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**Perception, Cognition and Ayahuasca:
A Multidimensional Analysis of Alter States of
Consciousness**

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Son olarak, anneme, babama ve canım dedeme sonsuz teşekkürlerimi sunmak istiyorum. Sizin sevginiz, inancınız ve hayattaki rehberliğiniz olmasaydı, bugünlere asla gelemezdim. İyi ki varsınız. Tezimi size ithaf ediyorum...

Anneme, babama ve canım dedeme...

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Abstract

My Ph.D. thesis comprises a series of experiments aimed at investigating the impact of a novel ayahuasca analog, pharmahuasca (PHA), on face perception and creative cognition. These studies were executed with a within-subject, double-blind, placebo-controlled design involving 30 healthy male participants. Chapter 2 centers on the effects of psychedelics on face perception, utilizing electroencephalography (EEG) during a visual oddball task with self, familiar, and unknown faces as stimuli. Notable changes induced by PHA in early visual processing, such as increased P1 and reduced N170 across all face categories, were observed. In late visual processing, a decrease in neural activation in response to the self-face, as indicated by the P300 wave, highlights the significance of psychedelics in altering self-referential information processing. Additionally, the impact of psychedelics on face discrimination was explored through a two-alternative forced choice (2-AFC) task, where faces are incrementally morphed to each other, revealing a decreased sensitivity for discrimination during psychedelic experiences across all face categories. Chapter 3 shifts focus to understanding how psychedelics influence creative cognition. Through task-based methodologies, the findings unveil a reduction in convergent thinking without affecting on divergent thinking. Next, we investigate how utilization of different thinking modes during the artistic creation, specifically in the domain of painting, under the influence of psychedelics. Importantly, there was a significant reduction in transitions between different creative thinking modes during the psychedelic-induced creative process, particularly affecting stages traditionally requiring convergent thinking, offered valuable insights into the phenomenological nuances of the interplay between psychedelics and the dynamics of creative thinking.

Abbreviations

AFC	Alternative Forced Choice
ANOVA	Analysis Of Variance
ASC	Altered State of Consciousness
AUT	Alternative Uses Task
BDNF	Brain-Derived Neurotrophic Factor
BF	Bayes Factor
BMI	Body Mass Index
BOLD	Blood Oxygen Level Dependent
CHF	Confoederatio Helvetica Franc
CI	Confidence Interval
CMS	Common Mode Sense
CORRMAP	Correlation Map
CRD	Creative Process Report Diary
CSTC	Cortico-Striatum-Thalamo-Cortical
CT	Convergent Thinking
DMN	Default Mode Network
DMT	Dimethyltryptamine
DRL	Driven Right Leg
DSLR	Digital Single-Lens Reflex
DT	Divergent Thinking
ECG	Electrocardiogram
EEG	Electroencephalogram
EOG	Electrooculogram
ERP	Event-Related Potential
FFA	Fusiform Face Area
FIR	Finite Impulse Response
FPN	Frontoparietal Network
GIMP	Gnu Image Manipulation Program

HAR	Harmine
HAR _{FAM}	Harmine Condition Familiar Face Category
HAR _{SELF}	Harmine Condition Self Face Category
HAR _{UNK}	Harmine Condition Unknown Face Category
HSV	Hue, Saturation, Value
HT	Hydroxytryptamine
ICA	Independent Component Analysis
IMT	Istituto Di Management and Technology
JASP	Jeffreys's Amazing Statistics Program
KG	Kilogram
LKM	Love And Kindness Meditation
LSD	Lysergic Acid Diethylamide
MANOVA	Multivariate Analysis of Variance
MAO	Monoamine Oxidase
MAOI	Monoamine Oxidase Inhibitor
MEG	Magnetoencephalography
MET	Creative Metaphors Task
MRI	Magnetic Resonance Imaging
OFA	Occipital Face Area
PCT	Picture Concept Task
PD	Pharmacodynamics
PET	Positron Emission Tomography
PFC	Prefrontal Cortex
PHA	Pharmahuasca
PHA _{FAM}	Pharmahuasca Condition Familiar Face Category
PHA _{SELF}	Pharmahuasca Condition Self Face Category

PHA _{UNK}	Pharmahuasca Condition Unknown Face Category
PK	Pharmacokinetics
PLA	Placebo
PLA _{FAM}	Placebo Condition Familiar Face Category
PLA _{SELF}	Placebo Condition Self Face Category
PLA _{UNK}	Placebo Condition Unknown Face Category
<i>PLOS</i>	Public Library of Science
PMT	Pattern Meaning Task
PSE	Point Of Subjective Equality
REBUS	Relaxed Beliefs Under Psychedelics
RGB	Red, Green, Blue
RMS	Root Mean Square
ROI	Region Of Interest
RSN	Resting State Network
SD	Standard Deviation
SE	Standard Error
SHINE	Spectrum, Histogram, And Intensity Normalization And Equalization
SN	Salience Network
pSTS	Posterior Superior Temporal Sulcal Regions
TGM	Thalamic Gating Model
TTCT	Torrance Tests Of Creative Thinking
VAS	Visual Analog Scale
WEIRD	Western, Educated, Industrialized, Rich, Democratic

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1 Introduction

Classic hallucinogens or psychedelics, such as lysergic acid diethylamide (LSD), psilocybin, dimethyltryptamine (DMT), and mescaline, induce a state of altered consciousness characterized by significant changes in sensory perception, mood, cognitive processes, perception of reality, and sense of self (Hofmann, 1968). In recent years, interest in the potential therapeutic applications of these substances has been resurgent. Clinical trials have proliferated, exploring their effectiveness in treating neuropsychiatric disorders, including depression, anxiety, migraines and obsessive-compulsive disorder (for review, see (Nutt & Carhart-Harris, 2021)). In controlled experiments, these substances exhibit antidepressant, anxiolytic, and anti-addictive effects akin to those observed with conventional antidepressant treatments (Anderson, 2012; Dos Santos et al., 2016; Hibicke et al., 2020; Palhano-Fontes et al., 2019). These effects persist for several weeks to months following administration (for review, see (Andersen et al., 2021)), with the proposed mechanism of action involving immunomodulatory and neuroplasticity processes in the brain (de Vos et al., 2021; Inserra et al., 2021). Although there has been growing interest in the therapeutic potential of psychedelic substances, our knowledge of their neurobiological and pharmacological mechanisms is still limited.

This dissertation aims to contribute to current research by exploring the impact of ayahuasca, a classical psychedelic substance, on perception and cognition using an innovative method of administration. The first section of this introduction will delve into the neurobiology and phenomenology surrounding the traditional use of ayahuasca and address the limitations that led to its adaptation of the novel administration method employed in this study within biomedical contexts. The subsequent section of this introduction chapter will focus on three experiments conducted throughout my Ph.D., encompassing the initial research questions, the methodological approach undertaken in these experiments, and a concise overview of the findings. The experimental work presented in this dissertation primarily focuses on two main dimensions: one, to investigate the impacts of ayahuasca on face perception and recognition, and two, to study its effect on creative cognitive processes. The overarching aim is to provide comprehensive insights into the neurobiological mechanisms underpinning the effects of psychedelics on perception and cognition and their potential therapeutic applications.

1.1. Neurobiological mechanisms, phenomenology and limitations of traditional ayahuasca use in medical settings

Ayahuasca, also known as yagé or hoasca, is a traditional medicine that has been utilized by indigenous communities in the Amazon valley of South America for centuries as a means of healing and spiritual exploration (Shanon, 2002). In the Quechua language, "ayahuasca" translates to "vine of the souls" or "vine of the dead," reflecting its profound impact on consciousness and perception (McKenna et al., 1984). It is prepared using the "ayahuasca vine" (*Banisteriopsis caapi*) along with leaves from either "chacrana" (*Psychotria viridis*) or "chaliponga/chagropanga" (*Diplopterys cabrerana*). *Psychotria viridis*, or *Diplopterys cabrerana*, contains a psychoactive compound called N,N-dimethyltryptamine (DMT) in their leaves, while *Banisteriopsis caapi* contains β -carbolines, including harmine, harmaline, and tetrahydroharmine which are known as "harmala alkaloids" (Ruffell et al., 2020). DMT is only psychoactive when smoked or infused intravenously because it is broken down by an enzyme in the stomach when ingested orally, thus becoming ineffective. However, β -carbolines present in the ayahuasca brew act as reversible inhibitors of monoamine oxidase-A, preventing the breakdown of DMT and allowing for its psychoactive effects (Agurell et al., 1968). When inhaled or injected, the onset is rapid, occurring within minutes and lasting approximately 15 minutes. However, when orally ingested as ayahuasca brew, the effects typically become noticeable after about 30 minutes. The duration of these effects can range from 4 to 6 hours, with a peak experienced around 1.5 to 2 hours after ingestion, coinciding with the highest concentration of DMT in plasma levels during this period (Riba et al., 2001, 2003).

Like other psychedelics (psilocybin, LSD, and mescaline), DMT shares a structural analog of serotonin and acts as an agonist at various serotonin receptors (particularly 5-HT_{2A}, 5-HT_{2C}, and 5HT_{1A}). Additionally, it has an affinity to glutamate, dopamine, acetylcholine, sigma-1 and trace amine-associated receptors (Nichols, 2016). Extensive evidence supports the hypothesis that the activation of 5-HT_{2A} receptors constitutes a fundamental mechanism in the formation of psychedelic symptoms in humans since these symptoms can be blocked by the preferential 5-HT_{2A} antagonists, ketanserin, and pirenperon (Vollenweider et al., 1998).

The consumption of ayahuasca induces powerful effects on the central nervous system, including changes in perception of oneself and the surrounding world and alterations in mood, cognition, and bodily sensations (Kjellgren et al., 2009; Shanon, 2002). These effects can result in transient introspective states characterized by heightened awareness, self-reflection, hallucinations, dream-like visions, recollection of personal memories, and intensified emotions (Riba et al., 2003; Shanon, 2010). Such experiences can potentially provide deep psychological and existential insights (Grob et al., 1996). Additionally, psychedelics have been associated with various psychological processes promoting pro-social attitudes (Roseman et al., 2022) and overall well-being (Mans et al., 2021), mindfulness (Smigielski et al., 2019; Soler et al., 2016), self-compassion (Fauvel et al., 2023), cognitive flexibility (Torrado Pacheco et al., 2023), creative problem-solving abilities and

divergent thinking (Kuypers et al., 2016), and openness trait (Erritzoe et al., 2019).

Repeated and regular use of ayahuasca is considered safe, lacking any addictive or abusive potential (Barbosa et al., 2012; Fábregas et al., 2010). Furthermore, it does not elicit pharmacological tolerance, even with repeated applications (dos Santos et al., 2018). When coupled with its ability to enhance psychological aspects such as self-awareness, empathy, compassion, and existential understanding, ayahuasca emerges as a highly promising candidate for psychotherapeutic interventions. However, there exist several obstacles when it comes to integrating ayahuasca into the Western healthcare system.

First of all, it is frequently observed that individuals may undergo physiological responses such as nausea and vomiting immediately following the consumption of ayahuasca (Bousso et al., 2022a; Fotiou & Gearin, 2019) due to emetic properties of beta-carboline alkaloids (Brito-da-Costa et al., 2020). While vomiting is considered a ritualistic purification process and a form of healing in traditional ayahuasca use (Friso & Mabit, 2021), it is regarded as an undesirable reaction to the toxins contained in ayahuasca (e.g., harmaline, harmine) and as an adverse side effect in the biomedical clinical setting (Loizaga-Velder & Verres, 2014). Secondly, the neurobiological effects of ayahuasca can be influenced by the variations in the levels and ratios of alkaloids in the preparation. Different recipes and preparation methods can lead to differences in the concentration of alkaloids such as harmaline, harmine, and tetrahydroharmine in ayahuasca tea. These variations can be attributed to factors such as the place and

time of collection of the plants, as well as the drying process (Kaasik et al., 2021; Rodríguez et al., 2022). A study conducted by Estrella-Parra and colleagues (2019) demonstrated that the variation in concentration of these alkaloids can impact their synergic activity, ultimately affecting the psychological and pharmacological effects (Estrella-Parra et al., 2019). Finally, variability in the bioavailability of the DMT is pronounced both among individuals and within them. This variability primarily arises from the MAO enzyme's extensive metabolic degradation of DMT during oral ayahuasca ingestion. This enzymatic activity can lead to unforeseen intensities in the psychoactive effects, potentially inducing overwhelming experiences and consequently heightening psychological risks (Bouso et al., 2022b).

1.2. Development of Ayahuasca Analogue Containing N,N-DMT and Harmine

For the reasons mentioned above, Dornbierer and colleagues developed a formulation similar to ayahuasca, containing DMT and harmine (Dornbierer et al., 2023). This formulation, known as "pharmahuasca," includes purified forms of DMT extracted from the *Mimosa hostilis* plant and synthesized harmine. To improve absorption kinetics and minimize side effects such as nausea and vomiting, harmine was administered in orodispersible tablets for buccal delivery, and DMT was formulated as an intranasal spray

solution for incremental dosing. By bypassing the gastrointestinal tract and first-pass metabolism, these administration routes enhance tolerability and offer significant advantages for clinical applications in psychedelic-assisted therapy. Detailed information on the study drug, administration, and pharmacokinetics/pharmacodynamics (PK-PD) results can be found in the following article (Michael J. Mueller et al., 2023). Acute subjective experiences, phenomenology, psychological change mechanisms measured using psychometric tools, psychological safety and tolerability, and persisting effects (1- and 4-months follow-up) results can be found in the pilot study (Helena Dorothea Aicher et al., 2023).

The experiments in this dissertation explored the effects of the pharmahuasca-administration-protocol mentioned above on both perception and cognition. In the forthcoming sections of the introduction chapter, I will provide an overview of the experiments conducted through my doctoral research. The first experiments investigate how psychedelic substances influence face perception, particularly emphasizing the differences between the perception of one's own and other faces. Subsequently, I will elucidate the second experiment, which delves into the profound impact of psychedelics on creative cognitive processes.

1.3. The effect of psychedelics on self-face perception

Two predominant models, the Thalamic Gating Model (TGM) and the Relaxed Beliefs Under Psychedelics (REBUS) Model, currently prevail in our understanding of psychedelic actions on the brain and the associated phenomenology. The TGM posits that the psychedelic state is achieved through alterations in information processing within cortico-striato-thalamo-cortical (CSTC) feedback loops (Vollenweider & Smallridge, 2022). The reduced thalamic gating allows sensory information to flood into the cortex as an amplification of ungated external sensory input, which changes the excitatory-inhibitory balance (Vollenweider & Geyer, 2001). In contrast, based on the hierarchical predictive coding, the REBUS model suggests that a psychedelic state results from the relaxation of the high-level priors or reduced top-down control, which in turn increases the flow of bottom-up information from the sensory regions (Carhart-Harris & Friston, 2019).

Both models share the fundamental concept that psychedelics relax constraints on the brain, albeit at distinct levels: at the lowest processing levels, in the form of reduced thalamic gating; at the highest levels, in the form of reduction of top-down priors. This relaxation of constraints contributes to an augmentation of sensory information richness and a reduction in cognitive rigidity. This fundamental transformation in the architecture of cognitive structures, combined with the amplification of information density, culminates in an experiential phenomenon often described as the "ego dissolution" or 'small self,' characterized by a diminished emphasis on self-centric

perceptions and self-focused cognitive processes (Carhart-Harris et al., 2014; Dourron et al., 2022).

In line with that, numerous neuroimaging studies have shown that psychedelics have a notable effect on reducing the activation of the Default Mode Network (DMN), the structures that are consistently associated with self-referential information processing (for review, see (Gattuso et al., 2023)). Moreover, the decreased focus on oneself is considered to be a critical therapeutic mechanism of these substances (Bouso et al., 2015; Smigielski et al., 2019a), as many mental disorders such as depression and anxiety are associated with heightened DMN activity and excessive self-focus (for review, see (Broyd et al., 2009)).

Besides the changes in one's sense of self, psychedelics are well-known for the induction of visual hallucinations (Aday et al., 2021). While there is considerable individual variation, some consistent characteristics of these alterations include heightened perception of colours with increased saturation, brightness, and contrast, flashes of light, intricate geometric patterns with recurring motifs, and the generation of highly detailed mental images, even without external sensory input (Kometer & Vollenweider, 2016).

Although existing research has yielded valuable findings regarding the effects of psychedelics on visual processing and perception, it is essential to acknowledge that there is a significant gap in the current literature when it comes to understanding how these substances impact the interaction between visual

processing and self-referential information. To fill this gap in Chapter 2, we investigated self-face perception and asked the following research questions:

Research Question #1= "How do psychedelics affect face recognition and the processing of self-face compared to familiar and unknown faces?"

To this end, we run a within-subject, double-blind, placebo-controlled design with separate sessions: we assessed in 30 subjects the impact of Pharmahuasca, Harmine, and Placebo on the spatiotemporal dynamics of face recognition by recording electroencephalography (EEG) during a visual oddball task, in which we presented self, familiar, and unknown faces as stimuli. Furthermore, we investigated whether psychedelics affected face discrimination at the behavioural level. Hence, our second research question was:

Research Question #2= "Do psychedelics alter face discrimination?"

To address this, we tested face discrimination between incrementally morphed face pairs (Self-Familiar, Self-Unknown, Familiar-Unknown) using a two-alternative forced choice (2-AFC) task. In addition to psychophysical measures such as point of subjective equality (PSE) and slope, we considered other critical behavioural factors, such as reaction times and the

intensity of self-reported visual hallucinations induced by pharmahuasca, such as elementary and complex imagery scores. Furthermore, we explored the relationship between electrophysiological data and behavioural outcomes. These investigations allowed us to quantitatively measure the effects of pharmahuasca and harmine on face recognition and discrimination, offering insights into both the neural and behavioural aspects of these effects.

Having addressed the intersection between visual processing and self-referential information in Chapter 2, my focus naturally progressed to examining the impact of psychedelics on creative cognition in Chapter 3. This transition was guided by personal drive and interest, as well as the recognized link between self-face perception and creativity. Studies have consistently demonstrated that individuals with a well-defined self-concept tend to exhibit greater levels of creativity (Kaufman et al., 2015). Given that self-face perception is intricately tied to self-awareness and emotional processing, alterations induced by psychedelics could potentially influence creative thinking abilities (Silvia et al., 2014). Additionally, self-face perception is closely intertwined with social cognition and interpersonal relationships, both of which play crucial roles in creative endeavors (Keyes et al., 2010). By exploring the effects of psychedelics on creativity, we aim to uncover the underlying mechanisms linking these phenomena, shedding light on the complex interplay between self-perception, cognition, and creativity.

1.4. The effect of psychedelics on creative cognition

Classical psychedelics are thought to reduce the rigidities of mental processing, promoting a cognitive style characterized by enhanced flexibility, creativity, and receptivity to novel information (Dourron et al., 2022). A pivotal element in this process is the role of rich sensory experiences that enable individuals to engage with a broader array of stimuli, even those typically considered irrelevant. This has led to a longstanding debate and curiosity surrounding the association between psychedelics and creativity (Baggott, 2015; Sessa, 2008). Furthermore, decreased serotonin levels have been associated with a decline in cognitive flexibility, which could indicate a connection to creativity (Clarke et al., 2004, 2007; Zhang et al., 2023). However, the connection between psychedelics and creativity remains complex and not entirely understood.

Creativity is a dynamic and multifaceted cognitive process that involves the generation of novel ideas and, making connections between seemingly unrelated concepts and fostering originality. (Young, 1985). The creative process encompasses two distinct cognitive modes: divergent thinking and convergent thinking (Guilford, 1961). Divergent thinking involves generating a wide range of unique and unrelated ideas, encouraging open and unconventional exploration. Conversely, convergent thinking focuses on evaluating and selecting ideas based on their connections and practicality, employing structured and

analytical approaches. The harmonious interplay between these cognitive modes is a fundamental underpinning of the creative process. Studies examining the influence of psychedelics on creative thinking have yielded fascinating but inconclusive insights. Some studies suggested that psychedelics may enhance creativity in the acute and subacute experience (K. P. C. Kuypers et al., 2016; Mason et al., 2019; Prochazkova et al., 2018; Uthaug et al., 2019). In contrast, others reported - an acute decrease in both convergent and divergent thinking (Mason et al., 2021). What is intriguing is that participants reported heightened feelings of creativity, even without measurable task-based changes.

Task-based methodologies, traditionally employed to assess creative thinking, pose limitations in capturing creativity's dynamic and multifaceted nature. These methods often focus on isolated tasks that may not adequately represent the complex, dynamic processes that underlie creative thinking. The very nature of creativity is elusive, context-dependent, and flexible, making it challenging to measure using static, one-dimensional tasks. As a result, the outcomes of such studies may not fully encapsulate the dynamic nature and the intricate interplay between two types of creative thinking during creation.

This paradox, where subjective feelings of heightened creativity persist despite decreased measured cognitive functions, raises fascinating questions about the nuances of creative thought in altered states of consciousness. It calls for re-evaluating how we approach and assess creative thinking during these unique experiences and emphasizes the importance of considering creativity's subjective, fluid, and phenomenological aspects,

which may elude traditional task-based assessments. To address this gap, we asked the following question in Chapter 3:

Research Question #3= "How do psychedelics influence the dynamism of creative thinking?"

To address this, we developed a comprehensive experimental methodology in a within-subject, double-blind, placebo-controlled design with separate sessions, and we assessed the impact of Pharmahuasca and placebo on creative cognition in 30 subjects. First, we investigated the two creative thinking (convergent and divergent) with traditional, task-based methodologies. Later, we investigate whether psychedelics altered the transitions of these creative thinking modes during the act of creation process, which allowed us to understand the phenomenological aspects of this relationship. Furthermore, our research extended to the examination of the effects of psychedelics on the aesthetic attributes of the artworks produced. We scrutinized elements such as colours, brightness, contrast, and more to discern whether the choices made during the creative process were influenced or determined by the administration of psychedelics. This study endeavours to fill this gap by exploring the phenomenological aspects of creativity under the influence of psychedelics. This work represents a step toward a more comprehensive understanding of the relationship between these substances and the creative mind.

2 Chapter

The effect of Ayahuasca on the Spatiotemporal Dynamics of Face Processing and Recognition

2.1. Introduction

Psychedelics (serotonergic hallucinogens) transiently alter perception and influence numerous cognitive processes, including consciousness and subjective experience of oneself. The alterations of sensory processing, such as visual perception, represent the main characteristic phenomenology of the psychedelic experience (Kometer & Vollenweider, 2016). The ability of psychedelic drugs to alter perception and their well-known neuromodulatory effect make them tools for causally investigating perceptual processes and their degree of flexibility (Aday et al., 2021). Psychedelics such as psilocybin, lysergic acid diethylamide (LSD), and N-dimethyltryptamine (DMT) produce hallucinogenic effects by agonizing serotonin (5-HT_{2A}) receptors in cortical pyramidal neurons and primary visual areas, since ketanserin, a 5-HT_{2A} receptor antagonist, abolishes these effects (Quednow et al., 2012). As shown by previous neuroimaging studies, psychedelics alter visual processes at several levels, such as augmenting functional connectivity between the primary visual cortex and the rest of the brain (Carhart-Harris et al., 2016), boosting fMRI BOLD signals in visual areas at rest (de Araujo et al., 2012; Roseman et al., 2016), increasing bottom-up traveling

waves (Alamia et al., 2020), and altering oscillatory activity (Komater et al., 2013a; Muthukumaraswamy et al., 2013; Timmermann et al., 2019) and visual evoked potentials in occipital cortex (Komater et al., 2011a, 2013a).

In addition to their effect on visual perception, psychedelics induce transient and dose-dependent reductions in one's subjective experience of self, namely ego dissolution (Letheby & Gerrans, 2017; Stoliker et al., 2022). An ego dissolution occurs when boundaries between subjective and objective realities disappear, and sentiments of oneness emerge, which may have therapeutic benefits such as enhancing mood, behaviour, altruism and overall well-being (Griffiths et al., 2008; Komater et al., 2015). It has been repeatedly shown that psilocybin, LSD and DMT alter the processing of the default mode network (DMN), an interconnected group of brain structures including the posterior cingulate cortex, medial prefrontal cortex (mPFC), and inferior parietal lobule, which is strongly associated with self-referential mental activity (Qin & Northoff, 2011). Several studies have aimed at capturing the relationship between 5-HT_{2A} receptor activation and ego dissolution reported that the degree of ego dissolution predicted decreased DMN "integrity" (Carhart-Harris et al., 2014, 2016; Lebedev et al., 2015; Palhano-Fontes et al., 2015).

Based on the effects mentioned above of psychedelic-induced serotonin modulations on visual and self-referential processing, it might be hypothesized that psychedelics also alter the visual processing associated with one's own face. Surprisingly, no study

has characterized the acute effect of psychedelics on neural and behavioural correlates of self and others' face processing. The present study was designed to fill these gaps and investigate the effects of a psychedelic drug, pharmahuasca, on *face recognition* and *discrimination*. Pharmahuasca is a pharmaceutical form of the entheogenic South American brew ayahuasca, which traditionally contains beta-carboline alkaloids containing *Banisteriopsis caapi* vine and the hallucinogenic DMT containing *Psychotria viridis* (McKenna et al., 1998). Orally, DMT is inactive due to the first-pass metabolism by visceral monoamine oxidase A (MAO-A). Therefore, the psychoactive properties of DMT depend on the simultaneous consumption of beta-carbolines, which inhibits the monoamine oxidase (MAO) action (McKenna, 2004). Chemically prepared pharmahuasca contains a crystalline form of DMT and pharmaceutical monoamine oxidase inhibitors (MAOI), such as harmine. In addition to its MAO inhibition, harmine also has moderate affinity at 5-hydroxy tryptamine 2A (5-HT_{2A}) (Grella et al., 2003), modest affinity at 5-HT_{2C} receptors (Glennon et al., 2000), and dopamine transporter (Drucker et al., 1990).

In the present study, we investigated the effects of Pharmahuasca and Harmine on the neural response to Self, Familiar, and Unknown faces. Additionally, we conducted face discrimination tasks during these sessions, wherein participants were asked to differentiate between incrementally morphed face pairs (Self-Familiar, Self-Unknown, Familiar-Unknown) using a two-alternative forced choice (2-AFC) task. Finally, we assessed the

association between electrophysiological and behavioural data, as well as the critical features of the psychedelic state, e.g., elementary and complex imagery. Ultimately, these investigations allowed us to measure the effects of pharmahuasca and harmine on *face recognition* and *discrimination* both at the neural and behavioural levels.

2.2. Methods

2.2.1. Experimental design

The present study followed a within-subject, double-blind, placebo-controlled design, with 3 sessions of counterbalanced drug administrations separated by 2 weeks (Pharmahuasca, Harmine, Placebo). The face processing EEG experiment and behavioural face discrimination task (2-AFC) were divided into three blocks presented sequentially. The order of the tasks was counterbalanced among participants.

2.2.2. Participants

Thirty-six right-handed healthy male volunteers (20-40y, BMI 18.5-25) were recruited for this study. Inclusion criteria comprised: (a) no current or previous history of neurological or psychiatric disorders and no family history of Axis-I psychiatric disorders (b) fluent German language (c) normal or corrected-to-

normal vision (d) normal hearing (e) little to no experience with hallucinogenic drugs. All participants underwent medical and psychological screening upon completing the initial telephone screening. On-site screenings were conducted in the same room as the experiments, ensuring familiarity with the surroundings, which was found conducive to the psychedelic experience (Hartogsohn, 2017). During the screenings, participants completed a training session to familiarize themselves with the tasks. The study enrolled 36 participants, 5 of whom were excluded because they did not complete the experimental procedure and one due to technical difficulties during data collection; thus, the final sample consisted of 30 participants. This study was approved by the ethical committee of the University of Zurich and carried out in compliance with the Declaration of Helsinki (2013). Participants gave written informed consent and were reimbursed commensurate with the time invested for participation (320.- CHF total, or 60.- per completed intervention day).

2.2.3. Drug and dosing

A counterbalanced order of (i) pharmahuasca, (ii) harmine, and (iii) placebo were administered in three different experiment sessions with a minimum 2 weeks of washout phase. (i) For the pharmahuasca condition (PHA), we used the standardized and quality-controlled pharmahuasca containing DMT (from *Mimosa tenuiflora*) and the monoamine oxidase inhibitor harmine (from Sigma-Aldrich / Merck KGaA). Thirty minutes after the sublingual administration of the 100 mg harmine capsule, the

DMT nasal spray was administered at intervals of 15 minutes. Each administration contained 10 mg of DMT, and the experiment started after 60 minutes of the first administration when participants were administered 50 mg of DMT. This procedure was preferred following a pilot study which showed that participants receiving doses within short time intervals had greater self-control and could cope better with the drug experience in an experimental setting (Helena Dorothea Aicher et al., 2023; Michael J. Mueller et al., 2023)(ii) For the harmine condition (HAR), participants were given 100 mg harmine capsules sublingually, along with a placebo nasal spray which was indistinguishable from Pharmahuasca as far as taste, smell, and appearance. (iii) In the placebo condition (PLA), both capsule and nasal spray were without active molecules and mimicked the natural drugs' appearance and taste. Please refer to *Supplementary Materials* Figure 14 for details of the study day, the timeline of the drug administrations and experiments.

2.2.4. Stimuli

2.2.4.1. Face processing EEG experiment

In the EEG experiment, the set of face stimuli consisted of 396 images pertaining to four different categories: (i) self faces, (ii) familiar faces, (iii) unknown faces (n=120 in each condition), and (iiii) target (n=36). (i) For self-face images, participants were photographed during on-site medical screening (Sony DSLRA350). (ii) Unknown-face images were chosen from the Chicago Face Database (Ma et al., 2015). (iii) For the familiar-face

images, we chose to use male celebrity pictures instead of participants' own family or friends to avoid additional biases that can arise in self-referential information processing from ingroup membership (Platek & Kemp, 2009). Additionally, we opted to utilize male stimuli in our experiments to prevent potential confounding results from morphing with female faces, which exhibit greater variability in facial features compared to male faces (Bruce et al., 1993; Burton et al., 1993). By selecting male stimuli, we aimed to ensure a more controlled and consistent manipulation of facial morphs, thereby enhancing the reliability and interpretability of our findings. Additionally, focusing on male stimuli allowed us to minimize potential gender-related differences in facial processing and familiarity, which are known to affect face recognition (Herlitz & Lovén, 2013; Wright & Sladden, 2003). This approach improved the internal validity of our study by reducing variability and potential biases related to gender differences in facial perception. A total of 262 male celebrity pictures were collected over the internet, including the faces of politicians, musicians, athletes, and actors. During the on-site medical screening, participants went through a pre-experiment familiarity test, where they rated each celebrity face as (a) *I do not recognize*, (b) *I recognize somehow*, (c) *I recognize*, and (d) *I can name the person*. Based on the ratings in (c) and (d), 120 celebrity pictures were selected to create participant-specific familiar-face stimuli. (iiii) Finally, scrambled images of participants' self-faces were used as a target (all image pixels were randomly oriented and placed). The selection of target stimuli, scrambled face, serves the purpose of maintaining attention during the oddball paradigm (Carmel & Bentin, 2002). In our

analysis, we deliberately excluded neural responses to scrambled images to focus specifically on investigating the discriminative neural response among various face stimuli (Bentin & Deouell, 2000). This decision was motivated by our aim to provide a targeted investigation into the neural correlates associated with facial recognition processes across a spectrum of familiarity, thereby enriching the interpretability of our findings within the context of face perception research under the influence of the psychedelics. Please refer to *Supplementary Materials* Figure 15 for the images of the stimuli.

2.2.4.2. Psychophysical Face Discrimination Task

For each participant, we created three sets of morphed faces (i.e., self-familiar, self-unknown, and familiar-unknown). The familiar face was selected based on individual ratings (from the "I can name this person" category) from the pre-experimental familiarity task. The unknown face was randomly chosen from the Chicago Face Database for each participant (Ma et al., 2015). Images were morphed in 10% steps, resulting in three sets (self-familiar, self-unknown, and familiar-unknown) of 9 morphed faces plus two original faces (self, familiar and the unknown category). Thus, every set contained 11 images in total (Please refer to *Supplementary Materials* Figure 16 for the images of the morphed stimuli). Each image was presented 12 times, for a total of 360 presentations. Morphed faces were generated by Abrosoft Fantamorph Deluxe 5.0. The software gradually merged facial features between any two of the three types of faces using 100-120

anatomical landmarks (e.g., points on eyes, nose, and mouth) that were manually aligned for each face pair. Since an increased reliance on the eye region correlates with a better ability to recognize faces, special attention has been given to the eyes by using 10-20 additional landmarks (Royer et al., 2018).

All stimuli (both for the EEG experiment and behavioural task) were converted to greyscale. An ellipse mask was placed around the face, the exterior of which was cropped, including the hairline and ears, leaving only the inner features of the face against a black background, using the open-source image editor GNU Image Manipulation Program (GIMP) (GNU Image Manipulation Program, 1995). The contrast and the luminance histograms of the images were equated by using the default function on the SHINE toolbox (Willenbockel et al., 2010), which was run under MATLAB R2020a (The Math Works, Inc., 2020). The spatial frequency (Self: Mean=0.179, SD=0.079; Familiar: Mean=0.169, SD=0.042; Unknown: Mean=0.175, SD=0.044) was not differed across face categories (ANOVA: $t(2,419)=1.245$, $p=0.289$).

Stimuli were presented electronically using E-Prime 3.0 software (Psychology Software Tools, Inc., 2016) at a constant viewing distance of 90 cm on a 25-inch screen, corresponding to an 11° x 15° (horizontal x vertical) visual angle. The E-Prime Chronos Device is used to collect button responses.

2.2.5. Procedure

2.2.5.1. Measures of Acute Subjective Effects

Participants' subjective state of consciousness was assessed using the 11-factor altered state of consciousness questionnaire (11DASC) (Studerus et al., 2010). The 11D-ASC is a well-validated self rating VAS developed to quantify the subjective experience of psychedelics and 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; Komter et al., 2015)). Before the experiment, respondents completed VAS-style ratings using a digital display screen and button press format. This paper specifically used elementary imagery and complex imagery scores from the 11D-ASC to focus on visual perception.

2.2.5.2. Face Processing EEG experiment

Subjects were instructed to keep their gaze on the fixation cross placed at the center of the screen for the entire block duration and were asked to press a button with their right index finger when the scrambled face (target) appeared. Targets could occur with a probability between 8 and 12%. This procedure ensured that participants attended each visual image and prevented eliciting motor responses for the relevant face categories (self-faces, familiar faces, unknown faces). The stimulus duration was 100 ms, and the interstimulus interval varied randomly between 1 and 1.4 seconds. The experiment was divided into 3 blocks, interleaved by a 3-minute break and a block of the behavioural

task. To prevent habituation, stimuli were presented pseudo-randomly so that no more than three faces of the same category could consecutively occur. On average, participants performed target detection with 98% accuracy. All conditions were presented in each experimental session (drug condition): PHA (Pharmahuasca), HAR (harmine) and PLA (placebo); thus, from now on, we will refer to the following conditions labels: PHA_{SELF}, HAR_{SELF}, PLA_{SELF}, PHA_{FAM}, HAR_{FAM}, PLA_{FAM}, PHA_{UNK}, HAR_{UNK}, PLA_{UNK}.

2.2.5.3. Psychophysical Face Discrimination Task

Participants made two alternative forced choices (2-AFCs) when presented with the face image to indicate whether the morphed face belonged to one of two possible categories. For example, when presented with an image from the self-unknown block, participants were instructed to determine whether a morphed face was more similar to a self or an unknown face. Choices were made by pressing one of two buttons of the Chronos Device using index fingers. Responses associated with left and right buttons were counterbalanced across sessions within each participant since previous studies showed a left-hand advantage over self-face recognition (Keenan et al., 1999). The face image remained on the screen for 3000 ms. Participants could only respond during that time; otherwise, no response was recorded, and the experiment continued. The EEG and the psychophysical tasks were always run within the same experimental session. Participants performed the psychophysical tasks between EEG recordings.

2.2.6. EEG recordings

Continuous EEG was recorded with the BioSemi Active 2 system with 64 Ag-AgCl pin-type active electrodes mounted on an elastic cap, according to the international 10-20 system. Eight additional flat-type active electrodes were used for body surface measurements. For horizontal and vertical electrooculography (EOG), electrodes were placed on each eye's outer canthus and the left eye's supraorbital and infraorbital. For electrocardiography (ECG), electrodes were placed on the end of the left collarbone and the lower left rib. Additional electrodes were placed on the right and left mastoid bones. Data were referenced to the Common Mode Sense (CMS) and the Driven Right Leg (DRL) electrodes, while the average voltage was kept in the range of ± 40 mV signal using Biosemi's electrodes offset tool. Signals were recorded with a 0.1 Hz high-pass filter and a 100 Hz lowpass filter, with a sampling rate of 2048 Hz. Triggers were sent to the Biosemi software and recorded using a parallel port along with the EEG data.

2.2.7. EEG preprocessing

The preprocessing was performed offline using EEGLAB (Delorme & Makeig, 2004) within the MATLAB environment (The Math Works, Inc., 2020). Data were pre-processed with a semiautomatic pipeline implemented in MATLAB (Stropahl et al., 2018). Data were re-referenced to the Fz electrode after they were imported. Stereotypical artifacts (eye blinks, lateral eye movements, and heartbeats) were detected by using an infomax independent component analysis (ICA) (Bell & Sejnowski, 1995).

To improve ICA decomposition, data were low-pass filtered (windowed sinc FIR filter, cut-off frequency 40Hz, filter order 256), resampled to 256 Hz and high-pass filtered (windowed sinc FIR filter, cut-off frequency 1Hz, filter order 512) and finally, segmented into consecutive dummy epochs of 1 second. The epochs with joint probabilities greater than 4 standard deviations were rejected (Bottari et al., 2020). ICA weights were then attributed to the *unfiltered raw data*. Topographies of each component were plotted and visually inspected for artifacts (eye blinks, saccades, and heartbeat). Across all datasets, components representing the best stereotypical artifacts were used as a template for a semi-automated CORRMAP algorithm to identify ICA components with similar topography across all datasets. A correlation of the ICA inverse weights was computed, and the components with a correlation coefficient higher or equal to 0.8 were removed (from the raw data). Artifact-free data were lowpass filtered (windowed sinc FIR filter, cut-off frequency 40Hz, filter order 256), resampled to 256 Hz and high-pass filtered (windowed sinc FIR filter, cut-off frequency 0.1Hz, filter order 5120). Bad channels were interpolated with the spheric spline. The proportion of interpolated electrodes was kept at <10% for each participant. Data were re-referenced to the average. Data were segmented as a function of stimulus category (Self, Famous, Unknown faces) and conditions (PHA, HAR, PLA), into epochs containing 200 ms pre-stimulus and 800 ms post-stimulus. Within the same stimulus category/condition, epochs that had a higher joint probability of 4 standard deviations were excluded from further analysis. Finally, epochs exceeding $\pm 100 \mu\text{V}$ were also excluded. The number of removed epochs did not differ across

conditions/stimulus categories (repeated-measures ANOVA ($F(4, 116)=0.35$, $p=0.843$, $\eta^2=0.013$; the mean and the $\pm$ SD of removed epochs for each conditions across stimulus categories were as follows: $5.9\% \pm 2.6$ for PHA_{SELF}, $5.8\% \pm 2.3$ for PHA_{FAM}, $5.7\% \pm 2.7$ for PHA_{UNK}; $5.4\% \pm 1.7$ for HAR_{SELF}, $5.4\% \pm 1.5$ for HAR_{FAM}, $5.5\% \pm 1.6$ for HAR_{UNK}; $5.8\% \pm 1.7$ for PLA_{SELF}, $5.6\% \pm 1.3$ for PLA_{FAM}, $5.4\% \pm 1.3$ for PLA_{UNK}). Finally, epochs were baseline-corrected from -200 to 0 ms.

2.2.8. Statistical Approach

2.2.8.1. Measures of Acute Subjective Effects

Elementary and complex imagery scores (11D-ASC) were analysed using repeated measure analyses of variance (rANOVAs; JASP) with the within-participant conditions as factors (PLA, HAR, PHA). The assumption of sphericity was tested using Mauchly's test. If epsilon (ϵ) values were <0.75 , then we used the Greenhouse-Geisser correction and if they were >0.75 , then we used the Huynh-Feldt correction. When the F-statistics were significant, post-hoc paired t-tests were performed using a Bonferroni correction (adjusted $\alpha=0.017$).

2.2.8.2. Face Processing EEG experiment

First, we assessed the main effects of the drug conditions (PHA, HAR, PLA) on each face category (Self, Familiar, Unknown). We employed cluster-based nonparametric permutation F-statistics

(MANOVA, Monte Carlo sampling method, 1,000 iterations, cluster alpha $p < 0.05$, maxsum criterion, cluster-based method for multiple comparison correction, minimum spatial extent 2 adjacent channels) to determine whether the three conditions differed. In case of significant effects in the MANOVA, we then employed cluster-based nonparametric permutation t-statistics (Monte Carlo sampling method, 1,000 iterations, two-tailed, cluster alpha $p < 0.025$, maxsum criterion, minimum spatial extent 2 adjacent channels) (Maris & Oostenveld, 2007) between pairs of conditions. The analysis was run within the whole time-window (0 – 600 ms). This data-driven approach allowed for identifying the significant difference between conditions without bias from a priori assumptions of a specific region of interest (ROIs) or time intervals while solving multiple comparison problems (Maris & Oostenveld, 2007). If the cluster-based p-value was less than .025 (corresponding to a critical alpha level of .05 for two-tailed testing, accounting for both positive and negative clusters), we rejected the null hypothesis that there was no difference between the conditions.

Secondly, we tested the specific hypothesis that the modulation of the self-face differed significantly from the modulation of familiar and unknown faces. The interaction effect of drug conditions (PHA, HAR, PLA) and face stimuli (Self, Familiar, Unknown) was investigated by running a series of nonparametric cluster-based permutation t-statistics (Monte Carlo sampling method, 1,000 iterations, one-tailed for negative clusters, cluster alpha $p < 0.05$, maxsum criterion, minimum spatial extent 2 adjacent channels) of the differential waves calculated by subtractions across face categories (e.g.

$PHA_{Self-Familiar}$ vs $PLA_{Self-Familiar}$), within the whole time-window (0 – 600 ms) across all electrodes.

2.2.8.3. Psychophysical Face Discrimination Task

To analyze the behavioural data, we fitted psychometric functions to each participant's responses, using Bayesian inference, implemented in the *Psignifit toolbox* (Version 4) for MATLAB, a software package that implements the maximum-likelihood method described by (Wichmann & Hill, 2001). Psignifit fits a beta-binomial model (instead of a binomial model), where the probability of a correct percentage is a random variable derived from a beta distribution (Schütt et al., 2016). The model has been shown to provide better fits for over-dispersed data, i.e., data in which answer probabilities are not independent as the conventional model assumes. We used the logistic function, 'YesNo' experiment design with four free parameters (μ , σ , λ , η): threshold, slope, lapse rate and guess rate.

We assessed the goodness-of-fit for each subject, using the Likelihood-ratio based *pseudo-R-squared* calculated by the proportional reduction in the deviance of the fitted psychometric model (D_{fitted}) compared to that of the null model (D_{null}):

$$R^2L = 1 - \frac{D_{fitted}}{D_{null}}$$

Deviance values for the fitted and null models were calculated using the *Psignifit* toolbox. If a participant's psychometric curves did not reach $R^2_L > 0.8$, that participant was removed from further analysis in that condition (Feigin et al., 2021). The data of 3 participants were excluded because of an unsuccessful fit. Thus, the final sample comprised 27 participants. Psychometric function threshold and slope were extracted for each subject separately.

Threshold or Point of Subjective Equality (PSE) indicates the stimulus level at which a participant is as likely to judge the stimulus with an equal probability. Any horizontal shift in the psychometric function describes the bias of the observer's internal estimate of the recognition. The psychometric function's slope determines the observer's discrimination threshold, defining their sensitivity to the stimulation (the bigger the value, the steeper the slope). For each measure of interest PSE and slope, we ran separated repeated measure analyses of variance (rANOVAs; JASP) with the within-participant drug conditions as factors (PLA, HAR, PHA). The assumption of sphericity was tested using Mauchly's test. If epsilon (ϵ) values were < 0.75 , then we used the Greenhouse-Geisser correction and if they were > 0.75 , then we used the Huynh-Feldt correction. When the F-statistics were significant, post-hoc paired t-tests were performed using a Bonferroni correction (adjusted alpha: 0.017).

Additionally, the effect of face identity (Self, Familiar Unknown) and drug condition (PHA, HAR, PLA) on response times was tested employing two-way repeated measures analysis of variance (ANOVA). Only trials including %100 images of self,

familiar and unknown faces were analyzed. Greenhouse-Geisser or Huynh-Feldt correction for non-sphericity was applied when required. We subsequently conducted post-hoc pairwise comparisons to detect differences between conditions. Effect sizes were estimated using the partial eta square (η^2p) method. All analyses were carried out with JASP software (JASP Team, 2023).

2.2.8.4. Correlations between EEG and Behavioural Data

To investigate the association between EEG and behavioural data collected during the psychophysics morphing experiment, the Pearson correlation coefficient between the differential EEG data and the relevant psychometric parameters (e.g., the EEG *PHA_{Self-Unknown}* was correlated with the slope of the behavioral data of the Self-Unknown morphed category). Coefficients were calculated using nonparametric cluster-based permutation Tstatistics (ft_statfun_correlationT, Monte Carlo sampling method, 1,000 iterations, cluster alpha $p < 0.05$, maxsum criterion, clusterbased method for multiple comparison correction, minimum spatial extent 2 adjacent channels) across all electrodes and time points (0-600 ms) (Oostenveld et al., 2011).

Additionally, we analyzed the correlation between the relevant psychometric parameters and P1, N170 and P300 ERP components. Occipital electrodes (OZ, O1, O2) were chosen within 90 to 150 ms for P1, posterior electrodes (P8, PO8) were chosen within 160 to 190 ms for N170, and central-posterior

electrodes (POZ, Pz, CPz) were chosen within 300 to 500 ms for P300 and Pearson coefficient was calculated using same nonparametric cluster-based permutation T-statistics.

2.3. Results

2.3.1. Measures of Acute Subjective Effects

We investigated the effect of the drug conditions (PHA, HAR, PLA) on the elementary and complex imagery scores using repeated measures ANOVA. In case Mauchly's test of sphericity indicated that the assumption of sphericity had been violated, Greenhouse-Geisser correction was used. There was a statistically significant effect of drug condition on elementary imagery scores ($F(1.23, 36.891) = 42.314, p < 0.001, \eta^2p = 0.585$). The post-hoc test revealed that PHA significantly increased the elementary imagery scores (Mean= 43.2, SD=33) compared to PLA ($p < 0.001$; Mean= 0.12, SD=0.7) and HAR ($p < 0.001$, Mean= 4.2, SD=13.2) (Figure 26). There was also a statistically significant effect of drug condition on complex imagery scores ($F(1.371, 41.141) = 47.524, p < 0.001, \eta^2p = 0.613$). The post-hoc tests revealed that PHA significantly increased the complex imagery scores (Mean= 51.1, SD=34.2) compared to PLA ($p < 0.001$; Mean= 0.39, SD=1.9) and HAR ($p < 0.001$, Mean= 6.9, SD=18.3; Figure 2-6).

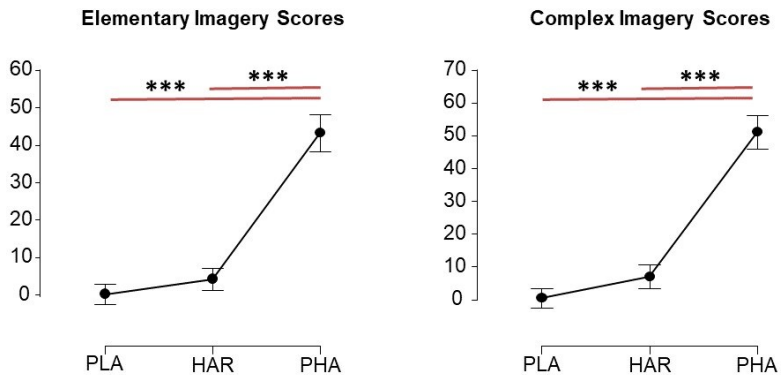


Figure 1- Plots showing the elementary and complex imagery scores

PHA significantly increased elementary and complex imagery scores (PHA vs. PLA and PHA vs. HAR: $p < 0.001$; PLA vs. HAR: n.s.).

2.3.2. Face Processing EEG experiment

Self-Face

First, we investigated the EEG response to self-faces. A nonparametric cluster-based permutation analysis was run to investigate the effect of drug conditions (PHA, PLA, and HAR) on the ERPs in response to self-face (refer to Table 1 in *Supplementary Materials* for all the detailed statistical results). Cluster-based analysis (MANOVA, comparing the three drug conditions) revealed 2 positive clusters at 140-199 ms and between 207-600 ms (all $p < 0.001$), suggesting a statistical

difference between the responses to self-faces across drug conditions. The direct comparison revealed that the PHA condition increased the neural response to self-face within the time window of 140-200 ms at posterior-occipital electrodes compared to the other drug conditions (PHA vs. PLA, $p=0.022$; PHA vs. HAR, $p<0.001$; Figure 2 A, B). The same analysis revealed a reduction of N170-P300 waves in the PHA condition compared to both PLA and HAR conditions (Figure 2 B). In addition, PHA increased neural responses within the time window of 200–600 ms at the frontal electrodes compared to the other drug conditions (PHA vs. PLA, all clusters $p<0.025$; PHA vs. HAR, $p<0.001$) (Figure 2 A). There was no significant difference between placebo and harmine drug conditions.

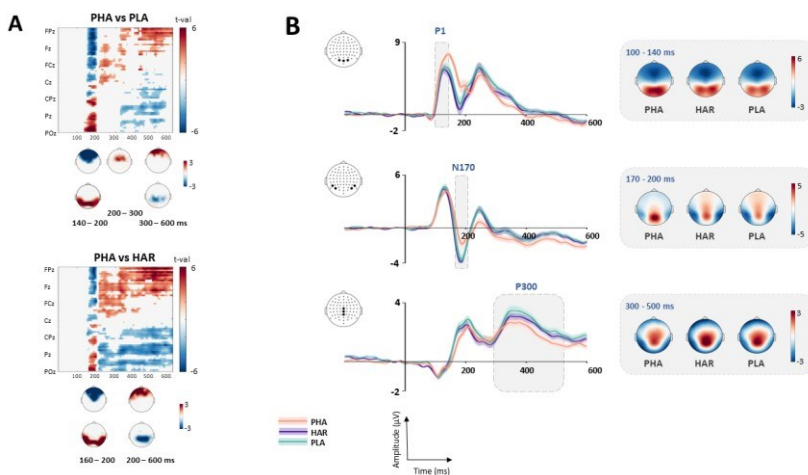


Figure 2- The effect of PHA on self-face

(A) Spatiotemporal matrices display the results of the cluster-based permutation test, comparing the responses across conditions (PHA vs. PLA and PHA vs. HAR) to self-face stimuli. Significant clusters are shown as topographic distributions at the bottom of the graphs. (B) Grand averaged ERPs (mean and SE) computed across all participants, averaged over O1, O2, Oz for P1 (*upper*), PO8, P8, PO7, P7 for N170 (*middle*) and Pz, CPz, Cz for P300 (*lower*) and scalp topography of each drug condition averaged within relevant time-windows on the right side. Electrodes were chosen based on the results of the cluster-based permutation test. PHA decreased N170 and P300 compared to both HAR and PLA. No significant differences emerged between PLA and HAR drug conditions.

Familiar Face

The same analytical approach was performed on the familiar face condition. Cluster-based analysis (MANOVA) revealed 2 positive clusters between 80-400 ms and 400-580 ms ($p < 0.001$ and $p = 0.017$), suggesting a statistical difference between the response to familiar face images as a function of drug condition. The direct comparison revealed that PHA increased the neural response to familiar faces within the time window of 90-200 ms at the posterior-occipital electrodes compared to the other drug conditions (PHA vs. PLA, $p = 0.013$; PHA vs. HAR, $p = 0.018$) (Figure 3 A). The effect revealed altered P1-N170 waves in the PHA condition compared to both PLA and HAR conditions (Figure 3 B). In addition, PHA increased neural responses within the time window of 200–600 ms at frontal electrodes compared to the HAR condition (all clusters $p < 0.025$) but not when compared to placebo ($p > 0.025$) (Figure 3 A). Interestingly, HAR increased

the neural response to familiar faces within the time window of 265-480 ms compared to the placebo condition ($p=0.01$) at right central-parietal-temporal electrodes (see Figure 17 in *Supplementary Materials* for the spatiotemporal matrix showing the significant effect of HAR on familiar faces).

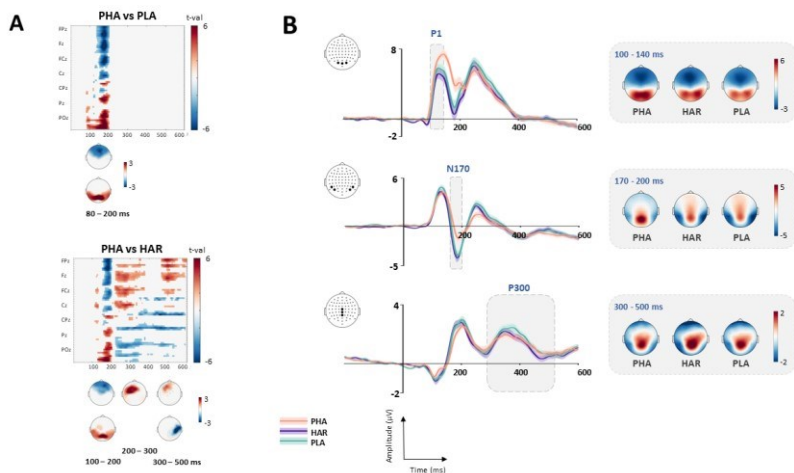


Figure 3 -The effect of PHA on familiar faces

(A) Spatiotemporal matrices display the results of the cluster-based permutation test, comparing the response to familiar face stimuli across drug conditions (PHA vs. PLA and PHA vs. HAR). Significant clusters are shown as topographic distributions at the bottom of the graphs. (B) Grand averaged ERPs (mean and SE) computed across all participants, averaged over O1, O2, Oz for P1 (*upper*), PO8, P8, PO7, P7 for N170 (*middle*) and Pz, CPz, Cz for P300 (*lower*) and scalp topography of each drug condition at relevant time windows on the right side. Electrodes were chosen based on the results of the cluster-based permutation test. PHA elicited increased P1 and decreased N170 compared to both HAR and PLA. PHA did not affect P300.

Unknown Face

Finally, a nonparametric cluster-based permutation analysis was run to investigate the effect conditions (PHA, PLA, and HAR) on the ERPs in response to unknown faces. Cluster-based analysis (MANOVA) revealed 2 positive clusters at 125-205 ms and between 215-600 ms (all $p < 0.001$), suggesting a statistical difference in drug conditions on an unknown face. The direct comparison revealed that PHA increased the neural response to an unknown face within the time window of 130-205 ms at the posterior-occipital electrodes compared to the PLA condition ($p = 0.02$) but not when compared to HAR ($p > 0.025$) (Figure 4 A). The effect revealed altered N1-P300 waves in the PHA condition compared to the PLA condition (Figure 4 B). In addition, PHA decreases neural responses within the time window of 300–600 ms at the right frontal central posterior temporal electrodes compared to both PLA ($p < 0.001$) and HAR ($p = 0.004$) conditions.

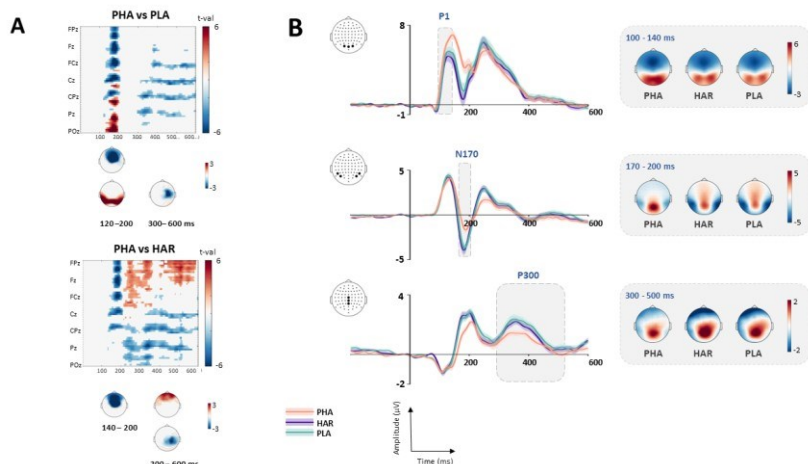


Figure 4-The effect of PHA on unknown faces

(A) Spatiotemporal matrices display the results of the cluster-based permutation test, comparing the conditions (PHA vs. PLA and PHA vs. HAR) response to unknown face stimuli. Significant clusters are shown as topographic distributions at the bottom of the graphs. (B) Grand averaged ERPs (mean and SE) computed across all participants, averaged over O1, O2, Oz for P1 (*upper*), PO8, P8, PO7, P7 for N170 (*middle*) and Pz, CPz, Cz for P300 (*lower*) and scalp topography of each drug condition at relevant time windows on the right side. Electrodes were chosen based on the results of the cluster-based permutation test. PHA elicited decreased N170 and P300 compared to PLA and decreased P300 compared to HAR. There were no significant differences between PLA and HAR drug conditions.

Interim Summary

In summary, our investigation revealed a consistent impact of pharmahuasca within the first 200 milliseconds across all face

categories (self, familiar, and unknown). During this time, there was an increase in neural response at parietooccipital electrode sites compared to the placebo (PLA) condition. Moving beyond the 200 milliseconds, subtle differences in the effects of pharmahuasca appeared to emerge among the various face categories, as observed through visual inspection. Notably, these effects remain to be tested. Therefore, in the subsequent section, we will investigate whether the influence of pharmahuasca distinctly modifies the processing of one's own face in comparison to familiar and unfamiliar faces.

Does pharmahuasca (PHA) reduce the self-referential information processing?

We tested the specific hypothesis that pharmahuasca (PHA) reduced self-face processing compared to other face categories. A nonparametric cluster-based permutation analysis was run for the interaction effect between drug conditions and the differential ERP waves calculated by subtracting the signal between face categories (e.g., $PHASelf-Unknown$ vs. $PLASelf-Unknown$;

$PHASelf-Unknown$ vs. $HARSelf-Unknown$; etc.) (Please refer to Table 2 in *Supplementary Materials* for all the detailed statistical results). The differential EEG responses for self-minus-unknown and self-minus-familiar faces were reduced in the PHA condition at the central-posterior electrodes compared to both other two drug

conditions. This corresponded to a negative cluster approximately between 320 and 550 ms (Self-Unknown: PHA vs. PLA, $p=0.024$; Self-Familiar: PHA vs. PLA, $p=0.004$; PHA vs. HAR, $p=0.002$) comprising several central-posterior electrodes (Figure 5 A). These results suggest that the neural response measured at centro-posterior electrodes when processing self-faces was more similar to familiar and unknown faces in PHA than in HAR/PLA conditions. A post-hoc cluster-based analysis was run to compare amplitudes of responses to self, familiar and unknown faces within a 300-500 ms time window (comprising the P300) at the central posterior electrodes (CPz, POz, Pz). Results revealed that the neural response to self-faces was increased in PLA and HAR conditions compared to the other unknown and familiar faces. This increase in neural response was substantially reduced in the PHA condition (Figure 5 C).

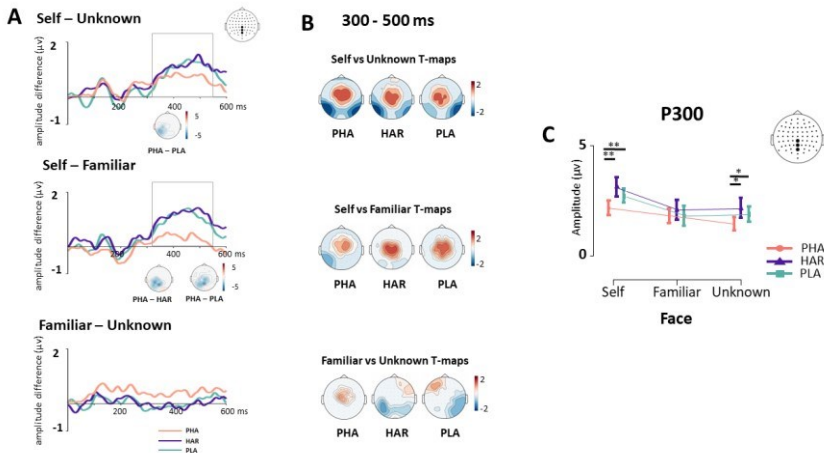


Figure 5- Interaction effect

Plots showing the significant differential ERPs of Self-Unknown (*upper*) and Self-Familiar (*middle*), and Familiar-Unknown (*lower*) at the posterior electrodes (POz, Pz, CPz) within 300-550 ms. Topographies of significant interaction effects of drug conditions are shown below the differential ERP plots. (B) Topographies of the difference responses for Self - Unknown, Self - Familiar and Familiar - Unknown for each drug condition (PHA, HAR, PLA). (C) Interaction plots show decreased responses to self and unknown faces in PHA condition compared to HAR and PLA conditions during the P300 time window over central-posterior electrodes (POz, Pz, CPz). Results revealed that the PHA condition dampened the neural response to self-faces, and in turn, the differences between neural responses to self-faces and the other face categories were reduced.

2.3.3. Psychometric Face Discrimination Task

After assessing PHA's effects on the neural response to face categories, we analyzed the data of the psychophysics 2-AFC task. To investigate whether the drug conditions (PHA, HAR, PLA) affected PSE values (the center of the psychometric functions, i.e., the thresholds), we compared them by employing a repeated measures ANOVA with drug condition as a factor. There were no significant effects of drug condition on the PSE values for all three morphing continuums (*Self-Unknown*: $F(2,52)=0.909$, $p=0.409$; *Self-Familiar*: $F(2,52)=1.748$, $p=0.184$, *Familiar-Unknown*: $F(3,52)=0.831$, $p=0.441$). This suggested that neither PHA nor HAR conditions affected PSE values, changing biases in face discrimination.

We then compared the slope values for psychometrics to investigate the drug's effect on face discrimination sensitivity.

For the Self-Unknown continuum, we observed a statistically significant effect of drug condition on slope values, $F(1.684, 43.792, \text{Huynh Feldt corrected}) = 6.128, p = 0.007, \eta^2p = 0.191$. The post-hoc test revealed that PHA significantly decreased the slope value (Mean= 20.5, SD=8.5) compared to PLA ($p=0.003$; Mean= 26.7, SD=7.2), but not HAR ($p=0.149$, Mean= 24.1, SD=8.5; see Figure 6 A).

Also, for the Self-Familiar continuum, we observed a statistically significant effect of drug condition on slope values, $F(2,52) = 3.172, p = 0.05, \eta^2p = 0.109$. The post-hoc test revealed that PHA significantly decreased the slope value (Mean= 22.3, SD=8.9) compared to PLA ($p=0.022$; Mean= 27.5, SD=7.8), but not HAR ($p=0.099$, Mean= 23.8, SD=7.8) (Figure 6 B).

For the Familiar-Unknown category, there was also a statistically significant effect of drug condition on slope values $F(1.739, 45.214)=5.090, p< 0.013, \eta^2p = 0.164$, Huynh Feldt corrected). The post-hoc test revealed that PHA significantly decreased the slope value (Mean= 18.4, SD=7.6) compared to both HAR ($p=0.017$; Mean= 23.5, SD=8.3) and PLA ($p=0.034$, Mean= 23.1, SD=8) (Figure 6 C).

Overall, results suggested that PHA decreased the slope for all morphing categories compared to PLA, suggesting that PHA reduced the sensitivity to face discriminations.

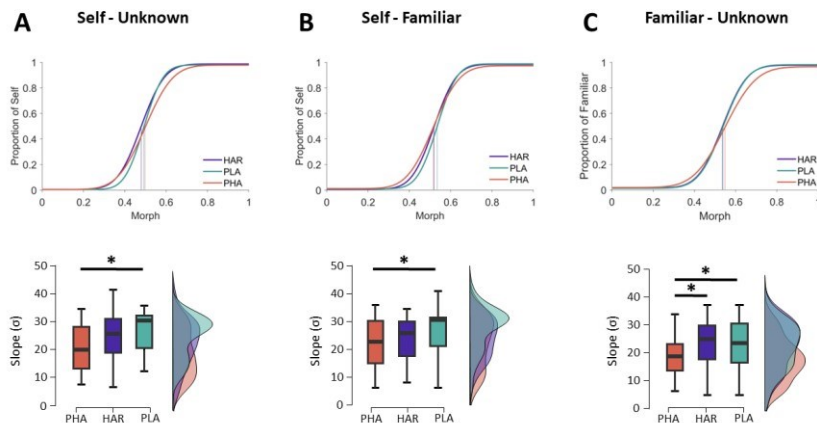


Figure 6-Psychometric functions illustrate the fit of the face discrimination results

Psychometric functions (*upper*) illustrate the average fit across participants of the face discrimination results. The X-axis represents the morphing continuum, and the y-axis represents the percentage of responses Self for Self-Unknown (A) and for Self-Familiar (B) continuum, and Familiar for the Familiar-Unknown (C) continuum. The point of Subjective Equality (PSE) was not changed by the drug conditions, suggesting no alteration of bias in face discrimination. (*Lower*) Box plot of the slope values for each morphing category. PHA reduced the slope values for all morphing categories compared to the PLA condition, indicating that PHA reduced the general discrimination sensitivity across face stimuli.

Additionally, we investigated whether PHA affected response times during face discrimination tasks. A two-way repeated measure of ANOVA was used to examine the effect of face category (Self, Familiar, Unknown) and drug condition (PHA,

HAR, PLA) on the reaction times (Figure 7). There were significant main effects of the face category ($F(2, 56) = 17.1, p < .001, \eta^2p = 0.379$) and drug condition ($F(1.72, 48.152) = 18.992, p < .001, \eta^2p = 0.404$). The interaction between the effects of face and treatment on reaction times was insignificant ($F(3.162, 88.526) = 2.3, p = 0.079, \eta^2p = 0.076$).

Post-hoc comparisons showed that reaction times were significantly higher in the PHA condition compared to other drug conditions across all face categories (*Self*: PHA vs. PLA, $p < 0.001$, PHA vs. HAR, $p < 0.001$ *Familiar*: PHA vs. PLA, $p < 0.001$, PHA vs. HAR, $p < 0.001$, *Unknown*: PHA vs. PLA, $p < 0.001$, PHA vs. HAR, $p < 0.001$).

Additionally, post-hoc comparisons showed an advantage of self-face in the discrimination task; that is, shorter response times for recognizing the self-face in comparison to an unknown-face category in all drug conditions (PHA: $p = 0.001$; PLA: $p = 0.034$; HAR: $p < 0.001$) and to familiar face in PLA condition ($p = 0.024$).

These results support the notion that self-face is processed distinctively and not simply as a familiar face. Notably, RTs to discriminate unknown faces significantly increased compared to familiar faces in the HAR condition ($p = 0.005$).

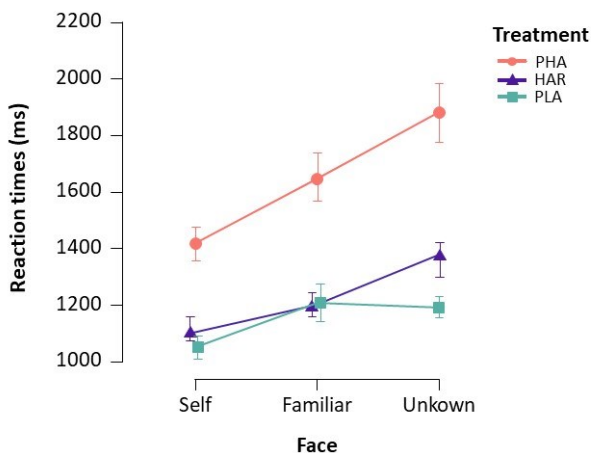


Figure 7- Mean reaction times on the facial recognition task.

The figure illustrates the mean response times (ms) with standard error bars (SE) for the three conditions: Self, Familiar, and Unknown faces and for 3 drug conditions (PHA, HAR, PLA) measured in the psychometric face discrimination task. Participants were slower under the influence of PHA than other drug conditions across all face categories (all $p < 0.001$). Self-face was recognized faster than unknown faces in all drug conditions (PHA: $p = 0.001$; PLA: $p = 0.034$; HAR: $p < 0.001$) and to familiar faces in PLA condition ($p = 0.024$), indicating a general faster discrimination of self-faces. Additionally, participants were slower in discriminating unknown faces in the HAR condition ($p = 0.005$).

2.3.4. Correlations between EEG and Behavioural Data

Without any a priori hypothesis, a correlation analysis was performed for the PHA condition between differential EEG waves (Self – Unknown, Self – Familiar, Familiar – Unknown) and

the slope values of corresponding morphing categories (Self – Unknown, Self – Familiar, Familiar – Unknown), which, as described earlier was reduced in PHA conditions. As an example, the differential ERP wave of *PHA_{Familiar–Unknown}* was correlated with the slope of the Familiar-Unknown category. First, a cluster-based correlation was performed across all electrodes and all time points (0-600ms). No significant correlation-clusters were observed between the slope values of Self-Unknown, Self-Familiar and familiar-unknown morphing categories and the entire time window (0-600 ms; all $p>0.05$). Additionally, no correlations were observed between the elementary/complex imagery scores and enhanced P1 (90-140 ms)/decreased N170 (170-200 ms) components (all $p>0.05$).

2.4. Discussion

The results of this placebo-controlled, double-blinded, within-subject design study provided novel insights into psychedelics' effects on face recognition and discrimination. Our findings demonstrate significant alterations in early visual processing during the pharmahuasca-induced psychedelic experience. Moreover, we observed specific modulation of the self-face perception compared to familiar and unknown faces, emphasizing the effect of psychedelics on self-referential information processing.

General effects of Psychedelics on Early Visual Processing

The primary finding of our study is that pharmahuasca administration leads to increased neural response in the posterior cortex during the early stages of visual perception (<200 ms) across all face categories (Self, Familiar, Unknown). This time range comprised both early P1 and N170 waves of the ERPs. Pharmahuasca increases the P1 at the medial occipital electrodes and reduces the N170 at the lateral occipital-temporal electrodes. The alterations observed in the early components of visual event-related potentials (ERPs), with an increase in medial P1 and a reduction in posterior N170 components, suggest that Pharmahuasca has different effects depending on the levels of face processing.

This finding shows that the effect of psychedelics can be dissected within the chronology of face perception, ultimately expanding our understanding of the opposite effects of serotonin modulation during visual processing. While our study didn't directly measure synaptic serotonin release, we can infer its involvement based on the well-established effects of psychedelics in the brain. Psychedelics primarily exert their effects through serotonin receptors, as demonstrated by the attenuation of their effects with serotonin receptor antagonists (Gonzalez-Maeso et al., 2007; Nichols, 2016). The relationship between serotonin and visual hallucinations is further supported by the high expression of 5-HT_{2A} receptors in the visual cortex (Dyck & Cynader, 1993; Gerstl et al., 2008; Watakabe et al., 2009), highlighting the importance of serotonin in visual processing and potentially in

the alterations observed during face perception under psychedelic influence.

Within the ventral occipitotemporal face processing network, faces are processed across different selective regions. The information process initiates in the inferior occipital region ("occipital face area", OFA), which is sensitive to the low-level features of the visual input (e.g., size, luminance, contrast, spatial frequency spectrum). The activity of this region has been associated with the P1 ERP component. Subsequently, the information reaches the lateral middle fusiform gyrus (commonly referred to as the fusiform face area, FFA) and the posterior superior temporal sulcus (pSTS), which are responsible for high-level structural encoding of faces and linked to the N170 component of the ERPs (Duchaine & Yovel, 2015; Haxby et al., 2000; Rossion & Jacques, 2011; Sadeh et al., 2010; Tsao & Livingstone, 2008). Our findings underscore significant alterations in the core system of face processing induced by psilocybin, as highlighted by the heightened P1 component, indicative of heightened visual sensitivity, juxtaposed with the attenuated N170 component, suggestive of impaired structural encoding of faces. However, the absence of control categories in this study, such as objects, impedes our ability to definitively attribute these effects exclusively to faces. Intriguingly, prior psychedelic research suggests that similar alterations in early visual processing extend beyond faces to encompass non-face stimuli (Kometer et al., 2011b, 2013b), hinting at a broader effect of psychedelics on visual processing mechanisms.

Kometer et al. (2011) have shown that psilocybin dose-dependently increases the medial P1 and decreases the N170 component in response to object completion task. Additionally, increased medial P1 was linked to subjective reports of enhanced brightness perception and reduction of the N170 was then associated with the perception of visual hallucinations (Kometer et al., 2011b, 2013b). Despite the significantly higher subjective ratings of visual distortions in the pharmahuasca condition compared to the other drug conditions, the correlation between the pharmahuasca-induced increase/decrease of the ERP components and the scores related to complex and elementary imagery did not reach statistical significance in our study.

Additionally, utilizing a forced-choice direction of motion discrimination task, Carter et al. showed that psilocybin specifically hinders coherence sensitivity for random dot patterns. This impairment is likely influenced by high-level global motion detectors. In contrast, there was no discernible impact on contrast sensitivity for drifting gratings, a function believed to be governed by low-level detectors (Carter et al., 2004).

Therefore, by integrating all of these EEG findings of the increase in P1 and concurrent decrease in N170, it could be speculated that psychedelics have opposite actions on low-level vs. high-level visual processing, namely enhancing the perception of simple visual features (e.g., brightness, contrast, local motion detection) and at the same time dysregulating higher-level integration processes (e.g., structural encoding of the faces, object recognition, global motion detection) (Condorelli, 2022). These

results offer a strong rationale for understanding the emergence of elementary visual experiences induced by psychedelics. However, further investigation is required to elucidate the underlying neural mechanisms behind intricate complex imagery phenomena, including visualizing autobiographical memories or entirely unfamiliar entities and locations (Davis, Clifton, et al., 2020; Lutkajtis, 2021).

Ultimately, the observed differential effects of the drug on the P100 and N170 components highlight the need to understand the specific mechanisms underlying these alterations in visual processing. The use of an oddball task, while effective for assessing general sensory processing and attention, might not be ideal for dissecting these nuanced effects (Polich, 2007). Understanding why the drug affects these components differently is crucial for elucidating its precise impact on neural activity during face perception. Future studies should focus on tasks specifically designed to probe face recognition mechanisms, such as face recognition tasks, holistic processing tasks, and studies involving the inversion effect. Face recognition tasks can directly assess the N170 component, which is specifically related to face processing (Eimer, 2011). Holistic processing tasks can help elucidate the distinct contributions of the P100 and N170 components to face recognition (Rossion, 2008). Additionally, the inversion effect, which disrupts holistic face processing and typically alters N170 responses, can provide valuable insights into the drug's impact on the visual system's adaptability (Yin, 1969). Exploring these specific aspects could reveal how the drug's effects on P100 and N170 relate to behavioral outcomes and subjective experiences, shedding light on the functional

significance of these neural responses and their role in shaping perceptual and cognitive processes.

Specific effects of Psychedelics on Self-referential Information Processing

The phenomenology of psychedelics is characterized by profound alterations in self-experience, encompassing the dissolution of the self/ego and blurring of the boundaries that delineate the self from the external world, ultimately fostering a sense of empathy and compassion towards self and others (Blatchford et al., 2020; Letheby & Gerrans, 2017; Tagliazucchi et al., 2022). According to social neuroscience, prosocial human traits like empathy and compassion are based on shared representations of self and others (Preston & Hofelich, 2012). Given this, we recorded ERPs elicited by the self, familiar and unknown faces with the hypothesis that, compared to controls, the pharmahuasca group would experience alterations of self-perception (or ego-dissolution), which could be associated with a reduction of self-face response compared to familiar/other-related face processing (i.e., smaller differences between self- and familiar/unknown faces). The spatiotemporal analysis of the EEG signal across the whole scalp and all the time window (0–600 ms) revealed significant drug-by-face interaction. The pharmahuasca significantly diminished the difference in neural responses between self-unknown and self-familiar faces at posterior midline electrodes during the 300-500 ms timeframe, namely the

P300 ERP component, compared to harmine and placebo conditions (Figure 5A).

P300 ERP component reflects attentional resource allocation (Polich, 2007, 2012). Source localization of this component typically corresponds with activations in DMN structures that are associated with self-referential information processing (Knyazev, 2013). Due to its high social/adaptive value, self-related information has preferential access to our attentional resources (Gray et al., 2004). Electrophysiological studies showed that the P300 amplitude is greater in response to participants' self-referential information, such as their own faces, than for famous and unknown faces (Scott et al., 2005; Sui et al., 2006; Tacikowski & Nowicka, 2010), for self-name than for other names (Tacikowski et al., 2011, 2014), even during sleep (Perrin et al., 1999) and during unconscious perception (Doradzińska et al., 2020). Our findings demonstrate that pharmahuasca significantly decreased the P300 amplitude for self-face and to a lesser extent for the unknown faces compared to harmine and placebo conditions. P300 amplitude for familiar faces remained consistent across all drug conditions (Figure 5B). Because the attention to self substantially decreased, the difference between self-unknown and self-familiar is blurred during the psychedelic experience.

Previous studies showed similar results on the relationship between psychedelics and self-referential information processing. A recent EEG-ERP study investigating the P300 mechanism using an auditory self-monitoring task found that psilocybin reduced the difference between self-other stimuli

(Smigielski et al., 2020). Additionally, the P300 effect significantly correlated with the intensity of the experience of unity and altered meaning of percepts. Moreover, meditators who practice Love and Kindness Meditation (LKM) displayed a smaller P300-amplitude difference in response to self- and other stimuli and this is negatively correlated with the duration of their practice (Trautwein et al., 2016). Therefore, it has been suggested that psychedelics primarily alter self-referential processing by inducing a decentring of the self and diminishing the responses between self and familiar/unknown face categories during the P300 processing stages. We speculate that this alteration of neural processing might be associated with feelings of unity, compassion, and empathy, the constructs continuously associated with the psychedelic experience's phenomenology (Preller & Vollenweider, 2018).

The current study provides evidence that psychedelics reduce the focus on the self and lead to a stronger self–other integration, which has been thought to be an underlying mechanism of improved social and emotional cognition (Dinulescu et al., 2021). Such a mechanism would have important implications as changes in self-processing play a vital role in the effectiveness of psychedelic-assisted therapy (Eisner & Cohen, 1958; Nayak & Johnson, 2021; Reiff et al., 2020). Many mental disorders, including depression and anxiety, are often characterized by excessive self-focus, feelings of isolation and decreased attention to others and the environment, which is attributed to heightened DMN resting-state activity and an altered balance between DMN

and executive network activity (Brakowski et al., 2017; Coutinho et al., 2016; Dixon et al., 2022). The temporary dissolution of self through psychedelics may lead to more flexible cognitive responses, particularly for individuals who experience negative self-attribution and ruminative thinking (Fauvel et al., 2023). Accordingly, it has been shown that psilocybin significantly decreases depression and anxiety in life-threatening cancer patients (Griffiths et al., 2016; Ross et al., 2016). Moreover, the encounter with self-dissolution, a sense of oneness, and disembodiment culminates in a realization that the intricate texture of emotions and thoughts is, in fact, nothing but a construction. This transformative shift in perception might serve as a catalyst for a more profound sense of self and existence, effectively dismantling dysfunctional self-perceptions. Furthermore, it might promote greater empathy toward others and facilitate social adaptation (Dolder et al., 2016; Pokorny et al., 2017), considered a key to authentic and enduring happiness (Dambrun & Ricard, 2011).

Behavioural Task

In this study, we investigated the impact of PHA (pharmahuasca) and HAR (harmine) on face recognition using a behavioural morphing task. As expected, participants consistently exhibited faster reaction times for their own faces than familiar and unknown faces across all drug conditions, indicating the self-face advantage regardless of the drugs administered (Bortolon & Raffard, 2018). Moreover, results showed that general face recognition was slower during a psychedelic experience. The

analysis of psychometric functions fitted along the morphing continuum revealed that neither PHA nor HAR affected the threshold of the psychometric functions, the point of subjective equality (PSE) values, indicating that none of the drug conditions resulted in a change of bias in face recognition.

Importantly, we observed a systematic reduction in slope values in the PHA condition across all morphing categories (Self-Familiar, Self-Unknown, and Familiar-Unknown), which suggests that the administration of pharmahuasca impaired the general sensitivity to discriminating between different faces. This impairment could potentially be attributed to the increased visual hallucinations; however, we did not find any correlation between the increased elementary or complex imagery scores and attenuated slope values. Additionally, there was no correlation between the P1/N170 visual evoked potentials and the attenuated slope values.

Future Directions

While our study has provided significant insights into the effects of psychedelics on face perception and recognition, it is crucial to recognize that the observed alterations in these processes may be influenced by the specific characteristics of pharmahuasca and the dosage utilized in our study. Variations in psychedelics or dosages may result in diverse effects on face processing. Consequently, future research should focus on investigating the generalizability of our findings to different psychedelics and

doses, aiming to gain a comprehensive understanding of the broader impact of psychedelics on face perception and recognition.

Secondly, in this study, celebrity faces were used as familiar stimuli. Given the expanding nature of the self (Aron & Aron, 2006; Aron & Fraley, 1999; Mattan et al., 2016), it has been proposed that personally familiar faces (e.g., a partner's face, family member) may be processed not only as familiar faces but also as self-related stimuli as if they were part of the self (Taylor et al., 2009). It would be interesting to explore the potential overlap between personally familiar faces and self-related stimuli during psychedelic experiences to understand better the intricate relationship between psychedelics, face perception, and self-referential processing.

Conclusion

In conclusion, this pioneering study provides valuable insights into the effects of psychedelics on self-face perception and recognition. Using a data-driven approach and taking advantage of the high temporal resolution of EEG, we observed the effect of pharmahuasca on early visual processing, namely increased P1 and attenuated N170 across all face categories. Furthermore, we discovered that pharmahuasca specifically modulated self-referential processing by reducing neural activation in response to the self-face, as revealed by the alteration of the P300 wave. These findings underscore the modulatory role of serotonergic neurotransmission in visual processing and face recognition. This

study addresses a critical gap in the existing literature by investigating the influence of psychedelics on the visual processing of faces across varying levels of familiarity, a domain that has been underexplored despite the hallucinatory aspect often associated with these substances. While previous research has predominantly focused on subjective self-experiences like ego dissolution and oceanic boundlessness, our study offers new insights into the neural mechanisms underlying altered self-perception induced by psychedelics. By examining the effects on face recognition across varying levels of familiarity, we reveal a reduction in neural activation in response to self-face stimuli and a blurring of the distinction between self and familiar or unknown faces during the psychedelic experience. These findings not only contribute to our understanding of how psychedelics impact self-perception and social cognition but also hold significant therapeutic implications. The ability to elucidate the mechanisms of self-other integration during the psychedelic experience could inform therapeutic approaches for disorders characterized by disturbances in self-focus and interpersonal relationships, such as depression or social anxiety. By bridging this research gap, our study advances the field of psychedelic research and underscores the complex interplay between psychedelics, cognition, and perception.

3 Chapter

The effect of DMT on creative cognition

3.1. Introduction

In a society marked by rapid advancements and constant transformation, creativity holds significant value in both personal and professional realms. The ability to think creatively and flexibly promotes adaptability, generates innovative ideas, and allows individuals to approach challenges with fresh perspectives. Additionally, it enhances communication skills through mediums like artistry, storytelling, and practical problem-solving in everyday life circumstances. Demonstrating cognitive flexibility is a fundamental attribute that enables an individual to adjust and adapt to their environment proficiently. Indeed, many mental health conditions, such as depression, anxiety, and substance abuse disorders are associated with impaired cognitive flexibility (Aldao et al., 2010; Todd et al., 2015; Yu et al., 2020). Psychedelic drugs' efficacy as a potential treatment option for mental disorders demonstrated encouraging outcomes. It has been theorized that the main therapeutic benefits stem from their capacity to stimulate cognitive flexibility and creative thinking (Davis, Barrett, et al., 2020; K. Kuypers et al., 2016; Sabucedo, 2017). While there exists a modest amount of anecdotal evidence and historical instances that suggest psychedelic drugs may enhance creative thinking (Baggott, 2015;

Huxley, 2010; Sessa, 2008; Sheldrake et al., 2001), quantitative research has not yet yielded a consensus regarding whether psychedelics can indeed enhance creativity or act as a catalyst for overcoming creative blocks.

Creativity is a complex, dynamic and multidimensional phenomenon described as micro and macro levels (Walia, 2019). Micro levels refer to the way of thinking and encompass the two modes of cognitive processes: divergent and convergent thinking. Divergent thinking (DT) refers to the ability to generate novel and original ideas (Runco, 1991). In contrast, convergent thinking (CT) implies the capacity to link different ideas, evaluate their usefulness, and find an effective solution to the problem (Simonton, 1999). Various task-based assessments can measure micro levels of creativity, for instance Torrance Tests of Creative Thinking (TTCT) (Kim, 2011), pattern meaning task (PMT) (Wallak & Kogan, 1966), alternate uses task (AUT) (Guilford, 1967), picture concept task (PCT) (David Wechsler, 2012), creative metaphors task (MET) (Wießner, Falchi, Maia, Daldegan-Bueno, Palhano-Fontes, Mason, Ramaekers, Gross, Schooler, Feilding, et al., 2022). So far, the research that examines the impact of psychedelics on micro levels of creativity has yielded inconclusive outcomes. Conducted in natural settings, some studies showed that psychedelics enhance either CT (Uthaug et al., 2019) or DT (Mason et al., 2019), or both (Prochazkova et al., 2018), while others indicate increased DT and decreased CT (K. Kuypers et al., 2016).

These mixed findings arise from employing diverse methodological designs, including variations in dosage (e.g., micro-dosing vs. high dosing), lack of placebo-control or lack of use of parallel task versions during the different drug/placebo administration (leading to increased learning effects), distinct timepoints of measurement (e.g., acute vs. a day after drug administration), and studies conducted on diverse socio-cultural populations. In a recent methodologically rigorous study, psilocybin has been shown to acutely decrease both DT and CT, measured by AUT and PCT, respectively, while subjective ratings of 'insightfulness' scores increased (Mason et al., 2021). According to authors, this discrepancy between acute increases in insight and decreased numbers of ideas may be explained by the fact that psychedelics increase spontaneous creative thinking (e.g. in mental states with defocused attention and unrestrained cognition) while decreasing deliberate creative thinking (e.g. mental state focused on meeting explicit task demands, for example, in guided, timed settings such as in AUT and PCT) (Dietrich, 2004; Mason et al., 2021). Additionally, it has been suggested that altered meaning attribution and the illusion of profoundness (Hartogsohn, 2018) might contribute to a sense of heightened creativity, even in the absence of demonstrable improvements in performance on creativity tasks during the acute effects of classic psychedelics (Mason et al., 2021). That is, psychedelics could only impact the metacognitive level associated with the perception of creativity without objectively impacting creative thinking. The noticeable disconnection between heightened creative sensation experienced during psychedelic states and the empirical findings can potentially be

attributed to a predominant focus on examining creativity in the context of isolated tasks instead of investigating how creative thinking unfolds within the creative process. Accordingly, recent investigations have highlighted the dynamic nature of creative thinking, emphasizing that it involves movement between different modes of thinking rather than being a singular mental state (Botella & Lubart, 2019; Girn et al., 2020). Therefore, the present research aimed to investigate how psychedelic substances influence macro stages of creativity as they occur during the act of creation itself while cognition is unrestrained, unfiltered, and unfocused.

Macro levels of creativity refer to the various stages essential for successfully completing a creative process. Historically, Wallas described these stages as preparation (gathering initial information), incubation (subconscious processing), illumination (insight or "Eureka" moment), and verification (idea evaluation and refinement) (Wallas, 1926). However, it is now acknowledged that the quantity and characteristics of these stages vary depending on the specific creative domain (artistic, scientific, writing, design) (Botella & Lubart, 2019). Furthermore, each macro stage is associated with a distinct mode of thinking; for example, divergent thinking is best suited for production, ideation, and illumination stages, while convergent thinking is best suited for preparation, incubation, and validation stages (Cropley et al., 2013; Lubart, 2001). During the creation process, individuals dynamically transition from one stage to another, adopting different thinking styles tailored to the unique demands of each phase (Girn et al., 2020). Perhaps psychedelics alter this

alignment of specific micro-level and macro-level stages, along with the dynamic transitions between them, which may optimize the creative process and enhance creative outcomes. However, there is currently no research examining the impact of psychedelic substances on macro levels of creativity. One of the main reasons for the lack of research on this matter was the absence of suitable tools to capture the dynamic transitions between stages during the creation process. For example, traditional methods like retrospective interviews enable participants to discuss their steps to achieve an outcome. However, they do not take into consideration or overlook the unsuccessful attempts and challenges encountered during the process (Botella et al., 2019). To address this limitation, Botella et al. have recently developed a Creative Process Report Diary (CRD), which utilizes experience sampling methodology to enable participants to self-report their engaged stages during the creation processes. CRD aims to capture the intricate interplay and feedback between different stages of creativity while enhancing the ecological validity. This approach offers a more dynamic understanding of creative cognition than conventional retrospective interviews.

Therefore, this study aimed to explore the effects of a pharmahuasca on both micro and macro levels of creativity using a traditional task-based and unconstrained cognition approach in a double-blind, placebo-controlled, within-subject design. Pharmahuasca is a pharmaceutical form of the entheogenic South American brew ayahuasca, which traditionally contains beta-carboline alkaloids containing *Banisteriopsis caapi* vine and the hallucinogenic DMT containing *Psychotria viridis* (McKenna et al.,

1998). Chemically prepared pharmahuasca contains a crystalline form of DMT and pharmaceutical monoamine oxidase inhibitors (MAOI), such as harmine.

1. Micro stages of creativity, CT and DT, are measured by using a Picture Concept Task (PCT), which involves selecting pictures from slides that belong to a common group (David Wechsler, 2012) and Alternate Uses Task (AUT) (Guilford, 1967) which involves stating as many uses as possible for everyday objects. We hypothesized that pharmahuasca will reduce the performance score in both PCT and AUT tasks.
2. Macro stages of creativity were investigated using a Creative Process Report Diary (CRD) (Botella et al., 2019). Painting was chosen as an artistic creation process because it is often considered an archetypal domain of creativity research, is easy to implement in the lab environment, and requires minimal prior technical expertise (Schlewitt-Haynes et al., 2002; Stanko-Kaczmarek, 2012). Macro stages of painting (preparation, incubation, ideation, illumination, production, and validation) were selected based on the previous literature (Botella et al., 2018). Using CRD, we collected the engaged stages every 3 minutes using the experience sampling method, and the transitions between the stages during painting were compared between pharmahuasca and placebo conditions. Importantly, this investigation was conducted without a prior hypothesis, allowing for an

open and exploratory approach to understanding the impact of pharmahuasca on the dynamics of the creative process.

3. Additionally, we investigated subjective feelings of spontaneous creative thinking by using altered state of consciousness questionnaire scores on "insightfulness" (Dittrich, 1998).
4. Furthermore, drawing inspiration from Oscar Janiger's historical work with LSD (Janiger & De Rios, 1989), we investigated the effects of pharmahuasca on various aesthetic experiences. In the late 1950s, Oscar Janiger collected over 250 drawings from artists under the administration of LSD, later analyzed by art historian Carl Herter, who concluded that drawings created during LSD experiences exhibited *"relative size expansion, involution, movement, alteration of figure/ground relationships, enhanced intensity of color and light, oversimplification, symbolic and abstract depictions of objects, and fragmentation, disorganization, and distortion"* (Janiger & De Rios, 1989). Building on these observations, we carried out a hypothesis-driven quantitative analysis on the participants' paintings. We aimed to determine whether paintings in the pharmahuasca condition exhibited characteristics such as increased brightness, higher contrast, expanded color choices and variety, a prevalence of more saturated colors, and a reduction in the percentage of empty space on the canvas compared to the placebo condition. Additionally, we analyzed whether

pharmahuasca affects the painting style (representational vs. non-representational). We hypothesized that participants would produce more non-representational style artwork in pharmahuasca condition.

3.2. Methods

3.2.1. Study design

The present study followed a within-subject, double-blind, placebo-controlled design, with 3 sessions of counterbalanced drug administrations separated by 2 weeks (Pharmahuasca, Harmine, Placebo). Three creativity tasks are presented with the following order: Picture Concept Task (PCT) and Alternative Uses Task (AUT) are used as a measure of CT and DT, respectively, and the CRD Questionnaire is used by experience sampling method during drawing to detect the occurrence and transitions of the macro levels of creativity. This research exclusively investigates the effects of both pharmahuasca (PHA) and placebo (PLA) conditions, with the deliberate restriction to compare the psychedelic state to the normal state. Notably, the harmine condition is intentionally removed from the analysis.

3.2.2. Participants

Thirty-six right-handed healthy male volunteers (20-40y, BMI 18.5-25) were recruited for this study. Inclusion criteria comprised: (a) no current or previous history of neurological or psychiatric disorders and no family history of Axis-I psychiatric

disorders (b) fluent German language (c) normal or corrected-tonormal vision (d) normal hearing (e) little to no experience with hallucinogenic drugs. All participants underwent medical and psychological screening upon completing the initial telephone screening. On-site screenings were conducted in the same room as the experimental sessions, ensuring familiarity with the surroundings, which was found conducive to the psychedelic experience (Hartogsohn, 2017). During the screenings, participants completed a training session to familiarize themselves with the tasks. Five participants failed to complete the 3 sessions of the experimental procedure, and one participant experienced technical difficulties during data collection in all sessions, leaving 30 participants in the study. The study was approved by the ethics committee of the University of Zurich and carried out in compliance with the Declaration of Helsinki. Participants gave written informed consent and were reimbursed commensurate with the time invested in participation.

3.2.3. Study Drug

A counterbalanced order of (i) pharmahuasca, (ii) harmine, and (iii) placebo was administered in three different experimental sessions. (i) For the pharmahuasca condition (PHA), we used the standardized and quality-controlled pharmahuasca containing DMT (from *Mimosa tenuiflora*) and the monoamine oxidase inhibitor harmine (from Sigma-Aldrich / Merck KGaA). Thirty minutes after the sublingual administration of the 100 mg harmine capsule, the DMT nasal spray was administered at intervals of 15 minutes. Each administration contained 10 mg of DMT, and the experiment started after 60 minutes of the first

administration when participants were administered 50 mg of DMT. This procedure was preferred following a pilot study which showed that participants receiving doses within short time intervals had greater self-control and could cope better with the drug experience in an experimental setting (Helena Dorothea Aicher et al., 2023; Michael J. Mueller et al., 2023) (ii) For the harmine condition (HAR), participants were given 100 mg harmine capsules sublingually, along with a placebo nasal spray which was indistinguishable from Pharmahuasca as far as taste, smell, and appearance. (iii) In the placebo condition (PLA), both capsule and nasal spray were without active molecules and mimicked the natural drugs' appearance and taste.

3.2.4. Randomization and blinding

An individual who had no direct interaction with the participants allocated treatments in a completely counterbalanced order and delivered to the experimenter in a closed container. The closed container guaranteed that both the experimenter and the participant remained unaware of the specific treatment administered. The study was fully unblinded only after whole experiment concluded.

3.2.5. Study Procedure and Setting

The study was conducted during the daytime in the Human Sleep Laboratories of the University of Zurich. The soundproof and temperature-controlled bedrooms were set up in a comfortable

living room atmosphere, with dimmable lights and a sound system. We conducted urine drug screening and breath alcohol screening on the morning of the test to confirm that no drugs or alcohol had been consumed. Participants were allowed to proceed after all tests were negative, and blood pressure monitors, venal catheters, and EEG caps were placed throughout the day to take blood samples and measure EEG activity. The study day started at 10 a.m. with the administration of a sublingual 100 mg harmine capsule. 30 minutes after the harmine administration, 100 mg DMT was administered at intervals of 15 minutes, 10 mg each. The same administration method was applied for the placebo condition, but both capsule and nasal spray were without active molecules and mimicked the natural drugs by appearance and taste. The experiments assessing creativity started 110 minutes after the last nasal spray administration. The study day finished at 5 p.m. Throughout all study days, a standardized playlist containing non-stimulating background music was played to provide comfort and relaxation. A medically trained experimenter was always in the room to supervise the participants.

3.2.6. Creativity tasks

3.2.6.1. Micro Levels of Creativity

Alternate Uses Task (AUT)

The AUT assesses divergent thinking (DT) and involves listing as many possible uses as possible for everyday objects (Guilford, 1967). Participants were also given three different versions of the

AUT for each condition (DMT, HAR, PLA). Participants were asked to come up with as many alternatives use as possible for "pen" for version A, "towel" for version B and "shoe" for version C. As the scope of this paper, the versions correspond to the PLA and DMT conditions analyzed. Four commonly used dimensions of creativity: originality, flexibility, fluency, and elaboration were analyzed by two independent raters using the following guidelines (Alhashim et al., 2020), and the average scores were used in the analysis. Originality scores, or uniqueness of the responses, were calculated as 2 points if the answer was given by less than 1% of the participants and 1 point if the answer was given by less than 5%. Flexibility scores, or how different the responses, were calculated by clustering the responses into categories; the sum of categories was used as the dependent variable. Fluency scores were calculated by counting the number of responses given to an object. Elaboration, or how detailed the responses were calculated by the number of meaningful words in the response.

Picture Concept Task (PCT)

The PCT is used to assess convergent thinking (CT) and involves selecting pictures from slides that belong to a common group. In brief, the PCT consists of 12 stimuli, each containing between 4 and 12 color pictures shown in a matrix of 2×2 , 2×3 , 3×3 , or 3×4 from the Wechsler Preschool and Primary Scale of Intelligence and the Wechsler Intelligence Scale for Children (David Wechsler, 2012) (Please refer to *Supplementary Materials* Figure 18 for the

example of stimuli). Participants are allocated 30 seconds per stimulus to find an association among the pictures in each row. For instance, in a 2x2 slide, the first row might display a *shoe* and a *leaf*, while the second row features a *tree* and a *smiley face*. The correct answer would be a leaf and a tree, as both images are nature-related. Participants are required to provide a single correct solution, as there is only one accurate answer. The number of correct answers served as the dependent measure of CT (K. Kuypers et al., 2016). Parallel versions of the task have been used to avoid the learning effect.

3.2.6.2. Macro Levels of Creativity and Artistic Production

Participants were instructed to draw on a Wacom One tablet (13.30", 2540 lpi) (Wacom One, 2020) using the oil painting feature on the Adobe Fresco Software (Adobe Fresco, 2019) without any subject matter given for 21 minutes. The Wacom One tablet was selected for its ability to simulate the texture of actual paper with natural surface friction, minimal reflection and not requiring a battery-powered pen with a natural feel. Meanwhile, Adobe Fresco software was chosen for its ability to replicate the real-life swirling, smudging, and layered effects of oil painting, creating a three-dimensional appearance. During the free creation time, CRD which includes the macro stages of the creative process (*Preparation = I think about the subject; Incubation = I leave my ideas to link with each other on their own; ideation = I think about new ideas; illumination = Suddenly, I know what I am going to do; production = I carry out/compose my ideas; validation = I check whether my work is finished*) were presented in every 3 minutes. Participants were

asked to select which of these stages (none or several) they were engaged in since the last evaluation (Botella et al., 2018, 2019). The answers were collected by the experience sampling method. The number of transitions between stages was analyzed as a dependent variable. At the end of the drawings, participants gave a title to their drawings.

3.2.7. Subjective Feelings of Creativity

The 11D-ASC scale (Dittrich, 1998), a tool developed to evaluate changes in consciousness, was employed 360 minutes after the first dose of drug administration to retrospectively measure the drug effects. This study focused specifically on the "insightfulness" subscale, which comprises three questions that are conceptually linked to spontaneous creative thinking: *"I felt very profound," "I had insights into connections that had previously puzzled me,"* and *"I had very original thoughts."*

3.2.8. Visual Features of the Paintings

We applied quantitative analysis to the paintings to identify standard, data-driven features between pharmahuasca and placebo conditions. The **overall brightness of the paintings** was calculated by converting the digital RGB image to grayscale and averaging on a scale from 0 (complete darkness) to 255 (maximum brightness). The overall contrast of the paintings was determined using the RMS (root-mean-square) method, scaling the results from 0 (indicating low contrast) to 100 (representing

high contrast). **The number of color choices** is counted manually from the drawing videos. Each color's red, green, and blue (RGB) values are converted to hue, saturation, and value (HSV) because it corresponds better to how people select colors from a color wheel than the RGB color space. The average **hue**, represented as a vector of values ranging between 0 and 1 (with 0 and 1 corresponding to red, and values in between indicative of orange, yellow, green, blue, indigo, and violet) and the average **saturation**, expressed as a percentage (where 0% denotes a shade of gray and 100% signifies full color), of the selected colors was calculated. **Empty space percentages** are calculated by dividing the size of white pixels (RGB = 255, 255, 255) by image size and multiplying by 100 (scale from 0 to 100).

The style of the art is examined in terms of representational or non-representational. Representative art represents something recognizable from the real world, such as people, animals, objects, places, and events. The meaning is quite obvious and may include a certain level of abstraction. Non-representational art does not represent anything from the real world, including shapes, colors, and lines. The meaning is subjective and abstract. Each drawing is categorized into two styles by two independent raters, with the assistance of a third opinion from a consultant if there is a disagreement.

3.2.9. Statistical Analysis

Statistical analyses were conducted with the aid of JASP (JASP Team, 2023). First, we analyzed the effect of PHA on the micro levels of creativity.

(1) Repeated measures ANOVA was employed to assess the effect of treatment (PHA and PLA) on the scores of the AUT (fluency, elaboration, flexibility, and originality) as the outcome measures. Treatment served as the between-subject factor. In the event of a significant treatment $\times$ score interaction, further post-hoc analysis was conducted using paired sample t-tests (one-tailed, $\text{PHA} < \text{PLA}$). Notably, due to missing treatment conditions for some subjects, only participants who completed both treatment conditions were included in the analysis ($n=17$).

(2) A paired sample t-test (one-tailed, $\text{PHA} < \text{PLA}$) was conducted to examine the effect of PHA on the performance scores on the PCT test. Additionally, in line with the missing treatment conditions for certain subjects, the analysis was restricted to participants who completed both treatment conditions ($n=22$).

(3) The explorative statistical approach was taken for a comprehensive understanding of the impact of PHA on the macro levels of creativity, considering both stage selections and transitions. We excluded 2 participants who did not comply with the task (they selected all choices for all time points; $n=28$). First, we counted each stage selection for both treatments.

We constructed transition tables to organize the data, where rows represent subjects and columns (12) represent the cumulative transition counts for each origin stage (e.g., from preparation, incubation, etc.) for both PHA and PLA treatments ("origin table"). Similarly, we created tables for destination stages as columns (e.g., to preparation, to incubation, etc., "destination

table"). To assess the impact of treatment (PHA and PLA) on both origin and destination stages, we employed two separate Friedman's two-way tests on both origin and destination tables. Subsequently, we conducted post-hoc analysis using the Wilcoxon test with Monte Carlo simulation (10000 iterations) to identify origin and destination stages where mean transitions significantly differed between PHA and PLA treatments.

To explore the directionality, we planned Wilcoxon test with Monte Carlo simulation (10000 iterations) between the previously found significant origin/destination stages and all stages on the distributions, covering the counts of transitions across the entire subject population. All p-values underwent FDR correction (Benjamini et al., 2001).

(4) Next, we observed the effect of PHA on the subjective feeling of creativity by analyzing "insightfulness" scores between treatments using paired t-test.

(5) Finally, we investigate the influence of PHA on the visual features of the paintings using paired t-tests. We tested whether PHA increases the overall brightness and overall contrast of the whole painting, the number of colors chosen during drawing, and the hue and saturation of the selected colors compared to PLA (one-tailed, $PHA > PLA$). Conversely, we predicted that PHA would decrease the percentage of empty space in the image compared to PLA (one-tailed, $PHA < PLA$). Finally, we explored the influence of PHA on drawing styles (representational vs. nonrepresentational) using a Chi-square test due to the categorical nature of this variable. The Shapiro-Wilk test

evaluated whether the data significantly deviated from a normal distribution. Wilcoxon's signed-rank (z) test was employed if the data violated the normality assumption.

In this study, the decision to conduct a one-tailed post-hoc analysis is based on several considerations. Firstly, theoretical expectations and prior evidence suggest the presence of a directional effect in our research. By aligning our analysis with these hypotheses, we can effectively explore specific anticipated effects, enhancing the interpretability of the results. Additionally, resource constraints necessitate a focused examination of the data. A one-tailed test maximizes statistical power within these limitations by concentrating our analysis on the direction of the effect of interest. Moreover, as an exploratory study, our aim is to uncover novel insights and generate hypotheses for future research. Adopting a one-tailed approach allows us to explore specific directional trends in the data, facilitating the generation of new research directions. However, it is crucial to acknowledge the limitations of this approach and to interpret the results cautiously, considering both the potential advantages and disadvantages of conducting a one-tailed analysis.

3.3. Results

Alternative uses test (AUT)

AUT is used to measure divergent thinking. AUT outcome measures followed a normal distribution. All four dimensions (flexibility, elaboration, flexibility, originality) followed the

assumption of homogeneity of variances. The analysis revealed no significant interaction effects between the treatment conditions and the dimensions of the AUT ($F(3, 96) = 21.868, p = 0.894$). Contrary to our hypothesis ($PHA < PLA$), The administration of PHA did not affect the fluency, elaboration, flexibility, and originality scores.

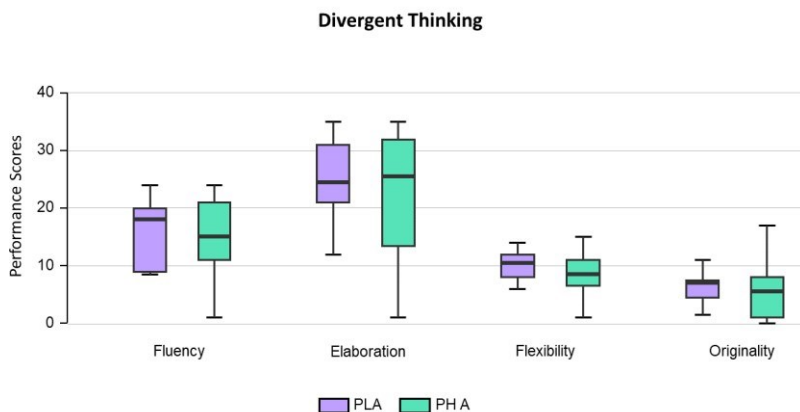


Figure 8- Divergent thinking dimensions as measured with the AUT.

The bars represent the mean ($\pm 95\%$ CI) of groups (PLA and PHA). The administration of pharmahuasca did not result in any significant changes in the dimensions of divergent thinking (all $p > 0.05$, one-tailed).

Picture Concept Task (PCT)

PCT is used to measure convergent thinking. PCT outcome measures followed the test for normal distribution assumptions and variance homogeneity. Paired samples t-test revealed PHA acutely decreased correct answer scores on PCT ($M=8.4, SD=1.6$)

compared to placebo (M=9.25, SD=1.26) condition ($t(21)=2.054$, $p=0.026$, one-tailed, $\text{PHA}<\text{PLA}$; Cohen's $d=0.438$).

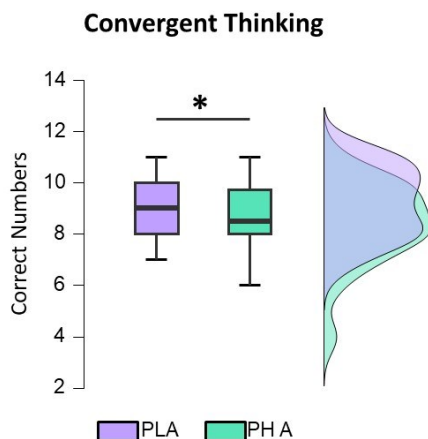


Figure 9- Convergent thinking as measured with the PCT.

The bars represent the mean ($\pm 95\%$ CI) of groups (PLA and PHA). The administration of pharmahuasca resulted in a significant decrease in convergent thinking ($p=0.026$).

Macro Levels of Creativity

The impact of pharmahuasca on macro levels of creativity and transitions between stages—preparation, illumination, ideation, incubation, production, and validation—was assessed using CRD. First, we explored the influence of PHA on stage selection counts (for the numbers of stage selection for each treatment, please refer to Table 4 in *Supplementary Materials*). Upon visual

inspection, it seemed that there was reduced engagement with the incubation stage in the PHA condition. To confirm this observation, a one-tailed t-test (PHA < PLA) was conducted, validating that the total number of Incubation stage selections was significantly smaller in the PHA condition ($t(27) = -1.986$, $p = 0.029$).

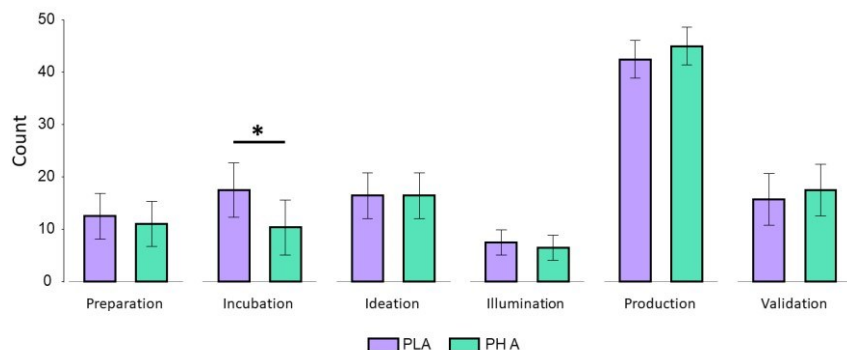


Figure 10- Bar plots show the number of macro-level stages selected for PHA and PLA conditions

The incubation stage is less selected during painting in the pharmahuasca condition ($p=0.029$, one-tailed).

Subsequently, we examined whether pharmahuasca influenced transitions between macro levels of creativity stages during the creative process. To gain an overview, we explored transition tables for both PHA and PLA conditions (please refer to Table 3 in *Supplementary Materials*).

Friedman's two-way ANOVA tests on origin table showed significant effect of treatment of the origin stages ($X^2(11)=111,451$, $p<.001$). A one-tailed Wilcoxon signed-rank test revealed a statistically significant change in transitioning from the incubation stage in PHA treatment ($Z = -2.205$, $p = 0.014$). Similarly, Friedman's two-way ANOVA tests on destination table showed significant effect of treatment of the destination stages ($X^2(11)= 89,668$, $p<.001$). A one-tailed Wilcoxon signed-rank test revealed a statistically significant change in transitioning from the incubation stage in PHA treatment ($Z = -1.781$, $p = 0.041$).

After identifying potential treatment effects on transitions to and from the incubation stage, we conducted a focused investigation into specific alterations. A one-tailed paired Wilcoxon test, with incubation as a constant origin stage, revealed that transitions from incubation to incubation ($Z=-2.409$, $p=0.021$) and from incubation to preparation ($Z=-2.202$, $p=0.044$) were significantly reduced in the PHA condition. Similarly, maintaining incubation as a constant destination stage, the one-tailed Wilcoxon test showed that transitions from preparation to incubation ($Z=-2.202$, $p=0.022$) were significantly reduced; from validation to incubation ($Z=-2.063$, $p=0.051$) were marginally significantly reduced in the PHA condition. Other comparisons did not survive FDR correction.

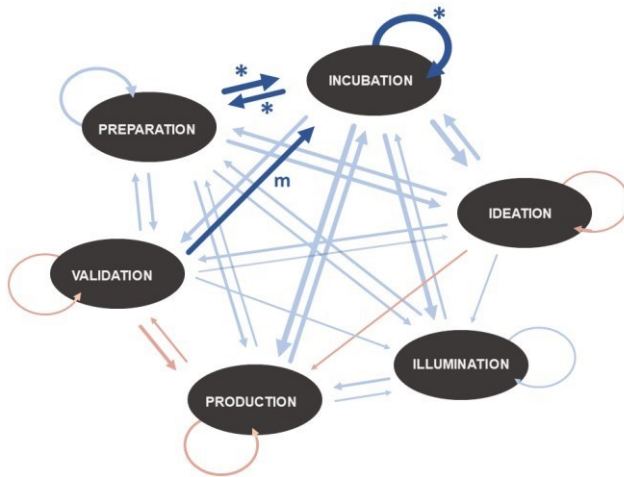


Figure 11- CRD Transitions during painting (PHA vs PLA)

The graph depicts the transitions in the PHA condition compared to the PLA condition. A red arrow indicates transitions that occurred more frequently in the PHA condition, while a blue arrow indicates transitions that occurred less frequently in the PHA condition compared to placebo. Significant transitions are shown in darker colors and asterisks. The transition lines are weighted according to the mean difference between PHA and PLA conditions. When there is no transition line (e.g., from illumination to validation stages), it indicates that the mean difference is close to zero. Our results indicated a significantly lower overall engagement with the incubation stage in the PHA condition, also affecting the transitions between the preparation and incubation stages and transitions from validation to incubation were marginally (m) reduced. Although there was an overall reduction in all transitions in the PHA condition, there was a trend of increased engagement in the ideation, production and validation stages; however, it did not reach the significance level.

To summarize, the test results indicate a substantial decrease in participant involvement with the incubation stage, where individuals usually allow their ideas to interconnect organically. Furthermore, transitions between the incubation and preparation stages involving convergent thinking show a noticeable reduction in the PHA condition. This decline aligns with the previous task (PCT) findings, which demonstrated lower creative thinking scores under the influence of PHA. As anticipated, our hypothesis regarding the impact of PHA administration on the dynamism between creative thinking modes, hence, on transitions between macro stages of creativity, has been confirmed. This suggests a noteworthy alteration in the phenomenology of the creation process when individuals are under the influence of PHA. Essentially, participants undergo a noticeable shift in how they experience and engage in the creative process during a psychedelic experience.

Subjective-Feelings of Creativity

We explored the impact of pharmahuasca on subjective feelings of creativity, specifically focusing on the "insightfulness" subdimension of the 11D-ASC. Insightfulness scores were significantly increased in the PHA condition ($t(29) = 4.313$, $p < 0.001$, Cohen's $d = 0.787$, two-tailed).

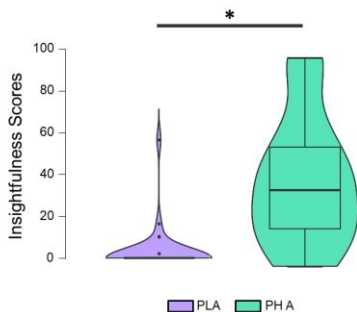


Figure 12- Box plot shows the insightfulness scores.

PHA significantly increased insightfulness scores measured by the 11D-ASC ($p < 0.001$).

Visual Features of the Paintings

We compared various features of paintings in both the pharmahuasca and placebo conditions (Please refer to *Supplementary Materials* Figure 19 for some examples of paintings). There were no significant differences in overall brightness ($t(29) = 1.007$, $p = 0.839$, one-tailed, PHA > PLA) or overall contrast ($t(29) = -0.494$, $p = 0.687$, one-tailed, PHA > PLA) between the paintings in the pharmahuasca and placebo conditions. As hypothesized, participants significantly selected more color during painting in the PHA condition compared to the placebo ($t(29) = 2.053$, $p = 0.025$, one-tailed, PHA > PLA). Moreover, we found a significant increase in the average hue in the PHA paintings, suggesting that participants used a more diverse range of high-hue colors, such as blues, violets, pinks, and

purples ($t(29) = 1.935$, $p = 0.031$, one-tailed, PHA > PLA). Additionally, their selected colors were significantly more saturated ($z = 1.800$, $p = 0.037$, one-tail, PHA > PLA). Then, we looked at the empty spaces in the paintings. As suspected, participants' drawings expanded on the canvas in the PHA condition compared to the placebo condition, yet it was insignificant ($z = 0.121$, $p = 0.457$, one-tailed, PHA > PLA) (Figure 13). Finally, we explored whether participants engaged in a more abstract art style during the psychedelic experience. However, the art style (representational vs. non-representational) did not change with the drug condition, as indicated by $X^2(1, N = 60) = 0.69$, $p = 0.794$. For detailed mean and standard deviation of the visual features mentioned above, please refer to Table 5 in

Supplementary Materials.

In summary, while visual features such as brightness, contrast, and art style showed no significant differences between pharmahuasca and placebo conditions, participants under pharmahuasca exhibited a distinctive preference for a richer and more varied color palette, choosing more colors during the creative process. These findings suggest that perceptual and sensory alterations during the psychedelic experience may influence artistic choices, particularly in the use of color.

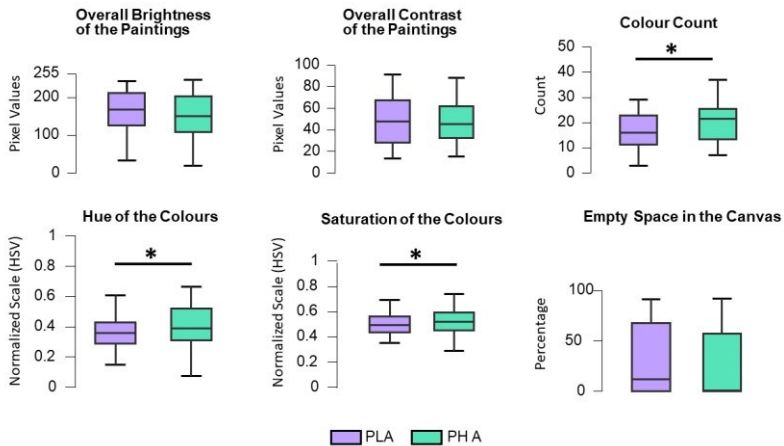


Figure 13- Histograms show the descriptive statistics of the visual features of the paintings

Individuals use significantly more amount and diversity (hue) of color, and the selected colors were more saturated in the PHA condition.

3.4. Discussion

In this study, we investigated the role of psychedelics in various domains of creative cognition

The Effect of Psychedelics on The Micro Levels of Creativity

The first objective of this study was to assess the impact of pharmahuasca on the micro-levels of creativity, specifically divergent and convergent thinking, using a task-based

methodology. None of the four aspects of divergent thinking – originality, elaboration, flexibility, and fluency – pertain to the idea-generation phase of the creative process and were not compromised during the psychedelic state. On the other hand, convergent thinking, the idea evaluation phase of the creative process, was reduced by psychedelic administration. Specifically, participants had difficulty identifying common images in the slides when under the influence of psilocybin, as evidenced by lower scores on the PCT. Therefore, our findings suggest that psilocybin acutely impairs an individual's ability to evaluate possibilities and engage in evaluation and logical thinking without diminishing the number of novel ideas and associations generated in response to goal-directed creativity tasks.

These results are consistent with prior research demonstrating a notable reduction in convergent cognitive processes following the administration of psilocybin (Mason et al., 2021) and LSD (Wießner, Falchi, Maia, Daldegan-Bueno, Palhano-Fontes, Mason, Ramaekers, Gross, Schooler, Feilding, et al., 2022). To understand the effects psychedelics on creative thinking, it is imperative to comprehend the role of the serotonin modulation of the brain structures associated with a distinct mode of creative cognition. Creative cognition is linked to the coordination of three resting-state networks (RSNs), namely, the default mode network (DMN, which supports idea generation), the frontoparietal control network (FPN, facilitating idea evaluation), and specific regions within the salience network (SN, involved in the transition between internally oriented DMN and externally-oriented FPN) (Beaty et al., 2015, 2018)). A consistent body of

research revealed that the administration of psychedelic substances acutely diminishes the integrity of the DMN and the modularity of the FPN (Carhart-Harris et al., 2016; Muthukumaraswamy et al., 2013; Palhano-Fontes et al., 2015; Timmermann et al., 2019). Therefore, it is reasonable to consider that both idea generation and evaluation phases may experience deterioration during the acute phase of the psychedelic experience. While some previous studies have reported impairments in divergent thinking during the acute phase, our research did not reveal such alterations in DT. This disparity could be attributed to several factors, including the novel administration method utilized in this study, the dose, or the measurement timing. Given that AUT (task for measuring DT) was conducted 150 minutes after the last DMT administration, it is plausible that any initial impairment in DT had restored by that point. This observation is consistent with the broader understanding that, despite the presence of cognitive impairments during the acute effects of classic psychedelics, these substances have been demonstrated to facilitate learning during the post-acute period (Calder & Hasler, 2023). This notion finds support in previous research, which indicates that psychedelics sub-acutely enhance the overall integrity of the Default Mode Network (DMN) (Barrett et al., 2020; Sampedro et al., 2017; Smigielski et al., 2019b), potentially through mechanisms involving neural plasticity (Ly et al., 2018; Vollenweider & Komater, 2010). In alignment with this, several longitudinal studies have reported positive developments in specific aspects of DT (higher number of novel ideas) (Mason et al., 2021) and CT (higher number of correct numbers) (Kiraga et al., 2021), as

evidenced by 1-week follow-up measurements. These results emphasize the need to evaluate both the immediate and lasting effects of psychedelics for obtaining a comprehensive understanding of how these substances influence various aspects of creative thinking.

The Effects of Psychedelics on Macro Levels of Creativity

The second objective of this study was to investigate the potential impact of psychedelics on the experience of the creative act, particularly their ability to influence the transition between different modes of creative thinking (CT and DT) throughout the creation process. To accomplish this, we adopted a unique approach, collecting participants' self-reported macro-levels of creativity using CRD as a tool through the experience sampling method while they were painting. Our findings indicate a significant reduction in participant engagement with the incubation stage (*"I leave my ideas to link with each other on their own"*) in the pharmahuasca (PHA) condition. Furthermore, transitions between the incubation and preparation (*"I think about the subject"*) stages are notably impaired in the PHA condition during the painting phase. As both the incubation and preparation stages are linked to convergent thinking, this observation aligns with the lower scores observed in the previous task (PCT), signifying a reduction in creative thinking (CT). The psychedelic experience led to a decline in convergent thinking, causing participants to dedicate less time to preparing ideas for

what they would draw or to allowing their ideas to naturally connect.

Exploring macro levels of creativity provided us with a closer examination of the phenomenology of the creative process during the psychedelic experience. Numerous transitions in this study tended to be slightly above the significance level, emphasizing the importance of both sample size and the extent of sampling. Nonetheless, it is crucial to acknowledge and highlight these trends in the results. Most transitions between macro stages of creativity were attenuated in the pharmahuasca (PHA) condition, suggesting that individuals under the influence of psychedelics exhibit a decreased propensity to shift between different cognitive thinking stages during the psychedelic experience. One particularly intriguing finding is the observed trend toward an increase time spend in the ideation (*'I think about new ideas'*), production (*'I carry out/compose my ideas'*), and validation (*'I check whether my work is finished'*) stages, although these trends did not reach statistical significance. However, the observed phenomenological alteration is particularly interesting. Unlike the placebo condition, where participants exhibited a continuous stream of adaptive thinking styles, involving planning what to paint, evaluating ideas, and allowing their ideas to link then produce; during the psychedelic experience, participants appeared to undergo a cyclical loop of thinking a new idea, producing and checking whether its finished. This suggests a more iterative creative process in line with the previous anecdotal evidence stating that artist who uses psychedelics felt "far more enthusiastic and productive, "seamlessly "merging" with the artistic process and experiencing a continuous "flow" of

creativity (Krippner, 2017). This raises the question of whether psychedelics could be considered a potential tool for unblocking creative productivity that may be inhibited or restrained, rather than just focusing on their potential to increase creativity.

Remarkably, participants reported significantly heightened feelings of creativity, as evidenced by increased scores in "insightfulness" during the pharmahuasca condition, despite the absence of empirical evidence. This outcome aligns with prior research suggesting that psychedelics diminishes deliberate creative thinking (e.g. characterized by a focused mental state directed towards explicit task demands encountered in guided, timed situations such as the AUT and PCT tasks) and enhance spontaneous creative thinking (e.g. marked by unrestricted cognition and a lack of focused attention) (Mason et al., 2021). This heightened sense of creativity may be explained by an increased emphasis on the meaning and salience of ordinary information (Hendricks, 2018), which could also account for the observed cyclical macro-levels of creativity stages during painting, indicating that numerous ideas are produced directly without undergoing immediate evaluation.

While spontaneous creative thoughts are integral to the creative process, it is crucial to acknowledge that these thoughts constitute only the initial phase in transforming novel combinations of information into creative output. Subsequent to an insight, higher-order cognitive functions come into play, involving attention, memory retrieval, information organization, abstract reasoning, and the evaluation of factors such as novelty and

usefulness (Dietrich, 2004). Without proper executive functioning, evaluation, and logical thinking, as evidenced by lower scores on PCT, many insights may ultimately prove inconsequential, incomplete, or insignificant. Therefore, future direction in research should adopt a temporal strategy when examining the relationship between psychedelics and creativity. This approach suggests generating ideas during the acute phase when individuals experience heightened openness, attention, and a sense of meaning, coupled with reduced self-criticism and inhibition. A few days later, revisiting these ideas when executive functioning is restored and enables a comprehensive evaluation of their practicality and utility. Only through such a sequential process might these substances potentially break down creative barriers and truly enhance creativity.

The Effects of the Psychedelics on the Aesthetic Experiences during Painting

In the final segment of our analysis, we focus on the aesthetic aspects of the paintings. It is important to note that the analysis of these artworks is not aimed at determining their level of creativity. Instead, the inclusion of art analysis, specifically focusing on the visual features of the paintings, serves the purpose of offering an additional perspective for understanding the participants' phenomenological experiences. We investigate the quantifiable aspects (e.g., number of color choices, brightness, contrast, color diversity etc.) because they represent the sensory experience of the painter and provide a window into a portion of

the creator's mental world. Building upon Oscar Janiger's historical precedent (Janiger & De Rios, 1989) with a hypothesis-driven approach, we employed objective measurements to assess the descriptive attributes of the paintings. Our analysis indicates no statistical difference in the overall brightness and contrast of the painting. However, a significant increase in the number of color choices, along with color diversity (increase in the number of high-frequency shades such as purples, pinks, and violets) emerged in the artworks in the pharmahuasca condition. These findings offer empirical validation of anecdotal reports (Krippner, 1985; Masters et al., 1968) that underscore 'an increased ability to work with colors' as a frequently cited outcome when individuals partake in psychedelic experiences. As one artist describes:

"I always had been afraid to use color in my work, but a single LSD session helped to conquer that fear." (Krippner, 2017)

As part of a broader experimental design, we noted a pronounced increase in enthusiasm for the painting task during the experiment. The designated painting time, recognized as a free period, showcased heightened playfulness among participants. This increase in color choice and diversity can be attributed to heightened playfulness and diminished inhibitions and self-criticism, thereby fostering enthusiasm for creative exploration (Hartogsohn, 2018). Moreover, participants in the PHA condition exhibited a preference for more saturated colors during the painting activity. This may be related to heightened sensory experiences such as elementary hallucinations characterized by

an amplification in the brightness and vividness of colors during the psychedelic experience (Preller & Vollenweider, 2018).

Finally, given the historical connection of psychedelic art to modern movements like abstraction and surrealism (Pisters, 2023), we classified paintings as either representational (depicting recognizable objects or concepts) or non-representational (utilizing abstract shapes, colors, and lines without an apparent real-world reference) to explore the potential influence of pharmahuasca on artistic style. Contrary to our hypothesis was no significant differences in art styles emerged between the pharmahuasca and placebo conditions. During categorization, we observed specific themes surfaced more frequently in the PHA condition, such as nature, love, animals, and landscapes, in contrast to the doodles and sketches seen in the placebo condition. This observed pattern coincides with the idea that psychedelics could enhance symbolic thinking (Wießner, Falchi, Maia, Daldegan-Bueno, Palhano-Fontes, Mason, Ramaekers, Gross, Schooler, & Feilding, 2022). Such insight holds promise for incorporating art production in psychedelic-assisted psychotherapies, providing a unique means of expression and contributing to a more comprehensive and personalized therapeutic intervention that acknowledges diverse modes of communication and processing experiences.

Future Directions

Future research should focus into the practical implications of using psychedelics as a means to enhance creative production

("flow") because of the contrast between the openness to experience, playfulness, and productive flow induced by psychedelics is especially relevant when considering the state of creative blocks commonly associated with feelings of depression, self-doubt, frustration, fear, and desperation (Hirst, 1992). Additionally, prioritizing the validation of these results among professional creatives, who often possess a well-developed introspective capacity and the ability to articulate subtle shifts in creative cognition and emotional states through years of practice and self-reflection, is crucial. This approach aims to enhance the reliability and validity of self-reporting. Such targeted investigations would not only improve the generalizability of findings but also offer valuable insights into the potential applications of psychedelics within creative industries.

Conclusions

In summary, this study reveals that psychedelics acutely diminish the phase of logical thinking and evaluation of creative ideas (convergent thinking), while idea generation (divergent thinking) remains unaffected. This reduction is consistent whether individuals are engaged in structured, goal-driven tasks or unstructured activities like painting. This shift in creative thinking patterns, combined with alterations in affective appraisal and shifts in the attribution of meaning, leads to a subjectively heightened perception of creativity during the psychedelic experience. Being the first study to investigate how psychedelics influence the macro levels of creation, our research

supports the hypothesis that the impact of psychedelics goes beyond creative thinking and extends to the dynamic interplay between cognitive modes throughout the entire creative process. This effort not only reveals new insights into how psychedelics and creative expression interact but also uncovers opportunities to observe dynamism in creative thinking during the acute phase of psychedelic experiences and underscores the necessity for more neurophenomenological models in comprehending creative cognition. This study highlights the potential significance of psychedelics in progressing the field of creativity neuroscience.

4 Conclusion

In concluding this dissertation, this final chapter directs attention towards the outcomes of the conducted experiments. It focuses on the critical role these results play in addressing gaps within the current body of literature. Furthermore, an exploration of the potential applications of psychedelic substances based on these findings is undertaken. This chapter examines the limitations inherent in the conducted experiments and provides insights into possible future directions.

The effect of psychedelics on face recognition and discrimination

Results and Potential Implications

In the first experiment, we explored the effects of pharmahuasca and harmine on the spatiotemporal dynamics of face recognition. Notably, pharmahuasca administration led to an increase in the P1 amplitude at medial occipital electrodes and a decrease in the N170 amplitude at lateral occipital-temporal electrodes within the first 200 milliseconds across all face categories, including self, familiar, and unknown faces. Our findings offer valuable insights into the diverse effects of psychedelics on various levels of visual organizational processes on the early phases of visual perception.

This underscores the significance of these substances as a versatile tool for unravelling the intricate role of serotonin modulation in the chronology of visual processing across diverse perceptual domains.

Our study is the first to reveal that psychedelics significantly decrease neural activation to the self-face during later processing stages. Additionally, these substances blur the distinction between the response to self and other faces at the neuronal level, particularly within the P300 component (300-500 ms). This suggests a notable alteration in the perception and processing of self-relevant information. These findings have significant implications for understanding self-referential information processing, social cognition, and the potential therapeutic use of psychedelics for clinical populations. For example, a meta-analysis conducted by Mor and Winquist (2002) illuminates a compelling relationship between increased self-focused attention/rumination and negative effects, including depression, anxiety, and negative mood (Mor & Winquist, 2002). In a parallel line, the concept of ego-dissolution is consistently connected to increased mental health and well-being. Ego-dissolution offers a unique perspective for individuals to transform themselves from an external vantage point. Negative emotions like guilt and shame, which are typically associated with self-perception in an unaltered consciousness state, can be released through the process of psychedelic-induced ego-dissolution. More psychologically beneficial associations can take root in this recalibrated mental state characterized by self-compassion,

fostering a positive shift in the person's self-image and worldview.

Our research findings indicate that the blurring of boundaries between self and external (both familiar and unknown) stimuli has fascinating implications for how psychedelics can affect interpersonal perception and social cognition. These results suggest that psychedelics have the potential to heighten feelings of interconnectedness while possibly diminishing social distinctions. This could significantly impact individuals' perceptions and relationships with others (Carhart-Harris et al., 2018). The concept of connectedness, denoting a profound sense of unity with one's surroundings and often referred to as oneness, has been extensively studied in clinically oriented psychedelic research (Carhart-Harris & Goodwin, 2017). It is particularly relevant due to its stark contrast to the state of disconnectedness frequently described by individuals suffering from depression before engaging in psychedelic therapy (Watts et al., 2017).

Although closely related, connectedness and ego dissolution are distinct phenomena (Kałużna et al., 2022). While ego dissolution typically fades after the psychedelic experience, individuals often reported enduring sensations of connectedness that lasted for days or even weeks following the session (Amada et al., 2020; Belser et al., 2017). It is important to note that while ego dissolution primarily affects self-perception, connectedness may play a more crucial role in healing interpersonal relationships. Participants in psychedelic studies found that experiences of connectedness resulted in improved relationships with loved

ones (Watts et al., 2017), and compassion induced by connectedness facilitated the processing of childhood trauma in some cases (Healy et al., 2021).

In the second experiment, our focus was on examining the impact of psychedelics on face discrimination. Our results unveiled that general face recognition exhibited a notable slowdown measured by reaction times during the psychedelic experience. Strikingly, participants consistently displayed faster reaction times for their own faces compared to familiar and unknown faces across all drug conditions, indicating a self-face advantage irrespective of the administered drugs, a phenomenon well-documented in prior research (Bortolon & Raffard, 2018). Additionally, none of the drug conditions introduced a bias in face discrimination. However, there was an overall impairment in sensitivity to face discrimination induced by psychedelics. This outcome was initially hypothesized to be linked with visual hallucinations. However, surprisingly, our analysis revealed that self-reported scores for both elementary and complex imagery or neural data did not correlate with impaired sensitivity, as measured by the psychometric function's slope. The possible reasons will be discussed in the *Limitations and Future Directions* section.

Limitations and Future Directions

While this study demonstrated meticulous data collection and rigorous analysis, it is crucial to recognize its inherent limitations. This section outlines some of these limitations and provides suggestions for future directions.

First and foremost, one of the objectives was to establish connections between behavioural outcomes (specifically, impaired discrimination sensitivity in the morphing task and scores on elementary and complex imagery) and neural data to elucidate the relationships between them. Regrettably, no such correlations were identified, prompting consideration of potential reasons for this absence. One possible explanation could be attributed to methodological errors or the variability of the data.

However, this does not clarify the lack of correlation between self-reported visual hallucinations (scores for elementary and complex imagery) and early neural activity components, as we initially theorized. This could be attributed to several factors. Variations in how participants individually perceive psychedelics, including differences in the type and intensity of visual hallucinations experienced, may play a significant role in explaining the observed absence of correlation. The inherently subjective nature of the psychedelic experience, expectations influenced by factors such as set and setting, may result in diverse perceptual outcomes among participants (Hartogsohn, 2017, 2022; Noorani, 2021). These variations may not align neatly with the chosen metrics, further complicating efforts to establish clear associations between behavioural and neural responses. Further investigation and refinement of experimental measures are essential to address these complexities. Tailoring assessments to capture the nuances of the psychedelic experience more precisely, including individual differences, could offer valuable insights in the future.

Secondly, while the research question did not specifically target the impact of harmine on familiar faces, our data unexpectedly revealed a noteworthy effect. Intriguingly, administering harmine resulted in heightened excitability in response to familiar faces within the right parietal temporal cortex (Figure 17 in *Supplementary Materials*). This cortical region has previously been associated with the recognition of celebrity faces (Borghesani et al., 2019; Elfgren et al., 2006; Jemel et al., 2010; Seidenberg et al., 2002). Similarly, one other study showed that the harmine alters the slow-gamma band in the right parietal cortex, which has been associated with attention and memory (Schenberg et al., 2015). Our results aligned with the behavioural reaction times, showing that participants using harmine discriminate the familiar faces much faster than the unknown faces. This finding is interesting, yet few studies have investigated harmine's effects on the human central nervous system and cognition. Preclinical studies involving hippocampal cell cultures and animal models suggest harmine may have cognitive-enhancing effects (see for the Review: Dos Santos & Hallak, 2017). Animal studies investigating the effect of acute harmine administration found an improved memory (Mennenga et al., 2015; Moura et al., 2006), and increased brain-derived neurotrophic factor (BDNF) levels in rat hippocampus (Fortunato et al., 2009), increased early response genes/transcription factors associated with memory/learning processes (He et al., 2015). The significance of this discovery extends to the broader context, suggesting a potential influence on the psychoactive effects of harmine, with specific relevance to memory processes. Considering the pressing demand for enhanced treatments

addressing neurodegenerative disorders and the related cognitive decline, additional human studies exploring the therapeutic potential of harmine are imperative. Such research has the potential to deepen our understanding of its therapeutic possibilities and how it could enhance cognitive function in individuals with neurodegenerative conditions.

Further, it is imperative for future research to prioritize and enhance sample diversity. The experiments, being the first to utilize novel pharmahuasca, had a limited sample diversity, primarily comprising young, healthy males, potentially rendering the findings less representative of the global population. The volunteers were predominantly WEIRD (Western, Educated, Industrialized, Rich, and Democratic), accentuating a limitation in generalizability (Henrich et al., 2010). The decision to include only male participants in the initial study was informed by considerations related to potential sex differences in hormonal fluctuations and brain structure. Research has suggested that females undergo hormonal fluctuations across the menstrual cycle, which can influence neurotransmitter levels and neural activity (Andréen et al., 2009). These hormonal fluctuations may interact with the effects of psychoactive substances, potentially leading to variability in drug response between males and females. Furthermore, studies have reported differences in brain structure and function between males and females, including variations in gray matter volume, white matter connectivity, and regional activation patterns (Cosgrove et al., 2007; Gong et al., 2011). These sex differences in brain structure and function may contribute to

differential responses to psychoactive substances, as neurobiological substrates underlying drug effects could vary between genders. By focusing exclusively on male participants in the initial study, we aimed to control for these potential sources of variability and enhance the internal validity of the findings. By excluding females, we minimized the influence of hormonal fluctuations on drug response and reduced variability related to sex differences in brain structure and function. While the decision to include only male participants may limit the generalizability of the results to female populations, it allowed for a more focused examination of the effects of the novel drug on the male brain, laying the groundwork for future research to explore potential sex differences in drug response. Future research should prioritize expanding participant diversity to elucidate potential sex differences and to enhance the external validity across diverse cultural and socioeconomic contexts.

Additionally, variations in psychedelics and dosages could yield diverse effects on face processing, necessitating further exploration of the generalizability of findings to different psychedelics and doses. Investigating the dose-dependent effects of psychedelics could provide valuable insights into the nuanced relationship between dosage and therapeutic outcomes. Understanding the optimal dosage for specific therapeutic goals could inform safer and more effective psychedelic-assisted therapies.

Like every study, this research is bound by the practical limitations inherent to the pursuit of knowledge, such as time

constraints stemming from limited funding and external factors like the COVID-19 pandemic. Moreover, it underscores the truth that as students, we often gain insight into optimal approaches only upon completion. Nevertheless, it's crucial to recognize the potential for future improvements, particularly given the wealth of EEG data suggesting the feasibility of a more comprehensive analysis approach. Moving forward, future directions for this study could involve expanding the analytical approach to incorporate time-frequency analyses to investigate oscillatory dynamics associated with face perception under psychedelic influence (Cohen, 2014; van Vugt & Sederberg, 2015). Furthermore, exploring connectivity patterns between brain regions using techniques like functional connectivity analysis or graph theory could elucidate the neural networks underlying altered face processing during the psychedelic experience (Bassett & Sporns, 2017; Friston, 2011). Additionally, source analysis techniques could be employed to localize brain activity and identify specific brain regions involved in face perception under psychedelic influence (Hämäläinen & Ilmoniemi, 1994; Michel et al., 2004). Furthermore, event-related spectral perturbation (ERSP) analysis could be utilized to examine changes in spectral power associated with specific events or stimuli, providing further insights into the temporal dynamics of brain activity during face perception tasks under the influence of psychedelics (Makeig et al., 2004; Tallon-Baudry & Bertrand, 1999). Moreover, the application of machine learning and artificial intelligence (AI) algorithms could provide valuable insights into EEG data, such as pattern recognition, classification

of brain states, or prediction of cognitive processes related to face perception under the influence of psychedelics (Bashivan et al., 2016; Marathe & Ries, 2013). Finally, integrating advanced neuroimaging methods, such as fMRI and MEG, will present valuable opportunities to enhance our understanding of the neural mechanisms underlying these effects. This serves to expand further our knowledge regarding the impact of psychedelics on self-referential information processing and its neural correlates in terms of functionality, structures, and network connectivity.

Embracing a holistic approach and integrating multidimensional analyses could yield a more nuanced and comprehensive understanding of the neural mechanisms underpinning the effects of psychedelics on face perception and cognition. This approach allows for a deeper exploration of how psychedelics may impact not only basic sensory processing but also higher-order cognitive functions, emotional processing, and social cognition. It also enables researchers to account for individual differences and contextual factors that may influence the effects of psychedelics on face perception and cognition. This enhanced understanding holds promise for refining therapeutic models based on the current knowledge of how psychedelics influence self-referential and interpersonal processing. These tailored models have the potential to optimize the therapeutic efficacy of psychedelics in treating mental health conditions, promoting personal growth, and enhancing overall well-being.

The effect of psychedelics on creative cognition

Results and Potential Implications

Our comprehensive examination of the influence of psychedelics on various aspects of creativity has yielded fascinating findings. Through the application of traditional creativity assessments like the PCT and AUT, we have found that while psychedelics impair convergent thinking, divergent thinking remains largely unaffected by these substances. Our results indicate that psilocybin consumption during acute states may impair an individual's ability to evaluate options and engage in logical reasoning while still allowing for a substantial generation of innovative ideas and associations during creative tasks with specific goals in mind. Furthermore, the observed reduction in convergent thinking aligns intricately with a significant decrease in the selection of the incubation stage, particularly evident during the act of painting. This association underscores a profound link between altered cognitive processes and the unfolding of macro-level creative cognition alterations. Building upon our findings, it becomes evident that the influence of psychedelics on creativity transcends mere cognitive processes, extending into the realm of creative expression. As the first study to investigate the impact of psychedelics on macro-levels creativity, our research provides a valuable perspective on the altered phenomenology that occurs during creative processes in psychedelic experiences.

The intriguing aspect of our findings lies in the reports from participants, who consistently expressed a heightened subjective

sense of creativity during the psychedelic state despite the absence of empirical results from specific tasks. The heightened sense of creative feeling observed during psychedelic experiences can be attributed to a distinctive shift in the perception of meaning and salience, a phenomenon commonly encountered in the psychedelic state (Hendricks, 2018). In this altered cognitive landscape, stimuli typically perceived as mundane or commonplace transform, becoming imbued with heightened significance and relevance. This shift in the interpretative framework contributes to an enriched and expansive cognitive environment, wherein the ordinary is redefined and infused with novel layers of meaning. In alignment with that, participants demonstrated active involvement in the ideation, production, and validation stages, although the level of engagement did not achieve statistical significance in our study (Possible reasons will be discussed in the *Limitations and Future Directions* section). Also, this active production may contribute to the heightened sense of creativity reported during the psychedelic state.

Secondly, our investigation into the aesthetic experience during the psychedelic state aimed to unravel how "psychedelic art" exhibits commonalities attributable to alterations in sensory phenomenology. A key revelation from our findings is the significant increase in color selection and the heightened color diversity and vividness. The broadening of the artistic palette can be attributed to the effects of psychedelics, which include an expansion of attention and a departure from the constraints imposed by conventional cognitive limitations. This leads to an increased enthusiasm and openness to the artistic experience.

While our study suggests that psychedelics may temporarily hinder specific aspects of cognitive evaluation and logical thinking, the preservation of divergent thinking and the reported heightened subjective creativity point to a nuanced interplay between altered cognitive states and creative processes. Our results don't necessarily directly link to increased creative thinking but seem to induce a productive mode of thinking and heightened openness during the acute phase, which is particularly intriguing. By disrupting established patterns of perception, psychedelics may facilitate a departure from the conventional, fostering a mindset conducive to tapping into untapped reservoirs of imaginative expression.

Limitations and Future Directions

A pivotal and primary direction for future exploration lies in shifting the focus towards harnessing psychedelics as unblocking agents rather than primarily as creative enhancers. This suggests a strategic pivot from viewing psychedelics solely through the lens of augmenting creative thinking capabilities to considering their potential role in overcoming creative obstacles and barriers. This shift in emphasis recognizes the observed phenomenon of production and heightened creativity during psychedelic experiences suggest that future directions seek to optimize the potential of psychedelics not only as enhancers of creative thinking but as deliberate tools for overcoming creative obstacles and fostering a more consistently uninhibited creative mindset.

Furthermore, future research should incorporate self-reported questionnaires specifically designed to target creative cognition to draw more definitive conclusions about the acute enhancements of creativity brought about by psychedelics. Although measures in this study are widely used in the literature, the degree to which these measures reflect creativity objectively is unclear. For instance, the 'insightfulness' scale, which comprises three questions focusing on feelings of profundity, insights into puzzling connections, and original thoughts, raises questions. The first two questions primarily convey a sense of deep introspection and insight, elements that contribute to the creative process but may also be associated with a reduction in self-focus, promoting a state of neutral introspection, understanding, or realization rather than a heightened sense of creativity (Dourron et al., 2022). To yield more definitive insights into the acute impact of psychedelics on subjective feelings of creativity, future studies should consider asking more straightforward questions, such as 'Do you feel more creative?' Finally, incorporating a variety of creativity tasks, including semantic and symbolic creativity, would assist in comprehending the nuanced effects of these substances on creativity.

Supplementary Materials

Figure 14- Overview of the study day.

Timeline of drug administrations and experiments.

measures	EEG	setting up			Baseline				
	tasks	task manual / instruction			eyes closed				
	interview								
	psychometry				explain		P acute		P acute
	psychometry	daily baseline			explain				
	vitals				BL vitals		vitals		vitals
	blood sample		prepare		BL blood		blood		blood
time (min)		t-120	t-90	t-60	t-45	t-30	t-15	t0	t15
treatment						HRM /		DMT /	DMT /
						100mg		10mg	10mg
Proband 1		08:30	09:00	09:30	09:45	10:00	10:15	10:30	10:45
Proband 2		09:30	10:00	10:30	10:45	11:00	11:15	11:30	11:45
									12:00

...

Resting	ERP				Resting		ECG!!!		Resting
eyes closed	self-other-task				eyes closed		karaoke		eyes closed
					microphenom enological interview				
P acute		P acute		P acute		P acute		P acute	P acute
keywords				keywords				keywords	
		vitals				vitals			vitals
blood		blood		blood		blood		blood	blood
t45	t60	t75	t90	t105	t120	t135	t150	t165	t180
DMT /	DMT /		DMT /	DMT /	DMT /	DMT /	DMT /		
0, 5 or 10 mg	0, 5 or 10 mg		0, 5 or 10 mg	0, 5 or 10 mg	0, 5 or 10 mg	0, 5 or 10 mg	0, 5 or 10 mg		
11:15	11:30	11:45	12:00	12:15	12:30	12:45	13:00	13:15	13:30
12:15	12:30	12:45	13:00	13:15	13:30	13:45	14:00	14:15	14:30
									14:45

...

FRN charity		Resting						
		eyes closed	social					
				painting task			micropheno & semi-structured interview	
	P acute keywords		P acute			P post		
			final vitals					
	blood		blood		final blood			
t210	t225	t240	t255	t270	t285	t300	t315	t330
14:00	14:15	14:30	14:45	15:00	15:15	15:30	15:45	16:00
15:00	15:15	15:30	15:45	16:00	16:15	16:30	16:45	17:00

Figure 15- Images of stimuli for the ERP experiment

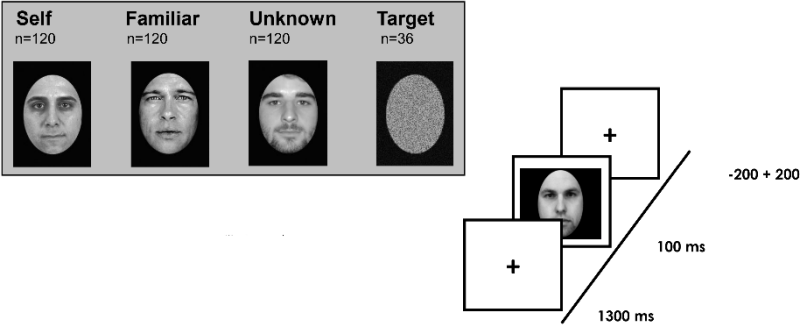


Figure 16- Images of morphed stimuli for the face discrimination experiment

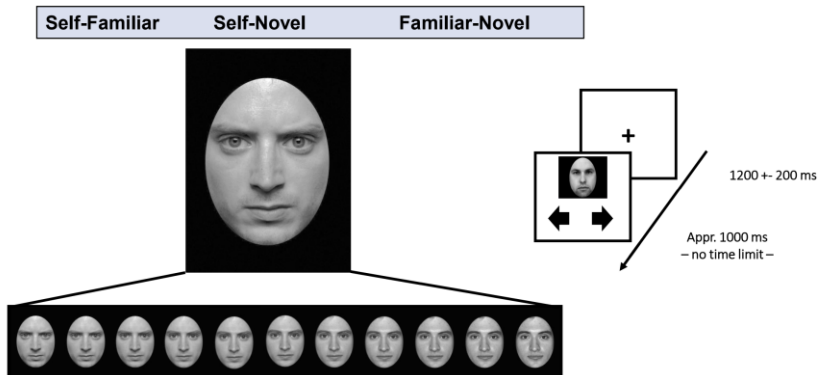


Figure 17- The effect of harmine on familiar faces

(A) Spatiotemporal matrix displays the result of the cluster-based permutation test, comparing the conditions HAR vs. PLA in response to familiar face stimuli. Significant clusters are shown as topographic distributions at the bottom of the matrix. (B) Interaction plots show that HAR increases the neural response to familiar faces ($p=0.004$, 332-523 ms) at the right posterior temporal cortex (T8, TP8, CP6, CP4, P4, P6, P8) and while the response to unknown faces does not change when compared to the placebo condition.

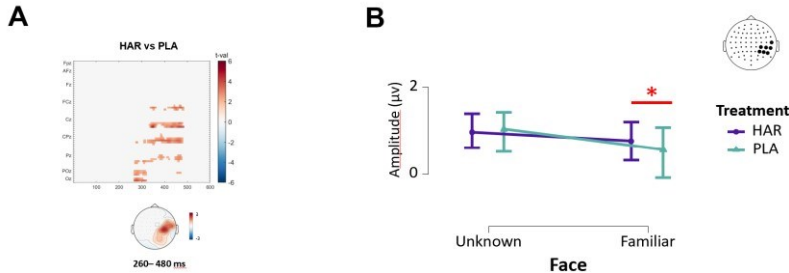


Table 1- Results of cluster-based permutation tests on the event-related potentials showing the significant effect of drug condition (PHA, HAR, PLA) on self, familiar and unknown faces.

<i>Main Effect</i>	<i>Comparisons</i>	<i>Probability</i>	<i>Statistics</i>	<i>Time (ms)</i>
<i>Self-Face</i>	MANOVA	p<0.001 p<0.001	Tsum=41383.9 Tsum=13633.7	140 - 199 ms 207 - 600 ms
	PHA vs. PLA	p=0.002997 p=0.015984 p=0.021978 p=0.004995 p=0.008991	Tsum=1852.0 Tsum=1187.2 Tsum=1046.8 Tsum=-2041.2 Tsum=-1662.2	398 - 601 ms 214 - 378 ms 136 - 199 ms 324 - 562 ms 148 - 203 ms
	PHA vs. HAR	p<0.001 p<0.001	Tsum=6559.2 Tsum=6278.1	160 - 601 ms 148 - 601 ms
	HAR vs. PLA	n.s.		
<i>Familiar Face</i>	MANOVA	p<0.001 p= 0.017	Tsum=31602.2 Tsum= 4250	82 - 398 ms 406 - 582 ms
	PHA vs. PLA	p=0.013 p=0.006	Tsum=1572.8 Tsum= - 2080.2	82 - 207 ms 121 - 203 ms
	PHA vs. HAR	p= 0.008 p= 0.017 p= 0.018 p= 0.001 p= 0.012	Tsum=1719.6 Tsum=1117.1 Tsum=1070.4 Tsum= - 2662.5 Tsum= - 1290.3	218 - 378 ms 464 - 597ms 113 - 210 ms 222 - 589 ms 152 - 203 ms
	HAR vs. PLA	p= 0.01	Tsum=1115.4	265 - 484 ms
<i>Unknown Face</i>	MANOVA	p<0.001 p<0.001	Tsum=24755.2 Tsum=18174.4	214 - 601 ms 125 - 207 ms
	PHA vs. PLA	p=0.02 p<0.001 p=0.003	Tsum=1078.9 Tsum= - 2574.6 Tsum= - 2161.5	132 - 203 ms 296 - 601 ms 121 - 207 ms
	PHA vs. HAR	p=0.004 p=0.004 p<0.001	Tsum=1741.5 Tsum=1610.8 Tsum= - 5501.8	214 - 363 ms 398 - 585 ms 132 - 601 ms
	HAR vs. PLA	n.s		

Table 2- Results of cluster-based permutation tests on the event-related potentials for interaction effects (one-tail=-1)

<i>Interactions</i>	<i>Comparisons</i>	<i>Probability</i>	<i>Statistics</i>	<i>Time (ms)</i>
<i>Self vs. Unknown Face</i>	PHA vs. PLA	p=0.023976	Tsum= -1267.5	312 - 562 ms
	PHA vs. HAR	n.s.		
	HAR vs. PLA	n.s.		
<i>Self vs. Familiar Face</i>	PHA vs. PLA	p=0.00399	Tsum=-2035.2	324 – 554 ms
	PHA vs. HAR	p=0.001998	Tsum=-2705.9	317 - 600 ms
	HAR vs. PLA	n.s.		
<i>Familiar vs. Unknown Face</i>	PHA vs. PLA	n.s.		
	PHA vs. HAR	n.s.		
	HAR vs. PLA	n.s.		

Figure 18- Example image from Picture Concept Task

Participants are asked to identify the common concept in each row. The correct answers are 3, 5, and 7, as they depict various representations related to water.



Table 3- Table showing the number of transitions (total count across participant) between each macro stage of creativity for pharmahuasca and placebo conditions.

Significant transitions are flagged by an asterisk (*).

<i>PHA condition</i>	<i>to Preparation</i>	<i>to Incubation</i>	<i>to Ideation</i>	<i>to Illumination</i>	<i>to Production</i>	<i>to Validation</i>	<i>Total</i>
<i>from Preparation</i>	10	5*	9	4	13	5	46
<i>from Incubation</i>	7*	9*	10	0	10	2	38*
<i>from Ideation</i>	15	18	24	9	30	9	105
<i>from Illumination</i>	5	6	10	6	10	5	42
<i>from Production</i>	21	23	29	14	90	23	200
<i>from Validation</i>	10	5	18	9	40	24	106
<i>Total</i>	68	66	100	42	193	68	537

<i>PLA condition</i>	<i>to Preparation</i>	<i>to Incubation</i>	<i>to Ideation</i>	<i>to Illumination</i>	<i>to Production</i>	<i>to Validation</i>	<i>Total</i>
<i>from Preparation</i>	15	17*	17	7	17	9	82
<i>from Incubation</i>	22*	29*	24	11	23	10	119*
<i>from Ideation</i>	22	27	25	8	29	13	124
<i>from Illumination</i>	9	9	10	8	13	5	54
<i>from Production</i>	23	33	30	15	86	21	208
<i>from Validation</i>	15	18	17	10	34	23	117
<i>Total</i>	106	133	123	59	202	81	704

Table 4- Table showing the mean number ($\pm$ SD) of selection for each macro stage of creativity for pharmahuasca and placebo conditions (one-tailed).

	PHA Mean $\pm$ SD	PLA Mean $\pm$ SD	Statistics	p
<i>Preparation</i>	11 $\pm$ 13.1	12.5 $\pm$ 16	0.478	0.318
<i>Incubation</i>	10.4 $\pm$ 12.6	17.5 $\pm$ 20.3	1.987	0.029*
<i>Ideation</i>	16.4 $\pm$ 17.6	16.4 $\pm$ 20.4	0	0.5
<i>Illumination</i>	6.4 $\pm$ 11.3	7.5 $\pm$ 13.8	0.648	0.261
<i>Production</i>	45 $\pm$ 13.7	42.5 $\pm$ 16	-1	0.837
<i>Validation</i>	17.5 $\pm$ 15.7	15.7 $\pm$ 17.1	-0.523	0.697
<i>Total stage choice</i>	106.8 $\pm$ 49.9	112.1 $\pm$ 75	0.544	0.295

Table 5- Table displaying the mean and standard deviation (SD) of measured visual features in the paintings.

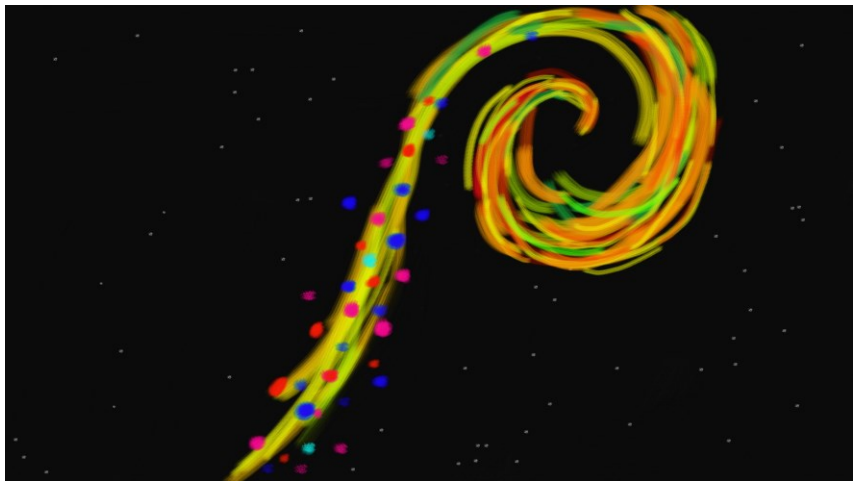
	PHA (Mean±SD)	PLA (Mean±SD)
<i>Overall Brightness</i>	149.2±67.9	161.8±52.2
<i>Overall Contrast</i>	47.4±20.5	49.7±22.9
<i>Number of colors selected</i>	20.6±8.9	16.7±7.5
<i>Hue</i>	0.406±0.147	0.354±0.132
<i>Saturation Empty Space</i>	0.533±0.11	0.484±0.12
<i>Percentage</i>	27±0.34	29±0.33
<i>Art Style</i>	Representational=19 Non-representational=12	Representational=18 Non-representational=13

Figure 19- Some examples of participants' paintings

Subject #43
Placebo Condition

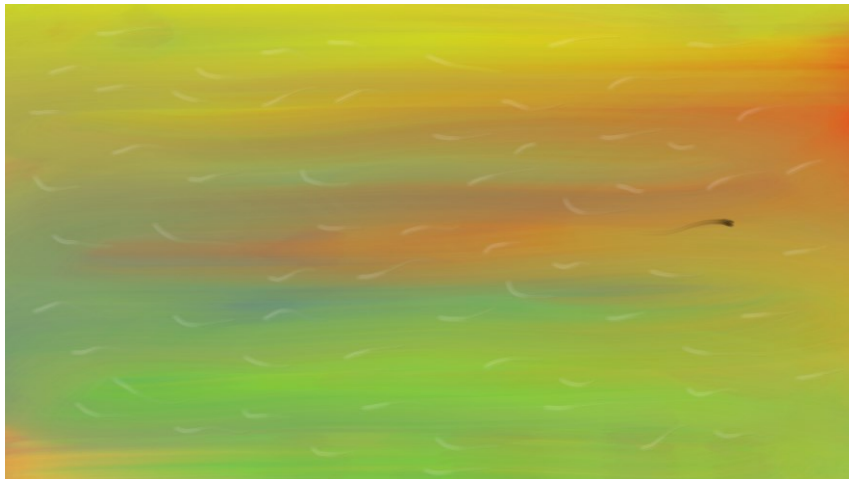


Pharmahuasca Condition

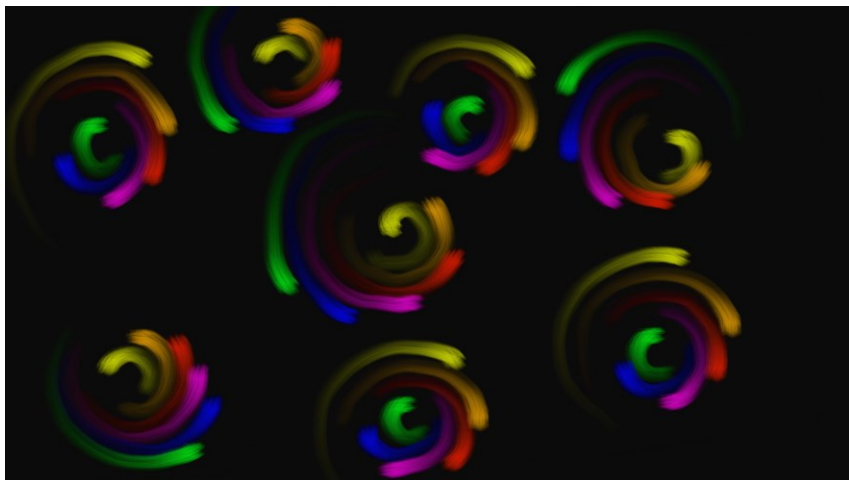


Subject #40

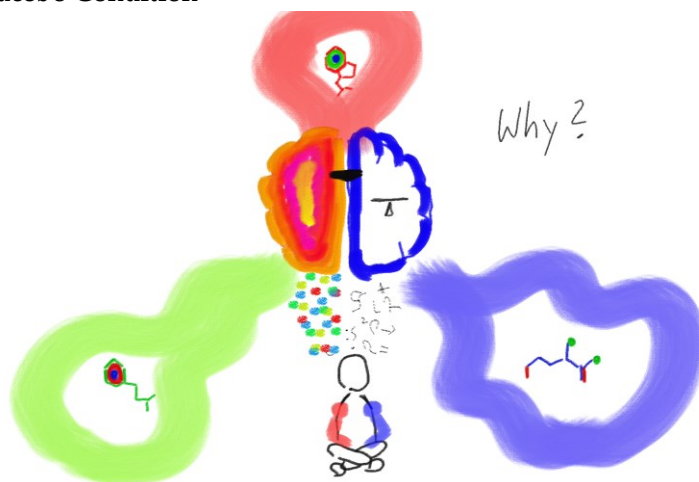
Placebo Condition



Pharmahuasca Condition



Subject #26
Placebo Condition



Pharmahuasca Condition

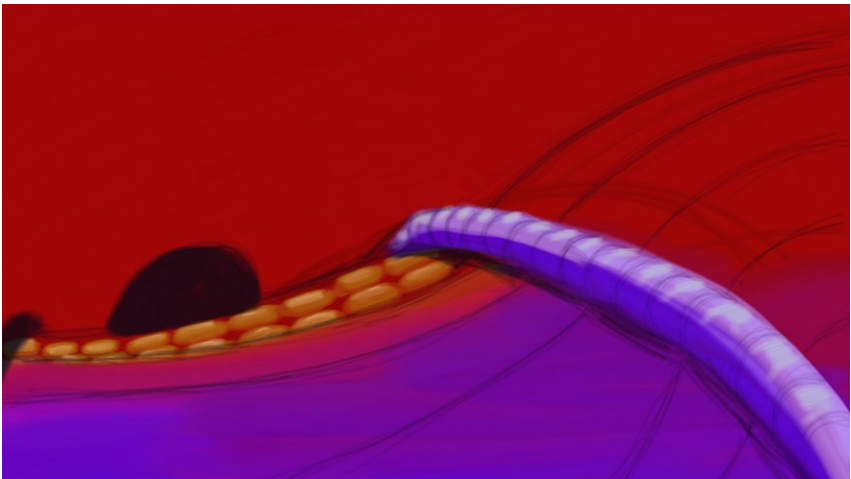


Subject #26

Placebo Condition



Pharmahuasca Condition



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