales (fear, grief, physical distress, insanity, isolation, death, and paranoia). In the present study, the validated Spanish version of the main scale was used (Davis et al., 2023), showing good internal consistency (Cronbach's $\alpha = .94$).

2.6.7. Psychological Insight Questionnaire (PIQ)

The PIQ is a recently developed questionnaire that assesses acute psychological insights that may occur during psychedelic experiences (Davis et al., 2021). The Psychological Insight Questionnaire consists of 23 items with a main scale and two subscales: (a) Avoidance and Maladaptive Patterns Insights and (b) Goals and Adaptive Patterns Insights. In the present study, the Spanish version of the main scale was used (Davis et al., 2023), showing good internal consistency (Cronbach's $\alpha = .96$).

2.6.8. The Acceptance and Action Questionnaire II (AAQ-II)

The Acceptance and Action Questionnaire II (Bond et al., 2011) measures psychological (in-) flexibility using seven items (e.g., "I am afraid of my feelings"). Lower scores on the AAQ-II indicate greater psychological flexibility. The Spanish-validated version (Ruiz et al., 2013) was used, after being adapted with statements in past tense to assess psychological flexibility retrospectively. Each participant completed two versions of this adapted questionnaire: one referred to the 3–4 weeks preceding the reported psychedelic experience, while the other referred to the 3–4 weeks following the experience. The difference score between both was used as an indirect measure of change in psychological flexibility (Davis et al., 2023; Wolff et al., 2022).

2.7. Data analysis

To favor comparability between different versions of the APEQ, and to test its underlying theoretical assumptions, this study followed the same analysis plan as was carried out in the original development of the English and German versions of the APEQ (Wolff et al., 2022).

2.7.1. Sociodemographic data and reported psychedelic experiences

The final sample that was subjected to analysis included all participants that completed the whole survey, after excluding the responses that indicated: (1) not being able to remember with clarity the selected psychedelic experience, (2) concomitant use of more than one psychedelic during the reported experience, or (3) open-item answers suggesting that responses were invalid. The survey was sequential and required completion of all data to be considered complete, ensuring that there was no missing data amongst the respondents that completed the whole survey and were included in the analysis.

The sociodemographic data gathered from the final sample was analyzed to assess its specific characteristics. The global sample was divided into three subsamples: (1) participants who reported living in Spain, (2) participants who reported living in Latin American countries (where Spanish is the primary language), and (3) participants who reported living elsewhere. Participants' responses related to the reported psychedelic experiences were also analyzed. The Spanish and Latin-American subsamples were then compared to assess for relevant differences.

2.7.2. Confirmatory Factor Analysis (CFA) of APEQ items

Confirmatory factor analyses (CFAs) were performed to test the factor structure that was previously found for the English and German versions of the APEQ (Wolff et al., 2022) in the translated Spanish version. CFAs were calculated using Mplus 8.9. We first calculated a baseline model including all 32 APEQ items, eight first-order factors (Accepting Response, Avoidant Response, Relief, Distress, Pro-Acceptance Insights, Pro-Avoidance Insights, Introspection, and Interaction), and the two complementary second-order factors AVE (representing the shared variance of the first-order factors Avoidant Response, Distress, and Pro-Avoidance Insights) and ACE (representing the shared variance of the first-order factors Accepting Response, Relief, and Pro-Acceptance insights). We then compared the baseline model to a more constrained alternative model where the two first-order factors Accepting Response and Pro-Avoidance Insights were collapsed into one single factor. In the original study that tested the psychometric properties of the German and English versions of the APEQ (Wolff et al., 2022), this more constrained model exhibited only insignificantly poorer model fit compared to the baseline model and was therefore selected for further analyses. Model fit was assessed using the root-mean square error of approximation (RMSEA), the standardized root mean square residual (SRMR) the confirmatory fit index (CFI), and the Tucker-Lewis index (TLI).

2.7.3. Principal component analysis (PCA) of use motives

Use motives were evaluated by means of a principal component analysis (PCA) to examine the underlying factor structure, following the same approach that was used previously (Wolff et al., 2022, 2024). Factor scores from this PCA were subsequently used to test the context-dependence of ACE and AVE (see below section on path analysis).

2.7.4. Path analysis testing context dependence and potential mediation effects

A path analysis was defined a priori to test the context-dependence and interaction assumptions: ACE and AVE scores were regressed onto component scores obtained from the previous PCA of use motives, which were introduced as context factors. Retrospective changes in psychological flexibility were regressed onto these component scores, ACE, AVE, and a latent variable accounting for the interaction between ACE and AVE. This last variable was included to test for the interaction assumption.

2.7.5. Reliability

Reliability was evaluated using the Cronbach's alpha coefficient, calculated using SPSS 23.0, to assess for internal consistency in all scales and subscales. This test was performed in the whole sample, as well as in the Latin-American and Spanish subsamples.

2.7.6. Convergent validity

Convergent validity with external scales was evaluated by examining correlations between APEQ scales and MEQ, CEQ, and PIQ scores.

3. Results

3.1. Description of the sample

Of the 2302 volunteers who agreed to participate and started the survey, 756 fulfilled the inclusion criteria and completed the survey. Out of these, 45 volunteers were excluded for one or more of the following reasons: Thirty-nine volunteers indicated concomitant use of more than one psychedelic during their reported experience, one volunteer left a feedback request stating that he had responded randomly, and two participants indicated that their used substance was 5-MeO-DMT, despite having selected another substance when responding to the inclusion criteria items.

Characteristics of the final sample of 715 participants are presented in Table 1. Four hundred and twenty participants (58.7 % of the total sample) reported living in Spain. 275 participants (38.3 %) reported living in Latin America, and 21 participants (2.9 %) reported living elsewhere. Countries in the Latin American subsample included Colombia (n = 155, 21.7 % of the total sample), Mexico (n = 33, 4.6 %), Argentina (n = 32, 4.5 %), Chile (n = 24, 3.4 %), Costa Rica (n = 11, 1.5 %), Ecuador (n = 7, 1 %), Peru (n = 5, .7 %), Bolivia (n = 2, .3 %), Venezuela (n = 2, .3 %), El Salvador (n = 1, .1 %), Guatemala (n = 1, .1 %), and Uruguay (n = 1, .1 %). Countries in the "Rest of the World" subsample included Germany (n = 4, .6 % of the total sample), USA (n = 3, .4 %), France (n = 3, .4 %), Italy (n = 3, .4 %), Andorra (n = 1, .1 %), Austria (n = 1, .1 %), Brazil (n = 1, .1 %), Canada (n = 1, .1 %), Moldova (n = 1, .1 %), the Netherlands (n = 1, .1 %), Portugal (n = 1, .1 %) and Romania (n = 1, .1 %).

Characteristics of the selected psychedelic experience are summarized in Table 2. Significant differences between the Spanish, Latin-American and "rest of the world" subsamples were found for some characteristics, albeit with mostly small effect sizes. Medium effect sizes were only found for the psychedelic used (with the Spanish sample reporting more ayahuasca use and less use of LSD and psilocybin mushrooms), presence of other people (with the Spanish sample reporting less unaccompanied psychedelic use and more use in larger groups) and previous psychedelic use (with a larger proportion of individuals in the Spanish sample reporting more than a hundred previous episodes of psychedelic use).

3.2. APEQ scores and comparison between Spanish and Latin American subsamples

Mean scores of all APEQ items, scales and subscales are listed in Table 3. Compared to the Spanish subsample, the Latin American subsample scored higher on both main scales (ACE and AVE) and on all subscales except for the AVE subscale Distress.

Several item scores were non-normally distributed, with univariate skewness ranging from −2.07 to 1.96 and kurtosis ranging from −1.54 to 4.21. Mahalanobis distance procedures (with $p < .001$) classified 49 participants (6.85 % of the sample) as multivariate outliers. Items deviating from univariate or multivariate normality were retained for further analyses. To account for nonnormality in the dataset, CFAs were calculated with the robust maximum likelihood (MLR) estimator in Mplus 8.9.

3.3. Confirmatory Factor Analysis

The baseline model with separate first-order factors Accepting Response and Pro-Acceptance Insights was rejected since the covariance matrix was not positive definite. The more constrained model where these two factors were collapsed into a single factor showed acceptable fit in terms of RMSEA (.054) and SRMR (.075), whereas CFI (.889) and TLI (.880) fell slightly below the commonly preferred threshold of .90. A summary of this model is shown in Fig. 1.

3.4. Use motives

After evaluating Bartlett's test of sphericity ($\chi2$ (253) = 5346.332; p < 001) and the Kaiser–Mayer–Olkin measure of sampling adequacy (.837), a PCA was calculated, using varimax rotation. Five components were found using PCA, but the scree-plot suggested that a three-component solution was more adequate, explaining 44.264 % of the variance. PCA results are shown in Table 4 Based on their content, the components were labeled (1) "hedonic/escapist", (2) "growth/well-being", and (3) "therapeutic". No significant differences between the

Table 1
Sociodemographic characteristics of participants.

	Global sample (*n* = 715)	Spain (*n* = 420)	Latin America (*n* = 274)	Rest of the world (*n* = 21)	*F* or $\chi2$	*p*	η^2 or Cramer's *V*
Mean (SD) age	36.41 (11.08)	39.72 (11.48)	31.75 (8.58)	31.24 (7.90)	51.66	<.001	.02
Gender					7.68	.263	.073
Female	50.2 %	47.6 %	53.3 %	61.9 %			
Male	47.8 %	51.0 %	43.8 %	38.1 %			
Non-binary	1.8 %	1.2 %	2.9 %	.0 %			
Other	.1 %	.2 %	.0 %	.0 %			
Highest educational level					23.181	.026	.127
Middle school or lower	3.5 %	5.2 %	1.1 %	.0 %			
High school	7.1 %	7.1 %	7.3 %	19.0 %			
Professional training/non finished college	25.5 %	22.4 %	30.7 %	19.0 %			
University	30.3 %	28.6 %	33.2 %	28.6 %			
Postgraduate degree	33.6 %	36.7 %	28.8 %	33.3 %			
Lifetime diagnosis of mental disorder							
None	66.0 %	68.8 %	62.0 %	61.9 %	3.546	.170	.070
Depression	23.2 %	21.4 %	25.5 %	28.6 %	1.926	.382	.052
Anxiety	23.2 %	20.0 %	27.7 %	28.6 %	5.917	.052	.091
SUDs	4.3 %	3.6 %	5.1 %	9.5 %	2.350	.309	.057
Mania	1.1 %	.5 %	2.2 %	.0 %	4.646	.098	.081
Psychosis	.6 %	.5 %	.7 %	.0 %	.314	.855	.021
ADHD	7.0 %	5.7 %	8.4 %	14.3 %	3.600	.165	.071
PTSD	2.7 %	3.6 %	.7 %	9.5 %	9.119	.010	.113
OCD	2.1 %	1.4 %	3.3 %	.0 %	3.245	.197	.067
Other	4.5 %	5.2 %	3.6 %	.0 %	1.992	.369	.053

SD: Standard deviation; SUDs: substance use disorders; ADHD: attention deficit/hyperactive disorder; PTSD: posttraumatic stress disorder; OCD: obsessive-compulsive disorder.

Table 2
Characteristics of psychedelic experience reported by participants.

	Global sample (n = 715)	Spain (n = 420)	Latin America (n = 274)	Rest of the world (n = 21)	*F or χ2*	*p*	η^2 *or Cramer's V*
Mean (SD) years since the experience	2.58 (4.19)	2.73 (4.26)	2.34 (4.12)	2.63 (3.77)	.704	.495	.002
Subjective quality of memory					7.979	.240	.075
Completely clear	39.9 %	36.7 %	44.2 %	47.6 %			
Very clear	37.9 %	40.0 %	35.0 %	33.3 %			
Clear	18.7 %	19.5 %	18.2 %	9.5 %			
Somewhat clear	3.5 %	3.8 %	2.6 %	9.5 %			
Psychedelic used					59.664	<.001	.204
LSD or derivatives	19.6 %	14.8 %	25.9 %	33.3 %			
Psilocybin or psilocybin mushrooms	31.5 %	26.2 %	39.8 %	28.6 %			
Ayahuasca	38.3 %	48.6 %	22.6 %	38.1 %			
Mescaline or mescaline-cacti	2.7 %	1.7 %	4.4 %	.0 %			
MDMA	6.7 %	7.1 %	6.6 %	.0 %			
Ketamine	1.3 %	1.7 %	.7 %	.0 %			
Strength of dose					11.913	.155	.091
Very weak	.7 %	.2 %	1.5 %	.0 %			
Weak	1.3 %	1.7 %	.7 %	.0 %			
Moderate	24.8 %	23.3 %	26.6 %	28.6 %			
Strong	48.4 %	52.4 %	42.7 %	42.9 %			
Very strong	24.9 %	22.4 %	28.5 %	28.6 %			
Valence of acute effects					12.851	.045	.095
Rather pleasant	57.5 %%	53.6 %	63.5 %	57.1 %			
Rather unpleasant	3.4 %	4.0 %	2.2 %	4.8 %			
Both pleasant and unpleasant	35.7 %	37.9 %	32.8 %	28.6 %			
Neither pleasant nor unpleasant	3.5 %	4.5 %	1.5 %	9.5 %			
Concomitant substance use							
None	59.0 %	62.1 %	53.3 %	71.4 %	6.757	.034	.097
Cannabis	24.6 %	21.2 %	30.3 %	19.0 %	7.764	.021	.104
Alcohol	8.4 %	9.0 %	7.3 %	9.5 %	.695	.706	.031
Stimulants	1.3 %	1.4 %	1.1 %	.0 %	.424	.809	.024
Benzodiazepines	.1 %	.2 %	.0 %	.0 %	.703	.704	.031
Opiates/opioids	.1 %	.2 %	.0 %	.0 %	.703	.704	.031
Inhalants	.7 %	.7 %	.7 %	.0 %	.153	.926	.015
Other substances	6.7 %	5.7 %	8.0 %	9.5 %	1.692	.429	.049
Length of the effects					21.911	.005	.124
Less than 1 h	1.8 %	2.1 %	.7 %	9.5 %			
1–2 h	2.1 %	2.6 %	1.5 %	.0 %			
2–5 h	38.6 %	43.1 %	32.5 %	28.6 %			
5–10 h	45.2 %	41.7 %	50.0 %	52.4 %			
Longer than 10 h	12.3 %	10.5 %	15.3 %	9.5 %			
Mood before the experience					16.133	.041	.106
Very bad	2.2 %	2.1 %	1.8 %	9.5 %			
Bad	6.3 %	6.2 %	6.9 %	.0 %			
Neither good not bad	19.6 %	17.9 %	22.6 %	14.3 %			
Good	40.0 %	53.3 %	42.0 %	52.4 %			
Very good	22.9 %	20.5 %	26.6 %	23.8 %			
Preparedness before the experience					11.380	.077	.089
Not at all	3.8 %	2.6 %	4.7 %	14.3 %			
A little	11.6 %	12.1 %	11.3 %	4.8 %			
Moderately	38.2 %	36.4 %	40.9 %	38.1 %			
A lot	46.4 %	48.8 %	43.1 %	42.9 %			
Setting							
Nature or close-to-nature environment	67.5 %	65.5 %	63.5 %	76.2 %	1.468	.480	.045
Setting designed for therapeutic purpose	65.0 %	70.2 %	65.0 %	52.4 %	4.429	.109	.079
Party, concert or festival	4.1 %	2.9 %	6.2 %	.0 %	5.689	.058	.089
Psychedelic retreat	46.5 %	46.2 %	36.2 %	38.1 %	15.855	<.001	.149
Ceremonial, religious or spiritual event	45.3 %	49.3 %	40.1 %	33.3 %	6.843	.033	.098
Presence of other people					102.367	.685	.268
Alone	8.7 %	6.9 %	12.0 %	.0 %			
2–5 people	41.1 %	36.2 %	46.4 %	71.4 %			
6–15 people	27.6 %	25.7 %	20.4 %	19.1 %			
16–30 people	15.5 %	18.3 %	12.1 %	.0 %			
31–100 people	11.2 %	12.9 %	9.1 %	9.5 %			
>100 people	.0 %	.0 %	.0 %	.0 %			
Guide/sitter present	74.4 %	78.3 %	69.7 %	57.1 %	9.864	.007	.117
Number of times of previous psychedelic use					364.177	.265	.505
0 (never before)	.1 %	.2 %	.0 %	.0 %			
1-5	19.6 %	20.0 %	19.3 %	14.3 %			
6-20	27.7 %	23.4 %	34.3 %	42.9 %			
21-50	24.1 %	23.1 %	24.9 %	19.0 %			
51-100	13.9 %	14.7 %	13.1 %	9.5 %			
>100	14.7 %	18.6 %	8.4 %	14.3 %			

SD: Standard deviation.

Table 3
Mean scores of the APEQ items in the whole sample and the Spain and Latin America Subsamples. T and p scores, as well as Cohen's d, refer to *t*-test comparison between the Spain and Latin America subsamples.

Scale/Item	Mean (SD)			*t*	*p*	Effect size (Cohen's d)	Skewness	Kurtosis
	Total	Spain	Latin America				Total	Total
Acceptance-Related Experience (ACE)	71.04 (21.18)	69.15 (21.98)	73.97 (19.58)	−2.943	.003	.234	−.854	.151
Accepting Response	66.67 (26.12)	64.67 (26.64)	69.91 (24.77)	−2.605	.009	.202	−.675	−.400
7. I was able to accept uncomfortable thoughts or memories	72.37 (29.78)	70.28 (30.18)	75.53 (28.74)	−2.281	.023	.177	−1.180	.376
13. I was open to difficult sensations or emotional states	77.10 (27.14)	76.11 (27.14)	79.08 (26.79)	−1.416	.157	.110	−1.443	1.311
18. I looked at painful memories with openness	53.93 (38.03)	52.25 (38.14)	57.20 (37.62)	−1.679	.094	.130	−.212	−1.538
32. I managed to confront a personal fear	63.28 (34.72)	60.03 (35.61)	67.84 (32.84)	−2.962	.003	.226	−.674	−.944
Relief	77.02 (20.74)	74.94 (21.54)	79.86 (19.58)	−3.044	.002	.236	−1.152	1.103
3. It seemed to me as if some kind of blockage was being resolved	70.96 (30.96)	68.97 (32.28)	74.26 (28.64)	−2.258	.024	.171	−1.024	−.102
9. I had a positive emotional breakthrough	84.54 (21.97)	83.11 (22.93)	86.51 (20.90)	−1.977	.048	.154	−2.035	4.207
22. I felt a sense of relief	78.78 (25.31)	75.82 (26.25)	82.61 (23.84)	−3.450	<.001	.268	−1.500	1.775
27 Things became easier for me in a liberating way	73.82 (26.68)	71.87 (27.38)	76.05 (26.03)	−2.006	.045	.156	−1.124	.546
Pro-Acceptance Insights	69.44 (23.81)	67.85 (24.34)	72.14 (22.40)	−2.341	.020	.182	−.966	.428
4. I learned to better understand certain emotional states.	76.57 (27.43)	74.78 (28.66)	79.76 (24.81)	−2.431	.015	.174	−1.372	1.083
11. I discovered a deeper acceptance of certain difficult feelings or sensations	77.62 (26.76)	76.88 (27.00)	79.45 (25.49)	−1.251	.211	.104	−1.554	1.713
20. I noticed that certain thoughts or memories are not as dangerous for me as I had previously thought	60.02 (33.62)	57.72 (34.13)	63.55 (32.50)	−2.266	.024	.176	−.556	−.994
30. I learned to appreciate certain uncomfortable feelings or sensations more	63.55 (30.72)	62.01 (31.07)	65.78 (29.88)	−1.588	.113	.123	−.779	−.480
Avoidance-Related Experience (AVE)	26.70 (20.24)	27.26 (19.63)	30.70 (21.07)	−2.192	.029	.172	.690	−.172
Avoidant Response	33.53 (24.17)	31.92 (23.50)	35.76 (24.89)	−2.052	.041	.162	.478	−.544
5. I tried to lessen, or rid myself of, certain perceptions or bodily sensations	43.54 (34.59)	41.72 (33.80)	46.34 (35.76)	−1.718	.086	.133	.158	−1.419
15. I tried to change my mood	35.48 (33.30)	34.24 (32.13)	37.69 (35.08)	−1.309	.191	.104	.464	−1.161
24. I attempted to suppress certain emotions of thoughts	25.26 (30.28)	22.79 (28.12)	28.71 (32.72)	−2.463	.014	.197	1.076	−.152
28. I made efforts to avoid or control difficult feelings	29.85 (31.78)	28.94 (30.83)	30.28 (32.50)	−.549	.583	.043	.857	−.611
Distress	28.89 (29.10)	28.36 (28.64)	29.35 (29.74)	−.440	.660	.031	.871	−.393
8. I felt tormented	28.29 (32.29)	28.38 (32.33)	27.98 (32.16)	.160	.873	.012	.917	−.519
14. I panicked	26.12 (32.79)	24.57 (31.90)	28.59 (34.12)	−1.554	.121	.122	1.058	−.319
23. I experienced a state of distress	32.28 (34.06)	31.27 (33.16)	33.01 (35.00)	−.662	.508	.051	.657	−1.063
31. I suffered from what I was experiencing	28.88 (33.05)	29.21 (32.99)	27.82 (32.80)	.542	.588	.042	.858	−.704
Pro-Avoidance Insights	23.64 (20.44)	21.50 (19.76)	26.99 (20.80)	−3.506	<.001	.273	.862	.204
6. I learned to fear or detest certain uncomfortable feelings or sensations more strongly	26.10 (31.30)	26.90 (31.20)	25.46 (31.65)	.589	.556	.046	1.009	−.356
16. I noticed that I can tolerate certain mental states less than I thought	31.31 (32.86)	24.56 (28.12)	41.30 (36.54)	−6.440	<.001	.528	.789	−.772
19. I learned that is better for me not to experience certain emotional states at all	15.67 (24.72)	14.03 (21.90)	18.34 (28.42)	−2.129	.034	.174	1.961	2.965
29. I learned that certain thoughts or memories are more dangerous for me than I previously thought	21.50 (27.62)	20.51 (27.07)	22.88 (28.20)	−1.106	.269	.086	1.330	.614
Ancillary scales								
Introspection	76.46 (20.70)	76.03 (21.61)	77.10 (19.10)	−.671	.503	.05	−1.248	1.431
2. I was engaged with what was going on inside me	78.86 (25.12)	77.55 (25.96)	80.42 (24.10)	−1.463	.144	.114	−1.548	1.922
12. I looked inside	84.88 (22.79)	83.99 (23.31)	86.31 (22.00)	−1.310	.191	.102	−2.066	4.031
17. My attention was turned inward	74.00 (27.72)	72.88 (28.46)	75.92 (26.02)	−1.422	.155	.110	−1.166	.519
25. I was absorbed in my inner experience	68.10 (29.94)	69.68 (29.28)	65.75 (30.95)	1.687	.092	.131	−.881	−.244
Interaction	65.05 (22.87)	61.85 (23.68)	69.61 (20.84)	−4.543	<.001	.34	−.489	−.502
1. I observed my external environment	67.71 (30.57)	63.87 (30.90)	73.47 (28.77)	−4.175	<.001	.319	−.716	−.645
10. I actively engaged with my surroundings	63.73 (31.61)	60.94 (32.11)	66.81 (30.78)	−2.392	.017	.186	−.557	−.900
21. I interacted with other people	58.42 (35.34)	54.79 (35.89)	63.97 (33.66)	−3.419	.001	.262	−.432	−1.238
26. I moved my body	70.36 (27.40)	67.79 (27.89)	74.19 (26.50)	−3.013	.003	.234	−.901	−.084

Each number refers to the order of each item in the original APEQ instrument.

Spanish and Latin American sample were found for the hedonic/escapist component (t(694) = −1.3424; p = .180; cohen's d = .51), and the therapeutic component (t(694) = −.883; p = .378; cohen's d = .27, whereas the Spanish subsample scored significantly lower in the growth/wellbeing component (t(694) = -4.353; p < .001; cohen's d = .34).

3.5. Path analysis of potential mediation effects

Fig. 2 summarizes the path model assessing associations between use motives, ACE, AVE, and retrospective changes in psychological flexibility. ACE was positively associated with growth/wellbeing (β = .33; $p < .001$) and therapeutic intention (β = .45; $p < .001$), and negatively associated with hedonic/escapist intention ($\beta = -.22$; $p < .001$). AVE was positively correlated with therapeutic (β = .26; $p < .001$) and hedonic/escapist intention (β = .11; $p < .001$), whereas no significant association was found with growth/wellbeing intention ($\beta = -.02$; p = .677). Retrospective changes in psychological flexibility were positively associated with ACE (β = .23; $p < .001$), and negatively associated with AVE ($\beta = -.08$; p = .032), but no significant effect of the interaction between ACE and AVE was found ($\beta = -.01$; p = .677). Furthermore, therapeutic intention had a positive direct effect on changes in



Fig. 1. Summary of Confirmatory Factor Analysis (CFA) of the global sample.

Table 4
Item loadings from the principal component analysis (PCA) of use motives for the global sample.

Item	1 – Hedonic/ escapist	2 – Growth/ wellbeing	3 - Therapeutic
To have fun	**.771**	−.037	−.375
For partying	**.747**	.042	−.319
To share my experience with my friends	**.625**	.063	−.420
To distract myself from problems	**.608**	−.194	.323
To relax	**.605**	.347	.117
To intoxicate myself	**.586**	−.063	.006
To increase my sexual pleasure	**.519**	.235	−.009
Out of boredom	**.501**	−.045	.008
Out of curiosity	**.341**	−.025	−.213
To fit in	**.269**	.192	.063
To have an experience with nature	.099	**.681**	.048
To increase my creativity	.357	**.647**	−.015
For spiritual reasons	−.293	**.625**	.224
To increase my performance	.145	**.583**	.288
For self-awareness	−.319	**.551**	.355
For personal growth	−.417	**.500**	.421
To connect with a community of people	.171	**.481**	.000
For religious reasons	−.041	**.444**	−.053
To confront difficult feelings	−.143	.150	**.785**
To escape from difficult feelings	.263	−.163	**.694**
To treat psychological problems	−.113	.088	**.693**
To increase my wellbeing	−.082	.454	**.523**
To treat physical problems	−.075	.210	**.371**

Note: The highest loading of each item is written in bold font.

psychological flexibility (β = .25; p < .001), whereas growth/wellbeing and hedonic/escapist intention were negatively associated with changes in psychological flexibility ($\beta = -.11$; $p = .003$) and $\beta = -.09$; $p = .012$, respectively). This points to the presence of associations between intentions and changes of psychological flexibility that are not completely mediated by ACE and AVE.

3.6. Reliability

Table 5 shows internal consistencies for all APEQ scales and subscales. All scales and subscales showed at least acceptable reliability.

3.7. Convergent validity

Table 6 summarizes correlations between scores of the APEQ mains scales, subscales and ancillary scales, and external scales. As hypothesized, ACE scores were found to positively correlate with MEQ and PIQ scores, while AVE scores were positively correlated with CEQ scores, supporting convergent validity.

4. Discussion

This study was conducted to evaluate the psychometric properties of the Spanish version of the APEQ. It also tested the theoretical model underlying this instrument and explored its value as a relevant measure that can help in understanding the relationship between the subjective effect elicited by a psychedelic, and the outcomes reported by a participant.

The Spanish version of the APEQ showed acceptable model fit after collapsing the first-order factors Accepting Response and Pro-Acceptance Insights into a single factor. In the original development of the APEQ scale, this more constrained model showed no worse fit than the baseline model with separate factors for the two scales (Wolff et al.,

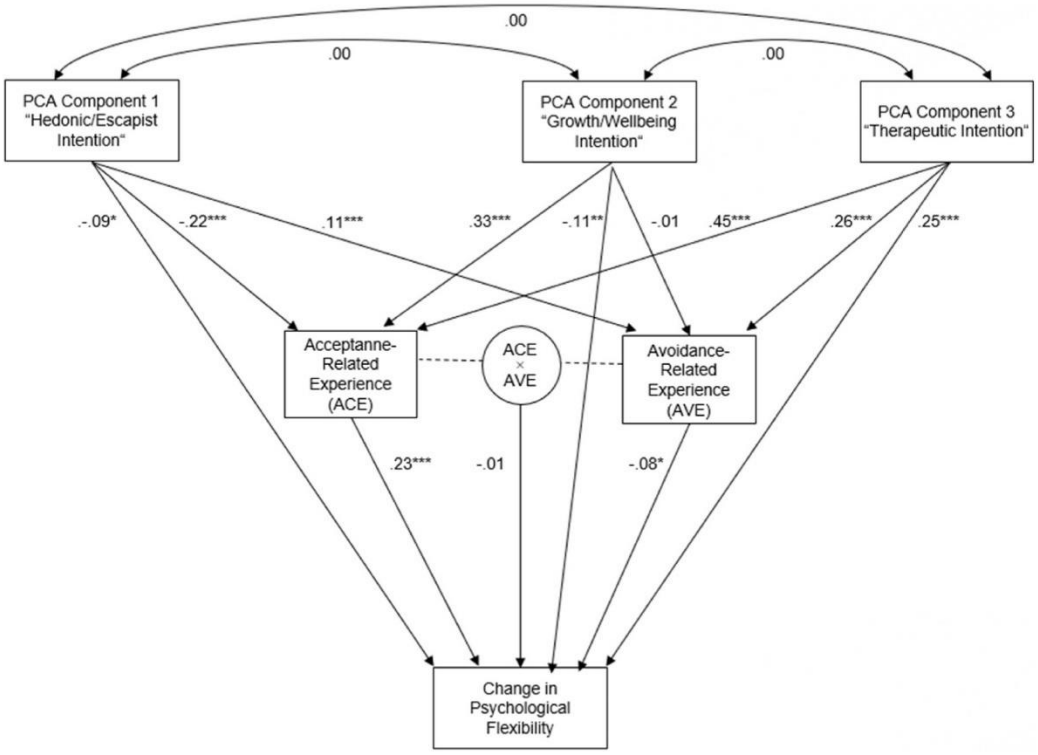


Fig. 2. – Path model showing associations between use motives, ACE, AVE, and changes in psychological flexibility.
PCA= Principal Component Analysis; ACE = Acceptance-related experience; AVE = Avoidance-related experience; * = p < .05; ** = p < .01; *** = p < .001. All coefficients are standardized. Correlations between use motives were all 0 since PCA component scores are by default uncorrelated.

Table 5
– Reliability test of APEQ scales and subscales are provided. Results show standardized Cronbach's alpha coefficients.

Scale	Global sample (n = 715)	Spain (n = 420)	Latin America (n = 274)
ACE	.92	.92	.90
Accepting Response	.82	.83	.79
Relief	.80	.80	.80
Pro-Acceptance Insights	.82	.82	.81
AVE	.87	.87	.87
Avoidant Response	.73	.75	.71
Distress	.90	.90	.91
Pro-Avoidance Insights	.65	.70	.59
Introspection	.79	.82	.73
Interaction	.71	.73	.64

ACE = acceptance-related experience; AVE = avoidance-related experience.

2022), hinting at the strong correlation between them. This could mean that accepting responses cannot be dissociated from acceptance-related cognitions, at least when a relatively long time has elapsed since the reported experiences (on average 2.58 years in the present study). Experimental and clinical studies administering the APEQ directly after psychedelic dosing sessions are needed to determine whether the two factors can be separated when less time has elapsed between psychedelic administration and test administration.

All APEQ scales and subscales showed good internal consistency in the global sample. Of note, the "Pro-Avoidance Insights" and the "Interaction" subscales of the Latin-American subsample performed slightly worse, perhaps indicating minor problems regarding transcultural translation or the influence of outliers, since the Latin American subsample was smaller than the Spanish subsample.

Using PCA, three main factors underlying psychedelic use motives were identified: "hedonic/escapist", "growth/wellbeing" and "therapeutic" intention. These results are largely consistent with previous studies of psychedelic use motives that used the same or similar items (Wolff et al., 2022, 2024), although the present study was limited to therapeutic and ceremonial uses of psychedelics. Also consistent with previous results (Wolff et al., 2022), path analysis showed that use motives were associated with ACE and AVE scores, providing further evidence for the assumed context-dependence of acceptance and avoidance in psychedelic states. While therapeutic intentions were positively associated with both ACE and AVE, growth/wellbeing intentions were positively associated only with ACE but unassociated with AVE. This is in line with the view that approach motives are conducive to therapeutic experiences in psychotherapeutic contexts and beyond, and that problem-focused therapeutic experiences additionally require a motivation to confront and work on problems (Wolff et al., 2024). In contrast, "hedonic/escapist intention" (at least in therapeutic or ceremonial settings) can be considered to reflect avoidance motives, involving the search for pleasure instead of confronting difficult feelings or situations. In line with this, hedonic/escapist intentions were negatively associated with ACE but positively associated with AVE.

Also replicating previous results (Wolff et al., 2022), path analysis showed that ACE was positively associated with retrospective changes in psychological flexibility, whereas AVE showed a negative association. These results further support the view that acceptance during psychedelic experiences has a therapeutic value and mediate longer-term effects (Wolff et al., 2020), and more generally is in line with the

Table 6
– Intercorrelations between APEQ scales and external scales in the complete sample.

	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.
APEQ main scales													
1. ACE													
2. Accepting Response	.903***												
3. Relief	.850***	.604***											
4. Pro Acceptance Insights	.938***	.787***	.736***										
5. AVE	.091*	.230***	−.131***	.106**									
6. Avoidant Response	.061	.153***	−.104**	.085*	.844***								
7. Distress	.101**	.258***	−.120**	.092*	.849***	.554***							
8. Pro Avoidance Insights	.055	.133***	−.095*	.083*	.762***	.536***	.443***						
9. Introspection	.607***	.599***	.460***	.563***	.176***	.106**	.227***	.075*					
10. Interaction	−.037	−.120**	.077*	−.033	−.038	.042	−.129**	.021	−.310***				
External scales													
11. MEQ	.566***	.436***	.577***	.529***	.014	.003	.012	.021	.471***	.021			
12. CEQ	.114**	.253***	−.100**	.113***	.712***	.487***	.799***	.401***	.250***	−.127**	.148***		
13. PIQ_AMP	.788**	.786***	.572**	.748**	.207**	.207**	.245**	.205**	.551**	−.112**	.277**		
14. PIG_GAP	.770**	.671**	.655**	.751**	.655**	.096**	.081**	.128**	.562**	−.038	.770**		
15 PIQ_total	.815***	.770***	.631***	.781***	.215***	.167***	.185***	.179***	.582***	−.089*	.607***	.227***	
16. AAQ II change	.321***	.316***	.269***	.276***	.001	−.009	.061	−.072	.257***	−.106***	.218***	.105***	.317***

*** = p < .001(two-sided); ** = p < .01 (two-sided); * = p < .05 (two-sided); ACE = Acceptance-Related experience; AVE = Avoidance-Related experience; MEQ = Mystical Experience Questionnaire; CEQ= Challenging Experience Questionnaire; PIQ= Psychological Insight Questionnaire; PIQ-AMP = maladaptative patterns insight; PIQ-GAP = goals and adaptative partnerns; AAQ-II-change = difference between pre- and post-experience Acceptance and Action Questionnaire II scores.

consistently replicated finding that the subjective experience plays a substantial role in the therapeutic benefits provided by psychedelics (e.g., Dahan et al., 2024). However, no interaction effect was found between ACE and AVE variables, contrary to previous findings (Wolff et al., 2022). This may be due to an overrepresentation of positive experiences in our sample, potentially reducing statistical power to detect such an effect. Another possible explanation lies in the fact that our survey only assessed therapeutic settings, which might have an attenuating effect on the impact of AVEs. This warrants the need to further research to assess the specific role of AVEs and their relationship with context.

In summary, the present results suggest that crafting a therapeutic, approach-oriented intention prior to a psychedelic experience can promote acceptance-related psychedelic experiences, which in turn can maximize therapeutic outcomes.

Correlations found between APEQ scales and external scales support the underlying theories proposed in the methodology: ACE scores were strongly correlated with mystical experiences and psychological insights. AVE scores, in turn, were strongly correlated with challenging experiences and significantly, but weakly, with psychological insights. It is worth noting that psychological insights are not necessarily positive or adaptative, and challenging experiences have been associated with avoidance-related psychological insights (Davis, Barrett, et al., 2021). Overall, the Spanish APEQ showed good convergent validity with external measures of the acute psychedelic experience.

The sample gathered had a similar proportion of female and male participants, and was balanced between subsamples, as no significant difference was found in any demographic indicator. Interestingly, 44 % of the whole sample presented with some type of mental health diagnosis, which points to a relevant naturalistic use of psychedelics for self-treating purposes. Participants resided in 25 different countries but were grouped in three subsamples to assess for differences between Latin-American and Spain.

Regarding the experience reported, there were relevant differences in relation to the substance used in the reported experience. Interestingly, the Spanish population reported a higher proportion of ayahuasca experiences than the Latin-American population, which reported more psilocybin mushrooms and LSD experiences. This finding is quite relevant and could point to a selection bias in the Latin American population, where ayahuasca use could be more restricted to collectives with less access to the means through which this survey was disseminated. Also, the Latin-American subsample scored significantly higher on ACE and all its subscales, AVE and its subscales Avoidant Response and Pro-Avoidance Insights, and the Interaction ancillary scale. Most reported experiences were of a strong or very strong dose with rather pleasant effects, which could have caused an underrepresentation of challenging or difficult experiences (AVE scores). Also, the Latin-American subsample had a higher proportion of participants with the diagnosis of a mental disorder, especially depression and anxiety, which could point to an intention to treat themselves. This is also supported by the fact that this subsample scored significantly higher in growth/well-being intentions, which likely had an impact on the reported subjective experience. Moreover, although cases where more than one psychedelic was used were excluded from the analysis, up to 41 % of the participants in the whole sample did take concomitantly other psychoactive substances, mainly cannabis and alcohol. This fact is not considered a confounding factor given the purpose of this study, but it merits closer attention. In the case of cannabis, for example, some authors consider that it can cause psychedelic effects, especially when used in high doses (Wolinsky et al., 2024). In the Latin-American subsample, a higher concomitant use of cannabis was reported (30.3 % vs 21.2 %); which could also partially explain the differences observed in the subjective effects experienced. Future studies should control for the concurrent use of other substances, as this may hinder causal interpretations of the subjective effects of specific psychedelic substances.The fact that most people reported being in a good or very good mood before the experience, felt moderately or

well prepared, had a guide or sitter present, and were not alone, supports the theory that the naturalistic use of psychedelics tends to be performed by well-informed people that takes care to ensure proper preparation and risk-prevention. Of note, most of the population had previously taken psychedelics more than once, and more that 50 % took them more than 20 times before the reported experience, which hints to a very experienced population. This is a relevant selection bias that is also present in the population participating in current and recent clinical trials (Hovmand et al., 2023; Ona et al., 2022). Future research should focus on assessing differences between naïve or almost naïve populations and experienced uses.

The main limitations of this study have to do with the fact that it was cross-sectional and retrospective, so it is not possible to properly test assumptions in a causal manner. Also, participants reported on the memory of a subjectively chosen experience, an average of 2.58 years before the completion of the survey. This could imply another selection bias that may explain some demographic findings, such as a majority of positive experiences, and should be taken into account when interpreting these data or crafting future studies.

Another limitation concerns the study's primary outcome: retrospective change in AAQ-II scores before and after psychedelic use. The validity of the AAQ-II as a measure of psychological flexibility has been debated, as it primarily captures psychological inflexibility, a construct not necessarily equivalent to the inverse of flexibility and is known to correlate with psychological distress (Wolgast, 2014). Moreover, retrospective self-assessments are prone to memory bias, reducing methodological rigor and limiting causal inference. Nonetheless, given the retrospective design of our study, chosen to ensure sufficient sample size, we considered this approach to be the most feasible. Despite its limitations, the AAQ-II has been widely used in psychedelic research (e.g., Davis, Barrett, et al., 2021; Pilecki et al., 2024) and has a validated Spanish version, whereas alternative instruments lack such validation. Future research would benefit from prospective designs and the use of more comprehensive tools, such as the Multidimensional Psychological Flexibility Inventory (MPFI; Rolffs et al., 2018).

Due to the design of this study, test-retest reliability could not be assessed, as participants remained anonymous and completed the survey only once. However, there is no clear consensus about evaluating test-retest reliability for instruments designed to capture complex experiences such as those assessed by the APEQ. Variability in participant responses over time may not necessarily indicate a flaw in the instrument but could instead reflect various biases, such memory bias or shifts in perception following an integration process.

Finally, the instruments used to test construct validity do not measure the exact same constructs as the APEQ instrument, but rather related and similar characteristics of the psychedelic experience. This is because there exist no other instruments to date that measure acceptance-related and avoidance-related experiences occurred during a psychedelic experience. However, given the phenomenological similarity of the experiences measured with the chosen instruments, as well as their relationship with similar outcomes, as explained in the "Objectives" section, we can conclude that the findings related to construct validity can be considered sufficiently valid and relevant.

In conclusion, this study evaluated the psychometric properties of the Spanish version of the APEQ, demonstrating good construct, criterion, and cross-cultural validity, along with high internal consistency. These findings support its use as a reliable instrument for assessing acceptance- and avoidance-related experiences during psychedelic states, providing insights into the contextual dependency of ACEs and AVEs and their association with long-term changes in psychological flexibility. Our results align with the existing literature by reinforcing the notion that the quality of the subjective psychedelic experience is central to therapeutic outcomes (Yaden & Griffiths, 2021). Beyond translation and validation, this study provides empirical support for the APEQ's underlying theoretical framework, showing that acceptance-related experiences mediate positive psychological outcomes across diverse cultural contexts; this contributes to the understanding of how contextual and experiential dimensions of psychedelic use affect psychological flexibility, a key therapeutic mechanism. By confirming the APEQ's theoretical model in a large, non-English-speaking population, this study expands the cultural generalizability of psychological flexibility as a therapeutic mechanism and offers a validated instrument to investigate experiential processes in psychedelic therapy. These findings may inform both future clinical applications and the design of context-sensitive interventions. For example, and although further research is needed to clarify the specific role of ACEs and AVEs in clinical settings, these findings suggest that intentionally promoting ACEs may enhance therapeutic effectiveness of psychedelic-assisted therapeutic interventions.

Finally, this study also explored patterns of psychedelic use across a broad international sample, revealing high rates of comorbid substance use and mental health conditions among naturalistic users. These data points to the importance of integrating risk-reduction strategies and epidemiological insights into future research and public health efforts in the psychedelic field.

CRediT authorship contribution statement

Óscar Soto-Angona: Writing – review & editing, Writing – original draft, Visualization, Validation, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Amanda Rodríguez-Urrutia:** Writing – review & editing, Supervision, Conceptualization. **Josep Antoni Ramos-Quiroga:** Writing – review & editing, Supervision, Conceptualization. **Óscar Álvarez-Bobo:** Writing – review & editing, Methodology, Investigation. **Genís Ona:** Writing – review & editing, Validation, Methodology, Investigation. **Sergio Pérez Rosal:** Writing – review & editing, Investigation. **Juan París-Pérez:** Writing – review & editing, Investigation. **Max Wolff:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Data sharing statement

Data is available upon reasonable request.

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Declaration of competing interest

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or advisory and travel reimbursement. Josep Antoni Ramos Quiroga reports a relationship with Shionogi that includes: consulting or advisory and travel reimbursement. Josep Antoni Ramos Quiroga reports a relationship with Sincrolab SL that includes: consulting or advisory. Josep Antoni Ramos Quiroga reports a relationship with BMS that includes: consulting or advisory. Josep Antoni Ramos Quiroga reports a relationship with Rubio that includes: consulting or advisory and travel reimbursement. Josep Antoni Ramos Quiroga reports a relationship with Uriach that includes: consulting or advisory. Josep Antoni Ramos Quiroga reports a relationship with Technofarma that includes: consulting or advisory. Josep Antoni Ramos Quiroga reports a relationship with Raffo Laboratories that includes: consulting or advisory. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ayahuasca-assisted meaning reconstruction therapy for grief: a non-randomized clinical trial protocol

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Background: Psychotherapy for Prolonged Grief Disorder (PGD), a condition characterized by an intense and persistent grief response, has received increased attention over the past decades. Evidence-based approaches to prevent PGD are currently scarce, and not always effective. This paper introduces a protocol for a clinical trial exploring the effectiveness of a Meaning Reconstruction psychotherapy approach (MR) assisted with ayahuasca, a traditional indigenous medicine.

Method: The outlined protocol is a three-arm, non-randomized controlled trial focused on reducing normal and pathological grief symptoms, comparing the effectiveness of Ayahuasca-assisted MR therapy (A-MR), MR therapy alone (MR) and No Treatment (NT). At least 69 people who lost a first-degree relative during the prior year, and with a Texas Revised Inventory of Grief score up 39 (TRIG $\geq$ 40), will participate in the trial. Participants will be allocated to an A-MR (n $\geq$ 23), MR (n $\geq$ 23) or NT (n $\geq$ 23) group. Those from the A-MR and MR therapy groups will undergo a therapeutic process involving 9 sessions of online psychotherapy. In addition, the A-MR condition involves 2 group sessions of ayahuasca. The primary outcomes will be normal and pathological grief severity as measured by the TRIG and Traumatic Grief Inventory Self-Report (TGI-SR), administered at baseline, post-treatment, and 3-month follow up. Measures of quality of life, post-traumatic growth, meaning-made, psychological flexibility, and self-belief consistency will be also included. In addition, subjective effects of ayahuasca and acceptance-avoidance promoting effects will be assessed following ayahuasca administration. Finally, we will analyze the potential mediating effect of meaning-made, psychological flexibility and self-belief consistency in grief symptoms (as measured by the TRIG and TGI).

Discussion: This trial is the first to empirically examine the potential of psychedelic-assisted psychotherapy for grief, as well as the potential processes of change that may account for it.

Clinical trial registration: https://clinicaltrials.gov, identifier NCT06150859.

KEYWORDS

psychedelic-assisted therapy, ayahuasca, psychedelics, meaning reconstruction, psychotherapy, protocol, bereavement, prolonged grief disorder

1 Introduction

Grieving the death of a loved one is a nearly universal experience, and one which may be experienced multiple times over the course of a lifetime. Recent studies have shown that, for each death, approximately nine relatives are directly affected (1). The loss of a first-degree family member significantly increases the risk of mortality, disease, and suicide for the mourner (2–6). Although grief is a natural process, and serves a key existential purpose (7), this psychological process can go awry. Over the last century, different theories have explored how grief itself can become complicated or pathological.

Prolonged Grief Disorder (PGD) has been recently incorporated as a diagnosis into the ICD (ICD-11; 8) and the DSM (DSM-5-TR; 9). PGD is characterized by (1) separation distress (i.e. a persistent grief response involving intense longing and preoccupation), (2) intense emotional reactivity (e.g. anger, denial, blame, emotional numbness, meaninglessness, avoidance), and (3) significant functional impairment (10, 11) according to the mourner's sociocultural context. This reaction should persist to a marked degree for a minimum of 6 months, following the ICD-11 (8), or 12, months following the DSM-5-TR (9).

The inclusion of PGD in the psychiatric diagnostic system is not without controversy. Besides the difficulties of distinguishing normal from prolonged grief, and the arbitrariness involved in categorizing continuous variables such as distress or time (10), it has been argued that the requirement for these diagnoses may lead to people experiencing acute grief not receiving appropriate healthcare (12). On the other hand, people in Western countries are rapidly losing the cultural knowledge, tradition, and rites to cope with the death of a loved one (13). In this social context, imposing a 6-to-12-month wait for receiving evidence-based psychological support can leave bereaved people abandoned in the most vulnerable state, especially for those at moderate or high health risk.

Despite the WHO's emphasis on the importance of preventive strategies for addressing the global burden of mental health issues (14), and on loneliness as a significant public health issue (15), evidence-based approaches to prevent PGD are still scarce. Moreover, meta-analyses have shown that preventive therapies for PGD are not currently effective (16, 17). Innovation is therefore necessary to provide effective psychotherapeutic and community support to people in the acute period of grief (18).

1.1 Psychedelic-assisted grief therapy

Psychedelic-assisted psychotherapy (PAP), a therapeutic approach augmenting talking therapy with psychedelic substances, has been recently classified as a potential breakthrough treatment for psychiatric illness (19). PAP is demonstrating promising outcomes in treating a wide range of mental health issues, ranging from depression to post-traumatic stress disorder, suggesting this efficacy may be transdiagnostic (20, 21). Controlled studies to date have been primarily focused on MDMA-assisted therapy for PTSD (22) and psilocybin-assisted therapy for treatment-resistant depression (23), but it has been proposed that psychedelics could also serve as a prophylactic or preventive intervention with the potential to improve quality of life, well-being, creativity, and personal and spiritual growth (24, 25).

Ayahuasca, a traditional indigenous medicine, has been investigated as a potential treatment for treatment-resistant depression (26). Several studies have evidenced that individuals who regularly use ayahuasca in a communal setting exhibit a higher level of general well-being, increased physical activity, and balanced diet than the general population (27–29). While ayahuasca may not cause physical or psychological dependence, and serious adverse effects are uncommon in healthy individuals (30), some users have reported experiencing psychological distress during its acute effects (31). In a global survey involving 10,836 participants, 2.3% reported requiring medical support following ayahuasca use (32). Additionally, there have been a few documented instances where its consumption has been associated with the emergence of psychotic episodes (33). Nevertheless, most adverse effects can be mitigated by conducting a thorough assessment of participants' health status prior to administration, ensuring the composition and purity of the ayahuasca preparation, administering an appropriate dosage, and avoiding potential drug interactions (30) (see Section Potential Adverse Effects Management).

Despite the promising outcomes reported in the treatment of several mental health issues, no controlled studies have been conducted testing the efficacy of PAP for PGD, nor have any evaluated PAP's potential in preventing prolonged grief when administered in the early course of bereavement. Previous observational research, however, has suggested that the ceremonial use of ayahuasca has therapeutic value in reducing the severity of grief (34–36). We therefore propose that ayahuasca assisted with an evidence-informed therapeutic approach, the meaning reconstruction model (37, 38), could show greater reduction in grief severity than psychotherapy alone.

The rationale behind this hypothesis is grounded in a wide range of neurobiological and psychological evidence. Ayahuasca is an Amazonian concoction, usually prepared from the *Banisteriopsis caapi* vine and the *Psychotria viridis* shrub, which has been utilized for healing and ritual purposes since pre-Columbian times (39). Regarding the neurobiological evidence, *in vitro*, animal and human studies have demonstrated how harmine, tetrahydroharmine, harmaline (all three present in *B. caapi*) and dimethyltryptamine (present in *P. viridis*) stimulate adult neurogenesis and neuroplasticity, similarly to other serotoninergic psychedelic substances (40–43). A window for neuroplastic changes would appear to open a few hours after administration, lasting from a few days to a month (44). This period has been related to improvement in grief, depressive mood, stress, mindfulness, acceptance, emotion regulation, social behavior, wellbeing, and quality of life (45). Moreover, elevated peripheral Brain-Derived Neurotropic Factor (BDNF) levels have been observed in healthy volunteers and clinically depressed patients two days following the ayahuasca administration, correlating with clinical improvement in those who were diagnosed with major depression (40). Recent studies have shown that psychedelics reopen a critical period to induce metaplasticity, which dynamically regulates the potential for synaptic plasticity (46, 47). This critical period is context-dependent and has been linked to the ability to induce social reward learning, psychological flexibility, cognitive reappraisal and new patterns of behavior (46, 48, 49). In sum, these studies highlight the importance of the post-treatment integration period to maximize the therapeutic effect of psychedelics.

Looking beyond the neurobiological evidence, several studies indicate that the therapeutic effect is experience-dependent (50, 51). Current research points toward specific traits of the psychedelic experience as relevant mediators of the therapeutic outcomes of PAP, such as acceptance-related experiences, the presence of mystical experiences, or the reappraisal of negative emotion (52–55). The altered state of consciousness induced by psychedelics is characterized by high sensitivity to the immediate and previous context, which can help actualize of the person's belief system with bottom-up information (56). The ayahuasca experience, therefore, could bring new information to the foreground to enrich the therapeutic process, providing an opportunity to transform maladaptive narratives about oneself, other people (including the deceased) or the world (56, 57). The preparatory psychotherapeutic work, moreover, could bring to light potential blockages or resistances, allowing for an appropriate preparation of the patient's mindset and intention before the administration of ayahuasca. Lastly, psychotherapy following ayahuasca administration (including, but not limited to, psychedelic integration) could likewise help to promote new behavior, in a way that is congruent with reappraised cognitive schemas derived from the assimilation and accommodation of the experience during this critical period.

We posit, in sum, that ayahuasca experiences, when taking place within the framework of an appropriate and effective psychotherapeutic intervention, could enrich the clinical treatment of grief. This would allow for the integration of new information evoked from the psychedelic experience, and for this to result in more adaptive behavior and coping. We also hypothesize this would favor grief adaptation through fostering psychological processes such as meaning reconstruction, experiential acceptance, or cognitive reappraisal during a period of heightened meta-plasticity.

2 Study protocol

2.1 Study design and hypotheses

This three-arm, non-randomized controlled trial investigates the efficacy of Ayahuasca-assisted Meaning Reconstruction therapy (A-MR) in decreasing normal and pathological grief symptoms in people who have lost a first-degree relative within the prior 12 months. Participants are sequentially allocated to the following treatment conditions: (1) a control group receiving Meaning Reconstruction therapy (MR), (2) a control group receiving No Treatment (NT), and (3) an experimental group receiving Ayahuasca-assisted Meaning Reconstruction therapy (A-MR).

The objective of this trial is two-fold. First, our aim is to compare the efficacy of A-MR with that of MR and NT by assessing differences in (a) the severity of normal grief symptoms, (b) pathological grief symptoms, (c) quality of life, and (d) posttraumatic growth. Moreover, we are also interested in analyzing how each condition may influence the proposed processes of change: (e) meaning-made (f) psychological flexibility, and (g) self-belief consistency. Additionally, we will explore the participants' (h) subjective effects of ayahuasca and the (i) acceptance-avoidance promoting effects.

The following hypothesis will be tested:

Hypothesis 1. The experimental group receiving A-MR will show greater improvement in normal and pathological grief symptoms, quality of life, and post-traumatic growth compared to both control groups (MR and NT), at post-treatment and 3 months follow-up. Moreover, MR group will show greater improvement than the NT group, expecting a medium clinical effect size.

Hypothesis 1.1. The experimental group receiving A-MR will show greater improvement in psychological flexibility, meaning-made, and self-believed consistency compared to both control groups (MR and NT), at post-treatment and 3 months follow-up. Furthermore, MR will also show greater improvement than the NT group, expecting a medium clinical effect size.

Hypothesis 2. Reductions in the severity of normal and pathological grief symptoms will be principally related to changes

in meaning- made, but also to changes in psychological flexibility and self-belief consistency. Moreover, a stronger relationship between changes in the severity of grief symptoms and meaning-made is expected in the A-MR group.

2.2 Participants

Participants eligible for this study will be English and Spanish-speaking adults experiencing grief symptoms due to the death of a loved one. Inclusion criteria involve: (1) people aged 18-65; (2) having experienced the loss of a first-degree relative; (3) within the past 12 months; and (4) with a Texas Revised Inventory of Grief score over 39 (TRIG ≥ 40). Exclusion criteria involve: (1) medically and mentally significant health conditions; (2) history of psychotic disorder (Axis I- DSM-IV-TR); (3) pregnant or breastfeeding women; (4) hypertension (SBP > 140 mmHg, DBP > 90 mmHg, HR >100 bpm); (5) substance use disorder, excluding nicotine; (6) alcohol consumption exceeding 40g/day; (7) concurrent psychological or pharmacological treatment for grief. Those who are not eligible will be referred to other mental health professionals specialized in bereavement.

2.3 Procedure

Participants will be recruited through the newsletter, webpage, and social media accounts of the Beckley Foundation, Beckley Med, MIND Foundation and the International Center for Ethnobotanical Education, Research and Service (ICEERS), all of them European institutions dedicated to psychedelic research and education. Upon receiving the request to participate in the trial, the participant will be prompted to complete a short online questionnaire to screen for inclusion criteria. Those who meet the inclusion criteria will attend a video-call interview with the principal investigator (DG) to learn more about what their participation would entail and to screen whether any exclusion criteria are met. They will also be informed about the need to verify their blood pressure range with a general practitioner to prevent potential ineligibility, given that blood pressure measurement is taken on-site before each ayahuasca session. Then, those who are eligible will provide informed consent. Assessments will be conducted online at baseline (T0), during treatment (T1 and T2), at post-intervention (T3), and at 3-month follow-up (T4) (see Figure 1).

Participants in the A-MR and MR group will undergo a 9-session online psychotherapy process, starting within 2 weeks after the baseline assessment is completed. Only those in the A-MR group will participate in up to two onsite ayahuasca sessions throughout the therapeutic process, preceded by an online preparation session, and followed by a 50-minute MR online integration session during the week after each ayahuasca experience. For ethical reasons, participants in either control group (MR or NT) have the option to participate in two ayahuasca sessions over a single weekend, once follow-up assessment is completed, if their grief symptom severity are still significant (TRIG ≥ 40), proceeded by a preparation session and followed by two integration sessions to process the experience. Table 1 shows the measures used at each of the time points.

2.4 Sample size

Given that no comparative trials analyzing the therapeutic effect of PAP on reduction of grief symptoms has been published to date, sample size was calculated based on the results of González et al. (35) observational study. The observed Cohen's d (0.84) for the study group between the baseline and the 15th-day-post-treatment assessment, and TRIG measurement correlation of 0.55, were used to estimate the sample size for this study. Therefore, sample size was calculated based on the assumption of a between groups differences at post-treatment of at least 9.4 points (TRIG score) in mean change between the A-MR and the NT groups. Sample size with power of 0.90 and an alpha of 0.05 was calculated using pwrss R package version 0.3.1 (58). To find at least the above effect size, a total sample of 69 participants is needed, but as drop-out rate of 20% were considered, 84 participants will be recruited.

2.5 Psychometric measures

2.5.1 Primary outcomes

2.5.1.1 Texas Revised Inventory of Grief (TRIG)

This self-report measure quantifies the severity of normal grief (59). In this trial, only one scale (the Present Feelings Scale, PFS) was used to assess the participant's emotional state. This 13-item scale is scored on a 5-point Likert-type scale (from 1 = "completely false" to 5 = "completely true") ranging from 13 to 65. Scores up to 39 (TRIG ≥ 40; above the 50th percentile), are defined as severe grief (60). The TRIG has been shown to have adequate psychometric properties, with the PFS having a Cronbach's coefficient alpha value of.90 (61).

2.5.1.2 Traumatic Grief Inventory Self-Report (TGI-SR)

A measure designed to assess markers of grief disorder as defined by the ICD-11 and the DSM- 5, using PGD criteria (62). This questionnaire focuses on a total of 18 symptoms experienced during the preceding month, assessed on a 5-point Likert-type scales (from 1 = "never" to 5 = "always"). A total score of ≥ 59 identifies those meeting criteria for PGD-caseness. Cronbach's alphas of the TGI-SR in the patient sample were.95 (all 18 items),.95 (17 PCBD items), and.93 (11 PGD items).

2.5.2 Secondary outcomes

2.5.2.1 Posttraumatic Growth Inventory-Short Form (PSGI-SF)

This questionnaire measures the degree of positive change experienced in the aftermath of a traumatic event (63, 64). The PSGI-SF is a 10-item self-report measure scored on a 6-point Likert scale (from 1= "no change" to 6 = "a high degree of change"). The five subscales are: (1) relating to others, (2) new possibilities, (3) personal strength, (4) spiritual change, and (5) appreciation of life.

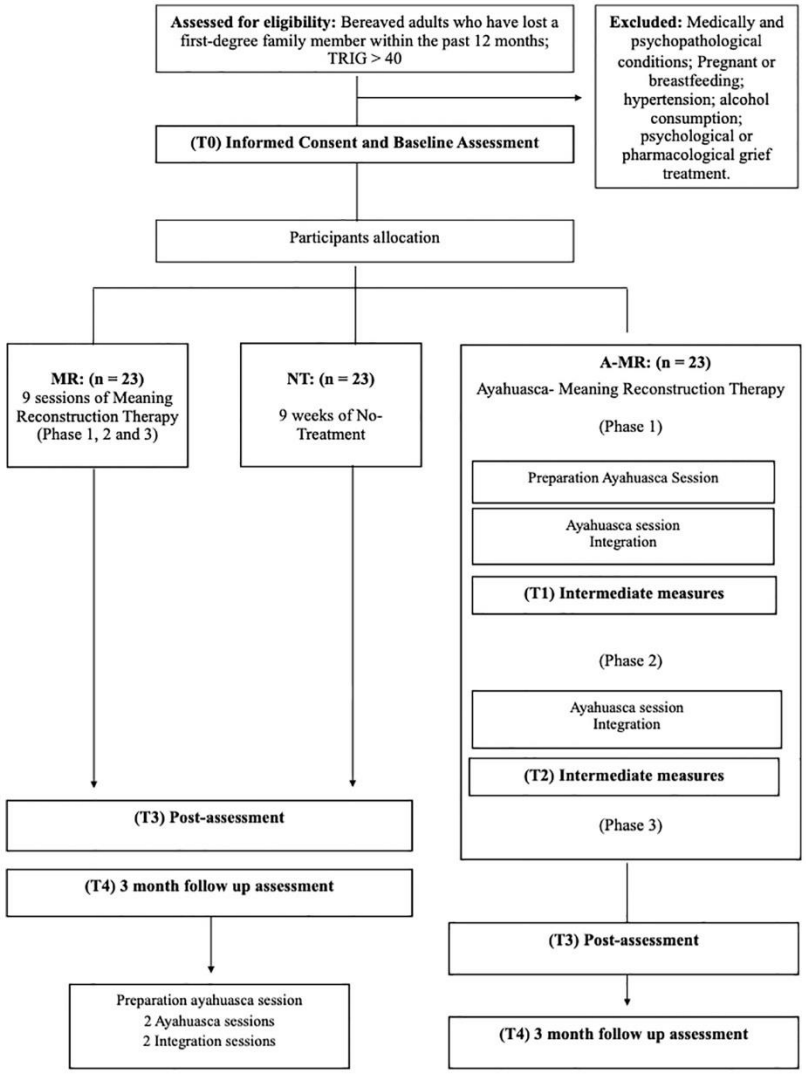


FIGURE 1
Flow-chart of the recruitment procedure.

Total scores ≥ 32 indicate probable personal growth (65). The internal consistency coefficient of the questionnaire is.86 -.89 (66).

2.5.2.2 World Health Organization Quality of Life-BREF (WHOQOL -BREF)

This questionnaire is a shorter version of the original WHOQOL-100 (67). The measure was designed to assess quality of life in four different areas: physical health, psychological health, social relationships, and environment. For this study, only the first three scales were used. The 24-item questionnaire is scored on a 4–20 scale, with higher scores indicating a better quality of life. The scale has been shown to have adequate psychometric properties, with Cronbach's coefficient alpha values ranging from.68 to.82 (68).

2.5.3 Measures of potential mediators

2.5.3.1 The Integration of Stressful Life Experiences Scale-Short Form (ISLES-SF)

This measure involves a self-assessment of "meaning made", as the successful outcome of meaning-making after stressful life experiences (69, 70). ISLES-SF is a 6-item version of the original 16-item measure, and it relies on a 5-point Likert response scale (from 1 = "strongly disagree" to 5 = "strongly agree"). Scores above 14 on the ISLES-SF have been found to reflect clinically significant functional impairment in family, occupational and social contexts (71).The scale has a validated bi-factorial structure, permitting overall assessment of challenges to meaning-making, as well as scoring of two subscales: (1) *Footing in the World* (a measure of

TABLE 1 Enrolment, intervention, and assessment schedule (SPIRIT).

	STUDY PERIOD									
	Enrolment	Baseline	Allocation	Treatment					Post-treatment	Follow-up
TIMEPOINT		(T0)		Phase 1	Ayahuasca (T1)	Phase 2	Ayahuasca (T2)	Phase 3	(T3)	(T4)
ENROLMENT										
Eligibility screen	x									
Informed consent	x									
Allocation			x							
INTERVENTION										
MR				x		x		x		
NT										
A-MR				x	x	x	x	x		
ASSESSMENT										
TRIG	x	x							x	x
TGI-SR		x							x	x
PSGI-SF		x							x	x
WHO-qol-BREF		x							x	x
AAQ-II		x							x	x
ISLES-SF		x							x	x
SCS		x							x	x
5D-ASC					x		x			
APEQ					x		x			
SA									x	

MR, Meaning Reconstruction Therapy; NT, No treatment; A-MR, Ayahuasca-assisted Meaning Reconstruction Therapy; TRIG, Texas- Revised Inventory of Grief; TGI-SR, Traumatic Grief Inventory self-report; PSGI-SF, Post-traumatic Growth Inventory-Short Form; WHO-qol-BREF, World Health Organization Quality of Life-Brief; AAQ-II, Acceptance and Action Questionnaire II; ISLES-SF, Integration of Stressful Life Experiences Scale Short-Form; SCS, Self-concept clarity Scale; 5D-ASC, Altered State of Consciousness Rating Scale; APEQ, Acceptance/Avoidance-Promoting Experiences Questionnaire Scale; SA, Level of Satisfaction and Adverse Effects

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personal disorientation following loss) and (2) Comprehensibility (an index of ability to make sense of the experience; 72). The ISLES-SF has shown to have strong psychometric properties, with a Cronbach's coefficient alpha value of.96 (73).

2.5.3.2 Acceptance and Action Questionnaire (AAQ-II)

This is a unidimensional scale to assess psychological flexibility (74, 75). The measure relies on a 7-point Likert-type scale (from 1 =" never true" to 7 = "always true"). The total score is calculated adding all individual scores, with lower scores corresponding to greater psychological flexibility. In terms of psychometric properties, the AAQ-II has good validity and reliability with the mean Cronbach's alpha being.84

2.5.3.3 Self-Concept Clarity Scale (SCS)

This 12-item scale measure the clarity and cohesiveness of the person's self-concept (76). Self-concept clarity is measured on a 5 point-Likert scale (from 1= "strongly disagree" to 5 = "strongly agree"), with higher scores corresponding to greater self-concept clarity. The SCS has been shown to have adequate psychometric properties, with a Cronbach's coefficient alpha value of .86.

2.5.4 Measures of subjective effects

2.5.4.1 The Altered State of Consciousness Rating Scale (5D-ASC)

This is a visual-analogue 94-item scale assessing five key dimensions of altered states of consciousness independently of their etiology (77). In this study, the 42-item version will be used (78), comprised of five different dimensions: (1) Oceanic Boundlessness, (2) Anxious Ego, (3) Visionary Restructuralization, (4) Auditory Alterations, and (5) Reduction of Vigilance (RV). The outcomes of the 5D-ASC data are percentage scores of maximum absolute scale values. This 42-item version has shown to have adequate psychometric properties, with Cronbach's coefficient alpha of.83 for the 11-factorial structure (78).

2.5.4.2 Acceptance/Avoidance-Promoting Experiences Questionnaire Scale (APEQ)

This psychometric instrument has been designed to measure experiences related to acceptance and avoidance, that occur during a psychedelic-induced altered state of consciousness. The questionnaire is self-reported and comprises 32 items, divided into two main scales: (1) the Acceptance-Related Experience (ACE) scale and the (2) Avoidance-Related Experience (AVE) scale, as well as two ancillary scales: Introspection and Interaction. The Acceptance-Related Experience (ACE) scale encompasses the subscales (1.1) Accepting Response, (1.2) Pro-Acceptance Insights, and (1.3) Relief. The Avoidance-Related Experience (AVE) scales comprise the subscales (2.1) Pro-Avoidance Insight, (2.2) Avoidant Response, and (2.3) Distress subscales. Cronbach's coefficient alphas are.92 for the ACE scale,.89 for the AVE scale,.84 for the Introspection scale, and.75 for the Interaction scale.

2.5.5 Level of Satisfaction and Adverse Effects Assessment (S.A)

In the post-assessment, participants will complete a survey comprising two satisfaction-related questions: (1) "To what extent are you satisfied with the therapeutic support provided during the psychotherapy sessions?"; (2) "To what extent are you satisfied with the ayahuasca sessions?". Responses will be rated using a 5-point Likert-type scale (from 1 = "Very dissatisfied" to 5 = "Very satisfied")

Adverse effects will be evaluated using the following questions: (3) "Have you experienced any negative effects from the psychotherapeutic sessions?"; (4) "Did you experience any negative effects during the ayahuasca session?"; (5) "Did you experience any negative effects in the week following the ayahuasca session?". Responses will be categorized as: (1) No, (2) Uncertain, or (3) Yes.

Each of these questions will be followed by an open-ended prompt encouraging participants to provide further details about their responses.

2.6 Data analyses

All the studied variables will be descriptively analyzed by means (SDs), medians (ranges) or n (percentages). Between groups baseline differences will be tested using 2-tailed t-test, Man-Whitney test or chi-square/Fisher's exacts test based on the type of variables compared.

Despite the trial being exploratory study, data will be analyzed following the intent-to-treat and/or completer strategies, based on the presence of drop-out. The first hypothesis (H1) will be tested using an independent two-way repeated measures analysis of variance (ANOVA) with 3 levels for each factor (Group: A-MR *vs* MR *vs* NT; Time: pre-treatment *vs* post-treatment *vs* follow-up) and/or Linear Mixed Models (LMM) for each primary and secondary outcome studied. The LMM will be used to analyze the possible effect of between groups differences at baseline measures as covariables, and to analyze the effect of the presence PGD diagnoses following the ICD-11 duration criterion at baseline. Bonferroni corrections will be applied to all analyses, and partial eta-square and Cohen's *d* effect sizes will be calculated for interaction effects and for between- and within-group comparisons, respectively. Confidence intervals for Cohen's *d* will be estimated at a 95% confidence level and 500 bootstrap samples.

The analysis of the second hypothesis (H2) will be based on the outcomes of testing H1, with reduction in grief severity (TRIG and TGI scores) as the dependent variable for mediation analyses. The mediation model will include all participants in the study and will only incorporate the potentially significant mediating variables (meaning-made, psychological flexibility, and self-belief consistency) identified in previous analyses. Power analyses for the mediation models will also be conducted based on a Monte Carlo simulation.

The statistical analyses will be conducted using R version 4.2.3 (79). The following R packages will be used for data exploration, description, and preprocessing if necessary: tidyverse (80), car (81),

moments version 0.14.1 (82), and nortest version 1.0-4 (83). The repeated measures ANOVAs and/or Lineal Mixed Models will be conducted using rstatix package version 0.7.2 (84). Finally, the mediation model will be tested using the lavaan package version 0.6-12 (85) and statistical power for the mediational analysis will be calculated using WebPower package version 0.9.4 (86).

2.7 Intervention

2.7.1 Meaning Reconstruction therapy

The psychotherapy protocol, part of both the A-MR and the MR group, is grounded in a meaning reconstruction approach to grief therapy (37, 38, 87). This model focuses on the crucial role of meaning-making in recovery and posttraumatic growth after the death of a significant person (69, 88–90). The intervention follows a tripartite approach that helps mourners overcome obstacles in making sense of the loss, reworking their attachment relationship to the deceased, and reconstructing their identities in light of the experience (37, 38). Open trials of the model with both unselected self-referred groups experiencing loss and transition (91) and mourners meeting criterial for PGD (92) have strongly supported the effectiveness of the model and, added to a growing literature, indicate that meaning-making prospectively predicts positive adaptation to bereavement (88, 92–95).

The 9-session A-MR and MR can be subdivided into the three domains defined in meaning reconstruction theory: the "event story" of the loss, the "back story" of the relationship with the deceased, and the "personal story" of self (37, 38) (Table 2):

1. The first phase is focused on the employment of non-directive narrative retelling to help the participant revisit the story of the loss, and the stressful or traumatic memories connected to it (37, 96, 97). This technique, when conducted in a safe and low-avoidance setting, can enable the bereaved to reconstruct a coherent narrative of the loss and its implications through introspection and deliberative processing and integration of its meaning. When necessary (e.g. when significant anxiety is present), relaxation and/or mindfulness techniques are introduced to manage activation and foster self-regulation.
2. The second phase is focused on promoting a secure attachment with the deceased (98), addressing unfinished business, or processing anger and guilt (37). Different techniques are employed to help reconstruct the internal representation of the deceased, such as introducing the deceased (99) and engaging in an imaginal conversation with them (100). When appropriate, and desired by the participant, a key aim is to establish and maintain a constructive continuing bond with the deceased (101).
3. The third and last phase prioritizes the reconstruction of the bereaved person's sense of self and their future as a survivor (7, 102). The Bull's-Eye Values Survey (BEVS), a contextual form of behavioral activation and values clarification, is employed to restore the participant's life orientation without the deceased (103).

Participants will complete a 50-minute session on a weekly basis, conducted online through a secure videoconference platform in compliance with HIPAA guidelines. Every therapist in the trial is a licensed psychologist, and all of them have received specialized training in the delivery of the treatment protocol. Furthermore, they have access to clinical supervision provided by DG and PS upon request. All the therapists have prior experience in PAP and/or psychedelic integration and are affiliated with the Spanish Society of Psychedelic Medicine (SEMPSi).

2.7.2 Ayahuasca-assisted Meaning Reconstruction therapy

The experimental group intervention (A-MR) adheres to the same online Meaning Reconstruction Therapy protocol, with the incorporation of up to two onsite ayahuasca sessions following phase 1 (session 3) and phase 2 (session 6) (see Table 2). The first ayahuasca session is preceded by a preparatory online group session (after session 1) and is followed by an online individual integration session during the week after the ayahuasca administration. This design is based on the contemporary structure of PAP, which typically involves a three-stage framework encompassing preparation, facilitation, and integration (104).

The objective of the preparation session is for participants to become familiarized with one another, address any uncertainties that might arise after reviewing the written information provided, and foster an appropriate expectation for the upcoming ayahuasca experience. Psychedelic integration following the ayahuasca session is conducted in alignment with the non-directive principles of restorative retelling (100, 105). Restorative retelling facilitates the assimilation of the phenomenology of the ayahuasca experience, while helping the person reconstruct their schemas and narratives about themselves, other people and the world, through a process of accommodation. A detailed outline of this method of psychedelic integration has been published elsewhere, in the form of a case study (106). Features of the psychedelic experiences that persist, or could gradually unfold, are further addressed during the remaining psychotherapeutic process.

2.7.2.1 Ayahuasca session procedure

Each ayahuasca session is conducted onsite over a 24-hour period, starting on Saturday morning. At 11:00 am, each participant is asked to attend an initial group meeting to discuss how the day will be organized. Immediately after that meeting, blood pressure and body weight are assessed by a medical doctor to ensure that this inclusion criterion is met, and to calculate the appropriate ayahuasca dose for each participant.

At 13:00h, a second meeting takes place to practice mindfulness exercises in a group format, which are aimed at promoting a low-avoidance and present-focused mindset during the psychedelic experience. Before the start of the first ayahuasca session at 14:30h, each participant takes part in a one-hour group dynamic during which they introduce their loved one to the rest of group, by sharing photos of the deceased (99). During the second ayahuasca session, this activity is replaced by an art-therapy activity, the dual rose technique, which can aid in the reconstruction of meaningful memories of the deceased and the relationship with them (107).

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TABLE 2 Ayahuasca-assisted meaning reconstruction protocol (A-MR).

Phases	Psychological content	Session	Techniques
Opening	Fostering therapeutic alliance; Exploring potential difficulties; Psychoeducation: Dual model of grief coping	1	
On-line preparation of ayahuasca session*			
Phase 1: The "event story" of the loss	Processing traumatic or stressing memories, and finding meaning in loss and in life	2	Narrative retelling
		3	Narrative retelling
First ayahuasca session*			
Integration of ayahuasca experience*			
Phase 2: The "back story" of the relationship with the deceased	Restoring attachment security through reconstructing a bond with the deceased and/or processing unfinished business	4	Introducing the deceased
		5	Imaginal conversation with the deceased
		6	Internal representation of the deceased's reconstruction
Second ayahuasca session*			
Integration of ayahuasca experience*			
Phase 3: The "personal story" of self	Reorganizing one's identity and life orientation as a survivor	7	Bull's-Eye Values Survey
		8	Bull's-Eye Values Survey
Ending	Summary of the psychotherapeutic process	9	

*Excluded in the MR intervention protocol.

Both activities help anchor the psychological content related to the loss in the participants' mindset, immediately before the ayahuasca administration takes place.

During the ayahuasca session in the afternoon, participants recline on a comfortable couch in a quiet, ample room, while listening to the same instrumental music through a loudspeaker. They are encouraged to focus their attention inward, and research staff are always present in the room to address participants' needs. Psychedelic effects typically last 5 hours, approximately, and participants are encouraged to describe their experience in writing during the 2 hours immediately afterward. Those who prefer to paint or draw to assimilate and express their experiences, instead of writing them down, are provided with the materials to do so.

After this period of rest and reflection, a healthy vegetarian dinner is provided. Subsequently, participants sleep under medical supervision. The following morning, a light breakfast is served. Participants are then invited to optionally share their ayahuasca experiences in a group setting, expressing themselves as they feel comfortable. During this sharing, non-directive principles are followed to validate their psychedelic experiences. Before the session is over, they are provided with general information and advice regarding the sensitive state they may find themselves afterward, and how to manage it.

Ayahuasca sessions will be conducted in groups of up to eight participants, supported by a team of four facilitators. The primary responsibility of the facilitators is to ensure the physical and psychological safety and trust of participants throughout the session. They also provide non-directive support to help participants engage openly with their internal experiences as they emerge. The facilitator team includes the head of the Santo Daime Church (Barcelona), a psychiatrist (JJ), a nurse, and the principal investigator of the study (DG). All facilitators have extensive experience supporting individuals through altered states of consciousness. Their expertise spans religious settings, clinics treating treatment-resistant depression with ketamine-assisted psychotherapy, and several psychedelic research studies. They have also collaborated with retreat centers administering ayahuasca and psilocybin, in both traditional and non-traditional contexts.

2.7.2.2 Potential adverse effects management

Ayahuasca has been demonstrated to be safe in naturalistic (35, 108) and clinical settings, across varying dosages and multiple administrations (26, 109–112). To enhance participant safety, individuals with a history of psychosis, medical complications, hypertension, or potential pharmacological interactions are excluded. While physically safe, the acute effects of ayahuasca are often challenging and not necessarily pleasant.

2.7.2.2.1 Acute effects

Nausea and vomiting are common during ayahuasca sessions (32), so each participant will have a bucket, tissue, and water placed next to their mat to facilitate vomiting without needing to leave for the restroom. If a participant experiences significant distress, agitation,

anxiety, fear, or paranoia, facilitators will provide reassurance and encourage acceptance and curiosity toward the challenging internal experiences. Grounding techniques, including deep breathing, mindful awareness (learned before the session), and progressive muscle relaxation, may also be suggested. Participants feeling overwhelmed by the group experience may be temporarily moved to a quiet space and remain under a direct facilitator's supervision.

2.7.2.2.2 Post-acute effects

The effects of ayahuasca are expected to last 5-6 hours, although participants may rest on their mats for up to 4 additional hours while listening to calming music under professional supervision. In cases of anxiety or distress, grounding techniques and emotional regulation strategies will be employed. If nausea or vomiting persists, antiemetic teas, such as ginger or chamomile, will be offered. Vital signs, including blood pressure, will be closely monitored in participants exhibiting adverse effects after the ayahuasca session.

2.7.2.2.3 Rescue medication

After monitoring post-acute effects for 4 hours, the medical team will evaluate the need for rescue medication if clinically indicated. In cases of severe anxiety, 1 mg of lorazepam may be offered, and in cases of agitation or psychosis, 5 mg of olanzapine may be administered, with the option to repeat the dose after an hour if symptoms persist. In extreme cases of severe agitation, where there is a risk of self-harm or the participant hurting other people, intramuscular administration of 0.5 mg of clonazepam may be required. For cases of severe and persistent hypertension (SBP > 180 mm Hg, DBP > 120 mm Hg), participants will be closely monitored and lorazepam 1mg may be administered. If the hypertension persists after 30 minutes, 25 mg of captopril may be administered, with a second dose after 30 minutes if necessary. If systolic/diastolic blood pressure persists above 180/120mmHg, 10mg of amlodipine may be administered, with a subsequent referral to an emergency service to assess for target organ damage. Metoclopramide (10 mg) may be offered for severe, persistent nausea and paracetamol (500 mg) if the participant experiences severe headaches. Participants will remain under medical supervision for at least 12 hours after the ayahuasca experience: any residual symptoms will be addressed during subsequent psychotherapy sessions.

The excitement component of the Positive and Negative Syndrome Scale (PANSS-EC) (113) will be evaluated by the physician 24 hours after ingestion for all participants.

2.8 Pharmacological analyses and dosification

A 10-liter batch of ayahuasca (i.e, *Daime* in Portuguese) will be donated by CEFLURIS (IDARIS), a Brazilian-based religious organization associated with the Santo Daime church. Following a ritual tradition, ayahuasca is prepared by boiling the stems of *B. caapi* (which are rich in harmine, tetrahydroharmine, and harmaline) together with the leaves of *P. viridis* (which are rich in N,N-dimethyltryptamine) for several hours. Analyses are conducted by Energy Control (energycontrol-international.org) using Liquid Chromatography-Mass Spectrometry (LC-MS). The ayahuasca will be stored in a refrigerator at -40°C to minimize degradation of DMT and alkaloids as much as possible (114).

A medium dose of ayahuasca (0.75 mg DMT/kg) will be orally consumed in two different intakes (0.30 mg DMT/kg as an initial dose and 0.45 mg DMT/kg after 30 minutes). With this method, it is expected that the monoamine-oxidase-inhibiting properties of the β-carbolines in the first dose will block the metabolic degradation of DMT by MAO-A, enabling full access to systemic circulation once the second dose is administered (115).

3 Discussion

This clinical trial is the first to examine the potential of psychedelic-assisted grief therapy and, more specifically, of ayahuasca-assisted meaning reconstruction therapy for the reduction of the severity of grief symptoms. The study also investigates whether the intervention promotes quality of life and post-traumatic growth, while exploring a series of processes of change that may mediate this therapeutic effect. If this intervention proves to be both feasible and effective upon completion of this study, a future clinical trial will be designed with a focus on (a) prioritizing the mechanism(s) of change that will be identified through mediation analyses.

A key limitation of the trial is that the sequential allocation of participants may have a bias influence on the outcomes. Another limitation is a threat to external validity connected to the recruitment process: the self-referral process relies on the social media presence of psychedelic research and education institutions and associations, which may limit the generalizability of the clinical outcomes to the general population. Moreover, the fact that ayahuasca is a plant concoction complicates the determination of which alkaloids and active compounds influence the outcomes. Finally, accepting bereaved people who meet the ICD-11 sixth-month-since-the-loss criterion for PGD disorder (instead of the more conservative 12-month criterion) could blur the distinction between prevention and treatment. Nevertheless, we will also analyze PGD criteria following the ICD-11 as a potential moderator.

Given the lack of grief literacy in the general population, the widespread loneliness in Western society, and lack of mental health support during the early stages of bereavement, it is imperative to improve bereavement support for acute grief (13). The scarcity of evidence-based therapies for the prevention of PGD indicates the urgent need for new interventions to support bereaved people at moderate-to-high risk, according to the four-tier model (116). We anticipate that the outcomes of this trial will significantly

contribute to the field of bereavement care, helping to reduce the time needed for the bereaved to receive evidence-based support, and promoting their adaptation. Moving beyond the context of grief and loss, this study will also contribute to advancing our understanding of PAP as way to prevent and reduce the global mental health burden (14).

Ethics statement

The studies involving humans were approved by Comité de Ética de la Investigación Clínica del Hospital Universitari Germans Trias i Pujol Pujol (CEIC PI-19-188). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

PS: Investigation, Methodology, Supervision, Writing – original draft. OA: Data curation, Formal analysis, Methodology, Software, Writing – review & editing. RN: Conceptualization, Methodology, Writing – review & editing. OS-A: Investigation, Methodology, Writing – review & editing. JJ: Investigation, Writing – review & editing. JH: Resources, Validation, Visualization, Writing – review & editing. MF: Conceptualization, Resources, Supervision, Validation, Visualization, Writing – review & editing. DG: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – review & editing.

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Conflict of interest

The authors declare that the research will be conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Ayahuasca-assisted meaning reconstruction therapy as an early resource for bereavement: a non-randomized clinical trial

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Preliminary evidence suggests that ayahuasca may alleviate severe grief symptoms. This three-arm, sequentially allocated, open-label study examines the therapeutic changes associated with ayahuasca-assisted meaning reconstruction therapy (A-MR) compared to meaning reconstruction therapy alone (MR) and a no-treatment control (NT). A total of 84 adults experiencing severe grief within 12 months of losing a first-degree relative were allocated to A-MR ($n=28$), MR ($n=28$), or NT ($n=28$). Grief severity, prolonged grief disorder symptoms, post-traumatic growth, and quality of life were assessed at baseline, after the intervention, and 3 months post-intervention. Ayahuasca was well tolerated, with no serious adverse events reported. All groups showed significant grief severity reduction (A-MR: $p<.0001$, $d=2.44$; MR: $p<.0001$, $d=1.84$; NT: $p<.002$, $d=0.74$). Greater reductions were observed in the A-MR compared to MR ($p=.012$, $d=0.86$) and NT ($p=.0008$, $d=1.07$). A-MR was also associated with significant improvements in prolonged grief symptomatology, post-traumatic growth, and quality of life, with medium-to-large effect sizes. This is the first controlled prospective study to provide preliminary support for A-MR as a safe and potentially effective intervention for severe grief, though replication in larger randomized trials is required.

Keywords Ayahuasca, Psychedelic-assisted therapy, Meaning reconstruction, Grief, Bereavement, Prolonged grief disorder, Clinical trial

The word "ayahuasca", meaning "vine of the soul" in Quechua, refers to a concoction that has been used by various Amazonian cultures for spiritual, communal, and healing purposes since pre-Columbian times[1]. Ayahuasca is a natural plant-based brew typically composed of the bark of the *Banisteriopsis caapi* vine and the leaves of the *Psychotria viridis* shrub[2]. The main psychoactive compounds in the bark are monoamine oxidase inhibitors (MAOIs), which enable N, N-dimethyltryptamine (N, N-DMT), present in the leaves of the shrub, to exert its effects on the central nervous system[3]. N, N-DMT is a tryptamine that acts primarily as an agonist of the 5-HT2A receptor, but also exhibits activity at trace amine-associated receptors (TAARs) and sigma-1 receptors, interacting with the serotonin, glutamate, dopamine, and acetylcholine systems[4].

Animal, in vitro, and human studies have shown that ayahuasca, like other serotonergic psychedelics, stimulates adult neurogenesis and neuroplasticity[5–7] within a temporal window ranging from a few hours after administration to several weeks[8]. Post-acute effects include enhanced mindfulness capacities[9]creative divergent thinking[10]psychological flexibility[11]and cognitive reappraisal[12]which may promote new behavioral patterns if taking place as part of a psychotherapeutic process. A single dose of ayahuasca has been shown to reduce depressive symptoms and suicidality, with effects lasting from 7[13] to 21 days[14]. The subjective perceptual effects

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evoked by ayahuasca have been correlated with reductions in depressive symptoms, underscoring the therapeutic importance of the phenomenological experience itself[13]. In addition to depression, preliminary evidence also indicates that ayahuasca may have the potential to alleviate grief symptoms after the loss of a loved one, although further research is needed[15,16]. Qualitative data suggest that ayahuasca may confer therapeutic benefits in the context of grief by eliciting subjective experiences that facilitate emotional processing, meaning-making of past events, and the reconstruction of identity and existential meaning[16]. Moreover, ayahuasca may facilitate the continuation of the bond with the deceased by evoking a new positive internal representation of them during its acute effects, thereby contributing to the redefinition of attachment to the deceased[17].

Grief, even when involving profound emotional turmoil and preoccupation with the deceased, is a normal and unavoidable aspect of human life. Most bereaved people experience moderate-to-high levels of grief shortly after the loss, often leading to disengagement from life and prior activities[18]. Although distress and avoidance normally decrease over time, a significant proportion of the population experiences different grief trajectories[19]. The fact that clinical research and intervention often focus on prolonged and functionally impairing grief, beyond 6 to 12 months after the loss, does not negate that the consequences of complex grief can be present earlier. The death of a close relative, for example, has been linked to an increased risk of suicide, self-harm, and psychiatric illness within the first year of the loss[20–22]. A decline in physical health, particularly cardiovascular health[23,24]has also been associated with recent bereavement, contributing to a heightened mortality risk within the first six-month period after spousal loss[25].

To date, meta-analyses have not found evidence supporting the effectiveness of any early psychological intervention in preventing Prolonged Grief Disorder (PGD)[26,27]. Additionally, there is no evidence that antidepressant medication is effective as a stand-alone treatment for PGD[28]. However, several studies have identified a notable increase in antidepressant prescriptions during the second month after bereavement, which tends to decline over the following year[29,30]. The development of effective and preventative early grief support therapies, therefore, could help decrease the risk of PGD, while also mitigating the early physical and emotional consequences for those who are most vulnerable.

This study aims to investigate the efficacy of an ayahuasca-assisted therapy based on a meaning reconstruction approach[31]focusing on bereaved people experiencing severe grief symptoms within the first year after the death of a loved one. Our primary hypothesis is that this intervention will lead to a significant reduction in grief symptom severity and PGD symptomatology, compared to the meaning reconstruction therapy alone and a no-intervention control group. In addition to this, we also hypothesize an increase in both post-traumatic growth and quality of life in the experimental group. We expect these changes to be sustained over a 3-month follow-up period.

Results

Participants and attrition

A total of 84 participants were allocated sequentially to the three study groups (Fig. 1).

A single participant dropped out of the experimental Ayahuasca-assisted Meaning Reconstruction therapy group (A-MR) following the first ayahuasca session, and a second participant in the No-Treatment group (NT) declined further participation before the post-intervention assessments (T3 and T4). Participants who dropped out had higher baseline grief scores compared to the mean score of those who completed the study (TRIG (T0): 63 and 60 vs. 52.4(7.1); $t_{(83)} \geq 9.86$; $ps \leq 0.001$; and TGI-SR (T0): 74 and 77 vs. 60.86 (12.2); $t_{(83)} \geq 9.87$; $ps \leq 0.001$). No participant dropped out of the Meaning Reconstruction group (MR). Total dropouts accounted for 2.4% of the total sample.

A total of fifty-five participants completed the 9-session-long psychotherapeutic component of the treatment (A-MR group: $n = 27$; MR group: $n = 28$). A total of 27 participants completed the first ayahuasca session, and 24 completed the second ayahuasca session in the A-MR group. No differences in any of the primary or secondary outcomes studied were observed when A-MR group participants who attended one or two ayahuasca sessions were compared (T0: $ps \geq 0.194$; T3: $ps \geq 0.353$; and T4: $ps \geq 0.538$).

A low frequency of missing values ($n = 15$; 0.40%) was observed. Moreover, missing values were observed only in 6 participants. Little's MCAR test ($c^2_{(72)}$ distance = 76.8; $p = .328$) and a logistic regression analysis were conducted to evaluate missing data, showing no relationships with the variables included in the study (all $ps > 0.999$).

The baseline characteristics of the total sample are presented in Table 1. No significant between-group differences were observed in any of the descriptive variables ($ps \geq 0.085$).

Safety

The acute effects of ayahuasca were well tolerated by all participants of the A-MR group, with no serious adverse events reported. The participant who declined further participation after the first ayahuasca experience claimed to see no meaning to ayahuasca sessions. Four participants did not take the second dose of ayahuasca, alleging not feeling psychologically prepared for another session so soon after the first one ($n = 1$), or due to a personal commitment on the day of the second administration ($n = 3$). Eight reported experiencing a negative effect during the ayahuasca session, and three were uncertain. Reported effects included nausea, vomiting or diarrhea ($n = 16$), headache ($n = 4$), fainting ($n = 2$), and anguish ($n = 2$) during the ayahuasca session. Only 3 participants perceived an adverse event the week following the ayahuasca session, including headache ($n = 1$), distraction, ($n = 1$) and minor sickness ($n = 1$). Open answers are shown in **Appendix 1.**

The average of the total PANSS-EC score was 5.07 (0.267) at 24 h post-administration. No participants required psychiatric medication within the 24-hour period following administration. Only two participants in the experimental group (A-MR) required Ibuprofen 8 h post-administration due to persistent headache.

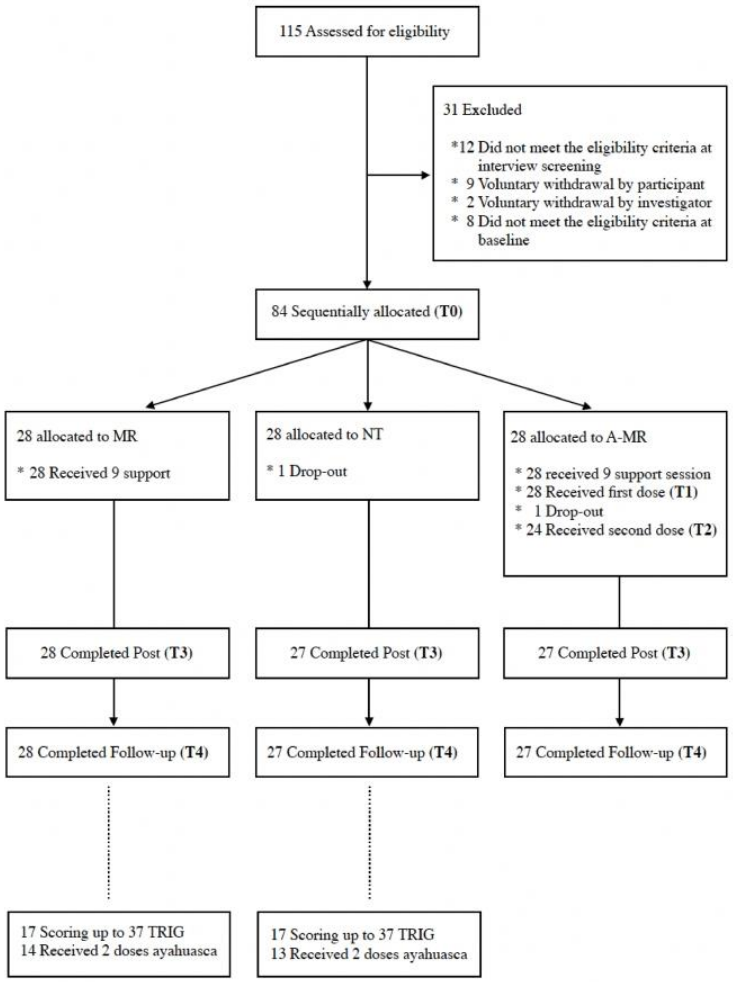


Fig. 1. Flowchart of participants.

Level of satisfaction with the support program and ayahuasca sessions

From the A-MR and MR groups Total sample ($n = 55$), 78.2% were very satisfied with the support program [A-MR: $n = 20$; MR: $n = 23$], 18.2% somewhat satisfied [A-MR: $n = 6$; MR: $n = 4$], 1.8% somewhat dissatisfied [A-MR: $n = 1$], and 1.8% were very dissatisfied [MR: $n = 1$]. Regarding the ayahuasca sessions in the A-MR group, 81.5% were very satisfied, 11.1% were somewhat satisfied, 3.7% were somewhat dissatisfied, and 3.7% were very dissatisfied. Open answers are shown in **Appendix 2.**

Primary outcomes

The descriptive statistics for the primary outcomes are reported in Table 2. For both measures studied, an *Intervention x Time* interaction was observed (TRIG: $F_{(3.57;\ 139.13)} = 22.70$; $p < .0001$; $\eta p^2 = 0.37$; TGI-SR: $F_{(3.57;\ 139.37)} = 24.88$; $p < .0001$; $\eta p^2 = 0.39$). However, no interaction effect of the covariate 'Months Since Death' was observed in the TRIG analysis ($F_{(1.78;\ 139.13)} = 2.47$; $p = .094$; $\eta p^2 = 0.03$ and $F_{(1;\ 78)} = 1.06$; $p = .307$; $\eta p^2 = 0.01$; respectively) or in the TGI-SR analyses ($F_{(1.79;\ 139.37)} = 1.25$; $p = .286$; $\eta p^2 = 0.02$ and $F_{(1;\ 78)} = 0.55$; $p = .461$; $\eta p^2 < 0.01$; respectively).

The analysis of the interactions observed for the severity of grief symptoms (TRIG) did not show differences between groups at baseline (T0: $ps > 0.999$), nor between the MR and the NT groups at post-intervention or at the 3-month follow-up (T3 and T4: $ps \geq 0.961$). However, a higher reduction in normal grief severity was observed in the A-MR group compared to the NT group [T3: $p < .0001$; Cohen's $d = 1.50$; T4: $p < .0001$; Cohen's $d = 1.25$] and with the MR group [T3: $p = .0001$; Cohen's $d = 1.20$; T4: $p = .0008$; Cohen's $d = 1.05$] at both post-intervention measures (Table 3).

	Total sample	A-MR	MR	NT	
	n = 84 (%)	*n* = 28 (%)	*n* = 28 (%)	*n* = 28 (%)	*p*
Age, mean (SD)	43.2 (11.7)	43.8 (10.8)	44.6 (12.4)	41.1 (11.9)	0.497
Months since death, mean (SD)	5.9 (3.4)	5.8 (3.7)	6.7 (3.1)	5.2 (3.3)	0.218
Female	54 (64.3)	19 (67.8)	18 (64.3)	17 (63.0)	0.856
Marital status					
Single	26 (30.1)	6 (21.4)	8 (28.6)	12 (42.8)	0.447
Married/stable partner	41 (48.8)	16 (57.1)	13 (46.4)	12 (42.8)	
Divorced	11 (13.1)	5 (17.9)	3 (10.7)	3 (10.7)	
Widowed	6 (7.1)	1 (3.6)	4 (14.3)	1 (3.6)	
With university studies	70 (83.3)	24 (85.7)	23 (82.1)	23 (82.1)	0.999
Caucasian	75 (89.3)	26 (92.8)	27 (96.4)	22 (78.6)	0.134
Religious	6 (7.1)	1 (3.6)	2 (7.1)	3 (10.7)	0.867
Relationship of the deceased					
Parent	50 (59.5)	20 (71.4)	15 (53.6)	15 (53.6)	0.389
Partner	8 (9.5)	1 (3.6)	5 (17.8)	2 (7.1)	
Son/daughter	15 (17.9)	4 (14.3)	6 (21.14)	5 (17.8)	
Brother/sister	11 (13.1)	3 (10.7)	2 (7.1)	6 (21.4)	
Cause of death					
Disease	46 (54.8)	19 (67.8)	16 (57.1)	11 (39.3)	0.269
Aging	10 (11.9)	4 (14.3)	3 (10.7)	3 (10.7)	
Suicide	4 (4.8)	1 (3.6)	2 (7.1)	1 (3.6)	
Accident	16 (19.0)	2 (7.1)	6 (21.4)	8 (28.6)	
Other/unknown	8 (9.5)	2 (7.1)	1 (3.6)	5 (17.8)	
Previous medication	8 (9.5)	3 (10.7)	4 (14.3)	1 (3.6)	0.520
Previous psychotherapy	22 (26.3)	8 (28.6)	7 (25.0)	7 (25.0)	0.940
Previous psychedelic use	62 (73.8)	25 (89.3)	18 (64.3)	19 (67.8)	0.085
Previous ayahuasca use	29 (34.5)	7 (25.0)	11 (39.3)	11 (39.3)	0.431

Table 1. Baseline sociodemographic characteristics of participants (total sample and by group).

	A-MR (*n* = 27)			MR (*n* = 28)			NT (*n* = 27)		
	T0	T3	T4	T0	T3	T4	T0	T3	T4
	Mean (SD) *	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)*	Mean (SD)	Mean (SD)
TRIG	52.0 (5.91)	34.1 (8.90)	33.2 (9.18)	53.2 (8.12)	45.2 (9.59)	43.2 (9.92)	51.3 (6.90)	47.7 (9.18)	45.0 (10.20)
TGI-SR	64.2 (9.43)	38.4 (8.86)	35.9 (11.10)	61.0 (10.78)	47.5 (12.14)	45.8 (14.62)	56.3 (14.72)	50.3 (12.95)	47.2 (13.15)
PSGI-SF	23.1 (9.82)	35.1 (9.62)	37.0 (10.92)	25.2 (10.82)	28.0 (8.01)	30.6 (11.05)	27.1 (13.77)	28.2 (10.96)	27.9 (12.44)
QoL-P. H	16.4 (2.89)	20.4 (3.09)	20.5 (3.37)	16.6 (3.34)	18.3 (3.35)	18.4 (3.54)	17.8 (2.82)	18.7 (2.22)	18.6 (2.56)
QoL-S. R	7.52 (2.46)	9.96 (2.93)	10.37 (2.68)	8.86 (2.49)	10.0 (2.45)	10.0 (2.74)	9.70 (1.92)	9.26 (9.26)	9.70 (2.25)

Table 2. Descriptive statistics for the primary and secondary outcomes at baseline (T0), post-intervention (T3) and 3-month follow-up (T4). Values are given as mean differences (with standard deviations). A-MR: Ayahuasca-assisted Meaning Reconstruction group; MR group: Meaning Reconstruction group; NT group: No treatment group. TRIG: Texas Revised Inventory of Grief total score; TGI-SR: Traumatic Grief Inventory Self-Report total scores; PSGI-SF: Post-traumatic Growth Inventory-Short Form total score; QoL-P.H: Psychological Health domain of the World Health Organization Quality of Life (WHOQOL-BREF); QoL-S. R: Social Relationships domain of the World Health Organization Quality of Life (WHOQOL-BREF).

The within-group comparison of TRIG showed a reduction in grief severity for all groups at post-intervention [A-MR (T0 vs. T3): $p < .0001$; Cohen's $d = 2.13$; MR (T0 vs. T3): $p < .0001$; Cohen's $d = 1.48$; NT (T0 vs. T3): $p = .02$; Cohen's $d = 0.59$] and at the follow-up assessment [A-MR (T0 vs. T4): $p < .0001$; Cohen's $d = 2.46$; MR(T0 vs. T4): $p < .0001$; Cohen's $d = 1.86$; NT (T0 vs. T4): $p = .004$; Cohen's $d = 0.86$]. No reductions were observed between T3 and T4 for any of the groups ($ps \geq 0.156$) (Fig. 2a).

The analysis of the *Intervention x Time* interaction for PGD symptoms (TGI-SR) showed no differences between groups at baseline (T0: $ps \geq 0.06$) or between the MR and NT groups at post-intervention or follow-up (T3 and T4: $ps \geq 0.990$).

	Between-groups							Within-group					
	A-MR vs. MR		A-MR vs. NT		MR vs. NT			A-MR		MR		NT	
	d	95%CI	d	95%CI	d	95%CI		d	95%CI	d	95%CI	d	95%CI
TRIG (**T0**)	0.17	0.16-0.19	0.10	0.08-0.13	0.24	0.23–27							
TRIG (**T3**)	1.20***	1.19–1.23	1.50****	1.51–1.55	0.27	0.26-0.30	TRIG (**T3** vs. **T0**)	2.13****	2.17–2.22	1.48****	1.48–1.52	0.59*	0.59-0.61
TRIG (**T4**)	1.05***	1.05–1.09	1.25***	1.26–1.29	0.21	0.19-0.23	TRIG (**T4** vs. **T0**)	2.46****	2.51–2.56	1.86****	1.90–1.95	0.86**	0.85-0.87
TGI-SR (**T0**)	0.32	0.31-0.34	0.64	0.63-0.67	0.36	0.36–39							
TGI-SR (**T3**)	0.86*	0.85-0.89	1.07**	1.07–1.11	0.22	0.20-0.24	TGI-SR (**T3** vs. **T0**)	2.44****	2.47–2.52	1.84****	1.87–1.91	0.74*	0.74-0.77
TGI-SR (**T4**)	0.76*	0.77–81	0.99**	0.98-1.02	0.15	0.14-0.17	TGI-SR (**T4** vs. **T0**)	2.48****	2.51–2.56	1.81****	1.86–1.89	0.96***	0.96-0.98
PTSG-SF (**T0**)	0.20	0.20-0.24	0.33	0.32-0.35	0.15	0.13-0.17							
PTSG-SF (**T3**)	0.80*	0.79-0.83	0.67*	0.66-0.70	0.02	0.003-0.04	PTSG-SF (**T3** vs. **T0**)	1.30****	1.31–1.33	0.28	0.28-0.31	0.10	0.09-0.11
PTSG-SF (**T4**)	0.59	0.57-0.61	0.77*	0.77–81	0.22	0.22-0.25	PTSG-SF (**T4** vs. **T0**)	1.78****	1.80–1.84	0.57*	0.58-0.61	0.09	0.08-0.10
QoL-P.H (**T0**)	0.06	0.04-0.08	0.47	0.45-0.50	0.36	0.36.-39							
QoL-P.H (**T3**)	0.66*	0.65-0.68	0.65	0.64-0.68	0.13	0.12-0.15	QoL-P.H (**T3** vs. **T0**)	1.18****	1.18–1.21	0.63**	0.62-0.64	0.42	0.41-0.44
QoL-P.H (**T4**)	0.60	0.60-0.63	0.64	0.64-0.67	0.05	0.04-0.07	QoL-P.H (**T4** vs. **T0**)	1.26****	1.26–1.30	0.89***	0.89-0.93	0.28	0.28-0.30
QoL-S.R (**T0**)	0.54	0.54-0.57	0.99**	0.99-1.03	0.38	0.37-0.40							
QoL-S.R (**T3**)	0.01	0.01-0.03	0.29	0.28-0.32	0.34	0.33-0.37	QoL-S.R (**T3** vs. **T0**)	1.11***	1.11–1.14	0.67**	0.67-0.69	0.22	0.21–23
QoL-S.R (**T4**)	0.14	0.12-0.15	0.27	0.26-0.30	0.12	0.11-0.14	QoL-S.R (**T4** vs. **T3**)	1.22****	1.24–1.27	0.56*	0.55-0.57	0.01	0.01-0.02

Table 3. Between-group and within-group effect sizes [Cohen's d (95% CI)] for the primary and secondary outcome variables. A-MR: Ayahuasca-assisted Meaning Reconstruction group; MR group: Meaning Reconstruction group; NT group: No treatment group. T0: pre-treatment assessment; T3: post-treatment assessment; T4: 3 months follow-up assessment. TRIG: Texas Revised Inventory of Grief total score; TGI-SR: Traumatic Grief Inventory Self-Report total scores; PSGI-SF: Post-traumatic Growth Inventory-Short Form total score; QoL-P.H: Psychological Health domain of the World Health Organization Quality of Life (WHOQOL-BREF); QoL-S.R: Social Relationships domain of the World Health Organization Quality of Life (WHOQOL-BREF). *: Bonferroni p-adjusted value < 0.05; **: Bonferroni p-adjusted value ≤ 0.01; ***: Bonferroni p-adjusted value ≤ 0.001; ****: Bonferroni p-adjusted value ≤ 0.0001.

However, differences were observed at both post-intervention assessment points between the A-MR and the MR groups [T3: $p = .012$; Cohen's $d = 0.86$; T4: $p = .018$; Cohen's $d = 0.76$], and between the A-MR and the NT groups [T3: $p = .0008$; Cohen's $d = 1.07$; T4: $p = .004$; Cohen's $d = 0.99$] (Table 3).

Within-group comparisons of TGI-SR showed reductions in all 3 groups at post-intervention [A-MR (T3 vs.T0): $p < .0001$; Cohen's $d = 2.44$; MR (T3 vs.T0): $p < .0001$; Cohen's $d = 1.84$; NT (T3 vs.T0): $p = .002$; Cohen's $d = 0.74$] and at follow-up [A-MR (T4 vs.T0): $p < .0001$; Cohen's $d = 2.48$; MR (T4 vs.T0): $p < .0001$; Cohen's $d = 1.81$; NT (T4 vs.T0): $p = .0001$; Cohen's $d = 0.96$]. No reductions were observed between T3 and T4 for any of the groups ($ps \geq 0.196$) (Fig. 2b).

Secondary outcomes

The descriptive statistics for the secondary outcomes are reported in Table 2. The RM-ANCOVA performed to test the effect of treatment on post-traumatic growth (PTSG-SF) showed an interaction of *Intervention* x *Time* ($F_{(3.55;\ 138.26)} = 9.51$; $p < .0001$; $hp^2 = .20$). However, no interaction effect of the covariate 'Months Since Death' was observed ($F_{(1.77;\ 138.26)} = 0.750$; $p = .474$; $hp^2 = 0.01$ and $F_{(1;\ 78)} = 0.062$; $p = .804$; $hp^2 < 0.01$; respectively).

The analysis of the interaction showed no significant differences between groups in PTSG-SF at baseline (T0: $ps \geq 0.650$). In addition, no significant differences were observed between the MR and the NT groups at post-intervention or follow-up (T3 and T4: $ps \geq 0.998$). However, higher PTSG-SF scores were observed for the A-MR group compared to the MR group at post-intervention [T3: $p = .023$; Cohen's $d = 0.80$], as well as compared to the NT group at post-intervention [T3: $p = .029$; Cohen's $d = 0.67$] and follow up [T4: $p = .014$; Cohen's $d = 0.77$] (see Table 2 and Fig. 3).

The within-group comparison performed to test the *Intervention x Time* interaction showed higher PTSG-SF scores for the A-MR group at both post-intervention time points [T0 vs. T3: $p < .0001$; Cohen's $d = 1.30$; T0 vs. T4: $p < .0001$; Cohen's $d = 1.78$]. The MR group showed higher PTSG-SF scores only at post-intervention assessment [T0 vs. T3: $p = .016$; Cohen's $d = 0.57$]. However, the NT group did not show significant improvement in PTSG-SF at any post-intervention time point (T3 and T4: $ps \geq 0.999$) (see Table 3 and Fig. 3a).

The RM-ANOVA performed to analyze the effect of treatment on the Psychological Health and Social Relationships domains of the WHOQOL-BREF showed *Intervention x Time* interaction ($F_{(4;\ 156)} = 7.01$; $p < .0001$; $\eta p^2 = 0.15$; $F_{(3.47;\ 135.2)} = 9.92$; $p < .0001$; $\eta p^2 = 0.20$; respectively). No main effect of the covariable "Months since death" was observed in Psychological Health ($F_{(2;\ 156)} = 1.72$; $p = .182$; $\eta p^2 = 0.02$; $F_{(1;\ 78)} = 1.29$; $p = .260$; $\eta p^2 = 0.02$), or in Social relationships domains ($F_{(1.73;\ 135.2)} = 1.09$; $p = .330$; $\eta p^2 = 0.01$; $F_{(1;\ 78)} = 0.571$; $p = .452$; $\eta p^2 < 0.01$).

The analysis conducted to assess the significant interaction of *Intervention x Time* for the Psychological Health domain of the WHOQOL-BREF did not show differences between groups at baseline (T0: $ps \geq 0.329$). Differences were only observed between A-MR and MR groups at post-intervention [T3: $p = .027$; Cohen's $d = 0.66$].

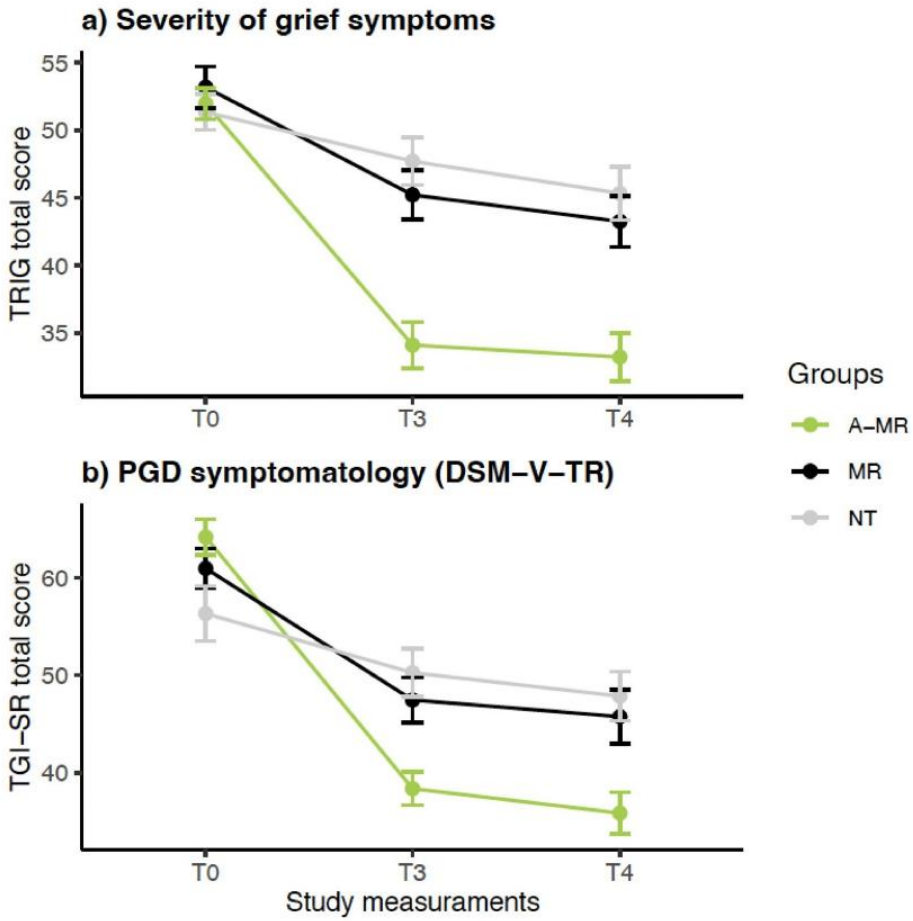


Fig. 2. Changes in primary outcomes at different time points. A-MR: Ayahuasca-assisted Meaning Reconstruction group; MR group: Meaning Reconstruction group; NT group: No treatment group; T0: Baseline; T3: Post-treatment; T4: 3 Months follow-up. TRIG: Texas Revised Inventory of Grief; TGI-SR: Traumatic Grief Inventory-Self Report; PGD: Prolonged Grief Disorder; DMS-V-TR: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision.

The within-group comparison did not show an improvement in the Psychological Health domain for the NT group at any post-intervention assessment (T3 and T4: $ps \geq 0.120$). On the other hand, both the A-MR and MR groups showed improvements at post-intervention [(T3 vs. T0): A-MR: $p < .0001$; Cohen's $d = 1.18$; MR: $p = .008$; Cohen's $d = 0.63$] and at follow-up [T4 vs. T0: A-MR: $p < .0001$; Cohen's $d = 1.26$; MR: $p = .0002$; Cohen's $d = 0.89$] (see Table 3 and Fig. 3b).

Finally, the between-groups comparison performed to analyze the interaction of *Intervention x Time* for the Social Relationships domain of the WHOQOL-BREF did not show differences at any post-treatment measurements (T3 and T4: $ps \geq 0.794$).

However, a lower Social Relationships domain score was observed for the A-MR group compared with the NT group at baseline [T0: $p = .002$; Cohen's $d = 0.99$]. The within-group comparison showed improvements in the Social Relationships domain at both post-intervention assessments for the A-MR group [T3 vs. T0: $p < .0001$; Cohen's $d = 1.11$; T4 vs. T0: $p < .0001$; Cohen's $d = 1.22$] and for the MR group [T3 vs. T0: $p = .005$; Cohen's $d = 0.67$; T4 vs. T0: $p = .019$; Cohen's $d = 0.56$]. No differences were found for the NT group at any post-treatment assessment ($ps \geq 0.807$) (see Table 3 **and** Fig. 3c).

Discussion

In this open-label, three-arm, sequentially allocated study, we evaluated the potential benefits of an ayahuasca-assisted meaning reconstruction therapy for grief. Our findings provide preliminary support for the safe use of ayahuasca within this therapeutic protocol, suggesting a reduction in the severity of grief symptoms and

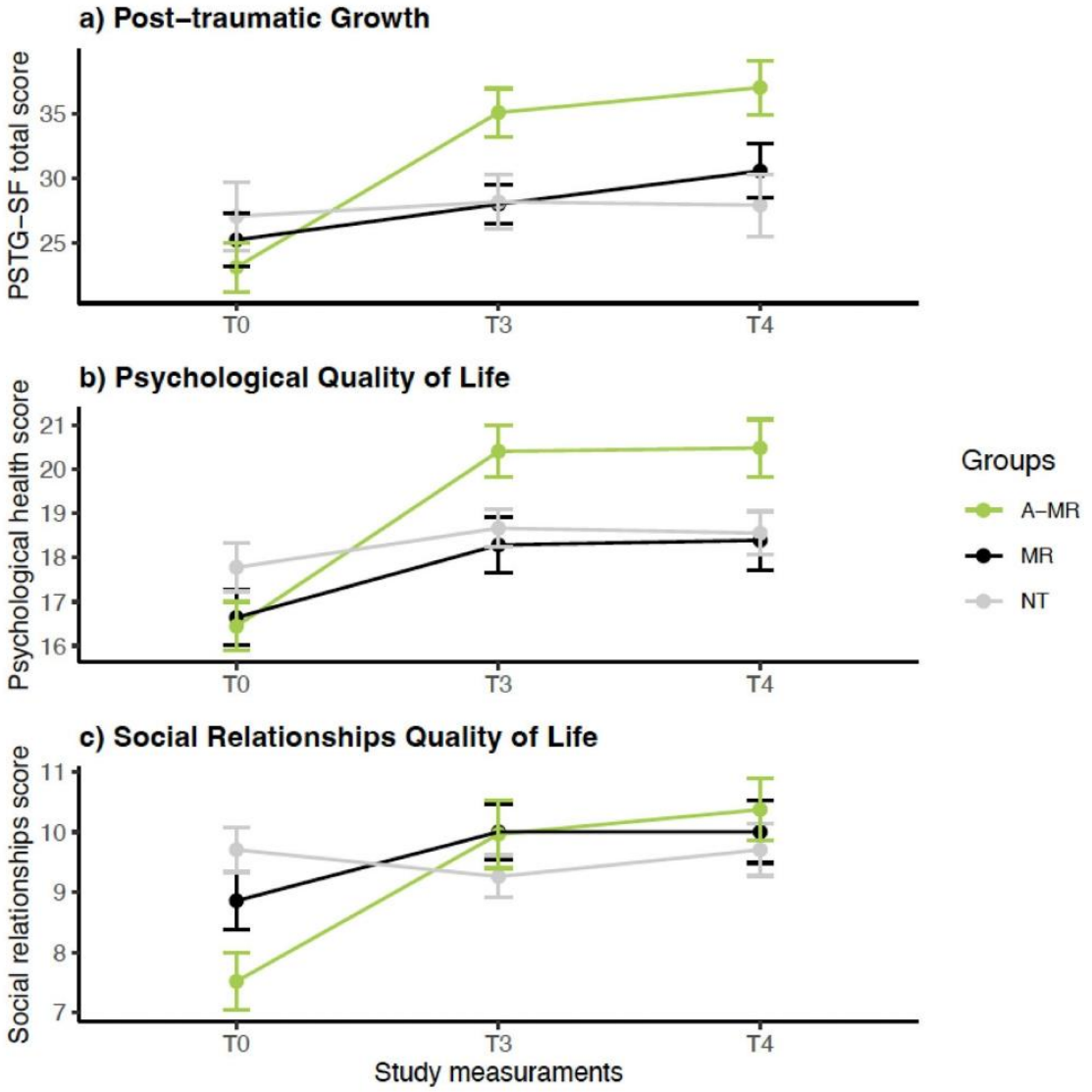


Fig. 3. Changes in secondary outcomes at different time points. A-MR: Ayahuasca-assisted Meaning Reconstruction group; MR group: Meaning Reconstruction group; NT group: No treatment group; T0: Baseline; T3: Post-treatment; T4: 3 Months follow-up; PTSG-SF: Posttraumatic Growth Inventory-Short Form; Psychological health: Psychological health domain of the World Health Organization Quality of Life (WHOQOL-BREF); Social relationships: Social relationships domain of the World Health Organization Quality of Life (WHOQOL-BREF).

PGD symptomatology, as well as the promotion of post-traumatic growth. The effects on these variables were superior to those observed with the therapeutic protocol alone, or the natural passing of time, and they remained stable for up to three months post-intervention. No serious adverse events were reported during the study. The incidence of minor adverse effects in the experimental group is aligned with prior research on ayahuasca use[32,33].

The magnitude of grief severity reduction observed in this study was consistent with the outcomes from previous observational research on the impact of ayahuasca on grief[15]. Notably, in this study, less than half the number of ayahuasca sessions were needed to achieve twice the effect size, which was maintained at follow-up. This may be because, in this study, the ayahuasca sessions were part of a specific meaning-oriented therapeutic protocol to address grief, which has demonstrated promise in previous open trials[34–37].

To our knowledge, only three studies have examined the efficacy of an early intervention on grief within the first year after the loss of a loved one[38–40]. Higher dropout rates, and lower intragroup effect sizes, were observed in such previous studies in comparison with the clinical outcomes reported here. In fact, the large effect size in the reduction of the severity of grief symptoms observed in the experimental group has not been found in any other intervention for PGD[26,41–44]. This may be attributable to the fact that one of the central challenges in grief is the meaningful integration of the loss into the bereaved individual's life narrative[34,38]. Interventions that emphasize narrative retelling and meaning-making processes have demonstrated efficacy in facilitating this integration. Within this therapeutic framework, ayahuasca may act as a potent catalyst by eliciting emotionally salient autobiographical memories involving both the bereaved and the deceased, while fostering insights into the loss and its existential dimension, and facilitating identity reorganization[15–17]. These emergent insights can then be further explored, processed, and integrated during post-experience integration sessions through structured restorative narrative retelling. The dynamic interplay between the acute subjective effects induced by ayahuasca, the psychotherapeutic integration sessions, and the broader meaning reconstruction therapeutic sessions may thus generate a synergistic effect, enhancing the intervention's capacity to address the complex psychological and emotional dimensions of grief.

Secondary outcomes also favored the Ayahuasca-assisted Meaning Reconstruction therapy group (A-MR) over control groups (MR and NT). Differences in post-traumatic growth were observed between the A-MR group and both control groups at post-intervention and over the NT group at follow-up assessments, with effect sizes ranging from medium to large. One of the psychological processes mediating post-traumatic growth when facing stressful events is the capacity to create meaning[45,46]. Several studies have proposed that psychedelics enhance the perception of meaning[47] which may function as a mediating mechanism underlying their therapeutic efficacy[48,49]. Our findings make it difficult to ascertain whether ayahuasca alone facilitates post-traumatic growth or if it results from the synergistic interaction with the integration and psychotherapeutic process. However, while an increase in post-traumatic growth is observed in the group that used ayahuasca (A-MR) at post-intervention assessment, the MR group needed a longer period to manifest this effect, only being observed at the follow-up assessment. The potential role of meaning-making as a mediator of primary and secondary outcomes will be analyzed in an upcoming publication[31].

Multiple studies have observed a negative relationship between grief and quality of life among bereaved people[50–52]. However, only a few studies have found an acceptable effect size on quality of life after a therapeutic intervention[53,54]. In this study, a moderate-to-large intragroup effect size was observed in the domains of psychological quality of life and social relating in the A-MR and MR groups, which was not observed in the NT group. The larger intragroup effect size observed in the experimental group aligns with the outcomes of other studies on the effect of ayahuasca on the quality of life in bereaved people[15] as well as studies on psilocybin and its impact on the quality of life of patients with life-threatening cancer[55,56] and depression[57].

Finally, although previous studies have found a moderating effect of time since death on the efficacy of bereavement therapies[27] the covariate "Months since death" did not have a significant effect on grief severity improvement or PGD symptomatology in our sample. However, we observed an improvement in bereavement symptoms across the different assessment points for the 3 groups once the study began. Since at the baseline assessment not enough time had passed to determine whether the sample exhibited chronic grief, these changes may be due to the natural course of the bereavement process, as well as unidentified biological and psychosocial variables that promote adaptation. In addition, it is known that enrollment in a clinical trial can lead to symptom improvement regardless of the treatment group in which the participant is included. This phenomenon is often attributed to the impact of being closely monitored, as repeated assessment of symptoms can alter those symptoms[58]. This is partly connected to the Hawthorne effect, where a person's behavior changes in response to the interest, care, or attention received by the study's personnel[59].

Limitations

It is important to note further limitations in this study. Foremost among these is the issue of internal validity. The non-randomization of groups was a direct consequence of the COVID-19 pandemic, during which restrictions on gatherings and sanitary requirements to enter Spain were enforced. These circumstances led us to sequence group allocation to start with the control groups (MR and NT), in which onsite ayahuasca sessions were not part of the intervention protocol, so they could be postponed at the conclusion of the follow-up assessment without a specific date. Nonetheless, sequential allocation inherently lacks the methodological rigor of randomization in controlling for selection bias. Consequently, there exists a substantive risk that temporal confounders, such as differential elapsed time since the COVID-19 pandemic between groups, or procedural variations, including evolving staff expertise, may have systematically influenced outcomes. These factors compromise intergroup comparability and challenge the attribution of observed effects exclusively to the intervention under study. Furthermore, the study's open-label design introduces a heightened potential for expectation bias, potentially impacting participant-reported outcomes, particularly given the reliance on self-report measures where subjective perception is paramount. Collectively, these design characteristics substantially limit the internal validity and generalizability of the findings, precluding definitive conclusions regarding the efficacy of the ayahuasca-assisted meaning reconstruction therapeutic protocol.

The second limitation involves external validity: the fact that three-quarters of the sample had used psychedelic substances in the past and were self-referred through the social media of psychedelic research institutions, may limit the generalizability of the outcomes. Expectancy effects could have influenced our results in the AM-R group, as prior use of psychedelics suggests that these participants may have had previous positive experiences.

The third limitation refers to the absence of standardized measures to capture the various dimensions of the negative effects associated with both psychological and pharmacological interventions, which leads to inconsistencies in the collected data and a potential underestimation of negative effects by participants.

Furthermore, the lack of an independent rater to assess whether adverse events are attributable to the intervention necessitates a careful assessment and interpretation of participants' reports of negative effects. This remains a critical issue in determining which patients may safely benefit from psychedelic therapy as a treatment alternative. Future studies would benefit from employing standardized assessment protocols that combine validated instruments with qualitative approaches to capture the complexity of potential adverse effects.

The fourth limitation has to do with the fact that no group received ayahuasca without therapeutic support, nor without preparation and integration sessions. Additionally, ayahuasca sessions were conducted in a group format, fostering the potential effect of mutual support and connection among bereaved participants. Moreover, the sessions took place in a natural setting, which may have influenced the participants' sense of well-being. These non-pharmacological factors prevent the effect of ayahuasca alone from being properly isolated from the effect of these components. However, the aim of the study was not the development of ayahuasca as a stand-alone drug treatment, but rather to assess potential benefits associated with an early supportive intervention for bereaved people that integrates two models that have shown promising results in preliminary studies: the psychedelic-assisted therapy framework[60] and meaning reconstruction approach to treat grief[35,61].

Finally, the short follow-up period of three months restricts the ability to explore the long-term sustainability of the intervention and to assess the potential for symptom relapse.

Conclusion

In conclusion, we aimed to examine the therapeutic changes associated with an ayahuasca-assisted meaning reconstruction therapy as an early resource to support bereaved people. We propose that the effects of ayahuasca may catalyze the psychotherapeutic work of meaning reconstruction, improving adaptation to loss. The magnitude and duration of the post-treatment reduction in the severity of grief and PGD symptoms, as well as the increase in post-traumatic growth, indicate the need for further research in this area. However, we would like to emphasize that consensual cooperation with Indigenous peoples and ayahuasca religious communities is essential to ensure the ethical and responsible use of ayahuasca in Western societies.

Method

Ethical considerations

The study was reviewed and approved by the Ethics Committee of the Hospital Universitari Germans Trias i Pujol (CEIC PI-19-188), Spain. The study was registered on clinicaltrials.gov on 2023-12-11 (NCT06150859). The trial protocol and statistical analysis plan have been previously published elsewhere[30]. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation, and with the Helsinki Declaration of 1975. Informed consent was obtained from all participants.

Trial design

This tree-arm sequentially allocated open-labeled study investigates the efficacy of ayahuasca-assisted meaning reconstruction therapy (A-MR) in decreasing grief symptoms severity and PGD symptoms in people who have lost a first-degree relative within the prior 12 months. Secondary outcomes involve post-traumatic growth, and the psychological health and social relationships domains of quality of life. Participants were sequentially allocated to the following treatment conditions, adhering to this predetermined order of assignment until the target sample size for each group was achieved: (1) a control group receiving Meaning Reconstruction Therapy (MR), (2) a control group receiving No Treatment (NT), and (3) an experimental group receiving Ayahuasca-assisted Meaning Reconstruction Therapy (A-MR). No measures were taken to achieve baseline equivalence between groups. Qualifying participants were assessed at baseline (T0), post-treatment (T3) and 3-month follow-up (T4). The subjective effects of ayahuasca were assessed in the experimental group (A-MR) on the following week after the ayahuasca administration (T1 and T2) (see Fig. 1). Results on the mediating potential of subjective affect and other mechanisms of psychological change will be analyzed in a future paper[31]. For ethical reasons, all participants who enrolled in either control group (MR or NT) and still showed severe grief after 3 months follow-up assessment (TRIG $\geq$ 40)[62], were offered 2 voluntary ayahuasca sessions conducted over a single weekend, preceded by one online group preparation session and followed by two online ayahuasca integration sessions, conducted over the two weeks following the ayahuasca session[31].

Sample size calculation

The sample size of 69 participants was calculated using the pwrss R package (version 0.3.158)[63] with a power of 0.90 and an alpha of 0.05. To account for a 20% drop-out rate, the final sample size was adjusted to 84. The sample size estimation was based on the effect size and the TRIG measurement correlation of 0.55, from a study by González et al.[15].

Participants

Participants were recruited from October 10, 2021, to April 15, 2024, advertising in the social media accounts of several international institutions related to psychedelic research. All participants met the following inclusion criteria: (1) aged 18 to 65, (2) having experienced the loss of a first-degree relative (3) within the past 12 months, and (4) with a Texas Revised Inventory of Grief score over 39 (TRIG $\geq$ 40). Exclusion criteria involved: (1) diagnosis of a medically significant health condition; (2) previous or current history of a psychotic disorder (Axis I- DSM-IV-TR); (3) pregnant or breastfeeding women; (4) hypertension (systolic blood pressure (SBP) > 140 mmHg, diastolic blood pressure (DBP) > 90 mmHg, heart rate (HR) > 100 bpm); (5) substance use

disorder, excluding nicotine; (6) alcohol consumption exceeding 40 g/day; (7) concurrent psychological or pharmacological treatment for grief.

All participants provided written informed consent prior to enrollment in the study. Informed consent was obtained by providing participants with clear and comprehensive information about the study's purpose, procedures, potential risks, and benefits. Risk disclosure included a detailed explanation of possible adverse effects or discomforts associated with the study. They also had the opportunity to ask questions during an online call prior to providing consent. Participants who gave written informed consent were screened for study eligibility and examined for psychiatric conditions by the principal investigator. Blood pressure was assessed by the medical doctor of the study on-site, before each ayahuasca session. Participant safety was monitored throughout the dosing session by trained staff to ensure their well-being.

Outcome measures

Severity of grief was assessed with the Texas Revised Inventory of Grief (TRIG)[64]and prolonged grief disorder symptoms following the DSM-5-TR[65] were assessed using Traumatic Grief Inventory-Self Report (TGI-SR)[66]. Secondary measures included posttraumatic growth, assessed with the Posttraumatic Growth Inventory-Short Form (PSGI-SF)[67] as well as Psychological Health and Social Relationships domains of quality of life, measured using the corresponding scales of the World Health Organization Quality of Life-BREF instrument (WHOQOL -BREF)[68]. Adverse events were collected 24 h after ingestion by a physician using the excitement component of the Positive and Negative Syndrome Scale (PANSS-EC)[69]. Moreover, participants answered the following questions at post-assessment: (1) "Have you experienced any negative effects from the psychotherapeutic sessions?"; (2) "Did you experience any negative effects during the ayahuasca session?"; (3) "Did you experience any negative effects in the week following the ayahuasca session?". Responses were categorized as: (1) No, (2) Uncertain, or (3) Yes. No standardized instruments were used to assess adverse events by the participants. Two satisfaction-related questions were added at post-assessment: (1) "To what extent are you satisfied with the therapeutic support provided during the psychotherapy sessions?"; (2) "To what extent are you satisfied with the ayahuasca sessions?". Responses were rated using a 5-point Likert-type scale (from 1 = "Very dissatisfied" to 5 = "Very satisfied"). These questions were followed by an open-ended prompt encouraging participants to provide further information about their responses. Responses are presented in the supplementary material to complement and illustrate the quantitative data. A qualitative analysis of these narratives will be undertaken in a subsequent sub-study.

Interventions

Components of the support program

The therapeutic protocol, part of both the A-MR and the MR groups, is grounded in a meaning reconstruction approach[38,70]. This model focuses on the crucial role of meaning-making in grief recovery, and posttraumatic growth, after the death of a loved one[71,72]. The intervention is structured around a three-phase framework aimed at supporting bereaved individuals in overcoming challenges related to sense-making and meaning-making around the loss, revising and redefining their attachment to the deceased, and reorganizing their sense of identity in response to the bereavement experience. Participants were offered a total of 9 online 50-minute sessions, on a weekly basis, conducted by a team of 4 clinical psychologists. Therapeutic sessions were conducted online through the Zoom for Healthcare platform, in compliance with HIPAA guidelines. Phase 1 (Session 2–3) addressed the "event story" of the loss, in order to process traumatic or stressful memories; Phase 2 (Session 4–6) focused on the "back story" of the relationship with the deceased, to restore attachment security through reconstructing a bond with the deceased (if appropriate) and to work through potential unfinished business; Phase 3 (Session 7–8) focused on the "personal story" of the participant's self, to reorganize their identity as a survivor (see[31,73]for a case report and a detailed therapeutic protocol respectively).

Ayahuasca sessions and integration

Ayahuasca sessions for the A-MR group were carried out at the IREHOM center in Barcelona, Spain. Ayahuasca sessions were conducted in groups of a maximum of 8 participants, supported by a minimum of 4 facilitators, after Phases 1 and 2 of the therapeutic protocol. Participants were encouraged to lie on a couch and listen to a standardized playlist of music on a speaker. An online individual psychedelic integration session was conducted after each ayahuasca session, during the following week, in alignment with the non-directive principles of restorative retelling[74,75]. Details of the procedure of the ayahuasca session have been previously published[31].

Ayahuasca analyses and dosage

A ten-liter batch of ayahuasca was donated by CEFLURIS (idaris.com.br/en), prepared by boiling the stems of *Banisteriopsis caapi* and the leaves of *Psychotria viridis*. Analyses were carried out by Energy Control (energycontrol-international.org) using liquid chromatography- mass spectrometry (LC–MS). The Ayahuasca brew used contained 0.6 mg/ml of N, N-dimethyltryptamine (DMT), 1.1 mg/ml of tetrahydroharmine, 0.03 mg/ml of harmaline, and 4.2 mg/ml of harmine and 0.01 mg/ml of N-methyltryptamine (NMT). A medium dose of ayahuasca (0.75 mg DMT/kg)[76] was orally consumed in two different intakes (0.30 mg DMT/kg as an initial dose and 0.45 mg DMT/kg after 30 min).

Safety measures

Blood pressure and heart rate were assessed one hour before each ayahuasca session and 6 h after administration. Medication was available to treat headaches, hypertension, severe anxiety, or psychotic symptoms. Participants remained in the center for a 24-hour period, under medical vigilance.

Statistical analysis

Statistical analyses were conducted following the best practice recommendations for clinical trials analysis[77,78]. As this is an exploratory study, a completer analysis strategy was used[79]. Before the study analysis, data were explored for outliers, missing variables and drop-out. To test the possibility that missing data could be considered as Missing Completely at Random (MCAR), Little's MCAR test and logistic regression analyses were used. Missing data were imputed simultaneously using Multivariate Imputation by Chained Eq.[80]. All the study variables were included for missing values imputation using the predictive mean matching methods and 5 multiple imputations.

Descriptive statistics were reported for the total sample and for the 3 groups studied: Meaning Reconstruction Therapy (MR), No Treatment (NT) and Ayahuasca-assisted Meaning Reconstruction Therapy (A-MR). Between groups differences at pre-treatment were analyzed using ANOVAs, Kruskal-Wallis, Chi-square or Fisher's exact test for the continuous, ordered and nominal variables, respectively. Drop-out participants for each group were reported and between drop-out and completers differences were tested using one-sample Student's *t*-test.

The effects of treatment on the primary (TRIG and TGI-SR) and secondary outcomes (PSGI-SF, WHOQOL-BRIEF Psychosocial Health and Social Relationships scales) were studied using repeated measures analysis of covariance (RM-ANCOVA). The RM-ANCOVA was used because time since death was included as a covariate in the analyses to test the effect of this variable on outcomes. Prior to performing the RM-ANCOVAs, applicability criteria for the test were analyzed. The RM-ANCOVAs included 2 fixed factors with 3 levels each (Time: pre, post-treatment and follow-up; Treatment: NT, MR and A-MR) and months since death as a covariate. Moreover, pre-treatment measures were also included as covariates in the RM-ANCOVAs, if significant differences at pre-treatment were observed. Greenhouse-Geisser correction was used when Mauchly's test for sphericity was significant with epsilon < 0.60, while Huynh-Feldt correction was used with epsilon values $\geq .60$[81]. The treatment effect was studied analyzing the Treatment x Time interaction. The effect of months since death on the participants' response was analyzed when a significant interaction with Time was observed. Significant interactions were analyzed by paired and unpaired Student's *t*-tests. Bonferroni corrections were applied to all analyses and only adjusted p values are reported in the Results section. Partial eta-square and Cohen's d effect sizes were reported for the interaction effects and for between and within groups comparisons, respectively. Differences between the ayahuasca group participants who attended to one or two ayahuasca sessions was tested using nonparametric independent samples test. Confidence intervals for Cohen's d was estimated with a 95% confidence level and 5000 bootstrap samples.

The statistical analyses were performed using R version 4.2.3[82]. The following R packages were used for data exploration, description, and preprocessing if necessary: tidyverse[83]car[84]moments version 0.14.1[85], and nortest version 1.0-4[86]. The RM ANOVAs and ANCOVAs were performed using the rstatix package version 0.7.2[87] and/or car package version[88]. Finally, missing variables were explored by naniar package[84] and missing data was imputed by MICE package version 3.16.0[89].

Data availability

Data from this study are available from the corresponding author upon reasonable request, subject to ethical and confidentiality considerations.

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Author contributions

OS-A: Investigation, Methodology, Writing original draft. OA: Data curation, Formal analysis, Methodology, Software, Writing – review & editing. PS: Investigation, Methodology, Supervision, Writing – review & editing. RN: Conceptualization, Methodology, Writing – review & editing. JH: Resources, Validation, Visualization, Writing – review & editing. JJ: Investigation, Writing – review & editing. MF: Conceptualization, Resources, Supervision, Validation, Visualization, Writing – review & editing. DG: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – review & editing.

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Declarations

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The authors declare no competing interests.

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DISCUSIÓN

Discusión general

La presente tesis se ha centrado en comprender los mecanismos psicológicos de cambio implicados en la acción de las sustancias psicodélicas sobre la mente. Partiendo de evidencia previa, se han planteado la flexibilidad psicológica y la atribución de significado como factores fundamentales, que se han evaluado mediante dos estudios orientados a cada uno de ellos. Las publicaciones resultantes presentan información novedosa que respalda las hipótesis planteadas y arroja luz sobre la dinámica de estos mecanismos y su potencial integración dentro de abordajes terapéuticos orientados a optimizar la eficacia de estas sustancias y maximizar su seguridad.

Estudio 1

El primer estudio abordó específicamente el mecanismo de flexibilidad psicológica mediante la validación de la versión en castellano del cuestionario *Acceptance/Avoidance-Promoting Experiences Questionnaire* (APEQ), un instrumento diseñado para evaluar experiencias subjetivas relacionadas con la aceptación (ACE) y la evitación (AVE) durante estados alterados de conciencia inducidos por psicodélicos. Este estudio no sólo se centró en evaluar las propiedades psicométricas de la versión en castellano de este instrumento, sino que también buscó verificar el paradigma teórico que lo sustenta y explorar la relación entre factores contextuales, elementos específicos de los estados alterados de conciencia causados por sustancias psicodélicas, y la flexibilidad psicológica. Se incluyó una muestra amplia (n = 715) de usuarios hispanohablantes procedentes principalmente de España y Latinoamérica, lo cual permitió además explorar patrones demográficos y motivacionales del consumo naturalístico de psicodélicos en estas poblaciones. No se observaron grandes diferencias demográficas entre ambas poblaciones, salvo por aspectos específicos como una mayor prevalencia del consumo de ayahuasca en España frente a Latinoamérica, donde predominaron las experiencias con LSD y psilocibina. Cabe destacar una alta prevalencia de diagnósticos de trastornos mentales en la muestra, lo cual apunta a un incremento en el número de personas que están recurriendo al uso de psicodélicos para aliviar su malestar fuera del ámbito clínico o institucional, y refuerza la importancia de avanzar en la investigación de estas sustancias para facilitar su acceso seguro para el tratamiento psiquiátrico. También cabe considerar

en este contexto la pertinencia de esfuerzos regulatorios que despenalicen su uso, de tal manera que los usuarios de estas sustancias tengan más acceso a iniciativas de reducción de daños, lo cual permitiría prevenir riesgos derivados del consumo de sustancias análogas o adulteradas, o en contextos no controlados donde existe un mayor riesgo de eventos adversos (Bremler et al., 2023).

Los resultados confirmaron la adecuada validez de constructo y criterio del cuestionario APEQ en población hispanohablante, que se mantuvo de manera transcultural cuando se evaluaron por separado las subpoblaciones latina y española. La escala presentó una estructura factorial satisfactoria, mostrando buena consistencia interna en todas sus subescalas. Cabe señalar que en este caso no se consideró necesario realizar una prueba de validez test-retest, ya que la escala APEQ evalúa experiencias subjetivas retrospectivas que, por su naturaleza, están sujetas a transformación con el paso del tiempo y con cada nueva evocación. En este contexto, que una misma persona otorgue puntuaciones diferentes en momentos distintos no implica una falta de fiabilidad del instrumento, sino que refleja el carácter dinámico y reconstructivo de la memoria autobiográfica. Lejos de representar un sesgo, esta variabilidad constituye una propiedad inherente del fenómeno que se pretende medir.

En conjunto, se puede considerar la versión en castellano del instrumento APEQ (Anexo 2) como un cuestionario válido para evaluar experiencias relacionadas con la aceptación y la evitación en estados inducidos por sustancias psicodélicas. Asimismo, se observó que la prevalencia e intensidad de las experiencias relacionadas con la aceptación estaban positivamente asociadas con la presencia de intenciones terapéuticas y orientadas al crecimiento personal, mientras que las experiencias relacionadas con la evitación se asociaron predominantemente con intenciones hedónicas o escapistas. Estos resultados replican y extienden los hallazgos previos obtenidos en las versiones originales en alemán e inglés del cuestionario (Wolff et al., 2022), confirmando la teoría subyacente según la cual los estados inducidos por psicodélicos están modulados por factores contextuales, como las intenciones *a priori* de consumo. Esto resulta relevante para el propósito de esta tesis, porque permite establecer una asociación entre el contexto y la fenomenología subjetiva de las experiencias psicodélicas.

Por otro lado, también se observó que las experiencias relacionadas con la aceptación durante el estado psicodélico fueron el predictor más robusto de cambios retrospectivos positivos en la flexibilidad psicológica. Aunque los resultados también indican que las experiencias de evitación se correlacionaron negativamente con cambios sobre la flexibilidad psicológica, no se confirmó una interacción estadísticamente significativa entre ambas dimensiones en nuestra muestra, uno de los supuestos teóricos propuestos en la validación original de la escala (Wolff et al., 2022). Esto podría tener relación con la sobrerrepresentación observada de experiencias predominantemente positivas, que habría dificultado la detección del impacto de las experiencias percibidas como negativas, lo cual respalda la necesidad de estudios prospectivos que evalúen directamente la dinámica de interacción entre aceptación y evitación en contextos clínicos reales. Otros estudios sobre experiencias similares apuntan a que, en algunos contextos, las experiencias difíciles, si se combinan con experiencias positivas posteriores, podrían desencadenar experiencias catárticas con valor terapéutico, algo que no se ha podido evaluar adecuadamente en este estudio (Roseman et al., 2019). En conjunto, tanto los factores contextuales (intenciones), y las experiencias relacionadas con la evitación y de aceptación presentaron valor predictivo sobre los cambios reportados en la flexibilidad psicológica.

Es importante no obstante contextualizar las limitaciones de este estudio, sustentadas principalmente en dos aspectos: por un lado, el uso de medidas retrospectivas de tipo pre-post, en las que se solicita a los participantes que valoren retrospectivamente su estado previo tras haber vivido la experiencia psicodélica. Este enfoque, aunque pragmático en contextos naturalísticos, conlleva varios sesgos que comprometen la validez interna de los hallazgos, ya que el recuerdo del estado previo puede estar sesgado por el estado actual, la intensidad de la experiencia psicodélica y la deseabilidad social. Esto puede dar lugar a una sobreestimación de las mejoras percibidas y a una reinterpretación más negativa del estado basal, limitando la validez interna y la posibilidad de establecer inferencias causales sólidas. Por otro lado, el análisis estadístico empleado se centró en evaluar las propiedades psicométricas de la escala APEQ y verificar los paradigmas teóricos subyacentes, lo cual pudo evitar el descubrimiento de nuevas asociaciones significativas. Por ejemplo, se recurrió a un *path analysis* para evaluar la relación entre

las intenciones, los valores de las distintas escalas, y los cambios en la flexibilidad psicológica, en lugar abordajes con un mayor valor para la exploración de relaciones desconocidas u ocultas, como un *latent class analysis.* Futuros estudios podrían beneficiarse de abordajes longitudinales prospectivos, que incluyeran análisis exploratorios o incluso entrevistas cualitativas.

Pese a las limitaciones descritas, estos hallazgos permiten plantear que determinados factores contextuales favorecen la aparición de experiencias relacionadas con la aceptación, las cuales ejercen a su vez un efecto positivo sobre la flexibilidad psicológica. Esto tiene implicaciones clínicas significativas, ya que plantea la posibilidad de desarrollar intervenciones específicas orientadas a modificar el contexto previo a la administración de un psicodélico, buscando así incrementar la presencia de experiencias que promueven la aceptación y, en consecuencia, potenciar la flexibilidad psicológica. Además, estas intervenciones podrían dirigirse selectivamente a participantes que presenten niveles iniciales bajos de flexibilidad psicológica o características clínicas particulares asociadas a patrones cognitivos rígidos, como ocurre en ciertos trastornos mentales específicos (Kashdan & Rottenberg, 2010). El cuestionario APEQ se presenta como una herramienta válida para evaluar tanto la eficacia de dichas intervenciones como su relación causal con los cambios terapéuticos observados posteriormente.

Además de su validez psicométrica, el cuestionario APEQ también demostró convergencia con otras medidas relevantes de experiencias psicodélicas, mostrando una fuerte correlación entre las experiencias de aceptación y fenómenos como las experiencias místicas, así como entre las experiencias de evitación y las experiencias desafiantes, lo que también permite plantear explicaciones causales a correlaciones observadas previamente entre experiencias subjetivas y cambios sobre la salud mental. Por ejemplo, como se ha abordado previamente, existe amplio consenso sobre el efecto beneficioso de las experiencias místicas (Ko et al., 2022), pero todavía no existe un claro marco teórico que explique el motivo de este efecto positivo, y lo mismo ocurre con las experiencias desafiantes y su posible impacto nocivo. Asimilarlas, al menos en parte, con experiencias de aceptación y evitación permitiría comprender mejor su valor dentro de un marco terapéutico.

Considerando que el castellano es la segunda lengua más hablada a nivel mundial, la traducción al castellano de la escala APEQ también facilita enormemente diversificar las poblaciones de estudio. Esto resulta especialmente relevante porque la mayor parte de la investigación actual sobre los efectos psicológicos de las sustancias psicodélicas proviene de poblaciones anglófonas, que además presentan importantes sesgos socioculturales, económicos y de género (Hovmand et al., 2023). Nuestro estudio es el primero en evaluar específicamente los efectos de los psicodélicos sobre la flexibilidad psicológica en población hispanohablante, lo cual aumenta la validez externa y generalizabilidad de los resultados previos y posibilita explorar cómo factores culturales específicos pueden modular la experiencia psicodélica y su eficacia terapéutica. Esta herramienta abre además la puerta a futuras investigaciones en una población que supera los 600 millones de personas.

En conjunto, los hallazgos del Estudio 1 aportan evidencia empírica que respalda uno de los ejes centrales de esta tesis: la flexibilidad psicológica no solo puede actuar como un mecanismo de cambio relevante en los efectos terapéuticos de los psicodélicos, sino que su expresión está mediada por variables fenomenológicas y contextuales que pueden ser operacionalizadas, medidas e incluso modificadas. Esto confirma la pertinencia del modelo integrador propuesto en la introducción, según el cual la acción de los psicodélicos sólo puede comprenderse si se tiene en cuenta su interacción con el contexto y la experiencia subjetiva.

Estudio 2

El segundo estudio de esta tesis se centró en evaluar el mecanismo de atribución de significado, mediante la aplicación de una intervención psicoterapéutica constructivista dirigida al duelo, y su posible sinergia con la administración de ayahuasca en un contexto grupal y terapéutico. En la publicación 2 se puede leer el protocolo completo del estudio, que consistió en un ensayo clínico abierto, con asignación secuencial a tres condiciones: grupo sin tratamiento (NT), grupo que recibió únicamente la terapia de reconstrucción de significado (MR), administrada a lo largo de 9 sesiones, y grupo que recibió la misma intervención psicoterapéutica combinada con hasta dos sesiones de ayahuasca (A-MR). Se asignaron 28 participantes a cada una de las ramas del estudio; además, se ofrecieron

dos sesiones de ayahuasca a aquellos participantes asignados a los grupos NT o MR que así lo desearan una vez finalizado el estudio, con la finalidad de minimizar el sesgo de expectativas y cumplir con estándares éticos. La intervención psicoterapéutica se basó en el modelo de construcción del significado del duelo (Neimeyer, 2019), que promueve la reconstrucción narrativa del evento de pérdida, la reelaboración del vínculo con la persona fallecida y la reorganización identitaria tras la muerte de un ser querido, lo cual permite modular la relación de la persona con la representación interna que tiene del ser querido que ha perdido.

Los resultados del estudio, sintetizados en la publicación 3, mostraron una mejora significativa en todos los grupos, pero de manera especialmente marcada en el grupo A-MR, que mostró una reducción de gran magnitud en la severidad del duelo y en los síntomas de trastorno de duelo prolongado, con tamaños del efecto muy superiores a los observados en las condiciones control y en la literatura previa. Estas mejoras se mantuvieron estables en el seguimiento a tres meses. Además, los participantes del grupo A-MR mostraron mayores incrementos en crecimiento postraumático y en bienestar psicológico, en comparación con los otros dos grupos. No se documentaron eventos adversos graves, sustentando la seguridad y tolerabilidad de todas las intervenciones.

Pese a lo prometedor de los resultados, estos hallazgos han de ser contextualizados dentro de las limitaciones inherentes a la metodología aplicada: en primer lugar, hay que tener en cuenta que se utilizó un procedimiento de reclutamiento secuencial no aleatorizado, consecuencia directa de las restricciones impuestas por la pandemia de COVID-19. Las medidas sanitarias y las limitaciones en reuniones presenciales en España obligaron a secuenciar la asignación de grupos, comenzando con los controles (MR y NT), ya que en estos las sesiones presenciales de ayahuasca no formaban parte del protocolo, por lo que podían posponerse hasta la finalización del seguimiento sin fecha definida. Esta asignación secuencial aumenta las probabilidades de sesgo de selección en comparación con la aleatorización. Además, no puede descartarse la influencia de factores de confusión temporales, como la diferencia en el tiempo transcurrido desde el inicio de la pandemia entre grupos, o de variaciones procedimentales, entre ellas la mayor experiencia adquirida por el equipo con el paso del tiempo. Dado que los participantes conocían de antemano

qué intervención recibirían, y no se añadió una intervención control con que comparar la administración de ayahuasca en el brazo de psicoterapia aislada, no es posible conocer con precisión el impacto de las expectativas en los resultados observados, o descartar una influencia significativa del efecto placebo. La decisión de no incluir esta intervención se basó en consideraciones éticas y metodológicas: se consideró que desplazar a los participantes hasta el lugar de dosificación sin ofrecerles un beneficio terapéutico claro resultaría perjudicial, mientras que el reclutamiento secuencial hacía imposible un verdadero cegado de las intervenciones. Incluso en un escenario con aleatorización, los efectos subjetivos intensos de la ayahuasca constituyen un obstáculo casi insalvable para lograr un cegado auténtico que elimine el sesgo por expectativas. Como posible estrategia futura, podría explorarse la administración aleatoria de ayahuasca o placebo dentro del mismo grupo y en una misma sesión, lo que permitiría evaluar de manera más precisa los efectos específicos de la sustancia, el contexto y las dinámicas grupales, aunque esta aproximación conllevaría el riesgo de incrementar fenómenos nocebo.

En segundo lugar, el tamaño muestral, aunque adecuado para detectar diferencias significativas, es aún limitado para extraer conclusiones generalizables o para realizar análisis de moderación más complejos que identifiquen qué perfiles de pacientes podrían beneficiarse más de esta combinación. Asimismo, la población del estudio estuvo compuesta por personas motivadas a recibir este tipo de intervención, lo cual puede haber introducido un sesgo de selección, limitando la aplicabilidad de los resultados a poblaciones clínicas más amplias o menos motivadas. Por otra parte, aunque se incorporó un riguroso protocolo de acompañamiento terapéutico, no se evaluó sistemáticamente la calidad del proceso terapéutico ni la adherencia al protocolo por parte de los facilitadores, lo cual podría haber influido en los resultados. Además, si bien se recogió información con instrumentos orientados a evaluar la atribución de significado como mecanismo específico, estos no formaron parte del análisis final debido a que el foco se centró en la eficacia clínica de la intervención, por lo que serían necesarios estudios posteriores que evaluaran la mediación o moderación específica de este mecanismo sobre los cambios observados. Finalmente, si bien se registraron efectos adversos menores (como náuseas, vómitos o malestar emocional transitorio), no se implementó un seguimiento a largo plazo

que permitiera detectar efectos negativos retardados o procesos de integración prolongada que implicaran cambios clínicos.

Si bien estas limitaciones obligan a mantener cautela a la hora de interpretar los resultados descritos, también cabe destacar la importante relevancia clínica y científica de los mismos: la superioridad de la condición combinada (A-MR) sugiere una sinergia específica entre la intervención psicoterapéutica sustentada en la reconstrucción de significado, y la experiencia inducida por la ayahuasca, que no sólo arroja beneficios terapéuticos: el efecto encontrado sobre el crecimiento postraumático y el bienestar psicológico apunta también a un posible valor salutogénico que podría facilitar la resiliencia y prevenir la aparición de futuros problemas de salud, como ya ha sido explorado previamente de manera incipiente (Spangemacher et al., 2024). Por lo tanto, este estudio aporta evidencia clínica de relevancia que sustenta la sinergia entre un modelo específico de psicoterapia basada en la construcción de significado, y el uso terapéutico de sustancias psicodélicas como la ayahuasca. Estos hallazgos respaldan la integración de sustancias psicodélicas dentro de marcos psicoterapéuticos estructurados, en los que el contenido fenomenológico de la experiencia se orienta hacia la reconstrucción narrativa de acontecimientos vitales significativos, como es el caso del duelo. A diferencia de los abordajes que entienden los psicodélicos como agentes catalíticos inespecíficos o como tratamientos exclusivamente farmacológicos, este estudio muestra que su potencial terapéutico puede amplificarse cuando se emplean como herramientas moduladoras de procesos psicológicos específicos, en este caso la atribución de significado.

Esta perspectiva tiene implicaciones importantes para el diseño de intervenciones clínicas efectivas. Por un lado, avala el uso de marcos terapéuticos que aprovechen la atribución de significado como mecanismo de acción de las sustancias psicodélicas. Por el otro, apoya la idea de que existen combinaciones específicas entre sustancia, contexto, preparación, acompañamiento e integración que permiten optimizar los resultados terapéuticos en función de la indicación o el perfil específico de los participantes. En particular, este modelo puede ser útil para abordar procesos de duelo complicado o prolongado, en los que los enfoques convencionales presentan eficacia limitada (Maass

et al., 2022), y donde el paciente muestra dificultades para reintegrar la experiencia de pérdida dentro de una narrativa vital coherente y significativa.

Finalmente, el diseño grupal y la combinación con intervenciones psicoterapéuticas breves representa un abordaje novedoso que aumenta la viabilidad y escalabilidad de este tipo de programas, frente a los modelos tradicionales, basados en intervenciones más intensivas administradas de manera individual por personal altamente cualificado.

Consideraciones generales

Tras analizar en detalle los hallazgos resultantes de los estudios 1 y 2, podemos considerar que la presente tesis ha abordado los objetivos planteados; por un lado, el primer estudio ha documentado el impacto de las intenciones previas sobre la fenomenología de las experiencias subjetivas, y ha establecido una relación entre estas y la flexibilidad psicológica, estableciendo de esta manera una asociación entre contexto, experiencia subjetiva y flexibilidad psicológica, en relación a los cambios ejercidos por las sustancias psicodélicas. El amplio tamaño muestral utilizado ha permitido de manera secundaria caracterizar los patrones de consumo naturalístico, y respaldar la validez externa de los hallazgos reportados. Además, se ha obtenido una versión española del cuestionario APEQ, que servirá como herramienta para documentar la presencia de experiencias relacionadas con la evitación y la aceptación, lo cual podrá facilitar futuros proyectos de investigación en esta dirección. Por otro lado, el segundo estudio se centró en evaluar una combinación específica de terapia y sustancia psicodélica (ayahuasca y terapia centrada en la reconstrucción de significado), diseñada para una población específica (personas con síntomas de duelo tras el fallecimiento de un ser querido). Esta intervención tuvo lugar en un contexto controlado y se sustentó en la hipótesis de que la atribución de significado es uno de los mecanismos psicológicos fundamentales para el efecto terapéutico de las sustancias psicodélicas. Este estudio se centró en evaluar la atribución de significado, con un énfasis en las implicaciones clínicas de incorporar este mecanismo. Por este motivo, utilizó un diseño centrado en evaluar el impacto clínico de la intervención, que se aleja del abordaje mecanicista utilizado en el Estudio 1, y tiene como limitación una mayor dificultad para establecer inferencias causales, ya que no evaluó aspectos clave considerados en el primero, como la influencia del contexto, o la

contribución de mecanismos psicológicos específicos. Sin embargo, estos aspectos sí se tuvieron en cuenta a la hora de elaborar la intervención terapéutica, con un control cuidadoso del entorno, incorporando aspectos como la música o la dinámica grupal, y la utilización de un abordaje psicoterapéutico centrado en la atribución de significado. En este sentido, cada estudio se centró en un mecanismo psicológico diferente, y ambos estudios también pueden considerarse complementarios a nivel metodológico y demográfico: el estudio 1 se centró en estudiar la flexibilidad psicológica desde un punto de vista explicativo, centrado en comprender su relación con otros aspectos claves de la experiencia psicodélica, y utilizó para ello población general y entornos naturalísticos, mientras que el estudio 2 se centró en explorar el impacto específico de la atribución de significado a la hora de diseñar intervenciones terapéuticas y optimizar los tratamientos asistidos con psicodélicos, y para ello utilizó población clínica y un entorno controlado. En conjunto, se han podido estudiar la flexibilidad psicológica y la atribución de significado, y se ha documentado su centralidad como factores clave a la hora de explicar los efectos de los psicodélicos.

Como se ha abordado en la introducción, para comprender de manera global estos hallazgos es importante tener en cuenta que la flexibilidad psicológica y la atribución de significado no pueden considerarse factores independientes y estancos, sino que probablemente interactúen de forma dinámica, sinérgica y bidireccional, lo cual dificulta su evaluación aislada (Yildirim et al., 2024). La distinción establecida para su estudio ha de considerarse desde el punto de vista operativo, no ontológico. En este marco, la flexibilidad psicológica puede entenderse como una capacidad facilitadora: permite al individuo sostener la experiencia interna sin necesidad de evitarla, y mantenerse abierto al contacto con emociones, recuerdos o pensamientos dolorosos. Esta apertura es esencial para que se produzca la atribución de significado, entendida como la capacidad de reorganizar la narrativa personal y resignificar experiencias vitales desde una nueva perspectiva. Desde este punto de vista, la flexibilidad psicológica proporciona las condiciones internas necesarias para que el proceso de atribución de significado ocurra. Por ejemplo, para que una persona pueda reinterpretar un evento traumático o una pérdida desde un lugar más integrado o compasivo, primero necesita tolerar el contacto con ese material emocional, y no bloquearlo a través de mecanismos de evitación experiencial. Sin esa disposición flexible hacia la experiencia, el acceso a nuevas perspectivas

significativas puede quedar bloqueado o distorsionado. A su vez, cuando el individuo logra atribuir un nuevo significado a una experiencia, esta nueva interpretación puede reducir la reactividad emocional asociada, aportar coherencia existencial, y reforzar la motivación para actuar desde los propios valores. Esto, en sí mismo, puede aumentar la flexibilidad psicológica, al desactivar creencias rígidas, narrativas disfuncionales o patrones automáticos de evitación (Boelen et al., 2006). Es decir, el significado no sólo es una consecuencia del proceso terapéutico, sino que también retroalimenta positivamente la capacidad del individuo para adaptarse con mayor flexibilidad. En resumen, la flexibilidad psicológica permite atravesar la experiencia sin evitarla, y la atribución de significado transforma esa experiencia en algo valioso y adaptativo que fomenta conductas activas de afrontamiento y aceptación. Por tanto, ambos mecanismos pueden considerarse parte de un ciclo recursivo de transformación psicológica, que podría explicar la profundidad y durabilidad del cambio observado tras intervenciones asistidas con psicodélicos, y que podría facilitarse mediante la intervención sobre factores contextuales o utilizando intervenciones terapéuticas específicas.

Ilustración 3- Interacción entre flexibilidad psicológica y atribución de significado



Limitaciones generales

Para interpretar adecuadamente los hallazgos presentados en esta tesis, es fundamental considerar también sus limitaciones generales, las cuales se derivan tanto de los enfoques metodológicos adoptados como de las limitaciones específicas de cada uno de los estudios, ya discutidas previamente.

En primer lugar, esta tesis se centra en dos mecanismos psicológicos centrales (flexibilidad psicológica y atribución de significado) que han sido evaluados por separado y aisladamente en dos estudios distintos. Esto no permite examinar directamente la interacción dinámica entre ambos, a pesar de que la evidencia teórica y clínica sugiere

que podrían estar profundamente entrelazados. Esta separación limita la posibilidad de construir modelos más integradores que expliquen con mayor precisión cómo se producen los efectos terapéuticos de los psicodélicos en contextos clínicos complejos. Además, la presencia de estos mecanismos no significa necesariamente que no haya otros implicados; en este sentido, cabría destacar la importancia de la identidad social y la conexión, mencionados en la introducción, como posibles aspectos clave para el cambio psicológico, que no han sido explorados en esta tesis.

En segundo lugar, las diferencias metodológicas entre ambos estudios (diseño, contexto, población y herramientas de análisis) dificultan su comparabilidad directa. Mientras que el Estudio 1 se basó en un diseño transversal retrospectivo en un contexto naturalístico, el Estudio 2 adoptó un diseño prospectivo experimental en condiciones clínicas controladas. Esta disparidad impide generalizar los hallazgos de forma conjunta y plantea retos para generalizar los resultados, especialmente poblaciones diferentes a las estudiadas.

Además, ambos estudios se sustentaron en metodologías cuantitativas basadas en autoinformes psicométricos. Si bien se utilizaron instrumentos validados y se obtuvieron datos de valor clínico, no se incorporaron metodologías cualitativas (como entrevistas fenomenológicas o análisis narrativos), que habrían permitido una comprensión más matizada de las experiencias subjetivas y del modo en que los participantes atribuyen significado o elaboran aceptación durante y después de la experiencia psicodélica. La ausencia de estos datos introduce un sesgo potencial, ya que ciertos elementos relevantes del proceso terapéutico podrían no estar siendo capturados por las escalas utilizadas.
Finalmente, los estudios no incluyeron medidas neurobiológicas ni biomarcadores objetivos, lo que impide establecer vínculos empíricos directos entre los cambios psicológicos observados y los mecanismos neurofisiológicos postulados en la literatura reciente. Esta desconexión limita la posibilidad de vincular los hallazgos de esta tesis con modelos neurocientíficos contemporáneos, y reduce su potencial explicativo.

Fortalezas

A pesar de las limitaciones mencionadas, esta tesis presenta varias fortalezas que contribuyen de forma relevante al campo emergente de la investigación psicodélica. En primer lugar, ofrece un enfoque innovador al situar los mecanismos psicológicos de cambio como elementos centrales en la explicación de los efectos terapéuticos de los psicodélicos, articulando un marco teórico integrador que conecta la experiencia subjetiva con procesos clínicos y fenómenos neurobiológicos, algo fundamental a la hora de abordar los desafíos metodológicos y regulatorios relacionados con la implementación de las terapias asistidas con psicodélicos.

En segundo lugar, el diseño complementario incorporado abarca tanto contextos naturalísticos como clínicos, lo que proporciona una visión más ecológica de los fenómenos estudiados. El Estudio 1 permite analizar patrones reales de uso en una amplia muestra internacional de habla hispana, mientras que el Estudio 2 aporta evidencia controlada sobre la sinergia entre psicoterapia y psicodélicos en un problema clínico relevante como el duelo. Si bien esta combinación presenta limitaciones ya descritas, también permite arrojar datos con implicaciones prácticas tanto para el desarrollo de políticas públicas como para el diseño de intervenciones clínicas.

Además, el desarrollo y validación de una herramienta psicométrica culturalmente adaptada (APEQ en castellano) constituye una contribución significativa, que abre nuevas posibilidades para la investigación y la evaluación sistemática de experiencias subjetivas en contextos hispanohablantes, una población hasta ahora infrarrepresentada en la literatura científica.

Finalmente, esta tesis emana de una perspectiva explícitamente transdisciplinar y no reduccionista que contribuye al necesario replanteamiento de los modelos metodológicos convencionales a la hora de comprender la mente y su sufrimiento, proponiendo alternativas viables para diseñar, evaluar y optimizar intervenciones cuyo efecto depende estructuralmente de la experiencia subjetiva y el contexto. En este sentido, la investigación psicodélica invita a superar los modelos actuales, centrados en la categorización diagnóstica rígida, y avanzar hacia un paradigma de psiquiatría de precisión (Vieta, 2015) capaz de integrar dinámicamente mecanismos psicológicos,

biológicos y contextuales en función de las características singulares de cada persona. Este cambio requiere reconocer a la mente no como una entidad aislada, sino como encarnada y situada, cuya salud emerge de la interacción entre procesos neurobiológicos, historia personal, vínculos intersubjetivos y entorno sociocultural (Dzwiza-Ohlsen & Kempermann, 2023).

Líneas de investigación a futuro

La investigación en psicoterapia asistida con psicodélicos enfrenta actualmente desafíos significativos (Aday et al., 2023). Por un lado, la intensidad y naturaleza inconfundible de los efectos subjetivos de estas sustancias dificulta la implementación de ensayos clínicos aleatorizados y doble ciego en su formato tradicional, comprometiendo la validez interna de los estudios. Por otro, los modelos terapéuticos empleados hasta ahora requieren múltiples sesiones de preparación, integración y acompañamiento intensivo, lo que limita su escalabilidad, accesibilidad y sostenibilidad en contextos clínicos reales. A ello se suma la ausencia de consenso sobre los modelos psicoterapéuticos óptimos, así como la falta de marcos regulatorios que contemplen estas intervenciones de forma integrada, lo que genera incertidumbre tanto a nivel clínico como normativo.

En este contexto, los hallazgos presentados en esta tesis ofrecen una contribución relevante, al proponer marcos conceptuales, estrategias metodológicas e instrumentos psicométricos que permiten diseñar, calibrar y evaluar intervenciones que integran sustancias psicodélicas con abordajes psicoterapéuticos específicos. No obstante, la complejidad inherente a la interacción entre los mecanismos implicados, el contexto y la experiencia subjetiva dificulta la identificación precisa de su contribución individual a los resultados clínicos. Validar los mecanismos propuestos requerirá diseños metodológicos más rigurosos, incluyendo estudios prospectivos con múltiples puntos de medida y análisis estadísticos robustos capaces de diferenciar entre variables mediadoras y moderadoras (Kangaslampi, 2020). La incorporación de modelos estadísticos que exploren variables latentes podría desvelar nuevos constructos que predijeran de manera más precisa los cambios clínicos y psicológicos.

Dado que, como se ha argumentado en esta tesis, el efecto de las sustancias psicodélicas no puede disociarse del contexto en que se administran, se propone focalizar la evaluación en las intervenciones psicoterapéuticas que acompañan su uso. Comparar abordajes estructurados centrados en mecanismos específicos (como la terapia centrada en el significado empleada en el estudio 2) frente a modelos de apoyo no directivo, permitiría esclarecer su valor añadido.

En cuanto a la experiencia subjetiva, su evaluación se beneficiaría de metodologías mixtas que combinen abordajes cuantitativos con análisis cualitativos o experienciales. Este enfoque permitiría no solo detectar efectos moderados, sino también captar dimensiones experienciales que difícilmente pueden ser aprehendidas por instrumentos psicométricos convencionales; algunas herramientas desarrolladas específicamente para recabar información precisa sobre experiencias subjetivas, como la microfenomenología, podrían ser especialmente eficaces para tal propósito (Petitmengin et al., 2019). Por otro lado, la inteligencia artificial ya se está utilizando para detectar patrones de significado en el lenguaje como posibles biomarcadores y predictores clínicos, y su incorporación incipiente a la ciencia psicodélica podría constituirse en un poderoso aliado para entender la implicación de la experiencia subjetiva (Sanz et al., 2021). Integrar estos datos con medidas neurobiológicas como la conectividad funcional, la entropía cerebral o los marcadores inflamatorios contribuiría a desarrollar las teorías explicativas actuales (como REBUS) y avanzar hacia modelos más sofisticados, con mayor poder predictivo, que permitieran optimizar y personalizar las intervenciones dentro de los paradigmas de la psiquiatría de precisión (Vieta, 2015) y de la psiquiatría estratificada (Arns et al., 2022). Mientras que la psiquiatría estratificada busca identificar subgrupos de pacientes con características compartidas para asignarlos a tratamientos ya disponibles, la psiquiatría de precisión persigue un ajuste terapéutico individualizado, basado en el perfil dinámico y singular de cada paciente. En el ámbito de los psicodélicos, la estratificación podría servir para identificar qué pacientes (por ejemplo, aquellos con mayor rigidez cognitiva o inflamación elevada) se beneficiarían más de estas intervenciones, e informar la decisión terapéutica (por ejemplo, escogiendo un psicodélico clásico o un psicodélico disociativo). Por otro lado, un enfoque de precisión permitiría adaptar de manera más fina el tipo de psicoterapia de apoyo, el contexto de uso y los objetivos terapéuticos en función de la

neurobiología, la fenomenología y la historia personal de cada individuo. En este sentido, los psicodélicos ofrecen un terreno particularmente fértil para avanzar hacia una verdadera psiquiatría de precisión, dado que su eficacia parece depender menos de parámetros farmacológicos uniformes y más de la interacción singular entre fármaco, contexto y experiencia subjetiva. El Anexo 3 de esta tesis presenta un estudio exploratorio sobre la fenomenología del 5-MeO-DMT, una sustancia psicodélica emergente con elevado potencial terapéutico, diseñado conforme a estas recomendaciones y que busca conectar marcadores neurofisiológicos con experiencias subjetivas específicas, lo cual podría servir como modelo de estudios que busquen integrar biomarcadores multimodales y cambios clínicos para alimentar modelos predictivos.

Como se ha argumentado a lo largo de esta tesis, no cabe entender los distintos niveles explicativos (neurobiológicos, psicológicos y fenomenológicos) como esferas independientes dentro de una perspectiva reduccionista, sino como factores codependientes que interactúan en un sistema dinámico. Para integrar esta complejidad, la psiquiatría computacional ofrece herramientas prometedoras que permitirían construir modelos capaces de predecir los efectos de las sustancias psicodélicas de manera más calibrada y personalizada. Un ejemplo notable es el modelo REBAS (*Revised Beliefs After Psychedelics*) (Zeifman et al., 2025), que amplía el modelo REBUS al incorporar explícitamente la revisión de creencias desadaptativas tras la experiencia aguda con psicodélicos, y su relación con mejoras sostenidas en el bienestar. Este modelo ha sido respaldado empíricamente mediante estudios que vinculan la relajación aguda de creencias negativas sobre uno mismo con un aumento de la entropía neuronal, experiencias de unidad *(oceanic boundlessness*), y cambios positivos en el bienestar semanas después de la administración de psilocibina. De este modo, REBAS proporciona un marco integrador que vincula marcadores neurofisiológicos, procesos psicológicos y resultados clínicos, y representa un ejemplo paradigmático de cómo avanzar hacia una psiquiatría de precisión basada en mecanismos.

Para estudiar la validez transdiagnóstica de los mecanismos planteados en esta tesis, sería recomendable también replicar y extender esta línea de investigación en otras poblaciones clínicas, como personas con trastornos de ansiedad, trastorno obsesivo-compulsivo,

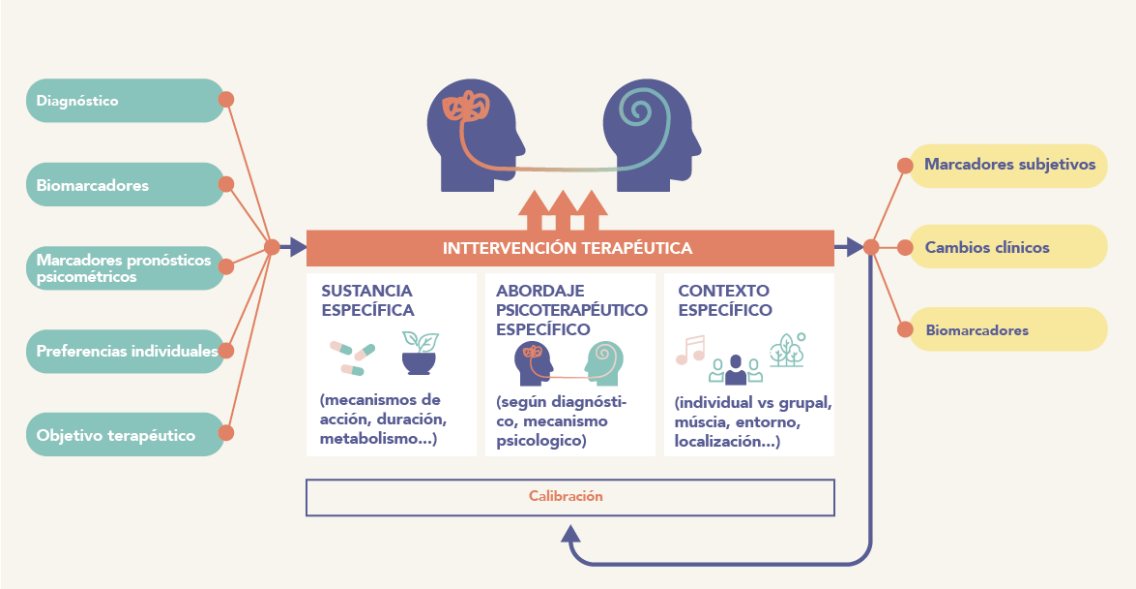
adicciones, o personas en situación de final de vida, donde los procesos de atribución de significado y flexibilidad psicológica también pueden desempeñar un papel central en la mejora clínica. Otro aspecto prioritario para futuras investigaciones es la exploración de modelos grupales de intervención que integren el soporte entre pares como componente terapéutico central. Incorporar de forma sistemática el soporte entre pares permitiría desarrollar modelos más accesibles y sostenibles, especialmente en entornos con recursos limitados, sin comprometer la contención emocional y la seguridad. (Marseille et al., 2023).

Por otro lado, es necesario explorar también los posibles efectos adversos derivados de los mecanismos psicológicos estudiados. Esta tesis se ha centrado en evaluar la relevancia de los mecanismos psicológicos de cambio para explicar los beneficios terapéuticos de los psicodélicos. Sin embargo, el mismo sustrato que justifica los beneficios de estas sustancias, podría explicar también los efectos adversos, siendo el contexto el principal modulador que inclinaría la balanza en un sentido o en otro (Brouwer & Carhart-Harris, 2020). Por lo tanto, resulta necesario explorar de manera sistemática los posibles riesgos de estos mecanismos psicológicos. Para explorar este aspecto, todos los estudios que incorporaran sustancias psicodélicas deberían incluir una recogida sistemática de eventos adversos, utilizando instrumentos validados específicos (Calder & Hasler, 2024) y datos cualitativos, así como realizar seguimientos longitudinales prolongados que permitieran documentar eventos de aparición tardía.

Finalmente, algunos resultados observados, como el aumento en la flexibilidad psicológica en población sana o el crecimiento postraumático tras experiencias con ayahuasca, abren la posibilidad de considerar estas intervenciones no sólo desde una óptica terapéutica, sino también preventiva o incluso promotora del bienestar psicológico. En este sentido, desarrollar intervenciones que favorezcan la salud mental desde un enfoque poblacional podría tener implicaciones relevantes no sólo individuales, sino también sociales y ecológicas, como sugiere la aplicación reciente del uso de ayahuasca para fomentar el entendimiento entre grupos en conflicto (e.g., israelíes y palestinos) (Roseman et al., 2021) No obstante, cualquier avance en esta dirección deberá estar

guiado por la prudencia, la ética y la evidencia sólida, bajo el principio de *primum non nocere*.

Ilustración 4- Uso de psicodélicos en el marco de la psiquiatría de precisión



CONCLUSIONES

Esta tesis doctoral se propuso explorar los mecanismos psicológicos de cambio implicados en los efectos terapéuticos de las sustancias psicodélicas, prestando especial atención a la flexibilidad psicológica y la atribución de significado como procesos centrales que median entre la farmacología, la experiencia subjetiva y los resultados clínicos. A través de dos estudios empíricos complementarios, uno centrado en el uso naturalístico de psicodélicos y otro en un contexto clínico controlado, se ha contribuido al desarrollo de un modelo integrador que reconoce la naturaleza compleja, interactiva y contextual de estas intervenciones.

Ambos estudios aportan evidencia convergente en torno a una idea fundamental: los efectos de los psicodélicos no pueden entenderse de forma aislada, sino que emergen de la interacción dinámica entre los efectos neurobiológicos de las sustancias, el contexto de uso, la experiencia subjetiva y los procesos psicológicos que estas experiencias movilizan. Esta perspectiva obliga a trascender los modelos reduccionistas clásicos y a incorporar marcos de análisis más complejos que incluyan dimensiones experienciales, narrativas y contextuales. En esta dirección, la tesis ofrece herramientas teóricas y empíricas útiles para diseñar, personalizar y optimizar intervenciones clínicas asistidas por psicodélicos, contribuyendo a la consolidación de un paradigma de psiquiatría más integrador, orientado en el proceso y centrado en la persona. Esta perspectiva no sólo es aplicable a las sustancias psicodélicas, sino a la práctica totalidad de las intervenciones que buscan aliviar el sufrimiento subjetivo, ya que toda experiencia personal se construye de manera coemergente en un contexto determinado. Entender cada uno de los aspectos que contribuyen al sufrimiento de manera codependiente e interrelacionada permitiría superar viejas dicotomías (naturaleza frente a cultura, reduccionismo materialista frente a relativismo, etc), y construir síntesis que permitan superar los importantes obstáculos que la investigación en psiquiatría ha encontrado en las últimas décadas, como la falta de biomarcadores, la dislocación entre nosología y etiología, o la aparente contribución de sistemas culturales y económicos sobre el sufrimiento humano.

Asimismo, los hallazgos presentados abren nuevas líneas de investigación que permitirán avanzar hacia modelos explicativos más robustos y personalizados, evaluar de forma más precisa los efectos de estas intervenciones en distintas poblaciones clínicas y no clínicas,

y diseñar políticas públicas que garanticen tanto la seguridad como la accesibilidad de estas terapias emergentes. Frente al sufrimiento psíquico que afecta a millones de personas, y ante la necesidad urgente de tratamientos más eficaces, esta tesis plantea que los psicodélicos, cuando son utilizados de forma cuidadosa y acompañada, pueden constituir una herramienta valiosa para facilitar procesos de cambio profundo, integrador y transformador.

Más allá de los datos, modelos y herramientas, esta tesis ha sido también un viaje de exploración sobre cómo las personas cambian, sufren y sanan. En el corazón de la investigación psicodélica late una pregunta fundamental sobre la capacidad humana para resignificar el dolor, abrirse a la experiencia y transformarse a través del encuentro con lo desconocido, poniendo de relevancia la mayor fortaleza de nuestra especie: nuestra capacidad fundamental para cambiar y adaptarnos, tanto a nivel neurobiológico como personal. Esta tesis ha querido acercarse a esa pregunta con rigor científico, pero también con una profunda sensibilidad hacia las dimensiones subjetivas y contextuales que atraviesan cualquier proceso de transformación psicológica. En un mundo marcado por el sufrimiento, la fragmentación y la búsqueda de sentido, el potencial terapéutico de los psicodélicos no radica únicamente en sus propiedades farmacológicas, sino en su capacidad para generar experiencias que (con)mueven, reordenan y despiertan. Explorar con honestidad y responsabilidad estas posibilidades es, quizás, una de las tareas más urgentes, y humanas, que hoy nos interpelan como científicos, clínicos y ciudadanos.

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ANEXOS

ANEXO 1

Do classic psychedelics increase the risk of seizures? A scoping review

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REVIEW

Do classic psychedelics increase the risk of seizures? A scoping review

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ABSTRACT

Seizures are a concerning adverse event frequently associated with the use of psychedelics, and hence, studies involving these substances tend to exclude patients with past history of epilepsy. This is especially relevant because epileptic seizures are markedly increased in the population suffering from mental disorders, and psychedelic assisted therapy is being researched as a promising treatment for several of them. To determine the extent of the current literature on the relationship between classic psychedelics and seizures, a scoping review was performed using the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews). The search was conducted in PubMed, Web of Science, Google scholar, LILACS and Scielo, and both animal and human models were included. A total of 16 publications on humans, and 11 on animals, were found. The results are heterogeneous, but globally suggest that psychedelics may not increase the risk of seizures in healthy individuals or animals in the absence of other drugs. However, concomitant use of other substances or drugs, such as kambo or lithium, could increase the risk of seizures. Additionally, these conclusions are drawn from data lacking sufficient external validity, so they should be interpreted with caution. Future paths for research and a summary on possible neurobiological underpinnings that might clarify the relationship between classical psychedelics and seizures are also provided.

1. Introduction

We are witnessing a renewed interest in the therapeutic potential of psychedelic-like drugs. Esketamine was the first of its kind to enter clinical practice (Kim et al., 2019), whereas other substances like psilocybin or 3,4-methylenedioxy-methamphetamine (MDMA) are in the last phases of drug development and it is expected that in 2023–2024 they will also obtain the commercialization approval by regulating agencies.

The enthusiasm with which these drugs are being received by both researchers and the general public is understandable in the light of the urgent need for innovative treatments in psychiatry (Insel, 2009). However, certain observations suggest that a cautionary approach should be adopted, as the available data are preliminary and sometimes not obtained from methodologically robust studies (Aday et al., 2022; dos Santos et al., 2022; Ona et al., 2022).

Due to the lack of data, it is common to observe certain practices in psychedelic research that are not based on evidence. For instance, although it is a common practice there are no trials informing about the need to exclude participants with dissociation traits or symptoms

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(Gasser et al., 2014; Johnson et al., 2008).

Another of those gaps that need further research is the safety profile of psychedelic drugs, which has been assessed and described in different reviews. For instance, Breeksema et al. (2022) did a systematic review to determine the adverse events in clinical treatments with serotonergic psychedelics and MDMA and concluded that adverse effects are poorly defined in the context of psychedelic treatments and are probably underreported in the literature due to study design (lack of systematic assessment of adverse effects) and sample selection. In addition, dos Santos et al. (2018) performed a systematic review of systematic reviews on efficacy, tolerability, and safety of serotonergic psychedelics for the management of diverse disorders and found good tolerability although only few included studies were RCTs, most had small sample sizes and a short duration, and there was a notable lack of long-term data. Therefore, adverse effects are an aspect that needs further research. Due to the fact that the therapeutic effects of psychedelics in psychiatric conditions are thought to take place in the central nervous system (CNS), the neurological safety related to the use of psychedelics is a pivotal subject.

Classic psychedelics, also known as serotonergic psychedelics, like *N, N*-dimethyltryptamine (DMT), lysergic acid diethylamide (LSD), mescaline or psilocybin (Sexton et al., 2020), exert their psychedelic effects by stimulating the serotonin 2A receptor (Vollenweider et al., 1998). They have increasingly demonstrated to generate promising results in anxiety, mood and substance use disorders. In healthy humans, psychedelics have been described to produce profound changes in perception and mood that are often associated with highly meaningful experiences (Griffiths et al., 2006). Reported adverse events are mostly benign and include a transient increase in blood pressure and tachycardia, anxiety, nausea and headache (Andersen et al., 2021; dos Santos et al., 2018, Leonard et al., 2018), it is important to note that real-life scenarios and users strongly differ from controlled clinical trials and highly selected patients. In that regard, in some studies there was a high rate of exclusion of participants, ranging from 90% to 96.3% of patients initially assessed (Griffiths et al., 2016, Davis et al., 2020).

Epileptic seizures, which refer to a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain according to the International League Against Epilepsy (ILAE), have emerged as a concerning potential adverse event to the use of psychedelic drugs (dos Santos and Hallak, 2021). Although apparently rare in frequency (Simonsson et al., 2022), people who are susceptible to seizures and/or are diagnosed with epilepsy (which is a disease characterized by an enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological, and social consequences of this condition) tend to be excluded from clinical trials or informal spaces where psychedelics are provided due to the potential adverse consequences of epileptic seizures (Lado et al., 2000). To date, only observational studies and case reports have informed about the potential of psychedelic drugs to induce seizures. Indeed, some early publications advised of cases of acute seizures provoked by LSD in subjects with epilepsy (Baker, 1964; Hollister et al., 1969). Leonard et al. (2018) performed a 16-year retrospective analysis of single-substance exposures of LSD or psilocybin-containing mushrooms reported to United States poison centers and found that 46 psilocybin mushrooms users (0.8%), and 129 LSD users (3.6%) experienced seizures and status epilepticus (15, 0.4%). In a similar study, Heise and Brooks, (2016) performed a retrospective analysis of calls to poison control centers over 10 years (September 2005–September 2015) in relation to ayahuasca use. A 2% of seizures (12 subjects) was observed, although some information was lacking: the type of seizures was not described nor if it were other exposures. Following on ayahuasca, a recently published study with the largest sample of ayahuasca users ever recruited (n = 8.216) showed that 1.3% (n = 106) of ayahuasca users experienced seizures (Bouso et al., 2022). One case of seizures was also reported in a small observational study (n = 40) with first-time ayahuasca users (Gómez-Sousa et al., 2021).

In this same line of thought, Houle et al. (2021) wrote a scoping review about ayahuasca use and concluded that evidence on benefits for the management of several mental health disorders is mixed, and multiple case reports suggested the potential for harm and interactions. This meant that serious adverse events were extremely rare but did occur. Therefore, when some concern is raised about the ability of classic psychedelics to cause seizures, it is urgent to gather more information about it, mostly because if the use of these compounds is currently increasing, the extremely rare adverse effects will occur more often.

It is worth noticing that epileptic seizures are markedly increased in the population suffering from mental disorders (Swinkers et al., 2005), even in drug-naive patients (Alper et al., 2007). Considering that psychedelic assisted therapy is showing to be very promising as a potential treatment for different mental disorders, assessing its safety in this regard seems relevant and could inform future design of clinical trials and treatment protocols.

Performing a scoping review on existing literature about classic psychedelics, we aimed to investigate the reality about classic psychedelic-related seizures. We deliberately chose to exclude other types of psychedelics, such as entactogens like MDMA, or dissociative psychedelics, such as ketamine or esketamine; their different underlying mechanisms of action would have hindered the possibility to draw conclusions regarding possible underlying pathways that could explain the relationship between these drugs and the presence of seizures. These data will provide for a more comprehensive understanding of the neurological safety of classic psychedelics, which can inform researchers, psychiatrists, neurologists and emergency doctors, as the use of these compounds continues to grow.

2. Experimental procedures

Literature search and data extraction were carried out following the guidelines of Arksey and O'Malley (Arksey and O'Malley, 2005) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-ScR) guidelines (Moher et al., 2009). The protocol of the scoping review has been previously registered in Open Science Framework. Two researchers conducted the search and data extraction independently and resolved discrepancies by consensus with a third researcher.

The process is described as a flowchart in Fig. 1.

2.1. Inclusion criteria

Studies were eligible for inclusion if they were peer reviewed studies investigating the effect of serotonergic psychedelics (LSD, lysergic acid amide or LSA, mescaline, peyote, San Pedro, DMT, 5-methoxy-N,N-dimethyltryptamine or 5-MeO-DMT, ayahuasca, psilocybin, *Psilocybe* mushrooms) on inducing seizures in both animals and humans. We set a language restriction to English, Spanish, French, Italian, Portuguese and German.

2.2. Search

The search was conducted in PubMed, Web of Science, Google scholar, LILACS and Scielo up to November 2022 with the following keywords: (psychedelics OR hallucinogens OR LSD OR psilocyb* OR mescaline OR peyote OR San Pedro OR DMT OR dimethyltryptamine OR classical psychedelics OR serotonergic psychedelics OR ayahuasca) AND (epilep*, OR epileptic seizures OR seizures). After removing duplicates, we screened the retrieved studies by title and abstract and, for those eligible studies, by the full text. Furthermore, private collections within the project group were also incorporated to the screening for a potential relevance in the review.

2.3. Data extraction

For each study, we extracted the author, year of publication, country

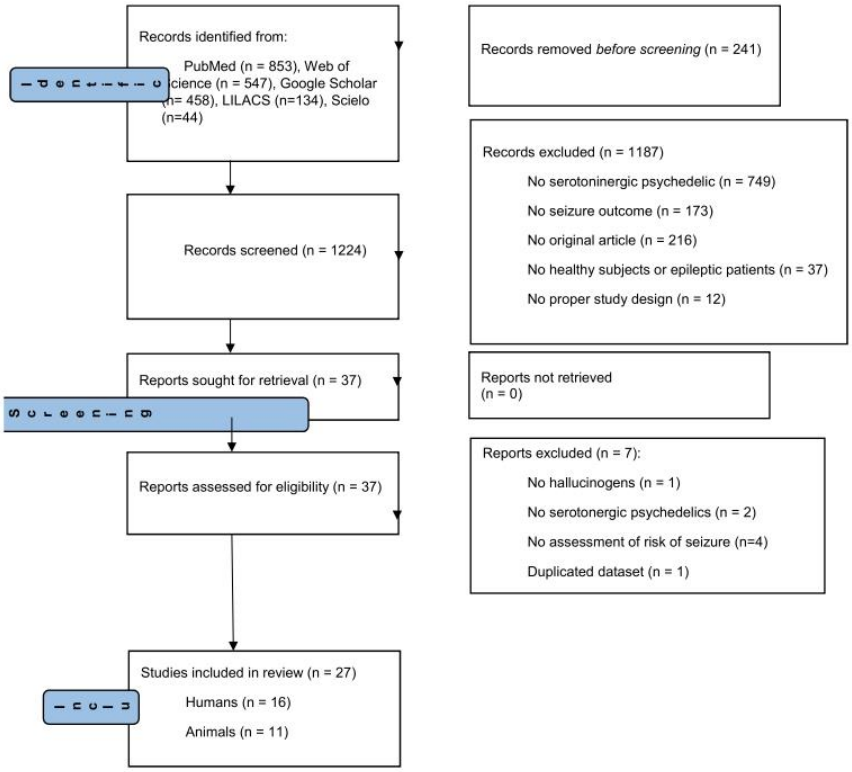


Fig. 1. Flowchart showing identification of studies via databases and registers.

of origin, type of article, studied substance, aim/objective, study population, used methodology, reported main results and conclusion.

3. Results

3.1. Findings on humans

We found 16 studies that explored a potential relationship between seizures and classic psychedelics in humans (see Table 2 for details). A total of 11.659 individuals who took psychedelics were included in the present review, of whom 83 had previous history of epilepsy. Age in the sample ranged from 0 to 83 years old. Assessed psychedelic drugs were LSD ($n = 10$), psilocybin ($n = 3$), ayahuasca ($n = 3$), mescaline ($n = 2$), DMT ($n = 1$) and LSA ($n = 1$). Studies reported different designs and methodology, including experimental and observational studies, and case reports. Older manuscripts were characterized by low quality and poor description of methodology.

Reports including patients with diagnosed epilepsy showed mixed results. Four studies reported no changes in EEG acquisitions after dosing of LSD between 50–200 μg (Schwarz et al., 1956, Balestrieri et al., 1957a, Balestrieri et al., 1957b, Serafetinides et al., 1965), with one of them describing five cases of "aura-like" phenomena during the acute effect of LSD (Balestrieri et al., 1957a). Another short report described increased focal epileptic activity registered in the EEG in seven out of 11 cases with neocortical origin and unchanged focal activity in 10 cases with temporal foci after administration of psilocybin at an average dose of 0.16 mg/kg (Kolarik et al., 1974). In addition, one study investigated the effect of mescaline (250–500 mg) in 12 patients with a previous history of either generalized tonic-clonic and/or focal seizures (Herman et al., 1955), in which one out of the 12 patients presented an absence seizure approximately four hours after mescaline administration. However, EEG records one hour after administration showed disappearance of previously present spike-wave patterns for variable periods of times in some patients. Another study reporting one case using mescaline showed no changes in post-administration EEG (Schwarz et al., 1956).

In a clinical context, several physicians using LSD for psychotherapy, back in the mid 50 s and 60 s, completed a survey on the adverse effects observed related to LSD administration during their sessions (Malleson et al., 1971). The data cover 4300 patients given a total of approximately 49,000 LSD doses, and 170 experimental subjects given a total of 450 administrations. Among all cases, there was only one report of a tonic-clonic seizure in a participant without a previous history of epilepsy. In addition, there were also two large articles (Heise et al., 2017; Leonard et al., 2018) that reviewed clinical histories of subjects who attended the emergency department due to an intoxication of LSD (554 admissions), ayahuasca (538), or psilocybin (5883). In these studies, 4% of individuals presented seizures after LSD intoxication (0.4% were epileptic), 2% after ayahuasca, and 0.8% after psilocybin. In these cases, doses could not be determined. In another smaller study, including 11 patients who attended the emergency department after LSD ingestion (Liakoni 2015), none reported seizures. Review of personal online reports by patients taking treatment for bipolar disorder together with self-administered psychedelics showed that 47% of 62 patients who reported taking lithium plus psychedelic involved the presence of seizures, while none of 34 lamotrigine reports did (Nayak et al., 2021).

Finally, among case reports, two authors described two cases of seizures associated with the combined use of ayahuasca and kambo (Mokhtari et al., 2022; Rodrigues et al., 2017), which is a toxin extracted from a frog, commonly used in healing rituals in South America. Other reports described two cases of tonic-clonic seizures after LSD recreational ingestion at probably high doses, one alone and the other in

association with fluoxetine (Fisher et al., 1997; Picker et al., 1992). Another individual also presented a status epilepticus due to a posterior reversible encephalopathy syndrome (PRES) after LSA in combination with clomipramine, probably in relation with hypertension (Legriel et al., 2008).

Results are summarized in Table 1.

3.2. Findings in animal models

Eleven studies (Alexander & Machis, 1972; Anlezark et al., 1976; Anlezark & Meldrum, 1978; Archer, 1987; Archer & Tandberg, 1984; Archer et al., 1985; Dizioli et al., 2011; Kaneko et al., 1960; Meldrum and Naquet, 1971; Rouse & Frank, 1974; Walter et al., 1970) explored the effects of different psychedelics in animal models. Specifically, they included mice (Alexander & Machis, 1972; Anlezark et al., 1976; Rouse & Frank, 1974), rats (Archer, 1987; Archer & Tandberg, 1984; Archer et al., 1985; Dizioli et al., 2011), baboons (Anlezark & Meldrum, 1978; Meldrum and Naquet, 1971; Walter et al., 1970), and cats (Kaneko et al., 1960).

The methodology used was heterogeneous, with six studies acutely administering psychedelic drugs and exposing animals to proconvulsant stimuli (Alexander & Machis, 1972; Anlezark et al., 1976; Anlezark & Meldrum, 1978; Meldrum and Naquet, 1971; Rouse & Frank, 1974; Walter et al., 1970), three studies administering psychedelics and assessing the rate of post-decapitation seizures (Archer, 1987; Archer & Tandberg, 1984; Archer et al., 1985), one study assessing EEG and ECG measures after the administration of psychedelics (Kaneko et al., 1960), and one study assessing the susceptibility to seizures in offspring after being exposed to psychedelics during pregnancy (Dizioli et al., 2011).

The psychedelics used consisted in LSD (Alexander & Machis, 1972; Anlezark et al., 1976; Anlezark & Meldrum, 1978; Kaneko et al., 1960; Rouse & Frank, 1974; Walter et al., 1970) (1.5–20 μg/kg in mice; 0.05–60 μg/kg in baboon; and 30–40 μg/kg in cat), 5-MeO-DMT (Archer, 1987; Archer & Tandberg, 1984; Archer et al., 1985) (0.125–4 mg/kg in rat), ayahuasca (Dizioli et al., 2011) (1.0 mL/100 g), DMT (Meldrum and Naquet, 1971) (0.5–4 mg/kg), mescaline (Alexander & Machis, 1972; Meldrum and Naquet, 1971) (0.5–75 mg/kg), and psilocybin (Meldrum and Naquet, 1971) (0.2–4 mg/kg).

In four studies, a certain degree of protection against seizures was observed upon administration of psychedelics, specifically LSD (Anlezark et al., 1976; Anlezark & Meldrum, 1978), psilocybin (Meldrum and Naquet, 1971), and DMT (Meldrum and Naquet, 1971). In the case of LSD, it seems that it reduced the rate of both myoclonic (Anlezark & Meldrum, 1978) and audiogenic (Anlezark et al., 1976) seizures. Psilocybin, at a dose of 0.2 mg/kg had no effect on myoclonic responses. At doses ranging from 1 to 4 mg/kg, the myoclonic activity was interrupted

Table 1
Summarizes findings in humans.

Reference	Study type	Subjects	Drug	Dose	N	Clinical finding
Herman et al. (1955)	Pre-post intervention	Epilepsy	Mescaline	0.25–0.5 g IV	12	Non-specific changes in EEG. No changes in seizure susceptibility
Schwarz et al. (1956)	Case series	Temporal lobe epilepsy	LSD & Mescaline	LSD (50mcg) and mescaline (5000 mg)	LSD (2) & mescaline (1)	Probably, LSD and mescaline does not influence temporal lobe epilepsy
Balestrieri et al. (1957)	Intervention	Psychomotor epilepsy	LSD	100–200 mcg	8	LSD may affect temporal lobes
Balestrieri et al. (1956–57)	Intervention	Epilepsy	LSD	100–200 mcg	6	Probably, LSD does not influence epileptic activity measured in EEG in epileptic patients
Serafetinides et al. (1965)	Pre-post intervention	Temporal lobe epilepsy	LSD	1 mcg/kg	34	Probably, LSD does not influence epileptic activity measured in EEG in epileptic patients
Fisher et al. (1967)	Case report	Healthy	LSD	~450 mcg	1	LSD may have reduced seizure susceptibility
Malleson et al. (1971)	Observational	Epilepsy Healthy	LSD	25–1500 mcg	Epilepsy (4300) & healthy (170)	Probably, LSD has a low risk of including seizures or epilepsy
Kolarik et al. (1974)	Pre-post intervention	Epilepsy	Psilocybin	0.16 mg/kg	30	Hyperexcitability of neurons after psilocybin seem to intensify focal epileptic manifestation at a cortical level
Picker et al. (1992)	Case report	Epilepsy	LSD + fluoxetine	?	1	Combination of LSD and fluoxetine may increase seizure susceptibility
Legriel et al. (2008)	Case report	Epilepsy	LSA	?	1	Seizures caused by a Posterior Reversible Encephalopathy Syndrome induced by LSA
Liakoni et al. (2015)	Observational	Epilepsy	LSD	? (intoxication)	11	Seizures not common during LSD intoxication
Rodrigues et al. (2017)	Case report	Healthy	Ayahuasca + kambo	Ayahuasca (100 mL) & kambo (5adms.)	1	Combination of ayahuasca and kambo may increase seizure susceptibility
Heise et al. (2017)	Observational	General population	Ayahuasca	? (intoxication)	538	A small proportion of seizures related to ayahuasca, 2% among those who called the ED, the real proportion should be less since the majority of people have a well tolerated experience.
Leonard et al. (2018)	Observational	Healthy	LSD & psilocybin	? (intoxication)	LSD (554) & psilocybin (5883)	Seizures are rare side effects in intoxications due to LSD and/or psilocybin. LSD has a higher percentage of seizures than psilocybin (4.0% vs 0.8%)
Nayak et al. (2021)	Observation self-reports	Healthy	Lithium + LSD, psilocybin & DMT	?	LSD (55), psilocybin (6), DMT (1)	Combination of LSD and lithium may increase seizure susceptibility
			Lamotrigine + LSD, psilocybin & DMT	?	LSD (22), psilocybin (9), DMT (2)	No apparent increased in seizures
Mokhtari et al. (2022)	Case report	Healthy	Ayahuasca + kambo	? (intoxication)	1	Ayahuasca might cause seizures through SIADH (severe hyponatremic encephalopathy) that might be due to serotonin agonism // Kambo might exacerbate the risk by causing polidipsia

LSD=dysergic acid dietilamide; DMT = *N*,N-dimethiltriptamine; EEG = electroencephalogram; ED = Emergency Department.

completely (Meldrum and Naquet, 1971). Regarding DMT, doses of 0.5 or 1 mg/kg diminished myoclonic activity. Higher doses completely abolished this activity (Meldrum and Naquet, 1971). In one study, the administration of LSD had no direct effect upon seizure susceptibility (Rouse & Frank, 1974). 5-MeO-DMT increased both the latency and duration of post-decapitation seizures, an effect that was antagonized by the co-administration of different substances: methergoline (5-HT antagonist), fluoxetine, amiflamine, ethyltryptamine, mianserin, cinanserin, and methysergide (Archer & Tandberg, 1984; Archer et al., 1985). Exposure to ayahuasca during pregnancy was found to increase the risk of seizures in offspring (Dizioli et al., 2011).

Results are summarized in Table 2.

4. Discussion

This scoping review provides an updated overview of the existing data on the relationship between the intake of classic psychedelics and the emergence of seizures. The findings reported in animal models are inconsistent, showing no evidence of a possible protective effect of LSD, psilocybin, and DMT over seizures, a partially protective effect of mescaline and an increased risk of seizures with ayahuasca and 5-MeO-DMT. However, the pooled sample size was low (in some studies it was not even reported), and methodologies were heterogeneous. In addition, all but one of these studies were carried out before 1990. Interestingly, the only recent study found an increase in seizure susceptibility of offspring after exposure to ayahuasca during pregnancy (Dizioli et al., 2011). It is noteworthy that ayahuasca is a mixture of different substances, so it is not possible to assess, in this particular case, the influence that DMT (the serotonergic psychedelic compound present in ayahuasca) alone might have had in the outcome, especially taking into account an opposite finding when DMT alone was investigated (Meldrum and Naquet, 1971). In contrast, a recently published study that could not be included in the review reported that *N*, *N*-Dipropyltryptamine (DPT) prevented seizures in an animal model of Fragile X syndrome inducing audiogenic seizures (Tyagi et al., 2023).

Data from human studies are also heterogeneous, both in terms of methodology and the reported outcomes. While psychedelics seem to exert changes in EEG, these were not consistent, and no clear relationship between them and seizures was found. On the other hand, observational studies report conflictual data. Malleson et al. (1971) carried out a nationwide survey pooling all the patients that received LSD therapeutically in the UK, and reported only one case of seizures. On the other hand, Leonard et al. (2018) conducted an observational study on intoxications in various Emergency Departments, and found an incidence of seizures ranging from 0.4% to 2.4%, reporting also a death after a grand mal seizure related to LSD intake. This disparity could be attributed to a selection bias, as the cases assessed in the first study refer to people receiving psychedelics therapeutically, with a previous medical assessment and a medical follow-up, whereas in the latter, patients consulted after an intoxication. Thus, possible concomitant use of other substances could not be assessed. Remarkably, a case report (Blond and Schindler, 2023) has been recently published informing about a seizure crisis confirmed by intracranial electrocorticography after the ingestion of a large dose of psilocybin mushrooms. This happened in a subject diagnosed with refractory focal epilepsy and taking daily doses of levetiracetam and pregabalin. It is worth noting that the lifetime prevalence of epilepsy in the general population is estimated to be around 0.76% (Fiest et al., 2017).

In modern clinical trials, no seizures have been reported as adverse events (Breeksema et al., 2022), which may reinforce the assumption that classic psychedelics are safe in this regard, when administered in a clinical environment and at controlled doses. However, the exclusion of subjects with epilepsy and the control for the presence of other drugs in these studies make it difficult to generalize this observation to the real-world seizure risk associated with recreational or self-medicating practices. For example, a recently published study assessing the safety

Table 2
summarizes findings in animal models.

Reference	Study type	Species	Drug	Dose	N	Main finding
Meldrum & Naquet (1971)	Acute administration and exposure to proconvulsant stimuli	Baboon	DMT, psilocybin, mescaline	DMT (0.5–4 mg/kg), psilocybin (0.2–4 mg/kg), mescaline (0.5–32 mg/kg)	20	DMT and psilocybin are the most effective at blocking the myoclonic and paroxysmal EEG responses. mescaline even at high doses did not interrupt it completely.
Walter et al. (1971)	Acute administration and exposure to proconvulsant stimuli	Baboon	LSD	0.5–400 mcg/kg	15	LSD blocks the paroxysmal responses to intermittent photic stimulation normally shown by baboons.
Alexander & Machis (1972)	Acute administration and exposure to proconvulsant stimuli	Mice	LSD & mescaline	LSD (20 mcg/kg) and mescaline (75 mcg/kg)	?	LSD and mescaline increase the seizure susceptibility
Rouse & Frank (1974)	Acute administration and exposure to proconvulsant stimuli	Mice	LSD	3.65mcg	685	LSD acts directly as an anticonvulsant when taken in high doses.
Anlezark et al. (1976)	Acute administration and exposure to proconvulsant stimuli	Mice	LSD	1.5 mg/kg	?	LSD reduces the seizure susceptibility
Anlezark & Meldrum (1978)	Acute administration and exposure to proconvulsant stimuli	Baboon	LSD	0.05–0.1 mg/kg	13	LSD reduces the seizure susceptibility
Archer & Tandberg (1984)	Acute administration before decapitation to analyze post-decapitation convulsions	Mice	5-MeO-DMT	0.125–4 mg/kg	?	The direct postsynaptic 5-HT agonist, 5-MeO-DMT, caused a prolongation of both the latency and duration of Post decapitation convulsions (PDCs) (5-HT depletion leads to a prolongation of PDCs)
Archer et al. (1985)	Acute administration before decapitation to analyze post-decapitation convulsions	Rat	5-MeO-DMT	2 mg/kg	?	repeated administration of 5-MeODMT to rats blocks almost completely the behavioral changes induced by an acute dose of 5-MeODMT.
Archer et al. (1987)	Acute administration before decapitation to analyze post-decapitation convulsions	Rat	5-MeO-DMT	0.5–4 mg/kg	?	5-HT antagonists methergoline, mianserin, cinanserin and methysergide blocked the prolongation effect caused by the 5-MeODMT substantially.
Dizioli et al. (2011)	Acute administration during pregnancy and exposure to proconvulsant stimuli	Rat	Ayahuasca	0.14 mL/100 g body weight	36	The treatment with ayahuasca during pregnancy and lactation period reduced the minimum convulsant dose of pentylenetetrazol in offspring.

LSD= lysergic acid dietilamide; DMT=N,N-dimethiltriptamine; 5-Meo-DMT= 5-metoxy-dimethiltriptamine; EEG = electro-encephalography.

of inhaled DMT in healthy participants, found no severe adverse effects, and no seizures were observed (Falchi-Carvalho et al., 2024) Hence, the eventual relationship between dose and emergence of seizures is yet to be established.

Drug-drug interactions may also modify psychedelics' safety profile, in particular with psychiatric medications, and seizures are most frequently reported in the context of polydrug use. It is relevant to the account of serious adverse events the combined use of ayahuasca with kambo (de Morais et al., 2018; Bayat Mokhtari et al., 2022), since both substances tend to be used simultaneously in different settings (Majić et al., 2021). Picker et al. (1992) reported a case of grand mal convulsion when mixing LSD and fluoxetine. However, the patient never experienced seizures although she used LSD around 30 times while on fluoxetine. Thus, it is plausible that the LSD sample was adulterated with other proconvulsant substances, such as 2,5-dimethoxy-4-chloroamphetamine (DOC) (Burish et al., 2015). Nayak et al. (2021) observed an increased risk of seizures with the co-administration of lithium (but not lamotrigine) and psychedelic compounds (LSD, psilocybin or DMT). Lithium was thought for a long time to be a proconvulsant drug, although these assumptions are currently challenged (Bojja et al., 2022), while lamotrigine is widely used as an anticonvulsant (Vajda et al., 2013), so these results are consistent on the independent effect of serotonergic psychedelics on the risk of seizures.

It is worth mentioning that temporal lobe epilepsy can induce altered states of consciousness that closely resemble those induced by psychedelics, including the presence of mystical experiences, or ego dissolution (Picard et al., 2021). Hence, some authors attempted to test whether psychedelics could exert its effect through similar underlying mechanisms as temporal lobe epilepsy, administering these compounds to epileptic patients (Balestrieri et al., 1956,1957; Herman et al., 1955; Kolarik et al., 1974; Schwarz et al., 1956; Serafetinides et al., 1965). Then again, the results are mixed, with no consistent effects in the EEG, or changes in seizure frequency or activity.

The divergent findings in this review could potentially be attributed to a dose-dependent mechanism of action. Certain serotonergic drugs have demonstrated an anti-epileptic effect when administered in lower doses, whereas they exhibit pro-convulsant properties at higher doses (Mula et al., 2009). Nevertheless, animal studies have shown antiepileptic properties of LSD, psilocybin or DMT at high doses (Meldrum and Naquet, 1971; Rouse & Frank, 1974). In the Rose & Frank study (1974), they even estimate the necessary anti-epileptic LSD-human dose "since 100 μg/kg represents the anticonvulsant threshold in mice, at least 300 μg/kg should be required to suppress motor seizures directly in the human epileptic".

According to Anlezark & Meldrum (1978), the protective action of LSD against photoparoxystic epilepsy can be explained in terms of action at a serotonergic synapse in the lateral geniculate. This hypothesis lacks conclusive evidence. Parenteral administration of LSD produces a reduction of transmission at the lateral geniculate nucleus and causes a decreased general motility, increased eye movements and transiently increased fast EEG activity, also seen when psilocybin and DMT are administered in doses with corresponding autonomic effects. This could be because psilocybin and DMT most closely resemble LSD in their mechanisms of action. Indeed, they were also reported to be effective at blocking the myoclonic and paroxysmal EEG responses whilst mescaline, although some low doses seemed to diminish the myoclonic activity, the highest dose did not interrupt it completely (Meldrum and Naquet, 1971). Those early publications suggested various theories as emerging from this phenomenon: the prevention by derivatives of lysergic acid of photically induced myoclonus may be the result of central anti-serotonin action (meaning that 5-HT depletion leads to a prolongation of convulsions (Archer & Tandberg (1984)) or these drugs block the photically provoked responses by acting synergistically with 5-HT (Meldrum & Naquet (1971). Anlezark et al. (1976) explained that LSD has been shown to activate the DA-sensitive adenylyl cyclase system and stimulate production of cyclic AMP in striatal homogenates. This generates a decrease in cerebral homovanillic acid concentration and increases turning behavior. LSD acts as a 5-HT agonist in several areas which receive a serotonergic input and also at serotonin containing cell bodies in the nuclei of the median raphe (where firing is inhibited by both 5-HT and LSD).

Additionally, it should be noted that not only dose-dependent mechanisms of action have been studied: the direct and acute postsynaptic 5-HT agonist, 5-MeO-DMT, caused a prolongation of both the latency and duration of post-decapitation convulsions (PDCs) from the 0.5 mg/kg dose upwards (Archer & Tandberg (1984), while the repeated administration of 5-MeO-DMT to rats prevented almost completely the PDCs (Archer et al., 1985). These findings offer evidence of 5-HT modulation by psychedelics probably via a direct postsynaptic mechanism.

The main limitation of this review has to do with the heterogeneity of the results and methodology of the studies reported, which hinder their comparability, and the external validity of the conclusions reached. However, it is the first review undertaken, to our knowledge, on the relationship between classic psychedelics and seizures, including all bibliography available in the reported databases.

Another relevant limitation is related to the term "seizure", that refers to a clinical syndrome that lacks a clear, consensual definition. Although it is generally thought to be the synonym of "epileptic seizure" (a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain) (Fisher et al., 2005), it is not always the case, since non-epileptic seizures are also common events that can arise due to different etiologic factors (Asadi-Pooya, 2017), and can have an identical clinical presentation. While some studies assess the neuroelectric underpinnings of the symptomatology observed, mainly through EEG measurements, especially those undertaken in animal models and in early research, others only report the observation of such clinical symptoms, which diminishes their validity to assess causal mechanisms. In addition, some studies employed the post-decapitation convulsion model, which is not a model for electrographic seizures. Although observing seizure susceptibility in these models can be intriguing, they are better suited for investigating brainstem and spinal activity. Nevertheless, we chose to include them as they met the search criteria for this review. Similarly, the studies involving baboons used a photosensitive epilepsy model and had small sample sizes, which may limit their generalizability to other conditions or exposures

In conclusion, the available data, although heterogeneous, generally indicate that the use of psychedelics alone does not increase the risk of seizures in healthy individuals devoid of additional drug interactions. However, the concurrent use of substances such as kambo or lithium may elevate seizure risks. These findings derive from datasets with limited external validity, necessitating cautious interpretation. Future discussions and debates should utilize this information to refine inclusion and exclusion criteria for clinical trials concerning seizure risk. It is imperative that these criteria adhere to stringent safety standards while striving to maximize inclusivity, equality, and ethical considerations.

CRediT authorship contribution statement

OSA, GO, AF, MMR and LF designed the study, wrote the protocol, managed the literature searches and analyses and wrote the first draft of the manuscript. **ES, FJGL,KNUDSEN** provided expert opinion, reviewed and provided critical comments of the manuscript. All authors contributed to and have approved the final manuscript.

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During the past three years, O.S.A has received travel awards (air tickets + hotel) for taking part in annual psychiatric meetings from Lundbeck and Janssen-Cilag. He also has acted as a speaker for Lundbeck, and as a consultant for MAPS Foundation. None of them are related to this publication.

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ANEXO 2

Versión en castellano del instrumento APEQ

APEQ

A continuación, se presenta una lista de afirmaciones que describen varios pensamientos, sentimientos y comportamientos que pueden haber ocurrido durante su experiencia. Por favor, califique el grado en que estas afirmaciones se corresponden con su experiencia o partes de ella.

Para ello, marque la posición apropiada de la línea bajo cada afirmación con una línea vertical.

1. Observé mi entorno externo.

NO, para nada — **SI**, extremadamente o absolutamente

2. Estuve ocupado/a con lo que ocurría en mi interior.

NO, para nada — **SI**, extremadamente o absolutamente

3. Me pareció que algún tipo de bloqueo estaba siendo resuelto.

NO, para nada — **SI**, extremadamente o absolutamente

4. Aprendí a comprender mejor ciertos estados emocionales.

NO, para nada — **SI**, extremadamente o absolutamente

5. Intenté atenuar o deshacerme de ciertas percepciones o sensaciones corporales.

NO, para nada — **SI**, extremadamente o absolutamente

6. Aprendí a temer o detestar con mayor intensidad ciertos sentimientos o sensaciones incomodas.

NO, para nada — **SI**, extremadamente o absolutamente

7. Fui capaz de aceptar pensamientos o recuerdos incómodos.

NO, para nada — **SI**, extremadamente o absolutamente

8. Me sentí atormentado/a.

NO, para nada — **SI**, extremadamente o absolutamente

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9. Experimenté una liberación emocional positiva.

NO, para nada — **SI**, extremadamente o absolutamente

10. Me involucré activamente con mi entorno.

NO, para nada — **SI**, extremadamente o absolutamente

11. Descubrí una aceptación más profunda de ciertos sentimientos o sensaciones difíciles.

NO, para nada — **SI**, extremadamente o absolutamente

12. Miré hacia adentro.

NO, para nada — **SI**, extremadamente o absolutamente

13. Estuve abierto/a a sensaciones o estados emocionales difíciles.

NO, para nada — **SI**, extremadamente o absolutamente

14. Me entró pánico.

NO, para nada — **SI**, extremadamente o absolutamente

15. Intenté cambiar mi estado de ánimo.

NO, para nada — **SI**, extremadamente o absolutamente

16. Me di cuenta de que puedo tolerar ciertos estados mentales menos de lo que pensaba.

NO, para nada — **SI**, extremadamente o absolutamente

17. Mi atención estuvo dirigida hacia adentro.

NO, para nada — **SI**, extremadamente o absolutamente

18. Observé abiertamente recuerdos dolorosos.

NO, para nada — **SI**, extremadamente o absolutamente

19. Aprendí que es mejor para mí no experimentar en absoluto ciertos estados emocionales.

NO, para nada — **SI**, extremadamente o absolutamente

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20. Me di cuenta de que ciertos pensamientos o recuerdos no son tan peligrosos como pensaba antes.

NO, para nada — **SI**, extremadamente o absolutamente

21. Interactué con otras personas.

NO, para nada — **SI**, extremadamente o absolutamente

22. Experimenté una sensación de alivio.

NO, para nada — **SI**, extremadamente o absolutamente

23. Experimenté un estado de angustia.

NO, para nada — **SI**, extremadamente o absolutamente

24. Intenté suprimir ciertas emociones o pensamientos.

NO, para nada — **SI**, extremadamente o absolutamente

25. Estuve absorto/a en mi experiencia interior.

NO, para nada — **SI**, extremadamente o absolutamente

26. Moví mi cuerpo.

NO, para nada — **SI**, extremadamente o absolutamente

27. Las cosas se volvieron más fáciles para mí de una manera liberadora.

NO, para nada — **SI**, extremadamente o absolutamente

28. Me esforcé por evitar o controlar sentimientos difíciles.

NO, para nada — **SI**, extremadamente o absolutamente

29. Aprendí que ciertos pensamientos o recuerdos son más peligrosos para mí de lo que pensaba antes.

NO, para nada — **SI**, extremadamente o absolutamente

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30. Aprendí a apreciar más ciertas sensaciones o sentimientos incómodos.

NO, para nada — **SI**, extremadamente o absolutamente

31. Sufrí con lo que estaba experimentando.

NO, para nada — **SI**, extremadamente o absolutamente

32. Conseguí enfrentarme a un miedo personal.

NO, para nada — **SI**, extremadamente o absolutamente

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APEQ Instrucciones para puntuar

Las escalas visuales análogas (EVA) de los cuestionarios APEQ impresos en papel DIN A4 (210 x 297 mm) deberían tener una longitud de exactamente 100mm. El rango de puntuaciones es de 0 a 100. La puntuación de cada ítem se lee midiendo la distancia horizontal entre el margen izquierdo de la EVA y la posición marcada por el sujeto en mm. Las puntuaciones de las escalas principales, las subescalas y las escalas de anclaje, se calculan como figura a continuación:

Subescalas:

Respuesta de aceptación	=	(Item 7 + Item 13 + Item 18 +Item 32) / 4
Alivio	=	(Item 3 + Item 9 + Item 22 + Item 27) / 4
Introspección pro-aceptación	=	(Item 4 + Item 11 + Item 20 + Item 30) / 4
Respuesta evitativa	=	(Item 5 + Item 15 + Item 24 + Item 28) / 4
Angustia	=	(Item 8 + Item 14 + Item 23 + Item 31) / 4
Instrospección pro-evitación	=	(Item 6 + Item 16 + Item 19 + Item 29) / 4

Escalas principales:

Experiencias relacionadas con aceptación (ACE) = (Respuesta de aceptación + Alivio + Introspección pro-aceptación) / 3

Experiencias relacionadas con evitación (AVE) = (Respuesta evitativa + Angustia + Introspección pro-evitación) / 3

Escalas de anclaje:

Introspección	=	(Item 2 + Item 12 + Item 17 + Item 25) / 4
Interacción	=	(Item 1 + Item 10 + Item 21 + Item 26) / 4

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ANEXO 3

Exploring 5-MeO-DMT as a pharmacological model for deconstructed consciousness

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Rapid Communication

Exploring 5-MeO-DMT as a pharmacological model for deconstructed consciousness

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Abstract

5-MeO-DMT is a short-acting psychedelic that is anecdotally reported to induce a radical disruption of the self and a paradoxical quality of aroused, waking awareness that is nevertheless devoid of any specific perceptual contents. Here, we conducted an exploratory observational study of the phenomenological and neuronal effects of this compound. We collected micro-phenomenological interviews, psychometric questionnaires, and electroencephalography (EEG) in naturalistic ceremonial settings where 5-MeO-DMT was ingested. Results revealed that the 5-MeO-DMT experience followed a dynamic progression that—only in the most extreme cases—manifested as a complete absence of self-experience and other phenomenal content with preserved awareness. Furthermore, visual imagery, bodily self-disruption, narrative self-disruption, and reduced phenomenal distinctions occurred in a variable fashion. EEG analyses revealed the 5-MeO-DMT experience was characterised by (global) alpha and (posterior) beta power reductions, implying a mode of brain functioning where top-down models are inhibited. Our preliminary phenomenological findings confirm the potential utility of 5-MeO-DMT as a pharmacological model for deconstructed consciousness while noting the limitations of employing retrospective questionnaires for this purpose. Considering the exploratory nature of this study and its limitations inherent to its naturalistic nature, further research employing real-time experience sampling and phenomenologically trained participants in controlled environments could expand our findings to meaningfully inform the potential of this tool for the scientific study of consciousness.

Keywords: psychedelic; serotonin; EEG; self; awareness; neurophenomenology

Introduction

Psychedelics are compelling tools for the study of consciousness, as they induce significant alterations in the contents of conscious experience while preserving wakefulness at commonly used doses (Timmermann et al. 2023a). 5-MeO-DMT is a classic, psychedelic compound which acts via agonism at the serotonin-2A receptor (Nichols 2016). However, it is atypical in comparison to other classic psychedelics, as preliminary reports suggest an especially potent and rapid disruption in self-related processing (Uthaug et al. 2019) while inducing comparatively less visual imagery, which may relate to its unusually high agonism at the serotonin-1A receptor (Ermakova et al. 2022).

The subjective effects of 5-MeO-DMT make it a promising molecule for the study of human consciousness, as it may not only reliably induce experiences of self-dissolution but also, in peak moments of intensity, lead to a further deconstruction of all

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contents of experience, including thoughts and perception, with wakefulness preserved. This is anecdotally described as a 'void' experience (Metzner 2013). These experiences resonate with the phenomenology of so-called 'nonduality' that has been reported in some forms of meditation. Such states have been proposed as an avenue to study the minimal constituents of subjectivity or a 'minimal phenomenal experience' (MPE; Metzinger 2020). Compared to meditation states, however, the administration of 5-MeO-DMT might represent an attractive alternative to study states of deconstruction in a controlled fashion. This is because studying such extreme conscious states using meditation might require participants with rare, advanced skills that take considerable time and training to acquire. Furthermore, when 5-MeO-DMT is inhaled, the onset of effects occur within seconds, and the resolution of these effects tends to resolve within 30 minutes (Metzner 2013), making this compound a useful tool to study the deconstruction of conscious experience.

While the pharmacological induction of deconstructed consciousness represents a significant opportunity for the neuroscience of consciousness, it is imperative first to determine to what extent 5-MeO-DMT experiences truly reflect these target states. Intense psychedelic experiences are particularly susceptible to reporting artefacts due to their ineffable character and the potential role of confabulation in subsequent descriptions (Timmermann et al. 2022). For researchers to meaningfully employ psychedelics in the scientific study of consciousness, innovative methods must be implemented to address these limitations. Rigorous first-person descriptions of subjective experiences, such as those produced during micro-phenomenological interviews (MPIs), have been found to quantitatively improve commonly reported issues associated with introspection and recollection (Petitmengin et al. 2013), and have become increasingly attractive in neurophenomenological studies linking subjective experiences of non-ordinary states of consciousness and brain activity (Timmermann et al. 2023a).

In this study, we performed a preliminary neurophenomenological naturalistic investigation of 5-MeO-DMT. We measured the brain activity of healthy volunteers using electroencephalography (EEG) before and during the administration of 5-MeO-DMT in naturalistic settings, followed by MPIs and psychometric questionnaires. We hypothesised that 5-MeO-DMT disrupts several features of the sense of self as well as the power of alpha brain rhythms.

Materials and methods

Participants

Participants in this observational study were recruited based on their intention to participate in a ceremony where psychedelics would be ingested. For this study, we focused on individuals planning to participate in a ceremony where either synthetic 5-MeO-DMT or parotoid gland secretions from the *Incilius alvarius* toad would be ingested (the main psychoactive component of these secretions is 5-MeO-DMT; Uthaug et al. 2019). Additional eligibility criteria included being 18 years or older and having a good understanding of English. Ethics approval was given by the Joint Research Compliance Office, the Imperial College Research Ethics Committee (ICREC reference 18IC4346), and the Ethical Review Committee Psychology and Neuroscience (ERCPN), Maastricht University. All participants gave informed consent.

Procedure

For this study, we collected data from participants in ceremonies occurring in the Netherlands and Spain. The research team was not involved with the organisation of the ceremonies or administration of 5-MeO-DMT. In both ceremonies, 5-MeO-DMT (either synthetic or from toad secretion) was inhaled, via a pipe, by participants assisted by a facilitator. The sample consisted of 14 participants (5 females, 8 males, average age 35.8 ± 11.8; 4 participants failed to complete data relative to age, and 1, to gender). Synthetic 5-MeO-DMT was used in the Netherlands ceremony (43% of participants), and toad secretions were used in the Spain ceremony (57% of participants). The facilitator of each ceremony chose the doses. The average dose for the Netherlands ceremony was 15.4 mg of 5-MeO-DMT. Chemical analyses from the Spain ceremony revealed the average dose to be 28.7 mg. In the latter ceremony, participants inhaled from multiple preprepared pipes (EEG data were analysed only after the last inhalation), allowing for the comparatively higher dose of 5-MeO-DMT (Supplementary methods and Supplementary Table S1 for details).

Phenomenology

Following our previous work (Timmermann et al. 2019), MPIs were conducted (by author C.T. for the Netherlands and Spain ceremonies and J.W.S. for the Spain ceremony), immediately upon return to baseline following the administration of 5-MeO-DMT. The MPIs were audio-recorded, then transcribed, and analysed (by J.W.S.) to capture time-dependent phenomenological features of the experience. The interviews lasted approximately 30–60 min. The MPI is beneficial to explore qualities of the experience which may go commonly unnoticed (Petitmengin 2006), and is shown to be helpful in reducing confabulation (Petitmengin et al. 2013) and the influence of posthoc interpretations of ineffable aspects of experience commonly encountered in non-ordinary states of consciousness (Timmermann et al. 2023a). In each interview, the trained interviewer guided the participant to immerse themselves in the memory of the 5-MeO-DMT experience and give a rich and systematic description of how it unfolded from moment to moment. Through an iterative line of questioning, the participant was invited to describe their experience in ever-more precise detail, focusing on the acute phenomenological qualities and structures while avoiding extraneous details such as posthoc explanations and judgements of the experience. Transcripts of the interviews were subjected to a combined micro-phenomenological and thematic analysis (Clarke and Braun 2017, Petitmengin et al. 2018), whereby micro-phenomenological analysis was used to parse each interview into a timeline of phenomenological phases according to linguistic indicators of temporal shifts, and thematic analysis was used to cluster these phases across participants according to the phenomenological characteristics described within each. These clusters formed categories that represent a distinct substate of the 5-MeO-DMT experience. Assessing transitions between these categories in the phase timeline of each interview supported the development of a flowchart model describing the pathways followed through the identified substates. The Altered States of Consciousness Questionnaire (ASC), a self-report retrospective measure lacking any temporal assessments, was completed after the interview to complement phenomenological findings (Studerus et al. 2010).

Electroencephalography

Brain activity was recorded continuously from baseline (for 5 min) as well as during and after 5-MeO-DMT administration (for up to 15 min) using a 24-channel wireless EEG cap (DSI-24 System, Wearable Sensing) with 21 dry electrodes (300 Hz sampling rate). Participants remained in a seated position for all recordings with their eyes closed. Electrodes were positioned following the 10–20

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international format with electrode Pz for online reference, and earlobe electrodes A1 and A2 to subtract noise in other channels. Data were recorded using a Bluetooth-connected DSI-Streamer-v.1.08.41 and processed using the Fieldtrip toolbox (Oostenveld et al. 2011) in MATLAB. Data were demeaned, bandpass filtered (1–30 Hz), and visually inspected for removal of gross artefacts. Independent Component Analysis was then employed, and components displaying electrocardiogram activity or ocular motion were removed. Five participants were removed from further analysis as no usable data survived preprocessing. Spectral analysis was performed using Hanning windowed Fast Fourier Transforms between 1 and 30 Hz at 0.5 Hz intervals, and averaged in delta (1–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), low beta (13–20 Hz), and high beta (20–30 Hz) bands. Gamma power and entropy metrics known to relate to fast rhythms (Mediano et al. 2023) are highly susceptible to muscle artefacts and were thus not included in analyses. Statistical analyses were performed by comparing power at each frequency band obtained in the 5-min immediately after administration against the 5-min baseline by performing cluster-based *t*-statistics testing (Oostenveld et al. 2011). Considering the sample size and variability of the data, a qualitative neurophenomenological analysis was employed to examine changes in brain activity (z-scored) of participants reporting a complete absence of the self compared to participants reporting some preservation of features of the self.

Results

Micro-phenomenology

Six categories characterising distinct phases of the 5-MeO-DMT experience were identified. Each was visited by a subset of the participants at some point. A description of each category is given below, along with the percentage of participants who reported it. The direction and frequency of transitions between categories were also identified (Fig. 1a).

Onset (86%)

The onset of the experience affected different modalities and dimensions of experience. The dynamic of 'onset' was rapid and variously described as 'fading', 'accelerating', 'expanding', 'compressing', 'tearing', 'fractalising', 'dissolving', 'shattering', or 'collapsing'. These were described as affecting the body, the visual field, the thinking mind, the self, or all of the above—with each potentially being affected by different processes (e.g. expanding body and shattering visuals).

> "At the very beginning, it was like something was crumbling … like, disintegrating … It was black. But I saw these … patterns … as if there was a pattern that was somehow crumbling, and it opened up to something big and enormous. And that was very quick." P14

Immersion/merging (43%)

Described as a reduction in awareness of immediate surroundings, accompanied by intense feelings moving through, or being released from, the body. Sometimes with a described sense of 'becoming' the feelings rather than just feeling them, or with sensations that are in between or beyond the senses. In some cases, feelings were identified as emotions, and at times those emotions were experienced as depersonalised (i.e. not connected to one's own personal narrative context). Feelings were described as either positive (blissful, sensual) or negative (fear, grief, discomfort). Sometimes, visuospatial language such as colour and shape was used to describe the state; however, in some cases this was qualified as being not truly visual.

> "I could feel energy centred in the torso … warm energy … very beautiful … The emotions are giving birth to energy within you … I was feeling like I'm letting go of something … I didn't really exist as a person … my surroundings didn't exist … like I was the emotions and the energy." P2

Abstract (43%)

A disembodied experience in which some elementary visuospatial form was described, using terms such as shape, colour, and movement. However, despite these visuospatial terms, the experience was sometimes further described as lacking spatial, visual, and also temporal dimensions. The form was sometimes described as being experienced through something akin to bodily sensations, but not in the everyday form of body at all (i.e.: felt sensations, but not feelings of the body). No other contents were described, including no narrative self and no capacity for thought or reflection.

> "There were no limits, or no objects, no dimensions even. I had no thought. I had no senses … But I had some feeling of … like a pyramid or something … And the colour … it was kind of a rose [colour]. [But] it is not that I saw this … it was more kind of feeling of the space … So there's a feeling of this kind of rose-coloured pyramid." P5

Everything/nothing (29%)

A state of extreme reduction in phenomenological distinctions such that, relatively, very little was described, and what was described was often done so in paradoxical terms. It featured no spatial or temporal qualities, no distinct sensory content, no capacity for thought or reflection, no narrative or bodily self, and no subject-object dichotomy. The experience was sometimes described as 'whole' or 'full', containing everything, despite a concurrent sense of 'void' or 'nothing'. It was sometimes described as luminous, or with a positive affective tone, though still lacking the structures of perception and selfhood that are implied by categories like vision and emotion.

> "I was not there. It was like I was accessing 'whiteness'. Quiet, blissful, enormous, whiteness … I was everything … There was no controller, or observer … It was not 'me'. I don't know what happened. I somehow had a glimpse of, of … of the wholeness." P6

Reconstitution (57%)

A gradual and sequential return of structures of experience, and sensory experience of the present environment. The order in which specific structures and content returned was variable across participants. An example sequence could be as such: sounds return first, followed by bodily sensations, followed by a broader awareness of the room, followed by thoughts and narrative self. Upon return, structures or content were sometimes described as distant or faint before gradually becoming clearer and more present. A rapid or discontinuous reconstitution was also described in some cases.

> "I started feeling my shoulders … it was a bit subtle, and I wasn't sure if [the feeling] was actually true … And then I was puzzled … like, 'why are there people [here]?' … This is where the duality

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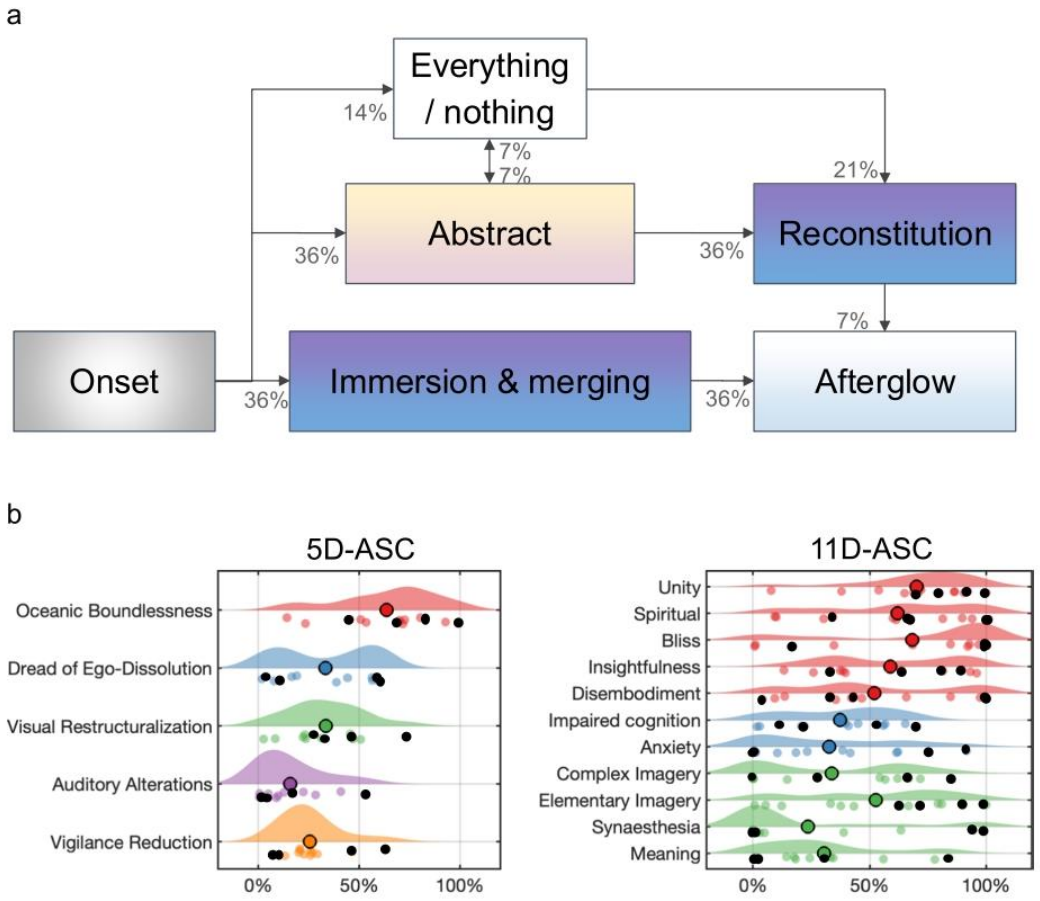


Figure 1 Characterisation of the 5-MeO-DMT experience. (a) Analysis of interviews following 5-MeO-DMT resulted in six categories of experience. Arrows and percentages describe the temporal progression between categories and their frequency of occurrence (initial transitions do not add to 100% because progressions were not identified for all participants). (b) Results from self-reported retrospective ASC questionnaire showing scores for the 5 (left) and 11 (right) dimensions (colours in the 11 dimensions are matched to their grouping in the 5 dimensions). These subscales revealed high variability in a wide range of phenomenological features, including for participants experiencing the 'everything/nothing' stage (shown as black dots), which are distributed in a wide range of scores (with the exception of the 'Unity' dimension), reflecting the inherent limitations of static, self-reported measures (Large coloured dots represent the mean).

started to happen. Like, that is me. And, that is the space. And, there are other things." P9

Afterglow (43%)

A state close to baseline consciousness but with a lingering sense of clarity, positive affect, and/or reduction in thought. Sometimes described as a meditative or peaceful state.

> "[It was] like a meditation. Just 'feel', and just 'be'. … the quality of my presence feels different … like I've been stretched out a bit." P13

Memory effects

Some participants described moments of the experience as being impossible or very difficult to recall, possibly related to amnesia or losing consciousness. This phenomenon was temporally associated with peak phases of the experience and exclusively by participants from the Spain ceremony (63%), who received higher doses. Therefore, categories such as 'abstract' and 'everything/nothing' may be underreported due to amnesia (see Supplementary Table S3 for the occurrence of phenomenological categories for each ceremony).

Questionnaire results

Average scores of the ASC questionnaire were variable across participants, including for those reporting peak experiences (i.e. the 'everything/nothing' category), possibly reflecting the limitations of self-report questionnaires lacking temporal precision (Fig. 1b). Further highlighting this point, whereas average scores of the Oceanic Boundlessness subscale—closely related to peak experiences of interest (Roseman et al. 2018)—were, on average, higher for the Netherlands ceremony (71.3% of total) compared to the Spain ceremony (58.7%) (Supplementary Fig. S1), the MPI analyses identified peak experiences occurring more frequently in the Spain ceremony (Supplementary Table S3), where a larger average dose of 5-MeO-DMT was used (however, it is important to note that nonpharmacological variables related to the setting of the ceremony may have also influenced this difference) (Supplementary Table S2).

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Table 1. Phenomenological categories of the 5-MeO-DMT experience as they typically relate to five broadly studied structures of experience

	Embodied self	Narrative self	Thought/reflection	Disconnection	Phenomenal distinctions
Onset	Present, undergoing transformation	Present, undergoing transformation	Present, undergoing transformation	Connected or in process of disconnection	Many
Immersion and Merging	Present with intense sensations, or reduced	Reduced	Reduced	Partially disconnected	Reduced
Abstract	Absent, or transformed beyond recognition	Absent	Absent	Disconnected	Few
Everything/Nothing	Absent, or universal and featureless	Absent	Absent	Disconnected	Minimal
Reconstitution	Transitioning from absent to present	Transitioning from absent to present	Transitioning from absent to present	Transitioning from disconnected to connected	Transitioning from minimal or few towards baseline
After(glow)	Present or slightly reduced	Present or slightly reduced	Present or slightly reduced	Connected	As per baseline or slight reduction

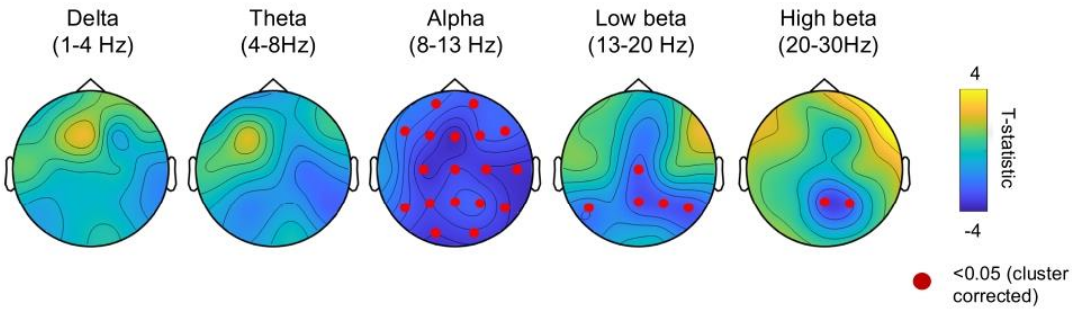


Figure 2 EEG effects of 5-MeO-DMT. Ingestion of 5-MeO-DMT resulted in global reductions of alpha power across most electrodes, and decreases in posterior beta band power.

The phenomenological categories were then associated with five broadly studied structures of experience in consciousness science, with results suggesting that 'abstract' and 'everything/nothing' experiences hint to a state of deconstructed consciousness (Table 1).

Electroencephalography

EEG results revealed that, compared to baseline, the 5-MeO-DMT state was associated with a global reduction of power in alpha brainwaves (max. $t[9] = 3.77$, $P = .0001$, cluster-corrected for multiple comparisons) and a posterior decrease in low (max. $t[9] = P = .007$, cluster-corrected for multiple comparisons) and high beta power was also observed (max. $t[9] = 3.18$, $P = .021$, cluster-corrected for multiple comparisons) (Fig. 2).

Neurophenomenology

To explore the impact of 5-MeO-DMT on the self, we inspected changes in EEG spectra separately for participants for which the 'abstract' and 'everything/nothing' categories were identified, as in these categories embodied and narrative features of the self were completely absent, compared to other participants for which only categories, where the self was preserved or only partially absent, were identified. Qualitative inspection of the spectra did not show a discrepancy between these groups. However, it is important to note that it was not possible to estimate when specific phenomenology corresponded to specific changes in brain activity within each subject as no real-time experience sampling was performed to estimate such changes and only averaged EEG activity throughout the whole period was used for neurophenomenological analyses (Fig. 3).

Discussion

In this exploratory, observational study, we investigated the effects of 5-MeO-DMT on experience and brain activity, based on the premise that 5-MeO-DMT may represent a useful model for deconstructed consciousness. Consistent with this notion, our results showed that peak 5-MeO-DMT experiences resulted in a state of disconnection, loss of narrative and embodied aspects of the self, and minimal phenomenal distinctions, while preserving wakefulness. However, these experiences occurred in approximately a third of participants and at specific moments only. EEG findings showed that a broad inhibition of alpha and posterior beta power was associated with the administration of 5-MeO-DMT.

Our phenomenological findings suggest that, during peak moments, 5-MeO-DMT induced a state of deconstructed consciousness. This state was not just linked to reductions in the embodied and narrative selves but also presented a state of heightened disconnection from the environment and (at times) associated with heightened levels of amnesia. Nonetheless, we found this state to be present only for some participants and at specific moments of the experience, something that could not be identified with the commonly used ASC questionnaire. A higher prevalence of this state among participants with larger doses indicates that the state may be dose-dependent, though amnesic effects may be similarly dose-dependent, and a dosing 'sweet spot' between the two may exist. Furthermore, these analyses revealed

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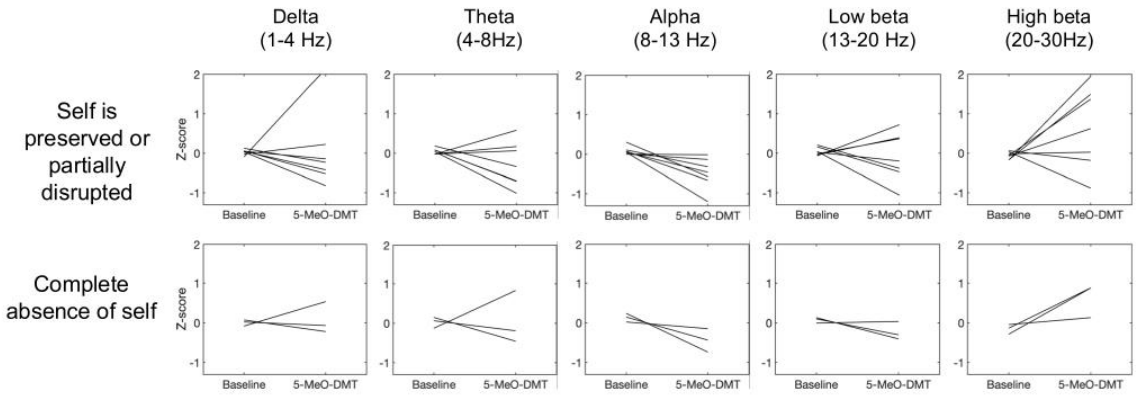


Figure 3 Relationship between self-disruption and EEG spectra. Qualitative inspection of EEG spectra of participants reporting a complete absence of the self (for which the 'abstract' or everything/nothing' stages were identified) did not show any overt differences compared to participants who reported some preservation of the self.

the 5-MeO-DMT state to be dynamic, with phenomenological trajectories varying between individuals. It is possible that this variability hindered the ability of neurophenomenological analysis to pick up on differences in brain activity of participants reporting the full absence of self, as opposed to participants reporting some preservation of features of the self. These results are consistent with the notion that temporal- and phenomenologically-guided analyses are required to establish the brain states associated with these experiences of deconstruction, which hold significant relevance to the study of self-experience and consciousness more broadly (Timmermann et al. 2023a). Future studies employing real-time sampling of experiences of interest are particularly relevant to detect the neural correlates of these states, especially considering the amnesic components of the 5-MeO-DMT experience that we report here.

In further support of temporal- and phenomenologically-guided analyses, self-report questionnaire results reflected somewhat counterintuitive differences in dosages of 5-MeO-DMT (synthetic vs. toad secretion) between the two ceremonies. Micro-phenomenological interviews more adequately captured these. We have established this sensitivity of micro-phenomenology to neurobiologically relevant dimensions of psychedelic experience in previous work (Timmermann et al. 2019); however, further work in a controlled lab setting should seek to validate these 5-MeO-DMT-specific phenomenological categories and potential dose-dependent effects against neurobiological data.

EEG findings of reduced alpha power are consistent with those of other psychedelics and dissociatives (Ona et al. 2022, Erritzoe et al. 2024). Alpha power has been linked to the encoding of high-level models (such as those related to the self), and thus, psychedelic-induced reductions have been linked with the reduced influence of these models on brain function (Carhart-Harris and Friston 2019). Our results suggest a similar inhibition of these models may also occur during the 5-MeO-DMT experience. Results of reduced posterior beta power under 5-MeO-DMT also resonate with similar decreases following the administration of DMT (Timmermann et al. 2019, 2023b), which correlate with bodily self-disruption (Timmermann et al. 2019). Intriguingly, disruptions of alpha and posterior beta power have also been found in the dissolution of bodily boundaries experienced during advanced meditation, with beta power reductions localised to the posterior cingulate cortex (Trautwein et al. 2024), a hub of the Default Network, which has a central role in self-related processing (Yeshurun et al. 2021). Apart from differences in these two bands, a high variability of effects was seen for other frequency bands. This variability resonates with contradictory results from different psychedelics on delta, theta, and gamma bands (Timmermann 2020). It is possible that such variability reflects phenomenological differences across subjects or variability in drugs, dose, or experimental setting. Future studies are required to establish the role of these variables in brain function.

Due to the uncontrolled environment of our study, we chose not to examine the effects of 5-MeO-DMT in brain entropy (see 'Methods' section). Entropy has been hypothesised to index the richness of an experience (Carhart-Harris et al. 2014). It is plausible that the increase in richness of contents in a high-intensity psychedelic experience (such as the one induced by 5-MeO-DMT) is such that it surpasses the attentional capacity required to perceive these in an organised fashion, and that this results in such minimal phenomenal distinctions we report here. Our phenomenological results seem to support such a hypothesis where participants recall a paradoxical experience of 'everything and nothing'. If this is correct, then such deconstructed experiences induced by 5-MeO-DMT would be indexed by an increase in neuronal entropy rather than a decrease.

Testing this neurophenomenological hypothesis requires employing both phenomenologically-guided analyses as well as adequate controls for EEG confounds. Increases in power of low and high brainwaves have been reported following naturalistic and lab reports of 5-MeO-DMT and - the closely-related compound - DMT (Acosta-Urquidi 2017, Pallavicini et al. 2021, Timmermann et al. 2023b, Blackburne et al. 2024). To confirm such reports (as well as our current EEG findings), it is imperative to control for potential physiological artefacts, especially considering that these compounds markedly increase cardiovascular and muscle-related artefacts known to impact measurement of these brain mechanisms.

It is relevant to note some limitations in our study. The naturalistic design of our study and relatively low sample prevented us from having experimental controls or performing experience sampling, which would have allowed us to refine the association between phenomenology and brain activity. Moreover, we

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averaged data from participants ingesting synthetic and natural sources of 5-MeO-DMT for EEG analyses. Future studies should aim for larger samples and would benefit from employing real-time experience sampling in controlled environments.

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Supplementary data

Supplementary data is available at *Neuroscience of Consciousness* online.

Conflict of interest

R.L.C. is a scientific advisor for Mydecine, Maya Health, Osmind, Synthesis Institute, Tryp Therapeutics, Journey Collab, Journey Space, Beckley Psytech and Usona Institute. J.G.R. is a scientific advisor to GH research. G.A. is a co-founder of Somnivore Pty Ltd. T.P., who declares to have shares in 'Psyon s.r.o.' and 'Společnost pro podporu neurovědního výzkumu s.r.o', founded the 'PSYRES—Psychedelic Research Foundation' and reports consulting fees from GH research and CB21-Pharma outside the submitted work. All other authors declare no competing interests.

Data availability

Data from this manuscript are available upon reasonable request to the corresponding author.

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