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Pharmacokinetics and Pharmacodynamics, Safety and Tolerability, and Therapeutic Potential of an Innovative Psychedelic Ayahuasca-Analogue containing N,N-Dimethyltryptamine and Harmine

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Michael Johannes Müller

MSc, ETH Zurich

born on 22.11.1992

accepted on the recommendation of

Prof. Dr. Johannes Bohacek

Dr. Dr. Milan Scheidegger

Prof. Dr. Boris Quednow

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Abstract

The psychedelic renaissance is a new wave of scientific research around psychedelics and their therapeutic potential as treatment options for mental health disorders. Specifically, psychedelic-assisted psychotherapy is a rapidly evolving field with significant therapeutic potential, and recent developments have focused on a class of serotonergic substances for their rapid-acting antidepressant and anxiolytic properties. Within this class, the Amazonian plant medicine “ayahuasca”, rich in the psychoactive compounds N,N-dimethyltryptamine (DMT) and β-carboline alkaloids like harmine or harmaline, has attracted substantial interest for its beneficial effects on affective and other mental health disorders. Yet, the use of traditional ayahuasca has been associated with several unpredictable distressing side effects in the Western medicine context, often attributed to suboptimal pharmacokinetic and pharmacodynamic (PK-PD) properties, overdosing, and intolerable plant constituents. These challenges have stimulated efforts towards refining the therapeutic application of ayahuasca components.

This dissertation presents an overview of the use of ayahuasca globally and elaborates on its pharmacological and therapeutic aspects. Furthermore, we present a pioneering approach involving the development of an ayahuasca-analogue formulation, a preparation consisting of only two isolated compounds, namely DMT and harmine. With a parenteral administration form, we sought to overcome the challenges of traditional ayahuasca, to further translate its therapeutic potential into the Western healthcare system. An initial pilot study has resulted in the development of an innovative formulation, with improvements seen in the PK-PD properties and tolerability compared to traditional ayahuasca. The subsequent 2 studies presented in this dissertation are part of a double-blind, randomized, placebo-controlled within-subject study involving healthy male subjects, with each participant receiving a combination of sublingual harmine and intranasal DMT, harmine alone, or a placebo. DMT was administered intermittently in increments over a period of time to establish a more patient-oriented and better controllable drug administration. All preparations were tolerated well and the pharmacokinetic profile of DMT showed a pronounced long-lasting plateau during the intermittent administration. Moreover, based on both psychometric self-assessments and pharmacokinetic profiles, we found that intranasal DMT can be effectively activated by sublingual harmine and is the main driver of subjective effects compared to the harmine only and placebo condition. Furthermore, the combination of DMT and harmine was shown to induce a phenomenologically rich psychedelic experience, characterized by psychological insights and emotional breakthroughs, with low scores reported in challenging experiences, suggesting a generally acceptable psychological safety profile. These effects were well tolerated and were not associated with changes in personality traits, psychological flexibility, or general well-being, nor were there increases in psychopathology. Importantly, participants attributed personal and spiritual significance to the experience, with mainly positive persisting effects observed at 1- and 4-months follow-ups.

These findings suggest that the standardized DMT and harmine formulation demonstrates promising PK-PD properties, psychological safety and tolerability, and induces beneficial

psychological processes that could potentially augment psychotherapy. The development of new treatments for mental health disorders based on this formulation warrants further investigation in clinical trials. The successful translation of this research into clinical settings could advance the treatment of mental health disorders, adding a potent therapeutic method to the existing options for treating affective disorders.

Zusammenfassung

Die psychedelische Renaissance ist ein neues Aufleben wissenschaftlicher Forschung über Psychedelika und ihr therapeutisches Potenzial für die Behandlung von psychischen Krankheiten. Insbesondere Psychotherapien, die mit der Einnahme von Psychedelika unterstützt werden, sind ein sich rasch entwickelnder Bereich mit grossem therapeutischem Potenzial. Die jüngsten Entwicklungen haben sich auf eine Klasse serotonerger Substanzen konzentriert, die aufgrund ihrer schnell wirkenden antidepressiven und anxiolytischen Eigenschaften bekannt sind. Innerhalb dieser Klasse hat «Ayahuasca», eine pflanzliche Medizin aus dem Amazonasgebiet, aufgrund positiver Auswirkungen auf affektive und andere psychische Störungen grosses Interesse auf sich gezogen. Dieser psychedelisch wirkende Aufguss ist reich an den psychoaktiven Komponenten N,N-Dimethyltryptamin (DMT) und β-Carbolin-Alkaloiden wie Harmin oder Harmalin. Dennoch wurde die Verwendung von traditionellem Ayahuasca im Kontext der westlichen Medizin mit mehreren unvorhersehbaren Nebenwirkungen in Verbindung gebracht, die oft auf suboptimale pharmakokinetische und pharmakodynamische (PK-PD) Eigenschaften, Überdosierung, und unverträgliche Pflanzenbestandteile zurückgeführt werden konnten. Diese Herausforderungen haben die Bemühungen zur Verbesserung der therapeutischen Anwendung von Ayahuasca-Komponenten gefördert.

Diese Dissertation gibt einen Überblick über die weltweite Verwendung von Ayahuasca und geht auf seine pharmakologischen und therapeutischen Aspekte ein. Darüber hinaus stellen wir einen wegweisenden neuen Ansatz vor, der die Entwicklung einer Ayahuasca-analogen Formulierung beinhaltet. Diese Formulierung besteht aus nur zwei isolierten Substanzen, nämlich DMT und Harmin. Mit einer parenteralen Verabreichungsform wollten gewisse Einschränkungen von traditionellem Ayahuasca überwinden und dazu beitragen, sein therapeutisches Potenzial im westlichen Gesundheitssystem zu implementieren. In einer ersten Pilotstudie wurde eine innovative Formulierung entwickelt, wobei Verbesserungen bei den PK-PD Eigenschaften und der Verträglichkeit gegenüber traditionellem Ayahuasca festgestellt wurden. Die beiden folgenden Studien, auf denen diese Dissertation basiert, sind Teil einer doppelblinden, randomisierten, Placebo kontrollierten Studie mit gesunden männlichen Probanden, wobei jeder Teilnehmer entweder eine Kombination aus sublingualem Harmin und intranasalem DMT, ausschliesslich Harmin oder ein Placebo erhielt. DMT wurde in Intervallen über einen bestimmten Zeitraum verabreicht, um eine patientenorientierte und besser kontrollierbare Behandlung zu ermöglichen. Alle Präparate

wurden gut vertragen und das pharmakokinetische Profil von DMT zeigte während der intermittierenden Verabreichung ein gleichmässiges, lang anhaltendes Plateau. Ausserdem zeigten sowohl die psychometrischen Selbsteinschätzungen als auch die pharmakokinetischen Profile, dass intranasales DMT durch sublinguales Harmin wirksam aktiviert werden kann und im Vergleich zur reinen Harmin-Bedingung und Placebo-Bedingung der Hauptfaktor für die subjektiven Effekte ist. Des Weiteren konnte gezeigt werden, dass die Kombination von DMT und Harmin eine phänomenologisch reichhaltige psychedelische Erfahrung hervorruft, die durch psychologische Einsichten und emotionale Durchbruchserfahrungen gekennzeichnet ist. Die Substanzerfahrungen wurden als nur leicht herausfordernd bewertet, was auf ein allgemein akzeptables psychologisches Sicherheitsprofil schliessen lässt. Die Verträglichkeit wurde als sehr gut bewertet und wir haben keine Veränderungen der Persönlichkeitsmerkmale, der psychologischen Flexibilität oder des allgemeinen Wohlbefindens gefunden. Ausserdem gab es auch keine Zunahme in der Psychopathologie. Im Gegenteil, die Teilnehmer haben der Erfahrung eine persönliche und spirituelle Bedeutung beigemessen, wobei bei den Nachuntersuchungen nach einem und vier Monaten hauptsächlich positiv anhaltende Effekte berichtet wurden.

Diese Ergebnisse deuten darauf hin, dass die standardisierte DMT- und Harmin-Formulierung eine vielversprechende Pharmakokinetik und Pharmakodynamik, psychologische Sicherheit und gute Verträglichkeit aufweist. Ausserdem werden positive psychologische Prozesse ausgelöst, welche möglicherweise die Psychotherapie unterstützen können. Die Entwicklung neuer Behandlungsmöglichkeiten für psychische Krankheiten auf der Grundlage dieser Formulierung sollte in klinischen Studien weiter untersucht werden. Die erfolgreiche Übertragung dieser Forschungsergebnisse in den klinischen Bereich könnte die Behandlung psychischer Krankheiten revolutionieren und die therapeutischen Möglichkeiten zur Behandlung affektiver Störungen um eine wirksame Methode erweitern.

Glossary

3-IAA	Indole-3-acetic acid
5/11D-ASC	5/11 Dimensions – Altered states of consciousness questionnaire
5-HT	Serotonin
5-MEO-DMT	5-Methoxy-N,N-Dimethyltryptamine
AAQ2	Acceptance and action questionnaire
(P)ACC	(Pregenual) Anterior cingulate cortex
ACN	Acetonitrile
AE	Adverse event
AMP	Avoidance and maladaptive patterns
AUC_{all}	Area under the curve from time zero to last time point
AUC_{inf}	Area under the curve from time zero to infinity
BDNF	Brain-derived neurotrophic factor
BT	Body temperature
C_{max}	Maximum plasma concentration
CBT	Cognitive behavioural therapy
CEQ	Challenging experience questionnaire
CFI	Cognitive flexibility inventory
CYP	Cytochrome P450
DA	Dopamine
DBP	Diastolic blood pressure

DMN	Default mode network
DMT/N,N-DMT	N,N-Dimethyltryptamine
EBI	Emotional breakthrough inventory
EEG	Electroencephalography
FMRI	Functional magnetic resonance imaging
GABA	Gamma-aminobutyric acid
GAP	Goals and adaptive patterns
GI	Gastrointestinal
HCL	Hydrochloride
(U)HPLC	(Ultra) High performance liquid chromatography
HPMC	Hydroxypropyl methylcellulose
IPIP	International personality item pool
LSD	Lysergic acid diethylamide
MAO	Monoamine oxidase
MAOI	Monoamine oxidase inhibitor
MEOH	Methanol
MDD	Major depressive disorder
MDMA	3,4-methylenedioxymethamphetamine
NE	Norepinephrine
NMT	N-methyltryptamine
NR6	Nature relatedness scale

ODT	Orodispersible
PCC	Posterior cingulate cortex
PEQ	Persisting effects questionnaire
(VM)PFC	(Ventromedial) Prefrontal cortex
PIQ	Psychological insights questionnaire
PK-PD	Pharmacokinetics-pharmacodynamics
PTSD	Post-traumatic stress disorder
QNMR	Quantitative Nuclear Magnetic Resonance
RCT	Randomized controlled trial
SBP	Systolic blood pressure
SCL-90-R	Symptom checklist 90 revised
SSRI	Selective serotonin reuptake inhibitor
SNRI	Selective serotonin-norepinephrine reuptake inhibitor
$T_{1/2}$	Plasma elimination half-life
T_{max}	Time to reach maximum plasma concentration
TCA	Tricyclic antidepressant
TRD	Treatment-resistant depression
TRKB	Neurotrophic tyrosine kinase receptor 2
VAS	Visual analogue scale
WEIRD	White, educated, industrialized, rich, democratic
WHO-5	World health organization well-being index

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Chapter 1. General Introduction

1.1 The Mental Health Crisis

The past two to three decades have seen a strong increase in mental disorders, accompanied by an impasse in pharmaceutical development (A. E. Becker & Kleinman, 2013; Benton et al., 2021). These psychiatric disorders cover a range of mental health conditions such as depression, anxiety, bipolar disorder, eating disorder, burnout, and post-traumatic stress disorder (PTSD). A subcategory of mental disorders, referred to as affective or mood disorders, encompass all behavioural and mental disorders, where a disturbance or disbalance in emotional regulation and mood is observed. This leads to a variety of symptoms such as anhedonia, persistent low mood, sleep disturbances, appetite changes, cognitive impairments, feelings of worthlessness, and fatigue (Gillberg et al., 2006). These disorders are widespread and have become leading contributors to global disability (Roehr, 2013; WHO, 2022). The most common mental health condition is major depressive disorder (MDD), also known as depression. MDD is characterized by decreased interest or enjoyment in activities, and persisting feelings of hopelessness and sadness. Its prevalence among millions worldwide significantly influences daily life, overall well-being, and social interactions (Roehr, 2013). Despite considerable research efforts, affective disorders, specifically MDD, remains highly prevalent in the general population and conventional treatments largely rely on antidepressant medications, often presenting limited effectiveness (Kirsch et al., 2008). The development of novel, more effective treatments has been an uphill battle due to the complexity of these diseases and the varying effectiveness of treatments among individuals (Cipriani et al., 2018; Cuijpers et al., 2013).

Additionally, the stigma associated with mental health disorders often acts as a barrier for seeking help, and many affected individuals may not receive appropriate care in time or at all (Clement et al., 2015). This issue has been further exacerbated in recent years by the ongoing capitalistic paradigm and changes in working environments, which has been hypothesized to increase stress and pressure on the individual, leading to an augmentation of the mental health burden (Davies, 2021; Zeira, 2022).

In spite of the unprecedented surge in psychiatric drug prescriptions, the incidence of mental health disorders is still escalating and was even more fuelled by the COVID-19 pandemic, which had a more severe effect among specific groups like younger adults (Ettman et al., 2022; Twenge et al., 2019). For instances, anxiety and depression have grown by over 25% in the pandemic's first year (WHO, 2022). This can be primarily attributed to factors such as existential dread, social isolation, emotional trouble due to illness, loss, unemployment, and financial instability (Armitage & Nellums, 2021; Inkster et al., 2020; Mahase, 2021). Stress-induced mood disorders pose a significant burden not only on individual health but also on societal and economic structures (WHO, 2022). Therefore, we are confronted with a predicament of ill individuals existing within unhealthy structures.

Existing antidepressants, which form the backbone of current MDD treatment protocols, often render inadequate clinical outcomes, exhibit delayed onset of action, and frequently

induce severe side effects (Holper & Hengartner, 2020; Kirsch et al., 2008; Munkholm et al., 2019). These pharmacological interventions rely predominantly on counteracting dysfunctional aminergic neurotransmission, which should lead to a daily relief of symptoms. However, they often fail to achieve full symptom remission, despite patients testing out a variety of medications (Munkholm et al., 2019). Consequently, there is an increasing need to explore alternative treatment approaches as the understanding of the underlying neurobiology of depression advances.

Additionally, the escalating prescription of pharmacological interventions, which bears an undeniable relation to the opioid crisis in the United States, has been the subject of criticism. The landscape of psychiatric drug discoveries since the 1950s has predominantly been characterized by reiterations of already existing medications, exhibiting a clear absence of innovation (Hillhouse & Porter, 2015). This has led to pharmaceutical companies discontinuing their investments in the development of psychiatric drugs, highlighting the state of crisis in which the field of psychopharmacology is currently in (Cressey, 2011). It has therefore become a priority to explore alternative therapeutic strategies for depression, which may offer more sustainable and long-lasting benefits to those suffering from these debilitating disorders.

1.1.1 Neurotransmitter Involved in Affective Disorders and Depression and Current State of Pharmacological Treatment

In the complex molecular landscape of depression, several neurotransmitter systems play a significant role. These include monoamines like serotonin (5-HT), norepinephrine (NE), and dopamine (DA), which are vital to various affective states and cognitive processes, including mood regulation (Krishnan & Nestler, 2008; Nestler et al., 2002). The monoamine hypothesis of depression, a prevalent conceptualization in the scientific community, suggests that depressive symptoms emerge from an imbalance in the neuronal equilibrium, functionality and availability of these neurotransmitters (Delgado, 2000; Liu et al., 2018; Schildkraut, 1965; Schildkraut & Kety, 1967). Given this understanding, the majority of contemporary antidepressants, encompassing selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and tricyclic antidepressants (TCAs), is designed to augment monoaminergic neurotransmission (Cipriani et al., 2018; Stahl, 2013). The primary mode of action of SSRIs, the most commonly prescribed class of antidepressants, involves selectively blocking the reuptake of serotonin. This leads to an increase of serotonin in the synaptic cleft and enhances serotonergic neurotransmission (van Harten, 1993). SNRIs, by contrast, inhibit the reuptake of both serotonin and norepinephrine, thus enhancing their synaptic availability and potentiating neurotransmission (Stahl et al., 2005). TCAs, although less selective, inhibit the reuptake of serotonin, norepinephrine, and to a lesser extent, dopamine. Additionally, they also interact with other receptor systems like histamine, muscarinic, and adrenergic receptors (Frazer, 1997). Moreover, current research indicates that apparently all antidepressants increase the signalling and expression of brain-derived neurotrophic factor (BDNF) by activation of the neurotrophic tyrosine kinase receptor 2 (TRKB) (Casarotto et al., 2021). It is important to note that the precise biochemical pathways

and mechanisms through which these alterations in neurotransmitter concentration generate antidepressant effects remain not fully understood. However, hypotheses suggest that long-term alterations in receptor responsiveness, downstream signalling cascades, and neuroplastic adaptations in specific cerebral regions are playing a crucial role driving therapeutic responses (Berton & Nestler, 2006; Duman et al., 2016).

Furthermore, current research suggests the involvement of other neurotransmitter systems in depression, such as glutamate and gamma-aminobutyric acid (GABA). Glutamate, being the primary excitatory neurotransmitter in the brain, is implicated in depression via its involvement in neuroplasticity and synaptic potency (Duman et al., 2019; Sanacora et al., 2012). Variations in glutamate receptor expression, metabolism, and signalling pathways have been identified in post-mortem cerebral samples from individuals with depression (Hashimoto, 2009). Similarly, the dominant inhibitory neurotransmitter GABA, shows dysregulation in individuals with depression, as supported by studies revealing diminished GABAergic functionality and expression (Luscher et al., 2011).

While the monoamine hypothesis has contributed significantly to the conceptual understanding of depression, it has been subject to criticism, primarily for its reductionist approach. The hypothesis presents affective disorder including depression as a straightforward biochemical imbalance, which may not fully capture the complexities of these diseases (Hirschfeld, 2000). Despite the extensive application of monoamine-based antidepressants, the global prevalence of mood disorders remains high, with fewer than half of all individuals with depression reaching full remission. This may be partially attributed to the limited efficacy of these conventional drugs (Kirsch et al., 2008; Munkholm et al., 2019). Moreover, it is increasingly acknowledged that affective disorders encompass a complex interplay of genetic, epigenetic, and environmental factors, which are shaping a person's psychological and biological state (Kendler et al., 2005; Sullivan et al., 2000). Additionally, there is growing acceptance that effective therapeutic strategies should combine psychopharmacological treatments with psychological and behavioural interventions towards a fully comprehensive treatment approach (DeRubeis et al., 2005; Hollon et al., 2005). For instance, therapeutic approaches like cognitive-behavioural therapies (CBTs) offer patients the tools to develop effective coping mechanisms, reframe maladaptive thinking patterns, and cultivate healthier behaviours. These interventions are crucial in maintaining and supporting the benefits of pharmacological treatments and preventing recurrence (Cuijpers et al., 2013, 2016; S. G. Hofmann et al., 2012). Furthermore, psychosocial interventions like social skills training can enhance interpersonal relationships and social functioning, thereby promoting recovery and increasing resilience to stress (Bellack, 2004).

In conclusion, while the monoamine hypothesis and its corresponding pharmacological interventions have significantly contributed to the understanding and treatment of depression, it is crucial to adopt a more holistic perspective that acknowledges the complex nature of these disorders (Hasler, 2010). Further investigations should continue to elucidate the underlying neurobiological mechanisms and explore the advantages of combining pharmacological and psychological treatment regimens (Insel, 2009; Nemeroff, 2007). This

evidence highlights the need for innovative, long-lasting drugs with better efficacy, and a more integrative and personalized approach for the treatment of affective disorders.

1.2. Psychedelic Substances

Psychedelic substances ("psychedelics") or hallucinogens encompass a range of both naturally occurring and synthetic compounds which alter perception, feelings, and thoughts of an individual. While the terms "psychedelics" and "hallucinogens" are often used interchangeably, there have been proposed several distinctions between these terms. The classification of drugs relies on several possibilities: chemical structure, mode of action (neurotransmission), origin (e.g., synthesized, plants, or mushrooms), or psychological effects and phenomenology. In that context, hallucinogens can be seen as a parent category of psychedelics, including a broad spectrum of substances that induce alterations in perception, but also feelings of dissociation, confusion, and euphoria (Abraham et al., 1996; Aghajanian & Marek, 1999; D. E. Nichols, 2004; Volgin et al., 2019). This includes classical serotonergic psychedelics like LSD or psilocybin, but also substances with different effect mechanisms such as ketamine (glutamate receptor antagonist), salvinorin A (κ-opioid receptor agonist) and muscimol (GABA-A receptor agonist), which are not defined as classical psychedelics, but rather as dissociative hallucinogens.

Consequently, psychedelics are a subset of hallucinogens, specifically identified by a classical serotonergic mechanism of action (D. E. Nichols, 2004, 2016) characterized by several criteria. They all act as a serotonin-2A receptor (5-HT2A) agonist (amongst many other receptors, see Chapters 1.2.4.1 and 1.3.2.) and induce strong alterations in consciousness, including changes in thought processes, mood, and perception accompanied by meaningful introspective experiences. Moreover, they not only change how we perceive the world around us, but also how we perceive ourselves and others (Dittrich, 1998). Additionally, psychedelics are known for producing transcendent and mystical experiences and are commonly referred to as "mind-expanding" substances (Barrett & Griffiths, 2018). Interestingly, these unique substances have specifically the capacity to temporarily change and disrupt the default mode network (DMN) of the brain, a network comprising of different interconnected brain regions which is involved in self-referential thought processes (Carhart-Harris, Leech, et al., 2014; Gattuso et al., 2023).

Psychedelics have a wide range of molecular structures, with phenethylamines and tryptamines being two of the main classes. Among the phenethylamine category, there are synthesized substances like dimethoxyphenethylamines ("2C psychedelics" e.g., 2C-B, 2C-I etc.), or dimethoxyphenylthylamines (e.g., DOI, DOM etc.), but also natural compounds such as mescaline, which can be found in cacti like San Pedro and Peyote. The more popular psychedelics typically belong to the tryptamine class, such as psilocybin and psilocin (psychoactive compounds of "magic mushrooms") and LSD (lysergic acid diethylamide), LSA (lysergic acid amide), and AL-LAD (an analogue of LSD) , all classified as lysergamines, a subclass of tryptamines (Baumeister et al., 2014). Other well-known tryptamine-based psychedelics are 5-MeO-DMT (5-methoxy-N,N,-dimethyltryptamine), and DMT (N,N-dimethyltryptamine), which is found in ayahuasca.

1.2.1. The Psychedelic Experience

The phenomenology of psychedelic experiences is highly subjective and show significant variabilities from person to person, but also from one experience to the next. Moreover, the experience can be significantly influenced by the social, physical, and psychological environment (Strickland et al., 2020). This creates difficulties to generalize the phenomenology of a psychedelic experience. However, the broad range of these experiences demonstrate many common features. The neuropharmacological activity of psychedelics induces modulations in waking consciousness, resulting in a broad spectrum of alterations including cognitive and affective processing, behaviour, mood, self-perception and self-awareness, and environmental perception (Dittrich, 1998). These alterations of consciousness can happen in opposing ways, simultaneously amplifying certain elements of consciousness while acutely impairing others, such as executive functions (Dolder et al., 2016). Users and study participants frequently report changes in their sensory perception, encompassing brightened colours, moving textures and patterns, synaesthesia, and pseudo-hallucinations. Emotional amplification over a diverse range of emotions is another often reported hallmark of psychedelic experiences. Psychedelics impact the subjective interpretation of temporal and spatial constructs, which can go as far as experiencing complete dissolution of time and space (Barrett & Griffiths, 2018). Individuals have described mystical and transcendental experiences, ego dissolution, feelings of interconnectedness, and profound experiences of unity (Barrett & Griffiths, 2018; Ko et al., 2022). Interestingly, the neurophysiological and phenomenological aspects of these experiences have been described as dream-like states, showing parallels with night sleep dreaming, specifically those occurring during rapid eye movement (REM) sleep (Carhart-Harris, Kaelen, et al., 2016; Carhart-Harris & Nutt, 2014; Fischman, 1983; Hobson, 2009). Additionally, the psychedelic experience is extremely dose-dependent, and the intensity and duration show huge differences among individuals (Holze, 2021; Holze et al., 2022; Liechti & Holze, 2022). Moreover, the duration of the psychedelic experience varies significantly across different substances and administration forms (e.g., inhaled/intravenous DMT – 10 minutes; oral mescaline – 11 hours; Lawrence et al., 2022; Ley et al., 2023)

1.2.2. Humans and Psychedelics

The human mind and the ability to alter waking consciousness constitutes a fascinating aspect of humanity. The human history is rich with examples of consciousness alterations, practices which have left a lasting impact on diverse cultures globally (Cardeña & Winkelman, 2011). There are different ways to achieve these states such as rhythmic dancing, breathing exercises, contemplative practices like meditation, music, extreme physiological circumstances including fasting, sensory or sleep deprivation, usage of psychoactive substances, and numerous other trance-inducing techniques (Barušs, 2020). Notably, the techniques, intentions, and contexts for achieving such alterations often exhibit variability across different cultures. Plant-derived or fungal psychoactive substances have been integrated into shamanistic rituals for centuries or possibly even millennia, used as mediums for the acquisition of wisdom, healing purposes and sacraments (Metzner, 1998).

In the realm of psychoactive substances, Albert Hofmann, a Swiss chemist working for the pharmaceutical company Sandoz, accomplished the first synthesis of lysergic acid diethylamide (LSD) in 1938. By 1943, Hofmann identified the substance's psychoactive properties, leading to the infamous "Bicycle Day", marking the day of his self-experiment on April 19th (A. Hofmann, 1979, 1980). Subsequent years witnessed the burgeoning first wave of psychedelic research in Western academia from the 1950s through the 1960s, with human-based LSD studies producing observations of significant consciousness alterations and substantial phenomenological experiences (McGlothlin et al., 1967; Pahnke & Richards, 1966; Stoll, 1947). The potential therapeutic benefits of psychedelics also underwent investigation (Sandison et al., 1954; Savage & McCabe, 1973; Smart, 1964), alongside the broader landscape of psychopharmacology, which reached its zenith from 1943-1958 (Braslow & Marder, 2019; Healy, 2004).

In the context of clinical trials, the 1950s were significant for the establishment of randomized, double-blind, placebo-controlled trial (RCT) methodologies as the gold standard for psychopharmaceutical approval (Oram, 2014; Wampold & Imel, 2015). Concurrently, the medical model of mental disorders solidified, with pharmacological treatments conceptualized as strictly biological processes (Healy, 2004; Schildkraut, 1965; Schildkraut & Kety, 1967). This also affected the treatment approaches for mental health disorders, as the monoamine hypothesis gained popularity (Schildkraut, 1965). Nonetheless, scientists postulated the role of psychedelics in therapy as a tool in the healing process rather than a pure physiological agent (Sandison et al., 1954). The rigorous implementation of RCTs as Gold Standard lead to a fundamental complication of the proof of efficacy of a psychedelic substance (Oram, 2014). Moreover, these difficulties continue to this day to prevail in clinical trials investigating psychedelics and their therapeutic potential.

In the 1960s, the countercultural hippie wave, partly accelerated by the ongoing Vietnam War, was responsible for increasing the popularity of psychedelic substances like psilocybin and LSD (Wesson, 2011). Due to the specific effects of psychedelics like feeling of interconnectedness, the call for peace was potentially even further increased throughout society. Yet, their widespread misuse as recreational drugs and associated destabilization of society's structures led to the implementation of stringent drug laws. This "war on drugs" in North America resulted in the prohibition of most psychedelics not only in the United States, but also in many other countries (Frydl, 2013). Moreover, an accompanying decline in the scientific credibility of psychedelics followed. However, the past two to three decades have seen a revival in interest towards psychedelic substances, often referred to as the "psychedelic renaissance" (Sessa, 2018). This resurgence, primarily accelerated by increasing public and scientific interest, has given rise to a surge in multidisciplinary research such as neuroscience, anthropology, biology, psychotherapy, psychology, medicine, and chemistry (Hadar et al., 2023). The scientific interest in psychedelics as a potential novel treatment approach for mental health disorders and initial findings has again sparked a sense of hope for addressing the escalating mental health crisis (Reiff et al., 2020; Tupper et al., 2015).

1.2.3. Psychedelic-assisted Therapy as a Novel Treatment Paradigm

The field of psychedelic-assisted therapy is witnessing a renaissance and occurs simultaneously with the global mental health crisis and the impeded progression in neuropsychiatric pharmaceutical advancements. Intriguingly, these concurrent crises are reciprocally intensifying this renaissance and the interest in psychedelic-assisted interventions. (A. E. Becker & Kleinman, 2013; R. E. Becker & Greig, 2010; Benton et al., 2021; Ona & Bouso, 2019). A range of novel glutamatergic (e.g., ketamine) and serotonergic psychoactive compounds (e.g., psilocybin, LSD, MDMA) emerge as promising drug candidates in the treatment of various mental health conditions. These substances have captured the interest of both clinicians and researchers, owing to their rapid-acting antidepressant and anxiolytic effects. This burgeoning area of research has led to a paradigm shift in our understanding of the potential applications of psychedelic substances in mental health care.

In recent years, intranasal esketamine (Spravato^{TM}, Janssen-Cilag) has been approved in combination with an oral antidepressant for treating adults with treatment-resistant depression (TRD). While ketamine is primarily utilized as a stand-alone drug treatment with a more biochemically driven mechanism of action, other psychoactive substances such as psilocybin, LSD, and MDMA are predominantly studied as adjuncts to psychotherapy (Reiff et al., 2020). Compared to conventional antidepressants, the therapeutic effects of psychedelics are mediated through entirely different drug targets and mechanisms of action. It has been observed that acute modulation of synaptic plasticity and brain network function provides an opportunity for resetting neural circuitry associated with maladaptive behaviours after a limited number of administrations (Carhart-Harris et al., 2017; D. E. Nichols, 2016; Olson, 2022). For instance, psilocybin has demonstrated rapid reduction of depressive symptoms in TRD patients after just two high-dose sessions, with sustained efficacy for up to six months (Carhart-Harris, Bolstridge, et al., 2016; Carhart-Harris et al., 2017). In a double-blind, randomized, controlled trial involving patients with long-standing, moderate-to-severe major depressive disorder (MDD), psilocybin was found to be non-inferior to escitalopram (an SSRI) regarding efficacy, and superior in terms of adverse effects and onset of action (Carhart-Harris et al., 2021). This has led the US Food and Drug Administration (FDA) to designate psilocybin as a Breakthrough Therapy for the treatment of both MDD (USONA, 2019) and TRD (Compass Pathways, 2018). Similarly, MDMA-assisted therapy for post-traumatic stress disorder (PTSD) has also received FDA Breakthrough designation (2017), with encouraging Phase 3 results indicating improvement in PTSD symptoms after just three dosing sessions (Mitchell et al., 2021). Moreover, in 2022 a phase 3 clinical trial for day psilocybin therapy with psychological support including close to 1000 participants has started (Compass Pathways, 2022). The success of these trials underscores the potential of psychedelic-assisted therapy to revolutionize mental health care, as we continue to explore the underlying mechanisms and optimize treatment protocols for these psychoactive substances.

However, there are several limitations regarding these clinical trials. Most of these trials were not blinded. Patients, funders and therapists were highly motivated due to the psychedelic hype and the follow-ups were relatively short. Moreover, the studies have still relatively small sample sizes and therefore the number of patients treated with psychedelics in these studies

is still comparably small. Besides the mentioned phase 3 clinical trials, most of the studies so far were open label or phase 2 clinical trials. This lead to increased open discussions about the potentially problematic hype around psychedelics and corresponding issues (Yaden et al., 2022).

Despite these limitations and scientific challenges mentioned above, initial results from clinical trials are promising and motivate to investigate the potentially beneficial effects of psychedelics further. Consequently, the field of psychedelics as an alternative treatment paradigm continues to captivate as an exciting field of research.

1.2.4. Decoding Psychedelics: A Deep Dive into Effect Mechanisms

The complex and layered mechanisms underpinning the consciousness-altering and therapeutic effects of psychedelic substances are influenced by molecular, cellular, and neurobiological changes in the brain, as well as neuropsychological changes in information and emotion processing within neural networks. The complexity extends to contextual, psycho-social, and psychological elements which shape and influence the subjective psychedelic experience (Ly et al., 2018; D. E. Nichols, 2016; Roseman et al., 2017; Scheidegger, 2021; van Elk & Yaden, 2022; Vollenweider & Kometer, 2010; Vollenweider & Preller, 2020). To assess the mechanisms of psychedelics, it is necessary to use a multifaceted approach, trying to explore different perspectives. Nonetheless, it is acknowledged that fully defining these mechanisms poses a significant challenge, underlining the need for continued extensive research in this dynamic field.

1.2.4.1. Pharmacological Properties and Pathways of Psychedelics

The interactions between classical serotonergic psychedelics and the complexity of the brain are a fascinating area of study, as the pharmacology of these substances involves a variety of different pathways and mechanisms. Research has identified a wide range of complex processes triggered by psychedelics (Aghajanian & Marek, 1999; D. E. Nichols, 2016; Vollenweider & Preller, 2020). As a primary mechanism of action of psychedelics for inducing hallmark effects in the psychedelic experience, the ability to act as a serotonin 2A (5-HT2A) receptor agonist was identified (Barrett & Griffiths, 2018; Dos Santos et al., 2021; López-Giménez & González-Maeso, 2018; D. E. Nichols, 2004, 2016; Vargas et al., 2023). The increased presence of 5-HT2A receptors in key brain areas like the cortex, striatum, hippocampus, and amygdala - which are all significant in the action of psychedelic drugs - reaffirms the importance of these receptors as mediators of the effects of psychedelics (Castelhano et al., 2021). The excitatory effects though 5-HT2A receptor activation with psychedelics like psilocybin, LSD, and DMT result in cortical glutamate release, causing destabilization of local network hubs and subsequent alterations in the overall connectivity of the brain (D. E. Nichols, 2016). However, the interaction of psychedelics is not exclusively bound to the 5-HT2A receptors; they also engage with a range of other serotonin (5-HT) receptors such 5-HT1A, 5-HT1B, 5-HT1D, and 5-HT2C. This multitude of interactions extends beyond the serotonergic system, incorporating other neurotransmitter networks including the glutamatergic and dopaminergic system, which potentially add to the diverse and

complex effects of psychedelics (Carbonaro & Gatch, 2016; Carhart-Harris & Nutt, 2017; D. E. Nichols, 2016; Ray, 2010; Smith et al., 1998; Vollenweider & Kometer, 2010). Moreover, some psychedelics (e.g., N,N-dimethyltryptamine) interact with many other neurotransmitter receptors, such as acetylcholine, sigma-1, BDNF, and trace amine-associated receptors (Carbonaro & Gatch, 2016; Moliner et al., 2023). The activation of the 5-HT2A receptor, primarily associated with excitatory synaptic transmission, triggers a chain of neurochemical events affecting several neurotransmitter systems, encompassing serotonergic, glutamatergic, and dopaminergic systems (D. E. Nichols, 2016; Vollenweider & Kometer, 2010). Accumulating scientific data suggests that psychedelics, upon activation of the 5-HT2A receptors located on cortical pyramidal cells, induce the release of glutamate (Vollenweider & Kometer, 2010; Vollenweider & Preller, 2020). These cells are the primary excitation units of the prefrontal cortex and are pivotal in the circuitry of glutamatergic neurons. Hence, the alteration in their excitability by psychedelics could potentially amplify functional connectivity, cortical activity, and neuroplasticity – the brain's capability to reorganize itself by forming new neuronal connections (Barrett et al., 2020; de Vos et al., 2021; Grieco et al., 2022; Ly et al., 2018; Preller et al., 2018; Vargas et al., 2023). Moreover, current research suggests that psychedelics can directly bind to the neurotrophic tyrosine kinase receptor 2 (TRKB), which can also promote plasticity (Moliner et al., 2023).

The diverse range of psychedelic substances each possess unique receptor profiles, providing a plausible explanation for the difference in the effects elicited by different substances (Carbonaro & Gatch, 2016; D. E. Nichols, 2016; Passie et al., 2002, 2008). Additionally, it is worth noting that the psychedelic experience is extremely dose-dependent, and the duration and intensity can vary significantly across individuals and substances (Holze, 2021; Holze et al., 2022; Liechti & Holze, 2022). Moreover, it has been shown that receptors exhibit several naturally occurring, random variations, also called single nucleotide polymorphisms. These receptor variations across individuals can affect the signalling cascade following the interaction with a psychedelic compound. Research suggests that specific variations in the 5-HT2A receptors lead to differences in efficacy and potency of several psychedelics (Schmitz et al., 2022).

1.2.4.2.Neurodynamic Modulation of Psychedelics

Shifting focus from the pharmacological effects of psychedelics, it becomes equally important to explore the resulting neurodynamic alterations and modulations of plasticity within the brain. As a starting point, a study proposed a model of a dualistic framework of brain serotonin function, differentiating the modulation exhibited by serotonergic psychedelics and common antidepressants (Carhart-Harris & Nutt, 2017). This model hypothesized that prolonged utilization of selective serotonin reuptake inhibitors (SSRI) exerts an influence on post-synaptic 5-HT1A receptor-mediated passive coping, leading to reduced limbic reactivity. This numbing effect can lead to diminished aggression, impulsivity, anxiety, and stress. On the contrary, psychedelics modulate 5-HT2A receptor-mediated active coping, linked with amplified cortical entropy, thus decreasing pessimism and rigid thinking. As a result, the theorized fundamental mechanisms of SSRIs encompass increased patience, stress tolerance,

emotional blunting, and patience. Especially the effect of emotional blunting is very common and perceived as unpleasant, as patients reporting to feel dull and no longer experiencing as much pleasure as they used to (Christensen et al., 2022). In contrast, psychedelics are proposed to enhance capacity for plasticity, learning and unlearning of different beneficial or maladaptive behaviours, adaptability, and environmental sensitivity (Barrett & Griffiths, 2018; Carhart-Harris et al., 2017; de Vos et al., 2021).

As the firing patterns of neurons change, there is a transformation in information processing. The influence of psychedelics onto this system adds an additional layer of complexity, leading to a disruption in the classical functioning and interactions of neural networks. What follows is an altered state of consciousness, characterized by changed interconnectivity between brain regions. As an example, this change and amplification of connections could be a potential explanation for psychedelic-induced synaesthesia, commonly reported during a psychedelic experience (Brogaard, 2013). Recent neurobiological models propose that psychedelics serve as a catalyst, escalating the overall entropy of neural brain activity, thereby induce a more chaotic, entropic state of neural brain networks (Carhart-Harris, Leech, et al., 2014). The entropy in neural activity is an indicator of the extent of randomness within neural activation patterns. During psychedelic stimulation, entropy increases in certain brain regions while diminishing in others, indicating a topographical reformation. There might be an association between lowered entropy with rigid thinking and more predictable activity patterns, commonly observed in internalizing mood disorders such as anxiety and depression (Winters & Ingwalson, 2022). Conversely, an elevated global brain entropy has been linked with altered consciousness, cognitive flexibility, enhanced creativity, and more interconnected, disorganized state of brain activity (Barrett & Griffiths, 2018; Petri et al., 2014).

Studies have shown that amplified connectivity between different sensory brain regions suggests a surge in sensory processing. Simultaneously, lower connectivity was observed within associative brain regions that integrate information and derive meaning (Daws et al., 2022; Gattuso et al., 2023; Preller et al., 2020, 2018; Tagliazucchi et al., 2016). This implies that during the psychedelic experience, sensory inputs are no longer as processed and integrated as they usually are. Moreover, brain regions which normally serve an inhibitory and controlling purpose on other brain regions show either reduced activity and enhanced entropy (Preller et al., 2020; Smausz et al., 2022). This profound altering effect of psychedelics is potentially explained by the thalamic filter model, which proposes a reduced activity in the filtering role of the thalamus (Müller et al., 2017; Preller et al., 2019; Vollenweider & Preller, 2020). Therefore, the cortex receives more sensory information which leads to more strongly coupled brain regions and altered patterns of connectivity between them.

Research evidence suggests a decrease in the activity within the default mode network (DMN) under the influence of psychedelics (Carhart-Harris, Leech, et al., 2014; Gattuso et al., 2023; Smigielski et al., 2019). The term DMN is used to describe a collection of interconnected brain regions characterized by strong coherent low-frequency oscillations at rest (van den Heuvel & Hulshoff Pol, 2010). Comprising key brain regions like the ventromedial prefrontal cortex (vmPFC), pregenual anterior cingulate cortex (pACC), and posterior cingulate cortex (PCC), the

DMN is linked with self-referential thought processes such as introspection, mind-wandering, self-reflection, daydreaming, and autobiographical memories, but also self-criticism and rumination, particularly when the brain is at rest (Raichle, 2015; Yeshurun et al., 2021). Moreover, it normally acts as a regulator of the information flow within the brain. Changes in the interconnectivity within the DMN have been linked to various neuropsychiatric disorders, including depression, anxiety, and PTSD, obsessive-compulsive disorder, schizophrenia, and attention deficit hyperactivity (Hou et al., 2020; Meda et al., 2014). The modulated DMN activity under the influence of psychedelics could potentially lead to decreased inhibition of other brain regions, thereby enabling increased functional connectivity between resting-state networks that are typically less interconnected (Gattuso et al., 2023). This effect was also underlined by the REBUS model (Relaxed Beliefs Under Psychedelics and the Anarchic Brain), which proposes that psychedelic-induced effects on neural brain activity might be attributed to a decreased effectiveness and functionality of the DMN (Carhart-Harris & Friston, 2019). Conclusively, psychedelics could disrupt or reset the hierarchical functions and constraints of the brain, leading to a more anarchic, decentralized, and chaotic state of neural brain activity. However, despite significant advances, the multifaceted and intricate effects of psychedelics on the brain are far from being comprehensively understood. The derived hypotheses based on these insights open up promising areas for further exploration into the mechanisms that underpin the psychedelic experience. Furthermore, they will enrich our understanding of the complex interplay between psychedelics, serotonin systems, and brain dynamics, and could open up new avenues for the treatment of psychiatric disorders.

1.2.4.3. Psychedelic Modulation of Cognitive and Affective Functions

Psychedelic substances have demonstrated to profoundly modulate cognitive and affective functions. They alter the processing and integration of information, thereby potentially affecting our perception of self and our surroundings with potentially clinical implications. For instance, LSD, even administered in low doses, has shown to modulate mood and emotions which was associated with a change in connectivity between the prefrontal cortex and the amygdala and with alterations in connectivity in the limbic circuits (Bershad et al., 2020). More studies underline these findings, demonstrating not only inhibited negative facial expression recognition, but also enhanced sociality and empathy during acute drug effects, a phenomenon also observed in patients after treatment with anxiolytics and antidepressants (Bershad et al., 2019; Dolder et al., 2016; Kometer et al., 2012; Rocha et al., 2019). The well documented sensitivity of the amygdala to emotional stimuli, regardless of their valence, may play an important role in the efficacy of psychedelic treatments (Adolphs, 2010; A. Santos et al., 2011; S. Santos et al., 2016). Research has shown substances such as psilocybin, and MDMA (not a classical psychedelic, but also a serotonergic psychoactive substance with empathogenic and entactogenic effects) acutely decreases reactivity of the amygdala to fearful faces and bad memories, and favour the processing of positive stimuli and emotions (Carhart-Harris, Wall, et al., 2014; Kometer et al., 2012). However, long-term effects remain ambiguous with partly contrasting findings on amygdala reactivity. While one study found increased amygdala reactivity 1 day after the psychedelic experience (Roseman et al., 2018), another study showed decreased amygdala reactivity lasting at least for 1 week after the

experience (Barrett et al., 2020). Interestingly, increases in amygdala responses shortly after psychedelic treatments were associated with a successful clinical outcome and, over time, they might enhance overall emotional reactivity (Roseman et al., 2018). This is in contrast with the emotional isolation commonly seen in depression or the emotional blunting caused by conventional antidepressants (specifically SSRIs), which is potentially associated with reduced amygdala activity (Felmingham et al., 2014; Ferri et al., 2017; Korem et al., 2022; Ma et al., 2021; Marazziti et al., 2019; Osler, 2022; Price et al., 2009).

A study investigating social pain processing under psilocybin showed decreased activation in the anterior cingulate cortex (ACC), a region associated with self-processing and the experience of social pain (Preller et al., 2016; Rotge et al., 2015). This decrease correlated with reports of universal feelings of oneness and unity. Other serotonergic substances, like LSD, psilocybin, and MDMA, have been associated with increased emotional empathy and prosocial behaviour, potentially mediated by an increased feeling of connectedness with others, oneself, and nature (Carhart-Harris, Erritzoe, et al., 2018; Dolder et al., 2016; Gandy et al., 2020; Hysek et al., 2014; Watts et al., 2022; Weiss et al., 2021). It is important to note that there was no increase in cognitive empathy, leading to the hypothesis that serotonin or serotonergic acting psychoactive substances seem to affect mainly emotional empathy (Hysek et al., 2014; Kuypers et al., 2017; Pokorny et al., 2017). In the context of exploring psychedelics as potential modulators for creative inspiration and spiritual experiences, a study positions the role of these substances as agents for enriched meaning within the boarder of societal framework of todays Western cultures (Hartogsohn, 2018). This underlines the hurdles associated with the fast technological progress, work settings dominated by stress, growing individualism, and the ongoing search for the meaning and purpose of life. Furthermore, the modulation of 5-HT2A receptors through LSD and psilocybin enhanced the fabric of meaning and increased perceived significance and meaning of the environment of an individual, including the emotional states of others (Pokorny et al., 2017; Preller et al., 2016, 2017).

The hallmarks of psychedelic experiences are generally associated with feelings of unity and ego-dissolution, boundary dissolution between self and others, and between self and the external world (Dittrich, 1998; Millière et al., 2018; D. E. Nichols, 2016; Studerus et al., 2010; Vollenweider & Kometer, 2010). These mystical-type experiences seem to lead to lasting positive changes in psychological functioning, spiritual significance, trait measures, and personal meaning, partly attributed to the afterglow effect after strong experiences (Barrett & Griffiths, 2018; Griffiths et al., 2018; Majić et al., 2015). The commonly observed loosening or even complete dissolution of self-other boundaries induced by psychedelics could be a significant therapeutic mechanism for the treatment of internalizing disorders like anxiety and depression, helping patients to break out of rigid thinking patterns and to develop new ways to view the world and themselves (Ho et al., 2020; Sarris et al., 2022; Scheidegger, 2021; Vollenweider & Preller, 2020). Psychedelics also enhance creativity and cognitive flexibility, offering patients broader perspectives on their life and challenges, potentially leading to the development of new adaptive thinking patterns including the change from avoidance to acceptance of emotions (Gallimore, 2015; Kuypers et al., 2016; Watts et al., 2017).

Overall, psychedelic experiences in supporting and safe environments are found to demonstrate short and long lasting positive effects on well-being, mood, prosocial behaviours, empathy, connectedness, forgiveness, gratefulness, mindfulness, cognitive flexibility, creativity, and other personality traits like value orientations, openness, nature relatedness, self-transcendence, self-compassion, and spirituality (Domínguez-Clavé et al., 2016; R. G. dos Santos et al., 2016; Forstmann & Sagioglou, 2017; Griffiths et al., 2018; Jungaberle et al., 2018). As a result, they may foster significant psychological improvements, contributing to an individual's overall psycho-spiritual development, self-acceptance, and their relationship with themselves and the world around them. Thus, this body of research underscores the compelling potential of psychedelics in enhancing positive psychology. It suggests a paradigm shift in mental health treatment with a more holistic approach, offering a complementary perspective to the traditional treatment approach of mental health disorders (Scheidegger, 2021).

1.2.4.4. Context Sensitivity and Set and Setting

In addition to the pharmacological, neurophysiological, and phenomenological attributes of psychedelic experiences, the role of context (e.g., physical, social, and psychological environment) in modulating the very nature of these experiences and even influencing psychotherapeutic results has been extensively explored (Eisner, 1997; Gukasyan & Nayak, 2022; Langlitz, 2023; Roseman et al., 2022; Strickland et al., 2020). An individual's perception, emotions, and thoughts can be significantly influenced by these contextual factors. Recent research has emphasized how these factors can significantly affect the safety and efficacy of psychedelic therapy (Carhart-Harris, Roseman, et al., 2018). These factors encompass both the mental framework or mindset of the user ("set"), and contextual elements ("setting"). To elaborate, the "set" involves elements like motivation, intentions, thoughts, expectations, prior experience, personal history, and current emotional state. This may even extend to the mindset of the potential therapist or trip sitter, who can profoundly influence the direction and outcome of the experience, highlighting the importance of the clinician-patient relationship in a therapeutic scenario (Hartogsohn, 2018; Tupper et al., 2015; Zinberg, 1984). The "setting", on the other hand, refers to the social and physical environment in which the psychedelic experience unfolds. This even includes the cultural and historical context, along with specific variables like the people present during the experience, the music playing, and the ambiance of the room or location. The influence of the "setting" on psychedelic experiences has been widely recognized, extending even to the smallest things such as the decoration of the room, ambient temperature, or available space in the room in which the trip is taking place (Doering-Silveira et al., 2005; Dollar, 2021; Gukasyan & Nayak, 2022; Muthukumaraswamy et al., 2021).

Understanding the profound interplay of personal and environmental factors in psychedelic experiences is crucial, which is reinforced by a growing body of research. This emphasizes the need for carefully controlled and supportive environments when administering psychedelics for therapeutic purposes (Tupper et al., 2015; Uthaug et al., 2021).

1.3 Ayahuasca

Ayahuasca, a plant-based psychoactive brew, traces its roots to the Indigenous communities of the Amazon rainforest, including parts of Brazil, Peru, Ecuador, Bolivia, and Colombia. It has been used by shamans for centuries or even millennia as a traditional indigenous medicine for holistic healing and spiritual rituals in Latin America (Domínguez-Clavé et al., 2016). Moreover, the entheogenic effects of ayahuasca have been utilized to understand the nature of reality, and connect with the spiritual world (Dos Santos & Hallak, 2021; Grob et al., 1996; Prue & Voss, 2014). The term "ayahuasca" is derived from the Quechuan language, and means "the vine of the soul", indicating that a specific vine is a major ingredient of the brew (discussed in Chapter 1.3.2.). Its documented use can be traced back to 1873, but archaeological evidence suggests consumption as early as 2400 B.C. (Rivier & Lindgren, 1972; Spruce, 1873). In the 1930s, Brazilian syncretic religions integrated ayahuasca into their rituals, expanding its influence throughout Brazil and beyond (Labate & Feeney, 2012; Lowell & Adams, 2017). Western scientific investigations into this substance began in the mid-20th century following discoveries of its Indigenous use in South America (Goldin & Salani, 2021). Later, the integration of ayahuasca into Western spiritual and therapeutic communities spurred additional scientific and cultural curiosity.

1.3.1 Globalization of Ayahuasca

As interest of ayahuasca continues to rise through online platforms and media outlets, the prevalence of retreats and ceremonial practices centred around the plant brew has expanded across urban areas in South and North America, Europe, Asia, and Africa (Horák & Verter, 2019; Tupper, 2008). A growing number of international visitors are traveling to countries such as Peru, Ecuador, Colombia, and Brazil to engage in ayahuasca ceremonies (Prayag et al., 2015). The increased popularity of ayahuasca's ceremonial use can be attributed to its perceived potential for natural healing, personal and spiritual growth and development, increased sense of connection, therapy of addictions, as well as its role as a religious sacrament (Dorsen et al., 2019; Halpern et al., 2008; Harris & Gurel, 2012). In recognition of its historical use as a traditional medicine, ayahuasca was designated as the Cultural Patrimony of Peru in 2008 (Instituto Nacional de Cultura, 2008). Furthermore, the consumption of ayahuasca for religious purposes (e.g. Santo Daime, UDV church) has been firmly established and legalized in Brazil (Labate et al., 2007; Labate & Jungaberle, 2011). Moreover, these religious movements have proliferated to the United States, Australia, and Europe and even received religious freedom protection to use ayahuasca in religious rituals (Labate & Feeney, 2012; Labate & Jungaberle, 2011; Tupper, 2008). As an example, although DMT is classified as a Schedule I drug, the United States implemented legislation in 2006 under the Religious Freedom Restoration Act to protect the religious use of ayahuasca (Bullis, 2008).

Ayahuasca has also gained attention in popular culture with public figures openly sharing their experiences, which has prompted media discussions on its potential therapeutic benefits and associated risks, including mental health implications, death, and instances of sexual assault

(BBC, 2020; The New York Times, 2014). Amidst the current psychedelic renaissance, scientific interest in ayahuasca has re-emerged, particularly for its potential therapeutic and beneficial effect for treating mental health conditions such as addiction, anxiety and depression.

1.3.2. Pharmacology of Ayahuasca

Due to the globalization of ayahuasca and its potential as a new treatment approach for mental disorders, scientific interest in the Amazonian brew has increased. It is typically made from the vine *Banisteriopsis caapi* and the leaves of *Psychotria viridis* or *Diplopterys cabrerana*, which contain the primary psychoactive compounds. The vine contains a variety of β-carboline alkaloids such as harmine, harmaline, and tetrahydroharmine, whereas the leaves of the of the other plant contain the indole alkaloid N,N-dimethyltryptamine (DMT) (Riba et al., 2003). The combination of these plants results in a unique pharmacological profile that sets it apart from other serotonergic psychedelics. The β-carbolines harmine and harmaline function as selective reversible monoamine oxidase inhibitors (MAOIs), mainly as MAO-A inhibitors, and tetrahydroharmine as selective serotonin reuptake inhibitor, respectively. DMT has no oral bioavailability because of the excessive metabolic first-pass degradation by the enteric MAO-A enzyme (Barker, 2018). Therefore, the MAOIs play a crucial role in preventing this degradation of DMT in the gastrointestinal tract and the brain, thus sustaining the effects of DMT in the body (Callaway et al., 1996). DMT, the main psycho active compound of ayahuasca, is a compound with a broad natural occurrence. It can be found in diverse biological systems including plants, mammals, human brains and body fluids (Barker, 2022). However, the precise function of naturally occurring DMT within human physiological processes is not fully understood. DMT is believed to exert its psychedelic effects as a structural analogue of serotonin and therefore acts as agonist at several serotonin receptors (mainly 5-HT2A, 5-HT2C, 5-HT1A), similar to other psychedelic substances such as psilocybin or LSD (R. G. dos Santos et al., 2016; D. E. Nichols, 2016; Vargas et al., 2023). Interestingly, changes in the cortical expression of these receptors have been identified in post-mortem studies of individuals with depression (Baumeister et al., 2014). Furthermore, DMT exhibits agonistic properties at glutamate, dopamine, acetylcholine, sigma-1, BDNF, and trace amine-associated receptors (Carbonaro & Gatch, 2016; Moliner et al., 2023; Riba et al., 2001, 2003). Similar to other classical serotonergic psychedelics, this interaction can trigger a cascade of downstream signalling pathways. These pathways are believed to produce the hallmark features of psychedelic experiences, such as modifications in emotional and cognitive processing and altered perception. However, MAO enzymes lead to a rapid breakdown of DMT in the body. Consequently, no subjective effects occur when DMT alone is ingested orally (Barker, 2018). However, with methods like smoking or intravenous injection, a robust alteration of consciousness can be induced by DMT without MAO inhibition, albeit short-lived due to the fast degradation by MAO enzymes and therefore short half-life of DMT (Vogt et al., 2023).

Due to the MAO inhibition of the β-carbolines of ayahuasca, DMT is able to cross the blood-brain barrier and induces a transient introspective state characterized by increased awareness, dream-like visions, recollecting of personal memories, and intensified emotions

(Riba et al., 2001, 2003). This powerful, transformative psychedelic experience has an average overall duration of 2-6 hours after 1 dose and therefore is more amenable for clinical applications compared to other psychedelics with longer lasting experiential profiles (Riba et al., 2001). Furthermore, the alkaloids present in the ayahuasca vine, *Banisteriopsis caapi*, have been shown to stimulate neurogenesis (Morales-García et al., 2017). Harmine, when ingested alone, has been linked to anti-inflammatory, neuroprotective, antidiabetic, antitumor, and other effects (L. Zhang et al., 2020). Other studies show neuroprotective and cognitive-enhancing effects induced by harmine (R. G. dos Santos & Hallak, 2017). The expression of neurotrophic factors (primarily BDNF) increased 48 hours after ingestion of ayahuasca in both healthy volunteers and patients (Almeida et al., 2019). Additionally, several animal and in-vitro studies have shown that some β-carbolines (e.g., harmine and tetrahydroharmine) exhibit a diverse range of pharmacological effects, including increases in brain-derived neurotrophic factor (BDNF) levels, modulation and amelioration of neurodynamic, proliferation of human neural progenitors, and alterations of dopamine transmission (Dakic et al., 2016; Fortunato et al., 2010; Li et al., 2018; Moliner et al., 2023; L. Zhang et al., 2020). While empirical evidence on harmine and other alkaloids is limited and largely preclinical, further systematic research is required to distinguish the effects of harmine and other β-carbolines alone from those produced by ayahuasca.

The metabolism of two main active ingredients of ayahuasca, namely harmine and DMT, was investigated in detail (Brito-da-Costa et al., 2020; Riba et al., 2015). DMT is metabolised through several different pathways. As mentioned in the section above, MAO-A is the main enzyme for the degradation of DMT and forms the inactive metabolite indole-3-acetic acid (3-IAA), which is either further conjugated to indole-3-aceturic acid or excreted renally. It is important to mention that 3-IAA is an endogenous substance, as it is a metabolite of the amino acid tryptophan, also broken down by MAO-A (Dragulska & Kańska, 2014; Martínez et al., 1983). MAO-A is expressed in the liver, spleen, stomach, kidney, brain, and intestines (Örlefors et al., 2003; Simão et al., 2019). After parenteral administration, DMT can rapidly reach the brain and is metabolised by MAO-A. This explains the rapid onset and short duration of subjective effects after administration forms like injection or inhalation. In contrast, after oral administration, DMT undergoes rapid and thorough oxidative deamination, driven by intestinal and hepatic MAO-A. This results in a high first pass effect, leading to the formation of the metabolite 3-IAA and no bioavailability of oral DMT (Barker, 2018). A second significant metabolic pathway of DMT is the cytochrome P450 (CYP) mediated N-oxidation, leading to the formation of DMT-N-oxide. Interestingly, DMT-N-oxide plasma levels after ayahuasca ingestion were significantly higher compared to plasma levels after pure DMT ingestion (intravenous or inhaled) (Brito-da-Costa et al., 2020; Vogt et al., 2023). This confirms the MAO-A inhibition of β-carbolines present in ayahuasca, leading to a slight shift from MAO-A to CYP mediated degradation of DMT (Riba et al., 2015). There are additional metabolic pathways documented for DMT, which includes the N-demethylation to form N-methyltryptamine (NMT). However, these pathways appear to play a minor role. Importantly, DMT appears to be excreted in urine in very small amounts after oral ingestion or inhaled, leading to the conclusion that DMT clearance is mainly driven by metabolic processes (Riba et al., 2015). The primary metabolic pathway responsible for the clearance of harmine is the

O-demethylation mediated by CYP isoforms, leading to the formation of harmol. Extensive studies have identified the CYP isoforms participating in this catalytic conversion, namely CYP1A1, CYP1A2, CYP2D6, CYP2C9, and CYP2C19 (Hamill et al., 2019). Moreover, reports have also highlighted the hydroxylation of harmine through unknown CYP isoforms (Yu et al., 2003; Zhao et al., 2012). After harmol is further metabolised by standard phase II conjugation reactions including glucuronidation and sulfation, it gets finally excreted (Zhao et al., 2012).

1.3.3. Phenomenology of Ayahuasca

Ayahuasca distinguishes itself from other serotonergic psychedelics, not only by its pharmacological profile due to the complex mixture of ingredients but also in its phenomenological characteristics and cultural context. However, to some degree the experience induced by ayahuasca share some overlaps with those produced by other serotonergic psychedelics. Ayahuasca users typically report a spectrum of psychedelic effects, including enhanced self-awareness, synaesthesia, visual hallucinations, anxiety and loss of control, depersonalization, modified emotion processing, and altered perception of time (Campagnoli et al., 2020; R. G. dos Santos et al., 2012; Grob et al., 1996; Riba et al., 2001). Furthermore, profound altered states of consciousness are induced, manifesting as introspection, spiritual revelations, visionary experiences, cognitive and emotional insights, and feelings of interconnectedness with oneself, others, and the universe (Frecska et al., 2016; Hamill et al., 2019; Loizaga-Velder & Verres, 2014; Palhano-Fontes et al., 2015).

Uniquely, ayahuasca usage is frequently coupled with pronounced physical sensations. Physiological responses can range from mild dizziness, agitation, and cardiovascular changes (increased blood pressure and heart rate), to involuntary muscular movements and gastro-intestinal effects like nausea, vomiting, and diarrhea (Bouso et al., 2022; Guimarães dos Santos, 2013). In traditional ayahuasca ceremonies, specifically the side effects nausea and vomiting are typically reported by over 60% of users (Bouso et al., 2022). In some cases, these side effects occurred in nearly all users (Halpern et al., 2008). This characteristic is likely attributed to the presence of β-carbolines like harmine and harmaline in the ayahuasca blend, which is hypothesized to generate an additional set of effects besides the classical psychedelic influences and effects of DMT (R. G. dos Santos & Hallak, 2017). These physiological responses, despite their potential perception as undesirable side effects in a Western medical context, are deemed crucial components of the purgative and ritual process in traditional ayahuasca cultures (Fotiou & Gearin, 2019; Politi et al., 2022). Especially vomiting is considered as purging of bad spirits and diseases in these cultures, contributing to their view of holistic healing. Research indicates that ayahuasca is physiologically and psychologically safe when delivered to healthy individuals in a supportive environment with appropriate psychological support (Barbosa et al., 2012; Bouso et al., 2022; R. G. dos Santos et al., 2012; Guimarães dos Santos, 2013). Over the last years, studies suggest that ayahuasca is considerably safe and has no addictive abuse potential (Fábregas et al., 2010). Moreover, even after several repeatedly administered doses, ayahuasca does not induce pharmacological tolerance and is generally considered safe (Barbosa et al., 2012; R. G. dos Santos et al., 2012).

Indigenous tribes, neo-shamanic groups, and ayahuasca churches have historically ascribed healing attributes to ayahuasca through plant spirits, often referred to as "mother" or "grandmother ayahuasca". These entities are considered powerful healers, mentors, and allies. Frequently, encounters with animals such as jaguars, condors, snakes, among others are reported (Hamill et al., 2019; Shanon, 2002). The ceremonial consumption of ayahuasca commonly involves religious or shamanic rituals that often feature the use of musical instruments, singing, and chanting. Moreover, due to the strong context-dependency of psychedelic experiences, an ayahuasca ceremony in a shamanic or religious ritual can have a strong influence on the whole experience and at least partly determine in which directions the trip will go (Carhart-Harris, Roseman, et al., 2018). Even differences in rituals between tribes from the same or different country can lead to variation in experiences, underlining the important cultural context (Pontual et al., 2022). Therefore, the cultural environment and group-specific settings, including the associated narratives and rituals, might significantly shape the unique phenomenological outcomes of the ayahuasca experience. This exotic mix of cultural context and phenomenology combined with the distinctive pharmacology of ayahuasca leads to a unique experience and fascinating field of research.

1.3.4. Therapeutic Potential of Ayahuasca

Ayahuasca and other mixtures containing DMT have been suggested as potential therapeutic interventions for a range of psychiatric disorders, including depression, anxiety, addiction, and PTSD (Domínguez-Clavé et al., 2016; Frecska et al., 2016; McKenna, 2004; Morillo et al., 2021; Palhano-Fontes et al., 2014; Sarris et al., 2021). Preliminary clinical studies have demonstrated that ayahuasca improves symptoms of depression and anxiety (Osório et al., 2015) and ameliorate brain network dynamics linked to the pathophysiology of depression (Palhano-Fontes et al., 2015). Multiple studies, including a randomized controlled trial (RCT), have reported a rapid and sustained antidepressant effect lasting up to 21 days following a single ayahuasca administration in patients diagnosed with TRD (R. G. dos Santos et al., 2016; Palhano-Fontes et al., 2019; Sanches et al., 2016). A recent systematic review including 21 clinical and preclinical studies concluded that the natural components present in ayahuasca consistently exhibit anxiolytic and antidepressant properties (R. G. dos Santos et al., 2016), as well as anti-addictive and neuroprotective effects (R. G. dos Santos et al., 2016; Moloudizargari et al., 2013; Morales-García et al., 2017; Szabo et al., 2016). Observational studies in naturalistic settings have reported positive effects of regular ayahuasca use on mental health and psychological well-being, including elevated mood, physical pain reduction, decreased impulsivity, reduced alcohol consumption or substance abuse, and fewer psychiatric/psychosocial problems (Barbosa et al., 2009; Fábregas et al., 2010; Lawn et al., 2017). In a large-scale global online survey, ayahuasca users filled out a survey to examine the perceived effect of ayahuasca on affective symptoms and potential adverse effects (Sarris et al., 2021). The overwhelming majority reported strong improvements or even complete cure of those who reported depression or anxiety, while just a very small number of ayahuasca users reported a worsening of symptoms, although these were minor and transient. Longitudinal observational studies have shown ayahuasca users to be well-adapted and integrated within their working, social, and familial environments, utilizing ayahuasca as

an instrument for personal growth. These findings are consistent with those found amongst practitioners of mindfulness or other personal development and wellness techniques (Bouso et al., 2012).

Moreover, an increased capacity for mindfulness-related abilities, such as acceptance and decentring, has been observed (Domínguez-Clavé et al., 2016; Soler et al., 2016). Additionally, there is evidence suggesting enhancements in traits such as optimism, confidence, and independence, as well as assertiveness (Barbosa et al., 2005, 2009). Ayahuasca was associated with supporting several aspects of emotion regulation such as self-compassion, mindfulness and empathy (Scheidegger, 2021). Different experiences during ayahuasca sessions like self-transcendent, emotional breakthroughs, or mystical-type were reported to support psychological well-being, quality of life and personal development. Furthermore, subjects have experienced a heightened state of compassion, love, tranquillity, and a reduction in judgmental attitudes, in addition to a sense of kindness and gratitude (Harris & Gurel, 2012). Highted self-awareness, purpose in life, valuable insights, and long-term alterations in personal belief systems underline the idea that ayahuasca elicits a complex series of beneficial psychological and social processes that can be considered independently of its pharmacology (Barbosa et al., 2012; Halpern et al., 2008; Harris & Gurel, 2012; Scheidegger, 2021). The reported effects like improved coping mechanisms in the face of serious health conditions, better psychosocial adjustments, and strengthened social solidarity emphasize the potential therapeutic effects of ayahuasca even more (Andritzky, 1989; Bouso et al., 2012; Schmid et al., 2010).

Associated enhancements in cognitive and creative capabilities have been documented with the use of ayahuasca (Kiraga et al., 2021; Shanon, 2002). On the cognitive level, increased levels of insightfulness and cognitive flexibility may help overcome maladaptive behaviours. The modulation of mood and cognition induced by DMT is primarily mediated by the activation of 5-HT2A receptors (Carbonaro & Gatch, 2016; Smith et al., 1998; G. Zhang & Stackman, 2015), which leads to extensive alterations in neuronal excitability and the disruption of maladaptive neurobehavioral patterns associated with mood disorders (Vollenweider & Kometer, 2010). Similar to the effects of psilocybin, ayahuasca has also been observed to decrease both the activity and the interconnectedness of the default mode network (DMN) (Carhart-Harris et al., 2012; Palhano-Fontes et al., 2015). The DMN, which is characterised by pathological heightened activity and connectivity in depression and associated with maladaptive patterns of ruminative self-referential information processing, has been suggested as a potential target for interventions focusing on network modulation (Sheline et al., 2010). This finding aligns with the entropic brain hypothesis, where an increase in the entropy of the functional connectivity within the brain was measured during the altered state of consciousness induced by ayahuasca, potentially leading to the therapeutic effects (Carhart-Harris, Leech, et al., 2014; Viol et al., 2017). DMT elicits agonistic properties to the 5-HT1A receptor (D. E. Nichols, 2016). It has been shown that therapeutic drugs which are 5-HT1A receptor agonists produce antidepressant and anxiolytic effects in humans and animals (Baumeister et al., 2014; Katzman, 2009; Nutt, 2005). Unlike the 5-HT2A/2C receptor, this receptor contributes to inhibitory neurotransmission, resulting in a decrease in serotonin release in other regions of the brain when activated (Blier et al., 1990; Cameron & Olson,

2018). The process of desensitizing these receptors and reinstating the normal function of serotonin in neurons is linked with antidepressant effects (Mann, 1999). Consequently. The documented antidepressant and anxiolytic qualities of ayahuasca or DMT may also be tied to their stimulating effects on 5-HT1A receptors (Cameron & Olson, 2018; R. G. dos Santos et al., 2016). Increased expression of neurotrophic factors, mainly BDNF, have been found 48 hours after administration of ayahuasca in both patients and healthy individuals (Almeida et al., 2019). The expression of BDNF is associated with cognitive activities such as memory (Inserra, 2018), synaptic plasticity (Lu et al., 2014; Moliner et al., 2023), and the modulation of the efficiency and adaptability of synapses (Olson, 2022). These cellular effects resemble those induced by the rapid-acting antidepressant ketamine, emphasizing the potential of DMT to treat depression and related disorders through TrkB (BDNF receptor), mTOR, and 5-HT2A signalling pathways. These pathways then increase the density of cortical neuron spines, promote spine growth, and synapse formation (Ly et al., 2018).

While there is rising interest in psychedelic compounds for treating various mental health conditions, there are major shortcomings of using compounds such as LSD for psychotherapy due to its long duration of action (~10 hours). Moreover, both LSD and psilocybin induce rapid tolerance in serotonergic receptors (D. E. Nichols, 2016), which is not favourable for repeated clinical dosing regimens. Regarding ketamine, it was shown that repeated administration lead to sustained antidepressant effects (aan het Rot et al., 2010), but puts patient at risk to its addictive potential (Liu et al., 2016). As mentioned before, ayahuasca is able to bypass these shortcomings and appears to be safe from a subjective and physiological perspective, with only few adverse reactions being reported (R. G. dos Santos et al., 2017). Moreover, no neuropsychological or psychopathological deficits have been identified in long-term ayahuasca users (Barbosa et al., 2012; Bouso et al., 2022; Gable, 2007).

Overall, this presents a potential alternative for treating stress-related affective disorders, as current antidepressant options are often associated with limited efficacy and delayed therapeutic onset (Cameron & Olson, 2018; Ly et al., 2018; Munkholm et al., 2019). Consequently, ayahuasca may be particularly well-suited for the comprehensive treatment of complex diseases, where conventional reductionist approaches have frequently been disappointing (Scheidegger, 2021). However, the research around ayahuasca as a therapeutical treatment is still evolving. Numerous research efforts conducted so far have primarily been observational, open label, often confined to religious context, and small scale, while results may differ depending on the context of use.

1.3.5. Challenges and Limitations of Ayahuasca as a Novel Treatment Paradigm in Western Society

Despite the encouraging evidence supporting the therapeutic potential and beneficial effects of ayahuasca, some limitations and uncertainties persist in incorporating this traditional brew into Western healthcare systems. For instance, when ayahuasca is used outside of clinical or established ceremonial contexts, the likelihood of unpredictable negative psychological outcomes may increase (de Rios & Grob, 2005). Moreover, ayahuasca consumption can lead to short-term emotional and physical distress, such as strong nausea, vomiting, diarrhea and

overwhelming visual sensations (Bouso et al., 2022). Physiological side effects such as sweating, nausea, and vomiting are perceived in Western medical context as very unpleasant and as adverse reactions to potentially toxic components like the β-carboline harmaline, although these effects are traditionally considered as an integral part of the healing process (Fotiou & Gearin, 2019). Moreover, these side effects can escalate due to anxiety or stress, potentially leading to dehydration (Bouso et al., 2022; Guimarães dos Santos, 2013). However, in a ceremonial context, vomiting can be experienced as part of a purging procedure, where individuals get rid of negative spirits and trauma. Therefore, these effects should not be prematurely dismissed as side effects but rather be reconsidered for its potential therapeutic effects (Fotiou & Gearin, 2019).

The modulation of the neurotransmitter homeostasis by ayahuasca could potentially induce negative psychological effects such as increased anxiety, paranoia, and depressive symptoms, or even longer-lasting psychological complications. Hence, thorough preparation and monitoring are crucial to mitigate the severity of these psychological effects and ensure safety. Additionally, the cardiovascular alterations observed after ayahuasca consumption such as increased body temperature, blood pressure, and heart rate can also pose potential risks for individuals with underlying cardiovascular conditions. Furthermore, individuals with existing health conditions like hepatic or renal diseases, mental health conditions, and cardiac problems could be susceptible to adverse reactions and should seek professional medical consultation before contemplating the use of ayahuasca.

Few instances of transient psychotic episodes have been documented, though these usually resolve spontaneously (de Araujo et al., 2012; Gable, 2007). Extended periods of psychosis are uncommon and primarily arise in individuals with specific vulnerabilities, such as a personal or family history of psychosis or bipolar disorders, or ongoing psychosis or mania (R. G. dos Santos et al., 2017). Severe harmful and toxic effects, potentially fatal, have only been reported for individuals with simultaneous use of other drugs or a personal or familial psychiatric history (R. G. dos Santos, 2013).

Another important point for discussion is the substantial variations in alkaloid concentration across different ayahuasca brews, attributed to different cooking receipts between tribes, and naturally varying alkaloid concentrations in plants. This poses a significant challenge, as the standardization of a dosage is nearly impossible, which makes a target-oriented medication in the sense of pharmaceutical treatment in the Western society very unlikely (Guimarães dos Santos, 2013). Furthermore, the oral administration and GI tract absorption of ayahuasca leads to great variability in bioavailability due to individual metabolism, diet, and health status. However, these side effects associated with ayahuasca occur rarely, are often related to insufficient preparation and medical clarification, and are transient in most cases, demonstrating the overall favourable safety profile of ayahuasca (Bouso et al., 2022; R. G. dos Santos, 2013; Guimarães dos Santos, 2013; Halpern et al., 2008; Riba et al., 2001, 2003; Scheidegger, 2021). In conclusion, the potential side effects of ayahuasca are generally well-understood, though their frequency, severity, and duration can vary based on a range of factors including the level of oversight during a study, medical and psychological histories, where and how the ayahuasca was used, the composition of the brew, and demographic

characteristics. However, due to possible self-selection bias and the limited sample sizes in observational studies on ayahuasca's adverse effects, it is challenging to definitively correlate reported side effects with clinical, personal, social, and environmental variables.

The social, cultural, and environmental aspects associated with traditional ayahuasca use pose additional hurdles for integration into Western medical practice. The incorporation of this indigenous practice, which expresses a whole worldview and medicinal framework for indigenous tribes, risks cultural appropriation (Brabec de Mori, 2021; Celidwen et al., 2022; Labate & Cavnar, 2018; Labate & Jungaberle, 2011). Additionally, increased ayahuasca tourism and export pose sustainability concerns due to over-harvesting of the constituent plants. These considerations form a complex dilemma, balancing the needs of ecological sustainability, cultural respect, and the urgent need to address not only the global mental health crises, but also the impasse in pharmaceutical development (Ona & Bouso, 2019; Scheidegger, 2021). It seems there might be no straightforward resolution for this predicament, hence all of these elements necessitate a mindful and respectful approach in the ongoing discourse and investigation into ayahuasca.

1.4. Ayahuasca and Beyond: The Journey to Ayahuasca-Analogues

The first studies with isolated compounds of ayahuasca, specifically DMT, were conducted between 1950 and 1970. DMT was identified for the first time in 1955, where a study analysed the indole alkaloids of ceremonial snuffs from indigenous tribes of South America (Fish et al., 1955). Subsequent studies described the psychoactive effects of DMT. For instance, a study has shown that intramuscular administration of DMT elicited hallucinogenic effects and can be used to induce "experimental psychoses" (Böszörményi & Szára, 1958). In this time period, it was well established that intramuscular administration of DMT produced hallucinogenic effects. Given the similarities between subjective effects of DMT and LSD, a study in 1964 explored potential cross-tolerance of intramuscular administered DMT in individuals tolerant to LSD, finding only mild cross-tolerance in mental effects and negligible effects in physiological parameters (Rosenberg et al., 1964). In the 1970s multiple studies of DMT's pharmacological effects in both human and animal models were published (Cole & Pieper, 1973; Dittrich et al., 1976, 1976; Szara, 1970; Waldmeier & Maître, 1977). DMT was also considered to be an endogenous substance despite its hallucinogenic effects, and studies discussed it as potential neurotransmitter and neuromodulator (Barker et al., 1981). In the 90s, several studies by Rick Strassman explored subjective effects, tolerance, dose-response effects and psychopharmacology of intravenous DMT in humans (R. J. Strassman et al., 1994; R. J. Strassman, 1995; R. J. Strassman et al., 1996; R. J. Strassman & Qualls, 1994). Alongside the demonstrated biological safety of DMT, they showed that DMT induces no tolerance and produces very intense and strong subjective effects in a dose-dependent manner.

Although research about DMT has been conducted since the 1950s, it was difficult to translate the strong subjective and physical effects of intravenous DMT into a therapeutic context and open questions remained regarding its clinical applicability. These challenges of therapeutic translation were described in detail in a book by Strassman (R. Strassman, 2000).

In parallel, the intriguing concept of ayahuasca-analogues has captured scientific interest. Ayahuasca-analogues, also referred to as "pharmahuasca", offer pharmacological alternatives to traditional ayahuasca. They often involve plant-based MAOIs and DMT or combinations of a synthetic MAOI and synthetic DMT (Clark, 2019; Kaasik et al., 2021; Ott, 1999). The traditional use of the different plant sources used is well-documented across different cultures (Lowe et al., 2022; Moloudizargari et al., 2013; Savoldi et al., 2023; Souza et al., 2008). As an example for such a plant-based ayahuasca-analogue, there is the combination of *Peganum harmala*, containing MAOIs, with *Mimosa hostilis*, containing DMT.

Ayahuasca-analogues gained popularity due to advancements in DMT synthesis, accessibility of pharmaceutical MAOIs, and cost-effectiveness of synthetic or plant-based alternatives (Kaasik et al., 2021; Labate et al., 2016; Ott, 1999). However, it is important to mention that much of our understanding about the effects and therapeutic benefits of ayahuasca-analogues and pharmahuasca is anecdotal or recent, and the scientific literature is limited. Their effects can be similar to traditional ayahuasca. However, this strongly depends on the exact active ingredients, due to the wide range of possible combinations with plants and/or synthetic DMT and MAOIs (Ott, 1999; St John, 2016). Some formulations may present fewer adverse effects, such as vomiting, thereby offering a potentially more suitable alternative for integration into Western medical practice. The prospect of these preparations offering a more refined and controlled approach to psychedelic-assisted therapy has sparked an increased interest in exploring therapeutic potential, subjective effects, and pharmacological characteristics. Emerging evidence suggests that the therapeutic potential of ayahuasca analogues may be similar to the beneficial effects of traditional ayahuasca. An observational study on the antidepressant effects of an ayahuasca-analogue recently showed a significant reduction in depressive symptoms (van Oorsouw et al., 2022).

As a response to the challenges and limitations of traditional ayahuasca listed in the previous chapter, and the challenges of intravenous DMT administration, we decided to develop an ayahuasca-analogue. We acknowledge that this analogue partly emulates ayahuasca pharmacologically but does not incorporate indigenous worldviews on healing and shamanism (Anderson, 2012; Kaasik et al., 2021; Ott, 1999). Prior to the clinical studies which constitute this doctoral thesis, we developed a standardized pharmaceutical formulation containing extracted DMT from *Mimosa hostilis* combined with synthesized harmine. In a first in-human pilot study, we tested several different dosages and administration routes, focusing on improving bioavailability, reduction of undesired drug effects, and better controllable dosing, while maintaining beneficial psychological effects comparable to those of traditional ayahuasca (Dornbierer et al., under review). Utilizing this approach, we established a unique ayahuasca-analogue formulation with a distinct administration procedure. This pharmaceutical formulation was employed within the framework of the following intervention study, serving as the foundation for the subsequent two chapters in this thesis. The intent was to further evaluate the formulation regarding its pharmacokinetic and pharmacodynamic properties, safety and tolerability, and explore its therapeutic potential. This endeavour marks an important step towards integrating the benefits of ayahuasca into Western medicine in an ethically and culturally respectful manner, while simultaneously addressing potential safety concerns.

1.5. Research Objectives and Aims

As ayahuasca continues to rise in popularity and global use, its scientific examination becomes increasingly relevant. There has been an increase in interest surrounding the influence of psychedelics, including ayahuasca, on psychological functioning and their potential as alternative treatment option for mental health disorders. Despite numerous studies on psychedelics as a broader category, systematic investigation into ayahuasca or ayahuasca-analogues are still relatively young. Thus, gaining a deeper understanding of their unique blends of psychoactive compounds, characteristics, and potential therapeutic applications is crucial, especially considering their possible utility in treating patients with internalizing or stress-related mood disorders.

The following two chapters are devoted to exploring the pharmacokinetics and pharmacodynamics, safety and tolerability profile, and therapeutic potential of an ayahuasca-analogue. Both manuscripts originate from an in-human, double-blind, randomized, placebo-controlled, within-subject study conducted in a laboratory setting, with focus on a uniquely formulated ayahuasca-analogue consisting of DMT and harmine (two psychoactive compounds of ayahuasca), previously developed and tested in a pilot study by our research group (Dornbierer et al., under review).

The first manuscript, described in Chapter 2, aimed to investigate the pharmacokinetics and pharmacodynamics of a controlled repeated-intermittent administration of a DMT/harmine formulation through a randomized controlled trial, comparing its safety and tolerability to a harmine only condition and a placebo condition. The goal was to establish a link between the plasma concentrations of DMT and harmine and the subjective acute effects to identify potential dose-response relationships. Moreover, we assessed if the administration protocol was able to maintain a continuous altered state of consciousness that is manageable for participants, rather than inducing overpowering alterations or side effects.

The second manuscript, elaborated in Chapter 3, aimed to explore the therapeutic potential of the same formulation, with a particular focus on the acute, post-acute, and persisting effects. The research hypothesized that the experience would be characterized by psychedelic phenomenology, leading to emotional breakthroughs, psychological insights, and minimal challenging experiences. The study also assessed positive and negative long-term effects, including trait changes and significant meaning attributed to the experience. The relationship between the persisting effects and the acute experience was also an area of exploration.

To sum up, our aim is to elucidate the molecular, physical, and psychological effects of a novel ayahuasca-analogue formula containing DMT and harmine, thereby guiding future research directions in this exciting field and potentially pave the way for future applications in clinical settings.

Chapter 2. Pharmacokinetics and Pharmacodynamics of an Innovative Psychedelic N,N-Dimethyltryptamine/Harmine Formulation in Healthy Participants: A Randomized Controlled Trial

*Michael J. Mueller[1,2,3], *Helena D. Aicher[1,3,4], Dario A. Dornbierer[1,5,6], Laurenz Marten[1,7], Dila Suay[1,8], Daniel Meling[1,9], Claudius Elsner[1], Ilhui A. Wicki[1], Jovin Müller[1], Sandra N. Poetzsch[6], Luzia Caflisch[1], Alexandra Hempe[1,10], Camilla P. Steinhart[11], Maxim Puchkov[12], Hans-Peter Landolt[3,5], Erich Seifritz[1,3], Boris B. Quednow[1], Milan Scheidegger[1,3]

*shared first authorship

[1]Department of Psychiatry, Psychotherapy and Psychosomatics, Psychiatric University Hospital Zurich, University of Zurich, Zurich, Switzerland
[2]Department of Health Science & Technology, ETH Zurich, Zurich, Switzerland
[3]Neuroscience Center Zurich, University of Zurich and Swiss Federal Institute of Technology Zurich, Zurich, Switzerland
[4]Department of Psychology, University of Zurich, Zurich, Switzerland
[5]Institute of Pharmacology and Toxicology, University of Zurich, Zurich, Switzerland
[6]Department of Forensic Pharmacology and Toxicology, Zurich Institute of Forensic Medicine, University of Zurich, Zurich, Switzerland
[7]Department of Chemistry and Applied Biosciences, ETH Zurich, Zurich, Switzerland
[8]IMT School for Advanced Studies, Luca, Italy
[9]Department of Psychosomatic Medicine and Psychotherapy, University Medical Center Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany
[10]Faculty of Psychology, TU Dresden, Dresden, Germany
[11]Institute of Neuroinformatics, University of Zurich, Zurich, Switzerland
[12]Institute of Pharmaceutical Technology, University of Basel, Basel, Switzerland

Author contributions

MJM[1,2,3,4,5,6,7,8], HDA[1,2,3,4,5,6,7,8], DAD[1,2,5,6,7,8,9], LM[4,8], DS[3,8], DM[3,8], CE[3,8], IAW[3,8], JM[3,8], SNP[4,5,8], LC[3,8], AH[3,8], CPS[3,8], MP[7,9] HPL[2,8], ES[1,8], BQ[1,5,7,8], MS[1,2,3,5,7,8]

[1]conception and design of the study; [2]study management; [3]data acquisition; [4]data analysis, [5]interpretation of results; [6]drafting the article; [7]revision of the article; [8]final approval of the version to be submitted; [9]manufacturing of study drug

Clinical trial registry name and URL incl. registration number: Neurodynamics of Prosocial Emotional Processing Following Serotonergic Stimulation With N,N-Dimethyltryptamine (DMT) and Harmine in Healthy Subjects. https://clinicaltrials.gov/ct2/show/NCT04716335

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2.1. Abstract

Investigating the medical potential of psychedelics has gained considerable interest in recent year, due to their rapid-acting and sustainable therapeutic effects on mood and quality of life. Among others, the Amazonian plant medicine “ayahuasca” - containing a synergistic mixture of the psychedelic N,N-dimethyltryptamine (DMT) and β-carboline alkaloids such as harmine - shows great promise in improving core symptoms of affective disorders. However, traditional ayahuasca use has been associated with a number of distressing effects like nausea, vomiting, and overwhelming hallucinations, which may be partially attributed to the complex pharmacokinetic/pharmacodynamic (PK-PD) interaction of its main constituents, potential overdosing, and intolerable plant constituents.

To this end, this study aimed at overcoming clinical limitations of artisanal ayahuasca preparations by means of pharmaceutical reformulation. In a double-blind, randomized, placebo-controlled, within-subject study the PK-PD properties of an innovative parenteral formulation containing high-purity forms of DMT and harmine were examined in 31 healthy male volunteers. Thereby, drug and metabolite blood plasma levels, subjective drug effects, adverse events and cardiovascular parameters were extensively sampled. On three separate study days, volunteers were administered in a randomized order 1) 100 mg buccal harmine plus 100 mg intranasal DMT, 2) 100 mg buccal harmine plus intranasal placebo, and 3) buccal plus intranasal placebo. Intranasal applications followed a repeated-intermittent dosing scheme, such that 10 mg of DMT (or placebo) were administered every 15 minutes.

Repeated-intermittent intranasal dosing of DMT resulted in sustained-release PK profiles with mean C_{max} values of 22.1 ng/ml (7.1 SD), t_{max} values of 2.7 hours (0.5 SD) and elimination half-life $t_{1/2}$ of 0.6 hours (0.3 SD). Likewise, buccal harmine administration produced sustained-release PK profiles with C_{max} values of 32.5 ng/ml (12.2 SD), t_{max} values of 1.4 hours (0.4 SD) and elimination half-life $t_{1/2}$ of 1.4 hours (0.7 SD). Acute subjective drug effects were primarily driven by DMT and resembled the psychological effects reported after ayahuasca use. By contrast, harmine alone was subjectively indistinguishable from placebo ($p > 0.05$). Vital sign and adverse effect assessment indicated a high tolerability of both buccal harmine and intranasal DMT administration.

In sum, the present work demonstrates the clinical pharmacological profile of a novel pharmaceutical formulation containing pure DMT and harmine. The precise and patient-oriented design of the formula may help mitigating risks associated with the use of DMT in vulnerable patient populations, and may thus be particularly well suited for therapeutic use in clinical settings.

2.2. Introduction

While mood disorders are on the rise, standard of care treatments often show limited efficacy and sustainability (Kirsch et al., 2008; Munkholm et al., 2019), leaving an urgent call for innovative, rapid-acting neuropsychiatric drugs with sustained efficacy. In this context, psychedelic compounds such as psilocybin, lysergic acid diethylamide (LSD), and N,N-Dimethyltryptamine (DMT) are currently experiencing renewed interest as potential treatments for various mental health disorders. In particular, the indigenous Amazonian plant brew "ayahuasca" containing the potent psychedelic compound DMT has become the focus of international research endeavours (R. G. dos Santos et al., 2016; Frecska et al., 2016; Palhano-Fontes et al., 2014; Sarris et al., 2021). DMT is increasingly being recognized as a promising drug candidate given its distinct effects on serotonergic homeostasis and neuroplasticity compared to conventional serotonergic antidepressants (Scheidegger, 2021; Vargas et al., 2023). Indeed, converging lines of evidence from preclinical and human studies suggest that oral formulations containing DMT such as ayahuasca are associated with substantial reductions in anxiety and depressive symptoms (R. G. dos Santos et al., 2016; Sarris et al., 2021). Notably, ayahuasca shows equally rapid but more sustainable antidepressant effects than ketamine (R. G. dos Santos et al., 2016; Osório et al., 2015; Palhano-Fontes et al., 2019; Sanches et al., 2016).

While the exact pharmacological mechanisms underlying the complex ayahuasca brew have not yet been fully revealed, a drug-drug interaction between the indole alkaloid DMT and the β-carboline alkaloids harmine, harmaline, and tetrahydroharmine is likely to be responsible for its therapeutic pharmacological effects. DMT shows no oral bioavailability due to excessive metabolic first-pass degradation by the enteric monoamine oxidase A (MAO-A) enzyme. Thus, herbal sources of DMT (e.g., from *Psychotria viridis*) are frequently combined with β-carboline containing plants (e.g., from *Banisteriopsis caapi*), serving as selective and reversible MAO-A inhibitors, ensuring reduced first-pass metabolism and prolonged duration of DMT action (Callaway et al., 1996). DMT interacts primarily with 5HT2A, 5HT2C, 5HT1A, and sigma receptors (Carbonaro & Gatch, 2016; Vargas et al., 2023), leading to widespread changes in neuronal excitability with pronounced effects on mood, perception, and cognition (Vollenweider & Kometer, 2010). While the effects of intravenous DMT are characterized by their rapid onset and experiential intensity (R. J. Strassman et al., 1994; Timmermann et al., 2019; Vogt et al., 2023), orally administered DMT in the form of ayahuasca evokes a state of introspective awareness, dream-like visions, intensified emotions and autobiographical memories, lasting up to 4-6 hours (Riba et al., 2001, 2003). Despite its high potency, DMT does not induce pharmacological tolerance like other psychedelics (e.g. psilocybin, LSD, mescaline, etc.), underlining the distinct pharmacological action on its receptors (Appel & Freedman, 1968; Barbosa et al., 2012; R. G. dos Santos et al., 2012; Isbell et al., 1961; Passie et al., 2002).

Although ayahuasca is considered safe when administered in a controlled setting (Guimarães dos Santos, 2013; Riba et al., 2001, 2003), traditional herbal ayahuasca can induce distressing somatic and psychological effects including strong nausea, vomiting, diarrhea, and overwhelming perceptive and psychological sensations (Bouso et al., 2022). While from the indigenous perspective these effects are considered key therapeutic factors of the ayahuasca experience, they may also limit the clinical applicability of ayahuasca in vulnerable patient population. A previous study comparing different DMT- and harmine-containing formulations (Dornbierer et al., *under review*) suggested, that some of the ayahuasca-typical intolerabilities

may be related to unpredictable pharmacokinetic and pharmacodynamic (PK-PD) profiles of the alkaloid mixtures, leading to overdosing and suboptimal drug-drug interactions. In particular, by-passing the gastro-intestinal (GI) tract by means of administering harmine via the oromucosal and DMT via the intranasal route was found to substantially reduce GI related side effects, but as well metabolic first-pass-related PK variabilities across the study sample.
Given these promising findings, the present work further investigates the clinical pharmacology of combined oromucosal harmine and intranasal DMT administration in 31 healthy male volunteers, using a placebo-controlled, randomized, placebo-controlled, crossover design. To evaluate the PD of combined DMT/harmine and harmine alone, all volunteers participated in 3 separate drug conditions: 1) 100 mg buccal harmine plus 100 mg intranasal DMT, 2) 100 mg buccal harmine plus intranasal placebo, and 3) buccal placebo plus intranasal placebo. DMT applications followed a repeated-intermittent dosing regimen, in which 10 mg were administered every 15 minutes. PK profiles of DMT (plus its metabolites N-methyltryptamine (NMT), DMT-N-oxide, and indole-3-acetic acid (3-IAA)) and harmine (plus its metabolite harmol) were assessed by means of continuous blood sampling. Moreover, vital signs and acute psychometric variables were assessed throughout the entire experience.
In sum, this study aimed at exploring the clinical pharmacological profile of a combined parenteral DMT/harmine formulation, thus contributing to the understanding of the mechanisms of action and clinical translation potential of ayahuasca.

2.3. Methods

Participants and Permission. Out of 37 healthy male volunteers, a total of 31 participants (25.4 ± 4.2 years) with a mean Body Mass Index (BMI) of 23.0 ± 1.9 SD participated in all 3 study days and experienced all 3 different conditions. Out of the 6 dropouts (27.4 ± 5.7 SD years), 4 volunteers dropped out before study day 1 and 2 volunteers dropped out after day 1 because of personal reasons. Following criteria were required for inclusion: male sex; age within the range of 20 to 40 years; body mass index between 18.5-30; no current or previous history of somatic, neurological, or psychiatric disorder according to case history and Structural Clinical Interviews for DSM (SCID-I; SCID-II); no family history of Axis-I psychiatric disorders; no acute or chronic medication intake; and no current drug use, no or little history of psychedelic experience (e.g., LSD, psilocybin, ayahuasca etc.). The study was approved by the Cantonal Ethics Committee of the Canton of Zurich (Basec-Nr. 2018-01385) and the Swiss Federal Office of Public Health (BAG-Nr. (AB)-8/5-BetmG-2019/008014). All participants provided written informed consent according to the declaration of Helsinki. All participants received monetary compensation.

Study setting. The study was carried out during daytime in the Human Sleep Research Laboratories at the Institute of Pharmacology and Toxicology of the University of Zurich. The soundproof and climate-controlled rooms were redesigned to create a cozy living room environment and fitted with adjustable lighting and sound systems. A standard playlist of background music was played throughout the study day. Participants were seated comfortably on a mattress leaning against the wall and supported by cushions. An experimenter was present at all times to oversee the participants.

Study design. The study was conducted as a within-subject, double-blind, randomized placebo-controlled trial. All participants underwent 3 randomized drug treatments on

separate study days, with an intervening washout period of at least two week: 1) DMT/HAR: harmine hydrochloride (HCl; 100 mg; buccal orodispersible tablet; ODT) plus DMT (as hemifumarate; 100 mg; intranasal: 10 mg every 15 min over 150 minutes), 2) HAR/PLA: harmine (100 mg, buccal ODT) plus placebo nasal spray (NaCl; at same dosing intervals), and 3) PLA/PLA: placebo buccal ODT plus placebo nasal spray. In all conditions, buccal tablets were premedicated 30 minutes. Food or water intake was not allowed 2 hours before drug administration. The detailed dosing scheme is depicted in Figure 1.

Study drug. DMT hemifumarate was obtained by acidic-basic aqueous extraction from the root bark of *Mimosa hostilis* (The Mimosa Company, 1069CL Amsterdam, NL), with n-heptane as organic solvent. DMT was purified by crystallisation and further recrystallized as DMT hemifumarate via salt precipitation. The DMT hemifumarate salt was then dried under vacuum. The final product was subjected to qualitative and quantitative analysis via quantitative Nuclear Magnetic Resonance (qNMR), liquid chromatography-tandem mass spectrometry (LC-MS/MS), and high-performance liquid chromatography (HPLC), revealing a purity of 98.20% ± 0.37%. Harmine hydrochloride (Harmine HCl, ≥98% HPLC-tested) was procured from Santa Cruz Biotechnology Inc. (Dallas, Texas 75220, USA) and further purified via basic precipitation, recrystallization and HCl precipitation.

Intranasal DMT Formulation. DMT hemifumarate was aseptically dissolved in NaCl 0.9% to form a nasal spray solution with concentration of 2.5 mg per puff. The solution was then transferred into nasal spray pump systems with a puff volume of 50 µl (Aptar Pharma, 78431 Louveciennes, France) containing a total of 100 mg (+20% excess) of DMT. The 20% excess volume was added to avoid aspiration of air and consequently dilution of the administered dose.

Buccal Harmine Formulation. Harmine HCl orodispersible tablets for buccal delivery were obtained by freeze-drying. Therefore, harmine HCl, mannitol, hydroxypropyl methylcellulose (HPMC) was dissolved in deionized water, volumetrically filled into aluminium blister moulds, and freeze-dried for 30 hours. For each study day, one ODT containing 100 mg was manufactured.

Intranasal Placebo Formulation. A fumaric acid (1% in NaCl 0.9%) was aseptically manufactured and transferred into nasal spray pump systems with a puff volume of 50 µl (Aptar Pharma, 78431 Louveciennes, France).

Buccal Placebo Formulation. Dextran-based orodispersible tablets were obtained by freeze-drying. Therefore, Dextran was dissolved in deionized water, volumetrically filled into aluminum blister molds, and freeze-dried for 30 hours.

Dose regimen. 30 minutes following buccal premedication with harmine HCl (100 mg) or placebo, respectively, the intranasal repeated-intermittent administration of DMT or placebo was initiated. Volunteers were incrementally administered a total of 100 mg DMT in intervals of 15 minutes with 10 mg at each time point (2x2 puffs per nostril) over a period of 150 minutes (except for one 30 minutes interval between 60 and 90 minutes after the first DMT administration because of a behavioural task performed between these two time points). Volunteers were allowed to discontinue DMT administration in case of intolerance or

unwanted effects. At each administering time point, either a dose of 0, 5 or 10 mg could be selected. Thus, volunteers were given the chance to control the psychedelic strength of the experience to enhance safety and tolerability. If there was no distress or adverse effect, participants were motivated to stick to the dose regimen. The option to skip one dosing time point was only chosen by two participants, the option of taking only 5 mg was never chosen. An overview of the administration time points is given in Figure 1.

Blood sampling. Blood samples were collected from the left or right antecubital vein at -30 (baseline), 0, 30, 60, 90, 120, 150, 180, 195, 210, 240, 270, and 300 min after first DMT/placebo administration for analysis of blood plasma levels of harmine, DMT, the three major DMT metabolites indole-3-acetic acid (3-IAA), DMT-N-oxide, and N-methyltryptamine (NMT) and the major harmine metabolite harmol. As long as DMT administration was still ongoing, blood drawing was always performed right before DMT administration (time point -1 minute). The venous catheter was connected to a 100 mm Heidelberger plastic tube extension in order to collect blood samples without disturbing the volunteers during their psychedelic experience. The intravenous line was kept patent with a slow drip (10 ml/h) of heparinized saline (1000 IU heparin in 0.9 g NaCl/dL; HEPARIN Bichsel; Bichsel AG, 3800 Unterseen, Switzerland). Blood samples were immediately centrifuged for 10 minutes at 2000 RCF. Then, plasma was transferred to Eppendorf tubes, shock-frosted in liquid nitrogen (~ -196°C) and stored at -80°C until assay. An overview of the blood withdrawal time points is visualized in Figure 1.

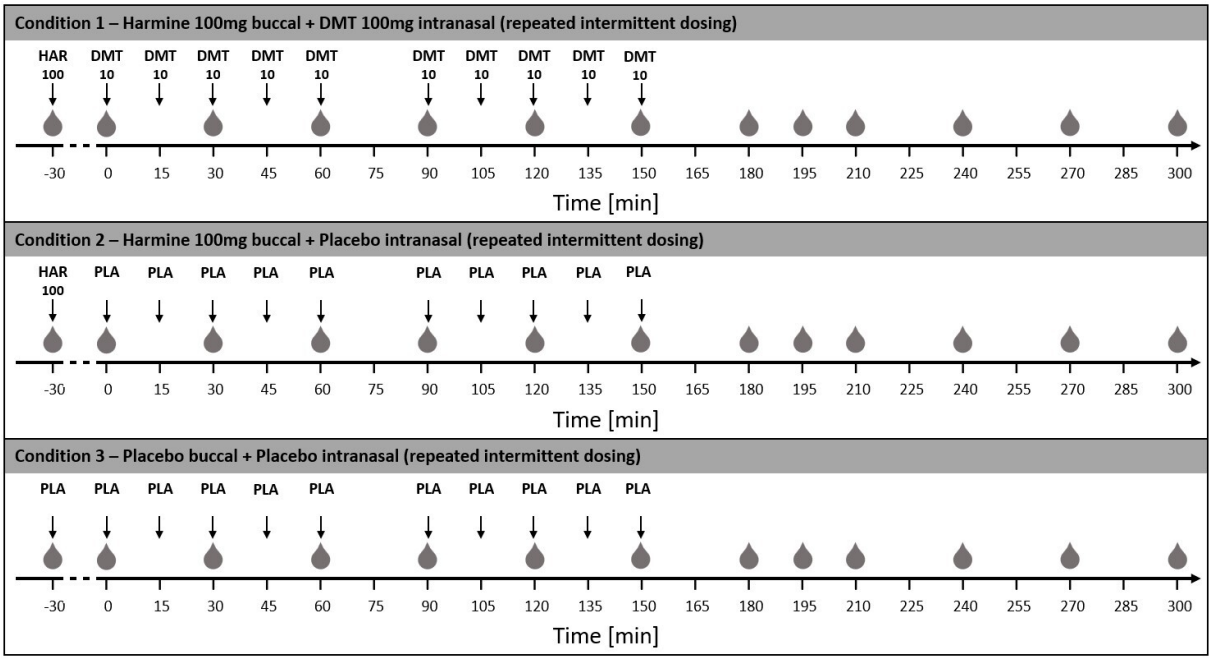

Figure 1: *Illustration of the study procedure. Time points of blood withdrawal are indicated as grey drops (🩸). On all study days, harmine (or corresponding placebo) was applied 30 minutes before first DMT (or corresponding placebo) dosing, to provide sufficient MAO inhibition at the time point of DMT administration. Harmine (or corresponding placebo) was given buccally, whereas DMT (or corresponding placebo) was administered intranasally in a repeated-intermittent manner. Thereby, volunteers were allowed to discontinue the DMT administration in case of tolerability issues or adverse effects. At each administering time point, either a dose of 0, 5 or 10 mg could be selected. Nevertheless, volunteers were motivated to stick to the original dosing protocol if they felt well.*

Analysis of blood levels. DMT was purchased from Lipomed (Arlesheim, Switzerland), NMT and 3-IAA were purchased from Sigma-Aldrich (St. Louis, USA), and harmine, harmol, DMT-N-oxide, harmine-d3 and DMT-d6 were purchased from Toronto Research Chemicals (Toronto, Canada). All other used chemicals were of highest grade available.
For the sample preparation 200 µl of plasma were spiked with 50 µl internal standard (IS) mixture (40 ng/ml DMT-d6 and harmine-d3) and 50 µl methanol (MeOH). Proteins were precipitated by adding 400 µl of acetonitrile (ACN). The samples were shaken for 10 minutes and centrifuged for 5 min at 10‘000 rpm. 350 µl of the supernatant was transferred into an auto-sampler vial, evaporated to dryness under a gentle stream of nitrogen at room temperature and reconstituted in 100 µl eluent-mixture (98:2, v/v). External calibrator and quality control (QC) samples were prepared accordingly, replacing the MeOH with calibrator or QC solution mixtures. Calibrator and QC samples containing 3-IAA were prepared separately, replacing plasma by water. The calibration ranges were 0.5–500 ng/ml for DMT and DMT-N-oxide, 2.5–120 ng/ml for harmine, 1–80 ng/ml for harmol, 0.015–10 ng/ml for NMT and 35–3000 ng/ml for 3-IAA.
Samples were analysed on an ultra-high performance liquid chromatography (UHPLC) system (Thermo Fisher, San Jose, CA) coupled to a linear ion trap quadrupole mass spectrometer 5500 (Sciex, Darmstadt, Germany). The mobile phases consisted of a mixture of water (eluent A) and ACN (eluent B), both containing 0.1% formic acid (v/v). Using a Kinetex C18 column 50 × 2.1 mm, 2.6 µm (Phenomenex, Aschaffenburg, Germany), the flow rate was set to 0.5 ml/min with the following gradient: starting conditions 98% eluent A, decreasing to 70% within 4 min, followed by a quick decrease to 5% within 1 min, holding for 0.5 min and returning to starting conditions for 1.5 min, resulting in a total runtime of 7 min. The mass spectrometer was operated in positive electrospray ionization mode with scheduled multiple reaction monitoring. The following transitions of precursor ions to product ions were selected as quantifier ions: DMT m/z 189→115, DMT-N-oxide m/z 205→117, harmine m/z 213→169, harmol m/z 199→131, NMT m/z 175→144 and 3-IAA m/z 176→103.

Psychometry. Intensity of acute subjective effects was monitored with visual analogue scales (VASs, range 0–100) on a touchscreen tablet throughout the study day at baseline (-90), 0, 30, 60, 90, 120, 180, 240, and 300 after the first DMT/placebo administration. At 360 minutes after first DMT/placebo administration, a phenomenological interview was conducted with participants to further explore acute subjective drug effects. For PK-PD analyses, we included VAS for intensity, liking, disliking, and arousal in the present paper. Further analyses on a set of neurophysiological, psychometric and phenomenological assessments will be presented in forthcoming manuscripts (e.g., Aicher et Mueller et al., in prep.).

Vital signs and adverse effects. The participants were monitored with regard to adverse effects throughout the experiment by the study physician, including questionnaire-based assessments (VAS, 0–100 or y/n) of physical and mental discomfort, breathing difficulties, racing heartbeat, chest or abdominal pains, unpleasant body sensations/muscle pain, headache, nausea, vomiting, and fainting at baseline (-105), 0, 30, 60, 120, 240, and 300 min after DMT/placebo administration. Vital signs (systolic/diastolic blood pressure, heart rate, body temperature) were assessed using a semiautomatic blood pressure and oral temperature recording device throughout the study at baseline (-45), 0, 30, 120, 150, 210, and 270 min after the first DMT/placebo administration.

Statistical analysis. The data were analysed and visualised with R Studio version 2021.09.2+382 (R Core Team, 2021). PK-PD parameters were computed using the R-package PKNCA (Denney, 2014/2023). For C_{max}, t_{max}, AUCs, and half-life calculations, non-compartmental analyses were performed (Gabrielsson & Weiner, 2012). According to the results of a Shapiro test (assumption test), non-parametric Friedman tests were used to compare drug conditions. Post-hoc pairwise comparisons were calculated using paired Wilcoxon signed-rank tests. P-values were adjusted using the Benjamini-Hochberg multiple testing correction method. Pearson or spearman correlations were performed (as appropriate according to Shapiro wilk tests) to analyse associations between DMT plasma levels and subjective effects.

2.4. Results

2.4.1. Pharmacokinetics

The course of the mean plasma concentrations over time of the study compounds N,N-dimethyltryptamine (DMT) and harmine and the metabolites of DMT, namely 3-IAA, DMT-N-Oxide, and NMT, and the metabolite of harmine, namely harmol, are shown in Figure 2, and the corresponding pharmacokinetic parameters are listed in Table 1.
On the study day with DMT plus harmine (DMT/HAR) and harmine plus placebo (HAR) administration, blood samples from 29 out of 31 participants could be analysed for each DMT/HAR and HAR. Exclusions of the plasma analysis were due to failure of sampling blood because of dislocation of the cannula venflon (1 cases in DMT/HAR; 2 cases in HAR) or due to accidental swallowing of the harmine ODT (1 case In DMT/HAR).

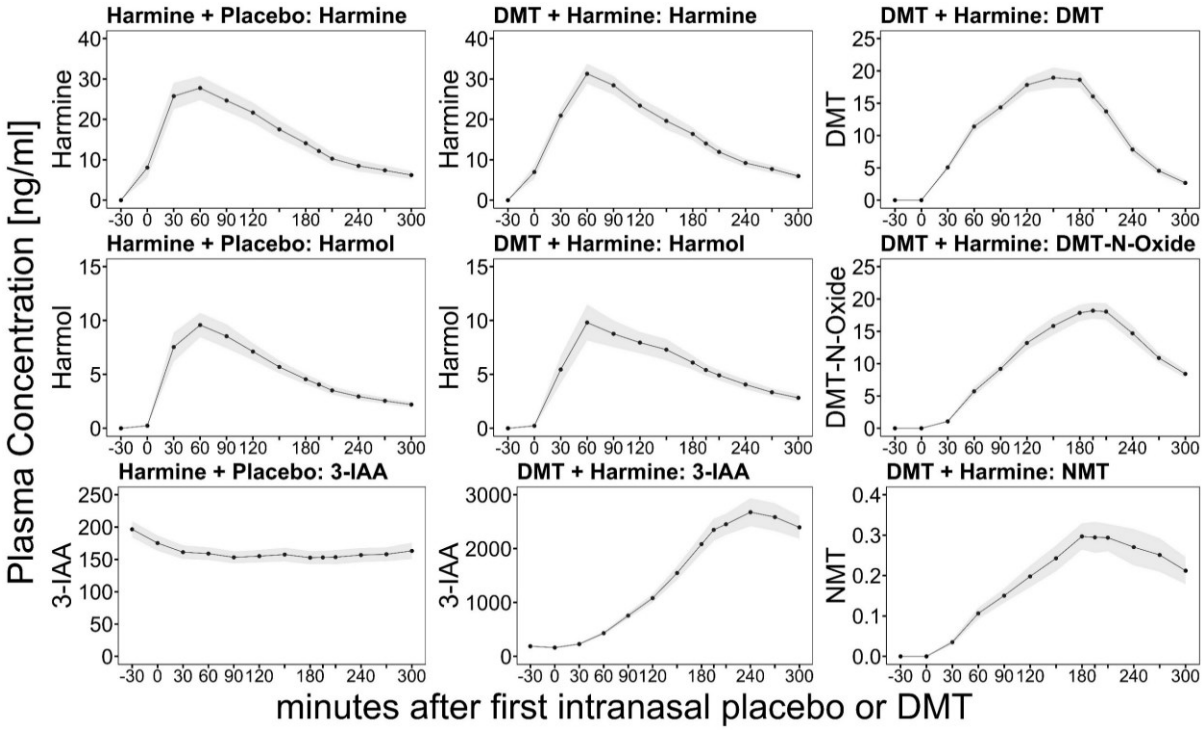

Figure 2: *Time course of the blood plasma profiles of DMT and harmine (1st row), DMT-N-oxide and harmol (2nd row), and NMT and 3-IAA (3rd row) after the administration of harmine + placebo (1st column) and DMT + harmine (2nd and 3rd column). The lines indicate mean analyte concentrations (displayed in ng/ml), shades indicated standard error of the mean (SEM). The x-axis displays the time (minutes) in relation to the start of the intranasal placebo/DMT administration at time point 0).*

In the DMT/HAR condition, the mean peak plasma concentration (C_{max}) of DMT was 22.1 ng/ml (7.1 SD). The time point with the maximum plasma concentration (t_{max}) of DMT was reached 2.7 hours (0.5 SD) after the initiation of repeated-intermittent intranasal DMT administration over a period of 150 minutes. We determined a mean elimination half-life ($t_{1/2}$) of 0.6 hours (0.3 SD) for DMT (when co-administered with harmine), with an AUC_{inf} of 59.9 ng*h/ml (19.4 SD). The mean peak plasma concentration (C_{max}) of harmine was 32.5 ng/ml (12.2 SD). The time point with the maximum plasma concentration (t_{max}) of harmine was reached 1.6 hours (0.6 SD) after harmine ODT administration. The mean elimination half-life ($t_{1/2}$) of harmine was 1.4 hours (0.6 SD), with an AUC_{inf} of 104.1 ng*h/ml (48.0 SD). The pharmacokinetic parameters of the metabolites of DMT and harmine are shown in Table 1.
In the HAR condition, we found a comparable C_{max} of 33.5 ng/ml (17.6) for harmine, and t_{max} was reached 1.4 hours (0.4 SD) after harmine administration with a mean $t_{1/2}$ of 1.5 hours (0.8 SD) and AUC_{inf} of 99.5 ng*h/ml (63.8 SD). 3-IAA levels decreased after harmine administration. The pharmacokinetic parameters of the metabolite of harmine are shown in Table 1.
The blood plasma profiles of DMT-N-oxide (metabolite of DMT) and harmole (metabolite of harmine), followed the profiles of their precursors with a slight time delay. In contrast, the blood plasma levels of the other DMT metabolites, namely NMT and 3-IAA, showed a more sustained increase and longer lasting plateau which corresponds to a longer elimination half-life. Notably, we observed a disproportional increase of the plasma concentrations of 3-IAA compared to the other metabolites.
Due to the fact that in some participants the blood concentration of some metabolites was not back to baseline at the later blood drawings, the elimination half-life ($t_{1/2}$) and AUC_{inf} of

the metabolites NMT, 3-IAA and DMT-N-oxide could not be calculated for all participants. This was most prominent for the metabolite 3-IAA, due to its prolonged elimination half-life, $t_{1/2}$ and the AUC_{inf} was only measurable in 5 participants, therefore, we do not report any mean values here. For NMT and DMT-N-oxide, $t_{1/2}$ and AUC_{inf} was measurable in 16 and 24 participants, respectively.

Table 1: *Pharmacokinetic parameters for N,N-DMT and its metabolites, and harmine and its metabolite in the DMT + harmine condition and harmine + placebo condition based on non-compartmental analyses. Temporal values refer to the administration time of DMT or harmine.*

Condition Marker	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC_{all} (ng*h/mL)	AUC_{inf} (ng*h/mL)
DMT+harmine					
DMT	22.1 (7.1)	2.7 (0.5)	0.6 (0.3)	56.6 (17.3)	59.9 (19.4)
DMT-N-oxide	21.0 (7.0)	3.2 (0.6)	1.2 (0.4)	55.4 (17.8)	69.2 (22.1)
NMT	0.4 (0.3)	3.3 (0.7)	2.4 (2.4)	1.0 (0.6)	1.6 (1.6)
3-IAA	2912.2 (1442.8)	4.1 (0.6)	-	7578.7 (3250.2)	-
Harmine	32.5 (12.2)	1.6 (0.6)	1.4 (0.7)	89.1 (36.1)	104.1 (48.0)
Harmole	12.0 (8.3)	1.6 (1.2)	1.8 (1.4)	29.5 (17.6)	36.8 (20.6)
Harmine+placebo					
Harmine	33.5 (17.6)	1.4 (0.4)	1.5 (0.8)	83.5 (47.7)	99.5 (63.8)
Harmole	12.5 (7.5)	1.6 (0.6)	2.0 (0.8)	26.4 (13.2)	32.6 (15.6)

Means and standard deviations (displayed in brackets) are shown. AUC_{all}: area under the plasma concentration-time curve from time zero to last time point; AUC_{inf}: area under the plasma concentration-time curve from time zero to infinity; C_{max}: estimated maximum plasma concentration; $t_{1/2}$: estimated plasma elimination half-life; t_{max}: estimated time to reach C_{max}

2.4.2. Pharmacodynamics

Subjective Effects. Compared to placebo (PLA) or harmine alone (HAR), combined DMT/harmine (DMT/HAR) administration induced significant alterations in the state of consciousness with psychedelic effects lasting up to 240 minutes (max. intensity ratings at 90 min: contrast DMT/HAR – HAR: effect size: 0.808; $p_{adj.} < 0.001$; contrast DMT/HAR – PLA: effect size: 0.847, $p_{adj,} < 0.001$; last significant difference at 240 minutes: contrast DMT/HAR – HAR: effect size 0.359, $p_{adj\ .} = 0.014$; contrast DMT/HAR – PLA: effect size 0.407, $p_{adj.} = 0.014$). We found no statistical differences in subjective ratings of acute drug effects between the harmine alone and placebo condition (max. intensity ratings at 90 min: contrast HAR-PLA effect size 0.133, $p_{adj.} = 0.307$; 240 minutes: contrast HAR-PLA: effect size 0.127, $p_{adj\ .} = 1$).
In Figure 3, acute subjective drug effects including A) intensity, B) liking, C) disliking and D) arousal are shown as visual analogue scales (VAS) at different time points throughout the study days. DMT/HAR induced robust increases in subjective intensity, liking, and arousal. Transient disliking was reported in some volunteers mostly during the first hour and is likely associated with the onset of acute DMT effects which may be distressing to drug-naïve participants, particularly while performing neurobehavioral tasks. The corresponding peak effects were reported around 90 min after the initiation of repeated intermittent intranasal DMT administration over 150 minutes, with a lasting plateau until 180 min, followed by a rapid decrease of subjective effects. Reported peak intensity reached on average 75.9% (22.2

SD) of the maximal possible score in DMT/HAR, considerably higher than in HAR (7.6% (15.9 SD)). Similarly, reported peak effects of liking reached on average 88.0 % (14.7 SD), considerably higher than in HAR (20.0% (35.2 SD)). Comparably lower levels of disliking were reported with mean peak effects of 41.7 % (28.9 SD) in DMT/HAR, considerably higher than in HAR (7.8% (21.9 SD)). Reported peak effects of arousal reached on average 66.2 % (30.2 SD) in DMT/HAR, considerably higher than in HAR (9.9% (23.1 SD)). Besides of a slight increase in liking with a reported peak effect reaching on average 11.0% (28.5 SD) of the maximal possible score, there were no notable changes in PLA.

The estimated time to peak effects after drug administration were all in the range between 80 to 120 min for both DMT/HAR and HAR, regardless of the subjective effect.

Acute subjective effects gradually subsided between 180-240 min after first DMT administration, but mild afterglow effects were still reported in the qualitative interviews taken after the last assessment around 360 min after drug administration (Meling et al. in prep.). Most subjective effects (except disliking) approximately followed the blood plasma concentrations of DMT, indicating that intranasal DMT is efficiently activated by buccal harmine. We observed a strong positive correlation between subjective intensity ratings and DMT plasma levels ($r = 0.59$, 95% CI [0.51, 0.66], $t(305) = 12.68$, $p < 0.001$).

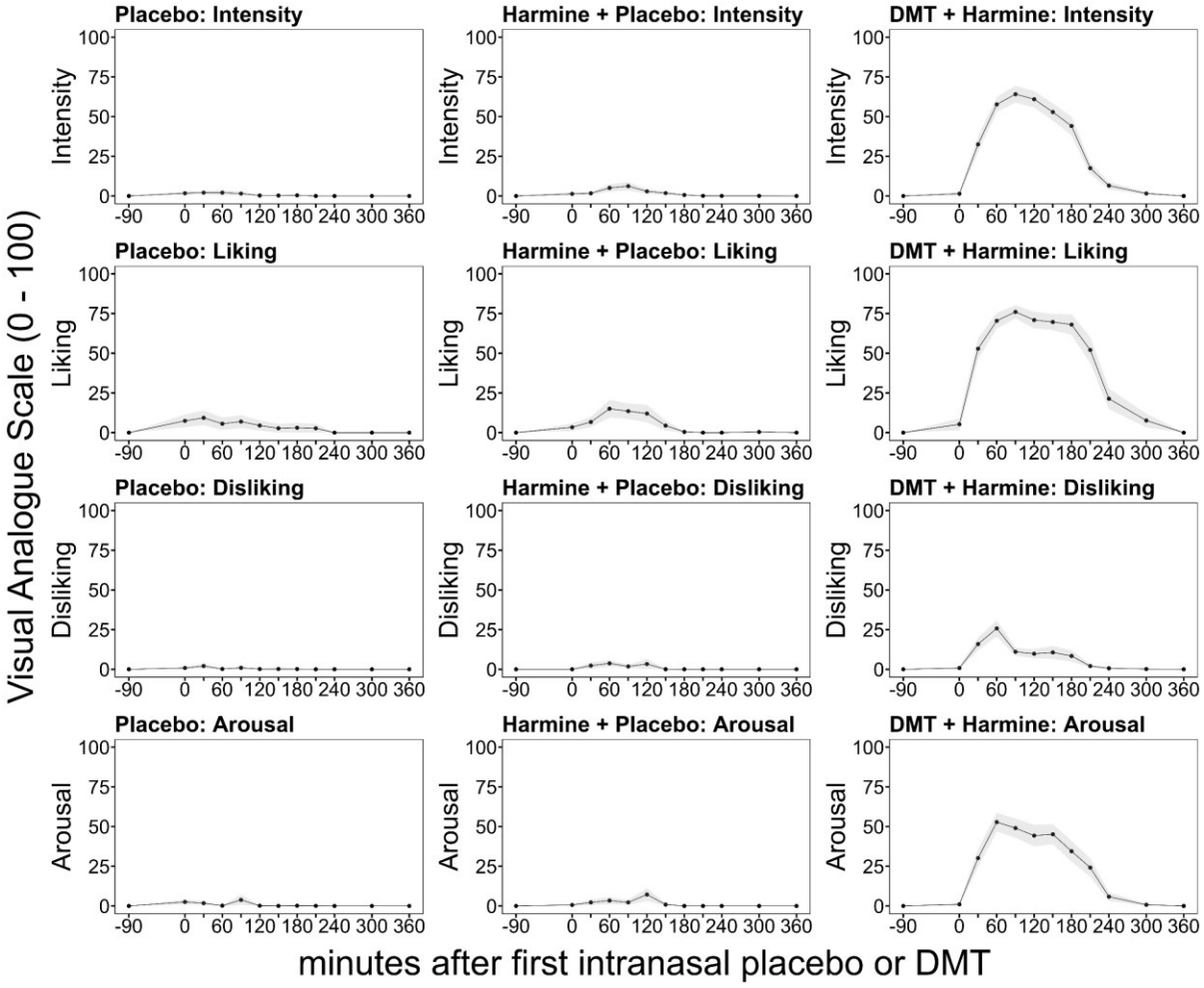

Figure 3: *Subjective drug effects for intensity (1st row), liking (2nd row), disliking (3rd row), and arousal (4th row) for placebo + placebo (1st column), harmine + placebo (2nd column), and DMT + harmine (3rd column). Black lines*

indicate mean ratings on visual analogue scales (VAS; 0-100), grey shades indicate standard error of the mean (SEM). The x-axis displays the time (minutes) related to the start of intranasal placebo/DMT administration at time point 0.

Vital signs. Mean values for body temperature (BT), systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate over time are shown in Figure 4. DMT/HAR induced low to moderate elevations of the cardiovascular parameters, no relevant changes were observed in HAR, nor in PLA. Mean heart rate values stayed in the range of 60 to 75 bpm. SBP increased on average by 16.5 (9.9 SD) mmHg, and DBP increased by 10.3 (10.2 SD) mmHg, with peak values at 120-150 min after initial DMT administration (values are likely confounded by neurobehavioral tasks). No relevant change was observed in BT.

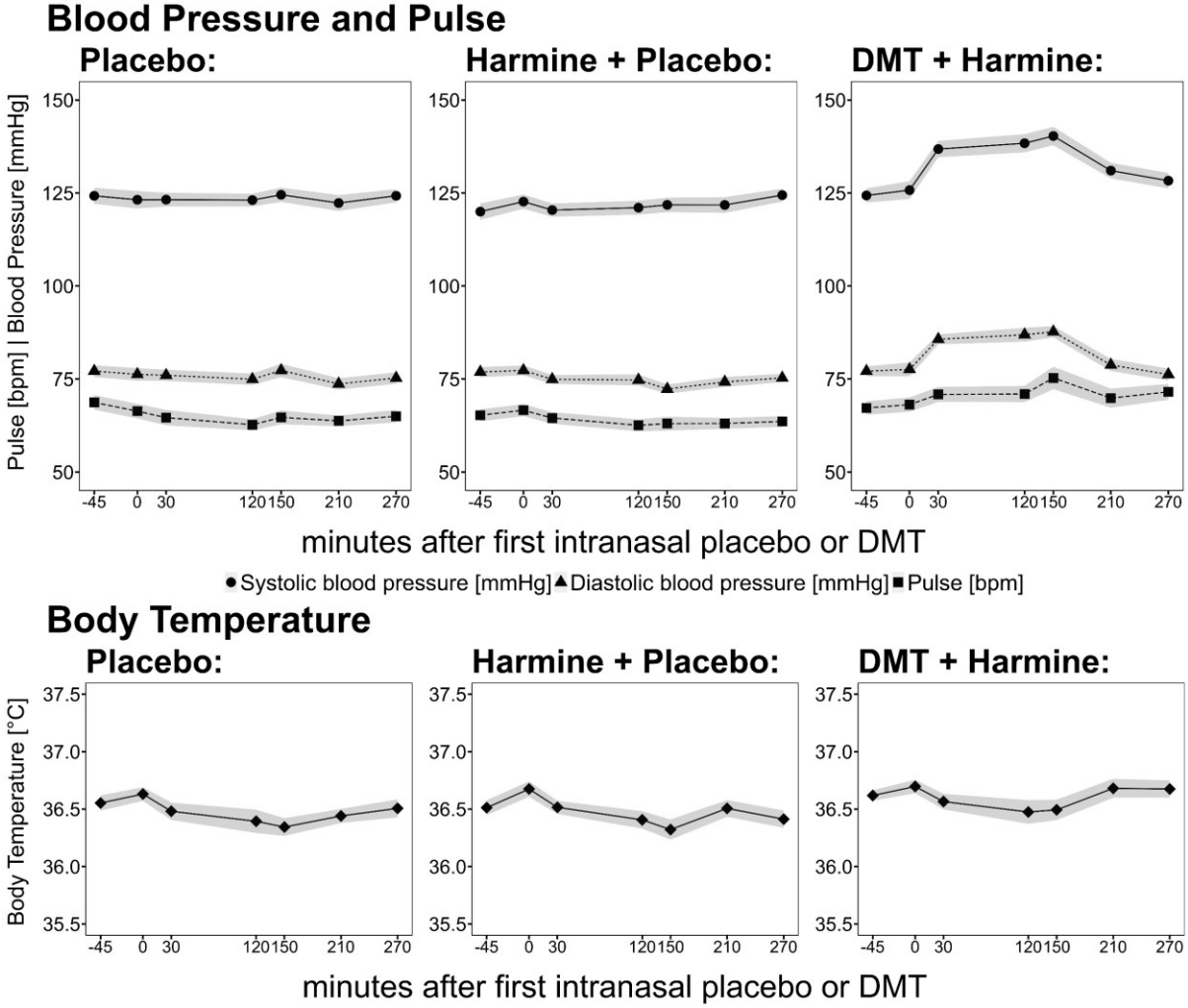

Figure 4: *Vital signs (● systolic BP; ▲ diastolic BP, ■ pulse, ◆ body temperature) during pharmacological challenge with placebo (left) vs. harmine (middle) vs. intranasal DMT/buccal harmine (right). Black lines indicate mean values, grey shades indicate standard error of the mean (SEM). The x-axis displays the time (minutes), based on the start of intranasal placebo/DMT administration at time point 0.*

Undesired drug effects. In Table 2 the number of participants reporting adverse effects (AEs) are shown for all drug conditions. Most AEs were observed in the DMT/HAR condition during the first hour when subjective drug effects increased. Around 30–40% of participants experienced transient AEs such as moderate levels of nausea (n=9/31; mean intensity 46.9/100), heart racing (n=12/31; mean intensity 29.8/100), and somatic distress (n=14/31;

mean intensity 26.1/100), which resolved rapidly and did not require medical intervention. Compared to the background noise in the reporting of AEs (e.g., placebo condition), the drug-induced AEs for both HAR and combined DMT/HAR can be considered as mild and well tolerated.

	minutes after first intranasal DMT administration						
	-105	0	60	120	180	240	300
Placebo							
Somatic distress	9; 13 (12)	8; 12 (11)	5; 21 (23)	4; 22 (25)	5; 20 (15)	6; 26 (15)	5; 18 (12)
Psychological distress	1; 11 (0)	2; 2 (2)	2; 14 (15)	0; 0 (0)	1; 8 (0)	2; 7 (3)	0; 0 (0)
Breathing difficulty	0; 0 (0)	2; 2 (1)	1; 2 (0)	3; 1 (1)	0; 0 (0)	1; 1 (0)	0; 0 (0)
Heart racing	2; 10 (3)	2; 1 (0)	1; 4 (0)	0; 0 (0)	2; 35 (45)	1; 54 (0)	2; 2 (1)
Chest pain	1; 3 (0)	0; 0 (0)	0; 0 (0)	1; 1 (0)	0; 0 (0)	0; 0 (0)	0; 0 (0)
Stomach ache	4; 28 (38)	3; 23 (34)	0; 0 (0)	0; 0 (0)	2; 33 (42)	0; 0 (0)	0; 0 (0)
Muscle ache	6; 21 (23)	4; 13 (9)	3; 18 (7)	4; 16 (12)	4; 14 (9)	4; 22 (10)	3; 14 (9)
Head ache	2; 3 (0)	5; 18 (13)	7; 12 (19)	4; 42 (35)	4; 28 (23)	6; 23 (12)	3; 29 (13)
Nausea	2; 4 (4)	3; 5 (4)	3; 7 (5)	1; 2 (0)	1; 5 (0)	0; 0 (0)	0; 0 (0)
Vomiting	0; 0 (0)	0; 0 (0)	0; 0 (0)	0; 0 (0)	0; 0 (0)	0; 0 (0)	0; 0 (0)
Fainting	0; 0 (0)	0; 0 (0)	0; 0 (0)	0; 0 (0)	0; 0 (0)	0; 0 (0)	0; 0 (0)
Harmine							
Somatic distress	7; 17 (12)	5; 18 (14)	5; 9 (5)	7; 7 (5)	4; 13 (3)	4; 16 (12)	3; 12 (5)
Psychological distress	4; 13 (8)	3; 6 (2)	2; 8 (8)	2; 4 (5)	1; 9 (0)	2; 3 (1)	1; 70 (0)
Breathing difficulty	2; 12 (15)	3; 18 (25)	2; 21 (28)	3; 7 (8)	0; 0 (0)	1; 6 (0)	1; 3 (0)
Heart racing	3; 9 (6)	2; 28 (35)	1; 9 (0)	3; 5 (5)	1; 1 (0)	1; 3 (0)	1; 49 (0)
Chest pain	0; 0 (0)	2; 24 (32)	2; 13 (8)	3; 4 (3)	0; 0 (0)	1; 1 (0)	0; 0 (0)
Stomach ache	2; 12 (15)	1; 2 (0)	1; 52 (0)	2; 30 (37)	0; 0 (0)	2; 32 (44)	1; 2 (0)
Muscle ache	5; 11 (9)	6; 9 (7)	2; 22 (0)	3; 10 (9)	4; 16 (14)	3; 21 (5)	2; 9 (11)
Head ache	3; 8 (7)	1; 3 (0)	2; 34 (47)	1; 11 (0)	1; 72 (0)	1; 27 (0)	0; 0 (0)
Nausea	1; 6 (0)	1; 2 (0)	3; 11 (10)	1; 15 (0)	1; 1 (0)	1; 2 (0)	2; 2 (1)
Vomiting	0; 0 (0)	0; 0 (0)	0; 0 (0)	0; 0 (0)	0; 0 (0)	0; 0 (0)	0; 0 (0)
Fainting	0; 0 (0)	0; 0 (0)	0; 0 (0)	0; 0 (0)	0; 0 (0)	0; 0 (0)	0; 0 (0)
DMT + Harmine							
Somatic distress	9; 13 (11)	7; 11 (5)	14; 26 (24)	11; 14 (12)	7; 25 (15)	3; 6 (3)	1; 37 (0)
Psychological distress	6; 9 (5)	3; 4 (4)	11; 9 (8)	5; 16 (11)	5; 32 (20)	1; 14 (0)	0; 0 (0)
Breathing difficulty	4; 6 (5)	3; 10 (8)	10; 19 (27)	3; 16 (21)	3; 12 (16)	1; 7 (0)	1; 4 (0)
Heart racing	2; 16 (8)	2; 17 (21)	12; 30 (26)	5; 17 (17)	6; 24 (18)	1; 1 (0)	2; 2 (2)
Chest pain	0; 0 (0)	2; 4 (0)	4; 24 (39)	4; 6 (6)	0; 0 (0)	1; 2 (0)	1; 2 (0)
Stomach ache	0; 0 (0)	5; 18 (21)	0; 0 (0)	4; 9 (13)	0; 0 (0)	0; 0 (0)	1; 4 (0)
Muscle ache	5; 20 (9)	8; 27 (24)	4; 34 (37)	5; 12 (9)	3; 22 (12)	2; 12 (16)	1; 3 (0)
Head ache	2; 6 (7)	6; 8 (4)	4; 15 (20)	1; 8 (0)	0; 0 (0)	4; 15 (10)	0; 0 (0)
Nausea	0; 0 (0)	2; 10 (5)	9; 47 (26)	5; 29 (33)	3; 43 (22)	2; 48 (64)	0; 0 (0)
Vomiting	0; 0 (0)	0; 0 (0)	1; 1 (0)	0; 0 (0)	0; 0 (0)	0; 0 (0)	0; 0 (0)
Fainting	0; 0 (0)	0; 0 (0)	0; 0 (0)	0; 0 (0)	0; 0 (0)	0; 0 (0)	0; 0 (0)

Table 2: *Number of participants reporting undesired drug effects with y/n and visual analogue scales, means of intensity [0–100], and standard deviations (displayed in brackets) over all participants are reported for the three drug conditions (placebo, top panel; 100 mg oromucosal harmine, medium panel; 100 mg oromucosal harmine with 100 mg repeated-intermittent DMT; bottom). Values greater than zero are highlighted in grey).*

2.5. Discussion

In the present study, an innovative psychedelic formula - comprising a synergistic combination of high-purity DMT and harmine - was pharmacologically examined in 31 healthy male volunteers. By means of pharmaceutical reformulation, the study aimed at mitigating pharmacological challenges associated with oral DMT preparations (such as herbal ayahuasca or so-called pharmahuasca), including inter-/intrasubject variability in bioavailability and metabolism, and gastro-intestinal side effects (Bouso et al., 2022; R. G. dos Santos et al., 2012). The developed pharmaceutical formula entailed the buccal premedication of a harmine ODT, followed by repeated-intermittent intranasal dosing of DMT over 150 minutes. To evaluate for the first time the pharmacological contribution of harmine to the overall subjective experience, this study compared the psychological effects of harmine and co-administration of harmine plus DMT.

DMT is one of the few short-acting psychedelics, that has recently gained considerable interest for the treatment of psychiatric and neurological conditions. DMT is not orally bioavailable due to excessive first-pass metabolism by the MAO enzyme system (Barker, 2018). In contrast, parenteral DMT administrations by means of inhalation or intravenous infusion yield high systemic exposure levels, followed by rapid elimination within minutes ($t_{1/2}$ between 5-16 minutes) (Carbonaro & Gatch, 2016; Vogt et al., 2023). However, the effects of DMT can be significantly potentiated and prolonged by reducing its metabolic breakdown through the concurrent inhibition of the MAO enzyme system (Callaway et al., 1996; Mckenna et al., 1984). This concept is the foundation of the indigenous Amazonian plant medicine ayahuasca, which combines plant-based sources of DMT with harmala alkaloid-rich plants, acting as selective and reversible MAO-A inhibitors. More recently, synthetic or purified sources of DMT and harmine have been used to create standardized versions of ayahuasca, also known as ayahuasca-analogue or pharmahuasca (Ott, 1999). While the synergistic principle underlying the combination of MAO inhibitors (e.g., harmala alkaloids) and DMT has been proven to work, several PK-PD challenges limit the usability of such preparations for pharmacotherapeutic purposes. In particular, dose-exposure relationship of ayahuasca was found to vary dramatically across individuals, which may be attributed to differences in gastro-intestinal absorption and first-pass metabolism. Consequently, strong adverse effects due to overdosing are not uncommon in traditional settings (R. G. dos Santos, 2013). From the indigenous perspective, ayahuasca-induced psychophysiological distress is considered a key therapeutic factor of the ayahuasca experience. On the other hand, these "side effects" may also limit the clinical applicability of ayahuasca-analogues in vulnerable patient populations. Thus, we hypothesized that optimizing dose-exposure predictability represents the first step towards a safe use of oral DMT formulations.
The GI tract and first-pass metabolism represents the major source of pharmacokinetic variations across individuals. To this end, in this study both harmine and DMT were pharmaceutically delivered in a non-oral fashion. In this sense and in line with PK data from a previous study (Dornbierer et. al, *under* review), we found that harmine was well absorbed buccally and produced blood plasma levels with low interindividual variability, in contrast to oral ayahuasca (Riba et al., 2003). Interestingly, the buccal route of administration favoured a sustained-release profile, which appeared to be particularly suited for the extended DMT administration protocol employed in this study.

Premedication of harmine significantly increased the elimination half-life of DMT ($t_{1/2}$ of 36 minutes), enabling continuous intermittent dosing of DMT over 150 minutes, resulting in an overall drug action of up to approx. 240 minutes. Unlike intravenous, inhaled, or oral preparations (ayahuasca/pharmahuasca), the repeated intermittent dosing of DMT yielded a sustained-release PK profile with a pronounced plateau. Moreover, by bypassing the first-pass metabolism through buccal administration, lower doses of harmine seem to be sufficient to prevent rapid clearance of DMT by MAO and to extend the psychedelic experience. After the last intranasal DMT dose, blood plasma levels remained constant for 30 minutes before starting to decrease. This is in strong contrast to inhaled or intravenous DMT, where half concentration is reached within minutes. Thus, the MAO inhibition of harmine is still in effect at 210 minutes after administration.
The ratio between a parent substance (DMT and harmine) and its main metabolite (3-IAA/N-oxide DMT and harmol, respectively) enables the estimation of the location of absorption. In more detail, oral administrations followed by excessive first-pass metabolism yield smaller ratios (higher metabolite level) compared to parenteral administration followed by slow systemic metabolism. Indeed, we found considerably higher harmine:harmol ratios (~3) compared to traditional ayahuasca, where in some cases even ratios below 1 were found (no detectable harmine levels; Riba et al., 2003). For DMT, we found that – despite co-administration of harmine - the majority was degraded to 3-IAA by MAO-A (Riba et al., 2015; Vogt et al., 2023). Anyhow, DMT-N-oxide plasma levels were significantly higher compared to plasma levels obtained after ayahuasca or pure DMT (i.v., smoked) administration (Brito-da-Costa et al., 2020; Vogt et al., 2023). This may indicate a slight shift from MAO-A to cytochrome P450 (CYP) mediated degradation in the presence of a MAO inhibitor (Riba et al., 2015). Anyhow, in the present study DMT was still predominantly metabolized via the MAO system, indicating that the MAO system was by far not completely blocked (but rather slowed down) in the measured harmine exposure range. This finding may indicate that the risks of drug-drug interactions following co-administration of monoaminergic drugs (e.g., SSRI) and combined harmine/DMT preparations may be less pronounced than generally anticipated, given the ability of MAO to degrade its substrates despite high harmine levels. Anyhow, further research is needed to verify this notion.
Moreover, we found that 3-IAA (which is not only the main DMT metabolite but also an endogenous metabolite of the amino acid tryptophan) levels were decreased in the harmine only condition, indicating a harmine-related decrease in tryptophan breakdown to 3-IAA by MAO (Dragulska & Kańska, 2014; Luethi et al., 2022; Martínez et al., 1983). This effect may account for some of harmine's indirect neuromodulating effects, given the role of tryptophan in the biosynthesis of serotonin and other neuroactive molecules.

In line with previous research, the subjective effects of the present DMT/harmine formulation were mainly driven by DMT. We found no significant difference for subjective ratings between HAR and PLA, suggesting that harmine at the administered dose strength acts primarily as a PK-enhancer of DMT. However, we observed a slight increase in liking, which may be in line with previously reported relaxing properties of harmine (Moloudizargari et al., 2013; Patel et al., 2012). Furthermore, the administered harmine dose and consequently the exposure levels were rather low in this study, compared to ayahuasca administrations reported in the past (Callaway et al., 1999). Thus, it can not be excluded, that harmine (and other harmala alkaloids) may have PD contributing effects at higher doses. Anyhow, DMT increases proprioceptive sensitivity, which may potentiate the sensation of subjective harmine effects.

Also, the isolated effects of DMT were not examined in this study, such that pharmacodynamic contributions of harmine to the overall experience can not be fully elucidated with the data at hand.
Overall, participants responded very well to the parenteral delivery of DMT, with high levels of intensity and liking as well as moderate arousal and comparably low and transient levels of disliking. Interestingly, the peak of the subjective effects slightly proceeded the peak plasma concentration of DMT and reached plateau levels despite continued DMT administration and still increasing plasma levels. A similar effect was observed with intravenous DMT (Vogt et al., 2023). While we found a clear exposure-effect relationship, the initial doses produced stronger changes in subjective rating compared to later dose increments. Thus, changes from baseline (ordinary consciousness) may be perceived stronger than changes occurring in a plateau. As such, bolus administrations of DMT (e.g., intravenous and inhaled) can rapidly perturb neurochemical homeostasis and may thus bear a pronounced risk potential compared to slow-release formulations or dosing protocols (Barker, 2022; Carbonaro & Gatch, 2016). Thus, in this study intranasal DMT was dosed incrementally in 15 min intervals over 150 minutes, which resulted in robust DMT exposure levels, closely corresponding to the subjective drug effects. Given the high degree of controllability of this approach, the dosing format was highly appreciated by all study volunteers and may also increase patient compliance in clinical settings.

While the reported undesired drug effects (such as mild levels of somatic or psychological distress, dizziness, headache, nausea, increased heart rate and blood pressure; Table 2, Figure 4) were similar in nature compared to ayahuasca typical side effects (Bouso et al., 2022), the frequency and intensity of AEs in the present study was considerably lower (e.g., nausea/vomiting: 29% of participants compared to 62% of traditional ayahuasca users). In some religious ayahuasca settings, vomiting can be as frequent as 97% of users (Halpern et al., 2008), compared to 3% of participants in our study. It is assumed, that this amelioration of AE intensity may be driven by reduced stimulation of serotonergic chemoreceptors in the GI tract, due to non-peroral dosing. It has to be mentioned, that some of the AEs observed this study could have been potentiated by the fact that participants were engaging in several neurobehavioral tasks (at 60, 150 and 210 minutes), posing additional challenges, specifically under the influence of a psychedelic. Furthermore, some reported AEs (e.g., headache, muscle ache) were even higher in the placebo (PLA) condition than in the HAR or DMT/HAR condition, possibly due to the study set up (EEG recordings). Overall, the AEs for both HAR and DMT/HAR were mild and well tolerated. Noteworthy, we observed a mild but asymptomatic increase in systolic and diastolic blood pressure and heart rate in the DMT/HAR condition, which is in line with previous studies (Barker, 2018; Callaway et al., 1999; R. J. Strassman et al., 1994). The increase cardiovascular activity may also have been confounded by some behavioural tasks (time window 120–150 minutes) that may have enhanced psychophysiological arousal levels. Ayahuasca as an extract of numerous plants contains a highly complex mixture of alkaloids, which makes it difficult to attribute pharmacological or AEs to any of the ingredients or microbiological contaminations. In contrast, the present formula formulation is fully standardized and by circumventing the GI-tract the predictability and tolerability of drug effects is further optimized (e.g., by reducing individual differences in GI absorption and hepatic first-pass metabolism, and by sparing intestinal 5-HT3 chemoreceptors on vagal afferent terminals).

Although there are many differences between botanical ayahuasca and DMT/harmine formulations, which obviously limits their direct comparison, we noticed a striking similarity in the reported subjective effects (e.g., intensity, liking, and duration) (Riba et al., 2001). Moreover, the improved PK-PD properties and the beneficial AE profile of this innovative DMT/harmine formulation may have clear advantages for clinical applications, as growing evidence shows that ayahuasca and DMT-based formulations have the potential to improve mental health (Frecska et al., 2016; Palhano-Fontes et al., 2014, 2019; Sarris et al., 2021). Although the combined administration of DMT and harmine is more complex, it is likely to yield more favourable experience profiles to support psychotherapy compared to DMT alone (Aicher et Mueller et al., in prep.). Given the need to reduce the psychological risks associated with the use of psychedelic drugs, this patient-controlled administration of a psychedelic substance is novel and seems particularly beneficial for future applications in the treatment of psychiatric patients. In sum, compared to the clinical data on traditional ayahuasca (Bouso et al., 2022) the clinical pharmacological profile can be significantly improved by means of pharmaceutical reformulation (Dornbierer et al., *under review*).

It is important to consider several limitations when interpreting the results of this study. Although double-blinded, randomized, placebo-controlled designs are widely used in therapeutic trials, they have limitations for the investigation of psychedelics. The potent and distinct effects of DMT potentially reduces the impact of a double-blinded randomization due to expectancy and reporting biases (Muthukumaraswamy et al., 2021), especially affecting self-report measures. Moreover, contextual setting variables such as behavioural tasks or music may significantly impact the overall subjective experience. In addition, we deliberately chose moderate dose levels to enable participation in behavioural experiments. To explore the full pharmacological range of effects of DMT/harmine, further dose-escalation studies are needed. Last but not least, the study sample consisted of Caucasian, male, young and average-weight individuals, thus not allowing for translation of the results to a more heterogenous population. Further research with a more diverse samples is needed to better ascertain the safety, tolerability, and efficacy of this intervention.

2.6. Conclusion

We here present the PK-PD properties of a novel combined parental administration of DMT as nasal spray and harmine as orodispersible tablet in a first double-blind, randomized, placebo-controlled, within-subject study in healthy male volunteers. Our PK-PD results are consistent with the pharmacological principle of herbal ayahuasca, wherein the rapid degradation of DMT in the body is slowed down by co-administration with the MAO-A inhibitor harmine, thereby prolonging DMT's psychedelic effects for the duration of 2-3 hours. Moreover, our results indicate that subjective psychedelic effects were primarily driven by DMT. Repeated-intermittent dosing of DMT further improves safety and tolerability compared to oral ayahuasca preparations and may represent a more reliable and controllable solution for administering DMT/harmine in clinical trials. The commonly reported psychosomatic side effects and distress with traditional oral ayahuasca could be strongly attenuated via parenteral administration bypassing the gastrointestinal tract. This novel approach appears to be valuable for clinical applications especially in vulnerable patient populations due to the improvement of dosing uncertainty and unpredictable side effects associated with the administration of psychedelic compounds. We conclude that combined

intranasal DMT and buccal harmine may become an innovative rapid-acting, safe, and patient-oriented treatment solution for affective disorders.

2.7. Acknowledgment

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Chapter 3. The Therapeutic Potential of an Ayahuasca-Analogue Containing N,N-Dimethyltryptamine and Harmine: A Controlled Trial in Healthy Subjects

*Aicher, H.D.[1,2,3], *Mueller, M.J.[1,3,4], Suay, D.[1,5], Elsner, C[1]., Wicki, I.A.[1], Meling, D.[1,6], Caflisch, L.[1], Hempe, A.[1], Steinhart, C.[1], Mueller, J.[1], Dornbierer, D.A.[1], Von Rotz, R.[1], Kleim, B.[2,7], Scheidegger, M.[1,3]

(*Shared first authors)

[1] Psychedelic Research & Therapy Development, Department of Psychiatry, Psychotherapy and Psychosomatics, Psychiatric University Hospital Zurich, University of Zurich, Switzerland
[2] Department of Psychology, University of Zurich, Switzerland
[3] Neuroscience Center Zurich, University of Zurich and ETH Zurich, Switzerland
[4] Department of Health Science & Technology, ETH Zurich, Switzerland
[5] MoMiLab, IMT School for Advanced Studies Lucca, 55100, Italy
[6] Department of Psychosomatic Medicine and Psychotherapy, University Medical Center Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany
[7]Experimental Psychopathology and Psychotherapy, Department of Psychiatry, Psychotherapy and Psychosomatics, Psychiatric University Hospital Zurich, University of Zurich, Switzerland

Contributions: HDA[1,2,3,4,5,6,7,8]; MJM[1,2,3,4,5,6,7,8,]; DS[3,8]; CE[3,8]; IAW[3,8]; DM[3,8]; LC[3,8]; AH[3,8]; CS[3,8]; JM[3,8]; DAD1[1,2,8]; RVR[1,8]; BK[1,7,8]; MS[1,2,5,7,8]

[1]conception and design of the study; [2]study management; [3]data acquisition; [4]data analysis, [5]interpretation of results; [6]drafting the article; [7]revision of the article; [8]final approval of the version to be submitted

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3.1. Abstract

Background: There is growing scientific evidence for the therapeutic benefits of the Amazonian plant-based psychedelic “ayahuasca” for mental disorders such as depression and anxiety. However, there are some translational challenges for using botanical ayahuasca in biomedical research and clinical treatment settings. Ayahuasca-analogue preparations, containing specific and standardized active ingredients, are a potential solution.

Methods: We investigated subjective acute and persisting effects of a novel formulation containing the reversible monoamine oxidase inhibitor harmine (orodispersible tablet containing 100 mg MAO-I) and N,N-dimethyltryptamine (incremental intranasal dosing of up to 100 mg DMT), compared with harmine alone and placebo, in a crossover RCT in 31 healthy male subjects.

Results: Overall, DMT + harmine and harmine alone were well tolerated. DMT + harmine, but not harmine alone, induced a phenomenologically rich psychedelic experience (assessed with the 5D-ASC rating scale and acute experience sampling), characterised by psychological insights (PIQ), emotional breakthroughs (EBI), and low scores on the challenging experience questionnaire (CEQ). Participants attributed personal and spiritual significance to the experience with mainly positive persisting effects (1 and 4 months follow up). Acute drug effects positively correlated with persisting effects. We found no changes in trait measures of personality, psychological flexibility, or general well-being, and no increases in psychopathology were reported.

Discussion & Conclusion: Our results suggest that the experience induced by the standardized DMT + harmine formulation demonstrates good psychological safety and tolerability, induces beneficial psychological processes that could possibly support psychotherapy, and should therefore be further investigated in clinical trials with patients.

3.2. Background

Scientific interest in the N,N-dimethyltryptamine (DMT) containing Amazonian psychedelic "ayahuasca" has increased due to the globalization of ayahuasca use (Tupper, 2008) and due to its potential therapeutic benefits (Frecska et al., 2016; Palhano-Fontes et al., 2014). This plant-based brew has been used by Indigenous cultures for centuries for ceremonial and medicinal purposes (Tupper et al., 2015). Ayahuasca contains the vine *Banisteriopsis caapi* and other ingredients such as *Psychotria viridis* or *Diplopterys cabrerana.* The vine contains a variety of β-carbolines, some of which are selective reversible monoamine oxidase inhibitors (MAO-Is; e.g., harmine and harmaline), or serotonin reuptake inhibitors (e.g., tetrahydroharmaline) (Callaway et al., 1996). The MAO-Is prevent the degradation of the N,N-dimethyltryptamine (DMT) contained in the *Psychotria viridis* leaves or other additional plants in the GI system, thereby DMT becomes bioavailable. DMT is a structural analogue of serotonin and has agonistic properties at a variety of serotonin receptors (mainly 5-HT2A, 5-HT2C, 5-HT1A), but also glutamate, dopamine, acetylcholine, sigma-1, and trace amine-associated receptors (Carbonaro & Gatch, 2016; Riba et al., 2001, 2003), similar to other psychedelic substances ("psychedelics") such as psilocin or lysergic acid diethylamide (LSD) (D. E. Nichols, 2016).

In contrast to the rapid onset and heightened experiential intensity associated with intravenous or inhaled administration DMT (Lawrence et al., 2022; Luan et al., 2023; R. J. Strassman et al., 1994; Timmermann et al., 2019), the subjective effects of orally ingested DMT found in Ayahuasca preparations exhibit a gradual onset and dissipation over a period of 4 to 6 hours (Riba et al., 2001, 2003). The ayahuasca plant composition induces subjective psychedelic effects, including alterations in perception of the self and the world, affective and cognitive changes, visionary experiences and bodily sensations (Kjellgren et al., 2009; Riba et al., 2001; Shanon, 2002). This transient introspective state is characterised by increased awareness, introspection, and self-reflection; dream-like visions, recollection of personal memories, and intensified emotions (Riba et al., 2001, 2003; Shanon, 2002), potentially leading to deep psychological and existential insights(Grob et al., 1996).

There are potentially beneficial effects of ayahuasca use for non-clinical populations: From a psychological perspective, enhanced cognitive flexibility, creativity, and imagination are generally found in psychedelic states, with long-term increases in psychological well-being, creative problem-solving abilities and divergent thinking, and trait openness (Kiraga et al., 2021; Kuypers et al., 2016; Perkins et al., 2022). Ayahuasca was also found to elevate levels of mindfulness and self-compassion (Sampedro et al., 2017; Soler et al., 2016). In supporting settings, drug-induced experiences have been found to facilitate enduring trait-level increases in pro-social attitudes and behaviours such as interpersonal closeness, gratefulness, forgiveness, compassion, and purposefulness, existential insights and a sense of self-awareness, thereby supporting psycho-spiritual development and personal growth (R. G. dos Santos et al., 2016; Griffiths et al., 2018).

First neuroimaging studies of ayahuasca highlight activations of cerebral areas associated with conscious experience of emotions (de Araujo et al., 2012; Riba et al., 2006), suggesting

that ayahuasca affects relevant neuronal circuitries for cognitive-emotional integration. The widespread changes in neuronal excitability resulting from 5-HT2AR activation are expected to disrupt maladaptive neurobehavior patterns associated with affective disorders and thereby result in marked effects on mood and cognition (Cameron & Olson, 2018; Ly et al., 2018; Vollenweider & Kometer, 2010). This offers an alternative for treating stress-related affective disorders, especially as currently available antidepressants often lack effectiveness, have a late onset and sometimes severe side effects (Kirsch et al., 2008; Munkholm et al., 2019). Hence, ayahuasca may be particularly well suited for the systemic treatment of complex affective diseases, where conventional reductionist approaches have often been disappointing (Scheidegger, 2021).

Indeed, converging evidence from preclinical and human studies suggest that oral formulations of DMT such as ayahuasca are associated with reductions in anxiety, depressive symptoms, addiction, and PTSD (Domínguez-Clavé et al., 2016; R. G. dos Santos et al., 2016; Frecska et al., 2016; Osório et al., 2015; Palhano-Fontes et al., 2014, 2019; Sarris et al., 2021; van Oorsouw et al., 2022; Zeifman et al., 2019). In small clinical pilot studies, ayahuasca has been shown to alleviate symptoms of depression and anxiety (Osório et al., 2015) and to resolve brain network dynamics associated with the pathophysiology of depression (Palhano-Fontes et al., 2015). Several studies, including one RCT, have highlighted a similar rapid onset and sustained antidepressant effect for up to 21 days after a single ingestion in patients diagnosed with treatment-resistant depression (Palhano-Fontes et al., 2019; Sanches et al., 2016). A recent systematic review of 21 clinical and preclinical studies found that the natural products contained in ayahuasca have consistently shown anxiolytic and antidepressant properties, as well as anti-addictive and neuroprotective effects (R. G. dos Santos et al., 2016).

There are major shortcomings of using psychedelic compounds such as LSD for psychotherapy, for example the long duration of action (~10 hours). Both LSD and psilocybin show rapid tolerance at serotonergic receptors (D. E. Nichols, 2016), which makes them less suited for repeated clinical dosing regimens. Repeated administration of ketamine was shown to sustain antidepressant effects (aan het Rot et al., 2010; Matveychuk et al., 2020), but puts patients at risk due to its toxic and addictive potential (Liu et al., 2018).

Ayahuasca with its overall duration of 2–4 hours (if not repeatedly administered, which is usually the case in ceremonial settings) is more amenable for clinical applications (Riba et al., 2001). Regular ayahuasca use is considerably safe and has no addictive abuse potential (Barbosa et al., 2012; Fábregas et al., 2010). Furthermore, it does not produce pharmacological tolerance even after repeated administration (R. G. dos Santos et al., 2012), which underscores the experimental utility of DMT for the investigation of brain serotonin function and its role in emotional processing and social cognition as well as potential candidate for pharmacological treatments in the context of psychedelic-assisted (psycho)therapy (PAT).

However, there are some challenges in the clinical implementation of ayahuasca in the Western biomedical system. First of all, there are physiological side effects, including nausea and vomiting (Bouso et al., 2022). While vomiting is considered a purification and one of the healing mechanisms of ayahuasca in traditional contexts (Wolff et al., 2019), in a biomedical

clinical setting, vomiting is seen as the body's reaction to the toxins contained in ayahuasca (e.g., harmaline) and is regarded an undesired and adverse side effect. Additionally, ayahuasca brew batches have varying levels and ratios of alkaloids due to different recipes including differences in plant combinations and ratios, variations in cooking duration and method, and naturally varying alkaloid levels in the plants used (Kaasik et al., 2021; Rodríguez et al., 2022). Furthermore, bioavailability varies greatly between and within individuals due to first pass effects associated with the oral ingestion and absorption via the GI tract. Consequently, targeted medication in the sense of standardizing pharmaceutical treatment is made difficult.

Additional significant cultural, sociological, and environmental factors make the use of traditional ayahuasca in the Western medical system questionable. In Indigenous tribes, ayahuasca refers to a healing system and a worldview that cannot be directly transposed to our cultural context (Anderson, 2012), also due to the inherent risk of cultural appropriation. The overuse of plants contained in ayahuasca is another consequence of ayahuasca tourism and plant export, that come along with the globalization of ayahuasca.

The latter cultural, social, and ecological reasons present us with an almost insoluble dilemma: While there is a pressing need to address the global mental health crisis and there is a potential in these substances for developing treatment options for patients in the Western world as well (Ona & Bouso, 2019), there is also a simultaneous aspiration to act sustainably and respect cultural traditions. Finding a solution to this dilemma demands navigating a multitude of ethical, cultural, and environmental considerations.

For the above reasons, we developed an ayahuasca-analogue formulation containing two of the main active compounds of ayahuasca – DMT and harmine – in order to obtain a well-tolerated, rather controllable preparation, with the aim of exploring its therapeutic potential, and ultimately to provide a treatment option for patients that could benefit from psychedelic-induced transformative experiences. We conducted a study with healthy participants and investigated acute, post-acute, and persisting effects of this DMT + harmine combination, with a focus on potentially therapy-relevant mechanisms including psychological safety and tolerability assessments. We hypothesized that the acute experience would be characterised by psychedelic phenomenology, and elicit psychological insights, emotional breakthrough, and only low levels of challenging experiences. Moreover, we expected no increases in psychopathological symptoms following the experience, but primarily positive persisting effects including respective trait changes, and an attribution of significance to the experience. We further expected the persisting effects to be associated with the acute experience.

3.3. Methods

3.3.1. Participants and Permissions

Thirty-seven healthy male participants were recruited, six dropped out (four before the first intervention day, two after the first intervention day). 31 participants (age 25.39 ± 4.21 years) completed all 3 intervention days. Following criteria were required for inclusion: (i) male sex

in order to avoid the potential impact of menstrual cycle on blood chemistry, (ii) age 20-40, (iii) BMI 18.5-30, (iv) no current or previous history of somatic, neurological, or psychiatric disorder, (v) no family history of psychosis, bipolar, or other severe psychiatric disorders, (vi) no acute or chronic medication intake that could interact with the study drug, (vii) no current or regular drug intake. Participants were required to abstain from caffeine on test days, as well as alcohol the day before; they had to refrain from using psychoactive substances or other medications for two weeks prior to the test days and throughout the study period. An extensive sample description can be found in the supplementary material (detailed demographics, motivation to participate, previous drug experience; Tables 3–6). Participants received monetary compensation (320.- CHF total, or 60.- per completed intervention day).

The study was approved by the Cantonal Ethics Committee of the Canton of Zürich (Basec-Nr. 2018-01385) and Swiss Federal Office of Public Health (BAG-Nr. (AB)-8/5-BetmG-2019/008014) All participants provided written informed consent according to the declaration of Helsinki.

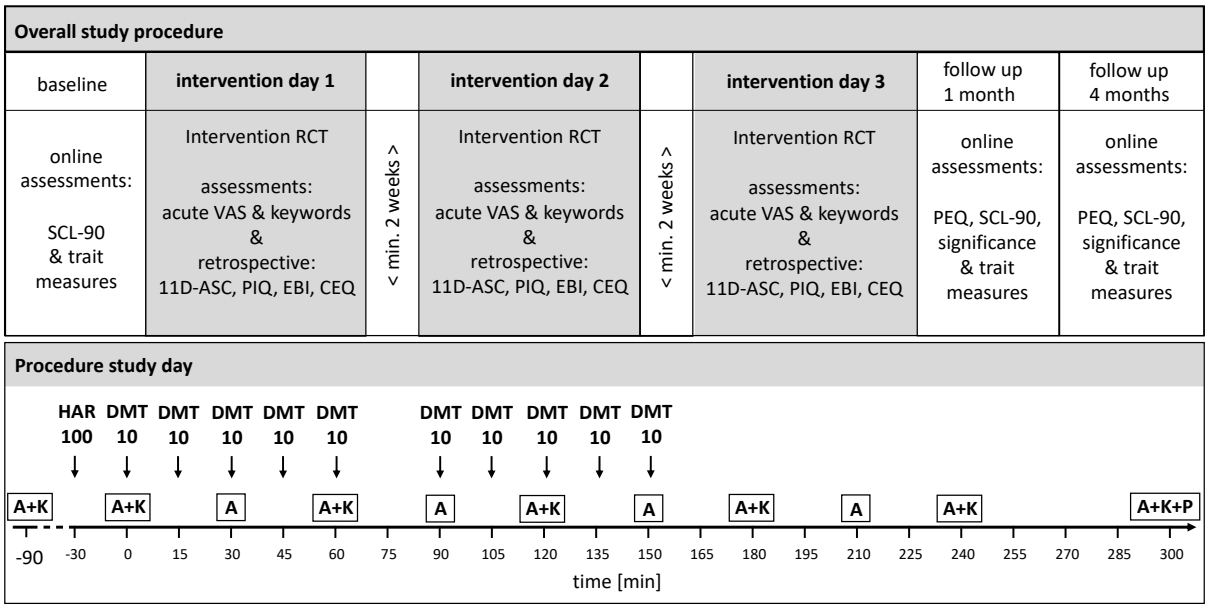
3.3.2. Study Design and Procedure

The study had a randomized, double blind, placebo-controlled crossover design with three conditions performed at three different intervention days with a washout phase of at least two weeks in between: 1) DMT + harmine ("ayahuasca analogue"), 2) placebo + harmine (for better readability, we will write harmine only condition), and 3) placebo + placebo (for better readability, we will write placebo condition). After informed consent, participants underwent a medical and psychiatric screening. Before the first intervention day, they filled out a baseline online assessment consisting of several questionnaires. At the intervention day, participants arrived at 10am or 11am. If possible, two participants completed the intervention day on the same day in two separate, but identical rooms, we therefore had two starting times, specified for each room, to enable the procedure for parallel testing, and to standardize timing and procedure. Participants filled out questionnaires regarding their current state. Measurement devices for further data collection (electroencephalography, electrocardiography, and venflon for blood sampling) were installed (results are presented in separate publications, e.g., Aicher et al.; Aicher & Wicki et al.; Mueller & Aicher et al.; Suay et al.; manuscripts submitted or in preparation). Dosing of the study drug was started at 11:30 (12:30 respectively). Throughout the day, acute experience sampling (acute items and keywords), blood withdrawal, and different behaviour tasks (results presented in separate publications) were performed. Around five hours (t300) after initial DMT (or placebo) administration (afterglow phase), retrospective questionnaires regarding the subjective drug-induced experience were filled out on a tablet. The procedure of the intervention day was identical for all three drug conditions. At one month and four months after the last intervention day, participants filled out online follow-up questionnaires.

An overview of the general study procedure including study visits and schematic procedure of the intervention day is shown in Figure 1.

Figure 1

Overview of study design and visits and intervention days procedure



Note. HAR = harmine (or placebo respectively); DMT = N,N-dimethyltryptamine (or placebo respectively). Drug conditions were randomized, double-blind, crossover: 1) Harmine 100mg buccal + DMT 100mg (10* 10 mg) intranasal; 2) Harmine 100mg buccal + Placebo intranasal; 3) Placebo buccal + Placebo intranasal. Intranasal: Repeated intermittent dosing. Washout-phase of at least 2 weeks between intervention days. A = acute assessment; K = keywords experience sampling; P = post-acute assessment. A & K experience sampling was assessed with VAS (visual analogue scale) items. SCL-90: Symptom check list; 11D-ASC: 11 dimensions altered states of consciousness rating scale; PIQ = psychological insights questionnaire; EBI = emotional breakthrough inventory; CEQ = challenging experience questionnaire; PEQ = persisting effects questionnaire. Only assessments relevant for this publication are shown.

3.3.3. Setting

The study was conducted during daytime in the Human Sleep Laboratories of the University of Zurich. The soundproof and temperature-controlled rooms were set up in a comfortable living room atmosphere and equipped with dimmable colourful lights and a sound system. Technical monitoring and measuring devices like blood pressure monitor, blood withdrawal materials, and EEG were installed. Throughout all study days, a standardized playlist (https://tinyurl.com/2p83pkze) containing mostly instrumental background music was played to provide a feeling of comfort and relaxation (music was switched off during tasks), while participants sat in a comfortable position on a mattress leaning against a sturdy pillow. A medically and psychologically trained experimenter was present in the room all the time to supervise the participants.

3.3.4. Study Drug and Dose Regimen

We applied parenteral administration routes and delivery mechanisms with purified forms of DMT (extracted from the plant *Mimosa hostilis*), and synthesized harmine. The combination DMT plus harmine is commonly called “ayahuasca analogue” or “pharmahuasca”. To bypass the GI tract and first pass effect in order to increase absorption and have better controllable absorption, harmine was administered in orodispersible tablets (ODT) fur buccal delivery, whereas DMT was formulated as intranasal spray solution to enable an incremental dosing. Moreover, this administration route ameliorates potentially undesired side effects of oral administration like nausea and vomiting. Detailed information on the study drug, administration, and PK-PD results can be found in Mueller & Aicher et al. (in prep.) and Dornbierer et al. (in prep.). Thirty minutes after administration of harmine HCl (100 mg) or placebo, respectively, the repeated intermittent dosing of DMT or placebo was initiated with a total of 100 mg DMT in intervals of 15 minutes (10 mg each timepoint) over a period of 150 minutes. At each dosing timepoint, participants had the possibility to discontinue DMT administration or chose only 5 mg and potentially continue at the next time point. The option to skip a dosing was chosen only twice over the full study, the option of taking only 5mg was never used. Administration timepoints are shown in Figure 1.

3.3.5. Outcome Measures

The measures included in this publication are widely used, validated psychometric instruments, or recently developed questionnaires specifically designed for studies investigating psychedelic substances (de Deus Pontual et al., 2023). For the acute experience sampling, we used an approach we developed in our dose-finding pilot study (Dornbierer et al.; Aicher et al.; in prep.). For questionnaires that were not available in English, we applied the state-of-the-art translation–back translation approach with two independent translators for each step to obtain a German version.

Online Baseline Measures. The Symptom Check-List-90-Revised (SCL-90-R; Derogatis et al., 1976) is a multidimensional psychological screening instrument where subjects rate 90 symptoms of distress and psychopathology on a 5-point Likert-scale with 0=“not at all” and 4=“extremely”. The subscales are somatization, obsessive compulsion, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism.

Intervention Days Experience Sampling. The overall acute psychedelic state was assessed at regular intervals throughout the day with single word & full sentence acute experience sampling items. The items were developed during a dose-finding pilot study (Dornbierer et al., in prep.) to capture the broader phenomenology of the experience during the dynamic progression over time. Participants rated the acute effect of the drug regarding experience of *any substance-induced effects* (yes/no), *progression since last assessment timepoint* (increase, same, decrease), *intensity, liking, disliking, frightening, arousing, relaxing*. Furthermore, they rated four sentences: “I am currently experiencing visual effects (patterns, colours, shapes) through the substance with my eyes open and closed.” (*elementary imagery*), “I currently experience through the substance sceneries, landscapes, stories in front

of my inner eye / in my imagination." (*complex imagery*), "I feel like I'm uncomfortably losing control." (*loss of control*), "I feel like I can comfortably let go / relinquish control." (*letting go*). Additionally, participants rated how easy/clear or how difficult/unclear it was for them to answer these single-word and sentence items (*ambiguity*), which referred to the experience of sometimes contradicting phenomenal experiences and a difficulty to define a clear value for each item. These items (single words and sentences) were rated on a 0–100 VAS scale (if not otherwise specified) on a tablet with touchscreen. Assessments took place at baseline, at t0 (right before the first DMT/placebo administration, which corresponds to 30 minutes after harmine/placebo administration), and then every 30 minutes until t240 (240 minutes after initial DMT/placebo administration), and a last time at t300 (300 minutes after initial DMT/placebo administration, corresponding to afterglow phase).

Complementary, at baseline, at t0, and then every 60 minutes until t300, participants rated 20 keywords (single word items) referring to the phenomenology of the experience on a 0–100 VAS, ten for psychedelic (*hallucinating, visuals, scary, patterns, multidimensional, dreamlike, colourful, loss of reality, powerless, oppressive, adventurous, sensory overload*) and ten for empathogenic (*compassionate, open, heart-warming, pleasurable, unity, loving, tolerant, stable, accepting, connected, harmonious*) phenomenological aspects, to get a better understanding of the phenomenological phase of the experience. The development of this psychedelic / empathogenic keywords experience sampling tool will be described in a separate publication (Aicher et al., in prep.). Additionally, at these timepoints, perceived body boundaries were measured with the Perceived Body Boundaries Scale (PBBS; Dambrun, 2016).

Intervention Days Post-acute Retrospective Measures. Around t300, participants started filling out retrospective questionnaires regarding the phenomenology of their experience: 11D-ASC, PIQ, EBI, CEQ.

Participants' subjective state of consciousness was assessed using the Altered States of Consciousness questionnaire (5D-ASC; Dittrich, 1998). The 5D-ASC is a well-validated self-rating VAS developed to quantify the subjective psychological effects of psilocybin. It has been widely used to assess the structure and phenomenology of altered states of consciousness induced by several psychedelic substances (e.g., Carhart-Harris et al., 2016; Griffiths et al., 2018; Kometer et al., 2015; Kraehenmann et al., 2015, 2017). However, Studerus and colleagues showed 11 subscales revealed by a confirmatory factor analysis (Studerus et al., 2010): Experience of unity, spiritual experience, blissful state, insightfulness, changed meaning of percepts, disembodiment, impaired control and cognition, anxiety, elementary imagery, complex imagery, audio-visual synaesthesia. We show results for the 11-dimensions solution.

The Psychological Insights Questionnaire (PIQ; Davis et al., 2021) assesses the degree to which acute insights were experienced. It consists of two subscales: Avoidance and maladaptive patterns insights (AMP), and goals and adaptive patterns insights (GAP), and a global score. Participants rated each of the 20 items on a six-point scale (with 0=no/not at all, 1=so slight cannot decide, 2=slight, 3=moderate, 4=strong / equivalent in degree to any other strong experience, 5=extreme / more than any other time in my life).

The Emotional Breakthrough Inventory (EBI; Roseman et al., 2019) is a reliable and validated scale to assess the degree to which a psychedelic experience was characterised by an emotional breakthrough. Participants answered the six items on a 0–100 VAS (with 0="not at all", and 100="very much").

The challenging experience questionnaire (CEQ; Barrett et al., 2016) was developed based on user's experiences with psilocybin (internet survey) and has been shown to have good internal consistency and external reliability. It consists of 26-items forming seven subscales: Fear, grief, physical distress, insanity, isolation, death, paranoia; and a global score. Participants rated the items regarding the challenging experiences on a 0–5 Likert scale (with 0="None, not at all" and 5="Extreme, more than ever before in my life"). Scores for each subscale were calculated as the mean of the items of the respective subscale, and results are presented in percentages.

Online Follow-up 1 Month and 4 Months. Approximately one and four months following the last study intervention day, participants filled out a set of online questionnaires. These included the SCL-90-R (for baseline-follow-up comparison; described above in the *online baseline measures* subchapter), and PEQ and significance ratings.

The Persisting Effects Questionnaire (PEQ; Griffiths et al., 2006) is used to measure long-lasting positive and negative effects (potential changes) subjectively attributed to the psychedelic experience. Items are rated using a 6-point Likert scale from 0 (=none / not at all) to 5 (=extreme / more than any other time in my life and more than a rating of 4). The subscales and the number of items associated with each subscale are positive attitudes about life and/or self (17 items), negative attitudes about life and/or self (17 items), positive mood changes (four items), negative mood changes (four items), altruistic/positive social effects (eight items), antisocial/negative social effects (eight items), positive behaviour changes (one item), and negative behaviour changes (one item). Two additional categories were comprised of one item each: positive behaviour change and negative behaviour change. Results are calculated as percentage of the maximum possible score.

Additionally, we assessed Griffiths' and colleagues three questions regarding the subjective significance of the experience: (1) "How personally meaningful was the experience?" (1=no more than routine, everyday experiences; 2=similar to meaningful experiences that occur on average once or more a week; 3=similar to meaningful experiences that occur on average once a month; 4=similar to meaningful experiences that occur on average once a year; 5=similar to meaningful experiences that occur on average once every 5 years; 6=among the 10 most meaningful experiences of my life; 7=among the 5 most meaningful experiences of my life; and 8=the single most meaningful experience of my life). (2) "Indicate the degree to which the experience was spiritually significant to you." (1=not at all, 2=slightly, 3=moderately, 4=very much, 5=among the 5 most spiritually significant experiences of my life, and 6=the single most spiritually significant experience of my life). (3) "Do you believe that the experience and your contemplation of that experience have led to change in your current sense of personal well-being or life satisfaction?" (7=increased very much, 6=increased moderately, 5=increased slightly, 4=no change, 3=decreased slightly, 2=decreased moderately, and 1=decreased very much).

According to a median split of the maximum subjective intensity ratings in the DMT + harmine conditions, participants were grouped into low vs. high sensitivity to the study drug, which was used to investigate potential intensity-response effects on significance at follow up and trait changes from baseline to follow-up.

Trait Measures. At baseline and at both follow up (one and four moths) timepoints, several trait measures were assessed: acceptance and action (AAQ2; Bond et al., 2011), cognitive flexibility (CFI; Dennis & Vander Wal, 2010), nature relatedness (NR6; Nisbet & Zelenski, 2013), World Health Organization – Five Well-being Index (WHO-5; Topp et al., 2015), openness and neuroticism (Big 5, measured with 10 items each from the International Personality Item Pool IPIP). We hypothesized that all trait measures would increase except for neuroticism, which was expected to decrease.

Qualitative Diary Reports. In order to complement the quantitative results and increase the tangibility, comprehensiveness, and the contextual understanding, we included some illustrative and representative quotes from the diary entries of our participants in the discussion of results.

Statistical Analyses. The data were analysed and visualised with R Studio version 2021.09.2+382 (R Core Team, 2021). Acute effect over time were visualised descriptively. Based on check of assumptions for ANOVAs (normality check, Shapiro wilk test), mixed model ANOVAs (Type 3 tests, Satterthwaite's method (S-method); calculated with the R-package afex, mixed function) and post-hoc estimated marginal means (emmeans R-package, degrees-of-freedom method: asymptotic; p-value adjustment for contrasts calculated with estimated marginal means: Tukey method for comparing a family of 3 estimates), or Friedman tests with post-hoc paired Wilcoxon tests (Multiple comparison contrasts with Benjamini-Hochberg correction) were performed to investigate drug effects and measurement timepoint (baseline, follow up) effects. For trait measures also interaction effects of sensitivity (low vs. high) * timepoint were calculated. Pearson or spearman correlations were performed (as appropriate according to Shapiro wilk tests) to analyse associations between acute and persisting effects.

3.4. Results

3.4.1. Acute Experience Sampling

The subjective experience induced by DMT + harmine could be clearly distinguished from the harmine only and the placebo condition, as assessed with acute experience sampling items over time. Figure 2 shows the dynamic evolution over time regarding the assessed experiential dimensions.

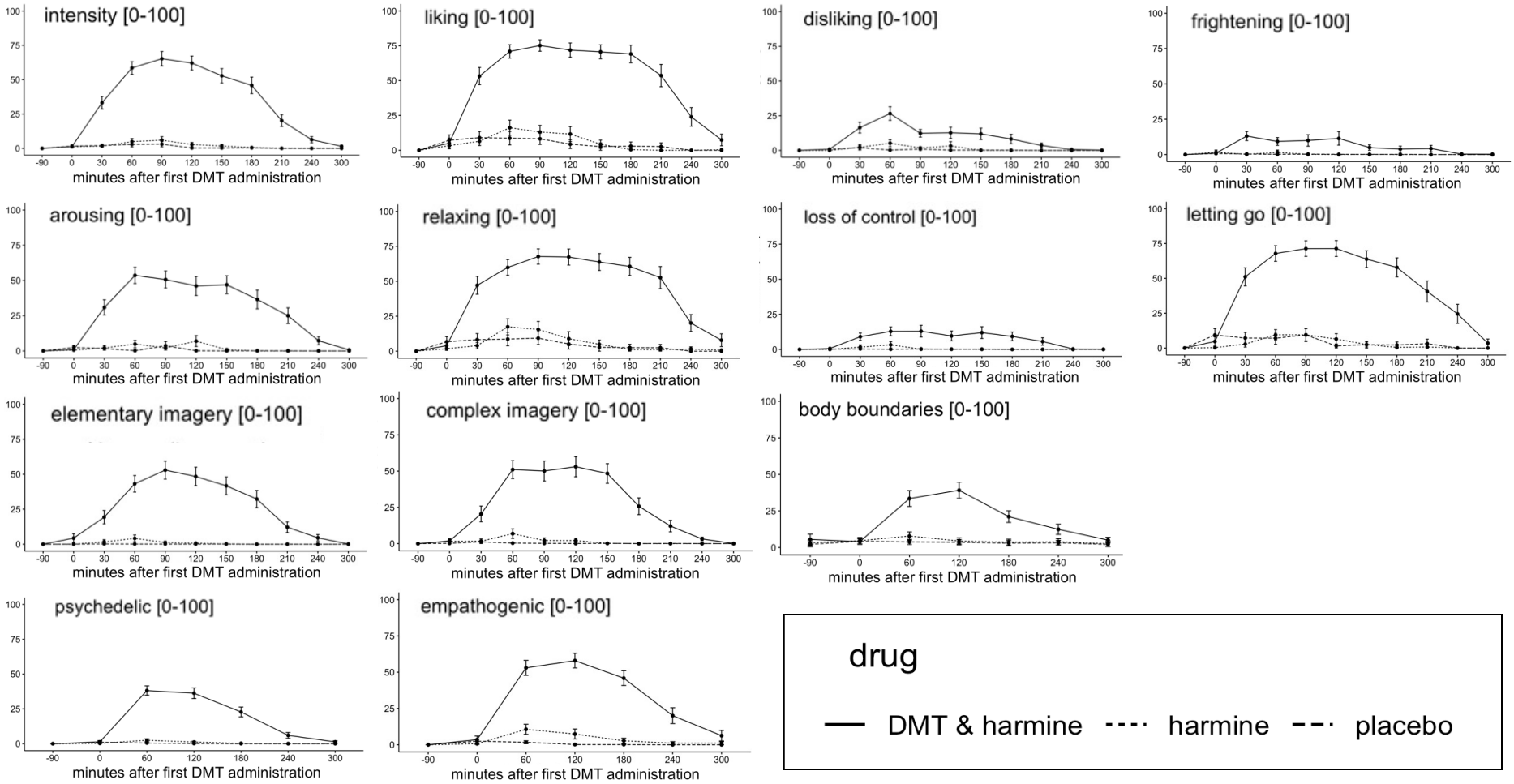
DMT + harmine Condition. In the DMT + harmine condition, participants' subjective peak intensity was on average at t90 after the initial DMT administration. An extensive overview of the PK-PD can be found Mueller & Aicher et and colleagues (in prep.).

Overall, stronger positive subjective effects (liking, relaxing, letting go) compared to weaker negative subjective effects (disliking, frightening, loss of control) were reported. The small values of disliking peaked around t60. Additionally, the subjective experience was experienced as arousing. Participants reported elementary (patterns, colours, shapes) and complex (landscapes, sceneries, visual memories) imagery. While the overall intensity decreased on average at t90, the positive phenomenal aspects were experienced with a prolonged plateau. Descriptively there were still afterglow residuals of some positive experiential aspects (liking, relaxing, empathogenic), however at t300 differences between DMT + harmine, harmine only, and placebo were not significant anymore.

While the psychedelic effects peaked on average at t60 and slowly decreased afterwards (stronger decrease after t120, almost back to baseline at t240), the empathogenic effects were generally stronger, increased similarly to the psychedelic effects, remained at a plateau with a peak at t120 and were still reported at t300 (positive afterglow effect).

Harmine Only Condition. Despite the harmine dose of 100mg, the subjective levels reported in the harmine only condition were not significantly different to the placebo-condition levels at any time, with a trend effect of harmine on empathogenic phenomenology at t60 (estimate 8.94, p = .062) being the strongest difference between harmine and placebo.

Figure 2 *Dynamic experience sampling of the acute subjective drug effects over time*



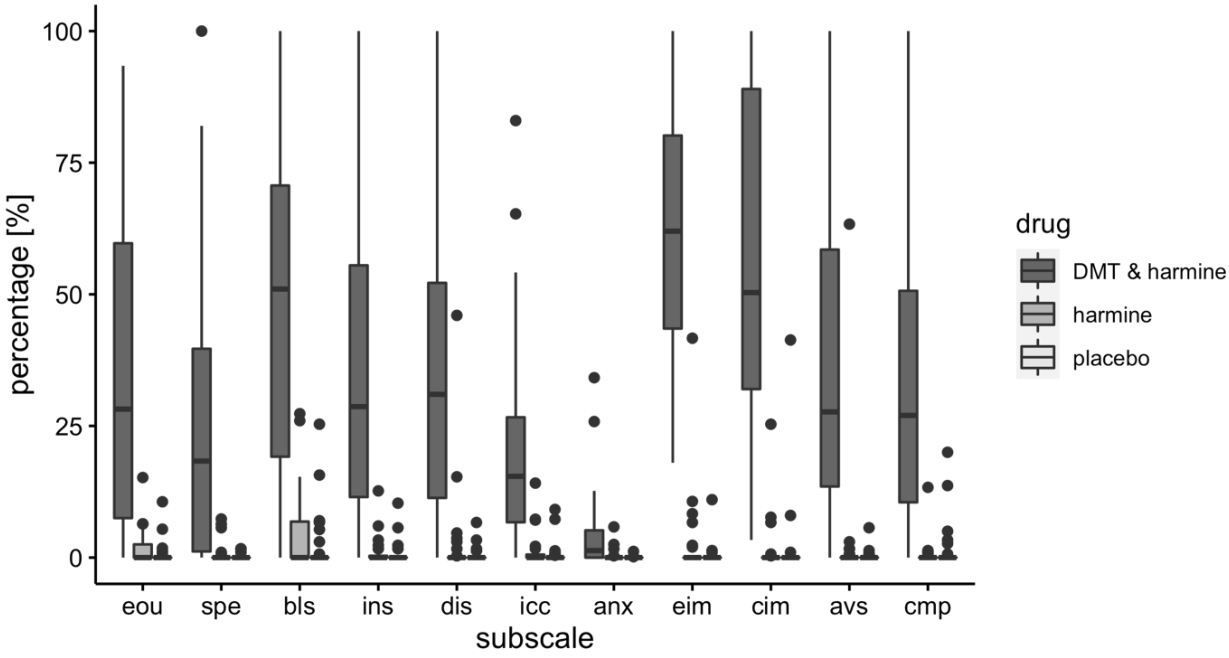
Note. Experience sampling: Dynamic ratings of the acute subjective drug effects over time for the 3 conditions DMT + harmine, harmine only, placebo. Single word acute items (intensity, liking, disliking, frightening, arousing, relaxing), full sentence acute items (loss of control, letting go, elementary imagery, complex imagery), and ambiguity (how easy/difficult was it to answer the questions) were assessed at baseline (t-90), at t0 (right before initial DMT administration, 30 minutes after harmine administration), and every 30 minutes until t240, and at t300. Psychedelic and empathogenic keywords (ten single words) and body boundaries were assessed at baseline (t-90), t0, and every 60 minutes until t300. Mean values and standard errors (SEs) are shown.

3.4.2. Post-acute Retrospective Description of the Acute Subjective Drug Effects

All subscales of the 11D-ASC were significantly increased by DMT + harmine compared to harmine only and compared to placebo. No differences were reported between harmine only and placebo. In the DMT + harmine condition, participants experienced significantly more psychological insights (global score PIQ and both subscales AMP and GAP) compared to harmine only and compared to placebo. No differences were reported between harmine only and placebo. Participants reported significantly higher levels of EBI in the DMT + harmine condition compared to harmine only and compared to placebo, with no difference between harmine only and placebo. The DMT + harmine experience was perceived as generally more challenging (global score CEQ) than the harmine only and the placebo experience (with no difference between harmine only and placebo), specifically regarding fear, physical distress, and insanity. Results are reported in Table 1 and visualised in Figure 3 (ASC) and Figure 4 (PIQ, EBI, CEQ).

Figure 3

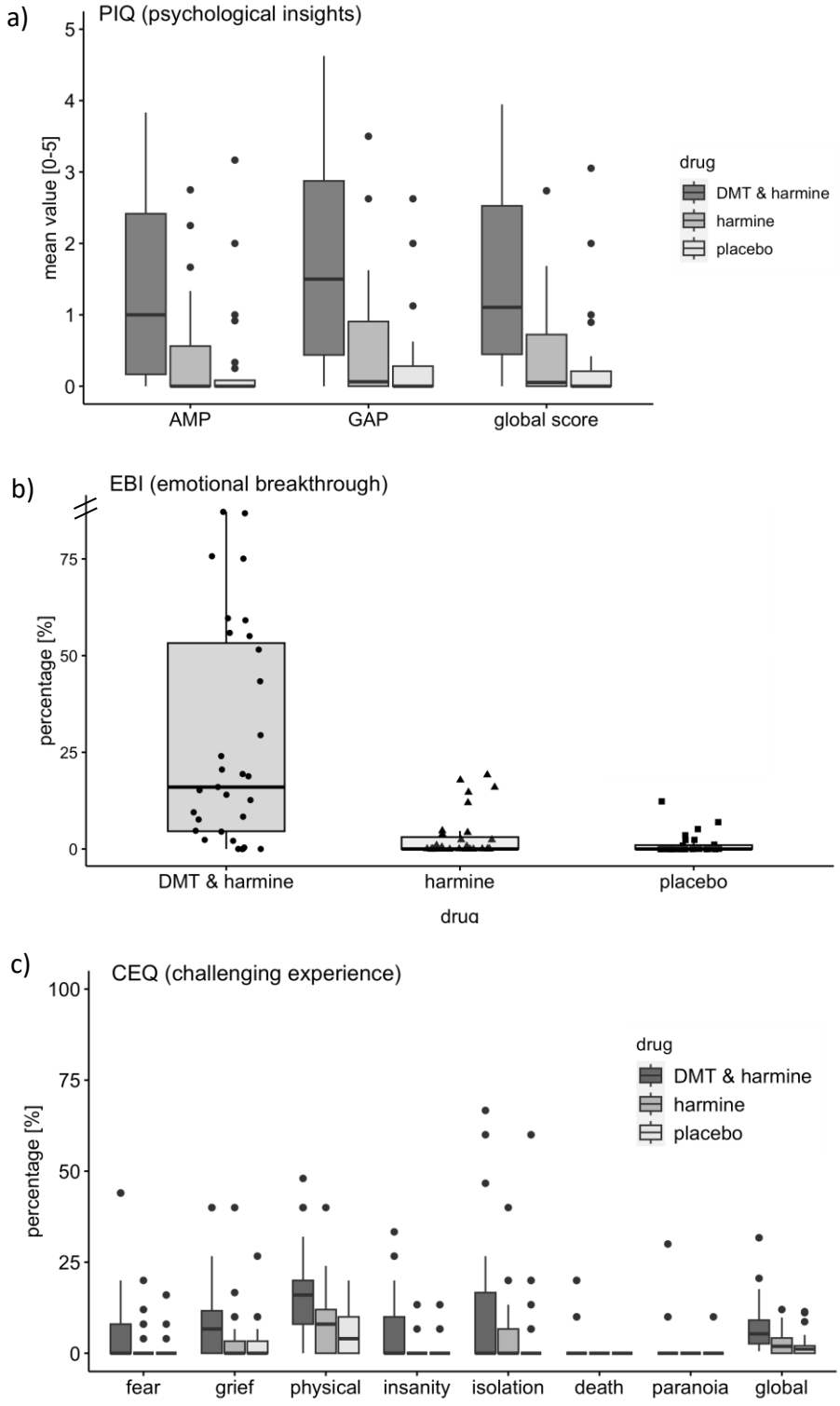
Retrospective 11-Dimensions Altered State of Consciousness rating scale



Note. 11-Dimensions Altered States of Consciousness rating scale (11D-ASC) for all three drug conditions (DMT + harmine, harmine only, placebo) with boxplots for all subscales: experience of unity (eou), spiritual experience (spe), blissful state (bls), insightfulness (ins), disembodiment (dis), impaired cognition and control (icc), anxiety (anx), elementary imagery (eim), complex imagery (cim), audio-visual synaesthesia (avs), changed meaning of percepts (cmp). Spider plot visualizations of the 11D-ASC and of the 5-dimension solution of the ASC (5D-ASC) for comparability with other trials using the same scale can be found in the supplementary material Figure 1.

Figure 4

Retrospective assessment of the subjective experience



Note. Retrospective assessment of the subjective experience induced by the three drug conditions DMT + harmine, harmine, placebo. PIQ = psychological insights (AMP: avoidance and maladaptive patterns insights, GAP: goals and adaptive patterns insights, global score); EBI = emotional breakthrough; CEQ =challenging experience (fear, grief, physical distress, insanity, isolation, death, paranoia, global score).

3.4.3. Persisting Effects

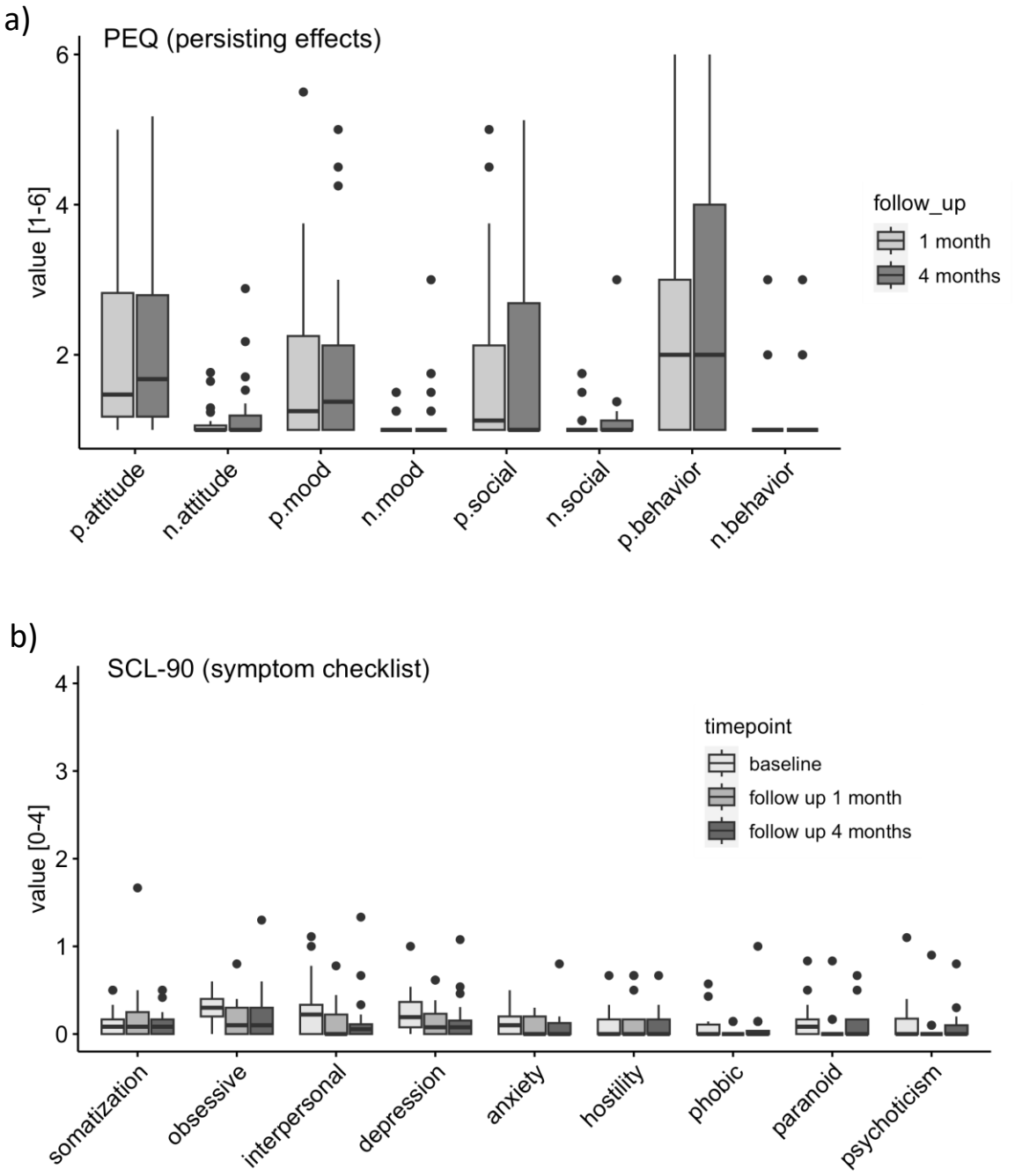
Participants reported significantly stronger positive compared to negative persisting effects for all four domains (attitude towards life, mood, social effects, behaviour change) of the PEQ at the follow up timepoints one and four months after the last study intervention day. Results are reported in Table 1 and visualised in Figure 5.

There were no increases on the SCL-90 from baseline to follow up. Overall (for the SCL-90 global score; obsessive compulsion and paranoid ideation subscales; and interpersonal, depression, and psychoticism subscales, but not after correction for multiple comparison), symptoms significantly decreased from baseline to follow up one month and stayed at the lower level (no differences between follow up one month to four months). Results are reported in Table 1 and visualised in Figure 5.

Four participants, all of which belonged to the high sensitivity group, reported that the experience was amongst the 5 most significant in their life (rating 7, of maximum 8), while it was no more than an everyday experience (rating 1) for one person (low sensitivity group), and most participants (10) indicated it was similarly meaningful as an experience happening approximately once a year (rating 4). For 7 participants (low sensitivity group), the experience was not spiritually significant at all, while it was the most spiritually significant experience of their life for 2 participants (high sensitivity group). While most participants (14) reported no change in their current sense of personal well-being or life satisfaction, 2 participants (high sensitivity group) reported very strongly increased personal well-being and life satisfaction (rating 7 of maximum 7), and no participants reported decreases in well-being or life satisfaction. Overall, the high sensitivity group reported higher levels of significance. Results are visualised in Figure 6.

Figure 5

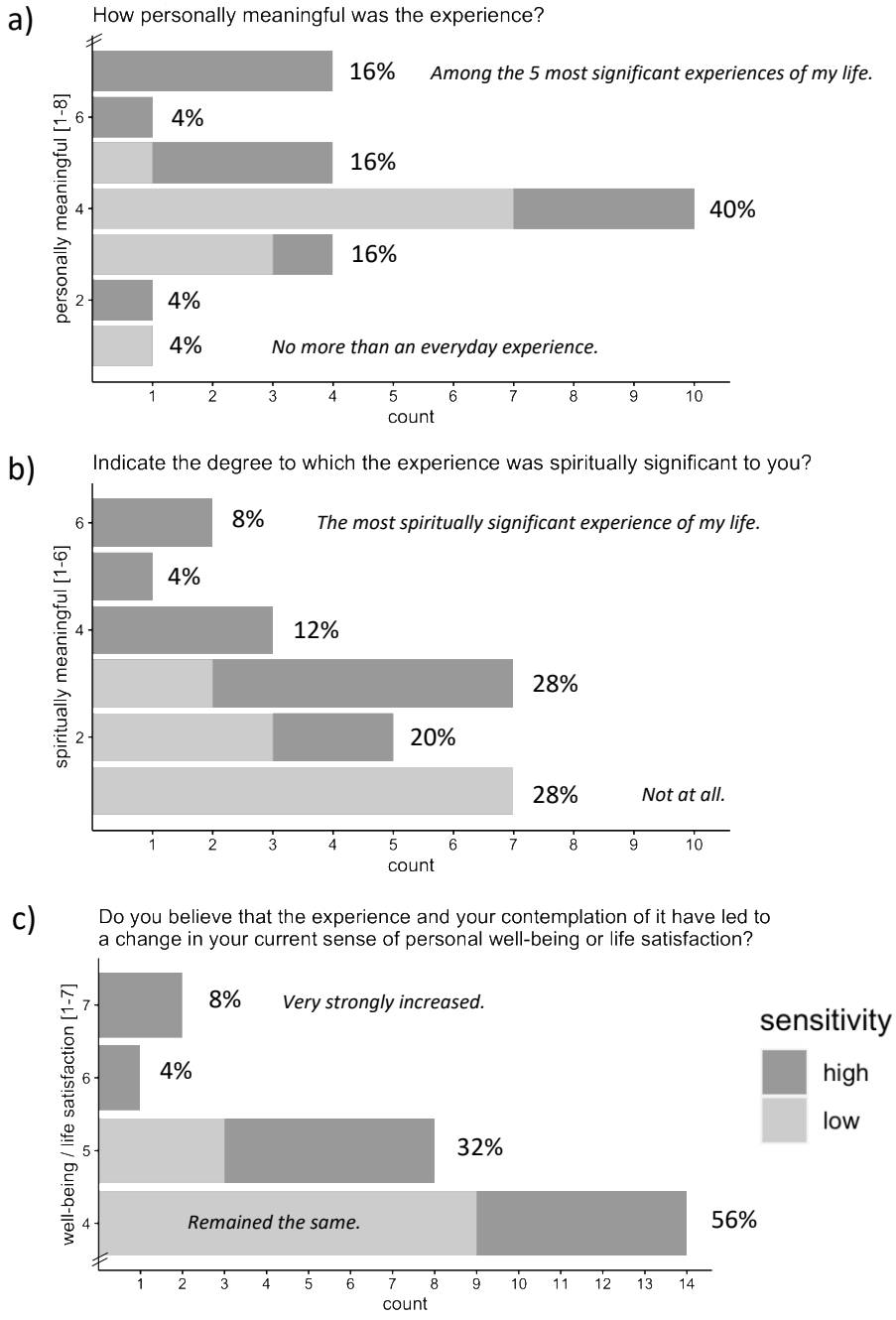
Persisting effects and symptoms



Note. PEQ (persisting effects) assessed at 1 month and 4 months follow up: n. = negative; p. = positive. SCL-90-R (symptom checklist) assessed at baseline, 1 month, and 4 months follow up: somatization, obsessive compulsion, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, psychoticism.

Figure 6

Significance of the experience rated at 1 month follow up



Note. N=25. Attribution of subjective significance of the experience at 1 month follow up: Personal meaning (a), spiritual significance (b), change in sense of personal well-being and life satisfaction (c), shown in number and percentage of participants. High vs low sensitivity group (median split according to maximum subjective intensity ratings) are marked in grey tones, participants of the high sensitivity group generally reporting higher significance. Significance ratings at 4 months follow up can be found in the supplementary material Figure 2.

Table 1a

Effects of the drug conditions on subjective experience and persisting effects

Subjective experience (retrospective assessment) by drug condition											
		drug condition main effect			contrasts						
					DMT+HAR – HAR		DMT+HAR – PLA		HAR – PLA		
Scale	subscale	*χ2*	*Kendall's W*	*p*	*r*	*p adj.*	*r*	*p adj.*	*r*	*p adj.*	
11D-ASC	global score	50.4	0.81	<.001	0.84	<.001	0.86	<.001	0.12	.126	
	experience of unity	50.7	0.82	<.001	0.74	<.001	0.81	<.001	0.24	.084	
	spiritual experience	40.6	0.65	<.001	0.66	<.001	0.71	<.001	0.10	.400	
	blissful state	45.1	0.73	<.001	0.72	<.001	0.78	<.001	0.16	.096	
	insightfulness	45.7	0.74	<.001	0.74	<.001	0.77	<.001	0.15	.506	
	disembodiment	41.2	0.67	<.001	0.7	<.001	0.76	<.001	0.1	.346	
	impaired cognition and control	43.0	0.69	<.001	0.72	<.001	0.78	<.001	0.18	.293	
	anxiety	33.3	0.54	<.001	0.51	<.001	0.59	<.001	0.11	.208	
	elementary imagery	57.4	0.93	<.001	0.88	<.001	0.90	<.001	0.15	.183	
	complex imagery	53.5	0.86	<.001	0.88	<.001	0.88	<.001	0.08	.944	
	audio visual synaesthesia	46.7	0.75	<.001	0.75	<.001	0.80	<.001	0.1	.127	
	changed meaning of percepts	50.1	0.81	<.001	0.8	<.001	0.76	<.001	0.10	.284	
EBI	emotional breakthrough	39.50	0.64	<.001	0.58	<.001	0.66	<.001	0.12	.433	
CEQ	global score	23.3	0.38	<.001	0.43	.001	0.56	.001	0.15	.170	
	fear	11.8	0.19	.003	0.26	.047	0.34	.034	0.1	.457	
	grief	9.2	0.15	.01	0.28	.054	0.24	.054	0.07	.766	
	physical distress	19.8	0.32	<.001	0.37	.006	0.53	<.001	0.17	.051	
	insanity	10.7	0.17	.005	0.39	.020	0.35	.020	0.06	.89	
	isolation	1.2	0.02	.545	0.07	.552	0.17	.426	0.13	.663	
	death	8.0	0.13	.018	0.26	.095	0.26	.095	NA	1	
	paranoia	4.7	0.08	.097	0.22	.522	0.13	.556	0.13	1	
			F	*p*	*EMM*	*p. adj.*	*EMM*	*p. adj.*	*EMM*	*p. adj.*	
PIQ	global score		28.51	<.001	1.12	<.001	1.28	<.001	0.16	.687	
	AMP		22.49	<.001	0.98	<.001	1.09	<.001	0.11	.816	
	GAP		32.59	<.001	1.26	<.001	1.48	<.001	0.22	.506	
Persisting effects											
					positive vs negative (both timepoints)		positive vs negative follow up 1 m		positive vs negative follow up 4 m		
Scale	subscale				*r*	*p*	*r*	*p*	*r*	*p*	
PEQ	attitude				0.83	<.001	0.91	<.001	0.79	<.001	
	mood				0.57	<.001	0.57	.004	0.05	.003	
	altruistic / social behaviour				0.46	.001	0.57	.004	0.39	.051	
					0.78	<.001	0.77	<.001	0.83	<.001	

Table 1b

Development of psychopathology symptoms measured with the Symptom Checklist (SCL-90) from baseline to follow up

Scale	subscale	timepoint main effect		contrasts					
				baseline – follow up 1 m		baseline – follow up 4 m		follow up 1 m – 4 m	
		χ2	*p*	*z*	*p adj.*	*z*	*p adj.*	*z*	*p adj.*
SCL	global score	27.32	<.001	5.05	<.001	3.55	.001	-1.58	.115
	somatization	0.64	.727	-0.18	.857	-0.77	1	-0.56	.867
	obsessive compulsion	11.88	.003	3.08	.006	2.79	.010	-0.37	.710
	interpersonal sensitivity	5.93	.052	2.17	.091	2.00	.068	-0.22	.824
	depression	5.85	.054	2.14	.098	2.00	.068	-0.19	.847
	anxiety	6.15	.046	1.89	.088	2.30	.064	0.34	.735
	hostility	1.01	.602	0.51	.608	-0.53	.900	-1.01	.943
	phobic anxiety	1.14	.564	1.02	.923	0.19	.857	-0.82	.618
	paranoid ideation	6.84	.033	2.56	.031	1.65	.148	-0.95	.344
	psychoticism	5.40	.067	2.32	.062	0.94	.349	-1.39	.249

Note (Table 1a and 1b). N=31. DMT+HAR = DMT + harmine; HAR = harmine only; PLA = placebo. 11D-ASC = 11 dimensions of altered states of consciousness; EBI = emotional breakthrough inventory; CEQ = challenging experience questionnaire; PIQ = psychological insights questionnaire (AMP = avoidance and maladaptive patterns; GAP = goal and adaptive patterns); PEQ = persisting effects questionnaire. Effect sizes: Kendall's W (Friedman's test) and r (Wilcoxon test). ASC, EBI, CEQ: Friedman tests and Wilcoxon test. Multiple comparison contrasts with Benjamini-Hochberg correction. PIQ: Mixed model Mixed Model Anova Table (Type 3 tests, S-method) and estimated marginal means (EMMs; degrees-of-freedom method: asymptotic. P value adjustment: tukey method for comparing a family of 3 estimates). PEQ: Wilcoxon rank sum test with continuity correction. 1m = 1 month, 4m = 4 months. SCL-90: Kruskal-Wallis test and Dunn test for multiple comparison of groups. Contrasts are shown between the drug conditions for the experiential variables, and between the assessment timepoints for the baseline–follow up changes (SQL-90). Baseline–follow up changes in

psychopathology (SCL-90) and persisting effects concern the full study participation (all drug conditions). χ2 is equivalent to Friedman's *Q*.

3.4.4. Trait Measure Changes from Baseline to Follow Up

We did not find increases from baseline to follow up 1 month and 4 months for the trait measures acceptance and action (AAQ2), cognitive flexibility (CFI), nature relatedness (NR6), and well-being (WHO-5), nor openness (IPIP), and no decreases in neuroticism (IPIP), for the full sample nor for the two subgroups of high vs. low sensitivity, nor for the drug-naïve subsample.

3.4.5. Correlations

We found correlations between most psychometric retrospective measures of the acute experience and persisting effects. However, CEQ did not correlate significantly with any of the other measures, potentially because of the low values of CEQ. The results are shown in Table 2. Furthermore, within the DMT + harmine condition, we found a significant correlation between *progression* (increasing effect) with the experience sampling items *disliking* (*rho* = 0.664, *p* < .001), *frightening* (*rho* = 0.577, *p* < .001), and *loss of control* (*rho* = 0.633, *p* < .001).

Table 2

Correlations of subjective experience with persisting effects

		Persisting effects				
		PEQ positive	PEQ negative	Significance: meaning	Significance: spiritual	Significance: well-being
Subjective experience	ASC	.725***	.268	.712***	.583**	.635***
	PIQ	.788***	.341	.529**	.582**	.746***
	AMP	.739***	.395	.488*	.482*	.662***
	GAP	.762***	.204	.504*	.647***	.776***
	EBI	.691***	.381	.471*	.521**	.735***
	CEQ	.431*	.286	0.361	.469*	.399*

Note. N=31. Pearson correlation coefficients. * *p*<.1, ** *p*<.5, *** *p*<.01. ASC: global score altered states of consciousness rating scale; PIQ: psychological insights questionnaire (AMP: avoidance and maladaptive patterns; GAP: goals and adaptive patterns); EBI: emotional breakthrough inventory; CEQ: challenging experience questionnaire; PEQ: persisting effects (positive and negative); significance: personally meaningful, spiritually significant, contribution to well-being.

3.5. Discussion

In our RCT, DMT + harmine and also harmine only were investigated regarding the characteristics of the acute experience (experience sampling, 11D-ASC), potential psychotherapy-relevant mechanisms (psychological insights [PIQ], emotional breakthrough [EBI]), psychological safety and tolerability (CEQ, SCL-90), persisting effects (PEQ), and attributed significance. Overall, the effects were positive. Importantly, DMT + harmine was the main driver for the effects, while harmine only led to only small or mostly negligible effects.

Dynamic Progression of Subjective Effects. Overall, the subjective experience shared phenomenological similarities with experiences induced by ayahuasca and other serotonergic psychedelics such as psilocybin, including alterations of consciousness captured by the 11 dimensions of the widely used ASC scale (Studerus et al., 2010; Uthaug et al., 2021). Acute qualities of the DMT + harmine experience over the course of the drug effect (experience sampling) were overall mainly positive, characterised by attributes such as liking, letting go, relaxation, visionary experiences (elementary and complex imagery). Some levels of arousal and only small levels of uncomfortable feelings (disliking, frightening, loss of control) were reported. The average peak of disliking was experienced at the timepoint of a task performed short before the average peak of the drug effect, which might have increased the negative sensations.

Our findings suggest that the incremental intermittent dosing regimen might have affected the subjective experience profile. The clear biphasic phenomenology described for ayahuasca such as discussed by Wolff as *"*bottleneck*"* phenomenon during the ayahuasca experience was less prominent in our study (Wolff et al., 2019). Hallucinogenic or classical psychedelic qualities increased early, and decreased rather rapidly, while being generally moderate. Empathogenic qualities appeared together with the psychedelic effects, were generally stronger, and lasted throughout the full drug-induced experience including some levels of empathogenic afterglow effects. Ayahuasca's somatic effects, primarily vomiting (*"*purging*"*), were discussed to contribute to the biphasic or *"*bottleneck*"* phenomenon but were not observed with our DMT + harmine formulation (Mueller & Aicher et al., in prep.). Based on our findings, we argue that our administration route and dosing regimen of DMT + harmine facilitates an adaptive process, which enables the organism to adjust its homeostasis, potentially leading to an acute psychological tolerance resulting in a less overwhelming and more empathogenic experience.

Therapy-relevant Psychological Processes. Of great relevance for a potential therapeutic application, DMT + harmine led to psychological insights (PIQ) and emotional breakthrough (EBI). Psychological insights refer to the understanding of own potentially maladaptive, but also goal oriented relational, behavioural, and cognitive patterns. Similarly, emotional breakthrough experiences describe moments of emotional clarification and uncovering of repressed affect. This combination of psychological insights and emotional breakthrough experiences represents an essential aspect of transformative psychotherapeutic processes. Indeed, definitions of catharsis – derived from the Greek word for cleansing or purification, which are terms often used in the context of ayahuasca rituals – emphasise two components:

emotional and cognitive (Bukar et al., 2019). It has been proposed that the development of insights following emotional catharsis is crucial for persisting improvement in psychosomatic functioning, while purely cognitive insights could result in increased psycho-physiological tension (M. P. Nichols & Efran, 1985). DMT + harmine could thus play a key role in substance-assisted psychotherapeutic approaches by eliciting both psychological insights and emotional breakthrough experiences.

The qualitative diary reports of the participants revealed further insights into beneficial and therapy-relevant effects of the intervention. Recurring topics were related to being present in the "here and now", clarity, trust, stillness, relaxation, contentment, non-judgement, awareness, universality, acceptance, gratitude, appreciation, and feelings of connectedness, as described in these representative examples:

"I notice how I try to look at emotions and thoughts from a greater distance without judging them. It is difficult, but since the trip one of my goals. I also try to build a greater acceptance for thoughts and decisions and to go through life with what is and not what is not. During the trip I had the strongest feeling ever that everything is ok the way it is."

"I lived completely in the moment. Perhaps this is a lesson that has been confirmed once again: All that matters is the here and now. Live in the moment!"

"…a great calm spread through me, and it felt like everything was settled and I could continue with what I like to do or where I was drawn to. My satisfaction and connection to my intuition is very great at the moment."

"Today I noticed a greater appreciation for everything. I was very aware of my thoughts, feelings & actions and tried to carry them out as lovingly as possible. I did everything I set out to do with joy & passion."

Psychological Safety and Tolerability. The mechanism of homeostasis adjustment discussed above might reduce potential adverse effects and allow for better controllability by the participant. We found that the acute escalation of drug effects (progression delta as assessed with experience sampling) was positively correlated with the sensation of fear (frightening) and loss of control, supporting the hypothesis that not only the overall intensity, but also the delta (dynamic change of intensity) could potentially be experienced as challenging. With the specific application form and the intermittent dosing regimen, the possibly overwhelming effects were attenuated and better controllable. One participant described this in his diary report:

"When I closed my eyes, I could dive into worlds and be really absorbed by that, but as soon as I opened my eyes I could focus on the now again. Talking and interacting with people went very well..."

While traditional ayahuasca is relatively safe, especially when consumed in a ritualised setting (Barbosa et al., 2012), its effects can be unpredictable due to varying combinations of ingredients and gastrointestinal absorption related to the oral intake. Sometimes, challenging experiences are reported including some levels of – mostly transient – adverse effects (Bouso et al., 2022). In our study setting, however, DMT + harmine stimulated only small levels of

feelings of loss of control (experience sampling), few side effects (Mueller & Aicher et al., in prep.), and only small levels of acute transient challenging experiences (CEQ). The brief half-life of DMT implies that the intensity of the experience can be effectively managed, when DMT is administered with this parenteral administration and the intermittent dosing regime. Moreover, in the absence of additional doses, the intensity of the experience subsides rapidly.

Overall, our DMT + harmine intervention had a good psychological safety and tolerability profile, which is an important aspect of any therapeutic intervention. These properties, including the flexible handling, make the DMT + harmine formulation an interesting candidate with potential utility for individualised clinical application in patients.

Persisting Effects, Integration, and Contextual Factors. Notably, persisting effects reported by participants were mainly positive, including positive attitudes about life and/or self, positive mood changes, altruistic/positive social effects, and positive behaviour changes (PEQ). Only small levels of negative persisting effects were reported. Overall, participants attributed personal and spiritual significance and perceived association with increased well-being to their study participation. Furthermore, psychopathological symptoms (SCL-90) in everyday life were stable or even decreased after the study participation, showing that participants did not deteriorate after the study participation. These primarily positive persistent effects further underline the potential of the substance to promote beneficial transformative experiences.

However, while other studies found lasting positive changes in personality traits such as openness, neuroticism, cognitive and psychological flexibility, or nature relatedness after use of psychedelics (Bouso et al., 2018; Erritzoe et al., 2018; Forstmann & Sagioglou, 2017; Kiraga et al., 2021), we did not find trait-related improvements in our study sample, despite the reported positive persisting effects. Considering the sample characteristics, the moderate dose, and the pharmacological study setting, the effects we found are still remarkable. Although our study setting was comfortable, there was no focus on embedding the processes within an integrative or therapy-oriented framework. Emphasising integration may have a positive impact on the sustainability of any potential positive effects brought about by a psychedelic experience. Integration refers to the process of making sense of and contextualise the insights and emotions that arise during a psychedelic experience into one's daily life (Bathje et al., 2022). While there were no integration sessions provided by the study protocol, some participants might have reflected on how to integrate the experience within their life, initiating a potentially beneficial process including lasting persisting effects, without yet being reflected in enduring trait changes. One participant wrote about the integration process in his diary report:

"The rest of the evening I felt very thoughtful, but in a positive sense. There was just a lot to process and think about again. On the one hand what I experienced, but also how I perceived it and what I can now do with it in everyday life."

Furthermore, and contrary to the notion of one single dose leading to sustainable changes (Osório et al., 2015), it might be valuable to offer several psychedelic sessions to deepen insights and processes, as one of our participants' reports states:

"… difficult to implement everything learned and not to fall back into the same patterns. I have the feeling that you need several such trips and states to be able to really change that sustainably."

Contextual factors, such as the environment in which the experience takes place (setting), the mindset of the individual (set), and the support available after the experience (setting), can also impact effects of psychedelics (Carhart-Harris, Roseman, et al., 2018; Eisner, 1997). Due to the potential of psychedelics to elicit profound psychological and emotional responses, providing empathetic support during and after a psychedelic experience represents a fundamental ethical requirement. The diary reports of our participants indicate that they felt safe and supported during the study, which might have contributed to the positive acute and persisting effects and might have prevented negative reactions. *"I felt very safe & comfortable knowing that everyone was there for me if I needed help."* Even though empathetic support was provided during the duration of the study, the setting was rather pharmacologically oriented. In such a context, the positive effects of psychedelics may be limited to the immediate physiological changes that occur as a result of the drug.

It will be important to carefully consider both integration and contextual factors when testing DMT + harmine for therapeutic purposes. Future studies, especially clinical trials with patients, should provide a setting that is targeted for psychological processes and integration, potentially even in group settings (Gasser, 2022). Such an environment would ideally support individuals to reflect on their experiences, process their emotions and challenging aspects of the experience, and incorporate their insights into their daily lives. This could minimize any adverse reaction and enhance the positive effects we found in our pharmacologically oriented study setting.

3.5.1. Limitations

To our knowledge, this is the first RCT investigating acute and persisting potentially psychotherapy-relevant effects of ayahuasca analogues containing DMT + harmine in healthy individuals. However, the study has some considerable limitations: First of all, our sample was Western, educated, industrialized, rich, democratic (WEIRD) (Henrich et al., 2010) and in our case even male because of the potential influence of the female cycle on pharmacological parameters that were measured. While other studies investigating psychedelics often include participants with a lot of previous psychedelic experience, we excluded such participants resulting in a sample consisting of participants with no or only little previous psychedelic experience. However, a selection bias remains, as studies including treatments with psychedelic substances require a rather high degree of motivation and openness by the participants. This might have contributed to a ceiling effect regarding potential changes in trait measures. We think that the blinding problem – prevalent in most psychedelic RCTs (Muthukumaraswamy et al., 2021) – might have been attenuated by the harmine only condition. Additionally, any potential long-term assessments might have been confounded by the impact that the COVID-19 pandemic and lockdowns had on people's daily routines, including isolation and decreased social interactions, and mental health (Armitage & Nellums, 2021; WHO, 2022), or by other life events such as exam periods of our student participants.

An important factor was discussed above: The pharmacologically oriented study set up was not targeted for transformative experiences, therapeutic or integration processes, but rather required participants to follow the study procedure including short psychometric assessments, blood withdrawal, and performance of behavioural tasks. For the experience sampling and the completion of the tasks, participants had to open their eyes, which also reduced the subjective intensity of the experience. While the intensity of the experience was rather moderate – consistent with the moderate dose and the incremental dosing of DMT – the study set up, including the experimental tasks, might have even attenuated the subjective effects and distracted participants from their inner processes, which was also reported in the diary texts:

"*I think that the whole setting and the tasks have/had a big effect, at least on me, that I probably could not get so involved in the profound questions. The many changes of persons and tasks were probably a contributing reason that I did not have an unpleasant feeling, but a feeling of not completely surrendering to the mind's eye and what was happening \'within me\'.*"

"In this setting, it was difficult for me to benefit optimally from the experience. I could never fully immerse myself in the experience. I experienced a lot of interesting thoughts & insights and experiences and in the next moment I was pulled out again by the experimental setting. This was to be expected and even though I would have liked to dive deeper into the experience to take more away from it, I realize that this was not the time & place for that. I was here in the context of a scientific investigation & trying my best to comply. To benefit optimally from the experience, it would probably have to be built into a psychotherapeutic context."

Further clinical trials in a therapeutic context including preparation and integration and with individualised doses are necessary to evaluate if the effects of our study translate to patient populations and thereby fully assess the clinical potential of this DMT + harmine formulation.

3.6. Conclusion

Taken together, our findings suggest that ayahuasca analogues containing DMT and harmine, but not harmine only, induce an experience with psychedelic and empathogenic characteristics, have the potential to elicit psychological insights (PIQ) and emotional breakthroughs (EBI), and lead to positive persisting effects, while showing good psychological safety and tolerability in a supportive setting. While we were able to reduce many of the potentially challenging or negative side effects, as well as the unpredictability and variability of effects between individuals, which are associated with traditional ayahuasca, the use of ayahuasca analogues should still be approached with caution and under the supervision of trained professionals. The fascinating phenomenology of psychedelic-induced experiences, the high context-sensitivity and complexity of these states, their underlying mechanisms, and their potentially therapeutic effects confront us with countless questions. While more research is needed to better understand the beneficial effects of DMT + harmine in therapeutic contexts, this work will always remind us to be humble, as written by one of our participants: *"Many questions. But I take everything so calmly at the moment that I would be satisfied even with the idea of eternal unknowing."*

Chapter 4. Discussion

The growing number of mental health disorders worldwide is a pressing contemporary concern that needs immediate attention (A. E. Becker & Kleinman, 2013). With psychedelic substances (e.g., the Amazonian plant brew ayahuasca) showing therapeutic potential in alleviating the burden of mental health disorders (Palhano-Fontes et al., 2019; Sanches et al., 2016; Sarris et al., 2021; van Oorsouw et al., 2022), the primary objective of this dissertation is to explore the pharmacokinetic and pharmacodynamic properties (PK-PD), safety and tolerability, and therapeutic potential of a novel parenteral ayahuasca-analogue formulation. This analogue comprises the serotonergic psychedelic substance DMT and the β-carboline alkaloid harmine, both constitutes of the Amazonian plant medicine ayahuasca, and was previously developed to improve the pharmacological profile of ayahuasca (Dornbierer et al., under review). This dissertation was in response to certain challenges linked with the use and implementation of traditional ayahuasca into Western medicine. By addressing these challenges, this research aims to contribute to our understanding of the potential benefits and applicability of this ayahuasca-analogue in a Western therapeutic context. Specifically, we conducted a double-blind, placebo-controlled crossover study in order to examine PK-PD as well as psychological effects of this novel formulation, allowing us to assess overall safety and tolerability. Moreover, to evaluate the pharmacological contribution of harmine to the subjective effects, this study compared psychological effects of co-administered DMT and harmine with harmine alone, and a placebo condition. Subjects were assigned to one drug condition (i.e., DMT + harmine = DMT/HAR, harmine + placebo = HAR, placebo + placebo = PLA) per study day, respectively, and the treatment order was randomized between participants. They all underwent every condition, with an intervening washout period of at least two weeks. The research employed a combination of physiological markers (i.e., blood pressure, heart rate, body temperature, blood analysis), psychometric measures, and qualitative diary reports. We expected the substance to exhibit both psychological and physiological safety and tolerability. Subjective effects were hypothesized to resemble those of traditional ayahuasca, while undesired side effects were assumed to be comparably reduced. Additionally, we expected the pharmacological induction of psychotherapy-relevant processes like emotional breakthroughs and psychological insights. The aim of this chapter is to provide an overview of key findings followed by an interpretation of the current results. Limitations of this research are discussed and, to conclude, an outlook regarding future scientific work and potential clinical application is given.

4.1. Overview and Interpretation of Key Findings

In line with formulated hypotheses, our results showed that parenteral administration of harmine and DMT produces consistent blood plasma levels. Furthermore, premedication of buccal harmine effectively potentiated and prolonged the effects of intranasal DMT through MAO inhibition, which is mirrored in an increased elimination half-life of DMT. Through buccal harmine administration, thus bypassing the first-pass metabolism, lower doses of harmine appear to be sufficient in preventing degradation of DMT by MAO compared to traditional

ayahuasca (Halpern et al., 2008). This indicates the feasibility and efficacy of activating intranasal DMT using buccal harmine, thereby improving the typical oral route of ayahuasca administration that often results in undesirable side effects (Guimarães dos Santos, 2013). Additionally, repeated-intermittent administration of DMT produced a pronounced plateau in the DMT blood plasma profile. Our study confirmed psychological and physiological safety of this novel and innovative ayahuasca-analogue formulation. As expected, compared to the background noise of undesired drug effects (i.e., PLA) induced by study setting, EEG, and behavioural tasks, the substance-induced side effects for both DMT/HAR and HAR were well tolerated and produced only mild side effects. Overall, less physical side effects compared to traditional ayahuasca were reported (Bouso et al., 2022). Although slightly more challenging experiences were observed in DMT/HAR compared to HAR and PLA, both physical and psychological side effects associated with traditional ayahuasca consumption could be reduced successfully (Hamill et al., 2019). The intermittent dosing regimen of intranasal DMT ensured better control of the subjective experience and a more subject-oriented drug administration. Intensity ratings correlated significantly with DMT blood levels in DMT/HAR, corroborating our assumption of DMT being the main driver for psychological and physiological effects, and harmine acting primarily as a PK-enhancer to increase the bioavailability of DMT. Harmine levels did not correlate with psychological and physiological measures. Moreover, there were no significant differences for subjective effects between HAR and PLA.

Although there are many differences between this formulation and botanical ayahuasca, the subjective experience profile produced by this analogue resembles that of traditional ayahuasca and other psychedelics (Ley et al., 2023; Riba et al., 2001, 2003; Wolff et al., 2019). It was characterized by classical psychedelic phenomenology at the beginning of the experience before emerging into a more empathogenic and less overwhelming spectrum of effects towards the end, which is a distinctive hallmark of ayahuasca experiences (Kjellgren et al., 2009; Wolff et al., 2019). Both emotional breakthroughs and psychological insights were acutely reported by subjects. Regarding long-term outcomes, we found that participants generally attributed significance to their experience up until 4 months later. A higher level of intensity of the psychedelic experience produced higher levels of significance. However, despite persisting effects being primarily positive, expected changes in personality traits were not found. No increases in psychopathological symptoms and no changes in psychological flexibility and general well-being were registered at follow-ups. In conclusion, this novel ayahuasca-analogue demonstrates good safety and tolerability, both psychologically and physiologically, and shows great potential for implementation into clinical applications. Specifically as adjuncts to psychotherapy, psychological changes could be enhanced by serotonergic stimulation with this formulation, especially in a process-oriented psychotherapy framework (Scheidegger, 2021)

The intermittent dosing of DMT combined with the parenteral administration form facilitates the personalization of both subjective and physiological effects. This feature is critically important for clinical applications, potentially increasing patient compliance and providing the ability to promptly respond in the event of heightened psychological or physiological distress or dangerously elevated blood pressure. The controlled amount of substances and the

circumvention of the gastrointestinal tract further ensures improved predictability and comparability, both intra- and inter-individually. Factors such as individual metabolic differences and dietary variations do not need to be rigorously accounted for. This contrasts with traditional ayahuasca use, as there are big differences in composition between different ayahuasca brews and individuals often have to follow a strict diet. Moreover, the standardization of the administered doses further increase the safety and predictability, as traditional ayahuasca can have huge differences of psychoactive and other plant constitute concentrations, caused by differences in preparation between tribes, cooking time, ingredients, and alkaloid content in plants (Guimarães dos Santos, 2013; Rodríguez et al., 2022).

These findings lay a critical foundation for the continued exploration and development of psychedelic-assisted therapies, specifically suggesting that combined DMT/HAR could serve as a potent, promising approach for novel treatments of mental health disorders. Nevertheless, despite these primarily positive outcomes, it is critical to acknowledge that our research inherently presents certain constraints that should be discussed, considered, and factored into subsequent analyses.

4.2. Limitations

The study faces several limitations that may affect the interpretation and generalizability of the results, some of which were already addressed above in the individual manuscripts. In anticipation of clinical applications of this novel ayahuasca-analogue in the future, this chapter thoroughly examines the limitations of the conducted study and the potential obstacles for the potential integration into Western medicine.

4.2.1. Sample Characteristics

One key restriction of our study pertains to the nature of our sample representation. The recruited participants were from WEIRD (western, educated, industrialized, rich, democratic) societies (Henrich et al., 2010), male, and young. They exhibited above-average motivation levels and an open personality trait, potentially introducing a selection bias into our findings. The nature of our sample poses a significant challenge to the generalizability of our results across broader and diverse populations. We therefore ask future research to emphasize inclusivity in sample selection, ensuring representation of diverse demographic and psychological profiles. Particularly with regard to future application in clinical settings, both a thorough investigation of pharmacokinetic and pharmacodynamic properties in female bodies and assessment of subjective effects in women are vital (Eisenberg & Lennon, 1983; Fattore et al., 2020; Soldin & Mattison, 2009).

4.2.2. Methodological Limitations

From a methodological standpoint, the reliance on self-report measures in both the acute phase and follow-up stages of our study poses a potential limitation (Rosenman et al., 2011). Self-report data can be influenced by factors like social desirability and inaccurate recall. To

mitigate these issues, we adopted a multi-method approach that integrated both quantitative measures (physiological and psychometric data) and qualitative measures (diary reports). Nonetheless, subsequent research could greatly benefit from incorporating third-party observations to cross-verify the authenticity and reliability of self-reported data. One practical approach could be to involve trip sitters in the data collection process, for example by having them undertake the same assessments as the participant. As for follow-up data, the inclusion of observations from friends and family members may yield significant insights. This mixed-method approach may result in a more comprehensive and trustworthy understanding of the findings.

4.2.3. Study Design

Furthermore, several study design-related limitations warrant discussion. Foremost is the challenge of blinding and placebo control in psychedelic research (Muthukumaraswamy et al., 2021). The distinct and profound effects induced by psychedelic substances often make it challenging to effectively blind participants and researchers, introducing potential bias in the interpretation of results. Although we included separate harmine only (HAR) and placebo (PLA) conditions in our study, we have to assume that both participants and study team members often became aware of the respective drug condition with progression of the study day. Intriguingly, psychotherapy faces similar challenges associated with randomized controlled trials, especially with the placebo condition (Wampold & Imel, 2015). Expectancy, social desirability and experimenter bias effects on self-report measures can therefore not be ruled out. Future studies should strive to improve blinding techniques by either employing active placebos that mimic some effects of the psychedelic substance or by using lower doses of the substance tested.

Another critical limitation lies in the absence of different dose ranges in our investigation. Both subjective and physiological responses to psychedelic substances are notably dose-dependent (Kaypak & Raz, 2022; Liechti & Holze, 2022). By only testing a single dose, our study fails to explore potential variations in response across a dose range, thus restricting the generalizability of our findings. Thus, the next logical step in this research would be to carry out dose-response analyses. This is critical for determining the optimal dosage that effectively promotes the desired therapeutic effects while minimizing the risk of adverse reactions, especially for clinical applications. Such investigations will provide a more comprehensive understanding of the substances' effects and guide the development of safe and effective therapeutic applications.

Moreover, we did not include a DMT only condition in our study, as DMT shows no oral bioavailability due to the excessive metabolic breakdown by MAO (Barker, 2022; Carbonaro & Gatch, 2016). Although we administered DMT intranasally, we expected no effects in a DMT only condition due to the slower onset of action in intranasal administrations compared to inhaled or intravenous routes, where DMT alone is typically able to elicit subjective effects. However, in anticipation of future clinical applications, it is also important to analyse the metabolic breakdown of intranasal DMT without a MAOI, as it might help to gain more insights into the metabolism of DMT in the body.

4.2.4. Context Sensitivity

Lastly, the effects of psychedelic substances on an individual's thoughts, perceptions, and emotions are significantly influenced by both the physical and social (i.e., setting), as well as the psychological (i.e., set) environment in which the psychedelics are consumed (Strickland et al., 2020). This impacts generalizability of results because the same substance at the same dosage could produce different effects in different contexts. It is therefore important to consider how set and setting in the study influenced the experience, especially if there are comparisons between different studies.

Many of our participants indeed mentioned the setting as an important factor shaping their subjective experience. Some reported, for instance, that outside influences like blood drawings, monitoring of vital signs, and behavioural tasks impacted their ability to fully surrender to the psychedelic experience. This raises questions about the potential impact of such interferences on the depth of participants' experiences and whether this could have contributed to the absence of long-term trait changes we observed. Furthermore, the experimental tasks performed at the peak of the psychedelic experience were described as very intense by many participants. The strong contrast of bright and dark stimuli, along with potent emotional cues such as facial expressions, appeared to shape the nature of their experiences, with several participants reporting challenging experiences at this time point (tasks discussed in separate manuscripts).

On the positive side, participants frequently mentioned the caring and supportive nature of the study team, which potentially contributed to the empathogenic feelings that subjects reported during the second half of their experiences and the subsequent afterglow period. In this regard, we cannot rule out that subjects in the DMT/HAR condition, compared to those in the HAR and PLA conditions, might have required and received more intensive care and support, resulting in a more empathogenic subjective experience. This bias relates to the frequently debated blinding problem in psychedelic research, which describes the issue of blinding in psychedelic trials being particularly challenging due to the distinct effects of psychedelic substances (Muthukumaraswamy et al., 2021).

The motivation of both researchers and volunteers in psychedelic trials could also impact study outcomes . Regarding our study, we found subjects to be highly motivated and open towards psychedelics, as assessed by pre-study measures, which could limit the generalizability of findings to a broader population. The high baseline levels of "openness to experience" among our participants and the pharmacologically oriented study environment might be further reasons we didn't observe long-term trait changes at follow-ups. Offering structured preparation and integration sessions could help to induce long-term therapeutic benefits from these substances.

To conclude, subjective effects reported by our participants have clearly been influenced by our study environment. Even though it is generally assumed that physiological effects of these substances can be traced back to their chemical interactions within the body and are not directly changed by set and setting, they can be modulated through psychosomatic processes (Eisner, 1997; Gukasyan & Nayak, 2022). However, the way the body processes and responds to the drug is usually thought to be more consistent across different environments than

psychological effects. This suggests that this ayahuasca-analogue will likely be physically safe across various contexts. However, we have seen that it remains difficult to entangle effects elicited by set and setting from those solely elicited by the substance itself. As it would be unethical not to provide certain aspects of set and setting, such as a safe, supportive environment, carefully screened participants, as well as trained and empathogenic trip sitters, we cannot say how subjective effects would be altered in the absence of these things. Likewise, our findings might have been different if the study environment would have put more emphasis on therapeutic change processes rather than pharmacological outcomes. Even though it is ethically not possible to omit certain aspects of set and setting, certain measures can be taken in scientific trials to account for the context sensitivity inherent to psychedelic substances. Firstly, future researchers are encouraged to assess those variables that cannot be controlled. This allows us to examine if they have an impact on the effects found. For example, one could register the amount and quality of support provided during sessions, as this may differ between and within subjects (psychedelic experiences are both highly inter-individual and intra-individual). Moreover, it is necessary to assess both researcher variables such as personality and mood, as well as participants' motivations, expectations, and personality traits. External influences, i.e., the setting, should be held constant if possible. This includes assigning fixed trip sitters to subjects and not changing the music, lighting, décor of the room, etc., across drug conditions.

From a clinical perspective, the context sensitivity of psychedelics has important implications for future psychedelic-assisted psychotherapy. The therapeutic alliance between patient and therapist, long recognized as a significant factor in the success of psychotherapy (Stubbe, 2018), could take on heightened importance in psychedelic-assisted therapy. As such, therapists working in this area need to be acutely conscious of their influence and be well-trained, not only in therapeutic techniques, but also in ethical practices. The potential for intensified transference and countertransference dynamics due to the profound emotional states facilitated by psychedelics makes this especially important. Given these dynamics, it may be beneficial to consider a model where two therapists are present, potentially offering greater support and balance in managing these complex therapeutic interactions. Offering extensive preparation before the psychedelic session, including discussing effects, expectations, fears, potentially setting intentions, is key to ensuring the patient is in a stable mental state when going into the experience (Guimarães dos Santos, 2013; Halpern et al., 2008). Furthermore, patients needs to be carefully screened regarding past history of mental illness, especially schizophrenic type, in order to make sure a psychedelic experience is safe for them (González-Maeso & Sealfon, 2009). Finally, one has to take into account that each person's experience with psychedelic substances is unique. Therapists should tailor their approach to meet the individual's specific needs, preferences, and circumstances. In essence, successful psychedelic-assisted psychotherapy involves a delicate interplay between the drug, the patient, and the context in which it is administered. A thorough understanding of the context sensitivity of psychedelics allows therapists to create a supportive environment that maximizes therapeutic benefits and minimizes potential risks.

In closing, it is likely that various elements, including the pharmacologically oriented study setting, the supportive nature of our study team, and participant predispositions, might have

influenced subjective experiences of our study participants. As psychedelics move towards therapeutic use, it is critical to address these issues through rigorous experimental design, ensuring ethical sitter and therapist training, careful participant/patient screening, and a clear focus on the drug-context interaction.

Despite the limitations discussed, our research offers significant insights into the effects of DMT and harmine. However, particularly with regards to future clinical application, more robust, large-scale clinical trials are needed to fully understand the safety and efficacy of these substances. The specific indications, effective doses, frequency of administration, and long-term effects are all areas that require more research. Recognizing the constraints discussed above will help refine future investigations, ensuring a more comprehensive understanding of psychedelic experiences. This will, in turn, advance the development and refinement of psychedelic-assisted psychotherapy, ensuring it is safe, effective, and accessible to diverse populations.

4.3. Implementation into Western Medicine

As we have seen, this novel ayahuasca-analogue formulation has allowed us to address several obstacles associated with traditional ayahuasca use. Nevertheless, bringing this powerful psychedelic into a Western psychotherapeutic context presents a unique set of challenges. The subsequent section will outline and discuss these concerns, acknowledging that while further research may provide additional solutions, thoughtful deliberation is required to integrate it effectively into Western medicine. This is crucial as we aim to harness the full potential of this innovative therapeutic approach to address the escalating challenges of mental health issues.

4.3.1. Legal Status

On of the main problems hindering both research and clinical application of psychedelic substances is their legal status. Many psychedelics, including DMT, apart from a few exceptions, are classified as Schedule I drugs under international law, meaning they are not currently accepted for medical use and are considered to have a high potential for abuse. Apart from hindering both research and therapeutic use, this causes further problems.

In the case of ayahuasca, many individuals, typically from Westernized countries, travel to regions in South America to participate in ayahuasca ceremonies (“ayahuasca tourism”) (Labate & Cavnar, 2018; Labate & Jungaberle, 2011). The resulting increased demand for the plants used to produce ayahuasca, specifically the *Banisteriopsis caapi* vine and the *Psychotria viridis* leaves, leads to overharvesting and depletion of these plant species in certain areas (Tupper, 2008). Apart from impacting local ecosystems, the lack of regulation and quality control in many ayahuasca ceremonies can lead to several potential problems that can impact the safety and well-being of participants. Ceremonies often take place in an unregulated setting, without thoroughly checking and preparing participants (Bouso et al., 2022; R. G. dos Santos, 2013). Further, the quality of the brew varies widely, which can lead to unpredictable effects. In unregulated settings, facilitators may lack the necessary experience or training, and unfortunately, there have been reports of so-called retreats taking advantage of the lack of

regulation to exploit or abuse participants, both financially and personally (BBC, 2020). The same issues caused by unregulated settings and lack of quality control can also be found in illegal underground therapy in the West (Pilecki et al., 2021).

To prevent these problems, a paradigm shift in regulatory approaches is imperative. The substantial evidence indicating favourable safety, tolerability, and positive impacts of ayahuasca and psychedelics in general - including the presented psychological insights, emotional breakthroughs, and empathogenic effects, but also lasting positive effects and significance - raises the questions about maintaining this rigid legal status. We ask regulatory authorities to attend to the scientific evidence and consider a reclassification of psychedelic substances as an alternative to mere prohibition. This change could foster a more informed public, capable of making educated decisions about their use of these substances. Moreover, it opens the avenue for disseminating science-based information to the public, encouraging dialogue, and promoting help-seeking behaviours. Furthermore, reclassification could pave the way for risk minimization through regulated usage settings and quality control measures. This may involve the involvement of trained professionals to facilitate sessions, rigorous participant screening processes, and an emphasis on the safety and wellbeing of users. We understand that changing these laws is a slow and challenging process that requires strong evidence of therapeutic benefit and safety. Nevertheless, we consider a reclassification necessary for mitigating risks while harnessing the therapeutic potential of psychedelic substances.

4.3.2. Danger of Cultural Appropriation

Aside from overcoming regulatory hurdles, a specific challenge concerning ayahuasca and analogues is the question of how to integrate the use of these substances into a Western therapeutic framework. Ayahuasca has been used for centuries in specific cultural and ceremonial contexts (de Rios & Grob, 2005; Fotiou & Gearin, 2019; Politi et al., 2022). Translating this into a Western therapeutic model raises questions about cultural appropriation and how to honour and preserve the traditional use and context of the substance.

Bringing ayahuasca into a Western therapeutic context carries a risk of disregarding its rich cultural heritage (Fotiou, 2016). This not only disrespects the Indigenous communities who have historically protected and preserved this tradition but also may impact the effectiveness of the treatment. As we have seen, the context in which ayahuasca is taken can significantly influence the experience and its outcomes (Carhart-Harris, Roseman, et al., 2018). It is plausible that some elements of traditional ayahuasca ceremonies, such as the use of music or a supportive community setting but also the act of vomiting which is considered as purging from bad spirits, may enhance the therapeutic process (Fotiou & Gearin, 2019). However, using ayahuasca outside of its traditional context, and incorporating these elements into a Western setting can be seen as cultural appropriation. This is especially the case when ayahuasca is commercialized or used in ways that are not respectful of its origins. There are ethical questions around the use of a sacred Indigenous practice in Western medicine, particularly given the history of exploitation and marginalization of these communities.

Additionally, the contrasting worldviews between Western and Indigenous cultures present a further challenge. While Western medicine tends to view healing in physiological terms, many Indigenous cultures approach healing more holistically, incorporating spiritual, emotional, and community aspects. These disparities can create misunderstandings and potentially limit the effectiveness of ayahuasca therapy if not properly addressed.

Our endeavour to develop a pharmacological ayahuasca-analogue aims to address some of these challenges pertaining to cultural sensitivity and incorporation into our Western healthcare system. However, this alone is insufficient. Despite the fact that we are using an ayahuasca-analogue instead of traditional ayahuasca, our version still draws inspiration from its traditional roots. Therefore, we must engage in the same considerations as those researching traditional ayahuasca use.

To address the challenges presented by introducing ayahuasca into Western therapeutic contexts, several measures could be implemented. First and foremost, active collaboration with Indigenous communities and respect for their wisdom and expertise is of utmost importance. Including them in decision-making processes and ensuring their perspectives and practices are authentically represented, can help facilitate a respectful cross-cultural exchange. This may also provide an opportunity for understanding and integrating holistic healing aspects into Western practice. A significant step toward resolving these issues is to establish fair and ethical agreements with these Indigenous communities. Securing their consent and devising compensation or benefit-sharing frameworks not only exhibits respect for their invaluable contributions but also sets a precedent for ethically sound practices.

In addition, focused research is required to discern which elements from traditional ayahuasca ceremonies might be beneficially transposed into a Western therapeutic setting. Whether it is the use of music, supportive community setting, or specific preparatory and integration practices, all can potentially enrich the therapeutic process and the patient's experience.

Lastly, while our development of a pharmacological ayahuasca-analogue is a step towards bridging cultural and medical systems, it is crucial to understand that it is not a complete solution. Even as we utilize this analogue, we must remain aware of its roots in traditional ayahuasca. These considerations about cultural sensitivity extend to our work as well, underscoring the ongoing responsibility to continually reflect on our practices, and make adjustments as necessary.

To conclude, this is a complex and sensitive issue with no easy solutions. However, ongoing dialogue, respect for Indigenous knowledge and rights, and culturally sensitive research practices can help navigate this challenge.

4.4. Conclusion and Outlook

In finalizing our thoughts and observations, it is apparent that while this research has some limitations and there are still challenges to overcome, the ayahuasca-analogue we developed offers significant solutions to many identified issues. The world is struggling with a mental health crisis, and the promising therapeutic properties of psychedelics have potential to be part of the solution. In the case of ayahuasca, a growing body of scientific literature

corroborates its potential therapeutic benefits. Nevertheless, the use of traditional ayahuasca is not without its unique challenges. To this end, we examined a novel parenteral ayahuasca-analogue formulation, designed to address these difficulties, particularly in terms of its integration into the Western medical framework. The objective of this dissertation was to examine the pharmacokinetic and pharmacodynamic characteristics of this innovative formulation, assess its physiological and psychological safety and tolerability profile, and explore its therapeutic potential for future clinical application. This was realized by conducting an extensive, randomized controlled trial to assess the molecular, physical, and psychological impacts.

Our research demonstrates that this ayahuasca-analogue effectively mitigates many of the challenges associated with traditional ayahuasca use. Our findings revealed a high degree of psychological and physiological safety and tolerability. Harmine effectively potentiated and prolonged the effects of DMT and the repeated intermittent dosing regimen of DMT produced long-lasting blood plasma levels. Subjective effects followed approximately the plasma levels of DMT, while there were no significant differences in effects between harmine only and placebo. Notably, many of the unwanted side effects commonly experienced with traditional ayahuasca consumption were significantly reduced, while the subjective effects remained largely similar. The subjective effects profile of this analogue demonstrates great therapeutic potential. One of the distinct advantages, relating to its specific form of repeated intermittent administration, is the enhanced controllability of the psychedelic experience. This patient-oriented aspect is crucial for therapeutic application, as it facilitates risk minimization while optimizing potential therapeutic outcomes.

Certainly, it is crucial to acknowledge that every research study has inherent limitations. In our work, these include potential biases related to the characteristics of our sample and the methodologies implemented. Notably in psychedelic research, context sensitivity and blinding present unique challenges. Future studies with this novel ayahuasca-analogue formulation should focus on diverse samples, with an emphasis on female representation. A multi-method approach, as adopted in our study, is beneficial for a comprehensive perspective. Moreover, subsequent research should examine dose-response relationships, perhaps considering active placebos or lower doses of the same substance to address blinding issues. Controlling variables where possible, like maintaining a consistent setting, and assessing those variables that cannot be controlled, including researcher and subject variables, can aid in managing context sensitivity. These improvements could contribute significantly to our understanding of ayahuasca-analogues and its therapeutic possibilities.

As we strive to integrate ayahuasca-analogues into Western psychotherapy, we encounter novel challenges, mainly around integrating these substances within Western medicine. Current prohibitions limit critical research and promote risky unregulated usage, along with related ecological issues. We urge for re-evaluation of these substances' legal status to enable safety guidelines and public education. Moreover, to avoid cultural appropriation given ayahuasca's deep roots in indigenous cultures, it is crucial to engage these communities in our processes, embracing profit-sharing and respecting their traditional knowledge.

To conclude this dissertation, this research is the first to investigate pharmacokinetic and pharmacodynamic properties, along with molecular, physiological, and psychological effects, of a novel and innovative ayahuasca-analogue, laying the groundwork for future clinical investigations. Moreover, for the first time the pharmacological contribution of harmine to the overall experience was evaluated by comparing the psychological effects of combined DMT/harmine to harmine alone and a placebo. Expanding upon this research, future studies will explore different settings, including group contexts, exploring dose-dependent relationships, prioritize more diverse samples, and progress towards controlled clinical trials. Despite persisting challenges, the promising therapeutic potential of ayahuasca and its analogues is paving the way for clinical investigations and, ultimately, integration into our healthcare systems. This will potentially provide access to essential mental health care for numerous patients in need. Our findings, while encouraging, present new questions that caution us against over-simplification of psychedelics as a straightforward solution to the mental health crisis. The transformation of healthcare cannot occur instantly, but rigorous research and thoughtful discourse will gradually lead us towards incorporating these substances in an ethically and scientifically informed manner. With both curiosity and a sense of optimism, we look forward to the revelations that future research holds.

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Supplementary Material

Supplementary Table 3

Demographics

		Participants	Dropouts
Number	n	31	6 (data from 5)
Gender	male sample		
Mother tongue	(Swiss) German speaking sample; in some cases an additional mother tongue		
Age (years)	*M (SD)*	25.39 (4.21)	27.4 (5.73)
	min, max, NA's	20, 37	22, 35
Sexual orientation	clearly heterosexual	15/25 (60%)	NA
	rather heterosexual	8/25 (32%)	
	bi-sexual	1/25 (4%)	
	rather homosexual	0	
	clearly homosexual	1/25 (4%)	
BMI	*M (SD)*	22.98 (1.89)	22.77 (1.51)
	min, max	19.59, 26.23, 2 NAs	20.9, 24.49
Physical fitness	very fit	9 (29%)	2 (40%)
	fit	17 (54.8%)	3 (60%)
	average	5 (16.1%)	
	no other fitness level ticked		
	sports on a regular basis	30 (96.8%)	5 (100%)
Education (years)	*M (SD)*	13.6 (6.08)	16.6 (4.16)
	min, max	1.5, 23	11, 21
Education (level)	Certificate of Secondary Education	2 (6.5%)	
	Higher School Certificate	14 (45.2%)	1 (20%)
	University Degree	15 (48.4%)	4 (80%)
	no other education levels ticked		
Work type	apprentice / trainee	1 (3.2%)	
	employee / officer	7 (22.6%)	1 (20%)
	self-employed / freelancer	3 (9.7%)	1 (20%)
	student	20 (64.5%)	3 (60%)
	no other work type ticked		
Employment (%)	fulltime	13 (41.9%)	1 (20%)

	part-time, *M (SD)*	13 (41.9%), 35 (24.66)	3 (60%)
	non-working	4 (12.9%)	1 (20%)
	other	1 (3.2%)	
	other: freelancer		
Income (CHF / month)	up to 2000	10/25 (40%)	NA
	2000 - 3000	6/25 (24 %)	
	3000 - 4000	2/25 (8%)	
	4000 - 5000	1/25 (4%)	
	5000 - 6000	3/25 (12%)	
	6000 - 7000	2/25 (8%)	
	7000 - 80000	0	
	more than 8000	1/25 (4%)	
Marital status	single	29 (93.5%)	5 (100%)
	partnership	2 (6.5%)	
	no other status ticked		
Living situation	alone	3 (9.7%)	5 (100%)
	with partner and/or children	2 (6.5%)	
	living community (excl. family)	17 (54.8%)	
	other	9 (29.5%)	
	other: family of origin (and/or siblings)		

Note. Characteristics of the participants sample and dropouts. Where information is not available for all participants, n or NA is specified.

Supplementary Table 4

Motivation to participate (multiple choice)

for intellectual or creative inspiration	13/25 (52%)
gaining insight into myself or parts of my life / self knowledge	19/25 (76%)
curiosity and adventurousness	21/25 (84%)
a general interest in psychedelic medicine or therapy	22/25 (88%)
a general interest in science	15/25 (60%)
simply because of the experience	9/25 (36%)
for more spiritual awareness, understanding or connection	13/25 (52%)
experience the visual effects	5/25 (20%)
someone else suggested/encouraged	1/25 (4%)
a sense of being called by dreams, synchronous events, etc.	1/25 (4%)
want to be high	2/25 (8%)
earn money	2/25 (8%)

Note. *N* = 31 participants, 6 dropouts. Motivation to participate variables are only available for N = 25 participants.

Supplementary Table 5

Drug pre-experience

Drug experience	tobacco	9/31 (29.5%)
	alcohol (mean per month)	28/31 (90.3%) (9.9 p.m.)
	caffeine	22/31 (71%)
within the last 3 months	THC	17/31 (54.8%)
	MDMA	2/31 (6.5%)
	Psilocybin / Magic mushrooms	3/31 (9.7%)
	LSD	2/31 (6.5%)
	Cocaine	1/31 (3.2%)
	Amphetamine / Methamphetamine	1/31 (3.2%)
	Ketamine	1/31 (3.2%)
	Opiates (heroine, morphium)	1/31 (3.2%)
	GHB	1/31 (3.2%)
	others	1/31 (3.2%)
in the past, more than 3 months ago	THC	31/31 (100%)
	MDMA	2/31 (6.5%)
	Psilocybin / Magic mushrooms	11/31 (35.5%)
	LSD	13/31 (41.9%)
	Cocaine	4/31 (12.9%)
	Amphetamine / Methamphetamine	6/31 (19.4%)
	Ketamine	1/31 (3.2%)
	Opiates (heroine, morphium)	1/31 (3.2%)
	GHB	1/31 (3.2%)
	others	1/31 (3.2%)

Note. N = 31 participants. Percentage of participants with pre-experience with the respective drugs. A detailed drug pre-experience overview can be found in Supplementary Table 7.

Supplementary Table 6

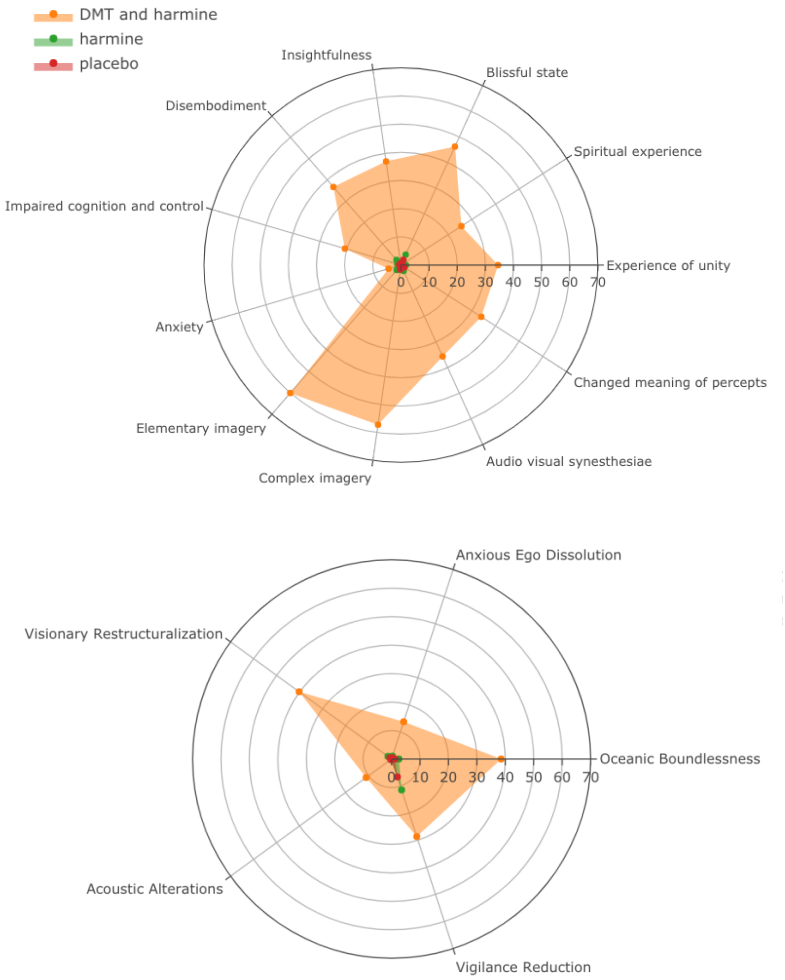
Detailed drug pre-experience

	min	max	mode	median	mean	SD
THC	0.3	168	4	6	26.4	39.45
MDMA	0	10	0	0	1.71	2.98
Psilocybin / Magic mushrooms	0	15	0	0	1.23	3.17
LSD	0	10	0	0	1.29	2.32
Cocaine	0	7	0	0	0.48	1.55
Amphetamine / Methamphetamine	0	10	0	0	0.48	1.81
Ketamine	0	1	0	0	0.03	0.18
Opiates (heroine, morphium)	0	2	0	0	0.06	0.36
GHB	0	3	0	0	0.1	0.54
Mescaline	0	1	0	0	0.03	0.18
2CB	0	1	0	0	0.06	0.25
Laughing gas	0	1	0	0	0.06	0.25
Ritalin	0	1	0	0	0.1	0.53

Note. N = 31 participants, 6 dropouts. All parameters are given in times / total_lifespan, except for THC in times / year. min = minimum, max = maximum, SD = standard deviation.

Supplementary Figure 1

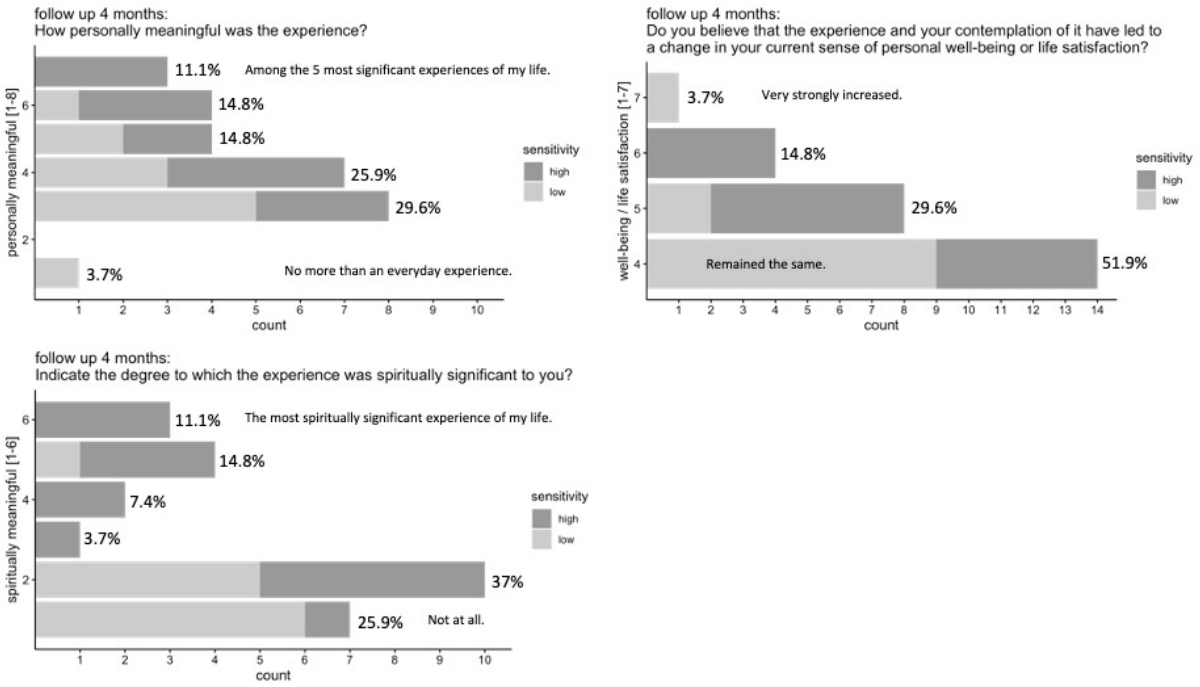
5D and 11D ASC spider plots



Note. Spider plots of 5D-ASC and 11D-ASC are shown for better comparability with other trials using this type of visualisation. Because of the small levels for harmine only and placebo, boxplots (drug conditions next to each other) are shown in the main paper.

Supplementary Figure 2

Significance ratings at the 4 months follow up



Note. N=27. In the main paper, significance ratings at the 1 month follow up are shown