

Subjective, physiological and EEG effects of extended DMT administration

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Statement of Originality

The author performed the work presented in this thesis, including study design, study coordination, participant recruitment, data collection, data preprocessing, data analysis, and write-up. The author confirms that the work is their own, and that all else is appropriately referenced.

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Abstract

DMT is a serotonergic psychedelic that induces rapid and unique alterations in consciousness. While traditionally short-acting, its unique properties make it suitable for continuous intravenous (IV) administration. This thesis investigated the feasibility, tolerability and neurophenomenological effects of continuous IV DMT infusions in healthy volunteers.

The first study phase established dose-response characteristics, evaluating tolerability and effectiveness across infusion rates. It was hypothesised that continuous IV DMT would be well-tolerated and maintain a steady-state psychedelic experience. A second phase examined subjective and electroencephalography (EEG) effects of a moderately high dose of continuous IV DMT. It was hypothesised that extended DMT would induce decreases in alpha power and increases in Lempel-Ziv (LZ) complexity, correlating with subjective intensity.

Continuous IV DMT was psychologically and physiologically well-tolerated. Infusions extended peak psychoactive effects, maintaining stable intensity throughout. Dose-dependent effects were seen for subjective intensity and plasma DMT concentrations, while heart rate increases normalised within 10-12 minutes of infusion. The extended DMT experience featured strong visual effects, immersion, and encounters with ‘entities’ (i.e., seemingly sentient beings). Experiences generally followed three stages: ‘struggles’, resolution, and positive experiences (‘fruits’).

EEG analyses showed widespread alpha (8-13 Hz) power reductions, correlating with a range of subjective effects. Occipital theta (4–8 Hz) power decreased during transition periods, while occipital low beta (13–20 Hz) power reductions persisted for up to 12 minutes, accompanied by increased low beta power in sensorimotor areas. Widespread high beta (20-30 Hz) reductions correlated with intensity of the experience. Increases in LZ complexity lasted up to 12 minutes post-infusion, correlating with a range of subjective effects. ‘Entity’ experiences displayed increased alpha and beta power and decreased LZ complexity compared to ‘No entity’ experiences. Together, these results suggest continuous IV DMT is an effective method for extending the DMT experience, with promising applications for research and clinical use.

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Abbreviations

11D-ASC	11-dimensions Altered States of Consciousness scale
2C-B	4-bromo-2,5-dimethoxyphenethylamine
5-HT	Serotonin
5-MeO-DMT	5-methoxy-N,N-dimethyltryptamine
5D-ASC	5-dimensions Altered States of Consciousness scale
AAL	Automated Anatomical Labelling
ACC	Anterior cingulate cortex
ANOVA	Analysis of Variance
BDNF	Brain-derived neurotrophic factor
BEM	Boundary Element Method
BOLD	Blood-oxygen-level-dependent
CAMKII	Ca ²⁺ /calmodulin-dependent protein kinase
CCC	Claustro-cortical-circuit
CEQ	Challenging Experiences Questionnaire
CSTC	Cortico-Striato-Thalamo-Cortical
CYP	Cytochrome P450
DAG	Diacylglycerol
DMN	Default mode network
DMT	N,N-Dimethyltryptamine
EBI	Emotional Breakthrough Inventory
ECG	Electrocardiogram
EDI	Ego Dissolution Inventory
EDTA	Ethylenediaminetetraacetic acid
EEG	Electroencephalography
ERP	Event-related potential
EPSP	Excitatory post-synaptic potential
ESM	Experience sampling method
FDR	False discovery rate
FFT	Fast Fourier Transform
fMRI	Functional magnetic resonance imaging

GFC	Global functional connectivity
GPCR	G-protein-coupled receptor
GWTs	Global workspace theories
HOTs	Higher-order theories
HR	Heart rate
HRA	Health Research Authority
ICRF	Imperial Clinical Research Facility
IIT	Integrated information theory
IP3	Inositol triphosphate
IPEG	International Pharmacology-EEG Group
ICA	Independent component analysis
IRASA	Irregular-Resampling Auto-Spectral Analysis
IV	Intravenous
JRCO	Joint Research and Compliance Office
LCMV	Linear constrained minimum variance
LORETA	Low-resolution electromagnetic tomography
LSD	Lysergic acid diethylamide
LME	Linear mixed-effects
LZ	Lempel-Ziv
MAO	Monoamine oxidase
MAPK	Mitogen-activated protein kinase
MEG	Magnetoencephalography
MEQ-30	Mystical Experience Questionnaire
mGlu	Metabotropic glutamate
MRI	Magnetic resonance imaging
NHS	National Health Service
NRES	National Research Ethics Service
NCCs	Neural correlates of consciousness
PCC	Posterior cingulate cortex
PCI	Perturbational complexity index
PET	Positron emission tomography
PIP2	Phosphatidylinositol-4,5-bisphosphate

PLC	Phospholipase C
PD	Pharmacodynamics
PK	Pharmacokinetics
PKC	Protein kinase C
PSD	Power spectral density
REBUS	Relaxed beliefs under psychedelics
REM	Rapid eye movement
RSC	Retrosplenial cortex
SD	Standard deviation
SEM	Standard error of mean
SOCQ	States of Consciousness Questionnaire
SPECT	Single-photon emission computed tomography
TAAR	Trace amine-associated receptor
TFR	Time-frequency representations
ToCs	Theories of consciousness
TOP	Transmodal association cortex pole
VAS	Visual Analogue Scale

1. Introduction

1.1 Classic psychedelics

1.1.1 Introduction

Psychedelics are a class of psychoactive substances that induce profound alterations in perception, mood, cognition, and consciousness (Nichols, 2004; Preller and Vollenweider, 2018). Naturally occurring psychedelics such as psilocybin mushrooms, peyote, and ayahuasca have been used by humans for centuries and are integral to religious and medicinal practices among cultures worldwide (Dos Santos and Hallak, 2021; Nichols, 2016). Indigenous tribes in the Amazon Basin, for example, have been using ayahuasca, a brew containing the potent psychedelic compound N,N-Dimethyltryptamine (DMT), in shamanic ceremonies and religious practices aimed at communication with spiritual entities, healing, and community cohesion (Dobkin de Rios, 1971; Labate and Cavnar, 2018; Luna, 1984; Luna, 2011). Similarly, Indigenous cultures in Mesoamerica have used psilocybin mushrooms in their religious ceremonies (Carod-Artal, 2015), referring to them as “teonanáctl” or “flesh of the gods” (Schultes et al., 2001). Likewise, Native American tribes have used the peyote cactus in spiritual and healing practices, with evidence dating back centuries (Bruhn et al., 2002; El-Seedi et al., 2005; Schultes et al., 2001). These traditional uses highlight the cultural significance of psychedelics and their historical role in spirituality and medicine.

The mid-20th century marked a significant turning point for psychedelics, bringing them into Western culture and the scientific community. After the synthesis of lysergic acid diethylamide (LSD) by Albert Hofmann in 1938 (Hofmann, 1979) and the isolation of psilocin from mushrooms by Hofmann in 1958 (Hofmann et al., 1959), they became the focus of psychiatric research due to their profound effects on consciousness, with the 1950s and 1960s seeing a surge of scientific interest in these substances. The psychiatrist Humphry Osmond reported on the potential of psychedelics to enhance psychotherapy, coining the term ‘psychedelic’ (‘mind-manifesting’; Osmond, 1957), while Pahnke’s (1963) Good Friday Experiment demonstrated the profound mystical experiences that psychedelics could induce. Other pioneering studies investigated the clinical potential of LSD and psilocybin for the treatment of various psychiatric disorders, including depression, end-of-life anxiety, and alcohol use disorder (Abuzzahab and Anderson, 1971; Grinspoon and Bakalar, 1979; Grof et al., 1973). Psychedelics were seen as potentially groundbreaking tools for psychiatry, and systematic reviews of these early studies suggest that

psychedelics could facilitate improvements in the treatment of these conditions, both given in repeated low doses combined with psychotherapy (psycholytic, ‘mind-loosening’ model) and given in a few high doses with psychological support (psychedelic, ‘mind-manifesting’ model; Rucker et al., 2016).

However, the sociopolitical climate of the 1960s and 1970s and the association of psychedelics with the ‘counterculture movement’ (Lee and Shlain, 1985), with its widespread recreational use and concerns over the misuse of psychedelics, led to a significant backlash. This resulted in the criminalisation of these substances under the Controlled Substances Act of 1970 in the United States in 1976, with other governments worldwide, including the United Kingdom, taking similar action. Since then, psychedelics have been classified as Schedule 1 drugs, indicating a high potential for abuse and no accepted medical use. The resulting stigmatisation and legal barriers to studying these substances led to a decades-long hiatus in scientific research (Carhart-Harris and Goodwin, 2017; Nichols, 2016; Pollan, 2018).

Human psychedelic research in healthy volunteers resumed in the 1990s, and recent years have seen a remarkable resurgence in interest in psychedelics from both scientific and public communities (Lieberman and Shalev, 2016), often referred to as the “Psychedelic Renaissance”. Modern-day research is driven by advances in brain imaging techniques and psychopharmacology, which have started to disentangle the molecular and neurophysiological processes involved in psychedelic action, providing insight into the potential mechanisms by which they affect brain function and exert their psychological effects (Vollenweider and Kometer, 2010). For instance, they have shown that psychedelics decrease activity in brain areas associated with self-referential thought processes, thereby facilitating a sense of connectedness and ego dissolution (Carhart-Harris et al., 2016b), and induce neural plasticity and connectivity changes, which may underpin the profound changes in perception and cognition, and potentially explain their long-lasting therapeutic effects (Carhart-Harris et al., 2012b; Vollenweider and Preller, 2020).

Recent years have also seen a growing number of studies revisiting the therapeutic potential of psychedelics. Contemporary clinical trials have shown that substances like psilocybin, LSD and DMT can produce significant reductions in symptoms of treatment-resistant depression, addiction, and anxiety symptoms in life-threatening cancer, often after just a single session (Carhart-Harris et al., 2016a; Carhart-Harris and Goodwin, 2017; Griffiths et al., 2016; Ross et al., 2016). Treatment for a range of other indications has also been tested (for a review, see Yao et al., 2024), and further studies with an increasing variety of psychedelic molecules are underway. Institutions such as Imperial College London have established dedicated centres for psychedelic research, and this is

paralleled with a growing interest of pharmaceutical companies developing and testing novel, patentable molecules (Phelps et al., 2022). As a result, the current wave of research is laying the groundwork for a potential paradigm shift in mental health treatment, aiming to integrate psychedelics into medical practice and offering alternative therapeutic options for conditions that are often resistant to conventional treatments (Nutt and Carhart-Harris, 2021; Nutt et al., 2023).

1.1.2 Biological mechanisms

1.1.2.1 Chemical structure and pharmacology

Classic, serotonergic psychedelics share a basic molecular structure that closely resembles the serotonin (5-HT) molecule (Nichols, 2016) and a common feature of partial agonism of 5-HT₂ receptors (Kim et al., 2020). They are further classified into three major groups based on their chemical structure. Phenethylamines (e.g., mescaline, 4-bromo-2,5-dimethoxyphenethylamine [2C-B]) are most selective for 5-HT₂ receptors, while tryptamines (e.g., psilocybin, DMT, 5-methoxy-N,N-dimethyltryptamine [5-MeO-DMT]) show a high affinity for most serotonin receptors. Ergolines (e.g., LSD) are structurally more complex and show the least selectivity, with high affinities for a broad range of receptor types, including serotonin, dopamine, adrenergic, and sigma receptors.

Psychedelics (e.g., psilocybin, LSD, mescaline, 2C-B) are typically administered orally, although some (e.g., DMT) are often inhaled or administered intravenously due to their rapid breakdown by monoamine oxidase (MAO) when ingested orally (for more details, see section [1.2.4](#), “*DMT – Routes of administration*”). Upon administration, they are absorbed into the bloodstream and distributed throughout the body; however, due to their small and lipophilic nature and resulting ability to cross the blood-brain barrier, they are concentrated in the brain. The onset and duration of action vary significantly between compounds and administration methods. Oral ingestion typically leads to peak plasma levels within 30 minutes to 2 hours (e.g., LSD reaches its peak effects about 60-90 minutes after ingestion; psilocybin is converted to psilocin within 30-60 minutes), while inhalation and intravenous (IV) administration lead to a significantly faster onset and peak of effects (e.g., onset < 1 minute and peak effects at 2-5 minutes for IV DMT). Likewise, the effects of oral LSD last up to 12 hours, whereas the effects of inhaled DMT last less than 30 minutes (Strassman and Qualls, 1994).

Psychedelics, including DMT, are metabolised primarily via liver enzymes such as cytochrome P450 (CYP) enzymes (Eckernäs et al., 2023a; Madrid-Gambin et al., 2023). The excretion of psychedelics

and their metabolites typically occurs through the kidneys, with half-lives varying widely between specific substances. While IV DMT has a half-life of 10-12 minutes (Good et al., 2023), oral LSD has a half-life of approximately two to four hours, with effects lasting much longer due to sustained interaction of its metabolites with brain receptors (Passie et al., 2008).

1.1.2.2 Receptor binding and molecular signalling pathways

Of the 5-HT₂ receptor subtypes, the 5-HT_{2A} receptor is the primary molecular target of most classic psychedelics, suggesting its crucial role in the emergence of psychedelic effects (Nichols, 2004; Nichols, 2016). In humans, it has been shown that 5-HT_{2A} receptor occupancy correlates with the intensity of subjective effects induced by psychedelics (Madsen et al., 2019), and that 5-HT_{2A} binding affinities of various psychedelics significantly correlate with their human hallucinogenic potencies (Glennon et al., 1984). A drug discrimination study revealed that the affinities of 5-HT₂ receptor agonists for 5-HT_{2A} receptors correlated better with their abilities to block the effects of LSD than 5-HT_{2C} receptors (Fiorella et al., 1995). Additionally, the administration of the 5-HT_{2A} receptor antagonist ketanserin diminishes the subjective effects associated with psychedelics (Becker et al., 2023; Holze et al., 2021; Preller et al., 2017; Quednow et al., 2012; Valle et al., 2016; Vollenweider et al., 1998), and this occurred in a dose-dependent manner (Preller et al., 2017; Vollenweider et al., 1998). Finally, it has been shown that baseline availability of 5-HT_{2A} receptors predicts the intensity and duration of the acute subjective effects of psilocybin (Stenbæk et al., 2021). These findings are supported by the results of animal studies. In rodent drug discrimination studies, a strong association has been shown between human hallucinogenic effects and the head-twitch response in mice (Halberstadt et al., 2020; Halberstadt and Geyer, 2013). 5-HT_{2A} receptor knockout mice do not show a head-twitch response following psychedelic administration (González-Maeso et al., 2007), while this effect was not seen in 5-HT_{2C} receptor knockout mice (Canal et al., 2010).

The 5-HT_{2A} receptor is a G-protein-coupled receptor (GPCR), and psychedelics and other 5-HT_{2A} receptor agonists activate intracellular Gq-like G proteins (Egan et al., 2000). This leads to a cascade of events, including phospholipase C (PLC) stimulation and the breakdown of phosphatidylinositol-4,5-bisphosphate (PIP₂) into the two secondary messengers inositol triphosphate (IP₃) and diacylglycerol (DAG). Intracellular Ca²⁺ ions are released from the endoplasmic reticulum via IP₃, and protein kinase C (PKC) is activated via DAG, ultimately activating Ca²⁺/calmodulin-dependent protein kinase (CAMKII), PKC and mitogen-activated protein kinase (MAPK) pathways (Roth et al., 1986). Other signalling pathways at 5-HT_{2A} receptors

include arrestin-signalling pathways (Gray et al., 2003; Kim et al., 2020; Wacker et al., 2013; Wacker et al., 2017) and arachidonic acid release (Felder et al., 1990). The binding affinity of different psychedelics for the 5-HT_{2A} receptor plays an essential role in their differing potencies. However, it should be noted that the activation of 5-HT_{2A} receptors and downstream signalling does not necessarily lead to psychedelic effects and various non-hallucinogenic 5-HT_{2A} receptor agonists have been discovered (Cameron et al., 2021; Cao et al., 2022; Cunningham et al., 2022; Lewis et al., 2023).

While the 5-HT_{2A} receptor is the primary target for psychedelics, pointing to their substantial role in producing the subjective effects of psychedelics, other receptors are likely to also play a role in the specific differential effects of different psychedelics (Hesselgrave et al., 2021; Pokorny et al., 2016). Many psychedelic substances, including LSD and psilocin, show high affinities for 5-HT_{2B} and 5-HT_{2C} receptors (Kim et al., 2020; Sard et al., 2005; Wacker et al., 2013). Outside of the 5-HT₂ receptor family, psilocin and LSD have also been shown to bind to many different sub-types of serotonin receptors (Halberstadt and Geyer, 2011; Klein et al., 2020; Kroeze et al., 2015; Pokorny et al., 2016). Additionally, LSD has shown affinities for dopamine receptors and adrenergic receptors (Kroeze et al., 2015). Some psychedelics, like DMT, also act as agonists at trace amine-associated receptors (TAARs; Bunzow et al., 2001) and sigma-1 receptors (Fontanilla et al., 2009). Recent work suggests that psychedelics may also bind to the tyrosine kinase receptor TrkB, thereby directly modulating brain-derived neurotrophic factor (BDNF) signalling (Moliner et al., 2023).

1.1.2.3 Neuronal and network-level activity

The 5-HT_{2A} receptor agonism of psychedelics and resulting downstream signalling leads to increased neuronal excitability and frequency of spontaneous and evoked excitatory post-synaptic potentials (EPSPs) of cortical layer five pyramidal neurons, resulting in enhanced synaptic transmission (Aghajanian and Marek, 1999; Araneda and Andrade, 1991).

The effects of psychedelics on neuronal excitability vary across different brain regions. 5-HT_{2A} receptors are expressed widely throughout the brain, but the highest densities are found in layer five of the cortex, especially in higher-order association areas such as the temporoparietal junction, medial prefrontal cortex (Beliveau et al., 2017), the striate and extrastriate visual cortex (Preller et al., 2018), the thalamus, reticular nucleus (Vollenweider and Preller, 2020), and the claustrum

(Weber and Andrade, 2010). These expression patterns may explain the specific effects of psychedelics on visual perception, attention and cognition, and emotional experience.

The effect of psychedelics on the human brain can be observed using neuroimaging methods such as electroencephalography (EEG), magnetoencephalography (MEG), functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and single-photon emission computed tomography (SPECT). Using these methods, studies showed differential effects of psychedelics in sensory and associative cortical brain areas. Psilocybin and other psychedelics reduced blood flow (Carhart-Harris et al., 2012a) and increased metabolism across the neocortex (Hermle et al., 1992; Vollenweider et al., 1997), with regional differences in cerebral blood flow (Lewis et al., 2017) and relative hypermetabolism in the prefrontal cortical areas and relative hypometabolism in subcortical and occipital brain areas (Vollenweider et al., 1997).

Psychedelics have also been shown to impact brain network dynamics. Studies on resting-state functional connectivity have consistently found that LSD and psilocybin decrease connectivity within associative networks, including the default mode network (DMN; Carhart-Harris et al., 2012a; Müller et al., 2018; Stenbæk et al., 2021; Madsen et al., 2021; Preller et al., 2018; Preller et al., 2020), and concurrently increase connectivity between sensory brain regions (Preller et al., 2018; Preller et al., 2020). Additionally, LSD has been shown to increase thalamocortical functional connectivity between the thalamus and the posterior cingulate cortex (PCC; Preller et al., 2019) and sensory regions of the somatomotor network (Müller et al., 2017; Preller et al., 2018), with concomitant decreases in connectivity from the thalamus to the temporal cortex (Preller et al., 2019). These findings suggest that the effects of psychedelics may, in part, be driven by increased (bottom-up) sensory processing and reduced top-down integration capacity of different brain networks under the influence of psychedelics.

MEG and EEG studies showed that psychedelics, including psilocybin, LSD and DMT, reduce the spontaneous power of low-frequency oscillations (1-13 Hz). Alpha band (8-13 Hz) power reductions in the DMN (including the anterior cingulate cortex [ACC] and PCC), parieto-occipital and posterior association cortices, as well as parahippocampal regions are the most consistent and pronounced effect (Kometer et al., 2015; Muthukumaraswamy et al., 2013; Riba et al., 2002; Riba et al., 2004; Schenberg et al., 2015), suggesting a widespread cortical disinhibition (Buschman et al., 2012). For a more detailed review of MEG/EEG studies of DMT and other psychedelics, see section [1.3.4](#) – “*Effects of DMT and other psychedelics on resting-state EEG*” and Chapter 4 – “*EEG effects of continuous IV infusions of DMT*”, section [4.1](#) “*Introduction*”.

Classic psychedelics have also been shown to promote neuroplasticity via enhanced dendritic branching and increased spine density, supporting synaptogenesis in various brain regions, including the prefrontal cortex and hippocampus. These changes appear to persist beyond the acute phase of drug action, suggesting a potential mechanism for the enduring psychological and therapeutic impact of psychedelics (de Vos et al., 2023). Mechanistic studies have revealed that the neuroplastic effects of psychedelics involve activation of intracellular 5-HT_{2A} receptors and tropomyosin receptor kinase B (TrkB) as well as brain-derived neurotrophic factor (BDNF) signalling pathways, with downstream mTOR pathway activation driving structural and functional changes in cortical neurons (Ly et al., 2018; Vargas et al., 2023).

1.1.3 Psychological effects

Psychedelics induce a range of characteristic changes in perception, mood and cognition (Nichols, 2004). They are known for their ability to induce altered states of consciousness, including mystical-type experiences and experiences of ego dissolution. Spiritual, mystical-type or ‘peak’ experiences are characterised by feelings of unity, transcendence, ineffability, and sacredness, often accompanied by profound positive emotions such as bliss and awe (Pahnke and Richards, 1966). These experiences are frequently rated as among the most meaningful in individuals’ lives, with enduring significance even decades later (Griffiths et al., 2006). Mystical-type experiences induced by psychedelics are often deemed ‘ineffable’, meaning they are difficult to articulate, escaping our ordinary concepts and language (Pahnke and Richards, 1966; Yaden et al., 2016). Despite their abstract nature, these experiences can generate profound personal insights and are perceived as having a noetic quality (i.e., an intuitive sense of understanding or experience of receiving objective insights and truths) that transcends ordinary awareness (Pahnke and Richards, 1966; Yaden et al., 2017a; Yaden et al., 2017b). Mystical-type experiences have been linked to positive outcomes, and their ability to offer a new perspective and enhance perceived meaning and purpose could, in part, explain the therapeutic potential of psychedelics (Griffiths et al., 2006).

At higher doses, psychedelics often occasion experiences of ‘ego-dissolution’. These experiences involve a complete loss of self-awareness or disintegration of the self and a potential sense of unity with the universe (Letheby and Gerrans, 2017; Millière, 2017; Nour et al., 2016; Nour and Carhart-Harris, 2017). This state is linked to specific neural changes, including increased connectivity between high-level association areas and the thalamus (Tagliazucchi et al., 2016) and decreased

activation of the DMN (Carhart-Harris et al., 2016b), as well as reduced alpha band power in the PCC (Muthukumaraswamy et al., 2013).

Psychedelics typically induce a wide variety of emotions, often encompassing intense positive but also negative emotions (Griffiths et al., 2006). Psychedelics have been suggested to act as non-selective amplifiers, bringing conscious and unconscious thoughts and emotions to the surface (Hartogsohn, 2018). In therapeutic settings, this can be harnessed to facilitate “emotional breakthroughs”, which have been shown to correlate with positive outcomes (Roseman et al., 2019).

While most research has focused on the positive aspects and transformative potential of psychedelic experiences, recent studies have started to investigate the adverse psychological reactions sometimes seen with psychedelics (Bremner et al., 2023; Schlag et al., 2022; Simonsson et al., 2023). Scales such as the Challenging Experiences Questionnaire (Barrett et al., 2016) have been developed to capture the adverse effects that can occur during a challenging psychedelic experience. Some studies have suggested that challenging experiences typically do not last the entire duration of the psychedelic experience (Andersen et al., 2021a) and that they can facilitate resolving personal issues and ultimately lead to positive outcomes (Carbonaro et al., 2016). Other work has focused on identifying predictors for the acute psychedelic experience (Aday et al., 2021) as well as its outcomes (Haijen et al., 2018).

Psychedelics are known to impair attention and cognitive control temporarily (Barrett et al., 2018; Bouso et al., 2013; Carter et al., 2005; Hecker et al., 2007; Quednow et al., 2012; Wittmann et al., 2007; Vollenweider et al., 2007). However, they can also enhance psychological and cognitive flexibility. Psychological flexibility (i.e., the ability to adapt to stressors and perform value-driven actions) has been shown to increase following psychedelic experiences and correlate with reductions in anxiety and depression (Davis et al., 2020a). Cognitive flexibility (i.e., the ability to switch between different cognitive operations; Uddin, 2021) has also been shown to improve after psychedelic use (Doss et al., 2021), although this effect was not consistently linked to depressive symptom reduction (Davis et al., 2021). It has been suggested that the trans-diagnostic effects of psychedelics may be partly explained by their impact on cognitive and psychological flexibility (van Elk and Yaden, 2022).

Psychedelic experiences can elicit increased suggestibility (Carhart-Harris et al., 2015) and encounters with supernatural forces, including “God encounters” (Griffiths et al., 2019; Yaden et al., 2017a; Yaden et al., 2017b) and encounters with divine or otherworldly beings (Strassman, 2000). The noetic quality and ineffability of psychedelic experiences can result in an ‘ontological shock’,

resulting in lasting changes in personal beliefs and metaphysical worldviews (Nour et al., 2016). In fact, psychedelics have been shown to increase beliefs in dualism (mind-body separation) and the afterlife (Timmermann, 2020) and shift people away from atheism (Davis et al., 2020b). Participants in psychedelic retreats frequently move from a physicalist or materialist worldview to more panpsychist or spiritual perspectives (Timmermann et al., 2021).

Psychedelics often induce strong feelings of social connectedness, empathy, and *communitas*, i.e., a sense of shared humanity and unity with others (Carhart-Harris et al., 2018; Kettner et al., 2021; Mason et al., 2019; Pokorny et al., 2017). This connectedness can enhance well-being (Forstmann et al., 2020), social connectedness (Kettner et al., 2021) and concern for nature (Forstmann and Sagioglou, 2017).

Finally, psychedelics may facilitate lasting behaviour changes. One study has suggested psychedelic use to be associated with a healthier lifestyle (Teixeira et al., 2022), and several clinical studies have found self-reported changes in behaviour in participants who underwent psychedelic-assisted therapy (Griffiths et al., 2006; Griffiths et al., 2011; Griffiths et al., 2016; Griffiths et al., 2018).

1.1.4 Models of psychedelic action

The current knowledge of neuronal and brain network changes induced by psychedelics gave rise to various theories attempting to explain the neurocognitive action of psychedelics in the brain that would account for the effects induced by psychedelics. Most popular are three theoretical frameworks, which explain the experiential effects of psychedelics through differing mechanisms at a brain level. However, it should be noted that these frameworks are not mutually exclusive and often complementary.

The Cortico-Striato-Thalamo-Cortical (CSTC) model (Vollenweider and Geyer, 2001) is based on the idea that the feedback loops between cortical regions and thalamic nuclei regulate exteroceptive and interoceptive information. The prefrontal cortex controls the thalamus, which acts as a filter to regulate the flow of external sensory and internal bodily information and, by extension, awareness and attention. According to this theory, psychedelics alter information processing in the brain through 5-HT_{2A} receptor activation in cortico-thalamic circuits (Geyer and Vollenweider, 2008). This leads to a release of inhibitory control mechanisms of the prefrontal cortex over the thalamic nuclei, thereby disrupting the normal gating mechanisms of the thalamus, allowing an increase of sensory and interoceptive information to be sent from the thalamus to cortical regions (Vollenweider and Preller, 2020). The resulting sensory overload may explain the perceptual and

cognitive changes observed with psychedelics. In support of this model, several studies have found that psychedelics increase thalamocortical functional connectivity (Müller et al., 2017; Preller et al., 2018) and synchronisation of cortical sensory regions (Preller et al., 2018; Preller et al., 2020; Roseman et al., 2016). Behavioural evidence for impaired sensorimotor gating in humans after administration of psychedelics, including psilocybin and LSD, has also been seen (Schmid et al., 2015; Vollenweider et al., 2007).

The REBUS model (relaxed beliefs under psychedelics; Carhart-Harris and Friston, 2019) integrates the free energy principle (Friston, 2010) with the ‘entropic brain hypothesis’ (Carhart-Harris et al., 2014; Carhart-Harris, 2018). The free energy principle proposes that living systems use predictive processes to reduce uncertainty. The entropic brain hypothesis proposes that higher levels of entropy (i.e., disorder or randomness) in neural dynamics and brain function, such as those found with psychedelics, result in more diverse and vivid subjective states. Taking these two theories together, the REBUS model proposes that the brain typically makes top-down predictions about the world based on past experiences and sensory input, which constrain neural processing and are used to interpret new information. According to this model, psychedelics reduce the precision of top-down predictions, making them less rigid while enhancing bottom-up processing of incoming sensory information, allowing for novel interpretations of sensory input and the experience of altered reality (Carhart-Harris and Friston, 2019). This model is supported by fMRI studies showing a disintegration of association networks, including the DMN (Carhart-Harris et al., 2012a; Müller et al., 2018), as well as MEG and EEG studies revealing increased complexity of neural signals following the administration of psychedelic substances such as psilocybin, LSD, and DMT (Ort et al., 2023; Schartner et al., 2017a; Timmermann et al., 2019; Timmermann et al., 2023b). Additionally, it has been shown that DMT changes the relative directionality of cortical travelling waves, decreasing alpha band (8-13 Hz) oscillatory signals in the top-down direction while increasing signals in the bottom-up direction (Alamia et al., 2020).

More recently, the claustrum-cortical-circuit (CCC) model has proposed the claustrum to play a mediating role in the effects seen with psychedelics (Doss et al., 2022). This model suggests that psychedelics activate 5-HT_{2A} neurons in the claustrum, thereby disrupting communication and coordination between the prefrontal cortex and claustrum and reducing cognitive control. Evidence for this model can be found in a study showing reduced functional connectivity of the claustrum and cortical networks and reduced activity in the claustrum, which correlated with measures of ‘ineffability’ of the experience (Barrett et al., 2020).

1.1.5 Psychedelics in the study of consciousness

There is substantial interest in using the unique effects and changes in consciousness induced by psychedelics to study the nature of human consciousness. However, the term “consciousness” is multi-faceted, and researchers use it in various ways to mean different things at different times. Much of the scientific debate on consciousness and its scientific study is dedicated to delineating the term and arriving at shared definitions of the subject of study.

A key concept in the scientific study of consciousness is what has been termed the “hard problem” of consciousness (Chalmers, 1995). It refers to the question that tries to explain the qualia (i.e., subjective sensations/experience; Dennett, 1988) of being, i.e., phenomenal consciousness, or “what it is like” to be an organism (Nagel, 1980), and how it arises out of observable phenomena such as brain activity. The “hard problem” of consciousness remains unanswered, and whether this “explanatory gap” (Levine, 1983) can be closed is debated. While some believe that the hard problem of consciousness can be solved (e.g., Searle, 1998), others remain agnostic about this possibility (e.g., Seth, 2021; Varela, 1996). In scientific disciplines such as cognitive science, neuroscience and psychology, the hard problem of consciousness is usually ignored, and materialism is adopted to address the various “easy problems” of consciousness, generally referring to distinct questions dealing with issues of perception, thoughts and attention, which are “plausibly explainable” and are sometimes used as proxies for the term “consciousness”.

Nevertheless, a number of philosophical theories have attempted to describe and define the nature of phenomenal consciousness. These can be broadly grouped into materialist, dualistic, and monistic theories (Chalmers, 2003). Materialist theories propose that all aspects of consciousness, including phenomenal consciousness and “qualia”, can be fully explained by physical processes occurring in the brain. According to this perspective, consciousness is not a separate entity but rather a direct result of neural activity and interactions among neurons and other physical structures in the brain. Proponents of materialism argue that advances in neuroscience will eventually allow us to understand how specific patterns of brain activity correspond to particular consciousness experiences. Dualistic theories of consciousness propose that consciousness is fundamentally distinct from the physical brain and body, suggesting the existence of a non-physical mind or soul interacting with the physical world. This perspective asserts that mental phenomena cannot be fully explained by physical processes alone and that consciousness possesses qualities that are not reducible to material interactions. Monistic theories of consciousness propose that consciousness and matter are not distinct entities but rather different manifestations of a single underlying reality. Within this framework, mental and physical phenomena arise from the same fundamental

substance or principle, which is neither purely mental nor purely physical. One well-known form of monism is neutral monism, which suggests that the basic substance of the universe is neutral and can manifest as either mind or matter, depending on the context. Panpsychism, a related view, suggests that consciousness is a fundamental aspect of all matter, not just a property of complex brains. In this way, monistic theories attempt to bridge the gap between physicalist and dualist perspectives by offering a unified explanation of how consciousness emerges from the same reality that gives rise to the physical world. While psychedelics cannot inform the accuracy of these philosophical theories, they have been shown to alter people's beliefs about the nature of consciousness, with some studies suggesting that psychedelics promote a shift away from materialist worldviews (Garcia-Romeu et al., 2015; Griffiths et al., 2019; Timmermann et al., 2021; Yaden et al., 2017a) to more dualist (Timmermann, 2020) and monistic perspectives (Timmermann et al., 2021), demonstrating their relevance in the study of consciousness.

The early scientific study of consciousness focused on 'neural correlates of consciousness' (NCCs; i.e., the minimal set of neural processes jointly sufficient for consciousness to arise; Crick and Koch, 1990; Metzinger, 2000; De Graaf et al., 2012), and this approach has been useful in arriving at a shared definition for the target and methodology of investigation across different philosophical traditions. However, scientists have faced difficulties, for example, in distinguishing NCCs from their neural preconditions and outcomes, revealing the limitations of this approach (Aru et al., 2012; De Graaf et al., 2012; Tsuchiya et al., 2015). As a result, there has been a shift towards the development of different theories of consciousness (ToCs), which aim to formulate empirically testable models to explain consciousness (Michel et al., 2019; Seth, 2018; Seth and Bayne, 2022).

ToCs generally aim to explain why certain systems are conscious and why different states of consciousness differ in the ways they do. However, they usually focus on specific aspects of consciousness and have different explanatory targets. For example, some theories focus on levels of consciousness, while others focus on the contents of specific states of consciousness. Similarly, some theories focus on the phenomenal properties of consciousness, while others focus on the functional properties (i.e., neural and cognitive processes) of consciousness. Therefore, comparisons between theories are not straightforward. A wide range of ToCs has been proposed, with the most prominent being higher-order theories (HOTs), global workspace theories (GWTs), and integrated information theory (IIT). HOTs explain consciousness through the interplay of representations of perceptual or internal content in lower-order brain regions and meta-representations in higher-order brain networks. As such, HOTs propose that consciousness involves the activity of higher-order brain networks (Cleeremans et al., 2020; Fleming, 2020).

GWTs propose that conscious content arises when perceptual information is “broadcast” within a neuronal ‘workspace’ that encompasses wide areas across higher-order cortical association areas, in particular the prefrontal cortex (Dehaene and Changeux, 2011; Mashour et al., 2020). IIT proposes that the degree of consciousness of a certain system is represented by the quantity “ Φ ” (i.e., the amount of integrated information a system generates; Tononi, 2008; Tononi, 2012; Tononi et al., 2016; Oizumi et al., 2014). According to the theory, Φ quantifies the degree to which a system’s parts are interconnected and unified, forming a whole that is more than the sum of its parts. A higher Φ value indicates a greater degree of integration and, according to IIT, a higher level of consciousness. As Φ is unfeasible to measure for complex systems, various related measures have been formulated (Mediano et al., 2018), including the perturbational complexity index (PCI), which measures transcranial magnetic stimulation evoked brain complexity (Casali et al., 2013). Contrary to HOTs and GWTs, it associates consciousness mainly with posterior cortical areas, including temporal, parietal, and occipital brain areas (Tononi et al., 2016). While not ToCs per se, predictive processing theories are notable for their potential usefulness in understanding consciousness (Hohwy and Seth, 2020). These theories propose that the brain operates with the aim of minimising prediction errors and employs Bayesian inference to mediate between (top-down) sensory input (i.e., predictions) and (bottom-up) prediction errors (Hohwy and Seth, 2020; Rao and Ballard, 1999). Psychedelics provide a valuable angle to the investigation of these ToCs by presenting an altered state of consciousness, which is rich in content and characterised by possibly higher levels of consciousness as compared to ordinary waking consciousness.

Models of psychedelic action, including the most prominent ones described above, have attempted to integrate explanations for phenomenal consciousness and how it may arise from the brain. For example, the free energy principle, which is one of the foundations of the REBUS model, suggests that prediction errors of interoceptive processes can explain phenomenal consciousness and why something feels like something to and for an organism (Solms and Friston, 2018; Solms, 2019). Proponents of the CSTC model, in turn, have suggested that activity in thalamocortical loops gives rise to conscious experience (Preller et al., 2019). Finally, the claustrum, which, according to the CCC model, is implicated in mediating the effects of psychedelics, has been proposed to act as a “conductor” to the cortex and be an essential brain structure for understanding how phenomenal consciousness may arise from brain function (Crick and Koch, 2005). While these models do not generate any specific testable hypotheses to answer the hard problem of consciousness, they generate predictions regarding various easy problems of consciousness, including perception,

attention and cognition. Using psychedelics as a research tool, these can be tested and may provide relevant insight into these easy problems of consciousness.

One avenue through which psychedelics have a strong potential to support the study of human consciousness is by reliably inducing significantly altered states of consciousness. This perturbation of normal states of consciousness allows for a better understanding of the cognitive and neuronal mechanisms involved in perception, self-consciousness, and other mental processes. Self-consciousness, for example, is a fundamental feature of human consciousness (Damasio, 1999), and psychedelics have been shown to substantially alter self-related processing at various levels and in different degrees of intensity. At higher doses, psychedelics induce profound changes in self-awareness, commonly described as ‘ego-dissolution’ (Millière, 2017; Nour et al., 2016; Nour and Carhart-Harris, 2017). Studying these psychedelic-induced changes in self-consciousness may provide important insights into the structure of the multidimensional construct of ‘self’ (e.g., ‘minimal self’ vs ‘narrative self’; Gallagher, 2000), and its neural correlates (Carhart-Harris et al., 2014; Letheby and Gerrans, 2017; Millière, 2017; Millière et al., 2018). For example, it has been shown that psychedelic-induced decreases in parahippocampal functional connectivity and reductions in alpha band power localised to the PCC correlated with ratings of ‘ego-dissolution’ (Carhart-Harris et al., 2012a; Carhart-Harris et al., 2016b; Palhano-Fontes et al., 2014). Both the parahippocampus and the PCC are important nodes of the DMN, suggesting an essential role of this network in self-related processing.

Recently, a neurophenomenological approach has been proposed for the study of altered states of consciousness (Timmermann et al., 2023a). While the standard approach to the study of altered states of consciousness usually investigates the changes induced by psychedelics and other methods as a whole, using average ratings across the entire course of the experience and relating them to average brain activity, the neurophenomenological approach aims to focus on dynamics and trajectories of an experience. It incorporates first-person subjective reports to inform meaningful units of analysis, allowing for a more fine-grained and specific investigation of potential sub-states within the experience. Several studies have used a neurophenomenological approach in the study of meditation (Berkovich-Ohana et al., 2013; Dor-Ziderman et al., 2013; Dor-Ziderman et al., 2016; Garrison et al., 2013), while two previous studies have employed a neurophenomenological approach in the study of the effects of DMT (Timmermann et al., 2019; Timmermann et al., 2023b). These studies used micro-phenomenological interviews (Petitmengin, 2006) to identify common dynamic features of the experience over time and correlated these to resting-state EEG data. Results showed that visual imagery was positively correlated with delta and theta band power and

inversely correlated with alpha band power. Changes in bodily awareness were inversely correlated with central and parietal beta band power. Therefore, the neurophenomenological approach allows a more in-depth and fine-grained study into the experiential and neurobiological aspects of consciousness, facilitating potentially significant insights for the field of consciousness research.

1.1.6 The therapeutic potential of psychedelics

Alongside their value in consciousness research, psychedelics have been extensively studied for their potential therapeutic applications. Research into psychedelic therapy dates to the early wave of psychedelic research, with studies focusing on mood disorders (Rucker et al., 2016), end-of-life anxiety (Grof et al., 1973; Richards et al., 1977), and substance abuse (Bogenschutz and Johnson, 2016). The recent years have seen a resurgence in studies investigating psychedelics in the treatment of various mental health disorders (for a review, see Yao et al., 2024). In fact, psychedelic medicine has become one of the most rapidly expanding fields in medical research (Nutt et al., 2023; Phelps et al., 2022).

While most clinical studies to date have focused on LSD and psilocybin (Yao et al., 2024), only a handful of studies have examined the potential therapeutic effects of ayahuasca, and the study into the possible use of DMT in therapy has only begun recently. Two phase 2 studies in major depressive disorder have been completed to date, using inhaled (D’Souza et al., 2022) and IV administration of DMT (Clinicaltrials.gov/NCT04673383; James et al., 2024), with promising results. Two further trials are in phase 1, employing inhaled DMT (Falchi-Carvalho et al., 2024a; Falchi-Carvalho et al., 2024b) and intranasal DMT in combination with an oral MAO inhibitor (Aicher et al., 2024; Dornbierer et al., 2023), respectively (for a discussion of DMT administration methods and respective strengths and limitations, see section [1.2.4](#) – “DMT – Routes of administration”).

The therapeutic effects of psychedelics are thought to be primarily mediated through their action as agonists at the serotonin 5-HT_{2A} receptor. Activation of these receptors disrupts normal neural network dynamics, leading to a state of increased brain connectivity and reduced modularity (Kwan et al., 2022). This disruption is believed to underlie some of the profound changes in consciousness in psychedelics and their therapeutic benefits observed in conditions such as depression (Carhart-Harris et al., 2014). Additionally, psychedelics like psilocybin have been shown to induce rapid and sustained neuroplasticity, promoting the growth of dendritic spines and enhancing synaptic

connections (De Vos et al., 2021; Ly et al., 2018). These structural changes in the brain are thought to contribute to the long-lasting therapeutic effects of these substances (Olson, 2018).

The modern approach to psychedelic therapy is informed by practices from early research from the 1960s and 1970s, which emphasised the importance of psychological support and the integration of psychedelic experiences into the patient's life. As a result, contemporary protocols often involve three phases: preparation, the psychedelic session itself, and integration (Johnson et al., 2019; Reiff et al., 2020). All three phases are thought to be important for achieving lasting therapeutic benefits (Carhart-Harris et al., 2018; Yaden et al., 2022).

Current research is also exploring the development of non-hallucinogenic analogues of psychedelics that could provide therapeutic benefits without the intense subjective experiences. These could make psychedelic therapy more accessible to a wider range of patients, particularly those who may be opposed to or unsuitable for the full psychedelic experience (Nutt et al., 2023; Yaden et al., 2022).

Despite the promising results of psychedelic therapeutics, the field is currently faced with a number of challenges. First, issues of methodological rigour (van Elk and Yaden, 2022), including unique challenges in blinding and expectancy effects (Aday et al., 2022; Muthukumaraswamy et al., 2022), have been raised and need to be addressed to ensure a high standard of research and resulting evidence. Specifically, the use of blinded control conditions is uniquely difficult in psychedelic research due to the nature of the subjective effects, and widespread media around drug effects and the positive promises of psychedelic therapy may introduce expectancy effects and influence trial results. Moreover, there are challenges to the scalability of psychedelic treatment models, which are usually cost- and resource-intensive (Aday et al., 2023; Muthukumaraswamy et al., 2022). For example, most therapy models require the presence of two therapists during the lengthy psychedelic experience (8-12 hours for LSD; 6-8 hours for psilocybin). As a result, the past years have seen a growing interest in short-acting psychedelics (e.g., DMT, 5-MeO-DMT [which has a similar chemical structure and duration of effects, yet widely different subjective effects from DMT]) for use in psychedelic therapy. Finally, psychedelic-assisted therapy contends with ethical challenges, including consent, the use of touch, and intercultural competencies (Johnson, 2021; Williams et al., 2024). As the field progresses, establishing clear guidelines and ethical standards will be crucial to ensure the safe and effective use of these powerful substances.

The safety profile of psychedelics is generally favourable. Still, the occurrence of adverse psychological reactions underscores the importance of the therapeutic setting and the presence of

trained professionals. The concept of ‘set and setting’ is crucial, and the patient’s mindset and the environment in which the therapy takes place play a significant role in the treatment outcome.

1.1.7 Contextual variables in psychedelic use and research

The altered states of consciousness elicited by psychedelics are influenced by a complex interaction of biopsychosocial variables, which can be categorised into pharmacological and non-pharmacological factors. Pharmacological factors encompass the specific psychedelic substance, its dose and chemical effects, including its potency and duration of action. Pharmacological factors largely determine the effects of a specific substance, although a considerable heterogeneity has been observed in the interaction with the unique individual (Moujaes et al., 2022). Non-pharmacological factors play an equally important role in shaping the psychedelic experience (Studerus et al., 2012). These include psychological factors (i.e., ‘set’), which consist of the individual’s mood, expectations, and intentions prior to the psychedelic experience (Aday et al., 2022; Hartogsohn, 2016), as well as the environmental context in which the experience takes place (i.e., ‘setting’). This includes the physical surroundings, social environment, and cultural background in which the psychedelic is consumed (Hartogsohn, 2016). The importance of setting has been recognised for a long time, with traditional shamanistic rituals including elements such as ‘icaros’ (ritual songs), whistles, and smoke blowing to alter the setting and thereby enhance the healing potential of psychedelic medicines (Golden et al., 2022; Hartogsohn, 2017; de Rios, 1975). While an intuitive understanding of the importance of non-pharmacological factors in shaping psychedelic experiences has existed for centuries, the importance of ‘set and setting’ in influencing the outcomes of psychedelic use was first highlighted by psychologist Timothy Leary in 1963, and this concept remains central in contemporary psychedelic research and pharmacology (Hartogsohn, 2017; Kaelen et al., 2018; Leary et al., 1963). Relatedly, psychedelics have been described as ‘nonspecific amplifiers’ (Grof, 1988; Hartogsohn, 2018). This has led to the development of guidelines for psychedelic therapy environments (Johnson et al., 2008).

In psychedelic-assisted therapy, preparation sessions are usually used to guide patients to a favourable (mind-) ‘set’. Psychedelic therapy sessions are usually conducted in a supportive environment with guidance from a therapist or facilitator, and this has been shown to be essential to ensuring a safe experience and facilitating positive outcomes (Carhart-Harris et al., 2018; Johnson et al., 2008). Furthermore, specific musical styles used during psychedelic sessions have been found to be particularly conducive to therapeutic outcomes (Kaelen et al., 2018; Strickland et

al., 2020). As set and setting are inherently cultural, it is also essential to consider a patient's background and adjust the set and setting accordingly to provide culturally competent and informed care (Williams et al., 2024).

1.1.8 Summary

Classic psychedelics induce deep shifts in perception and consciousness, including heightened emotional processing and experiences of emotional breakthroughs, mystical-type experiences, and ego-dissolution. These profound experiences have been shown to increase psychological and cognitive flexibility, social connectedness, and sometimes occasion shifts in worldview. The wide-ranging effects of psychedelics are thought to be mediated by 5-HT_{2A} receptor agonism and its downstream effects, leading to increased brain network connectivity and neuroplasticity.

Due to their effects, psychedelics have recently regained substantial interest in both neuroscience and medicine. The altered state of consciousness induced by psychedelics has been studied in the context of consciousness research and has provided insights into aspects of human consciousness and the concept of 'self'. While most previous research has studied the psychedelic experience as a whole, recent work has called for a more fine-grained examination of the dynamics and specific sub-states within these rich and oftentimes varied experiences, using methods such as neurophenomenology.

A wide array of ongoing and completed research is contributing to the field of psychedelic therapeutics, with overall promising results. However, the field contends with a number of challenges, including questions of scalability for psychedelic therapy models, which usually involve long therapist-facilitated treatment sessions and are, therefore, cost- and resource-intensive. As a result, there is growing interest in short-acting psychedelics, such as DMT, for use in psychedelic-assisted therapy.

1.2 N,N-Dimethyltryptamine (DMT)

1.2.1 History & culture

DMT is a naturally occurring classic psychedelic of the tryptamine family. It is endogenously synthesised in a wide range of species, including plants, animals, and humans (Barker, 2018; Barker

et al., 1981; Carbonaro and Gatch, 2016), with its presence documented in at least 50 different plant species (Domínguez-Clavé et al., 2016).

Although DMT is not orally active, various indigenous cultures have developed methods to harness its psychoactive properties. Early reports of DMT use primarily come from indigenous communities in the Amazonian regions of South America, where it was ingested orally in the form of ayahuasca (Samorini, 2019) as a form of medicine in healing ceremonies and spiritual practices (McKenna et al., 1998; Miller et al., 2019; Schultes et al., 2001; Shanon, 2002). The term ‘ayahuasca’ is of Quechua origin, translating to “vine of the souls” or “vine of the dead,” reflecting its spiritual significance (Santos et al., 2007). Additionally, some Native American cultures have created snuffs like yopo and epená, which contain enough DMT to induce altered states of consciousness (James et al., 2022).

Despite its ancient roots, DMT’s introduction to modern scientific research began much later. It was first synthesised exogenously by the Canadian chemist Richard Manske in the early 1930s (Manske, 1931), although it did not attract significant attention at the time. Interest in DMT only began to rise after the discovery of serotonin in the brain (Twarog and Page, 1953). This discovery prompted Hungarian chemist and psychopharmacologist Stephen Szára to extract DMT from the *mimosa hostilis* plant and administer it intramuscularly to himself, thereby discovering its potent hallucinogenic effects in humans (Szara, 1956).

Initial reports of DMT’s effects described them as similar to those of LSD or mescaline but with a much shorter duration (Szára, 1956), with hallucinogenic effects starting within five minutes of administration and typically lasting between 30 to 60 minutes (Böszörményi, 1958; Sai-Halász et al., 1958). Originally believed to be a schizotoxin (Osmond and Smythies, 1952; Szára, 2007), it was used to model schizophrenia. One study showed that DMT and (S)-Ketamine were better at modelling the positive and negative symptoms of schizophrenia, respectively (Gouzoulis-Mayfrank et al., 2005). Overall, the schizophrenia model of psychedelic action has largely fallen out of favour.

When interest in clinical psychedelic research revived in the 1990s, DMT studies were among the first to re-emerge, with notable work by Rick Strassman, who published a series of studies detailing the autonomic and subjective effects of DMT in humans (Strassman, 1995; Strassman and Qualls, 1994; Strassman et al., 1994b; Strassman et al., 1996). Strassman selected DMT for his studies mainly due to its relative obscurity as a psychedelic at that time. Despite its early role in the ‘psychedelic renaissance’, DMT remained underappreciated and understudied in comparison to

other psychedelics (Figure 1). It is only in recent years that a considerable rise in the number of publications has been seen, including studies on its neurophysiological and therapeutic effects.

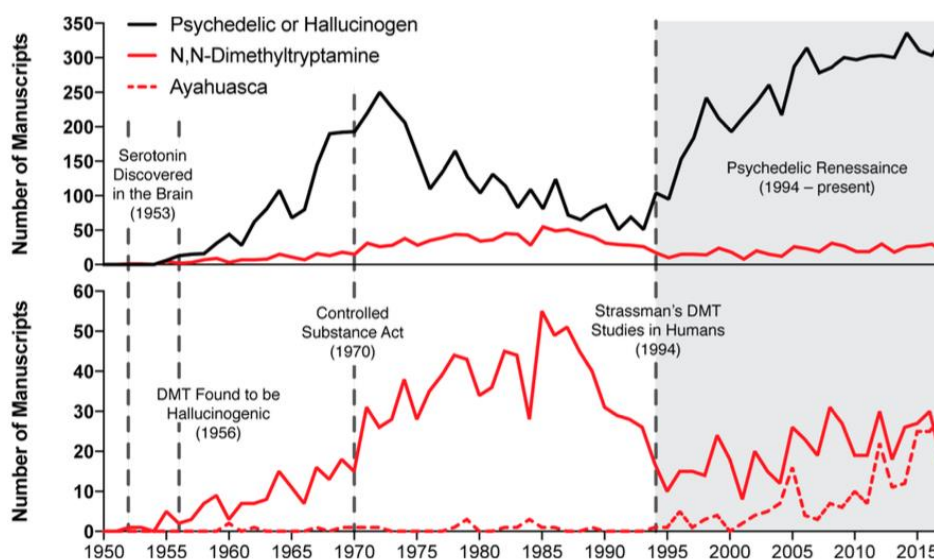


Figure 1. Overview of DMT research.

Timeline of significant events related to research on DMT and other psychedelics, and number of published manuscripts on psychedelics, DMT and ayahuasca from 1950 to 2018. Reprinted with permission from Cameron and Olson (2018). Copyright 2018 American Chemical Society.

1.2.2 Pharmacology

DMT interacts with a diverse array of receptors, with binding affinities to serotonergic receptors, sigma-1 receptors, TAARs, glutaminergic receptors, and dopaminergic receptors (Brito-da-Costa et al., 2020; Carbonaro and Gatch, 2016; Ray, 2010; Riba et al., 2002). DMT has been found to influence functional plasticity in prefrontal cortical neurons, which may be mediated via agonism at the 5-HT_{2A} receptor (Brito-da-Costa et al., 2020). In contrast, the administration of the 5-HT_{2A} receptor antagonist ketanserin inhibits many of DMT's subjective effects (Valle et al., 2016), suggesting the vital role of 5-HT_{2A} receptor agonism in producing the subjective effects of DMT. However, other compounds with higher affinity for 5-HT_{2A} do not induce hallucinations, suggesting that 5-HT_{2A} receptor agonism alone cannot fully account for DMT's unique

phenomenology (Barker, 2018; Brito-da-Costa et al., 2020; Carbonaro and Gatch, 2016; Nichols, 2016; Valle et al., 2016; Vollenweider and Preller, 2020; Wallach, 2009). Furthermore, pre-treatment with the 5-HT_{1A} partial agonist pindolol has been shown to significantly amplify the psychological response to DMT, suggesting that 5-HT_{1A} receptor agonism might modulate the psychedelic effects of DMT (Wallach, 2009).

DMT triggers a complex sequence of receptor activations, including modulation of the overall glutamate concentration through agonism of metabotropic glutamate (mGlu) receptors 2 and 3 in several brain regions, including the frontal cortex. This modulation is believed to contribute specifically to DMT's physiological and psychological psychedelic effects, although the exact mechanisms by which it induces hallucinations remain unknown (Barker, 2018; Carbonaro and Gatch, 2016; Dos Santos et al., 2016b; Dos Santos et al., 2016a; González-Maeso et al., 2007; González-Maeso et al., 2008; Nichols, 2004). Research using mGlu2 receptor knockout mice suggests that the mGlu2 receptor is necessary for psychedelic effects, as indicated by the head-twitch response, although this measure has its limitations (Canal and Morgan, 2012; Carbonaro and Gatch, 2016; Moreno et al., 2011). It has been suggested that the 5-HT_{2A} receptor-mediated intracellular pathway may require a complex involving both the 5-HT_{2A} receptor and the mGlu2 receptor to produce DMT's hallucinogenic effects (Frecka et al., 2016; González-Maeso et al., 2008; Moreno et al., 2011).

In addition to these mechanisms, DMT modulates sigma-1 receptors, although the relevance of this is not clear (Barker, 2018; Fontanilla et al., 2009; Frecka et al., 2013). It plays a role in neural plasticity, particularly through the formation of dendritic spines (Hayashi, 2019; Su et al., 2009). This process could be relevant to DMT's reported potential for promoting neurogenesis (Domínguez-Clavé et al., 2016; Morales-Garcia et al., 2020). Certain antidepressants also modulate the sigma-1 receptor, which may contribute to the antidepressant effects observed with DMT and ayahuasca (Domínguez-Clavé et al., 2016). At higher concentrations, DMT has been observed to inhibit voltage-gated sodium ion channels via sigma-1 receptor agonism (Fontanilla et al., 2009). The sigma-1 receptor has been associated with the psychopathology of various disorders, including addiction and depression. This connection suggests a potential link between sigma-1 receptor modulation and the subjective effects of psychedelics, particularly in therapeutic contexts (Carbonaro and Gatch, 2016).

DMT has also shown affinity for TAARs, particularly TAAR-6 (Brito-da-Costa et al., 2020; Wallach, 2009). However, the mechanisms following DMT's binding to TAARs are not well understood. Therefore, further research is necessary to elucidate the downstream processes that contribute to

DMT's complex effects (Barker, 2018; Carbonaro and Gatch, 2016). Table 1 provides a summary of DMT receptor activity and binding affinities.

Table 1. Overview of DMT receptor activity and binding affinities.

Receptors	Agonism/antagonism	Binding affinity	Functional relevance
5-HT _{2A}	Partial agonist	High	Principal mediator of psychedelic effects
5-HT _{1A}	Partial agonist	Moderate	May modulate intensity of psychedelic effects
mGlu _{2/3}	Indirect agonist (via 5-HT _{2A})	Moderate	Modulates glutamate transmission, required for hallucinogenic effects in mice
Sigma-1	Agonist	Moderate	Supports neuroplasticity, neuroprotection, neurogenesis
TAARs	Agonist	High	May modulate cAMP signalling and emotional responses
Dopaminergic	Partial agonist	Weak	Minor contribution; likely not central to DMT's psychedelic phenomenology

1.2.3 Phenomenology and subjective effects

DMT induces psychedelic effects that show similarities to those induced by other classic psychedelics, such as psilocybin and LSD, but with distinct and characteristic differences. Growing efforts are increasingly focused on characterising the hallmark effects and phenomenological features of DMT experiences (Cakic et al., 2010; Cott and Rock, 2008; Davis et al., 2020b; Gouzoulis-Mayfrank et al., 2005; Griffiths et al., 2019; Hase et al., 2022; Lawrence et al., 2022; Luke, 2011; Meyer, 1994; Michael et al., 2021; Richards, 2015; Timmermann et al., 2019; Timmermann et al., 2023b; Shanon, 2002; Strassman, 2000; Strassman et al., 1994a). While the pharmacology and pharmacokinetics (PK) of ayahuasca diverge significantly from that of pure DMT in inhaled or parenterally administered form (i.e., the DMT-containing brew ayahuasca contains an MAO inhibitor which prevents DMT catabolism in the gastrointestinal system and

makes ayahuasca orally active with subjective effects lasting for four to six hours), the consideration of ayahuasca phenomenology is of interest to elucidate the DMT experience more broadly.

The psychological effects of DMT were first recorded in the 1950s. Investigating the effects of intramuscular DMT, the Hungarian biochemist Stephen Szara described similar effects to those induced by LSD and mescaline. He noted the main difference being the temporal trajectory of the experience, with a much shorter onset (approximately five minutes) and duration of effects (approximately one hour). He describes DMT-induced visual imagery as ‘real’ hallucinations, pointing to their vividness and indistinguishability from external reality (as opposed to less vivid pseudo-hallucinations, which are recognised to be internally generated; Szara, 1956). Additionally, participants described extra-visual (auditory, somatosensory) hallucinations and strong emotional effects (both positive and negative; Sai-Halász et al., 1958; Szara, 1956).

In studies with IV DMT, Strassman reported a faster onset (within two minutes) and shorter duration (less than 30 minutes) of the effects compared to intramuscular administration (Strassman and Qualls, 1994; Strassman et al., 1996). Experiences were more intense, and participants reported strong visual imagery, which seemed to be overlaid on top of external visual input with eyes open. With eyes closed, visual effects progressed into intensely immersive, complex imagery. Additionally, participants reported strong bodily sensations, most commonly described as a bodily rush at the onset of effects, followed by feelings of disembodiment as the experience progressed. The physiological effects of IV DMT included increased blood pressure and heart rate (HR), as well as increased levels of β -endorphins and cortisol in the blood (Strassman and Qualls, 1994).

The subjective effects of DMT are often described as highly unpredictable, with anecdotal accounts suggesting that these effects are less consistent compared to other psychedelics like psilocybin (Brito-da-Costa et al., 2020; Strassman, 2000). As with other psychedelics, the subjective effects of DMT are strongly influenced by set and setting (Brito-da-Costa et al., 2020; Dos Santos and Hallak, 2021; Hartogsohn, 2016). Nevertheless, researchers have attempted to identify common themes of DMT experiences and to classify DMT experiences into subtypes. In his seminal work, Strassman classified DMT experiences into three subtypes: ‘Personal’, ‘Transpersonal’, and ‘Invisible Worlds’. According to findings from his research, each DMT experience can be a combination of any number of the three subsets in varying order (Strassman, 2000). In a survey study with 19 DMT users, Cott and Rock found nine common themes that captured the essential aspects of the DMT experience: hallucinations, entering other realms and contacting other sentient beings, lucidity, affective distortions, ineffability, intensity, spirituality and learning about truths; distortions in sense of time, space, and self; familiarity (Cott and Rock, 2008).

The most frequently reported features of DMT experiences include perceptual changes, such as simple imagery (vivid colours, geometric patterns) and complex imagery (objects, faces, scenes), which can occur with both open and closed eyes (Cott and Rock, 2008; Strassman et al., 1994b; Strassman, 2000). Comparing DMT-induced visual effects to those of other psychedelics, it appears that simple imagery most commonly occurs with LSD and psilocybin, while complex imagery is more commonly reported with DMT and ayahuasca (Shanon, 2002; Strassman, 2000). However, the intensity of visual imagery seems to be dose-dependent (Carbonaro et al., 2018; Liechti et al., 2017; Vollenweider and Kometer, 2010), making it conceivable that complex visual imagery also occurs with LSD and psilocybin at higher doses.

Other DMT-induced perceptual changes comprise somatosensory effects such as bodily sensations and auditory hallucinations, including a distinct sensation of what is described as a bodily ‘rush’ and the feeling of ‘leaving one’s body’ (Gouzoulis-Mayfrank et al., 2005; Strassman et al., 1994b; Strassman, 1995). As with other psychedelics, a range of emotional effects have also been observed with the DMT experience, ranging from anxiety, confusion, and overwhelm (Brito-da-Costa et al., 2020; Cott and Rock, 2008; Strassman, 2000) to a positive mood and feelings of bliss (Davis et al., 2020b; Strassman, 2000).

The DMT experience has been described as highly immersive and more so than with other psychedelics, with one of the most distinct features being a feeling of entering an alternate ‘world’ or ‘reality’, often deemed ‘more real than everyday reality’ (Cott and Rock, 2008; Strassman, 2000). The experience of immersion into these alternate worlds are usually deemed as deeply meaningful, sometimes leading to revisions in beliefs and worldviews (Amaringo and Luna, 1999; Strassman, 2000).

Another puzzling feature of the DMT experience is the sense of encountering seemingly autonomous, intentional and sentient ‘entities’ or ‘beings’, which are perceived as intelligent and wanting to communicate ‘useful information’ (Cott and Rock, 2008; Davis et al., 2020b; Luke, 2011; Michael et al., 2021; Strassman, 2000). These entities are described using various labels, such as ‘beings’, ‘aliens’, ‘guides’, or ‘helpers’ (Luke, 2011) and are often perceived as attempting to convey useful information (Cott and Rock, 2008; Davis et al., 2020b; Strassman, 2000). The initiation of these interactions is typically attributed to the entities themselves (Davis et al., 2020b). Entity encounters are common, with 94% of participants in a thematic analysis of 36 interviews of DMT users in naturalistic settings reporting such experiences (Michael et al., 2021). These encounters can evoke a range of emotions, from positive to threatening, or even a mix of both, contributing to the intense nature of DMT experiences (Sai-Halász et al., 1958; Strassman, 2000; Strassman, 1995).

Interestingly, more than 70% of individuals who encounter entities during a DMT experience believe these entities continue to exist beyond the experience itself. Many consider these encounters “more real than everyday waking consciousness” (Cott and Rock, 2008; Davis et al., 2020b). This contrasts with other psychedelic-induced hallucinations, which are often dismissed as illusory mental creations. Such experiences are considered profound and can lead to lasting changes in one’s perception of reality (Davis et al., 2020b). However, these enduring ontological shifts in worldview are less likely to be associated with positive long-term effects compared to mystical-type experiences (Davis et al., 2020b; Griffiths et al., 2019). Similar reports of encountering beings are found in ayahuasca experiences, which are integral to vegetalismo practices of the Peruvian Amazon. These practices, rooted in animism, involve attributing identities to plants used by ‘curanderos’ (healers) to treat health issues (Amaringo and Luna, 1999; Luna, 1984). The consistency of these encounters across different cultural contexts suggests that they may be influenced by pharmacological factors inherent to DMT rather than solely by participant expectations.

The immersive character of the DMT experience and the encounter of ‘entities’ is sometimes accompanied by a sense of familiarity, described as a ‘having been here before’, ‘belonging’, or ‘coming home’ (Cott and Rock, 2008; Davis et al., 2020b; Lawrence et al., 2022; Michael et al., 2021; Shanon, 2002; Strassman, 2000). In a qualitative analysis of 3778 experiences of inhaled DMT over a ten-year period, a sense of familiarity, including a sense of belonging or feeling at home, occurred in 227 (6%) of DMT experiences (Lawrence et al., 2022). Hence, even though these experiences of familiarity occur less frequently, they are still a distinct feature of DMT experiences, with no other psychedelics commonly eliciting this experiential phenomenon.

While most psychedelic experiences have been commonly described as ineffable (i.e. difficult to explain using words), this is perhaps particularly true for DMT experiences (Cott and Rock, 2008; Davis et al., 2020b; Strassman, 2000). Many DMT experiences satisfy the criteria for mystical-type experiences, with more than 70% of participants’ most memorable “God encounter experience” in a large retrospective survey study fulfilling the criteria of a complete mystical experience. These experiences were often rated as one of the most personally meaningful and spiritually significant lifetime experiences (Griffiths et al., 2019).

Mystical-type experiences are frequently accompanied by feelings of bliss and a loss of ego identity (Cott and Rock, 2008; Millière et al., 2018; Strassman, 2000). Relatedly, at higher doses, DMT experiences can induce profound alterations in self-related processing (Griffiths et al., 2019; Timmermann et al., 2018) to the point of complete detachment from the body and total dissolution

of sense-of-self and a merging into a unitive all-encompassing consciousness (Davis et al., 2020b; Strassman, 2000). These experiences are seen as profound, frequently leading to ontological revisions and lasting changes in attitudes and beliefs (Amaringo and Luna, 1999; Cott and Rock, 2008; Davis et al., 2020b; Griffiths et al., 2019; Strassman, 2000).

The subjective effects occasioned by DMT and other psychedelics have been compared to a range of other altered states of consciousness. They have been suggested to share similar features to those induced by hypnosis and sensory overload, rating high on the same subscales of the 5-dimensions Altered States of Consciousness scale (5D-ASC), including visual imagery and both positive and negative features of ego-dissolution (Dittrich, 1998). Other altered states of consciousness commonly compared with the psychedelic experience include meditation (Millière et al., 2018) and near-death experiences for DMT specifically (Timmermann et al., 2018). Due to its highly immersive character, DMT experiences have also been associated with experiences of ‘virtual reality’ and states of dreaming (Hobson et al., 2014; Shanon, 2002; Siclari and Tononi, 2016).

1.2.4 Routes of administration

1.2.4.1 Traditional administration methods

When DMT is ingested orally, MAO-mediated catabolism in the gastrointestinal system during first-pass metabolism leads to its degradation before it can reach the brain in sufficient concentrations to elicit a psychoactive response (Barker, 2018; Riba et al., 2015). As a result, oral ingestion of pure DMT does not produce psychoactive effects unless combined with substances that inhibit MAO.

In traditional settings, DMT is often administered in the form of ayahuasca (Domínguez-Clavé et al., 2016), a brew that contains both DMT and harmala alkaloids. Harmala alkaloids act as MAO inhibitors (Riba et al., 2015) and prevent the breakdown of DMT in the digestive system, allowing it to reach the brain and induce its psychoactive effects. When consumed as ayahuasca, the onset of DMT’s effects typically occurs within 60 minutes, peaks at around 90 minutes, and can last for approximately four to six hours (Cakic et al., 2010; Riba et al., 2003). In studies, doses ranging from 0.6 to 0.85 mg/kg of DMT derived from ayahuasca have been examined (Riba et al., 2001; Riba et al., 2003).

DMT is psychoactive when administered parenterally, bypassing the digestive system and avoiding MAO-mediated degradation (Barker, 2018; Riba et al., 2015). Parenteral routes of administration include IV and intramuscular (IM) injections, inhalation (vaporising or smoking) (Winstock et al.,

2014), and insufflation (nasal sprays, snuffs). These methods result in rapid onset and very short duration of subjective effects.

Snuffs such as ‘yopo’ and ‘epená’ are used by certain Native American cultures, containing enough DMT to induce altered states of consciousness (Fontanilla et al., 2009; Luke, 2011). In contemporary recreational settings, DMT is typically consumed via vaporisation or smoking (Winstock et al., 2014). In a comparative study of oral and vapourised DMT, oral ingestion of pure DMT produced no psychotropic effects, while vapourised DMT was found to be a highly psychoactive route of administration (Riba et al., 2015). Inhalation of DMT leads to a rapid onset of effects, typically within seconds, with the experience lasting less than 30 minutes (Davis et al., 2020b; Riba et al., 2015). The doses for vaporised or inhaled DMT are typically 40-50 mg, although higher doses (60-100 mg) have been reported (Jacob and Shulgin, 1994). A naturalistic study in 35 volunteers has shown that vaporisation of approximately 40 mg of DMT can produce mystical-type experiences (Pallavicini et al., 2020). Relatedly, a smoking blend known as ‘changa’, containing both DMT and MAO inhibitors derived from plant sources, has gained popularity within psychedelic subcultures (Lawrence et al., 2022).

DMT can also be administered intramuscularly, with the earliest recorded example conducted by Hungarian researcher Stephen Szára in the 1950s. Szára found that DMT produced powerful hallucinatory effects when administered intramuscularly (Barker, 2018; Domínguez-Clavé et al., 2016; Szara, 1956). The intramuscular effects of DMT, at doses ranging from 0.2 to 1 mg/kg, generally have a rapid onset of 2 to 5 minutes and last between 30 and 60 minutes (Barker, 2018; Szára, 2007). These effects are considered less intense than those achieved via IV administration.

Alternatively, DMT can be administered intravenously, leading to effects that begin within seconds, reach peak intensity within two to three minutes, and quickly subside thereafter, with negligible effects felt after about 30 minutes (Strassman, 1995; Timmermann et al., 2019). Strassman et al. (Strassman and Qualls, 1994; Strassman et al., 1994b) provided dose-response data for intravenously administered DMT fumarate in a group of experienced psychedelic users. This study administered doses of 0.06, 0.1, 0.2, and 0.4 mg/kg DMT fumarate. Peak blood levels and subjective effects were observed within two minutes after administration, with effects becoming negligible after 30 minutes. The study also reported that IV DMT elevated blood pressure, pupil diameter, rectal temperature, and blood concentrations of β -endorphin, corticotropin, and cortisol in a dose-dependent manner, while HR, prolactin, and growth hormone levels increased equally regardless of dose. The lowest dose of IV DMT that produced statistically significant

hallucinogenic effects relative to placebo was 0.2 mg/kg DMT fumarate (Strassman, 1995; Strassman and Qualls, 1994).

A recent development is the use of ‘pharmahuasca’, a pharmaceutical version of ayahuasca that combines DMT with harmaline and/or harmine (Brierley and Davidson, 2012; Ott, 1999) or other MAO inhibitors (e.g., the reversible MAO-A inhibitor moclobemide; (Kaasik et al., 2021; Ruffell et al., 2020). This method allows for the oral administration of DMT while preventing its degradation by MAO enzymes. For example, a common dosage for pharmahuasca might include 50 mg of DMT combined with 100 mg of harmaline, or a combination of 50 mg each of harmaline and harmine with 50 mg of DMT (Barker, 2022). The harmala alkaloids and DMT are typically placed in separate gelatin capsules, with the harmaline/harmine taken first, followed by DMT 15 to 20 minutes later, leading to an onset and duration of effects comparable to those of ayahuasca.

In addition to these traditional routes, other methods of DMT administration have been tested with limited success. For example, intranasal administration of free-base DMT has been found to be inactive at doses of 0.07 to 0.28 mg/kg (Turner and Merlis, 1959), as has rectal administration of DMT (De Smet, 1985).

1.2.4.2 Strengths and drawbacks of existing administration methods

While a range of administration routes for DMT have been tested and employed, they each present unique challenges and drawbacks.

The DMT-containing brew ayahuasca, for example, has a long history of use in many South American indigenous cultures and produces a gradual onset and long duration of effects, leading to a rich and long-lasting immersion which can facilitate therapeutic work. However, the need for an MAO inhibitor complicates the pharmacological profile of the experience, potentially increasing the risk of side effects. Additionally, the potency of ayahuasca can vary depending on the relative proportion of ingredients and preparation, making dosage control more difficult. Furthermore, ayahuasca is known to induce physical discomfort such as nausea, vomiting and diarrhoea, commonly known as ‘purging’, making it less suitable for use in controlled research and therapy settings.

Pharmahuasca has been proposed as a “cleaner” alternative to ayahuasca, offering an orally administered substitute that could be more practical and effective for conducting ayahuasca research. Pharmahuasca allows for a more controlled dosing than traditional ayahuasca, ensuring

chemical consistency without the need for lengthy preparation processes. However, as with traditional ayahuasca, the concurrent use of an MAO inhibitor remains a significant drawback, as it complicates the pharmacological profile of the experience and carries dietary restrictions and interactions with other substances, introducing potential risks.

Inhaled DMT leads to a rapid onset of effects, with intense but short-lasting effects. While inhalation can be more accessible than injections or the preparations involved in ayahuasca ceremonies and is the most common method of use in recreational settings, the intensity of the onset can be overwhelming, especially for less experienced users. Moreover, while the short duration of effects can be a benefit for some, it generally does not allow for deeper exploration and does not lend itself to therapeutic use. Additionally, inhaled DMT can be unpleasant and cause throat and lung irritation. Relatedly inhaled DMT is difficult to dose accurately, as the amount inhaled can vary. For these reasons, inhaled DMT is not used in research settings where accurate dosing is crucial. Insufflated, vaporised, and smoked DMT can frequently be harsh and are not always well-tolerated. Additionally, it is not always easy to ingest enough DMT to produce the desired psychoactive effects.

IV administration allows for precise dose control, beneficial in research and therapeutic settings, and is the preferred method of administration in research settings. It leads to an almost immediate onset and short duration of effects, providing an experience similar to inhalation. The precision in dosing achievable through IV administration makes it the preferred route for investigating the effects of DMT in humans (Gouzoulis-Mayfrank et al., 2005; Strassman and Qualls, 1994; Timmermann et al., 2019; Timmermann et al., 2023b). For the early studies of DMT, for example, Strassman chose IV injection over smoked administration, with one of the motivations being that it allowed for more precise dosing (Strassman, 2000; Strassman and Qualls, 1994). However, the psychoactive effects of DMT induced by IV injections are very short in duration, and the strong contamination by physiological effects presents a drawback for neuroimaging research. Similarly, the rapid onset and short duration are potential disadvantages for the use of IV injections of DMT in therapeutic settings, as they might not allow a comfortable settling into and processing of the experience.

1.2.4.3 Rationale for continuous infusion

Ultimately, none of the current methods of administration harnesses the unique properties of DMT, which make it suitable for continuous IV administration, thereby foregoing the unique strength of DMT within the classic psychedelics.

DMT is physiologically safe at effective doses and does not appear to induce psychological tolerance with repeated administrations (e.g., four doses of DMT have been safely administered in a single session, apparently without diminished psychological effects; Strassman et al., 1996), which supports its suitability for clinical research and therapeutic applications. This property, combined with the rapid onset, short duration, and specific character of its effects, make it unique among serotonergic psychedelics and potentially suitable for continuous IV administration (Gallimore and Strassman, 2016).

Continuous infusion of DMT would be an important development for allowing a more in-depth study of its phenomenology and neurobiological effects. By allowing control over the length, intensity, and dynamics of the DMT experience, with the potential for real-time adjustment, continuous DMT infusion could become a valuable tool in consciousness research, whereby these factors can be adjusted to test specific hypotheses and research questions. Additionally, extended DMT could be a valuable tool for psychedelic medicine, as the psychedelic effects could be tailored to the individual needs of each patient and their clinical condition.

In a previous study, continuous infusions of DMT were safely administered for up to 90 minutes (Gouzoulis-Mayfrank et al., 2005), with infusion rates determined via a prior pilot study involving six subjects. However, this report lacked information on how strong and sustained these effects were over time. Another proposed approach aimed to generate stable subjective effects via a continuous infusion of DMT (Gallimore and Strassman, 2016), but this protocol has not yet been implemented in human participants. To date, no pharmacokinetically-informed protocols of IV DMT have been tested in humans, indicating a significant area for future research.

1.3 Resting-state EEG and pharmacological interventions

1.3.1 The physiological and technical basis of EEG

EEG is a brain imaging technique that measures scalp electrical activity generated by the brain. While electrical currents in the brain were first discovered by Richard Canton in 1875, it was

decades later that Hans Berger laid the foundational work for EEG when he showed that the brain's electrical currents can be recorded non-invasively from the scalp (Adrian and Matthews, 1934). Several years later, Adrian and Matthews identified the first regular brain waves at 10 Hz, which are today known as 'alpha rhythms'. Since then, EEG has evolved into an essential tool for clinical diagnostics and neuroscience research, used for real-time monitoring of neuronal activity and oscillatory brain activity across various frequency bands.

The fundamental mechanisms underlying EEG are rooted in the electrical potential generated by neuronal activity within the brain. These potentials arise primarily from the synchronous activity of neurons, especially the excitatory and inhibitory postsynaptic potentials occurring in the apical dendrites of pyramidal cells, which are abundantly present in the cortex and oriented perpendicularly to the cortical surface. When large groups of these neurons become activated, the combined electrical activity produces fluctuations in voltage, which are detectable on the scalp's surface. These fluctuations at the scalp level are what EEG records through the placement of electrodes on the scalp. Each electrode acts as a sensor that captures tiny voltage fluctuations resulting from the sum of synchronous electrical activities of neurons. The EEG signal is a complex sum of these oscillatory activities, modulated by the conductive properties of the brain tissues, skull, and scalp. Over time, single-electrode systems developed into multi-electrode systems, nowadays featuring up to 512 electrodes strategically positioned to cover different areas of the brain according to standardised systems like the 10-20 system (Niedermeyer, 2011).

Nowadays, EEG and MEG are highly sensitive tools for monitoring changes in cognitive processes, alertness and consciousness, as well as identifying various pathologies, making them indispensable for clinical research as well as consciousness studies (Buzsaki, 2006).

Two approaches have been used in EEG research: Event-related potentials (ERPs) in the form of synchronisations or desynchronisations are fluctuations in electrical brain activity generated in response to a visual or auditory stimulus and are measured in experimental task paradigms through repeated stimulus presentation over a high number of trials, each lasting several seconds. Conversely, resting-state EEG is the brain's activity "at rest" (i.e., without the presentation of a stimulus), with resting-state EEG recordings typically being longer (e.g., sleep EEG recordings may cover several hours; Niedermeyer, 2011).

1.3.2 Pharmacology-EEG

Since Berger's early report on drug-induced alterations in visually inspected spontaneous human EEG (Adrian and Matthews, 1934; Gloor, 1969), researchers have used EEG to classify psychopharmacological agents and assess their effects on brain function. These studies into the EEG effects of psychoactive drugs have evolved significantly over time. Initially relying on qualitative evaluations, they soon evolved into quantitative analysis, first of single-channel EEG and later of multi-channel EEG systems (see Saletu et al., 2006 for an overview of studies). This allowed for a more objective and quantitative description of psychoactive drug effects on the brain and today is known as the 'pharmacology-EEG' method (Itil, 1974; Krijzer and Herrmann, 1996). Due to its ability to non-invasively and continuously assess the effects of drugs on the brain with high temporal resolution and relatively low cost, it has distinguished itself from more invasive and costly techniques. Additionally, the consistency of empirical observations captured by this method has made it an essential tool for providing a comprehensive quantitative description of a drug's effects on brain function (Herrmann and Irrgang, 1983).

The pharmacology-EEG method involves quantitatively evaluating a drug's effects based on its differentiation from placebo and its dose- and time-related EEG effects. Over the past four decades, systematic use of pharmacology-EEG in randomised double-blind, placebo-controlled studies has produced consistent findings, such as significant EEG changes within 1-3 hours after drug administration, similar EEG profiles for therapeutically equivalent drugs, and differing profiles for therapeutically inequivalent drugs (Itil, 1974; Itil and Itil, 1995; Itil and Krynicki, 1983). Pharmacology-EEG can also assess variations in drug formulations and their behavioural correlations through rating scales and cognitive tests. Efforts by groups such as the International Pharmacology-EEG Group (IPEG) have provided data acquisition and analysis standards (e.g., Jobert et al., 2012), which help ensure consistency across different research sites and comparability and generalisability of findings.

1.3.3 Resting-state EEG measures

1.3.3.1 Brain oscillations, frequency bands and spectral power

Brain oscillatory activity is traditionally classified into five main rhythms: delta (1-4 Hz), theta (4-8 Hz), alpha (8-13 Hz), beta (13-30 Hz), and gamma (30-100 Hz), and evidence suggests that these frequency bands are linked to specific cognitive, sensorimotor, and perceptual processes (Başar et al., 2000; Klimesch, 1996).

Delta oscillations (1-4 Hz) are thought to be primarily of cortical and thalamic origin (Dang-Vu et al., 2008; Murphy et al., 2009; Steriade and McCarley, 2013) and are associated with attention processes (Harmony et al., 1996), fatigue (Kirov et al., 1996), sleep onset (Dement and Kleitman, 1957; Goupil and Bekinschtein, 2012; Siclari et al., 2014a; Tanaka et al., 1997), and dreamless (non-rapid eye movement; NREM) or slow-wave sleep (Steriade and McCarley, 2013), with slow-wave sleep exhibiting additional low-frequency (<1 Hz) contributions (Achermann and Borbély, 1997; for a review, see Knyazev, 2012).

Theta rhythms (4-8 Hz) are closely linked to cortical sources in the hippocampus (De Araújo et al., 2002; Buzsaki, 2006). They have been associated with sleep onset (Dement and Kleitman, 1957; Goupil and Bekinschtein, 2012; Siclari et al., 2014b; Siclari et al., 2014a; Tanaka et al., 1997) and dreaming (Goupil and Bekinschtein, 2012; Siclari et al., 2014b; Siclari and Tononi, 2016; Siclari et al., 2017), thereby suggesting a role in transitional moments of consciousness and dream-like phenomena (Foulkes and Vogel, 1965; Nielsen, 2017). Additionally, they are linked to a broad spectrum of cognitive and mnemonic functions, including memory and spatial navigation (Sauseng et al., 2010).

Alpha oscillations (8-13 Hz) represent the most dominant brain rhythm, observed extensively across the occipital, somatosensory, and temporal areas. They were the first rhythm to be described and labelled after the invention of EEG (Adrian and Matthews, 1934). Alpha rhythms are dynamic, varying with human development (Başar et al., 2000), and play integral roles in a wide range of brain functions, from relaxed wakefulness (Adrian and Matthews, 1934; Buzsaki, 2006) to high-level cognitive functions like cognitive control and memory (Buzsaki, 2006; Jensen et al., 2002; Klimesch, 1997; Klimesch, 1999; Klimesch, 2012). Alpha oscillations have been associated with “idling” states (Pfurtscheller et al., 1996), with an amplification of this signal seen in closed-eyes wakeful states (Barry et al., 2007). They also lose their predominance during sleep and dreaming states, when slower frequency activity dominates (Siclari and Tononi, 2016). Therefore, it has been suggested that alpha may play a functional role in shifting cognitive processing from external stimuli to internal, endogenous activity (Buzsaki, 2006). Additionally, alpha oscillations might act as a general neuronal marker for ‘priors,’ which are the predictive mechanisms influencing perceptual processes and brain function (Bastos et al., 2012; Bastos et al., 2015; Mayer et al., 2015). The function of alpha oscillations varies depending on their cortical location and origin. Occipital alpha has been associated with wakeful rest and is often a marker of brain state changes, particularly in response to eyes opening or closing. Its origins have been identified in the cortex (Halgren et al., 2019) alongside contributions from the thalamus (Lőrincz et al., 2009). Alpha rhythms originating

from the somatosensory cortex and thalamic areas are referred to as ‘mu rhythms’ and have been associated with the blocking of motor activity (Pineda, 2005). Alpha rhythms in the auditory temporal cortex are referred to as ‘tau rhythms’ and are linked to auditory processing (Lehtelä et al., 1997).

Beta oscillations (13-30 Hz) are localised to different cortical sites, with high beta (20-30 Hz) activity specifically found in the somatosensory cortex (Roopun et al., 2006). As such, beta oscillations have been associated with the processing of sensory information and motor actions (Jasper and Penfield, 1949; Salenius and Hari, 2003; Zhang et al., 2008) as well as imagery of motor actions (Neuper et al., 2009; Pfurtscheller and Neuper, 1997). Additionally, frontal and temporal beta has been associated with emotional processes and emotional stress (Hayashi et al., 2009; Ray and Cole, 1985), while parietal beta is associated with cognitive tasks (Ray and Cole, 1985).

The precise role and origin of gamma oscillations are less understood compared to other brain waves. They have been linked to cognitive tasks (Fitzgibbon et al., 2004) and associative learning (Miltner et al., 1999). They have also been suggested to be implicated in mechanisms central to awareness and consciousness (Crick and Koch, 1990; Varela et al., 2001), with studies showing their role in meditative states (Lehmann et al., 2001) and dreaming (Llinas and Ribary, 1993). Recent studies have shown that high-frequency gamma oscillations occur in an area of the posterior cortex associated with conscious dreaming states (Siclari et al., 2017). Gamma activity has also been suggested to play an orchestrating function, providing timing mechanisms to modulate synaptic strength and facilitating the formation of neuronal assemblies in the cortex (Buzsáki and Wang, 2012), thereby potentially playing a critical role in the binding problem of consciousness (Singer, 1999; Singer, 2001). More generally, gamma oscillations have been associated with attentive wakefulness (Lutz et al., 2002; Steriade et al., 1996; Varela et al., 2001). As such, they may be the functional counterpart to the idling state characterised by increased cortical alpha band power (Pfurtscheller et al., 1996).

1.3.3.2 Fractal (1/f) activity

Human EEG signals are governed by scale-free dynamics (Buzsaki, 2006). Scale-free or 1/f dynamics in human EEG refer to the observation that the spectrum of electrical activity recorded from the brain follows a power law distribution over a wide range of frequencies. This means that large patterns of brain activity occur less frequently but with greater magnitude, while smaller patterns occur more often but with lesser magnitude. This characteristic is usually described as

“fractal” because it reveals self-similarity across different scales of time and space in the brain’s electrical activity. Scale-free dynamics reflect the inherent self-organisation and complexity of neural processes within the brain, which is critical for its functional flexibility. Deviations from typical $1/f$ behaviour in the human EEG have been associated with various neurological and psychiatric conditions (Klar et al., 2023; Niu et al., 2022), suggesting that scale-free dynamics might be a biomarker for brain health. Although the sources of non-oscillatory or fractal activity are poorly understood, and the mechanisms driving $1/f$ activity are still unclear, this type of activity constitutes the majority of power in the EEG power spectra (Freeman, 2004). Therefore, scale-free dynamics may be critical for understanding how the brain integrates information across various functional domains and adapts rapidly to environmental changes (Van de Ville et al., 2010).

1.3.3.3 Signal diversity and Lempel-Ziv (LZ) complexity

Resting-state EEG signals can reveal information about brain activity that extends beyond brain oscillations. In particular, the high temporal resolution of EEG makes it well-suited for assessing measures of signal diversity, entropy, or complexity in brain activity. Complexity in brain function generally refers to the randomness or unpredictability of brain activity. High entropy indicates a rich, complex pattern of brain activity with a high degree of randomness and variability, suggesting a state of high flexibility and information processing capacity. Conversely, low entropy suggests more predictable and less variable neural activity, often observed in certain pathological states or during reduced cognitive functioning. As such, measures of complexity are thought to index levels of consciousness (Sporns, 2007; Tononi and Edelman, 1998; Tononi et al., 1998).

LZ complexity is a measure of entropy from the field of information theory (Amigó et al., 2004). It quantifies the complexity of a data string by measuring how efficiently a sequence can be compressed without losing information. LZ complexity has been applied to EEG data to assess the complexity of brain activity over time by providing scalar measures for a chosen length of EEG recording. It is calculated by determining the instantaneous amplitude of the signal and then binarising it according to its mean. The LZ78 algorithm (Ziv and Lempel, 1978) is a dictionary-based compression method that incrementally builds a dictionary of substrings seen in the input data. In the context of EEG analysis, the LZ78 compression algorithm is applied to the binarised EEG data string, resulting in unique non-overlapping substrings. Thereby, LZ78 can be used to evaluate the complexity of the electrical activity recorded from the brain. Higher LZ complexity values denote a higher number of unique substrings and, hence, a larger diversity of a given EEG signal (Figure 2). Using LZ complexity, it has been documented that brain signal diversity changes

across the lifespan (Fernández et al., 2012) and that psychiatric and neurological conditions, as well as neurodiverse brains, show altered signal diversity (Abásolo et al., 2006; Fernández et al., 2009; Li et al., 2008).

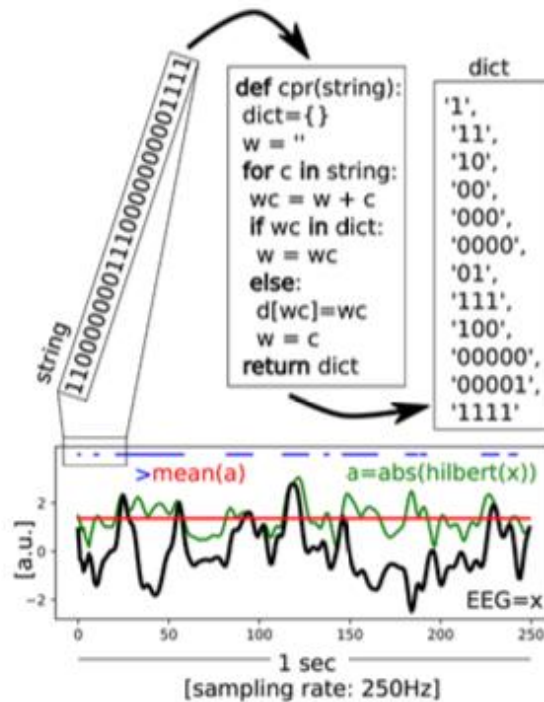


Figure 2. Computation of LZ complexity using the LZ78 algorithm (Ziv and Lempel, 1978).

EEG signal is binarised according to its mean to form a string, then unique non-overlapping substrings are identified. The higher the diversity of the string, the more substrings it contains and higher its LZ complexity. Figure reproduced from Timmermann et al., 2019, without need for permission: CC BY 4.0.

1.3.3.4 EEG source localisation

While EEG provides excellent temporal resolution, its spatial resolution is limited. As such, electrical signals measured at the scalp do not reflect the precise location of activated populations of neurons in the brain. Therefore, source reconstruction techniques are used to estimate the underlying brain activity from recorded EEG signals at the scalp level (Michel et al., 2004).

EEG source reconstruction involves two main steps, known as forward modelling and inverse solution. Forward modelling predicts the EEG signals at the scalp based on known sources within the brain. This requires knowledge of the conductive properties of different head tissues, often derived from MRI data. The inverse problem involves estimating the distribution of unknown sources within the brain that could have produced the observed EEG data. While forward modelling is relatively straightforward, the inverse problem is inherently ill-posed, as an infinite number of possible source combinations could have generated a given EEG signal. To solve the inverse problem, mathematical models are used to constrain the possible source combinations, taking into account the spatial arrangement of electrodes relative to the brain and the anatomical and conductive properties of the head. Additionally, regularisation techniques are applied to further increase the accuracy of the estimated sources (Grech et al., 2008).

The resulting source reconstruction allows for a more accurate association of EEG signals with underlying brain activity, thereby potentially providing important insights in clinical and research settings.

1.3.4 Effects of DMT and other psychedelics on resting-state EEG

A number of studies have used resting-state EEG to investigate the effects of psychedelics on brain function, with several consistent findings as well as some divergent results. Due to its short duration of action, DMT has offered the unique opportunity to study a psychedelic experience in its entirety. However, the transient nature of its phenomenology and a high contamination with physiological artifacts have also presented challenges to the study of its distinctive effects.

1.3.4.1 Effects on spectral EEG

Figure 3 presents a visual summary of spectral power findings from primary studies using EEG to investigate moderate to high doses of psychedelics.

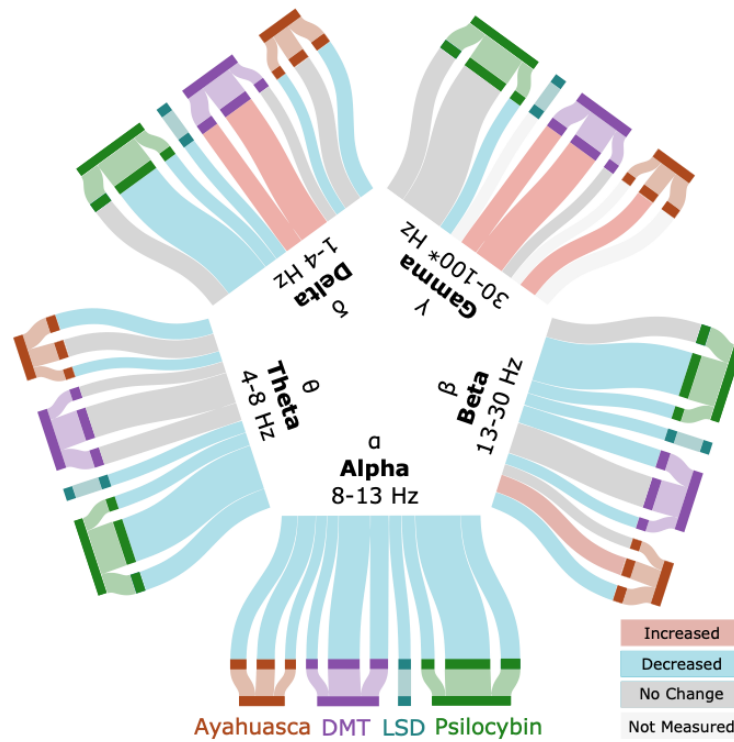


Figure 3. Effects of different psychedelics on EEG band power across frequency bands.

Each side of the pentagon corresponds to a specific frequency band (delta, theta, alpha, beta, and gamma), with projections from each side indicating individual publications. The projections are grouped by drug (ayahuasca, DMT, LSD, and psilocybin) and are colour-coded accordingly. The thickness of each line denotes the relative sample size of the study. Blue lines indicate decreases in band power, red lines represent increases, dark grey lines show no change, and light grey lines indicate that the band power was not measured or reported. Figure reproduced from Godfrey et al., 2025, without need for permission: CC BY 4.0.

The most consistent finding in human EEG and methodologically related MEG studies of classic psychedelics is a significant reduction in alpha band power, which has been consistently observed with various psychedelics, including psilocybin (Muthukumaraswamy et al., 2013; Ort et al., 2023), LSD (Carhart-Harris et al., 2016b; Murray et al., 2022), ayahuasca (Riba et al., 2004; Riba et al., 2002; Schenberg et al., 2015; Valle et al., 2016), and DMT (Acosta-Urquidi, 2015; Pallavicini et al., 2020; Timmermann et al., 2023b; Timmermann et al., 2019; Tagliazucchi et al., 2021). These reductions are especially pronounced in the occipital cortex (Carhart-Harris et al., 2016b;

Muthukumaraswamy et al., 2013; Riba et al., 2002; Schenberg et al., 2015), with psilocybin and ayahuasca also showing decreases in alpha localised to parietal brain areas (Muthukumaraswamy et al., 2013; Valle et al., 2016). Additionally, ayahuasca-induced decreases in high alpha (10-12 Hz) have been localised to the temporal-parietal junction (Riba et al., 2004). Notably, these decreases in alpha band power following ayahuasca administration have been negatively correlated with plasma DMT levels (Schenberg et al., 2015) and correlated with visual imagery and ego dissolution in LSD studies (Carhart-Harris et al., 2016b). Pretreatment with the 5-HT_{2A} antagonist ketanserin inhibited these reductions in alpha power following psilocybin and ayahuasca administration, suggesting that 5-HT_{2A} receptors play a critical role in mediating these alpha reductions induced by psychedelics (Kometer et al., 2015; Valle et al., 2016).

This reliable suppression of alpha band activity has been interpreted within the context of a predictive processing model of psychedelic action. According to this model, the brain operates by using Bayesian inference, continuously generating predictions about incoming sensory input. When there is a mismatch between these predictions and actual sensory input, the brain is said to update its models through prediction errors (Friston, 2010; Hohwy, 2013). Alpha and beta bands are thought to be a marker of top-down predictions, while gamma band activity is associated with bottom-up prediction errors (Bastos et al., 2012; Bastos et al., 2015; Mayer et al., 2015; Van Kerkoerle et al., 2014). Additionally, top-down predictions associated with alpha and beta waves are thought to be linked to activity in deep cortical layers, while prediction errors associated with gamma activity are found in superficial cortical layers (Bastos et al., 2020; Bastos et al., 2012). The reduction in alpha activity induced by psychedelics may signify a decrease in top-down processing (i.e., a relaxation of priors), allowing for increased bottom-up prediction errors to ascend the cortical hierarchy. This may contribute to the characteristic effects of psychedelics, such as increased cognitive flexibility, emotional reactivity, psychological insight, and a heightened sense of novelty (Carhart-Harris and Friston, 2019).

Beyond alpha, psychedelic administration often results in a broadband decrease in spectral power across lower frequency bands, including delta, theta, alpha, and beta frequency bands (1-30 Hz; Carhart-Harris et al., 2016b; Kometer et al., 2015; Muthukumaraswamy et al., 2013; Riba et al., 2002; Timmermann et al., 2019; Valle et al., 2016; Murray et al., 2022). For instance, LSD has been shown to reduce broadband oscillatory power across key hubs of the DMN, including the PCC, medial prefrontal, and temporoparietal cortices, spanning multiple frequency bands (Carhart-Harris et al., 2016b; Murray et al., 2022). However, other studies have reported increases in certain frequency bands, such as delta (Ort et al., 2023; Pallavicini et al., 2020; Tagliazucchi et al., 2021;

Timmermann et al., 2023b), theta (Acosta-Urquidi, 2015; Tagliazucchi et al., 2021), and beta (Schenberg et al., 2015; Tagliazucchi et al., 2021).

Inconsistencies in delta band activity could be attributed to contamination from physiological signals like cardiac activity, which typically occurs in the 0.6-2 Hz range and could be amplified by psychedelics' effects on HR and sympathetic tone (Bonnelle et al., 2024; Olbrich et al., 2021; Pasquini et al., 2024). Beyond this potential source of artifactual change in delta band activity, psychedelic-induced changes in delta may suggest that these substances push the brain into a state that shares similarities with deep sleep or introspective/meditative states, during which delta activity is also more prominent (Frohlich et al., 2021; Lee et al., 2018; Steriade and McCarley, 2013).

A few studies found increases in theta band power following DMT and 5-MeO-DMT administration (Acosta-Urquidi, 2015; Tagliazucchi et al., 2021), potentially suggesting that this signal is unique to certain psychedelics. Similar increases in theta power have been noted in studies involving ketamine (McMillan et al., 2019; Muthukumaraswamy et al., 2015), temporal lobe epilepsy (Carhart-Harris and Nutt, 2014; Carhart-Harris, 2007), altered states of consciousness induced by olfactory stimulation (Piarulli et al., 2018), and dreaming (Siclari and Tononi, 2016), suggesting a potential common neuronal mechanism underlying various altered states (Carhart-Harris and Nutt, 2014; Carhart-Harris, 2007). Increased theta power following psychedelic administration has been associated with immersive aspects of the experience, especially with compounds that induce intense effects. For example, increased theta power has been observed following DMT and 5-MeO-DMT administration (Acosta-Urquidi, 2015), likely due to their profound effects that shift focus from external stimuli to internally generated experiences. Higher doses of other psychedelics, such as psilocybin, LSD, and ayahuasca, or recordings taken during the peak intensity of the experience, might also reveal increased theta activity, which is often averaged out in typical EEG and MEG studies. Theta waves, often originating from deeper brain regions like the medial temporal lobes and hippocampus, are less accessible to scalp electrodes, which may account for some inconsistencies in findings.

High-frequency gamma band activity (> 30 Hz) has mostly been found to be increased following psychedelic administration (Acosta-Urquidi, 2015; Ort et al., 2023; Pallavicini et al., 2020; Schenberg et al., 2015; Tagliazucchi et al., 2021; Timmermann et al., 2023b). However, some studies have found either no gamma effects (Timmermann et al., 2019) or decreased gamma power (Murray et al., 2022; Muthukumaraswamy et al., 2013). Discrepancies in findings regarding gamma activity may be due to contamination from muscle artifacts, as muscle activity often falls within the gamma frequency range, potentially leading to false-positive results (Muthukumaraswamy, 2013).

1.3.4.2 Effects on signal complexity

Recent neuroimaging research has increasingly focused on understanding the effects of psychedelics through measures of brain complexity. The ‘entropic brain’ hypothesis suggests that psychedelics increase brain entropy, thereby enhancing functional plasticity and flexibility (Carhart-Harris, 2018; Carhart-Harris et al., 2014). Under this hypothesis, psychedelics push the brain into states of higher entropy. Studies utilising LZ complexity have provided empirical support for this hypothesis. Increased LZ complexity has been observed following the administration of psychedelics such as psilocybin, LSD, ketamine, and DMT (Ort et al., 2023; Pallavicini et al., 2020; Schartner et al., 2017a; Timmermann et al., 2019; Timmermann et al., 2023b). These findings align with fMRI studies that have also shown increased entropy during psychedelic experiences (Kaelen et al., 2016; Tagliazucchi et al., 2014; Viol et al., 2017). For example, fMRI studies have demonstrated that music listening during LSD administration correlates with increased entropy (Kaelen et al., 2016), and similar increases have been observed with ayahuasca and psilocybin in networks involving the ACC and hippocampus (Tagliazucchi et al., 2014; Viol et al., 2017). Other psychoactive drugs which induce changes in entropy-related measures include propofol (Schartner et al., 2015) and Tetrahydrocannabinol (THC; Cortes-Briones et al., 2015). LZ complexity is not unique to pharmacologically induced states; it has been observed across a wide range of conscious states, including non-REM sleep (Schartner et al., 2017b) and flow states induced by activities like musical improvisation (Dolan et al., 2018). Notably, while psychedelics induce an increase in LZ complexity, states of reduced consciousness, such as non-REM sleep and propofol-induced loss of consciousness, show a reduction in LZ complexity (Schartner et al., 2015). In sum, the consistent increase in brain complexity and entropy during psychedelic experiences supports the ‘entropic brain’ hypothesis, which argues that non-ordinary states of consciousness exhibit higher levels of disorder (Carhart-Harris, 2018; Carhart-Harris et al., 2014). This enhanced entropy may reflect a more flexible and functionally plastic brain state, potentially contributing to the therapeutic effects and the richness of subjective experiences reported by users.

Another concept related to brain complexity is self-organised criticality, which suggests that the brain typically operates in a balance between order and disorder (Chialvo et al., 2008). Studies have shown that certain states, such as focused attention, exhibit subcritical dynamics, while mind-wandering states show increased criticality (Fagerholm et al., 2015). This suggests that brain criticality varies depending on task demands. Psychedelics also appear to push the brain to increased criticality. For example, psilocybin and LSD induce increases in the fractal dimension

and a stronger alignment with power laws of fMRI blood-oxygen-level-dependent (BOLD) timeseries (Atasoy et al., 2017; Varley et al., 2020), and fractal structures have been shown to emerge near a critical point (Stinchcombe, 1989). This suggests that the brain, during a psychedelic state, operates closer to criticality, allowing for a broader exploration of potential states of consciousness.

1.3.4.3 EEG source reconstruction in psychedelic research

Several neuroimaging studies have employed source reconstruction techniques to localise the effects of psychedelics on brain activity, revealing specific changes in oscillatory power across various frequency bands and brain regions.

In an MEG study on psilocybin, researchers observed a widespread decrease in oscillatory power across a broad frequency range following psilocybin infusion. This decrease was primarily localised to association cortices, with significant reductions in areas of the DMN, such as the PCC. In posterior brain regions, decreases were seen in the delta (1–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (13–30 Hz), and low gamma (30–50 Hz) frequency bands. Additionally, in bilateral prefrontal cortices, there was a decrease in power ranging from the alpha band to high gamma (50–100 Hz) (Muthukumaraswamy et al., 2013).

In an MEG study on LSD, significant decreases in delta, theta, alpha, and beta bands (1–30 Hz) were source localised to specific cortical areas. These included the left fusiform gyrus, left temporoparietal junction, and left superior temporal gyrus for delta; the cingulate cortex and several frontal and parietal structures for theta; the ACC, superior occipital gyrus and precuneus for alpha; and select frontal, occipital, and temporal areas, as well as the cingulate cortex, for beta. Notably, significant correlations were identified between simple hallucinations and decreases in alpha power, as well as between ego dissolution and decreases in both delta and alpha power (Carhart-Harris et al., 2016b). A study on LSD further elaborated on these findings by showing a reduction in broadband oscillatory power (1–80 Hz) across four major hubs of the DMN, including the medial prefrontal cortex, PCC, and left and right temporoparietal cortices (Murray et al., 2022). The effects of LSD were most pronounced in electrodes over the PCC, with notable reductions in power in the left and right temporoparietal cortices as well (Murray et al., 2022).

Another study using low-resolution electromagnetic tomography (LORETA) after ayahuasca administration found decreases in alpha band power density in the parietal, occipital, temporal, and limbic lobes. Decreases in delta band power were also observed in a small region at the border between the left occipital and temporal lobes (Riba et al., 2004).

Further insights into the effects of psychedelics were provided by a study employing source localisation techniques on inhaled DMT. This study found widespread decreases in alpha band power and increases in delta band power. In contrast, increases in gamma band activity were localised to the temporal, parietal, and occipital areas. The study also revealed an occipital increase in theta band activity and increased beta band power in the temporal, parietal, and occipital regions, co-occurring with decreased frontal beta band power (Tagliazucchi et al., 2021).

Kometer et al. (2015) conducted a study on psilocybin and reported consistent, significant reductions in current source density across low-frequency bands (below 20 Hz) in the PCC and the retrosplenial cortex (RSC), both in eyes-open and eyes-closed conditions. These reductions also extended to the ACC, precuneus, cuneus, parahippocampal gyrus, and additional areas of the RSC. Particularly in the theta (4–8 Hz) and alpha1 (8–10.5 Hz) frequency bands, the reductions were more widely distributed, including the insular cortex, occipitotemporal area, and parahippocampal regions. Decreases in the alpha1 and alpha2 (10.5–13 Hz) frequency bands were also observed across large areas of the posterior occipital-parietal cortex, especially in the right hemisphere. Interestingly, psilocybin induced significant increases in high-frequency oscillations (55–100 Hz) in the left RSC during the eyes-closed condition (Kometer et al., 2015).

1.3.5 Summary

Resting-state EEG is a widely employed neuroimaging method and has a long history of use in studies investigating psychoactive drugs and their effects on the brain. It has been used extensively in psychedelic research and has consistently revealed widespread reductions in alpha band power and increases in signal diversity associated with the psychedelic state. DMT is an especially practical substance in the study of psychedelic brain effects due to its significantly faster onset and shorter duration of action compared to other classic psychedelics. However, this transient nature of DMT's psychological effects, coupled with its strong physiological effects, also presents a drawback, making it difficult to capture the full effects without a high contamination by physiological artifacts. Physiological activity such as eye movements, cardiac activity, muscle activity and movement contribute to EEG contamination and can mask or distort recorded EEG signal, thereby reducing signal-to-noise ratio and potentially altering spectral properties of the signal. An extended DMT experience may address these challenges and enable a more refined exploration into the rich substates of psychedelic experiences.

1.4 Thesis outline

1.4.1 Aims, objectives, and hypotheses

DMT and other psychedelics are valuable tools in the study of consciousness and have recently regained scientific interest for their potential therapeutic effects for various mental health disorders. DMT induces striking alterations in human consciousness; however, its effects are short-lived. The most commonly used methods of administration are inhalation and bolus IV administration, both producing substantial psychoactive effects within the first minute of administration, peaking within 2-5 minutes, and completely resolving in less than 30 minutes.

This thesis aims to investigate the use of continuous IV administration of DMT, its tolerability and effectiveness in extending the otherwise short-lived DMT experience at different doses, and its phenomenology, subjective, and neurophysiological effects in healthy human volunteers. The objectives were

- 1) To evaluate the tolerability and dose-response characteristics of continuous IV DMT, using measures of the subjective intensity of drug effects, anxiety, HR, and plasma DMT concentrations
- 2) To characterise the phenomenology of the extended infusion experience, using validated questionnaires, VAS scales, experience sampling, and micro-phenomenological interviews
- 3) To assess the neural dynamics of continuous IV DMT using EEG.

It was hypothesised that

- 1)
 - a. Using an infusion model based on previously determined PK parameters of DMT, continuous IV infusions of DMT will be safe and well-tolerated
 - b. Continuous IV infusions of DMT will allow the maintenance of a steady-state psychedelic experience over the period of the infusion and will be significantly different from placebo for the infusion period and a minimum of five minutes beyond
- 2)
 - a. Extended DMT will induce significant alterations in subjective experience, including significant increases in ratings of altered states of consciousness, mystical-type experience, ego dissolution, and emotional breakthrough

- b. Dose-response relationships are hypothesised for the effects of doses on the resulting subjective effects
- 3)
 - a. Extended DMT will induce decreases in alpha band power and increases in LZ complexity
 - b. These changes will be positively correlated with subjective ratings of intensity of the experience.

When the work for this thesis started, no previous research had implemented a pharmacokinetically-informed approach to develop continuous infusion protocols for the extended administration of DMT. To date, no research has systematically studied the subjective and neurophysiological effects of extended DMT infusions and their phenomenology.

1.4.2 Study overview

Two studies were conducted to address the above objectives. In an initial dose-finding study, five different doses of continuous infusions of DMT were tested in eleven healthy volunteers in a single-blind, fixed-order, placebo-controlled, within-subjects repeated measures design. Each participant received up to four doses of continuous IV DMT. The main outcome measures were subjective ratings of intensity and anxiety during the drug infusion, as well as HR and PK data. This study aimed to investigate the tolerability and effectiveness of continuous infusions of DMT at different doses and to find an optimal dose for the second study.

In a second high-dose imaging study, a single dose of continuous IV DMT was administered to an additional 15 healthy volunteers for a total sample size of $n = 20$ in a single-blind, fixed-order, placebo-controlled design. The main outcome measures were subjective (experience sampling, questionnaires, interviews) and resting-state EEG data. This study aimed to characterise the phenomenology and subjective and neurophysiological effects of a moderately high dose of continuous DMT. Figure 4 provides the study design for both studies, and Figure 5 shows participant inclusion in different parts of the study in a consort diagram.

The studies were approved by the National Research Ethics Service (NRES) Committee London-Brent and the Health Research Authority (HRA) and were conducted in accordance with the revised Declaration of Helsinki (World Medical Association, 2013), the International Committee on Harmonization Guidelines in Good Clinical Practice, and the National Health Service (NHS) Research Governance Framework. The studies were sponsored and approved by Imperial College

London's Joint Research and Compliance Office (JRCO), and the National Institute for Health Research/Wellcome Trust Imperial Clinical Research Facility (ICRF) gave site-specific approval for the studies. The studies were conducted under a Home Office license for research with Schedule 1 drugs.

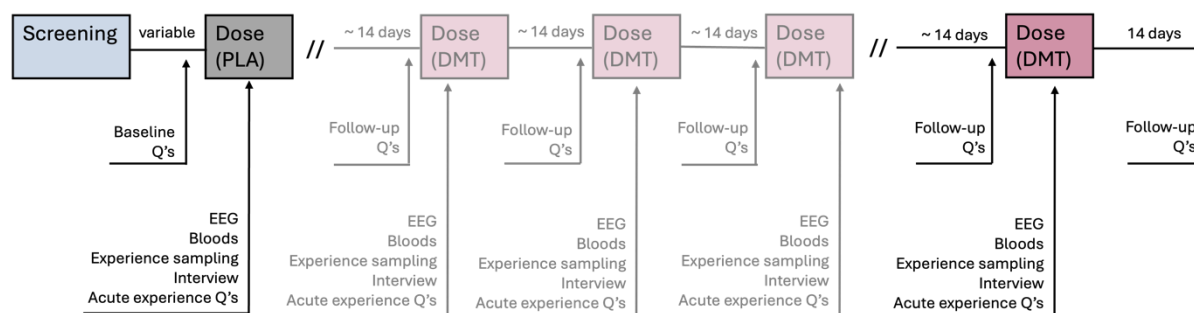


Figure 4. Study design.

Participants received a placebo dose and either one or up to four different doses of extended DMT. On dosing days, EEG, blood samples, and experience sampling data were collected acutely during the infusion. Interviews and questionnaires about the acute experience were completed following the end of the infusion. Baseline and follow-up questionnaires were completed approximately two days before and approximately 14 days after each dosing visit.

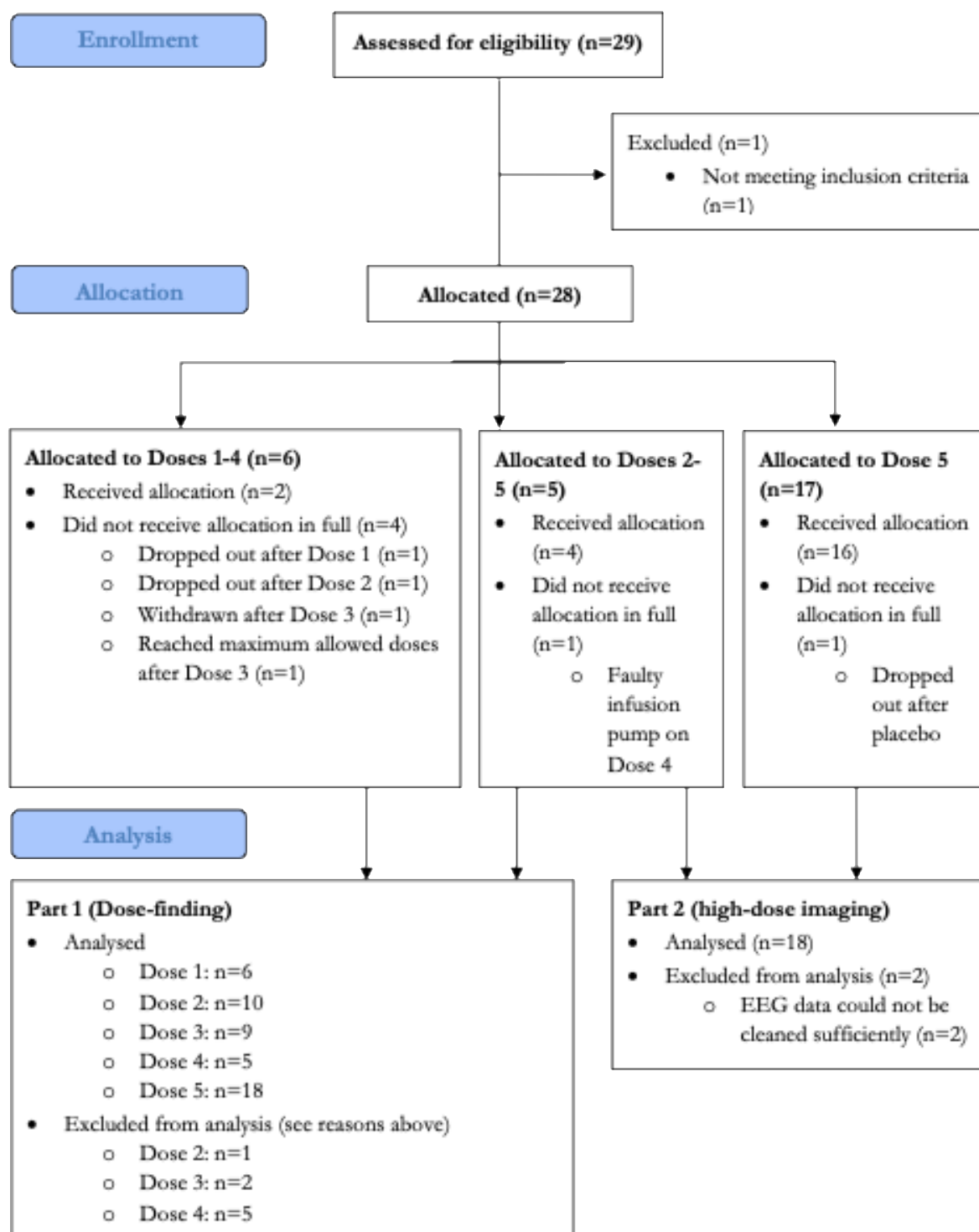


Figure 5. CONSORT flow of participants through the study.

29 participants were assessed for eligibility. After exclusions for ineligibility ($n = 1$), 28 participants were allocated to different parts of the study. Drop-outs and withdrawals are shown per group with reasons. Five participants contributed to both the dose-finding part and the high-dose imaging part of the study; per-part total therefore do not represent unique individuals, whereas the enrolment total does.

1.4.3 Ethical and safety considerations

1.4.3.1 Doses

The main aim of the presented work was to characterise the effects of continuous IV DMT administration at a moderately high dose. As this was the first study to test extended DMT administration at this dose range, and no previous data detailing the effects of different doses of continuous IV administration existed at the conception of this work, a dose-finding study was used to identify a suitable dose which produces the desired psychological effects while maintaining safety and tolerability. Relatedly, a single-blind, fixed-order study design was used with the saline placebo administered during the first session to provide additional safety and allow participants to become familiarised with the research team and environment before any DMT administration. While participants were blinded to the order of doses, the study did not assess any potential unblinding effects.

1.4.3.2 Set and setting

Psychedelic experiences are known to be influenced by contextual factors known as ‘set’ and ‘setting’ (Carhart-Harris et al., 2018; Hartogsohn, 2017). Therefore, guidelines proposed by (Johnson et al., 2008) were followed where possible. Care and attention were given to the space in which DMT administration took place. While the context of medical research limits the range of control over the room used for dosing sessions, white and light-coloured sheets were used to cover medical equipment as much as possible, and mood lights and decorations were placed to soften the space. Ambient music was played in the room, and staff at the research facility were informed about the delicate nature of the research taking place. As such, attention was given to all interactions between medical and research staff and study participants to provide a sense of safety, respect, care, and calmness. Where possible, the same researchers and medical staff attended all study visits, including screening visits of a single participant, to foster a trusting alliance throughout study participation.

1.4.4 Thesis structure

Chapter 2 will present an initial dose-finding study in which several dose regimens of continuous IV infusions of DMT were tested for their tolerability and effectiveness to produce sustained psychedelic effects over the duration of the infusion. Chapter 3 will present the acute

phenomenology and subjective effects of different doses of continuous IV infusions of DMT. Chapter 4 will focus on the effects of continuous IV infusions on the brain, as assessed with resting-state EEG. Chapter 5 will conclude the thesis with a summary of the analyses and results and a discussion of possible interpretations, implications, and future directions for research.

2. Dose-finding study of continuous IV infusions of DMT

2.1 Introduction

When ingested orally, DMT is rapidly metabolised in the gastrointestinal system by MAO (Riba et al., 2015), rendering it psychologically inactive. In both recreational and ritual settings, DMT is commonly given in the form of ayahuasca (Domínguez-Clavé et al., 2016), a brew containing DMT and harmala alkaloids that inhibit MAO (Riba et al., 2015), which, upon oral ingestion, leads to alterations in consciousness lasting for four to six hours. Alternatively, DMT can be inhaled (vaping/smoking; Winstock et al., 2014) or administered parenterally (e.g., intramuscularly or intravenously as a bolus). These forms of administration result in a very short duration of action: the subjective effects of intramuscular DMT have an onset of 2 to 5 minutes and last between 30 and 60 minutes (Barker, 2018; Szára, 2007), while those of bolus IV injection begin within seconds, reaching their peak intensity within two to three minutes and subsiding thereafter, with negligible effects felt after about 30 minutes (Strassman, 1995; Timmermann et al., 2019). IV DMT administration allows for precise control over dosing, which makes it the preferred route of administration for investigating its effects in humans (Gouzoulis-Mayfrank et al., 2005; Strassman and Qualls, 1994; Timmermann et al., 2019; Timmermann et al., 2023b). DMT appears to be physiologically safe at effective doses, and repeated administration of bolus IV DMT does not produce any apparent psychological tolerance – e.g., four doses of DMT have been safely administered in a single session apparently without diminished psychological effects (Strassman et al., 1996); this property, combined with an apparent lack of tachyphylaxis, a rapid onset, short time-course and specific character of its effects, makes DMT possibly unique among serotonergic psychedelics and suitable for continuous IV administration (Gallimore and Strassman, 2016).

Developing a prolonged DMT experience (i.e., longer than the duration of effects seen with inhalation or bolus IV injection) would be an essential step towards allowing for a closer study of its phenomenology and neurobiological effects. It would make it possible to control the length, intensity, and dynamics of the DMT experience, with the potential for real-time adjustment. This could make extended DMT a valuable tool in conjunction with therapy, to tailor the psychedelic effects to the individual needs of each patient and their clinical condition, as well as for

consciousness research, whereby the intensity of the DMT experience can be adjusted according to specific hypotheses and research questions. In a previous study, continuous infusions of DMT were safely administered for up to 90 minutes (Gouzoulis-Mayfrank et al., 2005), and the infusion rates were reported to be determined via a previous pilot study with six subjects. However, this report lacked information on the nature and duration of effects DMT induced. Another approach was proposed, aiming to generate stable subjective effects via a continuous infusion of the drug (Gallimore and Strassman, 2016). Still, unfortunately, this protocol has not been implemented in human participants. Overall, no pharmacokinetically-informed protocols of continuous IV DMT have been tested in humans to date.

The present study developed the first systematic protocol for the continuous IV infusion of DMT and tested its effectiveness in healthy volunteers. The main goal of the study was to provide first steps toward establishing infusion parameters for maintaining a steady state of DMT effects for a chosen length of time. A further goal of the study was to test different doses of continuous IV infusions and to identify a suitable moderately high dose for use in subsequent studies investigating the phenomenology, subjective and EEG effects of extended DMT administrations, detailed in Chapters 3 and 4.

2.2 Methods

2.2.1 Study design

In a single-blind, placebo-controlled study using a within-subjects repeated measures design, eleven healthy volunteers received up to four different doses of bolus plus slow-rate infusions of DMT over 30 minutes. Dosing sessions were separated by at least two weeks. On dosing visits, EEG activity, as well as subjective and autonomic effects, were measured acutely and retrospectively, and blood samples were collected for PK modelling purposes. Figure 4 in Chapter 1 – “*Introduction*”, section [1.4.2](#) – “*Study overview*”, provides an overview of the study procedures.

2.2.2 Dose regimens

Different dose regimens were simulated based on a separate population PK reanalysis of data from a previous study (Strassman and Qualls, 1994), yielding new two-compartment model parameter estimates (unpublished). Four dose levels of a combination of an IV loading bolus dose followed

2. Dose-finding study of continuous IV infusions of DMT

by a constant-rate infusion were tested, with the aim to induce and sustain moderate-to-high intensity effects over 30 minutes while maintaining psychological safety (i.e., low levels of anxiety). These doses were chosen based on subjective effects observed with comparable bolus IV doses of DMT in a previous study (Timmermann et al., 2019). The bolus IV injection was delivered over 30 seconds, followed by a saline flush for 15 seconds. The constant-rate infusion was started one minute after the beginning of the bolus injection and lasted 29 minutes, for a total of 30 minutes of DMT administration (i.e., bolus plus constant-rate infusion). Table 2 shows the doses administered to subjects in this study. To ensure safety, a pilot session involved the first participant receiving a dose of 1.5 mg bolus plus 0.2 mg/min of DMT fumarate. The data for this dose is not included here as it was not repeated across participants, induced negligible psychological effects, and was not intended for analyses. The following infusions initially followed the lowest calculated dose regimen, with the first subject receiving a bolus dose of 6 mg of DMT fumarate, followed by a constant rate infusion of 0.63 mg/min, corresponding to projected low doses according to previous research (Strassman and Qualls, 1994). For each participant, doses were increased for subsequent dosing sessions if the last dose was well-tolerated, with the overall aim of identifying a dose that produces an average peak subjective intensity of < 7.5 (scale 0-10). This rationale was used based on the procedures of a previous study (Timmermann et al., 2019), to identify a dose that sustains a moderate-to-high level of intensity throughout the infusion to be used in future studies investigating the phenomenology and brain activity related to states of immersion commonly reported for DMT.

Table 2. Dosing schedule of continuous IV infusions of DMT.

Doses are expressed for DMT fumarate. A bolus injection was given over 30 seconds, followed by a saline flush over 15 seconds. The continuous slow-rate infusion was started one minute after the beginning of the bolus injection and maintained for 29 minutes.

	Bolus (mg)	Inf (mg/min)	Total (mg)	Participants (n)
Dose 1	6	0.63	24.19	6
Dose 2	10	1.05	40.32	10
Dose 3	14	1.46	56.45	9
Dose 4	18	1.88	72.58	6
Dose 5	20	2.27	85.83	5

2.2.3 Study drugs

Freebase DMT (Cole Parmer Instrument Company Limited, United Kingdom) was transformed into DMT fumarate (Onyx Scientific, United Kingdom) as done in previous studies of IV DMT (Gouzoulis-Mayfrank et al., 2005; Strassman and Qualls, 1994; Timmermann et al., 2019; Timmermann et al., 2023b). On dosing days, DMT fumarate (Cole Parmer Instrument Company Limited, United Kingdom; Onyx Scientific, United Kingdom) was reconstituted with saline to give a 5mg/ml solution and sterile-filtered into sterile vials. For each dose, the corresponding amount of DMT solution was drawn into separate syringes for the bolus injection and slow-rate infusion, then saline was added to create a 5 ml bolus injection and 15 ml slow-rate infusion, respectively. The bolus injection and saline flush were administered by a study physician, and the constant-rate infusion was delivered with a BD Alaris GH plus syringe pump (BD Switzerland Sàrl, Switzerland), with the infusion rate set to 30 ml/h.

2.2.4 Participants

Eleven healthy participants (seven male, four female, mean age $\pm$ SD = 37.09 $\pm$ 8.93 years, range = 26-51 years) took part in this study. Participants were recruited via word of mouth. Exclusion criteria for study participation were age < 18, current or previously diagnosed psychiatric disorder as assessed using the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998), family history of psychotic disorder, a medically significant condition which rendered them unsuitable for the study, e.g., heart condition, diabetes), and abnormal physical exam, electrocardiogram, or blood test, no prior experience with a psychedelic drug, previous adverse response to a hallucinogenic drug, blood or needle phobia, a positive pregnancy test at screening or during the study, and excessive use of alcohol or other drugs (> 40 units per week). A complete list of inclusion and exclusion criteria can be found in Table 3. Participants were asked not to consume any alcoholic drinks 48 hours before each study visit and to not consume any illicit drugs two weeks before their first study visit until two weeks after their last study visit. Drugs of abuse tests and pregnancy tests (where applicable) were performed before each dosing visit. All subjects gave written informed consent in accordance with the revised Declaration of Helsinki (2013).

Table 3. List of inclusion and exclusion criteria for the study.

Inclusion criteria	Exclusion criteria
Physically and mentally healthy	A current or previously diagnosed psychiatric disorder
18+ years old	One or more immediate family members with a current or previously diagnosed psychotic disorder
Good command of the English language	A medically significant condition which renders them unsuitable for the study (e.g., hypertension, diabetes, severe cardiovascular disease, hepatic or renal failure etc.)
Prior experience with a psychedelic without experiencing adverse events	MR contraindications (e.g., metal implants, pacemakers, claustrophobia etc.)
	No prior experience with a psychedelic drug
	Previously experienced an adverse response to a hallucinogenic drug
	Blood or needle phobia
	A positive pregnancy test at screening or during the study
	Excessive use of alcohol or other drugs
	Currently using a psychoactive medication

2.2.5 Study procedures

All volunteers attended a screening visit to determine eligibility for the study. During this visit, volunteers provided informed consent to be enrolled in the study. A physical examination (weight, ECG, blood pressure, HR, neurological examination) and routine blood test were performed, as well as a psychiatric interview (see [section 2.2.3](#) ‘Participants’ for exclusion criteria). Subsequently, volunteers completed questionnaires.

The dosing visits took place in a calm, decorated hospital room at the ICRF. On dosing days, two researchers, one medic and one participant were present. Participants were reminded of the study procedures and were asked to verbally provide re-consent if they wished to continue. Urine screens for drugs of abuse and pregnancy were performed. Participants were fitted with a high-density

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EEG cap, an ECG was taken (to ensure safety), and cannulation took place on both arms. Blood samples were drawn from one cannula, and continuous infusions of DMT/placebo were administered via the other cannula. Participants were made comfortable in a semi-supine position, and baseline EEG recordings were taken (eyes-open and eyes-closed). Shortly before dosing started, a body scan meditation was performed to help participants relax. During dosing, participants wore an eye mask and were instructed to keep their eyes closed. Low-volume ambient music (<https://soundcloud.com/user-202717649-642667767/colour-field-94>) was played through headphones to ensure psychological comfort. Dosing occurred around noon, during which DMT was administered for 30 minutes (see Table 2). EEG and acute subjective and autonomic effects were recorded for 8 minutes pre-dosing and 52 minutes post-dosing. The EEG recorded in this phase of the study is not included in the present analyses, but is included in Chapter 4 – “*EEG effects of continuous infusions of DMT*”.

2.2.5.1 Experience sampling of subjective effects

2.2.5.1.1 Intensity. Subjective intensity of effects was assessed acutely via an experience sampling method (ESM) from 8 minutes before to 52 minutes after the start of the bolus injection. For this, audio prompts were played through headphones, and participants were instructed to verbally give subjective ratings of the intensity of the experience (from 0 = “no effects” to 10 = “most intense imaginable”). These were collected at minutes -8, -6, -4, -2, 0, 1, 2, 3, 4, and every two minutes thereafter, with minute 0 being the start of the bolus injection.

2.2.5.1.2 Anxiety. For Doses 1-4, subjective ratings of anxiety were also collected every four minutes using a similar procedure (from 0 = “no anxiety” to 10 = “most anxiety imaginable”) to assess the psychological safety of DMT infusions.

2.2.5.1.3 Entities. For Dose 5, ratings of entity experiences (“yes”/“no”) were collected at minutes -8, -4, 0, 1, 2, 3, 4, 6, and every four minutes thereafter, to use for neurophenomenological analysis (for analysis and results, see [Chapter 3](#) – “*Phenomenology and Subjective effects of continuous IV infusions of DMT*” and [Chapter 4](#) – “*EEG effects of continuous IV infusions of DMT*”).

2.2.5.2 Heart rate

HR was measured and monitored from 8 minutes before until 52 minutes after the beginning of the bolus injection with an E4 Empatica wristband (Empatica Srl, Milan, Italy), which participants

wore on their wrist during the dosing period. The results reported here correspond to the recorded HR at two-minute intervals.

2.2.5.3 Plasma DMT concentrations

Plasma levels of DMT were repeatedly assessed at baseline and 2, 5, 10, 20, 29, 32, 37, 40, 50, 60, 80, 100, 120, 150, and 180 minutes after the beginning of bolus injection of DMT. Blood samples (up to 6 ml) were collected into EDTA tubes, kept on wet ice, and centrifuged within one hour of collection. The harvested plasma was stored at -80°C before being shipped on dry ice to the University of Gothenburg for analysis. Samples were analysed using a previously published liquid chromatography tandem mass spectrometry method (Eckernäs et al., 2022a). In brief, a methanolic solution containing internal standards was added to plasma samples, followed by protein precipitation with acetonitrile. The samples were centrifuged, and supernatants were transferred to new tubes and evaporated to dryness before reconstitution in aqueous mobile phase. Chromatography was performed using a diphenyl column with gradient elution (0.1% formic acid in methanol/water), and the mass spectrometer was operated in multiple reaction monitoring mode (Eckernäs et al., 2022a).

2.2.6 Statistical analysis

Linear mixed-effects (LME) models were constructed to test the relationship between doses, timepoints, and the response variables of intensity, anxiety, HR, and DMT plasma concentrations. LME models exhibit several advantages over repeated measures ANOVAs in dealing with the present data: 1) LME models control for the potential influence of random variables (i.e., subject-driven interindividual variability) by including them as random effects; 2) LME models can cope with missing data; and 3) they are able to include grouping hierarchies such as the present partially-crossed groups (i.e., each subject received multiple but not all DMT doses).

LME analyses were run in R (version 4.2.2; R Core Team, 2013) using the *lme4* (Bates et al., 2015) package. Models included subjective intensity, anxiety, HR, and plasma DMT concentration as the dependent variable, respectively. For all models, the participant ID was accounted for via a random intercept. Dose and timepoint were added as fixed effects, and the dependent variable was assessed via change scores from the placebo condition for the same subject at that given timepoint. Both dose and time were treated as categorical variables, and the earliest timepoint (minute -8) of Dose 1 was specified as a reference. While investigating the differences between each pair of doses is of

interest, the small sample size led to the decision to reduce the number of comparisons by focusing the statistical analyses on contrasting higher doses against Dose 1. Consequently, the summary statistics of Dose 1 compared to placebo and the added effects of higher doses compared to Dose 1 are reported here. The resulting model for these outcome variables was specified as follows:

$$\text{Outcome variable} \sim \text{Dose} + \text{Timepoint} + (1 \mid \text{Subject}).$$

For all mixed models, significance was estimated via the *lmerTest* package (Kuznetsova et al., 2017), and false discovery rate (FDR) correction was used to adjust for multiple comparisons (Benjamini and Hochberg, 1995), with significance established at $p < 0.05$.

2.3 Results

In total, six participants received Dose 1, ten participants received Dose 2, nine participants received Dose 3, six participants received Dose 4, and five participants received Dose 5. Two participants reached the maximum amount of dosing sessions allowed by the protocol without reaching the goal average peak intensity of > 7.5 (Participant 1 received a pilot dose [see above], and Dose 1 was repeated for Participant 3 due to a faulty infusion pump), and three participants dropped out without completing all dosing sessions. Due to the lack of differential effects between Dose 1 and Dose 2 (see Figure 6), Dose 1 was omitted from Participant 7 onwards to allow a focus on higher doses (i.e., Dose 4 and 5) while ensuring compliance with the study protocol. An overview of doses administered and any adverse reactions that occurred during and after dosing can be found in Table 4.

Based on the apparent reduction of sensory effects over time and peak effects lower than the target peak intensity of > 7.5 , Dose 5 was added to the initially planned Doses 1, 2, 3, and 4. For this dose, a higher amount of DMT was chosen for the bolus dose to reach the target peak intensity of > 7.5 . Additionally, the bolus dose was paired with a relatively higher infusion rate for the continuous infusion to counteract the reduction of subjective effects over time and achieve a more stable immersion in the DMT state. At the conception of this study, DMT plasma concentration data was only available from one previous study using bolus IV injections of DMT (Strassman and Qualls, 1994). Therefore, Doses 1-4 were designed based on only that data. Our team has since collected and analysed further plasma DMT data, including a previous study (Timmermann et al., 2019), which has been used to model the relationship between DMT PK and its effects (Eckernäs

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et al., 2022b; Eckernäs et al., 2023b) and the initial four doses of continuous IV infusions described here. For Dose 5, data from all three studies mentioned above were included for an updated PK model of DMT, which resulted in the dose parameters for Dose 5. In a subsequent study, Dose 5 was given to an additional 15 participants. For completeness, the results reported here include all data collected from Dose 5.

Table 4. Overview of completed doses.

The table shows participants, completed doses, adverse events, and data included in the analysis. On one occasion, the participant requested to terminate the continuous infusion at minute 26. Parameters for the doses are given in Table 2.

Participant	Doses received	Adverse events	Notes
1	1, 2, 3		Received an initial pilot dose of 1.5 mg bolus plus 0.2 mg/min of DMT (not reported here) and thus completed the four doses the protocol allowed and could not receive Dose 4
2	1, 2, 3	Dose 3: anxiety with chest discomfort (nothing abnormal was found on an ECG performed immediately after the infusion)	Dose 3 terminated at minute 26 upon request – all data up to minute 26 included in analysis
3	1, 2, 3		Dose 1 was repeated due to infusion line blocking on the first attempt and thus completed the four doses the protocol allowed and could not receive Dose 4
4	1, 2, 3, 4		
5	1, 2		Dropped out after Dose 2 due to personal reasons not related to adverse events
6	1		Infusion line blocked at minute 27 and 29 on Dose 1 – all data up to minute 26 included in analysis Dropped out after Dose 1 due to personal reasons not related to adverse events
7	2, 3, 4, 5		
8	2, 3, 4, 5	Dose 4: slight nausea	
9	2, 3, 4, 5		Infusion line blocked on Dose 4 – excluded from analysis
10	2, 3, 4, 5		
11	2, 3, 4, 5		

Note: Participant 2 experienced anxiety and chest pains on Dose 3 starting from approx. minute 20 and requested to terminate the infusion at minute 26. Anxiety and chest pains subsided within 10 minutes of the end of infusion, and follow-up examinations (ECG, blood tests) did not show any abnormalities, suggesting that chest pains were psychogenic. Dose 1 was omitted for participants 7-11 to prioritise higher doses (Dose 2, 3, 4, 5).

2.3.1 ESM of subjective effects

2.3.1.1 Intensity

Substantial increases in intensity ratings were observed with all tested doses, as shown in Figure 6. Using a bolus IV injection paired with a constant-rate infusion, participants were maintained at relatively stable levels of drug effects over the period of infusion. The onset of subjective effects was quick, occurring within the first minute of the beginning of the bolus IV injection being administered. After an initial peak, the subjective effects remained relatively stable throughout the continuous infusion, with the plateau of effects stabilising at a slightly lower level than the initial peak (Figure 6). LME analysis showed the temporal profile of the effect, revealing first a significant increase in intensity for Dose 1 compared to placebo at minute 1 ($\beta = 4.31, t = 14.89, p < 0.001$), which lasted until minute 46 ($\beta = 0.83, t = 2.83, p = 0.006$), with peak intensity reached at minute 2 ($\beta = 4.584, t = 15.84, p < 0.001$). Additionally, other doses exhibited significant average increases when compared with the changes observed in Dose 1 (Dose 2: $\beta = 2.52, t = 19.20, p < 0.001$; Dose 3: $\beta = 3.21, t = 23.31, p < 0.001$; Dose 4: $\beta = 4.39, t = 26.25, p < 0.001$; Dose 5: $\beta = 4.91, t = 46.62, p < 0.001$), resulting in a significant dose-effect relationship throughout the whole 30 minutes infusion and for 16 minutes following the end of infusion ($p < 0.05$, FDR corrected for multiple comparisons). Summary statistics can be found in Table 5.

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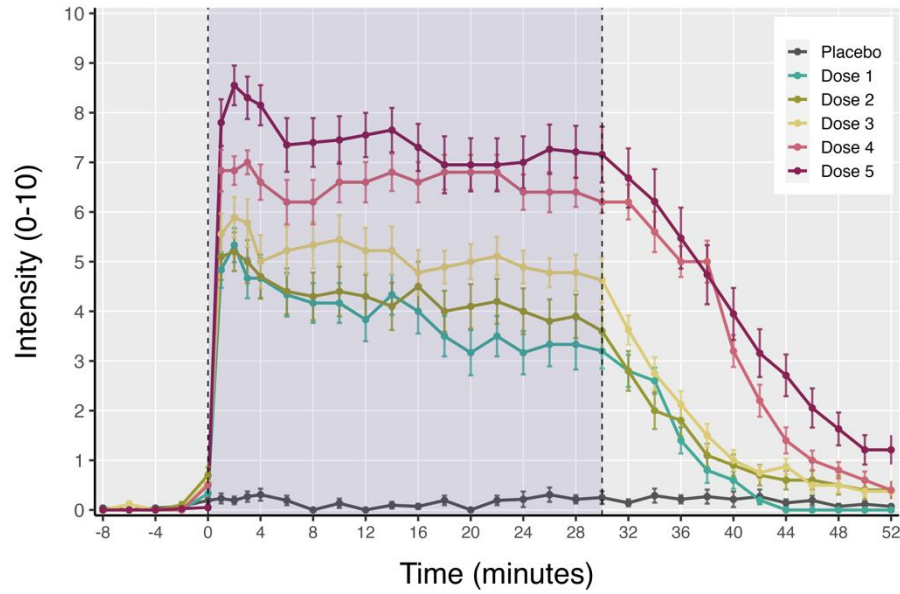


Figure 6. Subjective intensity of DMT and placebo infusions.

ESM of subjective effects induced by continuous infusions of placebo and different doses of DMT. The bolus IV injection was administered at time 0. The constant-rate infusion started at min 1 and was maintained until min 30. Peak effects of DMT were successfully extended via continuous infusion. A significant dose-response relationship for Intensity was found for minutes 1-40 (assessed using a 0-10 scale with 0 = “no effects” and 10 = “most intense effects imaginable”). The data are expressed as the mean $\pm$ SEM.

Table 5. Summary table for the LME model of subjective intensity.

Random effects	σ^2	SD		
Subject intercept	0.992	0.996		
Residual	3.227	1.796		
Fixed effects	<i>b</i>	SE	<i>t</i>	<i>p</i>
Intercept	-2.338	0.288	-8.109	< 0.001 ***
Dose 1	1.647	0.167	9.885	< 0.001 ***
Dose 2	2.518	0.131	19.202	< 0.001 ***
Dose 3	3.210	0.138	23.311	< 0.001 ***
Dose 4	4.394	0.167	26.246	< 0.001 ***
Dose 5	4.913	0.105	46.615	< 0.001 ***
Min -6	0.000	0.290	0.000	1.000
Min -4	0.000	0.290	0.000	1.000
Min -2	-0.337	0.303	-1.111	0.298

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Min 0	0.286	0.290	0.987	0.352
Min 1	4.312	0.290	14.893	< 0.001 ***
Min 2	4.584	0.290	15.835	< 0.001 ***
Min 3	4.436	0.290	15.273	< 0.001 ***
Min 4	4.252	0.290	14.639	< 0.001 ***
Min 6	3.982	0.290	13.552	< 0.001 ***
Min 8	4.231	0.304	13.906	< 0.001 ***
Min 10	3.982	0.290	13.710	< 0.001 ***
Min 12	4.184	0.304	14.008	< 0.001 ***
Min 14	3.713	0.290	13.710	< 0.001 ***
Min 16	4.184	0.304	13.752	< 0.001 ***
Min 18	4.713	0.290	12.781	< 0.001 ***
Min 20	4.965	0.304	13.033	< 0.001 ***
Min 22	4.765	0.290	12.963	< 0.001 ***
Min 24	3.965	0.304	13.033	< 0.001 ***
Min 26	3.741	0.291	12.837	< 0.001 ***
Min 28	4.004	0.306	13.103	< 0.001 ***
Min 30	3.619	0.294	12.331	< 0.001 ***
Min 32	3.431	0.308	11.130	< 0.001 ***
Min 34	2.879	0.294	9.810	< 0.001 ***
Min 36	2.497	0.308	8.099	< 0.001 ***
Min 38	2.031	0.295	6.895	< 0.001 ***
Min 40	1.513	0.308	4.909	< 0.001 ***
Min 42	1.283	0.294	4.373	< 0.001 ***
Min 44	0.849	0.308	2.755	0.007 **
Min 46	0.831	0.294	2.833	0.006 **
Min 48	0.382	0.308	1.240	0.284
Min 50	0.516	0.294	1.759	0.093
Min 52	0.186	0.308	0.602	0.578

Note: Number of observations: 2320, 26 subjects. P-values are FDR-corrected for multiple comparisons. Significance codes: $p < 0.05 = *$, $p < 0.01 = **$, $p < 0.001 = ***$.

2.3.1.2 Anxiety

Overall, participants experienced low levels of anxiety before and throughout dosing, indicating that extended administration of DMT was well tolerated (Figure 7). LME analysis showed no significant increases in anxiety during the peak of the experience under Dose 1 with respect to placebo, and only showed significant differences at minutes 8 ($\beta = 0.60$, $t = 2.99$, $p = 0.019$), 12 ($\beta = 0.70$, $t = 3.49$, $p = 0.008$) and 28 ($\beta = 0.69$, $t = 3.38$, $p = 0.008$, all FDR corrected) possibly due to a quicker drop of the initial anxiety in the placebo condition. Moreover, the model revealed no significant effect associated with Dose. These results suggest that the initial increase in anxiety was

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related to psychological anticipation rather than direct dose-dependent drug effects. This is apparent considering that the highest mean anxiety scores occur at minute 0, at the beginning of administration, when no subjective effects are apparent. Summary statistics can be found in Table 6.

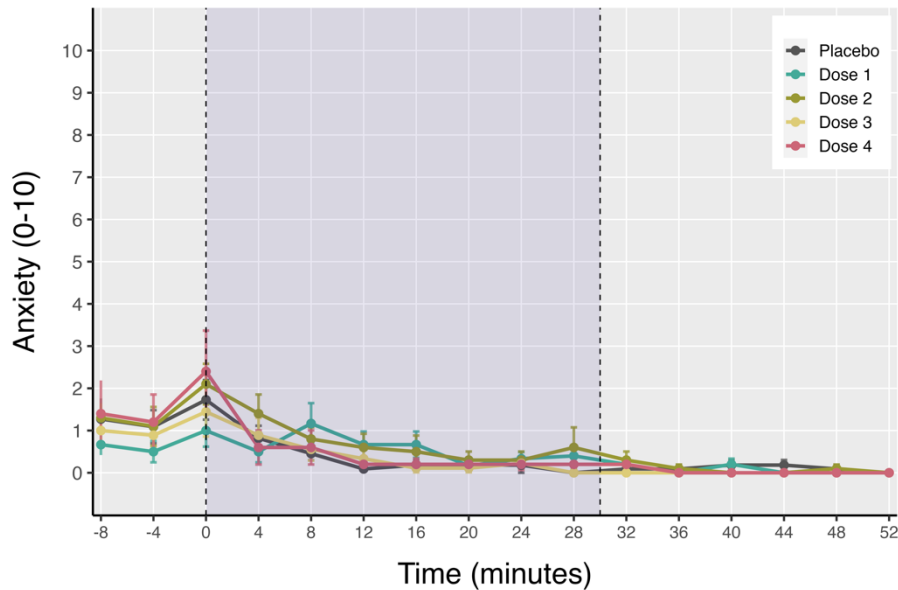


Figure 7. Ratings of anxiety following DMT and placebo infusions.

ESM of subjective effects induced by continuous infusions of placebo and different doses of DMT. The bolus IV injection was administered at time 0. The constant-rate infusion started at min 1 and was maintained until min 30. Anxiety ratings were given on a scale from 0-10, with 0 = “no anxiety” and 10 = “most intense anxiety imaginable”. The data are expressed as the mean $\pm$ SEM.

Table 6. Summary table for the LME model of anxiety.

Random effects	σ^2	SD		
Subject intercept	0.2958	0.5439		
Residual	0.6044	0.7774		
Fixed effects	<i>b</i>	SE	<i>t</i>	<i>p</i>
Intercept	-0.312	0.232	-1.341	0.316
10 mg + 1.1 mg/min	0.106	0.113	0.938	0.473
14 mg + 1.5 m/min	-0.087	0.121	-0.717	0.530
18 mg + 1.9 mg/min	-0.024	0.144	-0.166	0.868
Min -4	0.100	0.201	0.498	0.653
Min 0	0.200	0.201	0.996	0.467
Min 4	0.400	0.201	1.993	0.152
Min 8	0.600	0.201	2.989	0.019 *
Min 12	0.700	0.201	3.487	0.008 **
Min 16	0.467	0.201	2.325	0.098
Min 20	0.300	0.201	1.495	0.276
Min 24	0.333	0.201	1.661	0.232
Min 28	0.691	0.204	3.380	0.008 **
Min 32	0.405	0.204	1.983	0.152
Min 36	0.263	0.204	1.284	0.316
Min 40	0.155	0.204	0.760	0.530
Min 44	0.155	0.204	0.760	0.530
Min 48	0.298	0.204	1.459	0.276
Min 52	0.370	0.204	1.808	0.193

Note: Number of observations: 466, 11 subjects. P-values are FDR-corrected for multiple comparisons. Significance codes: $p < 0.05 = *$, $p < 0.01 = **$, $p < 0.001 = ***$.

2.3.2 Heart rate

Changes in HR following DMT dosing with respect to placebo are shown in Figure 8. LME analysis showed significant increases in HR for Dose 1 compared to placebo, starting at minute 0 ($\beta = 8.29$, $t = 2.75$, $p = 0.013$), peaking at minute 2 ($\beta = 35.5$, $t = 11.8$, $p < 0.001$), and lasting until minute 24 ($\beta = 8.95$, $t = 2.97$, $p = 0.007$). Additionally, there were added effects of Dose, which, however, were only significant after FDR correction for Dose 3 ($\beta = 4.28$, $t = 3.22$, $p = 0.003$) and Dose 4 ($\beta = 8.67$, $t = 5.24$, $p < 0.001$). Summary statistics can be found in Table 7. Overall, these findings

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reveal that HR increases induced by continuous DMT stabilise following the bolus period, while subjective effects remain elevated, suggesting physiological safety.

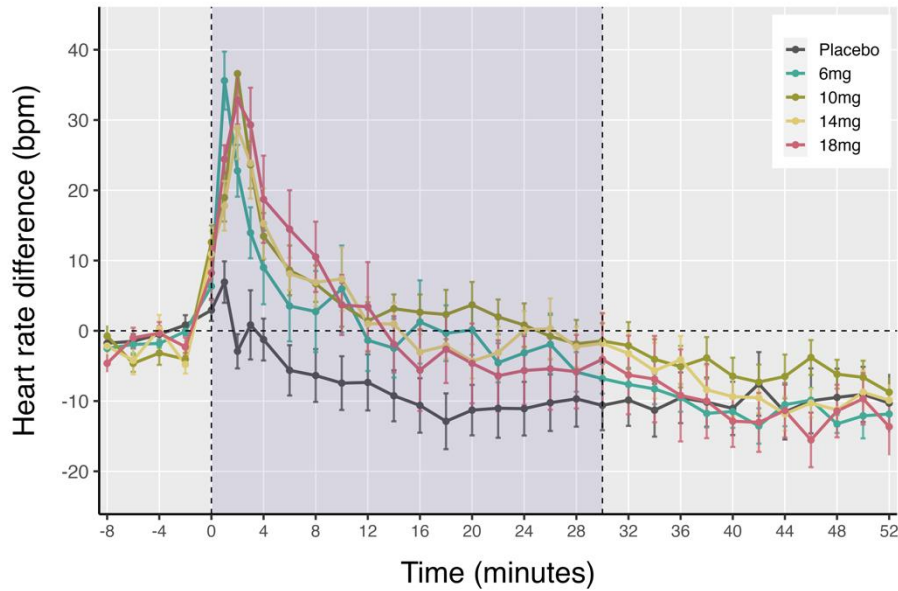


Figure 8. Acute changes in HR following placebo and DMT infusions.

While the initial period of DMT administration is associated with an elevated HR, this then returns to baseline levels and stabilises. Values are expressed as average differences in beats per minute (bpm) from baseline HR, defined as the average HR between minutes -8 and 0, $\pm$ SEM.

Table 7. Summary table for the LME model of HR.

Random effects	σ^2	SD		
Subject intercept	52.09	7.217		
Residual	113.89	10.672		
Fixed effects	<i>b</i>	SE	<i>t</i>	<i>p</i>
Intercept	3.543	3.257	1.088	0.404
10 mg + 1.1 mg/min	2.461	1.245	1.976	0.085
14 mg + 1.5 m/min	4.281	1.330	3.219	0.003 **
18 mg + 1.9 mg/min	8.671	1.655	5.239	< 0.001 ***
Min -6	-2.164	3.018	-0.717	0.531
Min -4	-0.894	3.018	-0.296	0.825

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Min -2	-4.073	3.018	-1.349	0.263
Min 0	8.294	3.018	2.748	0.013 *
Min 1	16.542	3.018	5.480	< 0.001 ***
Min 2	35.548	3.018	11.777	< 0.001 ***
Min 3	23.650	3.018	7.835	< 0.001 ***
Min 4	16.437	3.018	5.446	< 0.001 ***
Min 5	16.075	3.018	5.326	< 0.001 ***
Min 6	14.344	3.018	4.752	< 0.001 ***
Min 8	14.520	3.018	4.810	< 0.001 ***
Min 10	10.358	3.018	3.431	0.002 **
Min 12	11.464	3.018	3.798	< 0.001 ***
Min 14	11.457	3.018	3.796	< 0.001 ***
Min 16	13.057	3.018	4.326	< 0.001 ***
Min 18	11.447	3.018	3.792	< 0.001 ***
Min 20	8.811	3.018	2.919	0.008 **
Min 22	10.559	3.050	3.462	0.002 **
Min 24	8.949	3.018	2.965	0.007 **
Min 26	6.279	3.018	2.080	0.070
Min 28	7.853	3.121	2.516	0.024 *
Min 30	5.632	3.161	1.782	0.126
Min 32	5.288	3.121	1.694	0.146
Min 34	3.208	3.121	1.028	0.417
Min 36	3.034	3.121	0.972	0.423
Min 38	2.876	3.121	0.921	0.440
Min 40	-0.204	3.121	-0.065	0.965
Min 42	4.384	3.121	1.404	0.248
Min 44	3.052	3.121	0.978	0.423
Min 46	0.872	3.121	0.279	0.825
Min 48	2.330	3.121	0.746	0.527
Min 50	-0.137	3.121	-0.044	0.965
Min 52	2.462	3.121	0.789	0.514

Note: Number of observations: 809, 10 subjects. P-values are FDR-corrected for multiple comparisons. Significance codes: $p < 0.05 = *$, $p < 0.01 = **$, $p < 0.001 = ***$.

2.3.3 Plasma DMT concentrations

Plasma concentrations of DMT over time for all doses of DMT are shown in Figure 9. LME analysis showed an increase in plasma concentrations of DMT for Dose 1 compared to placebo,

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which remained significant for all timepoints following bolus injection until minute 50, exhibiting a first peak at minute 2 ($\beta = 77.12, t = 9.80, p < 0.001$) and a second peak at minute 29 ($\beta = 104.59, t = 13.25, p < 0.001$) – the latter coinciding with the last blood sampling timepoint before the end of the infusion. On average, peak concentrations at the end of infusion were slightly higher than those achieved by the bolus dose. Moreover, results show added effects for all higher doses compared to Dose 1 (Dose 2: $\beta = 39.30, t = 7.22, p < 0.001$; Dose 3: $\beta = 61.72, t = 12.28, p < 0.001$; Dose 4: $\beta = 74.97, t = 11.99, p < 0.001$; Dose 5: $\beta = 99.30, t = 25.54, p < 0.001$), resulting in a significant dose-effect relationship for all doses, for all measured timepoints until minute 50 (all FDR corrected for multiple comparisons). Following the end of the infusion, plasma concentrations of DMT decreased quickly, reaching < 1 nM 90 minutes after the end of the infusion. Summary statistics can be found in Table 8. The increase in plasma levels of DMT from minutes 10-30, while subjective effects remain sustained, suggests the development of short-term psychological tolerance induced by DMT.

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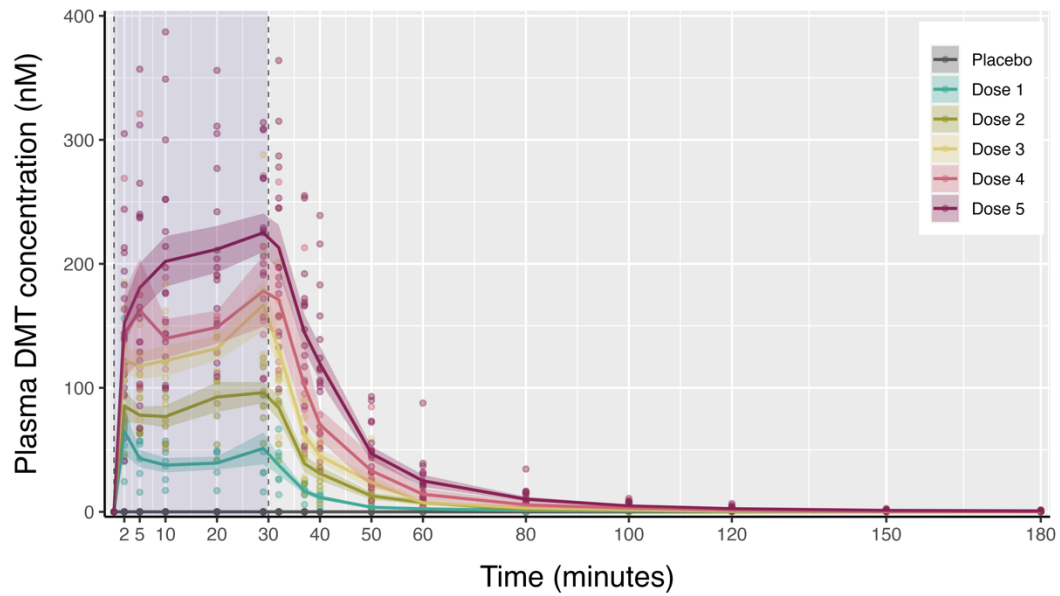


Figure 9. Plasma DMT concentrations following DMT and placebo administrations.

DMT plasma concentrations after administration of DMT fumarate IV bolus dose followed by constant-rate infusion at four dose levels (minutes 0-30). Plasma concentrations peak after bolus IV injection and before the end of the continuous IV infusion. There was a significant dose-effect relationship for all doses and measured timepoints until minute 50. The data are expressed as the mean $\pm$ SEM.

Table 8. Summary table for the LME model of plasma DMT concentrations.

Random effects	σ^2	SD		
Subject intercept	137.8	11.74		
Residual	2197.4	46.88		
Fixed effects	<i>b</i>	SE	<i>t</i>	<i>p</i>
Intercept	-42.280	6.300	-6.711	< 0.001 ***
Dose 1	21.524	5.889	3.655	< 0.001 ***
Dose 2	39.300	5.446	7.216	< 0.001 ***
Dose 3	61.722	5.026	12.281	< 0.001 ***
Dose 4	74.965	6.254	11.987	< 0.001 ***
Dose 5	99.296	3.889	25.535	< 0.001 ***
Min 2	77.117	7.868	9.802	< 0.001 ***
Min 5	82.070	7.868	10.432	< 0.001 ***
Min 10	85.494	7.868	10.867	< 0.001 ***
Min 20	93.583	7.896	11.851	< 0.001 ***
Min 29	104.588	7.896	13.245	< 0.001 ***
Min 32	91.318	7.926	11.522	< 0.001 ***
Min 37	55.309	7.956	6.952	< 0.001 ***
Min 40	43.543	7.926	5.494	< 0.001 ***
Min 50	18.067	7.958	2.270	0.033 *
Min 60	9.566	7.987	1.198	0.304
Min 80	4.297	7.987	0.538	0.689
Min 100	2.473	7.987	0.310	0.799
Min 120	1.761	8.019	0.220	0.826
Min 150	2.452	8.051	0.305	0.799
Min 180	4.841	8.155	0.594	0.683

Note: Number of observations: 1092, 26 subjects. *P*-values are FDR-corrected for multiple comparisons. Significance codes: $p < 0.05 = *$, $p < 0.01 = **$, $p < 0.001 = ***$.

2.4 Discussion

The present dose-response study tested a novel methodology to extend the typically transient DMT experience via continuous IV infusion. This was combined with a bolus loading dose to achieve prolonged effects within a short period. The results showed that IV infusions of DMT – at doses ranging from 6 mg + 0.6 mg/min to 20 mg + 2.3 mg/min – were psychologically and physiologically well tolerated, and that the protocol was effective at extending the duration of the psychological effects of DMT, achieving a steady-state of subjective effects, with low-to-negligible

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changes in anxiety. Subjective drug effects appeared within one minute of the start of the bolus injection, peaked at two minutes, and settled at a slightly lower-than-peak intensity for the duration of the infusion. Subjective drug effects decreased in intensity shortly after the end of infusion, resolving almost entirely 20 minutes after the end of infusion. Intensity of the drug effects increased dose-dependently. Ratings of anxiety generally remained low during the duration of the infusion, with a transient increase in anxiety seen just around the start of DMT administration, suggesting psychological tolerability of the tested continuous infusion protocol. An initial peak in average plasma DMT concentrations was observed corresponding to the bolus IV injection. A second increase was observed corresponding to the continuous infusion, starting at minutes 5-10 and continuing steadily until the end of infusion, at which point plasma levels dropped exponentially, reaching < 1 nM within 90 minutes of the end of infusion. Plasma DMT concentrations increased dose-dependently. Finally, HR peaked quickly after the bolus IV injection, then exhibited significant decreases with respect to baseline within 10 minutes of the start of the bolus injection, suggesting it was in part anxiety-related and showing that more prolonged infusions do not overload the autonomic system. This habituation of physiological effects, while subjective effects remain elevated, indicates the physiological safety of extended DMT infusions and is consistent with previous findings showing the development of physiological tolerance following the administration of four closely-spaced bolus injections of 20 mg of DMT fumarate (Strassman et al., 1996).

Compared with previous studies of bolus IV administration of DMT (Timmermann et al., 2019; 2023b), the duration of DMT effects in the present study was successfully extended over the course of the continuous infusion. At the end of the infusion, subjective effects resolved within a similar period of approximately 20 minutes. Compared with a previous study of bolus IV administration of DMT at different doses (Timmermann, 2020), the onset of effects appears to be comparable, with similar peak intensities reported for comparable doses. Specifically, a 7 mg bolus IV DMT dose in the previous study produced an average peak intensity of approximately 5.5 at minute 3, compared to a peak intensity of approximately 5.5 at minute 3 for Dose 1 (6mg + 0.6 mg/min) in the present study. A 14 mg bolus IV DMT dose in the previous study produced an average peak intensity of approximately 7.5 at minutes 2-3, while the peak intensity for Dose 3 (14 mg + 1.5 mg/min) at minute 2 in the present study was approximately 6. Lastly, a 18-20 mg dose in the previous study showed an average peak intensity of approximately 9.5 at minutes 2-3, whereas Dose 5 (20 mg + 2.3 mg/min) in the present study led to an average peak intensity of approximately

8.5 at minute 2. Figure 10 shows the intensity of drug effects following bolus IV administration of 20 mg DMT fumarate.

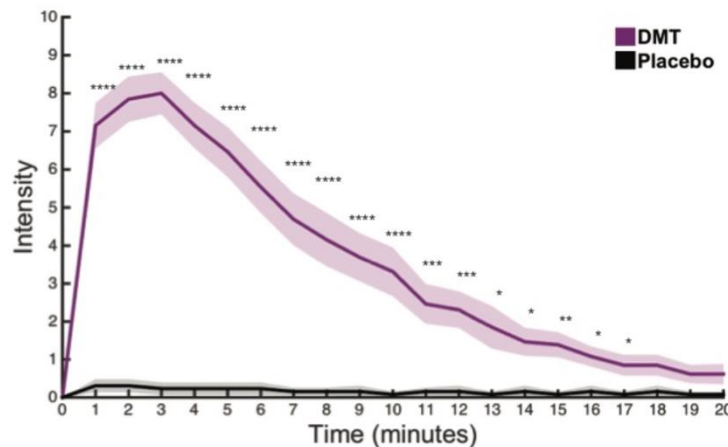


Figure 10. Intensity of effects following bolus IV administration of 20 mg DMT fumarate.

Data are shown for DMT and placebo conditions. Figure reproduced from Timmermann et al., 2019, without need for permission: CC BY 4.0.

Importantly, although subjective intensity ratings largely followed plasma concentrations of DMT during the first 15 minutes, a decoupling was observed during the second half of the infusion. While subjective intensity of drug effects decreased after an initial peak and remained stable – at specific doses with a slight downward slope – for the remainder of the infusion, plasma levels of DMT generally increased throughout the infusion. These findings may suggest a progressive development of acute psychological tolerance to DMT during continuous infusion, a finding not seen in previous studies employing this compound. One potential explanation for the dissociation between subjective intensity and DMT plasma concentrations in the later part of the infusion is the development of psychological habituation to the effects over time, i.e., effects of the same strength loose salience over time. In contrast, sharp transitions (i.e., as the one induced by the bolus) induce a stronger psychological response. However, the observed individual variability makes it difficult to draw final conclusions based on this analysis. Future studies are needed to address the

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cause and extent of short-term tolerance induced by continuous DMT to better understand and develop infusion protocols that elicit desired subjective effects.

While the initially planned Doses 1-4 did not elicit the desired effects, peak effects of Dose 5 reached the targeted subjective intensity > 7.5 , making it a moderately high yet tolerable dose. Additionally, the effects of Dose 5 remained relatively stable over the duration of the infusion, resulting in a stable extended immersion in the DMT state. Therefore, Dose 5 was chosen for use in the subsequent studies investigating the phenomenology, subjective, and EEG effects of extended DMT, detailed in Chapters 3 and 4.

This pilot study tested a novel method of DMT administration and assessed the stability and tolerability of different doses of the drug delivered via continuous IV infusions. DMT exhibits PK properties that make it suitable for continuous IV infusion, and this study demonstrated the safety and feasibility of this method of administration. Continuous IV infusions of DMT administered in doses of up to 20 mg + 2.3 mg/min were psychologically and physiologically well-tolerated in healthy, psychedelic-experienced volunteers. No significant acute or persistent adverse effects were observed. It is important to note some limitations of this study. Firstly, this study was conducted on a small sample of eleven participants. Due to the small number of resulting observations, the effects of Dose 1 compared to placebo were tested, and the added effects of higher doses compared to Dose 1. Dose-related effects between higher doses were only assessed qualitatively. Future studies with larger sample sizes may be able to investigate the differences between each pair of doses of interest. Secondly, due to safety considerations (i.e., participants receiving a maximum of four DMT doses) and dropouts, there was variability in doses administered, with not all participants receiving all doses investigated. Relatedly, although several of the dropouts occurred for personal reasons, it is impossible to rule out the possibility that participants did not wish to receive more doses. However, it is essential to acknowledge that all tested doses seemed psychologically safe for most participants, as can be seen from ratings of anxiety and the adverse events presented in Table 4. Lastly, this study adopted a fixed-order design and thus, order effects may have occurred. While the results are not consistent with the development of long-term tolerance to DMT, it is still possible that some order effects may have occurred due to psychological reasons (i.e., participants guessing the order of administration). Future studies could directly test the occurrence of order effects by asking participants to guess the order of doses administered.

This study lays the groundwork for the subsequent studies detailed in Chapters 3 and 4, which explore the phenomenology, subjective, and neurobiological effects of extended DMT administration and its unique state of consciousness.

3. Phenomenology and subjective effects of continuous IV infusions of DMT

3.1 Introduction

The phenomenology of altered states of consciousness induced by psychoactive substances has long been a topic of specific interest for philosophers, researchers, and clinicians and has provided important information in the context of consciousness research. Among the classic psychedelics, DMT holds a unique position due to its short duration of action and its profound and often ineffable effects. Traditionally, DMT has been studied primarily in the context of brief experiences induced through inhalation or IV injections (Strassman, 1995; Timmermann et al., 2023b; Timmermann et al., 2019). Reports which characterise the psychedelic effects of ayahuasca lend themselves to the study of DMT, even though these related substances exhibit strikingly different pharmacological and PK properties (for details, see Chapter 1 – “Introduction”, section [1.2.4](#) – “Routes of administration”). Specifically, these reports have described the visual phenomena (geometric motifs, story-like “visions”, occasional entity encounters), and prominent somatic effects, with purging often interpreted as cleansing and integral to the process. Additionally, experiences frequently involve emotional catharsis or existential insight, and a sense of guidance or “teaching” (Shanon, 2002; Wolff et al., 2019).

Early investigations into the phenomenology and subjective effects of DMT can be found in the form of anecdotal reports, editorial, non-peer-reviewed contributions and popular science literature (Richards, 2015; Shanon, 2002; Strassman, 2000). More recently, efforts to understand the unique DMT experience and its specific characteristics have increased, and more rigorous methodologies have been employed, including interventional clinical research studies (Gouzoulis-Mayfrank et al., 2005; Timmermann et al., 2023b; Timmermann et al., 2019; Valle et al., 2016), naturalistic field research (Pallavicini et al., 2020), and large-scale retrospective surveys (Cott and Rock, 2008; Davis et al., 2020b; Griffiths et al., 2019; Lawrence et al., 2022; Michael et al., 2021).

Methods applied to investigate the psychedelic effects of DMT include validated psychometric scales, retrospective surveys and qualitative interviews. Using these methods, various characteristic

3. Phenomenology and subjective effects of continuous IV infusions of DMT

changes in perception, mood and cognition have been associated with the DMT experience. The most frequently reported features include perceptual changes, such as simple imagery (vivid colours, geometric patterns) and complex imagery (objects, faces, scenes), which can occur with both open and closed eyes (Cott and Rock, 2008; Strassman, 2000; Strassman et al., 1994b). Other perceptual changes include somatosensory effects such as bodily sensations and auditory hallucinations. A range of emotional effects have also been observed with the DMT experience, ranging from anxiety, confusion, and overwhelming feelings (Brito-da-Costa et al., 2020; Cott and Rock, 2008; Strassman, 2000) to positive mood and feelings of bliss (Davis et al., 2020b; Strassman, 2000). The DMT experience has been described as highly immersive, with one of the most distinct features being a feeling of entering an alternate ‘world’ or ‘reality’, often deemed ‘more real than everyday reality’ (Cott and Rock, 2008; Strassman, 2000). Another puzzling feature of the DMT experience is the sense of encountering sentient ‘entities’ or ‘beings’, which are perceived as intelligent and wanting to communicate ‘useful information’ (Cott and Rock, 2008; Davis et al., 2020b; Luke et al., 2011; Michael et al., 2021; Strassman, 2000). This is sometimes accompanied by a sense of familiarity, described as a ‘having been here before’, ‘belonging’, or ‘coming home’ (Cott and Rock, 2008; Davis et al., 2020b; Lawrence et al., 2022; Michael et al., 2021; Shanon 2002, Strassman, 2000). Many DMT experiences satisfy the criteria for mystical-type experiences (Griffiths et al., 2019) and are seen as profound, frequently leading to lasting changes in attitudes and beliefs (Cott and Rock, 2008; Davis et al., 2020b; Griffiths et al., 2019; Amaringo and Luna, 1999; Strassman, 2000; Timmermann et al., 2021).

Most of the measures employed to date investigate the DMT experience as a whole, and little research has explored the trajectory and dynamics of the DMT phenomenology throughout its psychoactive action. This is further exacerbated by the short duration of DMT’s subjective effects – the effects of IV DMT peak within 2-5 minutes after administration and subside within 20 minutes. Inhaled DMT shows a similar time course. IM DMT, although showing a more prolonged activity, has been less frequently studied. As a result, little data describes the dynamics of DMT experiences over time. Attempts have been made to map the ayahuasca experience and its progression over time, with suggestions that experiences tend to progress from faint elementary imagery of colours and shapes towards clear, complex and figurative imagery of scenes and alternate realities, higher richness, higher narrative complexity, higher levels of immersion and interaction, and more psychological significance and spiritual impact (Shanon, 2002). More recently, Timmermann et al. (2019) employed micro-phenomenological interviews and three identified

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dimensions of experience (i.e., visual, bodily, metacognitive/emotional) to inform EEG analyses in a neurophenomenological approach.

While inhalation is the preferred method of consumption in recreational settings (Winstock et al., 2014) and bolus IV administration has been the method of choice in clinical research settings, recent studies, including the one outlined in Chapter 2, have started to explore continuous IV infusions as a novel method of administration for DMT (Luan et al., 2023; Vogt et al., 2023). Using constant slow-rate infusions, with or without a bolus loading dose, the psychedelic effects of DMT were found to be maintained over time. Given the novelty of this DMT administration method, no studies exist investigating the phenomenology and subjective experience of extended DMT administration. Characterising its effects and drawing comparisons to those seen with other methods of DMT administration is an important avenue to explore.

The current chapter aims to investigate the phenomenology and subjective effects of continuous IV administrations of DMT in healthy participants, with the objective to characterise the phenomenology of the extended infusion experience, using validated questionnaires, VAS scales, experience-sampling, and micro-phenomenological interviews. This chapter combines the data from the first study detailed in Chapter 2 with data from an additional study which investigated the effects of a moderately high dose of extended DMT, resulting in a rich dataset of subjective effects and phenomenology of extended DMT infusions at different doses. In these studies, the main goal was to extend the peak effects of DMT in a stable fashion over the duration of the infusion, and this was achieved with dosing regimens of different target intensities of effects.

The effects of extended DMT will be described using a combination of an acute ESM, post-acute static (averaging the experience over time) and dynamic (following the trajectory of the experience over time) psychometric scales, and post-acute micro-phenomenological interviews. The chosen measures are a combination of validated psychometric scales (i.e., the Altered States of Consciousness [ASC] Scale, the Mystical Experience Questionnaire [MEQ-30], the Ego Dissolution Inventory [EDI], the Emotional Breakthrough Inventory [EBI], and the Challenging Experiences Questionnaire [CEQ]) and measures that cover the most characteristic facets of the DMT experience, as judged from results of previous studies on the subjective effects of DMT. This approach will allow for a comparison of the effects of extended DMT with previous findings of inhaled and IV DMT, as well as for a closer exploration of the dynamics of the extended DMT experience over the duration of the infusion, harnessing the unique opportunity provided by the prolonged immersion into the DMT experience provided by the current method of DMT administration. It was hypothesised that 1) extended DMT infusions will induce significant

alterations in subjective experience, including significant increases in ratings of altered states of consciousness, mystical-type experience, ego dissolution, and emotional breakthrough, and 2) dose-response relationships will be found for the effects of doses on the resulting subjective effects.

3.2 Methods

3.2.1 Study design and participants

In two single-blind, placebo-controlled fixed-order studies using a within-subjects repeated measures design, 11 healthy volunteers (seven male, four female, mean age $\pm$ SD = 37.09 ± 8.93 years, range = 26-51 years) received up to four different doses of extended IV DMT, and an additional 15 healthy volunteers (ten male, five female, mean age $\pm$ SD = 41.54 ± 11.75) received a single moderately high dose of extended DMT. Extended IV DMT administrations consisted of a bolus loading dose plus slow-rate infusions of DMT over 30 minutes. Dose regimens and participant inclusion criteria are detailed in Chapter 2 – “*Dose-finding study of continuous IV infusions of DMT*”, [section 2.2](#) – “*Methods*”. Table 9 shows the doses administered to subjects across both studies.

Table 9. Dosing schedule of continuous IV infusions of DMT across both studies.

Doses are expressed for DMT fumarate. A bolus injection was given over 30 seconds, followed by a saline flush over 15 seconds. The continuous slow-rate infusion was started one minute after the beginning of the bolus injection and maintained for 29 minutes.

	Bolus (mg)	Inf (mg/min)	Total (mg)	Participants (n)
Dose 1	6	0.63	24.19	6
Dose 2	10	1.05	40.32	10
Dose 3	14	1.46	56.45	9
Dose 4	18	1.88	72.58	6
Dose 5	20	2.27	85.83	20

3.2.2 Study procedures

A detailed description of the study procedures can be found in Chapter 2 – “*Dose-finding study of continuous IV infusions of DMT*”, section [2.2.4](#) “*Study procedures*”. All dosing visits took place in a calm, decorated ICRF hospital room. Participants were in a semi-supine position for dosing, and a body scan meditation was performed shortly before dosing to help participants relax. During dosing, participants wore an eye mask and were instructed to keep their eyes closed. Low-volume ambient music was played through headphones throughout the infusion. DMT was administered for 30 minutes, and acute effects were recorded for at least 52 minutes following the start of administration. Once the acute drug effects had subsided, participants completed a range of measures inquiring about their experience, which comprise the data presented in this chapter.

3.2.2.1 Static measures

A range of rating scales and validated questionnaires were used to capture the extended DMT experience as a whole. Visual Analogue Scales (VAS), the ASC Scale and the MEQ-30 were completed once the acute drug effects had subsided (approximately 30 minutes following the end of administration). The EDI, EBI, and CEQ were completed approximately three hours following the end of the DMT administration to prioritise other dynamic measures (see below).

3.2.2.1.1 VAS scales. To characterise the subjective experiences induced by DMT, participants were asked to complete a series of VAS scales. Items were based on psychedelic effects seen in previous studies on both other classic psychedelics (Carhart-Harris et al., 2012a; Carhart-Harris et al., 2016b; Muthukumaraswamy et al., 2013) and DMT (Gouzoulis-Mayfrank et al., 2005; Sai-Halász et al., 1958; Strassman et al., 1994b; Timmermann et al., 2019; Timmermann et al., 2023b). In total, 28 items were administered. Items were rated on a scale from 0 (“no, not at all”) to 100 (“most imaginable”). The wording for each item can be found in Table 10.

Table 10. Wording of VAS items.

Items were rated on a sliding scale from 0 (“no, not at all”) to 100 (“most imaginable”).

Item	Wording
1	How intense was the overall drug experience?
2	I experienced a disintegration of my usual sense of ‘self’ or ‘ego’
3	I saw geometric patterns
4	I experienced elaborate/complex visual images
5	I experienced the presence of another sentient being or beings, not including the people in the room
6	I experienced a different reality or dimension
7	The experience felt more “real” than this reality
8	I felt unusual bodily sensations
9	My sense of size or space was altered
10	I felt that energy was flowing through my body
11	I saw a white light
12	I lost consciousness at some point during the experience
13	I felt I was going to die, or that I was dead
14	My sense of time was altered
15	I felt a general sense of gratitude
16	I felt open/sensitive to all emotions (good or bad)
17	I felt I was displaced from my body
18	The experience was pleasurable
19	The experience was challenging
20	The experience was meaningful
21	How ‘rich’ was your conscious experience
22	How ‘rich’ was your visual experience
23	I felt I was experiencing everything one could ever possibly experience, all at once
24	I experienced beauty
25	I was able to let go of fixed ideas or notions that were limiting my thinking
26	I was able to let go of anxious feelings that I previously had
27	I had valuable insights concerning myself or my relationships
28	I had insights concerning the nature of reality or consciousness

3.2.2.1.2 Altered States of Consciousness (ASC) scale. The ASC scale is a validated measure widely used to assess various dimensions of altered states of consciousness. The 94 items make up five dimensions (5D-ASC; ‘Oceanic boundlessness’, ‘Anxious ego dissolution’, ‘Visionary restructuration’, ‘Auditory alterations’, and ‘Reduced vigilance’ (Dittrich, 1998), and 11 lower-order scales (11D-ASC; ‘Experience of Unity’, ‘Spiritual Experiences’, ‘Blissful State’, ‘Insightfulness’,

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‘Disembodiment’, ‘Impaired Control and Cognition’, ‘Anxiety’, ‘Complex Imagery’, ‘Elementary Imagery’, ‘Audio-Visual Synesthesia’, and ‘Changed Meaning of Percepts’ (Studerus et al., 2010). Items are scored on a Likert scale ranging from 0 (not at all) to 100 (extremely). Scores for each dimension are calculated by averaging the ratings of the items within that dimension. Higher scores indicate stronger experiences of the particular aspect of altered states of consciousness.

3.2.2.1.3 Mystical Experience Questionnaire. The Mystical Experience Questionnaire assesses the characteristics and intensity of mystical-type experiences. It was initially developed by (Pahnke and Richards, 1966) and based on the anthropological research and theoretical writings of philosopher Walter Stace (1960), who posited common and universal experiential components of mystical-type experiences. The revised Mystical Experience Questionnaire includes 30 questions (MEQ-30; Barrett et al., 2015; MacLean et al., 2012), sorted into four scale scores: ‘Mystical’, ‘Positive mood’, ‘Transcendence of time and space’, and ‘Ineffability’ (Barrett et al., 2015). Items are rated on a Likert scale ranging from 0 (none, not at all) to 5 (extreme; more than ever before in my life). Scores for each dimension are calculated by averaging the ratings of the relevant items. The total MEQ-30 score is calculated as the average of all 30 items and then multiplied by 20 to provide a 0-100 value. The MEQ-30 has been validated in several studies, demonstrating good psychometric properties, and has been shown to predict positive outcomes in therapeutic settings (Barrett et al., 2015; MacLean et al., 2012).

3.2.2.1.4 Ego Dissolution Inventory (EDI). The EDI measures the extent of ego dissolution experienced in the context of altered states of consciousness, with ego dissolution referring to a temporary reduction or loss of the subjective sense of self, leading to a feeling of unity with the surroundings or universe. The EDI includes items that reflect different dimensions of ego dissolution, such as ‘Loss of boundaries between self and environment’, ‘Feeling of unity with surroundings’, ‘Altered sense of time’, ‘Diminished self-importance’, and ‘Transcendence of personal identity’. Items are rated on a Likert scale ranging from 0 (“not at all”) to 100 (“extremely”), with higher scores indicating greater levels of ego dissolution. The scores of each item are averaged to produce an overall EDI score, with higher scores indicating more intense experiences of ego dissolution. The EDI has been validated and has been shown to effectively characterise and test the subjective experience of ego dissolution and correlate with other measures of altered states of consciousness (Nour et al., 2016).

3.2.2.1.5 Emotional Breakthrough Inventory (EBI). The EBI assesses the extent of emotional breakthrough experiences by individuals, with emotional breakthroughs being defined as profound emotional experiences that can lead to significant personal insights, emotional release, and

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psychological transformation. The six items are rated on a Likert scale ranging from 0 (“not at all”) to 4 (“extremely”). Average scores are calculated by summing up all item ratings and dividing by six to produce a 0-100 value (Roseman et al., 2019).

3.2.2.1.6 Challenging Experience Questionnaire (CEQ). The CEQ assesses the nature and intensity of challenging or difficult experiences during altered states of consciousness (Barrett et al., 2016). The CEQ is derived from ‘challenging’ items from the Hallucinogen Rating Scale (HRS; Strassman et al., 1994b), the ASC (Dittrich, 1998), and the States of Consciousness Questionnaire (SOCQ; Griffiths et al., 2006). The CEQ includes 26 items that reflect seven dimensions of challenging experiences, including ‘Fear’, ‘Grief’, ‘Physical Distress’, ‘Insanity’, ‘Isolation’, ‘Death’, and ‘Paranoia’. Items are rated on a Likert scale, ranging from 0 (“not at all”) to 5 (“extremely”), with higher scores indicating more intense challenging experiences. Scores for each dimension are calculated by averaging the ratings of the relevant items. The total CEQ score is calculated as the average of all items and then multiplied by 20 to provide a 0-100 value.

3.2.2.1.7 Statistical analyses. The data were analysed using R (version 4.2.2; R Core Team, 2013). LME models were used to investigate the effect of Dose on the above dependent variables. LME models exhibit several advantages over repeated measures ANOVAs in dealing with the present data: 1) LME models control for the potential influence of random variables (i.e., subject-driven interindividual variability) by including them as random effects; 2) LME models can cope with missing data; and 3) they can include grouping hierarchies such as the present partially-crossed groups (i.e., some subjects received multiple but never all DMT doses).

LME models were fitted using the *lmer* function from the *lme4* package (Bates et al., 2015). Models included ‘Dose’ as the fixed effect and ‘Participant’ as a random effect to account for individual differences. The resulting model was specified as

$$\text{Dependent variable} \sim \text{Dose} + (1 | \text{Participant}),$$

where dependent variables were VAS items, 5D-ASC subscales, 11D-ASC subscales, MEQ-30 subscales, EDI total score, EBI total score, and CEQ total score, respectively.

For all mixed models, significance was estimated via the *lmerTest* package (Kuznetsova et al., 2017), and FDR correction was used to adjust for multiple comparisons (Benjamini and Hochberg, 1995), with significance established at $p < 0.05$.

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3.2.2.2 Dynamic measures

Several dynamic measures were employed to complement the above detailed static measures and explore the trajectory of the extended DMT experience over time, including an acute ESM of 'Entities', Micro-phenomenological interviews, and dynamic VAS scales.

3.2.2.2.1 ESM of 'Entities'. ESM was used to assess several key subjective effects acutely. For this, audio prompts were played through headphones, and participants were instructed to respond verbally. Resulting ratings of 'Intensity' and 'Anxiety' were presented in Chapter 2 (*"Dose finding study of continuous IV infusions of DMT"*). For Dose 5, ratings of 'Anxiety' were replaced by ratings of 'Entities' to study this intriguing phenomenon more closely. Ratings were collected at -8, -4, 0, 1, 2, 3, 4, and every four minutes thereafter, with minute 0 starting the bolus injection. Participants were instructed to consider the period since the last rating and give a "yes" or "no" answer whether they had experienced a sentient presence or 'entity'.

3.2.2.2.2 Micro-phenomenological interviews. Micro-phenomenological interviews (Petitmengin, 2006; Petitmengin and Lachaux, 2013) were conducted approximately one hour after the end of DMT administration to gather a systematic retrospective account of the experience and its progression over time. To facilitate remembering the fleeting experience, acute subjective ratings of intensity (see [Chapter 2](#) – *"Dose-finding study of continuous IV infusions of DMT"*) were used to anchor the experience. A thematic data analysis approach was used to identify key categories of the experience, and a micro-phenomenological-inspired analysis (Petitmengin et al., 2019) was used to assess the temporal progression of categories and to reveal possible generic diachronic structures of the experience. Specifically, the interviews were transcribed, and sections that did not describe the acute subjective experience were removed. The remaining sections were re-ordered to represent the timeline of the experience. The transcript was then broken down into subsections, and each subsection was assigned to a phenomenological category in an iterative, bottom-up fashion. After completing this for all interviews, similar categories were grouped and assigned to a theme. As a next step, separate phenomenological phases within each experience were identified using linguistic indicators of temporal shifts (i.e., "then", "after"), and the order in which categories emerged was compared between interviews to identify common patterns across interviews. The analysis presented here will focus on the process of acclimation, i.e. the progression of struggle and its resolution within the experience. For this, 20 interviews conducted after Dose 5 were included in the analysis.

3.2.2.2.3 Dynamic VAS scales. After the conclusion of the micro-phenomenological interview, participants were asked to complete VAS scales with a time dimension to retrospectively provide

ratings of various categories of their experience over time. Ratings were given on a scale from 0 = “none/not at all” to 10 = “an extreme amount/extremely”. Categories included ‘Immersion’, ‘Entity encounters’, ‘Ego dissolution’, ‘Visual imagery’, ‘Emotional experience’, ‘Auditory hallucinations’, ‘Bodily dissociation’, ‘Bodily sensations’, ‘Meaningfulness’, ‘Metacognition’, ‘Overall richness’, and ‘Visual richness’ over time. The definitions for each item can be found in Table 11.

Table 11. Definitions for dynamic VAS items.

Items were rated on a scale from 0 = “no/not more than usual” to 10 = “most imaginable”.

Item	Definition
Immersion	Feeling of being immersed or absorbed into a ‘space’ separate from the experimental environment
Entity encounters	Intensity of sensing a presence
Ego dissolution	Loosening of the distinction between the ‘self’ and the environment
Visual imagery	Perception of images with eyes closed
Emotional experience	Intensity of emotional content
Auditory hallucinations	Hearing sounds not originating from the experimental environment
Bodily dissociation	Losing awareness of the body
Bodily sensations	Effects felt in the body
Meaningful	How meaningful did the experience feel?
Metacognition	‘Processing’ the experience
Overall ‘richness’	How ‘rich’ did the experience feel in terms of richness of contents?
Visual ‘richness’	How ‘rich’ did the visual experience feel in terms of richness of contents?

3.3 Results

Figure 2 shows the number of datasets collected for each dose. Additionally, some missingness was observed. One participant did not complete the EDI, EBI, CEQ, and dynamic VAS scales after the placebo dose. One participant did not complete the ‘Metacognition’ and ‘Overall richness’ items of the dynamic VAS scale after the placebo dose. One participant did not

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complete the EDI, EBI, CEQ, and dynamic VAS scales after Dose 4. Finally, one participant did not complete the EDI, EBI, and CEQ after Dose 5.

3.3.1 Static measures

3.3.1.1 VAS-scales

Figure 11 shows VAS scores for all items and all doses of DMT and placebo. The highest ratings were seen on items related to the intensity and richness of the drug experience, visual effects, bodily effects, and experiencing a different reality. Conversely, the lowest ratings were seen on items related to seeing a white light, losing consciousness, and feeling like one was dying. Ratings were generally higher for higher doses, although Dose 1 showed higher ratings than Doses 2 and 3 on several items. LME models showed significant dose-response relationships between dose levels and scores on all VAS items except 'I lost consciousness at some point during the experience'. Summary statistics for the LME analyses can be found in Table 12.

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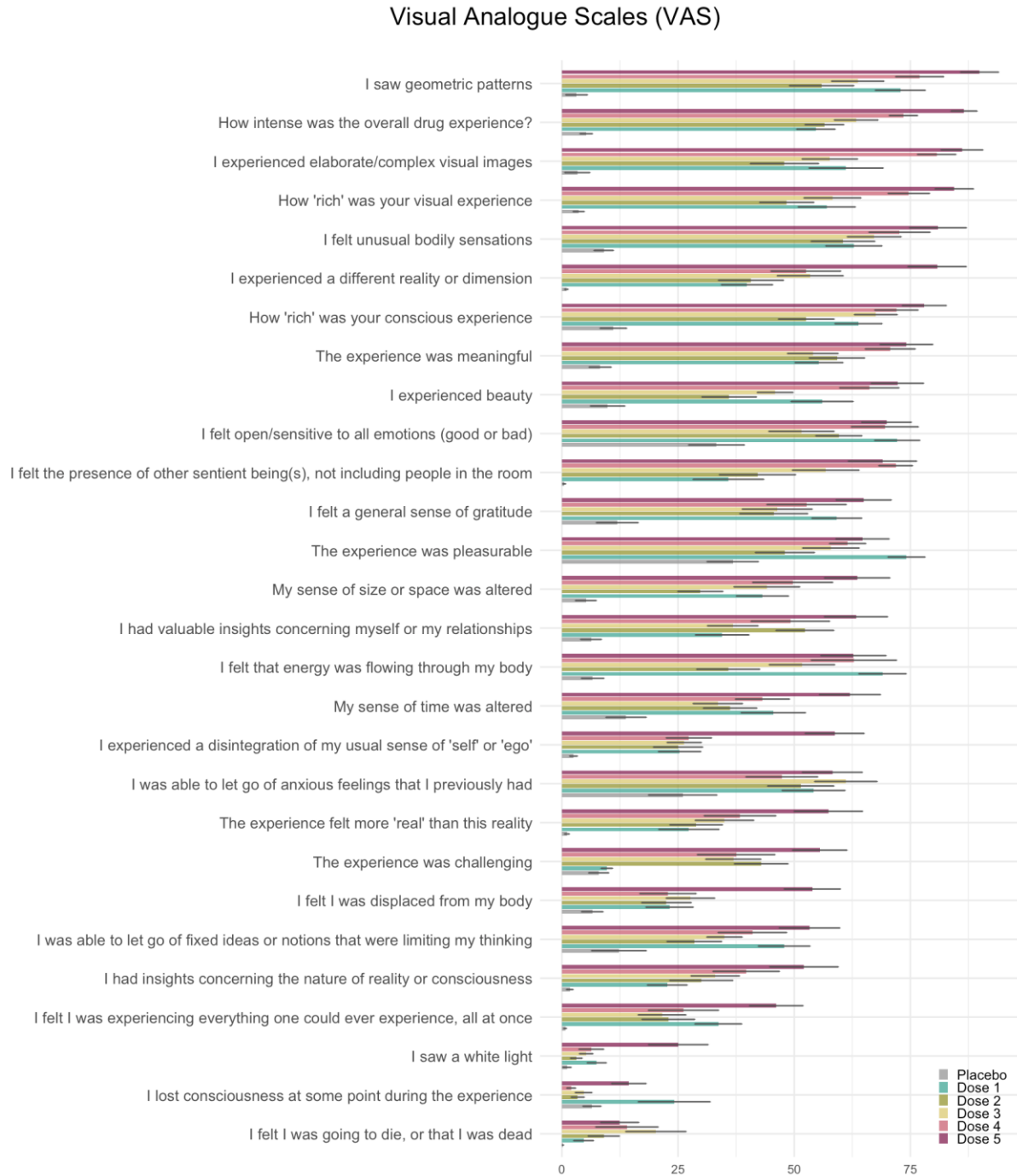


Figure 11. Effects of different doses of DMT and placebo on VAS scales.

Mean scores $\pm$ SEM are shown for all VAS items, sorted by the mean score of Dose 5. Placebo (n=26), Dose 1 (n=6) = 0.6 mg + 0.6 mg/min, Dose 2 (n=10) = 1.0 mg + 1.1 mg/min, Dose 3 (n=9) = 1.4 mg+ 1.5 mg/min, Dose 4 (n=6) = 18 mg + 1.9 mg/min, Dose 5 (n=20) = 20 mg + 2.3 mg/min.

Table 12. Summary table for the LME models of VAS items.

VAS item	<i>b</i>	<i>SE</i>	<i>df</i>	<i>t</i>	<i>p</i>
How intense was the overall drug experience?	0.961	0.045	56	21.39	< 0.001
I experienced a disintegration of my usual sense of 'self' or 'ego'	0.613	0.064	55	9.63	< 0.001
I saw geometric patterns	0.993	0.069	59	14.34	< 0.001
I experienced elaborate/complex visual images	0.971	0.074	56	13.20	< 0.001
I felt the presence of other sentient being(s), not including people in the room	0.834	0.086	58	9.71	< 0.001
I experienced a different reality or dimension	0.908	0.073	57	12.53	< 0.001
The experience felt more 'real' than this reality	0.648	0.070	56	9.20	< 0.001
I felt unusual bodily sensations	0.858	0.070	55	12.32	< 0.001
My sense of size or space was altered	0.688	0.072	55	9.53	< 0.001
I felt that energy was flowing through my body	0.666	0.087	56	7.69	< 0.001
I saw a white light	0.237	0.049	49	4.81	< 0.001
I lost consciousness at some point during the experience	0.045	0.055	65	0.81	0.419
I felt I was going to die, or that I was dead	0.183	0.052	58	3.53	0.001
My sense of time was altered	0.512	0.089	60	5.78	< 0.001
I felt a general sense of gratitude	0.593	0.086	57	6.91	< 0.001
I felt open/sensitive to all emotions (good or bad)	0.422	0.088	58	4.81	< 0.001
I felt I was displaced from my body	0.528	0.071	58	7.41	< 0.001
The experience was pleasurable	0.313	0.081	54	3.86	< 0.001
The experience was challenging	0.557	0.075	59	7.44	< 0.001
The experience was meaningful	0.795	0.068	57	11.65	< 0.001
How 'rich' was your conscious experience	0.812	0.063	53	12.81	< 0.001
How 'rich' was your visual experience	0.947	0.059	56	16.09	< 0.001
I felt I was experiencing everything one could ever experience, all at once	0.507	0.068	56	7.43	< 0.001
I experienced beauty	0.744	0.064	51	11.58	< 0.001
I was able to let go of fixed ideas or notions that were limiting my thinking	0.462	0.087	54	5.32	< 0.001
I was able to let go of anxious feelings that I previously had	0.384	0.101	56	3.80	< 0.001
I had valuable insights concerning myself or my relationships	0.643	0.083	59	7.88	< 0.001
I had insights concerning the nature of reality or consciousness	0.592	0.066	55	9.00	< 0.001

3.3.1.2 5D-ASC

Figure 12 shows the scores of all 5D-ASC dimensions for each dose of DMT and placebo. The highest ratings were given on the dimension 'Visionary restructuralization'. All DMT doses show higher ratings than placebo on all dimensions except 'Vigilance reduction'. Higher doses generally show higher ratings for the remaining dimensions, with Dose 5 ratings showing the biggest visible difference to lower doses. LME modelling indicated significant dose-response relationships for 5D-ASC dimensions 'Oceanic boundlessness' ($b = 0.471$, $SE = 0.045$, $t[53] = 10.44$, $p < 0.001$), 'Dread of ego dissolution' ($b = 0.169$, $SE = 0.031$, $t[55] = 5.52$, $p < 0.001$), 'Visionary restructuralisation' ($b = 0.426$, $SE = 0.038$, $t[56] = 11.28$, $p < 0.001$), and 'Auditory alterations' ($b = 0.146$, $SE = 0.022$, $t[52] = 6.650$, $p < 0.001$). No dose-response relationship was found for 'Vigilance reduction'.

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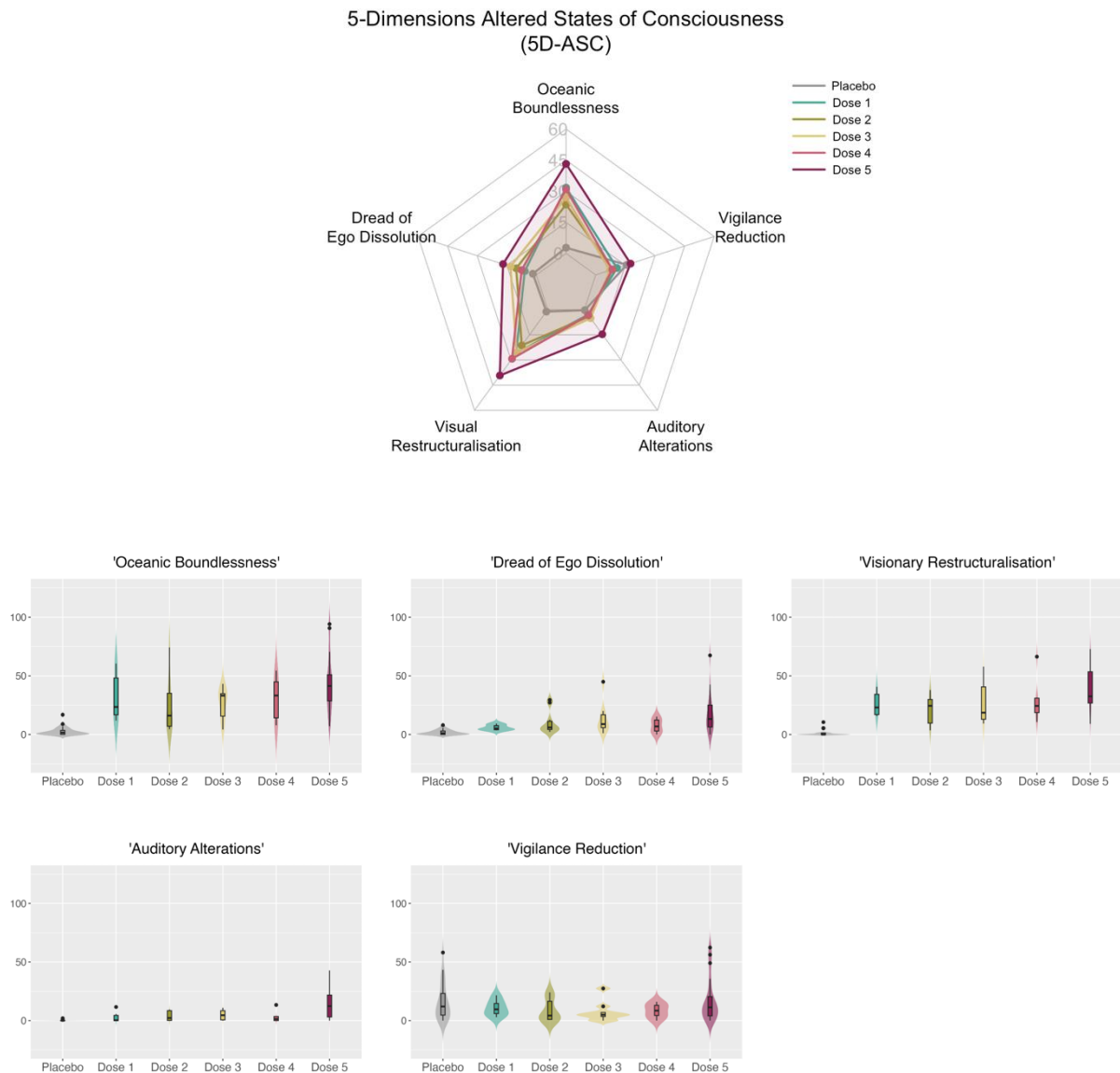


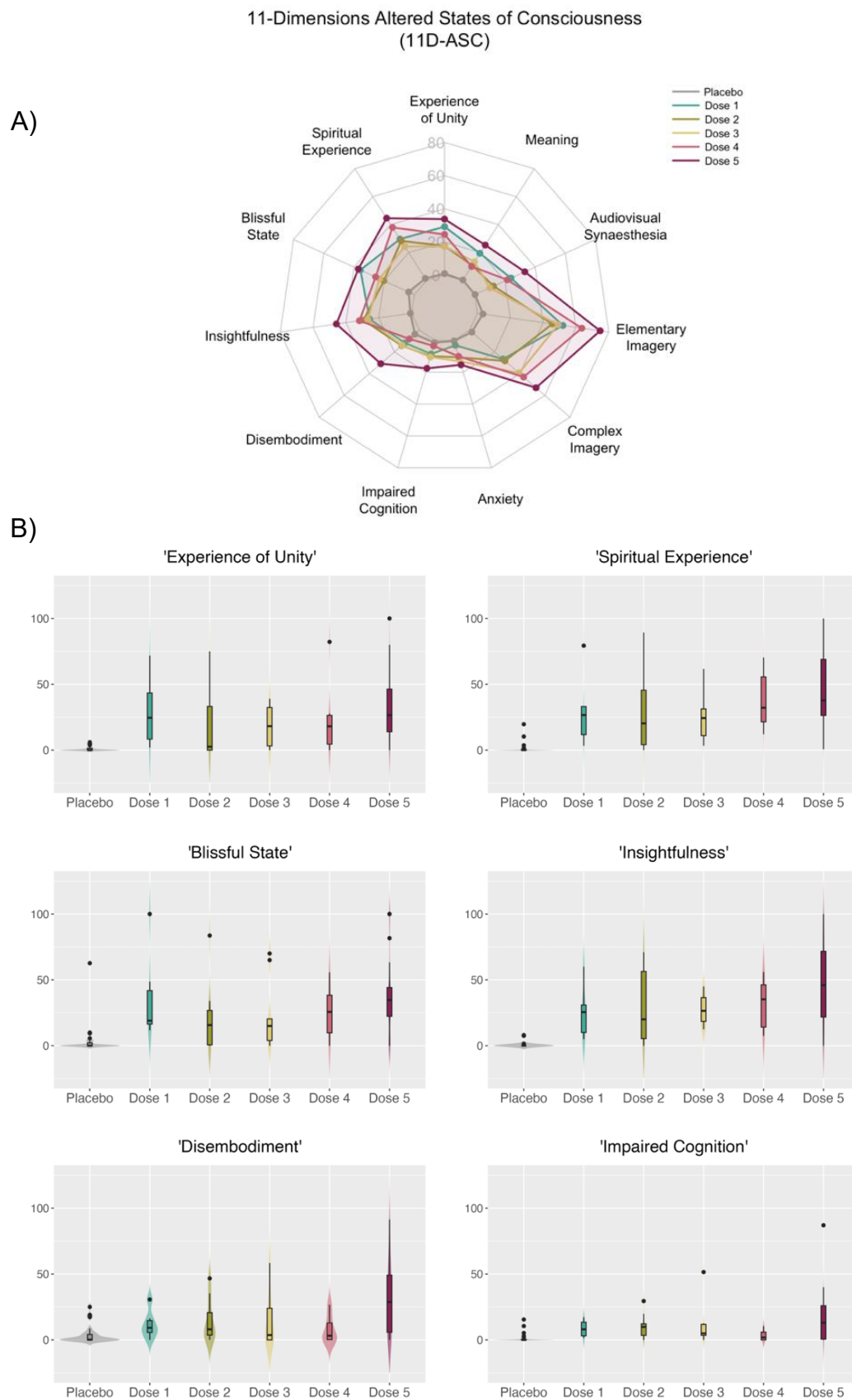
Figure 12. Effects of different doses of DMT and placebo on 5D-ASC dimensions.

(A) Radar chart showing mean scores of each 5D-ASC dimension for each dose, (B) Scores of each 5D-ASC dimension and each dose presented as boxplots, indicating the median and interquartile range, overlaid with violin plots outlining the distribution of data. Placebo (n=26), Dose 1 (n=6) = 0.6 mg + 0.6 mg/min, Dose 2 (n=10) = 1.0 mg + 1.1 mg/min, Dose 3 (n=9) = 1.4 mg + 1.5 mg/min, Dose 4 (n=6) = 18 mg + 1.9 mg/min, Dose 5 (n=20) = 20 mg + 2.3 mg/min.

3.3.1.3 11D-ASC

Figure 13 shows the scores of each 11D-ASC dimension for all doses. All DMT doses show higher ratings than placebo on all 11D-ASC dimensions, and higher doses generally score higher than lower doses. Several dimensions show higher ratings on Dose 1 than on higher doses, including ‘Experience of unity’, ‘Blissful state’, ‘Elementary imagery’, ‘Audio-visual synaesthesia’, and ‘Meaning’. ‘Elementary imagery’ and ‘Complex imagery’ were scored highest, to the degree that a ceiling effect is visible with higher doses. LME modelling indicated significant dose-response relationships for all 11D-ASC dimensions. Specifically, ‘Experience of unity’ ($b = 0.386$, $SE = 0.055$, $t[54] = 7.06$, $p < 0.001$), ‘Spiritual experience’ ($b = 0.508$, $SE = 0.054$, $t[54] = 9.47$, $p < 0.001$), ‘Blissful state’ ($b = 0.401$, $SE = 0.062$, $t[50] = 6.458$, $p < 0.001$), ‘Insightfulness’ ($b = 0.519$, $SE = 0.059$, $t[55] = 8.78$, $p < 0.001$), ‘Disembodiment’ ($b = 0.286$, $SE = 0.050$, $t[53] = 5.77$, $p < 0.001$), ‘Impaired cognition’ ($b = 0.173$, $SE = 0.037$, $t[52] = 4.67$, $p < 0.001$), ‘Anxiety’ ($b = 0.179$, $SE = 0.039$, $t[57] = 4.61$, $p < 0.001$), ‘Complex imagery’ ($b = 0.584$, $SE = 0.056$, $t[57] = 10.40$, $p < 0.001$), ‘Elementary imagery’ ($b = 0.808$, $SE = 0.063$, $t[57] = 12.82$, $p < 0.001$), ‘Audio-visual synaesthesia’ ($b = 0.344$, $SE = 0.068$, $t[58] = 5.09$, $p < 0.001$), and ‘Meaning’ ($b = 0.269$, $SE = 0.045$, $t[52] = 6.00$, $p < 0.001$).

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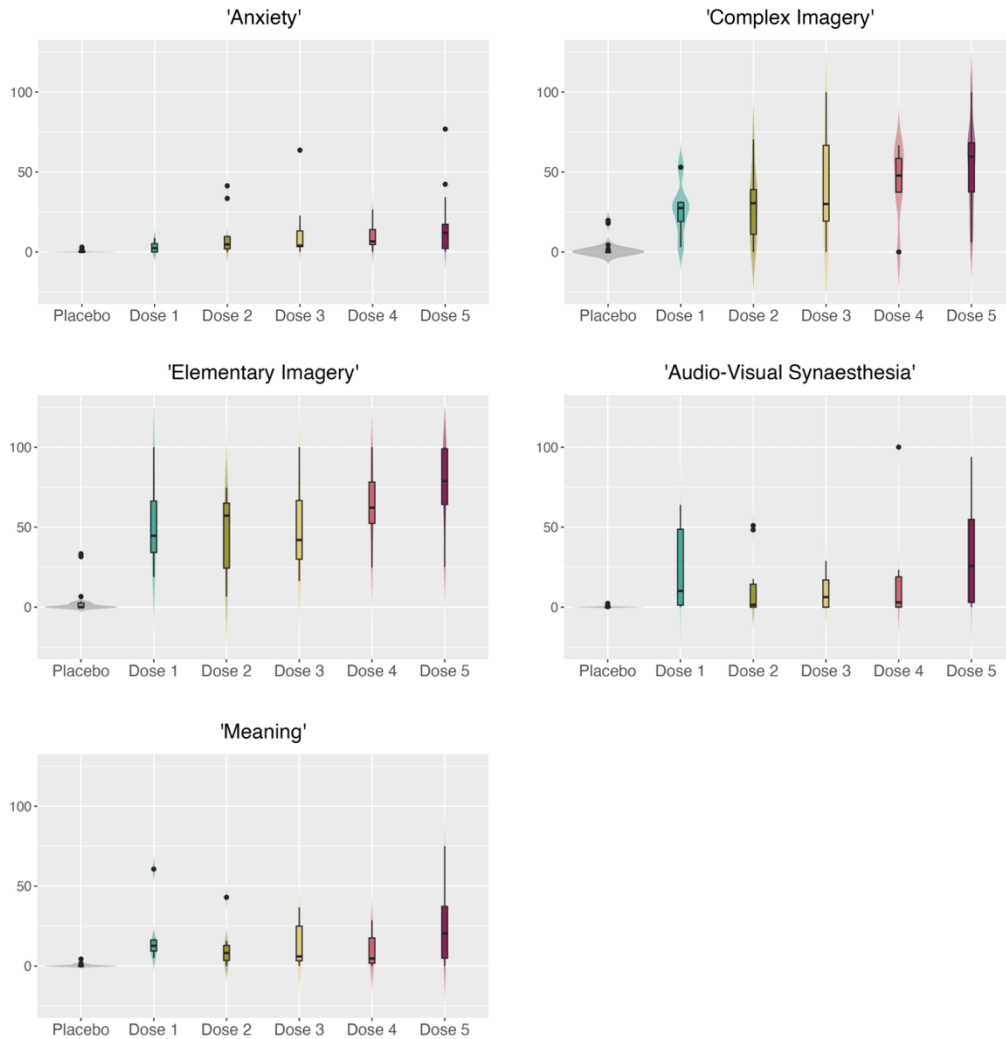


Figure 13. Effects of different doses of DMT and placebo on 11D-ASC dimensions.

(A) Radar chart showing mean scores of each 5D-ASC dimension for each dose, (B) Scores of each 11D-ASC dimension and each dose presented as boxplots, indicating the median and interquartile range, overlaid with violin plots outlining the distribution of data. Placebo ($n=26$), Dose 1 ($n=6$) = 0.6 mg + 0.6 mg/min, Dose 2 ($n=10$) = 1.0 mg + 1.1 mg/min, Dose 3 ($n=9$) = 1.4 mg + 1.5 mg/min, Dose 4 ($n=6$) = 18 mg + 1.9 mg/min, Dose 5 ($n=20$) = 20 mg + 2.3 mg/min.

3.3.1.4 MEQ-30

Figure 14 shows the scores for all MEQ-30 subscales and all doses. Although higher doses tend to show higher ratings on all MEQ-30 subscales, Dose 1 does not follow this trend. Additionally, a ceiling effect can be observed with the subscale 'Ineffability', which received the overall highest

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scores on average. LME analysis revealed a significant dose-response relationship between dose levels and scores on the MEQ-30 total ($b = 0.566$, $SE = 0.059$, $t[60] = 9.54$, $p < 0.001$) as well as all subscales ('Mystical', $b = 0.550$, $SE = 0.064$, $t[59] = 8.65$, $p < 0.001$; 'Positive', $b = 0.49$, $SE = 0.068$, $t[62] = 7.12$, $p < 0.001$; 'Space time', $b = 0.58$, $SE = 0.063$, $t[57] = 9.13$, $p < 0.001$; 'Positive', $b = 0.49$, $SE = 0.068$, $t[62] = 7.12$, $p < 0.001$; 'Ineffability', $b = 0.795$, $SE = 0.077$, $t[77] = 10.392$, $p < 0.001$).

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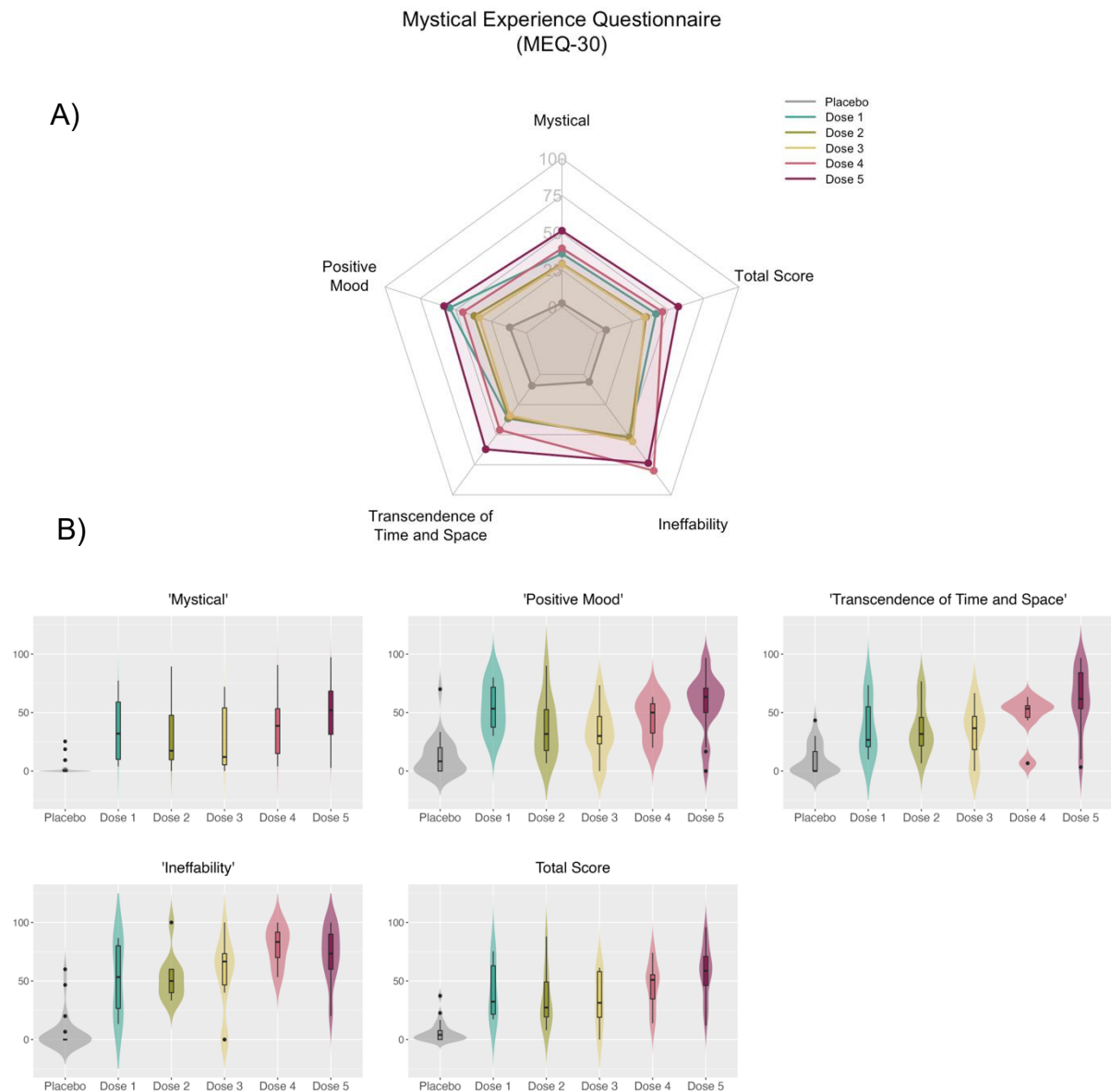


Figure 14. Effects of different doses of DMT and placebo on MEQ-30 subscales.

(A) Radar chart showing mean scores of each MEQ-30 subscale for each dose, (B) Scores of each MEQ-30 subscale and each dose presented as boxplots, indicating the median and interquartile range, overlaid with violin plots outlining the data distribution. Placebo ($n=26$), Dose 1 ($n=6$) = 0.6 mg + 0.6 mg/min, Dose 2 ($n=10$) = 1.0 mg + 1.1 mg/min, Dose 3 ($n=9$) = 1.4 mg + 1.5 mg/min, Dose 4 ($n=6$) = 18 mg + 1.9 mg/min, Dose 5 ($n=20$) = 20 mg + 2.3 mg/min.

3.3.1.5 EDI

Total scores on the EDI for all doses are shown in Figure 15. Overall, EDI scores remained below 25 for all doses except for a few outliers and Dose 5. EDI median scores are similar for Doses 1, 2, and 3. They are slightly lower for Dose 4 and significantly higher for Dose 5. Additionally, Dose 5 exhibits a significantly bigger interquartile range than the lower doses. LME modelling revealed a significant dose-response relationship between ‘Dose’ and ego dissolution as measured with the EDI ($b = 0.381$, $SE = 0.053$, $t[51] = 7.14$, $p < 0.001$).

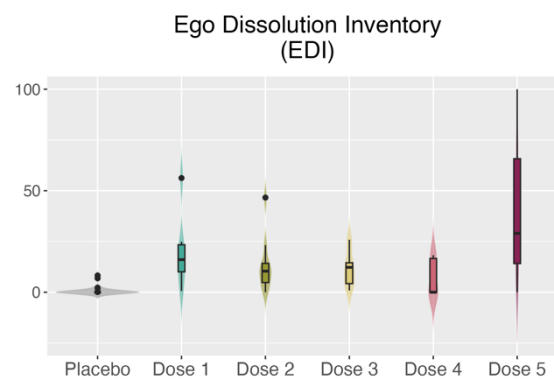


Figure 15. Effects of different doses of DMT and placebo on EDI total score.

EDI scores and each dose are presented as boxplots, indicating the median and interquartile range, overlaid with violin plots outlining the data distribution. Placebo ($n=25$), Dose 1 ($n=6$) = 0.6 mg + 0.6 mg/min, Dose 2 ($n=10$) = 1.0 mg + 1.1 mg/min, Dose 3 ($n=9$) = 1.4 mg + 1.5 mg/min, Dose 4 ($n=5$) = 18 mg + 1.9 mg/min, Dose 5 ($n=19$) = 20 mg + 2.3 mg/min.

3.3.1.6 EBI

Figure 16 shows the EBI total scores for each dose of DMT and placebo. Emotional breakthrough remained relatively low, with the median for all doses below 20 and an interquartile range below 40. Higher doses of DMT tend to lead to higher occurrence of emotional breakthrough, and LME modelling revealed a significant dose-response relationship between ‘Dose’ and emotional breakthrough as measured with the EBI ($b = 0.273$, $SE = 0.071$, $t[52] = 3.84$, $p < 0.001$).

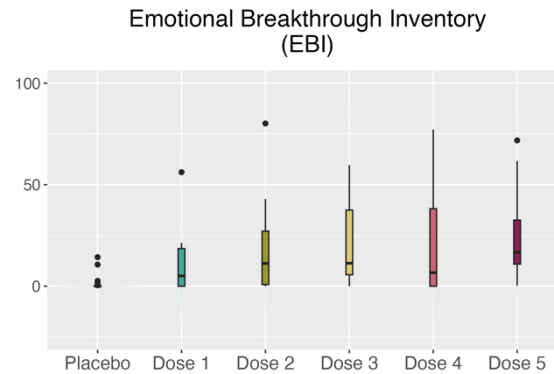


Figure 16. Effects of different doses of DMT and placebo on EBI total score.

EBI scores and each dose are presented as boxplots, indicating the median and interquartile range, overlaid with violin plots outlining the data distribution. Placebo ($n=25$), Dose 1 ($n=6$) = 0.6 mg + 0.6 mg/min, Dose 2 ($n=10$) = 1.0 mg + 1.1 mg/min, Dose 3 ($n=9$) = 1.4 mg + 1.5 mg/min, Dose 4 ($n=5$) = 18 mg + 1.9 mg/min, Dose 5 ($n=19$) = 20 mg + 2.3 mg/min.

3.3.1.7 CEQ

Figure 17 shows the CEQ total scores for all doses of DMT and placebo. Although scores generally remained low, higher doses of DMT tend to lead to higher occurrence of challenging experiences, and results of the LMM analysis showed a significant dose-response relationship between ‘Dose’ and CEQ total scores ($b = 0.174$, $SE = 0.031$, $t[59] = 5.66$, $p < 0.001$).

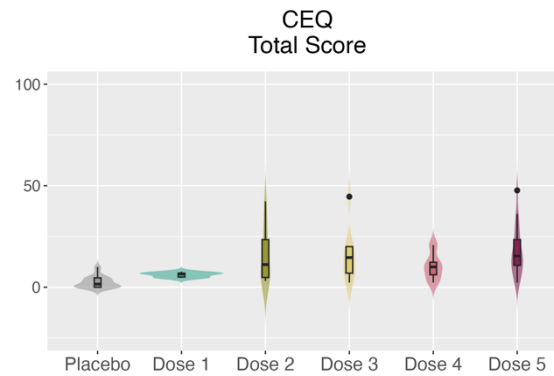


Figure 17. Effects of different doses of DMT and placebo on CEQ total score.

CEQ scores and each dose are presented as boxplots, indicating the median and interquartile range, overlaid with violin plots outlining the data distribution. Placebo (n=25), Dose 1 (n=6) = 0.6 mg + 0.6 mg/min, Dose 2 (n=10) = 1.0 mg + 1.1 mg/min, Dose 3 (n=9) = 1.4 mg + 1.5 mg/min, Dose 4 (n=5) = 18 mg + 1.9 mg/min, Dose 5 (n=19) = 20 mg + 2.3 mg/min.

3.3.2 Dynamic measures

3.3.2.1 ESM of ‘Entities’

Figure 18 shows the results from the ESM of ‘Entities’. 16 out of 20 participants had encounters with entities during the DMT experience. Out of those, six experienced entities throughout the entire DMT administration, two experienced entities only at the beginning of the infusion, and two experienced entities only at the end. The remaining participants reported entities intermittently or at specific time points. Overall, entities are experienced about half the time, with entities being more prevalent at the beginning and the end of DMT infusion.

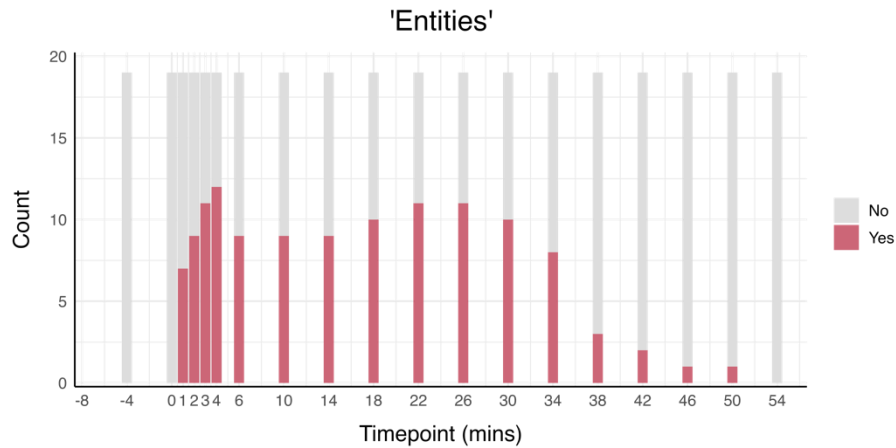


Figure 18. Results of the ESM of ‘Entities’.

The data are visualised as the total count for each timepoint sampled.

3.3.2.2 Micro-phenomenological interviews

The accounts gathered from the micro-phenomenological interviews generally reflect classic tropes of DMT experiences, including immersion into complex, otherworldly realities, strange encounters with other beings, and deep states of introspection, insight, and emotional release. Nonetheless, some participants also described chaos, confusion, and meaninglessness, sometimes lasting the entire length of the infusion.

Focusing on the process of acclimation within the experience, three common qualitative categories of the experience were identified: 1) ‘Struggle’ (i.e., trying but failing to change, avoid, or resist an undesired aspect of the experience), 2) ‘Resolution’ (i.e., resolution of struggle), and 3) ‘Fruits’ (i.e., high valence or otherwise meaningful and desirable state). Figure 19 shows a schematic of three identified common pathways through the phases of the experience. These are: 1) going through all three phases (approximately 60% of participants), 2) extended period of struggle and bypassing the fruits (approximately 15% of participants), and 3) bypassing any extended periods of struggle and going straight to the fruits for the entire duration of the infusion (approximately 25% of participants). It is important to note that all participants experiencing ‘Struggle’ eventually reach ‘Resolution’, and the return to baseline plasma concentration of DMT ultimately resolved struggles that were not resolved by the end of the infusion.

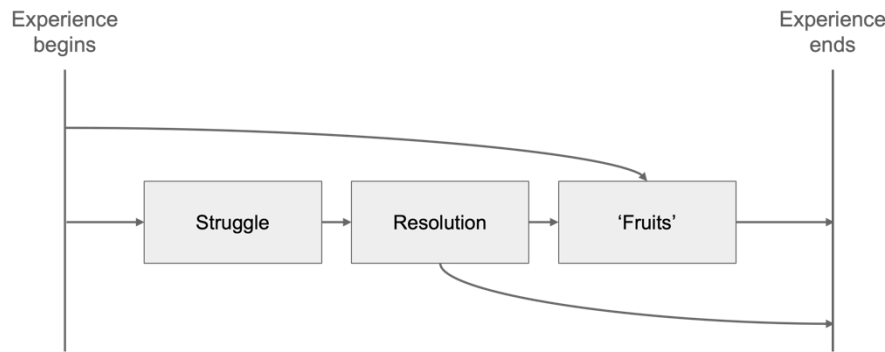


Figure 19. Common pathways through the DMT experience.

Boxes represent a selection of broad themes for qualitative categories that characterise participants' experiences. 'Struggle' = an extended period of struggle, 'Resolution' = resolution of struggle through some means, 'Fruits' = the 'fruits' of the experience, i.e., some high valence or otherwise meaningful and desirable state.

Seven categories were identified for the contents of 'Struggle': 1) 'Agency' (the ability to make a desired bodily or mental action), 2) 'Trust/safety' (struggling with losing a sense of trust/safety), 3) 'Know-how' (knowing, remembering, and implementing know-how), 4) 'Perceptual clarity', 5) 'Clarity/coherence of thought', 6) 'Coherence of self in narrative context' (not knowing who/where one is, what one is doing, and not being satisfied with that), and 7) 'Narrative flow of experience' (how much the experience seems to string together into a meaningful sequence of events).

Struggles were resolved in three distinct ways: 1) 'Incidental relief' (e.g., "The drug became less intense and suddenly I could speak again"), 2) 'Relief via successful implementation of know-how' (e.g., "The visuals became more intense, so I focused on my breathing to ground myself"), and 3) 'Social relief' (e.g., being comforted by supportive touch from one of the researchers when it was requested, engaging with a perceived entity in the experience).

Five categories of 'Fruits' were identified as potential outcomes of acclimation: 1) 'Bliss/sensual pleasure', 2) 'Aesthetic/neophilic experience (i.e., an enjoyment of beauty or novelty in the experience), 3) 'Insight' (i.e., coming into personally meaningful insight), 4) 'Healing/catharsis', and 5) 'Connectedness' (either as a generic feeling of connectedness, an intimate engagement with an entity, or feeling connected while the participant is reflecting on people from their lives).

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To examine the distribution of ‘Struggle’ and ‘Fruit’ categories over time, three time periods were defined as ‘Early infusion’ (first half of the infusion), ‘Late infusion’ (second half of the infusion), and ‘Post infusion’ (up to 20 minutes after the end of infusion). Figure 20 shows the approximate prevalence of the ‘Struggle’ and ‘Fruit’ categories for these periods. This analysis is preliminary and was not tested for inter-rater reliability. Results show that ‘Struggle’ is experienced most often in the ‘Early infusion’ period, while ‘Fruits’ are most often experienced in the ‘Late infusion’ and ‘Post infusion’ periods.

Struggle category	Early	Late	Post
Agency	55%	20%	00%
Trust/safety	20%	05%	00%
Know-how	55%	30%	00%
Perceptual clarity	25%	15%	00%
Clarity of thought	20%	20%	05%
Self coherence	25%	05%	05%
Narrative coherence	45%	25%	05%

Fruit category	Early	Late	Post
Bliss/pleasure	00%	15%	25%
Aesthetic/neophilic	25%	35%	00%
Insight/knowledge	10%	40%	20%
Healing/catharsis	05%	20%	15%
Connectedness	00%	20%	20%

Figure 20. Prevalence of ‘Struggle’ and ‘Fruit’ categories across different infusion periods.

Data presented as percentage of participant interviews coded for each category. ‘Struggles’ are most densely concentrated in the early infusion phase, while ‘Fruits’ are most concentrated in the late infusion phase.

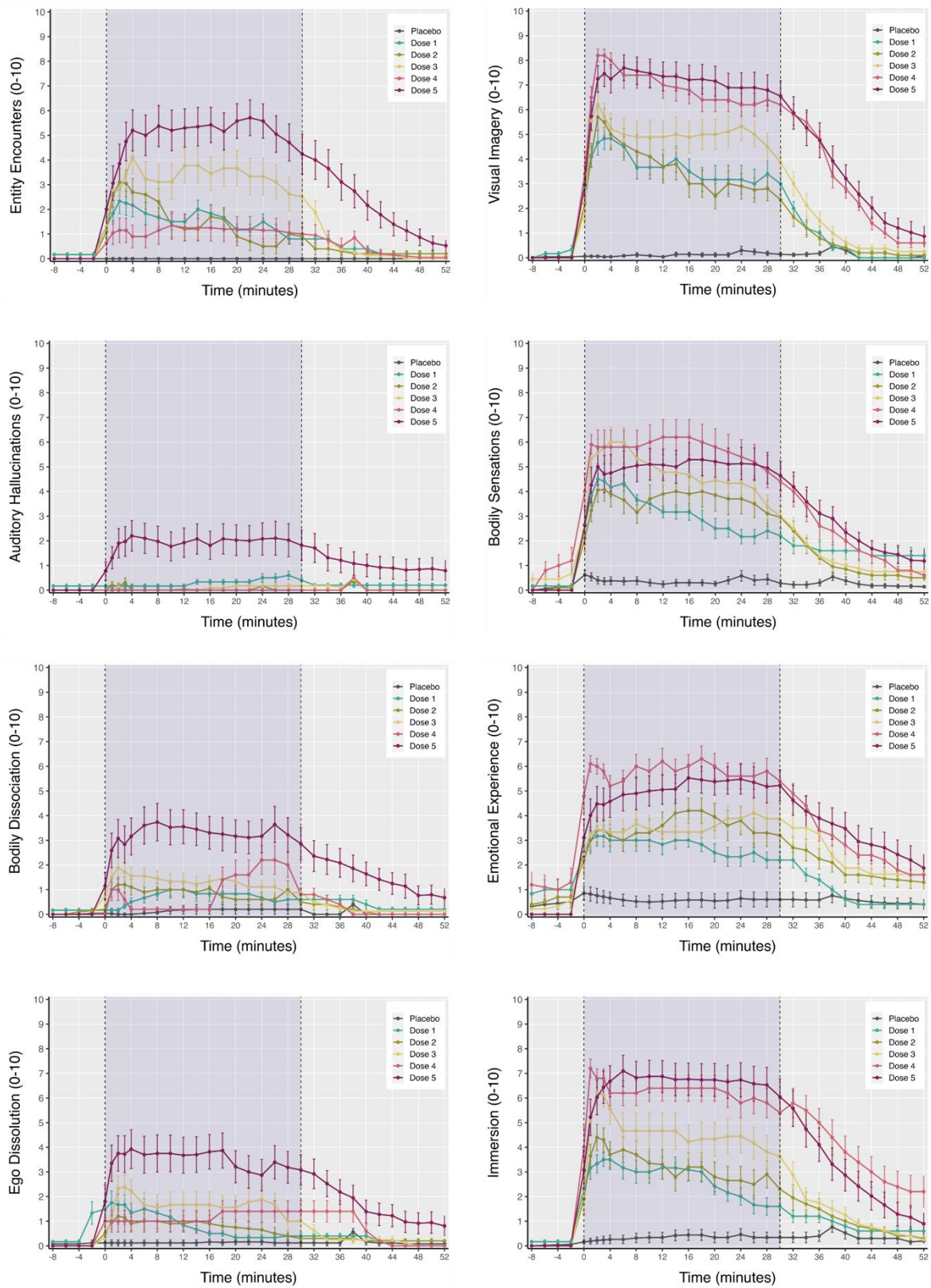
3.3.2.3 Dynamic VAS scales

As a complement, the micro-phenomenological interviews were followed by participants self-reporting their DMT experiences on various dimensions over time. Figure 21 shows the average ratings for each dimension over time. Qualitative assessments of the mean scores indicate that overall, ‘Visual imagery’, ‘Immersion’, ‘Overall richness’, and ‘Visual richness’ were rated as most pronounced, followed by ‘Entity encounters’, ‘Bodily sensations’, ‘Emotional experience’, and ‘Meaningful’. ‘Visual imagery’, ‘Immersion’, ‘Meaningful’, ‘Overall richness’ and ‘Visual richness’

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follow a dose-response relationship, although there is some overlap between certain doses. Specifically, 'Visual imagery', 'Immersion', 'Overall richness' and 'Visual richness' were rated similarly for Doses 1 and 2 and for Doses 4 and 5, and 'Meaningful' showed similar ratings for Doses 2 and 3 and for Doses 4 and 5, respectively. Several items showed a dose-response relationship, but with higher ratings on Dose 4 than on Dose 5, including 'Bodily sensations' and 'Emotional experience'. 'Entity encounters' did not exhibit a dose-response relationship, with equally low ratings for Doses 1, 2, and 4 and higher ratings for Dose 3, followed by highest ratings for Dose 5. Ratings of 'Auditory hallucinations', 'Bodily dissociation', and 'Ego dissolution' were low for all doses, albeit significantly higher for Dose 5. Generally, the experience seems to remain relatively stable over the duration of the infusion. Several dimensions, including 'Visual Imagery', 'Bodily sensations', 'Immersion', 'Overall richness', and 'Visual richness', exhibit a decrease over time, more pronounced with lower doses. Others slightly increase over time, including 'Emotional experience' and 'Meaningful'. 'Metacognition' (i.e., processing of the experience) shows a distinctly different profile compared to the other items, with low ratings at the beginning of the experience and increasing towards the end of the experience and beyond on all doses except for Dose 1.

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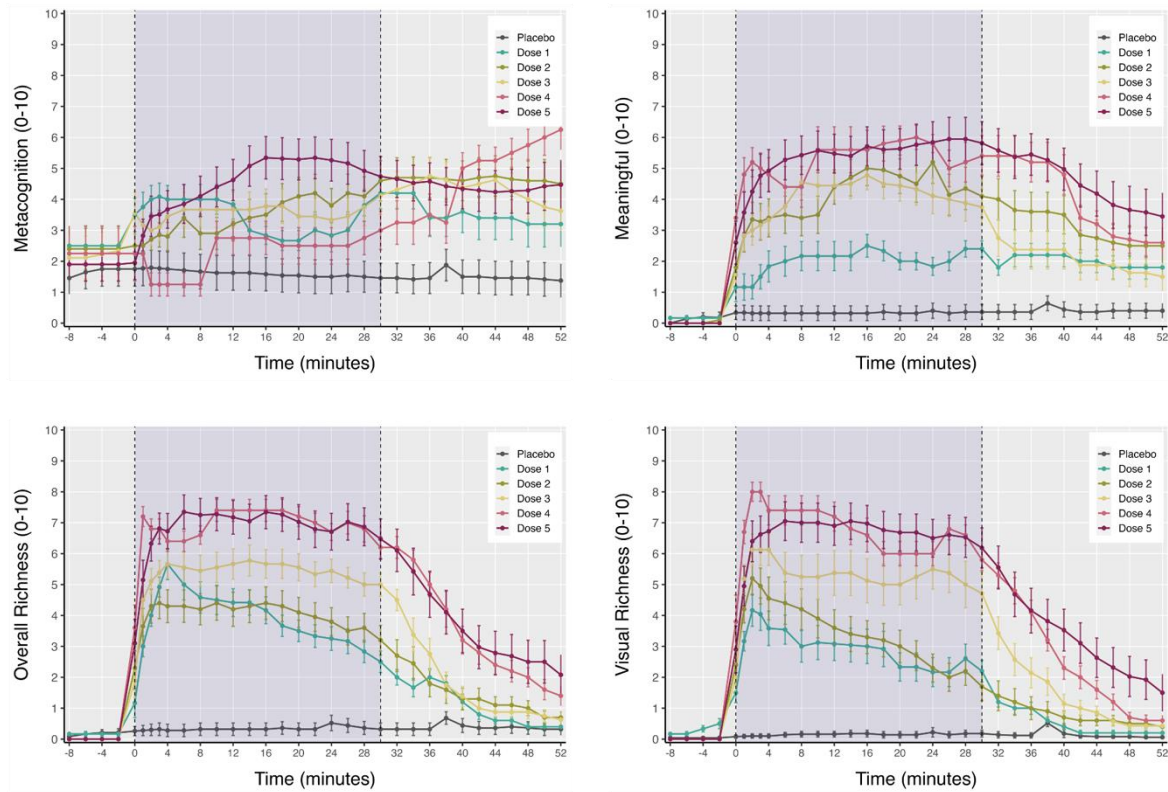


Figure 21. Average ratings of dynamic VAS items over time.

Continuous infusion of DMT/placebo took place during minutes 0-30. The data are expressed as the mean $\pm$ SEM. Placebo ($n=25$), Dose 1 ($n=6$) = 0.6 mg + 0.6 mg/min, Dose 2 ($n=10$) = 1.0 mg + 1.1 mg/min, Dose 3 ($n=9$) = 1.4 mg + 1.5 mg/min, Dose 4 ($n=5$) = 18 mg + 1.9 mg/min, Dose 5 ($n=20$) = 20 mg + 2.3 mg/min.

3.3.3 Post-hoc correlation of visual imagery and entity experiences

Given the observed results, follow-up correlations were conducted to examine the relationship between visual imagery and entity experiences.

3.3.3.1 Static correlation

A first correlation was conducted between the static VAS item 'I felt the presence of other sentient being(s), not including people in the room' and the 11D-ASC subscale 'Complex imagery'. A Shapiro-Wilk test of normality showed that one of the variables was not normally

distributed; hence, Spearman's rank-order correlation was used. A significant positive association was observed between these two measures, $r = 0.78$, $p < 0.001$ (Figure 22).

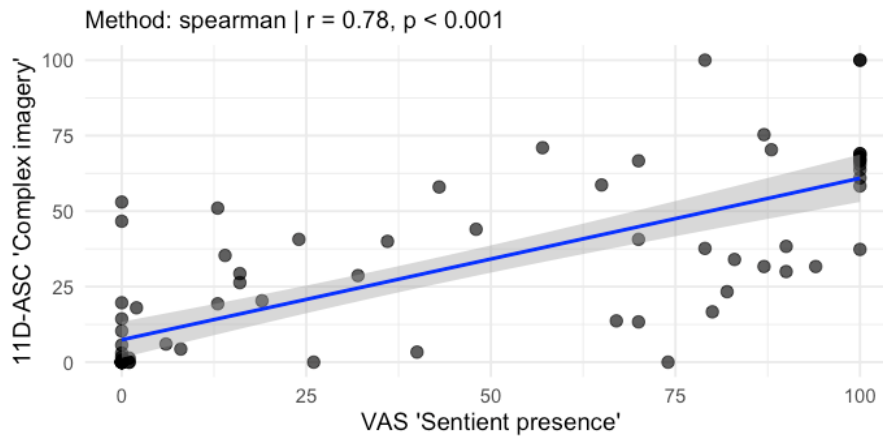


Figure 22. Correlation between the static VAS item ‘Sentient presence’ and the 11D-ASC subscale ‘Complex imagery’.

A Spearman's rank-order correlation was used, and a significant positive correlation was observed between these two measures, $r = 0.78$, $p < 0.001$.

3.3.3.2 Dynamic correlation

A second repeated-measures correlation was performed between the dynamic VAS items ‘Entities’ and ‘Visual imagery’. Because these items include multiple acute observations across different timepoints, a repeated-measures correlation was used to quantify the common within-subject association between these two items. This approach controls for inter-individual differences by fitting parallel regression lines for each participant and estimating a single overall correlation coefficient that reflects the strength of the within-subject association. Analyses were conducted in R using the ‘rmcorr’ package (Bakdash & Marusich, 2017). Repeated-measures correlation indicated a strong positive within-subject association between the dynamic VAS items ‘Entities’ and ‘Visual imagery’, $r_{rm} = 0.70$, 95% CI [0.67, 0.72], $p < 0.001$ (Figure 23).

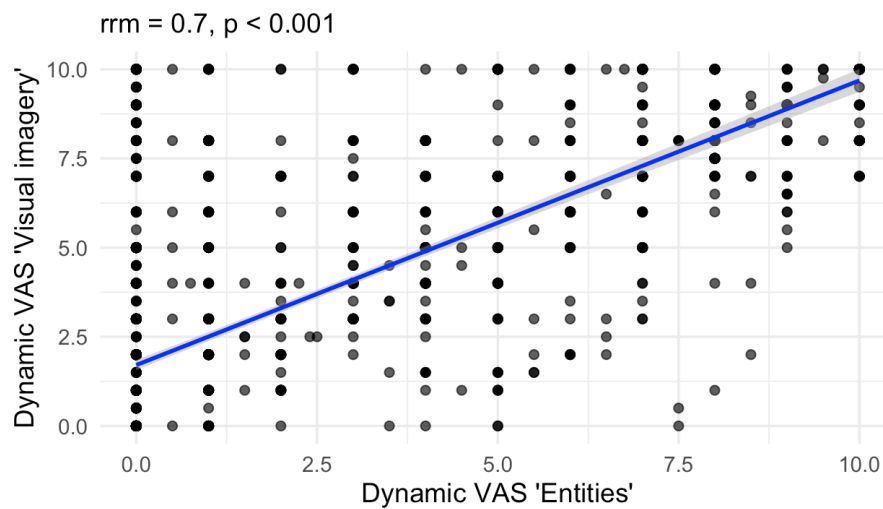


Figure 23. Repeated-measures correlation between the dynamic VAS items ‘Entities’ and ‘Visual imagery’.

Results showed a positive within-subject correlation between these measures, $rrm = 0.9$, 95% CI [0.67, 0.72], $p < 0.001$.

3.4 Discussion

The present study investigated the phenomenology and subjective effects of extended DMT administration at different doses in healthy volunteers. Measures employed included psychometric scales commonly used in research on psychedelics and initial attempts to characterise the dynamics of the extended DMT experience through ESM, micro-phenomenological interviews and dynamic VAS scales.

Results from the static VAS scales indicate that the extended DMT experience is characterised by a high occurrence of geometric patterns and elaborate/complex visual imagery, experiences of conscious and visual richness, unusual bodily sensations, and experiencing a different reality or dimension. Participants also reported experiencing beauty, feeling open and sensitive to emotions, and the experience being pleasurable. They felt a general sense of gratitude and felt the experience to be meaningful. Extended DMT infusions also frequently induced a feeling of encountering other sentient beings, not including people in the room with them. Participants experienced altered states of consciousness in line with the phenomenology suggested in the 5D-ASC and 11D-ASC scales.

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Most pronounced were visual effects in the form of both elementary and complex imagery ('Visionary restructuralisation', 'Elementary imagery', 'Complex imagery'), experiences of ego dissolution ('Oceanic boundlessness'), mystical-type experiences ('Spiritual experience'), and experiences of insight ('Insightfulness'). Extended doses of DMT induced mystical-type experiences as measured by the MEQ-30 scale, with especially high scores on the 'Ineffability' subscale. While participants reported experiencing emotional breakthroughs and ego dissolution, these occurred less often and less strongly. Although participants reported higher degrees of pleasure, beauty, insight and meaning with higher doses of extended DMT, these higher doses also led to more challenging experiences.

Results from the dynamic VAS scales indicate that visual imagery, immersion and richness of the experience are most pronounced with the extended DMT experience, followed by bodily sensations, emotional experience, and a sense of meaning. Entity encounters were also reported and rated significantly higher for Dose 5 than lower doses. While most aspects of the experience remain stable over time, 'Emotional experience' and 'Meaning' increase towards the end of the infusion, with 'Meaning' sustaining the longest after the end of the infusion. 'Metacognition' shows low ratings at the beginning of the infusion and increases towards the end and beyond, potentially suggesting metacognitive processes (i.e., thinking about the experience) as a tool for experiential acclimation and navigation, as well as for meaning-making.

The ESM of 'Entities' revealed that encounters of sentient 'beings' were reported by 80% of the participants; however, their occurrence over time was less predictable. While half of the participants reporting entities experienced them throughout the duration of the infusion, the remaining participants reported them either in the first or the second half of the infusion or intermittently at various time points. Preliminary analysis of the micro-phenomenological interviews unveiled three common categories of experience participants passed through in their extended DMT experiences: 1) 'Struggle', 2) 'Resolution', and 3) 'Fruits'. While most participants passed through all three categories during the experience, approximately 15% did not reach any 'Fruits', and approximately 25% went straight to the 'Fruits' without passing through 'Struggle' and 'Resolution'. Regarding the temporal distribution of the categories, 'Struggle' was significantly more prevalent in the first half of the infusion. In contrast, 'Fruits' were significantly more prevalent in the second half of the infusion and the post-infusion period.

Results across the different employed measures are broadly consistent, with the extended DMT experience characterised by strong visual effects (both elementary and complex imagery), bodily sensations, high immersion and richness (both visual and conscious content), the experience of a

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different reality or dimension, and heightened emotions and emotional processing. Participants generally felt the experience was positive, including experiencing a positive mood, finding the experience pleasurable, and experiencing beauty. This was accompanied by a general sense of gratitude, spiritual/mystical-type experiences, and finding insights and meaning in the experience. Participants experienced the presence of sentient beings in about half of the experiences and reported the overall DMT experience to be particularly ineffable. Effects generally followed a dose-response relationship, with higher doses leading to stronger experiences, rating higher on all the above-detailed effects. The relationship between doses and effects tends to follow a linear relationship, with effects increasing linearly with increasing doses. Several categories of experience do not follow this trend, showing a much higher prevalence at the highest tested dose of extended DMT (Dose 5). These include domains relating to the body ('Feeling displaced from one's body', 'Disembodiment', 'Bodily dissociation'), the ego/self ('Disintegration of the usual sense of self/ego', 'Ego dissolution'), auditory processing ('Auditory hallucinations', 'Audio-visual synaesthesia'), and the experience of a different reality or dimension. This suggests that there might be a threshold for certain effects, which only occur with stronger DMT experiences. This would align with findings from previous studies (e.g., earlier observations of bolus IV DMT suggested that the threshold for experiences of 'breakthrough' into alternate realities be at 14 mg; Strassman, 2000). Although it is possible that the significantly higher ratings for the higher dose stem from a response bias (explained below), the clustering of effects on several distinct domains suggests that the observation might reflect (at least partly) a true effect of nonlinearity in the dose-response relationship.

The present results are largely consistent with findings from previous studies on the subjective effects of IV DMT (Gouzoulis-Mayfrank et al., 2005; Strassman and Qualls, 1994; Strassman et al., 1996; Timmermann et al., 2019; Timmermann et al., 2023b). The use of several identical measures in a previous dose-response study of bolus IV DMT (Timmermann, 2020) offers a direct comparison of the effects of DMT delivered as a bolus vs continuous infusion. Comparing results from the ASC scale, extended DMT showed lower ratings on ASC dimensions compared to similar doses of bolus DMT. This might point towards the effect of acclimatisation as the infusion progresses, weakening the perceived alteration of consciousness over time. Comparing the response profiles on the 11D-ASC dimensions, extended DMT shows lower ratings of disembodiment and unity and relatively higher ratings of insightfulness and meaning compared to similar bolus DMT doses. This may suggest that feelings of disembodiment and unity occur beyond a certain threshold of intensity of the experience, more likely to be achieved by a bolus dose and

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less likely to be maintained by a continuous infusion. Continuous infusions, on the other hand, allow more time to progress through and process the experience, leading to more experiences of insight and meaning in the later part of the extended DMT experience. Alternatively, recency effects and a biased remembering of the experience in favour of the later infusion period characterised by increased acclimation may lead to an understating of potential experiences of disembodiment and unity earlier on. This is in line with the results of the micro-phenomenological analysis, which showed acclimation and the increased occurrence of ‘Fruits’ in the later period of the infusion. Comparing the results from similar VAS items, extended DMT was rated lower on displacement from one’s body, which aligns with the above ASC results. At the same time, higher ratings of entity encounters were shown compared to bolus DMT doses. This fits the qualitative results obtained from the ESM of ‘Entities’, which pointed to the unpredictability of entity encounters in time. Several participants reported experiencing entities only towards the later part of the infusion, suggesting that an extended DMT infusion may increase the likelihood of ‘encountering an entity’. In contrast with the results from Timmermann (2020), the present study found dose-response relationships for most tested measures. The present study employed a within-subjects repeated measures design with a larger sample size, yielding 51 observations (vs. 33 in the bolus DMT study), potentially explaining the more robust effects found in this study.

Several of the employed measures show uncharacteristically high, potentially inflated measures for the lowest tested dose of extended DMT (Dose 1). Additionally, several measures show significantly higher ratings on the highest DMT dose (Dose 5) than on lower DMT doses. While the considerably higher ratings on Dose 5 may be explained by a threshold for specific effects to appear (see above), the inflated ratings on Dose 1 point to an additional response bias introduced by the study design employed in the present study. The data presented here were collected from two partially overlapping studies. The first was a dose-finding study with eleven participants who received up to four doses of extended DMT infusions. The second study was a single-dose study with an additional 15 volunteers. Being the first study to administer DMT as a continuous IV infusion over an extended time at moderate and high doses, a fixed-order design was employed, with doses administered in ascending order. Several participants in the dose-finding study did not receive any of the higher doses (for an overview of participants and completed doses, see Table 4 in Chapter 2 – *“Dose-finding study of continuous IV infusions of DMT”*, [section 2.3](#) – *“Results”*), and participants in the single-dose study only received Dose 5 (the highest dose). Therefore, the lack of sufficient comparison from repeated dosing could explain the potentially inflated ratings given for participants’ first dose (i.e., Dose 1 and Dose 5). Additionally, sample sizes were small for

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several of the tested doses, with only 6 participants receiving Doses 1 and 4 (for a complete overview of number of participants receiving each dose, see Chapter 2 – “*Dose-finding study of continuous IV infusions of DMT*”, [section 2.2.2](#) – “*Dose regimens*”). This makes the results of Doses 1 and 4 arguably less reliable than those of Doses 2, 3 and 5.

In summary, the present study investigated the phenomenology and subjective effects of extended DMT at different doses. Results were generally consistent with previous studies describing the effects of bolus IV DMT while pointing towards increased occurrences of ‘Insight’ and ‘Meaning’, especially towards the later periods of infusion. This aligns with the preliminary results of a micro-phenomenological analysis of the extended DMT experience, which revealed common trajectories of the experience in the process of acclimation over time. While experiences of ‘Struggle’ occurred more frequently in the early infusion period, the ‘Fruits’ of the experience were accessed more commonly in the late infusion period. This potentially reveals two distinct phases of the extended DMT experience, with a first phase showing comparable effects to those seen with inhaled and bolus IV DMT – characterised by overwhelming sensory experiences and possibly a lack of agency – and a second phase showing a process whereby individuals were able to reflect and make meaning (demonstrated in increased scores of meaningfulness and metacognition). This suggests that extended DMT may lend itself better to use in psychedelic-assisted therapy. Future studies are needed to further explore the specific characteristics and dynamics of the extended DMT and test the effects of different infusion regimens (i.e., bolus loading dose vs. no loading dose, more prolonged infusion regimens, and reflexive infusion rates), to gain a better understanding of how the favourable effects of extended DMT can be emphasised and harnessed.

The present study is the first to extensively investigate the phenomenology and subjective effects of extended infusions of DMT, revealing potential similarities and differences to other methods of DMT administration. A series of measures were employed to characterise the extended DMT experience both as a whole and dynamically over time, with dynamic measures revealing important information about processes occurring within an experience, as well as potentially distinct phases of the experience. The study was mainly limited by its study design, which was chosen with issues of safety in mind. Future studies employing a randomised dose design and larger sample sizes will be able to test the robustness of the current findings.

4. EEG effects of continuous IV infusions of DMT

4.1 Introduction

Psychedelics induce a range of characteristic psychological effects and alterations in consciousness, thereby offering a unique window into the study of human consciousness. Neurophysiological and neuroimaging studies allow the investigation of the underlying brain effects induced by these substances, thereby aiding our understanding of potential mechanisms involved in the generation of the effects of psychedelics and different aspects of consciousness. Due to its non-invasive nature and its high temporal resolution, EEG lends itself to investigating the transient states that psychedelics induce. In the past two decades, an increasing number of studies have employed this method to understand the neural mechanisms involved in psychedelic brain action.

The most robust effect found across all previous studies investigating the effects of classic psychedelics on resting-state EEG is a significant decrease in alpha band power, and this has been seen for all studied classic psychedelics, including psilocybin (Komater et al., 2015; Muthukumaraswamy et al., 2013; Ort et al., 2023), LSD (Carhart-Harris et al., 2016b; Murray et al., 2022), ayahuasca (Riba et al., 2004; Riba et al., 2002; Schenberg et al., 2015; Valle et al., 2016), and DMT (Acosta-Urquidi, 2015; Pallavicini et al., 2020; Tagliazucchi et al., 2021; Timmermann et al., 2023b; Timmermann et al., 2019). Functionally, alpha oscillations are thought to support top-down inhibitory control and cortical information gating (Klimesch, 2012). A reduction of alpha activity under psychedelics has been interpreted as a breakdown of these constraints, consistent with increased sensory flooding and the destabilisation of high-level priors described in predictive processing accounts of psychedelic action (Carhart-Harris & Friston, 2019). In line with this, reductions in alpha power have been correlated with increases in overall subjective intensity (Timmermann et al., 2019, Timmermann et al., 2023b), the intensity of visual effects (Valle et al., 2016), the ‘supernatural quality’ of the experience, as well as experiences of ego dissolution (Carhart-Harris et al., 2016b; Muthukumaraswamy et al., 2013). The reduction in alpha band activity extended into a broadband decrease in spectral power across all lower frequency bands (delta, theta, alpha, beta; 1-30 Hz) in several studies (Carhart-Harris et al., 2016b; Komater et al., 2015; Murray et al., 2023; Muthukumaraswamy et al., 2013; Riba et al., 2002; Timmermann et al., 2019; Valle et

al., 2016). Decreases in delta and theta were correlated with subjective ratings of ‘contact with external reality’ (Valle et al., 2016), while decreases in beta power were correlated with higher intensity ratings (Timmermann et al., 2019; Timmermann et al., 2023b) as well as higher scores on ‘anxiety’ and ‘cognition’ (Pallavicini et al., 2020).

However, other studies have found contradicting results. A number of studies found increases in delta (Ort et al., 2023; Tagliazucchi et al., 2021; Pallavicini et al., 2020; Timmermann et al., 2023b), with these increases positively correlating with intensity ratings (Timmermann et al., 2023b) and visual effects (Timmermann et al., 2019). A few studies showed increases in theta (Acosta-Urquidi, 2015; Tagliazucchi et al., 2021) and increases in beta (Schenberg et al., 2015; Tagliazucchi et al., 2021). Most studies found an increase in high-frequency activity (gamma band; > 30 Hz; Acosta-Urquidi, 2015; Schenberg et al., 2015; Ort et al., 2023; Tagliazucchi et al., 2021; Pallavicini et al., 2020; Timmermann et al., 2023b), correlated with higher ratings on a wide range of subjective measures, including several 5D-ASC subscales and MEQ-30 subscales, and the Near Death Experience questionnaire (Greyson, 1990) item ‘cognition’ (Pallavicini et al., 2020). Only a handful of studies found no gamma effects (Timmermann et al., 2019) or decreased gamma band power (Murray et al., 2023; Muthukumaraswamy et al., 2013). Several studies employed different doses in their investigations, and dose-dependency of EEG effects has been shown (Eckernäs et al., 2023b; Murray et al., 2022; Riba et al., 2002).

Signal diversity has been investigated with an array of compounds, and an increase has been found for all tested compounds, including psilocybin, ketamine, LSD (Schartner et al., 2017a) and DMT (Pallavicini et al., 2020; Timmermann et al., 2019; Timmermann et al., 2023b). This makes increased signal diversity the most robust signature of psychedelic-induced changes in resting-state EEG, along with decreases in alpha band power. Signal diversity measures have been interpreted as indices of the richness of conscious experience and the brain’s dynamical repertoire (Schartner et al., 2017a), correlating with subjective intensity ratings and the richness of conscious experience (Timmermann et al., 2023b).

Although the past two decades have seen an abundance of electrophysiological and neuroimaging studies investigating the neural correlates induced by DMT and the related compound ayahuasca (Acosta-Urquidi, 2015; Alamia et al., 2020; Alonso et al., 2015; Alves et al., 2024; Alves et al., 2022; Daumann et al., 2010; de Araujo et al., 2012; Palhano-Fontes et al., 2015; Pallavicini et al., 2020; Pasquini et al., 2020; Pasquini et al., 2024; Riba et al., 2004; Riba et al., 2002; Riba et al., 2006; Schenberg et al., 2015; Singleton et al., 2023; Stuckey et al., 2005; Tagliazucchi et al., 2021; Timmermann et al., 2023b; Timmermann et al., 2019; Valle et al., 2016; Viol et al., 2017; Vohryzek

et al., 2023; Vohryzek et al., 2024), only five studies have focused on the effects of DMT on resting-state spectral EEG (Acosta-Urquidi, 2015; Pallavicini et al., 2020; Tagliazucchi et al., 2021; Timmermann et al., 2019, Timmermann et al., 2023b). Table 13 summarises the spectral EEG effects of DMT observed in these studies.

Table 13. Previous studies investigating the effects of DMT on resting-state EEG.

Administration methods, doses, sample sizes, EEG systems, and spectral EEG results are shown.

Study	DMT and sample size	EEG system	δ	θ	α	β	γ
Acosta-Urquidi, 2015	Inhaled DMT, ca. 20-30 mg (n = 23)	19-channel EEG, 250 Hz sampling rate	↓	↑	↓		↑
Pallavicini et al., 2020	Inhaled DMT, ca. 40 mg freebase (n = 35)	24-channel mobile EEG, 500 Hz sampling rate	↑		↓		↑
Tagliazucchi et al., 2021	Inhaled DMT, ca. 40 mg freebase (n = 35)	24-channel mobile EEG, 500 Hz sampling rate	↑	↑	↓	↑↓	↑
Timmermann et al., 2019	Bolus IV DMT, 7 mg, 14 mg, 18 mg, 20 mg (total n = 13)	32-channel EEG, 1000 Hz sampling rate			↓	↓	
Timmermann et al., 2023b	Bolus IV DMT, 20 mg fumarate in 10 ml saline	31-channel EEG, 5 kHz sampling rate	↑		↓		↑

Note: The study by Acosta-Urquidi (2015) is not peer-reviewed and has never obtained ethics. The analyses and results from Pallavicini et al. (2020) and Tagliazucchi et al. (2021) are based on the same sample.

In a study of inhaled DMT in 23 healthy volunteers, Acosta-Urquidi (2015) found robust suppressions of alpha (ca. 10 Hz) and significantly increased gamma (30-40 Hz) power at parietal and occipital sites following DMT ingestion. In some participants, DMT increased theta band (6-8 Hz) activity. An alpha rebound (i.e., increased power in the alpha band) at 15-25 minutes was found in some cases.

A more recent study of inhaled DMT in 35 volunteers (Pallavicini et al., 2020) found significantly decreased power in the alpha (8-12 Hz) band throughout all scalp locations, as well as increased power in the delta (1-4 Hz) and gamma (30-40 Hz) frequency bands. Gamma power increases were correlated with subjective ratings of altered states of consciousness (5D-ASC dimensions ‘Complex imagery’, ‘Oceanic boundlessness’, ‘Dread of ego dissolution’) and mystical-type experiences (MEQ-30 subscales ‘Mystical’, ‘Transcendence of time and space’, ‘Ineffability’).

Using the same sample and employing source localisation techniques, the authors found widespread decreases in alpha band power and increases in delta band power. In contrast, increases in gamma band activity were localised to temporal, parietal, and occipital areas. Additionally, source localisation revealed an occipital increase in theta band activity and increased temporal, parietal and occipital beta band power co-occurring with decreased frontal beta band power (Tagliazucchi et al., 2021).

The effects of bolus IV DMT on spectral EEG have been tested in two studies (Timmermann et al., 2019, Timmermann et al., 2023b). In the first study, DMT administered at different doses (7-20 mg, total $n = 13$) led to spatially widespread decreases in alpha band power and reductions in beta band power. A decomposition of the signal into its fractal ($1/f$) and oscillatory components revealed a significant decrease in fractal power in all low-frequency bands (1-30 Hz) and decreases in oscillatory alpha and beta band power, consistent with the total power decreases. Additionally, signal diversity was found to increase significantly following DMT administration. Following the temporal development of effects over time, a decrease in delta and theta band power was observed for the first minute following DMT administration, followed by increases peaking at minutes 2-3.

Significant relationships were found between subjective intensity ratings and decreased alpha and beta band power as well as increased signal diversity, with additional relationships found between intensity and increased oscillatory power in the delta and theta frequency bands. Using a neurophenomenological approach (Timmermann et al., 2023a), the authors found significant relationships between alpha and beta power reductions and signal diversity increases, and the visual and emotional/metacognitive components of the experience. Bodily effects were associated with reductions in central beta band power.

In a second, combined fMRI-EEG study in 20 healthy volunteers, reductions in alpha band power and increases in signal diversity were replicated. Moreover, the authors found increases in delta and gamma band activity. Increases in delta band activity were significant for four minutes following DMT administration, while alpha decreases remained significant for eight minutes following DMT administration. Increases in signal diversity were significant between minutes 2-13. Additionally, signal diversity was found to be correlated with 'Richness of the experience'.

Several studies have used source reconstruction techniques to localise the observed sensor-level activity to brain areas. In an MEG study on psilocybin, results showed that the decreased oscillatory power observed across a wide frequency range after psilocybin infusion was mainly localised to association cortices, especially areas of the DMN, such as the PCC. Furthermore, in posterior

regions, a decrease was observed in all frequency bands between delta and low gamma (1 – 50 Hz), while in the prefrontal cortex, the reduction in power ranged from alpha to high gamma frequency bands (8 – 100 Hz; Muthukumaraswamy et al., 2013). A second study found that psilocybin-induced reductions of current source density across low-frequency bands (<20 Hz) were localised in the PCC, RSC, and ACC, the precuneus, the cuneus, and the parahippocampal gyrus. Theta (4–8 Hz) and alpha1 (8–10.5 Hz) reductions were also found in the insular cortex, the occipitotemporal area, and parahippocampal regions. Additionally, decreases in the alpha1 frequency band and partially the alpha2 frequency band (10.5–13 Hz) also encompassed large areas of the posterior occipital-parietal cortex (Kometer et al., 2015). In a low-dose (13–26 µg) LSD study, broadband reductions (1–80 Hz) were localised to DMN structures, including the PCC, medial prefrontal, and temporoparietal cortices (Murray et al., 2022). In an MEG study on LSD, significant decreases in delta, theta, alpha, and beta bands (1 – 30 Hz) were source localised to specific cortical areas, including the left fusiform gyrus, left temporoparietal junction, and left superior temporal gyrus for delta, the cingulate cortex and several frontal and parietal structures for theta, the ACC, superior occipital gyrus, and precuneus for alpha, and select frontal, occipital, temporal areas as well as the cingulate cortex for beta. Significant correlations were found between simple hallucinations and decreases in alpha power, as well as ego-dissolution and decreases in both delta and alpha power (Carhart-Harris et al., 2016b). Using LORETA after ayahuasca administration, one study found decreases in alpha band power density in the parietal, occipital, temporal and limbic lobes. Additionally, decreases in delta band power were found for a small area in the border between the left occipital and temporal lobes (Riba et al., 2004). Finally, one study employed source localisation techniques on a dataset of inhaled DMT (Tagliazucchi et al., 2021). The results are outlined in the paragraph above.

In a combined fMRI-EEG study, the authors used regression models to investigate parallel changes in EEG frequency band activity and global signal diversity (LZ complexity) and fMRI measures of functional connectivity (Timmermann et al., 2023b). Results showed that delta power increases were associated with increases in global functional connectivity (GFC) incorporating widespread cortical areas, including frontal, temporal, parietal, motor, and visual association cortices. Parietal reductions in alpha power were associated with GFC increases in the transmodal association cortex pole (TOP), decreased coupling between visual and somatomotor regions, and increased coupling between these sensory and TOP regions. Occipital gamma power increases were associated with increases in GFC in frontoparietal regions and the limbic network. Finally, LZ complexity increases were associated with increases in GFC in TOP networks and the limbic network.

Extended infusions of DMT induce a range of profound and unique psychological effects in healthy human volunteers (For an overview of the phenomenology and subjective effects of extended infusions of DMT, see [Chapter 3](#) – “*Phenomenology and subjective effects of continuous IV infusions of DMT*”). Participants reported a rich visual experience of both geometric patterns and complex visual imagery of what felt like a different reality or dimension. They also described unusual bodily sensations, openness to emotions, and encounters with other sentient beings (‘entities’). Overall, extended DMT infusions were experienced as beautiful and meaningful. While the extended administration aimed and achieved to keep the intensity of subjective drug effects stable over the duration of the infusion, analysis of dynamic VAS scales and micro-phenomenological interviews revealed that experiences commonly progress through distinct phases. The early infusion period, with its fast onset of drug effects, can lead to an experience of ‘struggle’, which is commonly resolved with an acclimation to the experience, leading to the ‘fruits’ of the experience, usually experienced in the late or post-infusion periods, which can take shape as pleasurable or blissful states, a neophilic experience, insights, healing, catharsis, or a sense of connectedness.

The main objective of the present study was to investigate the effects of extended infusions of DMT on resting-state EEG spectral power and signal diversity. A handful of previous studies have tested the effects of DMT administered through inhalation or as a bolus IV injection, with largely consistent results (robust decreases in alpha band power and increases in signal diversity, potential increases in theta and gamma band power) and a few inconsistencies (both increases and decreases were reported for delta and beta band power). These results are also broadly consistent with the wider literature on the effects of classic psychedelics on resting-state EEG spectral power and signal diversity. With the current study, the author aims to add to the existing literature by implementing previously used measures (spectral EEG and signal diversity measures) while employing a novel method of DMT administration. The concurrent use of a bolus IV injection followed by a continuous infusion will allow a comparison of the initial effects of the DMT administration to those previously seen with bolus IV DMT while also investigating the unique effects of a prolonged DMT infusion over time. The analysis will focus on EEG spectral power and signal diversity changes over time following extended DMT administration. A high-density EEG system was used to provide increased spatial resolution compared to previous studies. The data will be analysed on both sensor and source levels to localise any observed differences in EEG signal following DMT administration to potential underlying brain activity. Additionally, the data will be decomposed into its fractal ($1/f$) and oscillatory components to compare to a previous

analysis of bolus IV DMT (Timmermann et al., 2019; Timmermann et al., 2023b). Furthermore, the relationship between any emergent changes in spectral power and signal diversity and measures of subjective experience will be explored using subjective measures collected after DMT administration (for a full description of subjective measures employed and results obtained, see [Chapter 3](#) – “*Phenomenology and subjective effects of continuous IV infusions of DMT*”). Finally, a neurophenomenological approach will be used to study the occurrence of ‘entity encounters’ during DMT administration by combining EEG with an ESM. As this is the first study on the neurophysiological effects of extended administrations of DMT, analyses are mainly exploratory and hypothesis-free. However, based on previous effects observed with inhaled and bolus IV DMT, an acute decrease in alpha band power and an increase in signal diversity are hypothesised. Additionally, it is hypothesised that these effects will be correlated to the subjective intensity of drug effects.

4.2 Methods

4.2.1 Study design and participants

In two single-blind, placebo-controlled fixed-order studies using a within-subjects design, 20 healthy volunteers (twelve male, eight female, mean $\pm$ SD age 39.38 ± 10.23) received one dose of saline placebo and one moderately high dose of extended IV DMT. Extended IV DMT administrations consisted of a 20 mg bolus loading dose delivered over 30 seconds plus a slow-rate continuous infusion of 2.27 mg/min DMT over 29 minutes. Dosing sessions were separated by a minimum of one week. Participant inclusion criteria can be found in Chapter 2 – “*Dose-finding study of continuous IV infusions of DMT*”, [section 2.2.3](#) – “*Participants*”. Table 14 provides demographic data of the study participants.

Table 14. Demographics of the study participants.

	Participants (n = 26)
Age, mean (SD)	40 (10.3)
Sex, n (%)	
Male	17 (65.4)
Female	9 (34.6)
Ethnicity, n (%)	
White	21 (80.8)
Black	1 (3.9)
Asian	1 (3.9)
Mixed	2 (7.7)
Other	1 (3.9)
Alcohol consumption (n, %)	
0 units/week	8 (30.8)
1-5 units/week	4 (15.4)
6-10 units/week	8 (30.8)
11-15 units/week	5 (19.2)
16-20 units/week	0 (0)
21-25 units/week	1 (3.9)
Smoking status, n (%)	
Never smoked	2 (7.7)
Ex-smoker	17 (65.4)
Current smoker	6 (23.1)
Previous DMT experiences, n (%)	
0	2 (7.7)
1-10	16 (61.5)
11-25	7 (26.9)
>25	1 (3.9)

4.2.2 Study procedures

A detailed description of the study procedures can be found in Chapter 2 – “*Dose-finding study of continuous IV infusions of DMT*”, section [2.2.4](#) “*Study procedures*”. All dosing visits took place in a calm, decorated hospital room at the ICRF. During dosing, participants were in a semi-supine position, and a body scan meditation was performed shortly before dosing to help participants relax. During dosing, participants wore an eye mask and were instructed to keep their eyes closed. Low-volume ambient music was played through headphones throughout the infusion. DMT was administered for 30 minutes, and acute effects, including EEG, plasma samples, and ‘Intensity’ and ‘Entities’ ratings collected via ESM, were recorded for eight minutes before until 52 minutes following the

beginning of drug administration. Once the acute drug effects had subsided, participants completed a range of psychometric measures inquiring about their experience.

4.2.3 EEG acquisition

Continuous EEG was recorded from EGI 256-channel HydroCel Geodesic Sensor Nets and Net Station NA3 amplifiers (Magstim EGI, Eugene, OR, USA). Figure 24 shows the electrode placement of the EGI 256-channel sensor nets. EEG was acquired at a sampling rate of 500 Hz using the Net Station Acquisition tool (Magstim EGI, Eugene, OR, USA). Cz served as reference electrode, and electrode impedance was kept below 50 k Ω for all electrodes before the start of the recording. EEG was recorded for eight minutes before and 52 minutes following the start of the DMT/placebo infusions for a total of 60 minutes of recording. EEG data were collected on all dosing sessions and for all doses; however, only data from placebo and Dose 5 were analysed for this thesis.

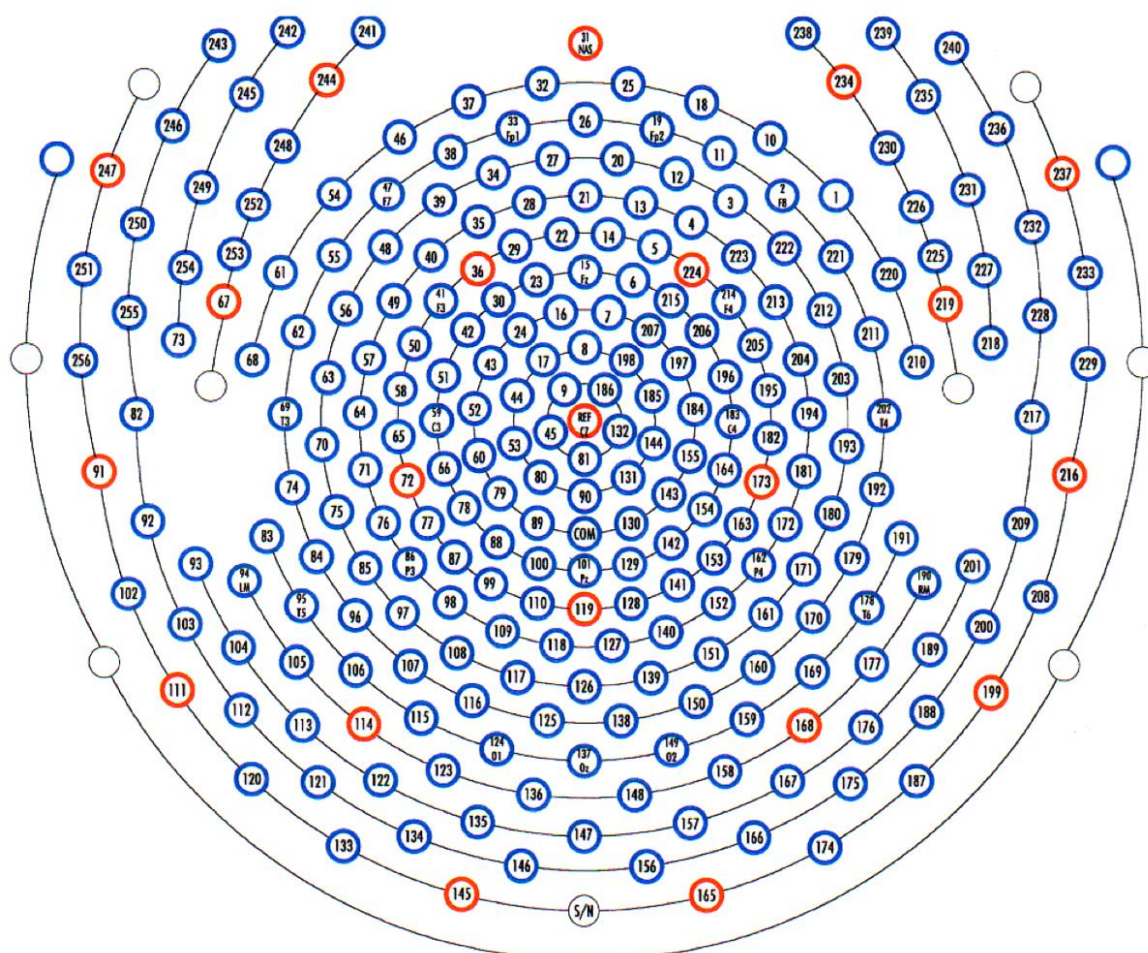


Figure 24. EGI 256-channel HydroCel Geodesic Sensor Net channel map.

4.2.4 EEG pre-processing

EEG pre-processing was conducted using the Fieldtrip toolbox (Oostenveld et al., 2011). First, a temporary version of the EEG data was created for optimised identification of muscle artifacts in the data. This data was demeaned and bandstop-filtered between 48 and 52 Hz and its harmonics (98-102 Hz), to remove line noise from the mains electricity at 50 Hz. The data was not lowpass-filtered to keep muscle activity intact, which is most pronounced at 110 to 140 Hz. The data was visually inspected using the summary view of *ft_rejectvisual*, and channels with a high variance were marked as noisy. To identify muscle artifacts, the data were filtered between 110 and 140 Hz, z-transformed and averaged over channels. A threshold of 20 was applied to the accumulated z-scores, and all timepoints above or below this threshold were marked as muscle artifacts. Additionally, a minimum of 6 seconds (up to 13 seconds) of data were marked as rating artifacts following each ESM prompt occurring at mins -8, -4, 0, 1, 2, 3, 4, and every two mins thereafter. Lastly, the timecourse of all channels was visualised to confirm the above-identified artifacts and adjust where necessary.

Next, the raw data was demeaned, bandstop-filtered between 48 and 52 Hz and its harmonics at 98-102 Hz, and bandpass-filtered between 1 and 100 Hz. The above-identified artifacts were removed from this data to exclude noisy channels and timepoints.

As a next step, independent component analysis (ICA) was used to decompose the data into independent components. This was done using the ‘runica’ method of *ft_componentanalysis*. ICA was performed on the continuous data, including eight minutes of eyes-closed baseline, 30 minutes of acute dosing, and 22 minutes of post-dosing recording. All channels remaining after artifact removal were included in the ICA, including one ECG electrode, and an equivalent number of components minus one were extracted. Components were reviewed and those identified as eye movements, cardiac artifacts, muscle artifacts, line noise and channel noise were removed from the data. To confirm the quality of the ICA cleaning, the timecourse of the data was reviewed, and more noisy channels and timepoints were rejected, where necessary.

Prior excluded channels were interpolated, and 186 channels corresponding to scalp locations most closely associated with brain regions were selected for analysis, excluding channels located on the face and neck. This approach is consistent with the conventions used in previous studies with the

same EEG system (e.g., Murphy et al., 2009; Murphy et al., 2011; Riedner et al., 2007). The selected channels were re-referenced to average reference, thereby recovering the signal at channel Cz.

4.2.5 EEG source reconstruction

MRI data were acquired on a Siemens Magnetom Verio 3T scanner (Siemens Healthineers, Erlangen, Germany) running syngo MR software platform B17 using a 32-channel head coil. A T1-weighted MPRAGE sequence was acquired using the ADNI protocol with the following parameters: TR = 2300 ms, TE = 2.98 ms, TI = 900 ms, flip angle = 9°, FOV = 256 x 256 mm, voxel size = 1 x 1 x 1 mm³, slices per slab = 192, bandwidth = 240 Hz/Px, echo spacing = 7.1 ms, phase encoding direction = A >> P. Acquisition was accelerated using GRAPPA with an acceleration factor of 2, resulting in a scan time of approximately 5 minutes. Images were acquired in the sagittal plane.

Source reconstruction was performed using the Fieldtrip toolbox to estimate brain activity from the EEG signal measured from electrodes placed on the scalp (Oostenveld et al., 2011).

Boundary Element Method (BEM) volume conduction models of the head were created for each participant by segmenting individual structural MRI into brain, skull and scalp tissues. Triangular meshes were generated in the boundaries between different tissues to represent the brain, skull, and scalp surfaces, and each tissue type was assigned a specific conductivity value. Head models were constructed using these meshes, based on the implementation from Thom Oostendorp ('dipoli'; Oostendorp and Van Oosterom, 1989).

To determine sensor positions, the GSN HydroCel 257-channel electrode template was manually realigned to each individual's headmodel, and 186 sensors were included, excluding neck and face electrodes, complementing the procedure used for the sensor-level EEG data.

Source models were created by generating grid points of the individual MRIs based on coordinates from the Montreal Neurological Institute (MNI) standard brain template and mapping these points to the corresponding regions in the Automated Anatomical Labelling atlas (AAL; Tzourio-Mazoyer et al., 2002), which divides the brain into 90 cortical and subcortical regions, ensuring that the source points are anatomically aligned with AAL regions to provide a meaningful anatomical context for source reconstruction.

Forward solutions were computed using the individual headmodels, source models and sensor positions. For each source point in the source models, leadfield matrices were computed that

describe how electrical currents originating from that specific source point are projected to each sensor to affect sensor measurements.

Averaged data for each channel and channel covariance matrices were calculated from the sensor-level EEG data. The inverse solution for the averaged data was calculated using beamforming with linear constrained minimum variance (LCMV; Van Veen et al., 1997). The covariance matrices were used to weigh the contribution of each sensor, to account for noise and the spatial correlation of the EEG signals and improve accuracy of the source estimates.

Spatial filters for voxels inside the headmodel were extracted and normalised to improve source localisation accuracy and stability (Hillebrand et al., 2012). Normalised spatial filters were applied to the sensor-level EEG data to reconstruct the source-level activity at each voxel inside the head as estimated from the recorded sensor-level EEG data, effectively transforming the data from the sensor space to the source space.

Source reconstruction was repeated using a template MRI instead of individual MRI scans to test the validity and robustness of results. Both procedures produced comparable results. Since the use of individual MRI scans is the preferred method in the literature and the individual MRI scans had a higher spatial resolution, results will be reported from the analysis using individual MRI scans.

4.2.6 Spectral power analyses

4.2.6.1 Sensor-level TFR

Time-frequency representations (TFRs) of power were calculated to inspect the data visually. EEG data was segmented into two-second epochs without overlap. The power spectrum for each trial was computed separately for low (1-30 Hz) and high (30-100 Hz) frequency ranges using the ‘mtmfft’ method. A hanning taper was used for low frequencies, and for high frequencies, a dpss taper with a smoothing parameter of 1.5 Hz was applied. Data around the notch filter range (48-52 Hz) was interpolated to correct for previous line noise filtering. The low- and high-frequency spectra were concatenated to form a continuous frequency representation, and missing data in the power spectra were linearly interpolated. Grand averages of the TFR data across all subjects were computed for each condition separately and plotted for visual inspection.

4.2.6.2 Sensor-level time course of EEG rhythms

To visualise spectral activity over time, continuous EEG data was segmented into two-second trials, and an Irregular-Resampling Auto-Spectral Analysis (IRASA) algorithm (Wen and Liu, 2016) in Fieldtrip toolbox (Oostenveld et al., 2011) was used before computing the Fast Fourier Transform (FFT) using dpss tapers, to separate rhythmic activity from concurrent power-spectral $1/f$ (fractal components) modulations. The IRASA algorithm compresses and expands the time-domain data with a set of non-integer resampling factors, redistributing the rhythmic components in the power spectrum while leaving the arrhythmic $1/f$ distribution intact. The data is then passed onto the FFT. By taking the median of the resulting auto-spectral distributions, the power-spectral $1/f$ component was extracted. A power-spectral estimate of rhythmic content (i.e. the oscillatory component) in the recorded signal was calculated by subtracting the power-spectral $1/f$ component from the original power spectrum.

Frequency bands were extracted, and for each frequency band, the data was thresholded to remove ± 3 standard deviations (SD) from the mean. Missing data was linearly interpolated, and the data was lowpass-filtered with a cutoff frequency of 0.08 Hz. Channel and frequency averages were taken, and a baseline correction was applied. The data was then z-scored across DMT and placebo conditions and smoothed using moving means with a sliding window of 21 trials. Spectral activity in the DMT and placebo conditions was plotted for each frequency over time.

4.2.6.3 Sensor-level time-averaged spectral power

To investigate the differences between DMT and placebo conditions over time, the continuous EEG data was cut into epochs, and the DMT vs placebo data of each block was compared. Based on the average subjective intensity of DMT over the duration of the infusion (Figure 25), epochs of six minutes were chosen for the analysis. The pre-processed sensor-level EEG data was cut into six-minute epochs, resulting in the following epochs: minutes -6 – 0 (baseline), minutes 0 – 6 (infusion), minutes 6 – 12 (infusion), minutes 12 – 18 (infusion), minutes 18 – 24 (infusion), minutes 24 – 30 (infusion), minutes 30 – 36 (post-infusion), minutes 36 – 42 (post-infusion), and minutes 42 – 48 (post-infusion). This resulted in one pre-dosing epoch of eyes-closed baseline, six acute infusion epochs, and three post-infusion epochs.

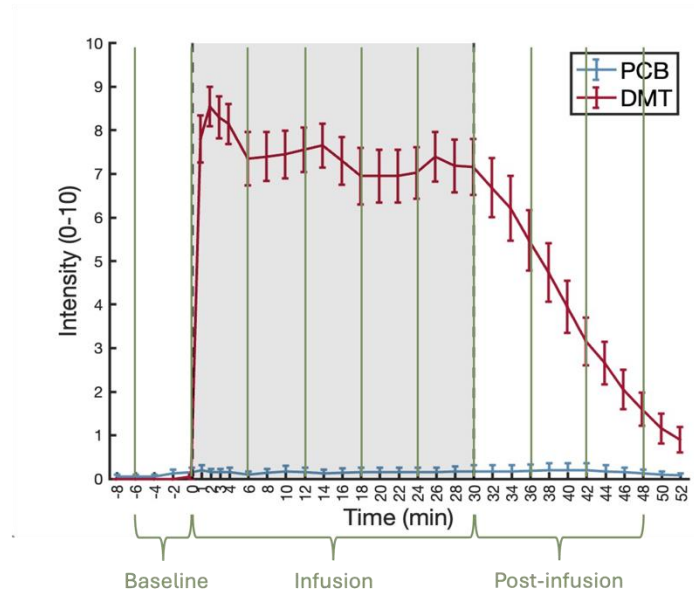


Figure 25. Average subjective intensity of the DMT and placebo experience over time.

Based on the average trajectory of intensity ratings, 6-minute epochs (delineated by green lines) were used for the time-averaged spectral EEG analysis, resulting in one baseline epoch, five acute infusion epochs, and three post-infusion epochs.

For each epoch, the EEG data was segmented into two-second trials with a 0.5-second overlap. In Fieldtrip toolbox, an IRASA algorithm (Wen & Liu, 2016) was used before computing the FFT using dpss tapers, to separate rhythmic activity from concurrent power-spectral 1/f (fractal components) modulations. The data was then passed onto the FFT. By taking the median of the resulting auto-spectral distributions, the power-spectral 1/f component was extracted. A power-spectral estimate of rhythmic content (i.e. the oscillatory component) in the recorded signal was calculated by subtracting the power-spectral 1/f component from the original power spectrum.

Power spectral density (PSD) values were averaged across each epoch, and grand averages were calculated across all subjects for each condition, epoch, and the original, fractal, and oscillatory power spectra separately. These were plotted to visually compare DMT and placebo effects over time.

Baseline correction was performed by subtracting the average power spectrum of the baseline (minutes -6-0) from the power spectrum of each of the following epochs, and statistical analysis was performed on each of the remaining infusion and post-infusion epochs and for original, fractal

and oscillatory power spectra separately. This was done to avoid potential order effects, following previous work (Muthukumaraswamy et al., 2013). Frequency bands were defined as delta (1-4 Hz), theta (4-8 Hz), alpha (8-13 Hz), low beta (13-20), high beta (20-30), low gamma (30-45 Hz) and high gamma (45-95 Hz). Frequency band definitions were chosen to avoid notch filter effects between 45 and 55 Hz and above 95 Hz. For the statistical comparisons, the DMT infusion and post-infusion epochs were compared to the first placebo infusion epoch (minutes 0-6). This was done as participants reported increased drowsiness after the 6-minute mark during placebo doses, which led to changes in the EEG recordings in the later infusion and post-infusion epochs characteristic of sleep onset, thereby not providing a sensible comparison for the DMT dose.

Statistical analysis was performed using two-tailed paired-samples Monte Carlo cluster permutation t-tests with an initial cluster-forming threshold of $p = 0.05$ repeated for 7500 permutations to identify significant differences between DMT and placebo conditions across the defined frequency bands and different sensor locations and time points. A cluster-based correction was used to control the family-wise error rate while considering spatial and temporal correlations in the data, and the significance level was set to $\alpha = 0.025$. The statistical results of the comparison between DMT and placebo conditions for each frequency band over time were visualised using topographical plots.

4.2.6.4 Source-level time-averaged spectral power

Spectral power analysis was also performed on source-reconstructed EEG data. For this, IRASA FFTs were performed on the source-level EEG data, with the approach identical to the one used for the sensor-level data. Grand averages were calculated across all subjects, for each condition, epoch, and the original, fractal, and oscillatory power spectra, separately. Baseline correction was performed by subtracting the average power spectrum of the baseline (minutes -6-0) from the power spectrum of each of the following epochs. Frequency bands were defined as delta (1-4 Hz), theta (4-8 Hz), alpha (8-13 Hz), low beta (13-20), high beta (20-30), low gamma (30-45 Hz) and high gamma (45-95 Hz).

For each epoch, the power spectrum data for the DMT and PCB conditions were averaged across the specified frequency bands. Paired-samples t-tests were used to compare the frequency band power between the DMT and placebo conditions across different epochs. For each frequency band and epoch, a paired t-test was performed. FDR correction was used for multiple comparisons, and statistical significance was set to $p < 0.05$.

The BrainNet Viewer tool (Xia et al., 2013) was used to plot the results on a standard brain mesh. To visualise the significant differences in brain activity, the AAL mask was used to map significant areas of interest in the brain. For each frequency band and epoch, significant AAL regions were identified, and their corresponding t-statistics were mapped onto a 3D brain mask.

4.2.7 LZ complexity analysis

4.2.7.1 Sensor-level time-course of LZ complexity

To visualise the effects of DMT on spontaneous signal diversity over time, continuous EEG data was segmented into two-second trials. For each trial, LZ complexity was calculated using the open-source LZ76.c code available for MATLAB (Mediano et al., 2021). This function computes LZ complexity of a binary sequence by counting the number of distinct substrings encountered as it scans through the sequence, reflecting the complexity of the sequence. Each continuous 2-second signal of each channel was transformed into a string of 1000 binary digits, using its mean activity over the two seconds as binarisation threshold. The resulting matrix was concatenated into one binary string, then the LZ compression algorithm was applied, which divides the string into non-overlapping and unique substrings. Hence, the more diverse the binary string, the more substrings it will be divided into, and the number of these substrings will be referred to as the LZ complexity index LZc.

The LZc data was thresholded to remove ± 3 SD from the mean, and missing data was linearly interpolated. The data was lowpass-filtered using a cutoff frequency of 0.08 Hz, averaged across channels, and a baseline correction was applied by subtracting six minutes of recorded baseline activity from the signal. Data was z-scored across DMT and placebo conditions and smoothed using a moving mean with a window size of 21. The resulting signal was plotted for both DMT and placebo conditions over time.

4.2.7.2 Sensor-level time-averaged LZ complexity

To compare spontaneous signal diversity between DMT and placebo conditions, LZc was calculated for 6-minute epochs of averaged data starting 6 minutes before the infusion, resulting in a total of nine epochs (one baseline, five infusion, and three post-infusion epochs).

For this, pre-processed EEG data was segmented into 6-minute epochs, and for each of these epochs, the data was segmented into two-second trials. For each trial, Lempel-Ziv complexity was

calculated using the open-source LZ76.c code available for MATLAB (see above). Grand averages over subjects were computed for all epochs and both conditions separately. Baseline correction was performed on the grand-average results by subtracting the baseline (first epoch) values from each subsequent epoch.

Cluster-based permutation tests were conducted to compare the baseline-corrected LZc values between the DMT and PCB conditions. The analysis was performed for each epoch, excluding the baseline. The second placebo epoch was used to compare against each of the DMT epochs. Two-tailed paired-samples Monte Carlo permutation t-tests with 7500 permutations were used to identify significant differences between DMT and placebo conditions across different sensor locations and time points. A cluster-based correction was used to control the family-wise error rate while considering spatial and temporal correlations in the data, and the significance level was set to $\alpha = 0.025$. The statistical results of the comparison between DMT and placebo conditions over time were visualised using topographical plots.

4.2.7.3 Source-level time-averaged LZ complexity

Spontaneous signal diversity analysis was also performed on source-reconstructed EEG data. For this, LZc values were computed for each region and timepoint following the same approach as for the sensor-level data. Grand averages were calculated across subjects for each epoch and condition separately. Baseline correction was performed by subtracting the baseline (minutes -6-0) data from each subsequent epoch. Paired-samples t-tests were used to compare LZc between the DMT and placebo conditions across different time points. For each region and time point, a paired t-test was performed. FDR correction was used to correct for multiple comparisons, and statistical significance was set to $p < 0.05$. The BrainNet Viewer tool (Xia et al., 2013) was used to plot the results on a standard brain mesh. To visualise the significant differences in brain activity, the AAL mask was used to map significant areas of interest in the brain. Significant AAL regions were identified for each time point, and their corresponding t-statistics were mapped onto a 3D brain mask.

4.2.8 Neurophenomenology of ‘Entities’

A neurophenomenological approach was employed to investigate the EEG effects of ‘entity encounters’. For this, ESM ratings of entities were used to identify specific moments during the DMT infusion in which experiences of entities occurred vs moments during the DMT infusion in

which experiences of entities did not occur. Therefore, the data were split into three conditions: 1) placebo, 2) ‘No entities’, and 3) ‘Entities’.

The DMT EEG data were segmented, extracting segments of ten seconds of data before each ESM of ‘Entities’ prompt. The prompts occurred at minutes 1, 2, 3, 4, 6, and every four minutes thereafter. For this analysis, only acute infusion timepoints were considered (minutes 0-30), as this ensures that the levels of DMT are stable while the only changing variable is that of the experience of entities. FFTs were performed on these data epochs and then assigned to either the ‘Entities’ or ‘No entities’ category. For the placebo EEG data, a six-minute epoch following the start of the placebo infusion was used (see above).

The resulting three conditions were compared against each other in separate t-tests. Comparisons were all performed within subjects, i.e., the placebo vs ‘No entities’ comparison included only participants who had given ratings of ‘No entities’ at any moment during the infusion ($n = 11$), the placebo vs ‘Entities’ comparison included only participants who had given ratings of ‘Entities’ at any moment during the infusion ($n = 13$), and the ‘No entities’ vs ‘Entities’ comparison included only participants who had given both ‘No entities’ and ‘Entities’ ratings at any point during the infusion ($n = 8$).

For each of these subsamples, separate grand averages were calculated for both conditions and baseline-corrected before statistical analysis. Two-tailed paired-samples Monte Carlo cluster permutation t-tests were performed with an initial cluster-forming threshold of $p = 0.05$ repeated for 7500 permutations, to identify significant differences between the conditions across the defined frequency bands as well as LZc and different sensor locations and time points. A cluster-based correction was used to control the family-wise error rate while considering spatial and temporal correlations in the data, and the significance level was set to $\alpha = 0.025$. The statistical results of each comparison for each frequency band and LZc were visualised using topographical plots.

4.2.9 Psychometric correlations

4.2.9.1 Static psychometric correlations

Correlational analysis was performed using 6-minute averaged EEG data and static subjective measures, i.e. static VAS scale items (for a detailed description of the items, see Chapter 3 – “*Subjective effects and phenomenology of continuous infusions of DMT*”, [section 3.2.2.1.1](#)). VAS scale items with an average score of 70 or higher on Dose 5 were identified, and correlations were performed between these items and each 6-minute average of EEG frequency band and LZc. For each

correlation, Shapiro normality tests were performed for both variables (EEG and subjective measure). A Pearson correlation was performed if both variables were normally distributed; if at least one variable was not normally distributed, a Spearman correlation was chosen instead. P -values were adjusted using FDR correction to correct for multiple comparisons.

4.2.9.2 Dynamic psychometric correlations

Dynamic correlations were performed between the dynamic VAS scales and EEG frequency bands and LZc across time. For the DMT condition, Pearson correlations were calculated between each VAS item and each EEG frequency band and LZc across time, for each subject and each channel separately, then normalised and grand-averaged across subjects. As a control variable, a matrix of the same structure was filled with null values, following previous work (Timmermann et al., 2019; Timmermann et al., 2023b). Resulting r -values were compared between DMT and control conditions using two-tailed paired-samples Monte Carlo cluster permutation t -tests, to identify significant differences in the above correlations between VAS items and EEG variables between the DMT and control condition. The initial cluster-forming threshold was set to $p = 0.05$ across 7500 permutations, and a cluster-based correction was used to control the family-wise error rate while considering spatial and temporal correlations in the data, and the significance level was set to $\alpha = 0.025$. The results of the statistical comparison for each VAS item and EEG frequency band and LZc were visualised using topographical plots.

4.3 Results

4.3.1 Data quality and inclusion

Out of the initial 20 participants, data from 18 were included in the final analysis. Two participants were excluded due to excessive artifacts that could not be satisfactorily corrected. One participant's DMT infusion was terminated at minute 24; therefore, data beyond that point were not included in the analyses. The remaining datasets were confirmed to meet the quality standards for minimal noise and artifact interference, ensuring reliable analysis. During ICA, an average of 151.7 components (SD = 22.9, range 104-191) were removed from each dataset in the placebo condition, and an average of 160.8 components (SD = 13.9, range = 127-176) were removed from each dataset in the DMT condition. Figure 26 shows example traces of each EEG frequency band obtained after EEG preprocessing.

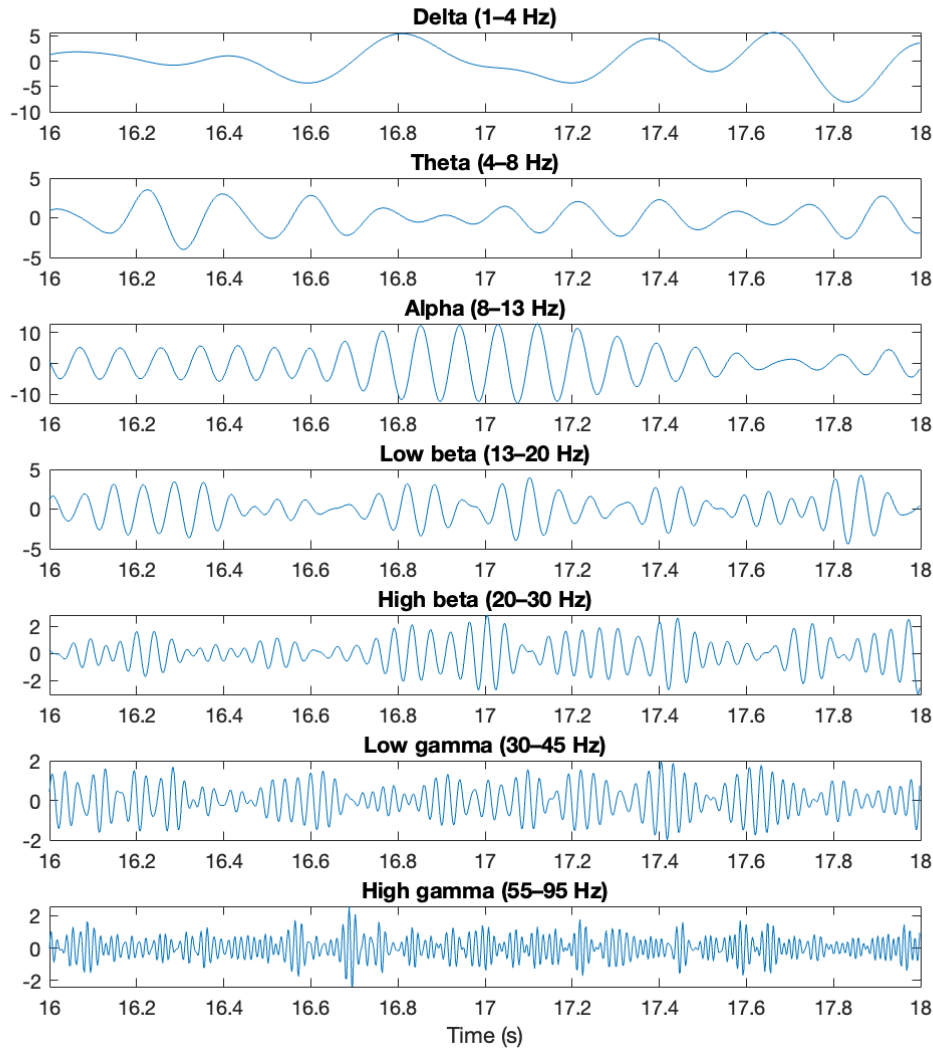


Figure 26. EEG traces obtained for each frequency band after EEG preprocessing.

Two seconds of example eyes-closed baseline EEG recording from Participant 08 are shown.

4.3.2 Spectral power analyses

4.3.2.1 Sensor-level TFR

TFR plots were generated to visualise spectral activity in the DMT and placebo conditions over the course of the EEG recording (Figure 27). The data is shown for 1–45 Hz and for six minutes of eyes-open baseline recording, eight minutes of eyes-closed baseline recording, 30 minutes of infusion, and 22 minutes of post-infusion.

During the baseline period, the TFRs of both DMT and placebo conditions appeared similar across all frequency bands, with characteristic alpha band power attenuations during the eyes-open baseline period and increased alpha band power in the eyes-closed baseline period. Following drug administration, distinct patterns emerged in the DMT condition. An attenuation of alpha band activity is visible acutely and up to 10 minutes following the end of infusion, as well as a decrease in theta band activity, which lasts until the end of the EEG recording. Additionally, beta band activity is decreased in the first two minutes following bolus IV injection.

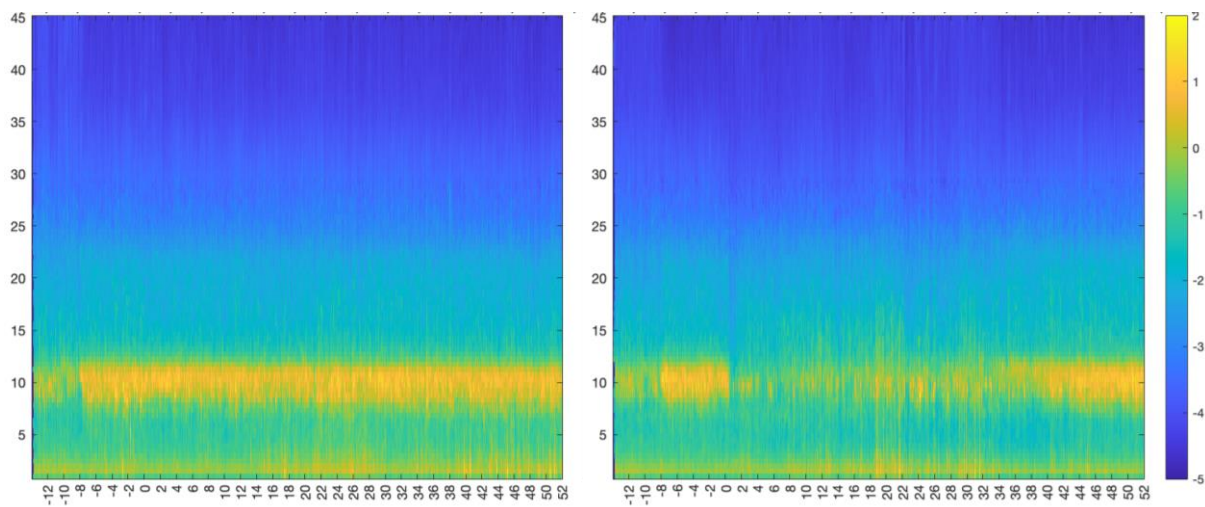


Figure 27. TFR of placebo (left) and DMT (right).

The data are shown on a log scale. The x-axis shows time (minutes) and the y-axis shows frequencies (Hz). Data is shown for 6 minutes of eyes-open baseline (minutes -14 to -8), 8 minutes of eyes-closed baseline (minutes -8 to 0), infusion (minutes 0 to 30), and post-infusion (minutes 30 to 52).

4.3.2.2 Sensor -level time-course of EEG rhythms

Continuous average spectral activity for different frequency bands in the DMT and placebo conditions over time, overlaid with average ratings of intensity over time, is shown in Figure 28. The data was thresholded to remove outliers ± 3 SD from the mean, lowpass-filtered with a cutoff frequency of 0.08 Hz, baseline corrected, z-scored across DMT and placebo conditions, and

smoothed using sliding window means. Results show an increase in delta and theta band activity throughout the infusion in both DMT and placebo conditions, with the DMT condition showing a sharper drop following the end of the infusion. Alpha band activity in the DMT condition shows a characteristic substantial decrease almost immediately following the bolus IV injection and remaining low throughout the infusion and for approximately eight minutes beyond, mirroring ratings of subjective intensity over time. Both low and high beta band power show a distinct decrease in the first two minutes following DMT administration, then slowly increase over the course of the infusion. Low gamma band power slowly increases towards the second part of the infusion. In contrast, high gamma shows strong increases starting with DMT administration and sustaining until the end of the infusion, roughly following the trajectory of subjective intensity ratings. Increases in delta and theta power over time in the placebo condition are consistent with the onset of drowsiness reported by participants, further justifying the decision to compare all EEG epochs of the DMT condition against the first infusion epoch of the placebo condition.

4. EEG effects of continuous IV infusions of DMT

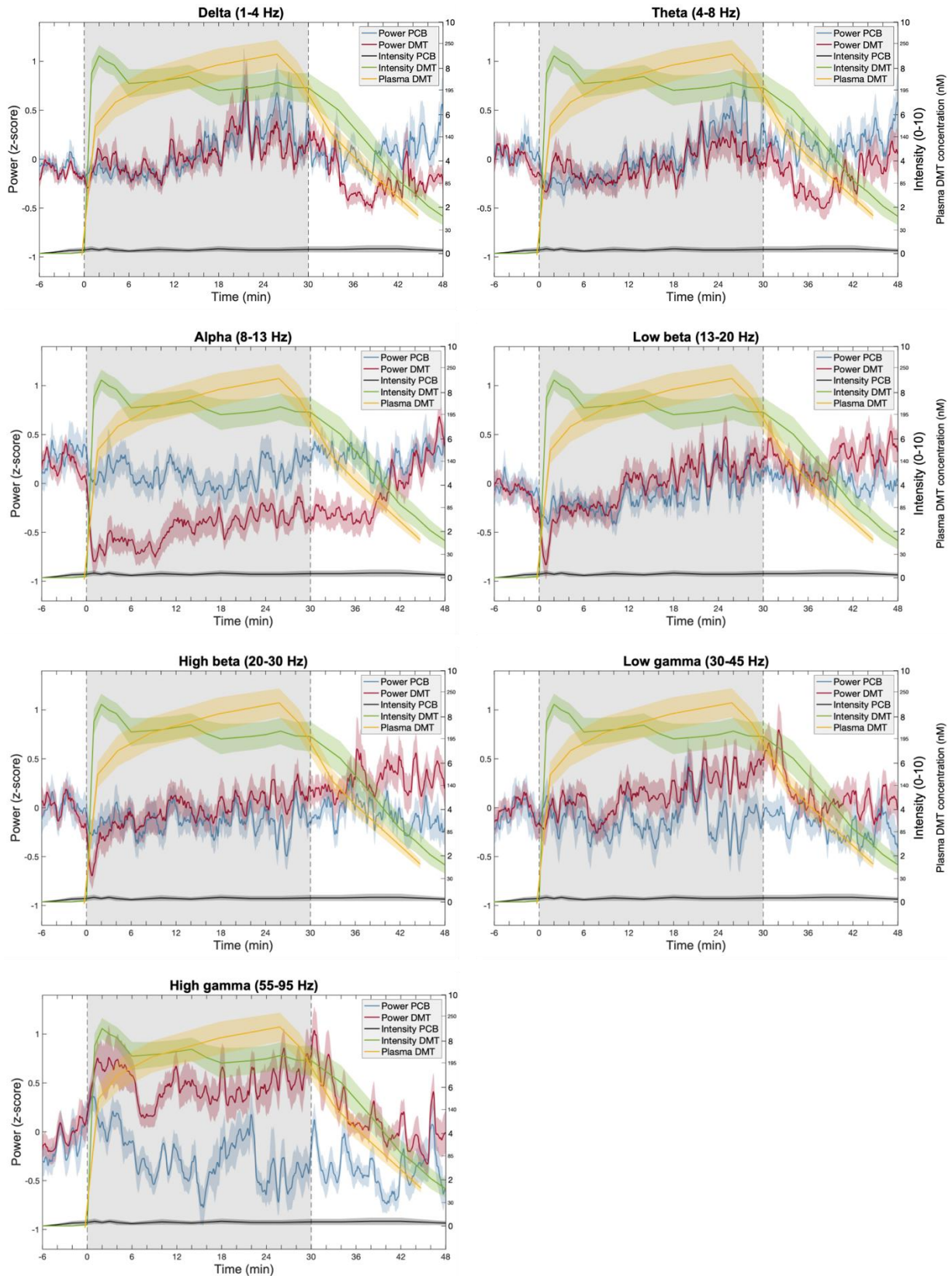


Figure 28. Spectral power in defined frequency bands over time.

The DMT condition is shown in red and the placebo condition is shown in blue. Average subjective intensity over time is shown in green. Values are plotted as smoothed means $\pm$ SEM.

4.3.2.3 Sensor-level time-averaged spectral power

Statistical comparisons between spectral power in DMT vs placebo conditions were conducted for 6-minute averages of spectral power in the defined frequency bands. The EEG data were processed using the IRASA method to separate fractal and oscillatory components. Cluster-based permutation t-tests were used to identify significant differences in spectral power between the DMT and placebo conditions across various frequency bands (delta [1-4 Hz], theta [4-8 Hz], alpha [8-13 Hz], low beta [13-20 Hz], high beta [20-30 Hz], low gamma [30-45 Hz], and high gamma [55-95 Hz]) and epochs. (ranging from 0 to 48 minutes post-infusion). Averaged EEG of 6-minute epochs of resting state activity following bolus injection of DMT was contrasted against the first 6-minute epoch following placebo injection.

4.3.2.3.1 Original signal. Figure 29 shows the power spectra for placebo and DMT conditions across the different epochs. During the baseline period, the PCB and DMT conditions showed similar spectral profiles, exhibiting a peak in power within the alpha band (8-13 Hz). There were no discernible differences between the two conditions during this period. In the initial phase of the infusion, there was a noticeable decrease in power for the DMT condition compared to the PCB condition, particularly evident in the alpha band (8-13 Hz), along with visible decreases in the theta band (4-8 Hz) and beta band (13-30 Hz) power. This trend persisted until the end of the infusion period. In the post-infusion period, the DMT condition showed a recovery in power during minutes 36-42, although power in the alpha band remained lower than in the placebo condition. Notably, there is an increase in delta band (1-4 Hz) activity starting here and continuing until the end of the post-infusion period.

4. EEG effects of continuous IV infusions of DMT

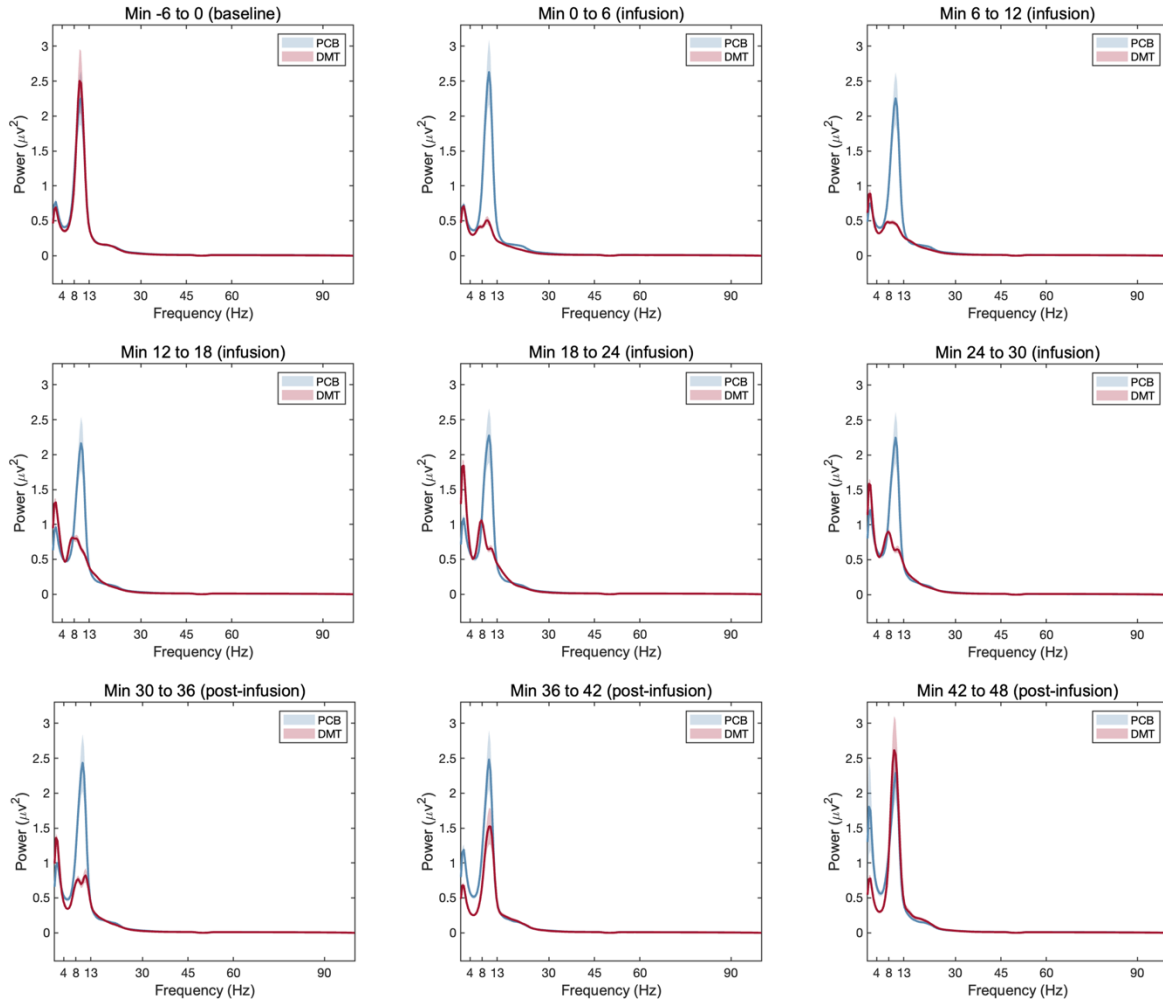


Figure 29. Time-averaged frequency spectra (original data).

Original data before separation into fractal and oscillatory components. Each subplot represents a 6-minute epoch, with the x-axis indicating frequency (Hz) and the y-axis indicating power ($\mu\text{V}^2/\text{Hz}$). The placebo condition is depicted in blue, and the DMT condition is depicted in red. Values are plotted as means $\pm$ SEM.

The results of the statistical analysis comparing DMT and placebo conditions are presented in the topographical plots in Figure 30. These plots show the spatial distribution of significant differences in power spectra between DMT and placebo across different frequency bands and time points during the infusion and post-infusion periods.

Using cluster-based permutation tests, significant differences in power between the DMT and placebo conditions across various frequency bands were identified. Significant clusters in the theta

frequency band (4-8 Hz) were found at minutes 0-6 (max. $t[17] = -102.26$, cluster $p = 0.019$) and 36-42 mins (max. $t[16] = -84.36$, cluster $p = 0.022$). In the alpha band, a significant cluster was identified, encompassing all timepoints from minute 0 to minute 42, with the most considerable difference occurring at timepoint 0-6 mins (max. $t[17] = -730.88$, cluster $p = <0.001$). The decrease in alpha band activity shows a weakening in the middle of the infusion, at timepoint 18-24 mins (max. $t[17] = -413.39$, cluster $p = 0.004$), before resuming to decrease until minutes 30-36 (max. $t[16] = -573.53$, cluster $p = <0.001$).

In the low beta (30-45 Hz) frequency band, power initially decreased during minutes 0-6 (max. $t[17] = -323.68$ cluster $p = 0.003$) and minutes 6-12 (max. $t[17] = -117.87$, cluster $p = 0.017$), and later showed an increase compared to placebo, significant during minutes 12-18 (max. $t[17] = 98.09$, cluster $p = 0.021$) and minutes 24-30 (max. $t[16] = 130.97$, cluster $p = 0.015$). In the high beta band, decreases compared to placebo were seen throughout the infusion epochs, most powerfully and widespread during minutes 0-6 (max. $t[17] = -384.64$, cluster $p = 0.005$), weakening and posteriorising over time (max. $t[16] = -91.55$, cluster $p = 0.016$ at minutes 30-36). Slight decreases in low gamma band activity were seen at the beginning of the infusion (max. $t[17] = -125.13$, cluster $p = 0.013$ at minutes 0-6) and weakening over time, while increases in activity around the temporal channels became significant at minutes 30-36 (max. $t[16] = -51.86$, cluster $p = 0.023$, all cluster corrected).

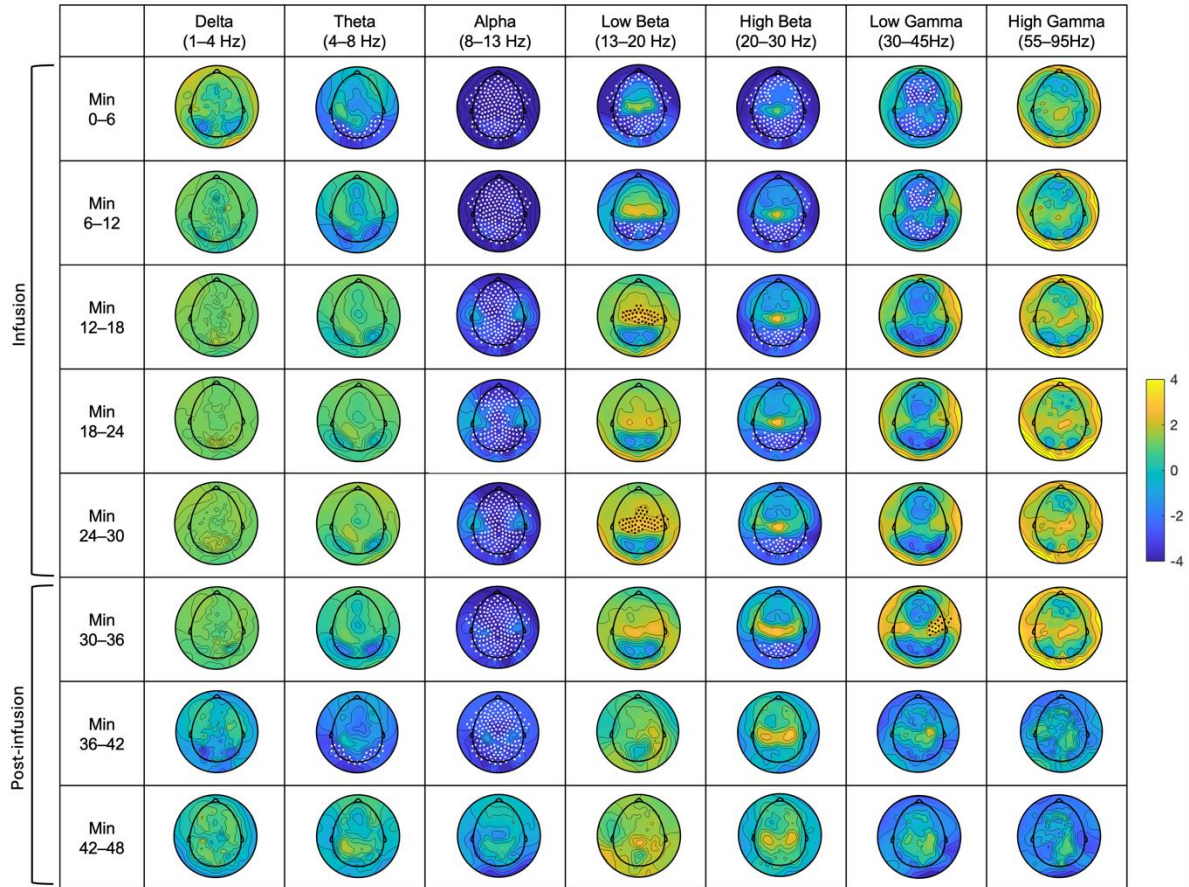


Figure 30. Sensor-level time-averaged spectral power (original data).

Topographic distributions of significant differences in the original data (before separation into fractal and oscillatory components). Frequency bands are shown in the columns, and 6-minute epochs are shown in the rows. T-statistic values of the t-tests between DMT and placebo conditions are represented on a colour scale, and significant differences are represented as dots corresponding to the electrode locations of significant p -values after cluster correction.

4.3.2.3.2 Oscillatory signal. The oscillatory component of the signal was obtained by subtracting the fractal ($1/f$) component from the original data. Power-spectral oscillatory activity in the DMT and placebo conditions across time are shown in Figure 31. Following DMT administration, a substantial attenuation of oscillatory power is seen in the alpha band (8-13 Hz), lasting until minute 36, after which it quickly normalises. In contrast, slight increases in power are seen in theta (4-8 Hz) and beta (13-30 Hz) frequency bands.

4. EEG effects of continuous IV infusions of DMT

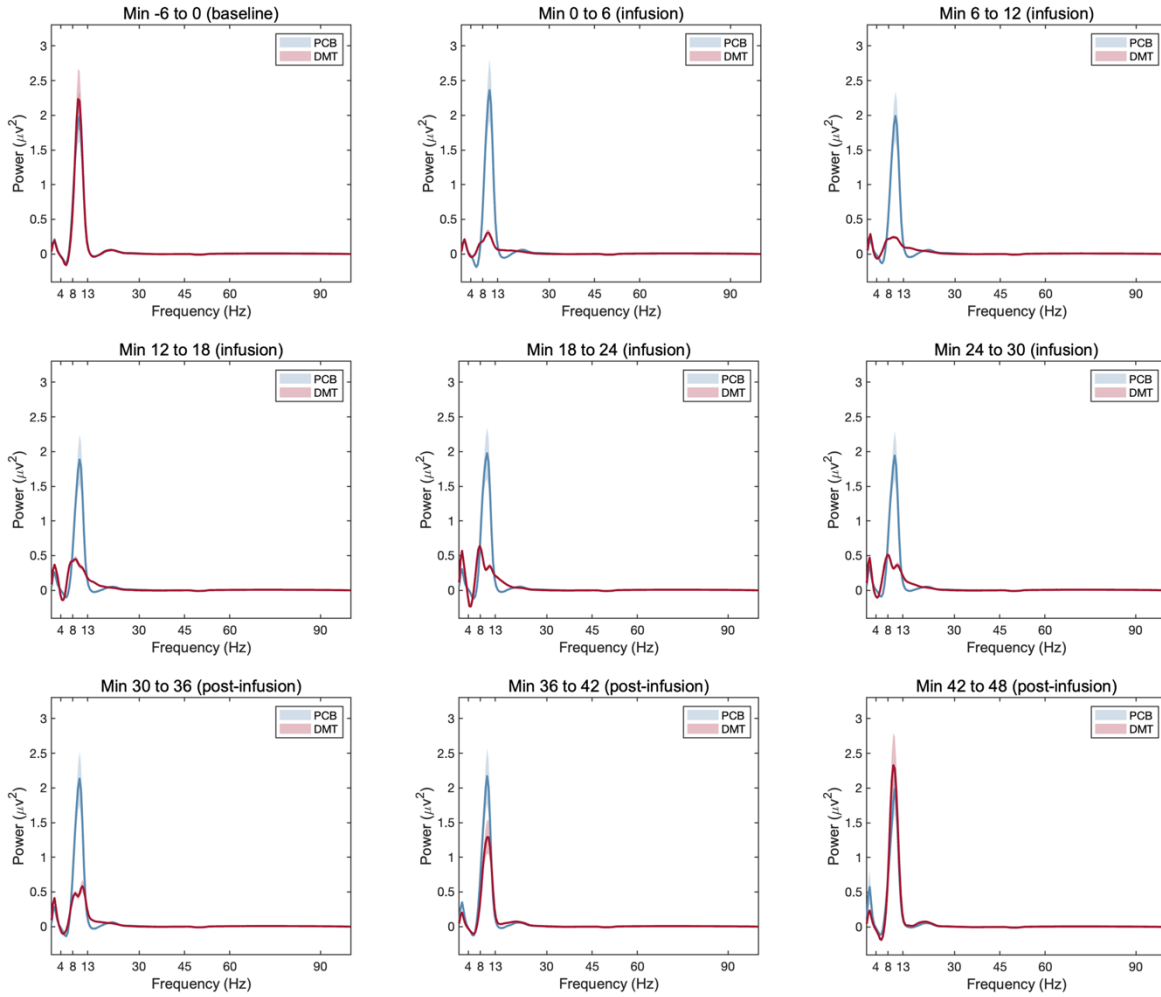


Figure 31. Time-averaged frequency spectra (oscillatory data).

Oscillatory signal after separation of the fractal component from the original data. Each subplot represents a 6-minute epoch, with the x-axis indicating frequency (Hz) and the y-axis indicating power ($\mu\text{V}^2/\text{Hz}$). The placebo condition is depicted in blue, and the DMT condition is displayed in red. Values are plotted as means $\pm$ SEM.

Cluster-based permutation t-tests were conducted to identify significant differences in oscillatory activity between DMT and placebo conditions. Following DMT administration, oscillatory theta band activity increased compared to placebo, and these increases persisted throughout the infusion and post-infusion periods, being strongest and most widespread during minutes 0-6 (max. $t[17] = 398.95$, cluster $p = 0.003$) and minutes 30-36 (max. $t[16] = 320.68$, cluster $p = 0.001$). Oscillatory alpha activity was highly significantly decreased during all epochs from minutes 0-6 to minutes 26-

42, with the most substantial effects observed at minutes 0-6 (max. $t[17] = -723.36$, cluster $p = <0.001$). Oscillatory low beta activity was significantly increased in the DMT condition compared to placebo, with strongest effects found at the beginning (minutes 0-6, max. $t[17] = 625.79$, cluster $p = <0.001$) and the end of infusion (minutes 24-30, max. $t[16] = 635.45$, cluster $p = <0.001$). Conversely, high beta oscillatory activity was found to be decreased compared to placebo at temporal and posterior locations, and this effect was most pronounced in the middle of the infusion, at minutes 18-24 (max. $t[17] = -242.27$, cluster $p = 0.005$). In the low gamma frequency band, oscillatory activity was decreased in the DMT compared to the placebo condition at central electrodes and only during the infusion period (0-30 minutes), with the strongest effect at minutes 12-18 (max. $t[17] = -260.27$, cluster $p = 0.002$, all cluster corrected). No differences were seen in delta and high gamma oscillatory activity. Topographical maps corresponding to these results are depicted in Figure 32, illustrating the distribution and intensity of significant differences across various frequency bands and time points.

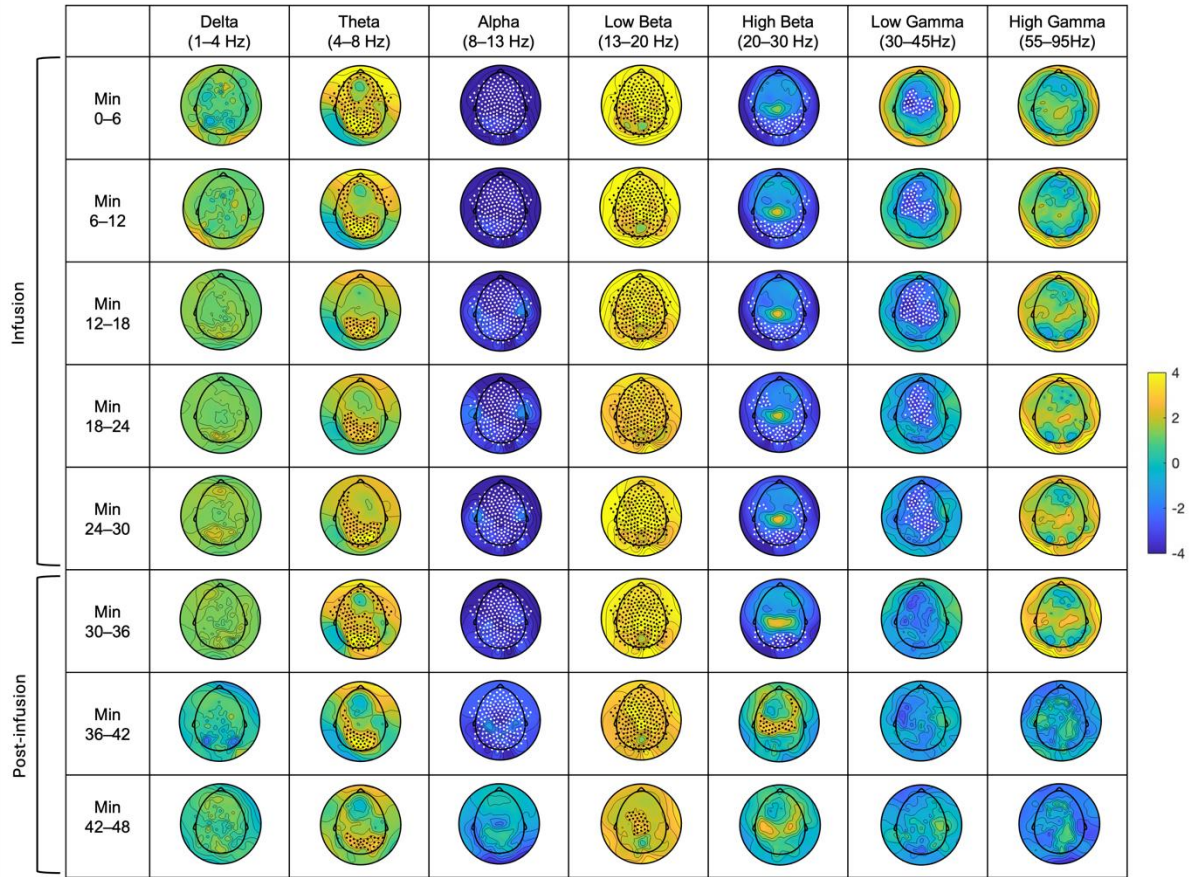


Figure 32. Sensor-level time-averaged spectral power (oscillatory data).

Topographic distributions of significant differences in the oscillatory signal (after subtracting the fractal component from the original data). Frequency bands are shown in the columns, and 6-minute epochs are shown in the rows. T-statistic values of the t-tests between DMT and placebo conditions are represented on a colour scale, and significant differences are represented as dots corresponding to the electrode locations of significant p -values after cluster correction for multiple comparisons.

4.3.2.4 Post-hoc analysis of alpha peak frequency changes following DMT administration

An exploratory analysis was conducted to investigate potential changes in alpha peak frequency following DMT administration. For this, the data were averaged over the duration of the infusion, and alpha peak frequencies were identified for each subject and each condition separately. A visual check was conducted to verify the alpha peaks, and five subjects were excluded at this stage, as

they did not show any discernible alpha peak in either the DMT condition or both conditions. A paired-samples t-test with the remaining subjects showed no significant difference in peak alpha frequency between DMT and placebo conditions, $t(12) = 0.15$, $p = 0.886$. A visual inspection of the boxplots for each condition shows that peak alpha frequency ‘spreads’ following DMT administration, resulting in two somewhat distinct groups centering around 11 Hz and 9 Hz, potentially explaining the double peak observed in the alpha band following DMT administration (Figure 33).

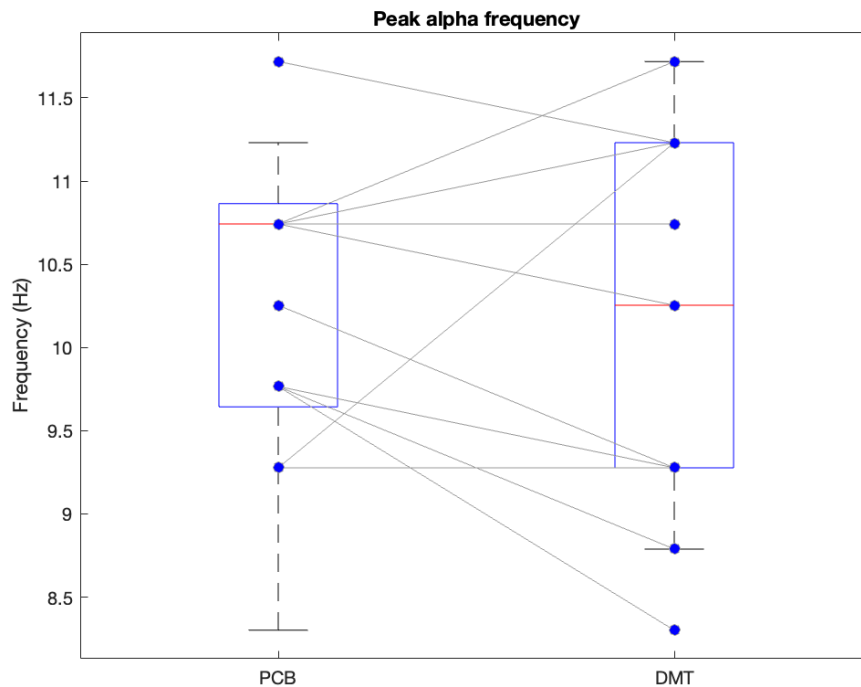


Figure 33. Alpha peak frequency in placebo and DMT conditions.

The data are shown as boxplots for each condition, indicating the median and interquartile range, as well as individual datapoints linked between conditions, visualising individual changes.

4.3.2.5 Source-level time-averaged spectral power

Spectral power analysis was performed on source-reconstructed EEG data to estimate the locations of differences in EEG activity between DMT and placebo conditions. The source-reconstructed EEG data were processed using the IRASA method to separate fractal and oscillatory components.

Cluster-based permutation t-tests were used to identify significant differences in spectral power between the DMT and placebo conditions across various frequency bands (delta [1-4 Hz], theta [4-8 Hz], alpha [8-13 Hz], low beta [13-20 Hz], high beta [20-30 Hz], low gamma [30-45 Hz], and high gamma [55-95 Hz]) and epochs (ranging from 0 to 48 minutes post-infusion). Averaged EEG of 6-minute epochs of resting state activity following bolus injection of DMT was contrasted with the first 6-minute epoch following placebo administration. FDR correction was used for multiple comparisons, and statistical significance was set to $p < 0.05$.

4.3.2.5.1 Original signal. Results of the cluster-based permutation t-tests are visualised in Figure 34. Significant decreases in alpha band power were observed in the DMT condition compared to the placebo condition at minutes 0-6 (max. $t[17] = -4.51, p = 0.001$), minutes 6-12 (max. $t[17] = -4.19, p = 0.001$) minutes 18-14 (max. $t[17] = -4.14, p = 0.002$), and minutes 24-30 (max. $t[16] = -3.98, p = 0.002$, all FDR corrected) during the infusion. These effects initially comprised a wide range of brain regions, including parts of the frontal, temporal, parietal, and occipital lobes, as well as the motor cortex, insula, parts of the cingulate cortex, the basal ganglia, hippocampus, and thalamus. Effects posteriorized over time, only encompassing the occipital lobe and right PCC, as well as the left superior parietal lobule, right fusiform gyrus, and left angular gyrus in the parietal lobe. No significant differences were found at the post-infusion timepoints. A significant decrease in high beta power was observed in the DMT condition during the initial time interval (minutes 0-6; max. $t[17] = -4.69, p < 0.001$, FDR corrected), encompassing broad areas of the occipital and temporal lobes, some frontal lobe structures, and additionally, the insula, limbic system, and basal ganglia, leaving the parietal lobe completely intact. No significant differences were observed in the delta, theta, low beta, low gamma, or high gamma frequency bands at any of the epochs evaluated.

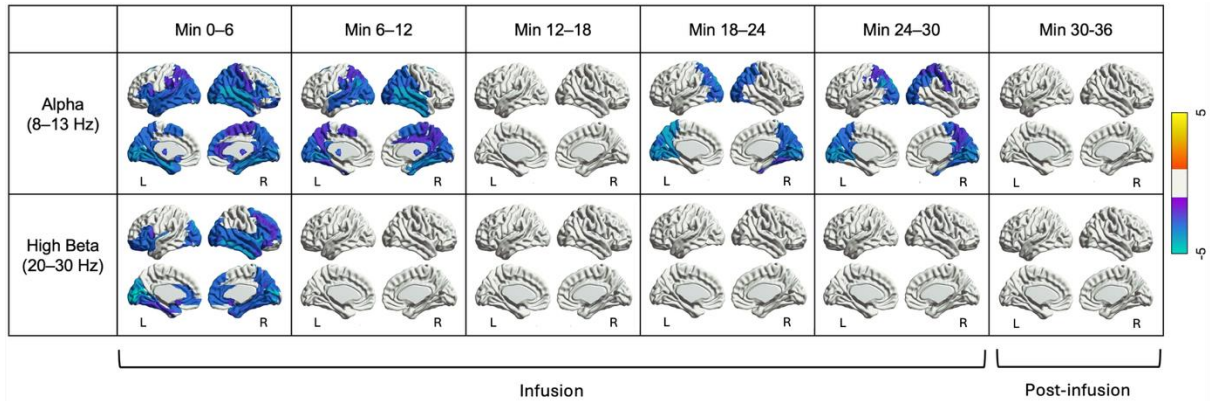


Figure 34. Source-level time-averaged spectral power (original data).

Locations of significant ($p < 0.05$, FDR corrected) changes in source-level spectral power of the original signal (before separation into fractal and oscillatory components) plotted on a cortical surface. Contrasts represent the difference between DMT and placebo during 6-minute epochs during and after the infusion. Frequency bands are shown if significant differences were found (here alpha [8-13 Hz] and high beta [20-30 Hz] frequency bands). L = left, R = right.

4.3.2.5.2 Oscillatory signal. The oscillatory component of the signal was obtained by subtracting the fractal ($1/f$) component from the original data. Significant increases in theta band power were observed in the DMT condition compared to the placebo condition during the initial phase of the infusion (minutes 0-6, max. $t[17] = 4.54$, $p = 0.001$, minutes 6-12, max. $t[17] = 4.48$, $p = 0.001$), initially encompassing the occipital cortex, and parts of the parietal lobe (more right than left), then only a small part of the occipital lobe (left superior occipital gyrus and right middle occipital gyrus. An additional increase is seen in these areas at the end of the infusion (minutes 24-30, max. $t[16] = 4.48$, $p = 0.001$). Significant decreases in alpha band power were noted during the initial 12 minutes of infusion (minutes 0-6, max. $t[17] = -4.09$, $p = 0.002$, minutes 6-12, max. $t[17] = -3.98$, $p = 0.002$), initially encompassing almost all of the brain, except the straight gyri, and precentral and orbitofrontal areas in the frontal lobe, the middle cingulum, and the left postcentral cortex. Additionally, significant decreases were also seen in the later parts of the infusion (minutes 18-24, max. $t[17] = -4.15$, $p = 0.002$, minutes 24-30, max. $t[16] = -4.20$, $p = 0.001$). These were localised to the occipital lobe, excluding the cuneus, right superior occipital gyrus, and left middle occipital gyrus. In the low beta band, significant increases were observed during minutes 0-6 (max. $t[17] =$

4.65, $p = 0.001$) and minutes 12-18 (max. $t[17] = 4.17$, $p = 0.001$, all FDR corrected) in a small occipital area including the right calcarine sulcus and right middle occipital gyrus. Results of the paired-samples t-tests are visualised in Figure 35.

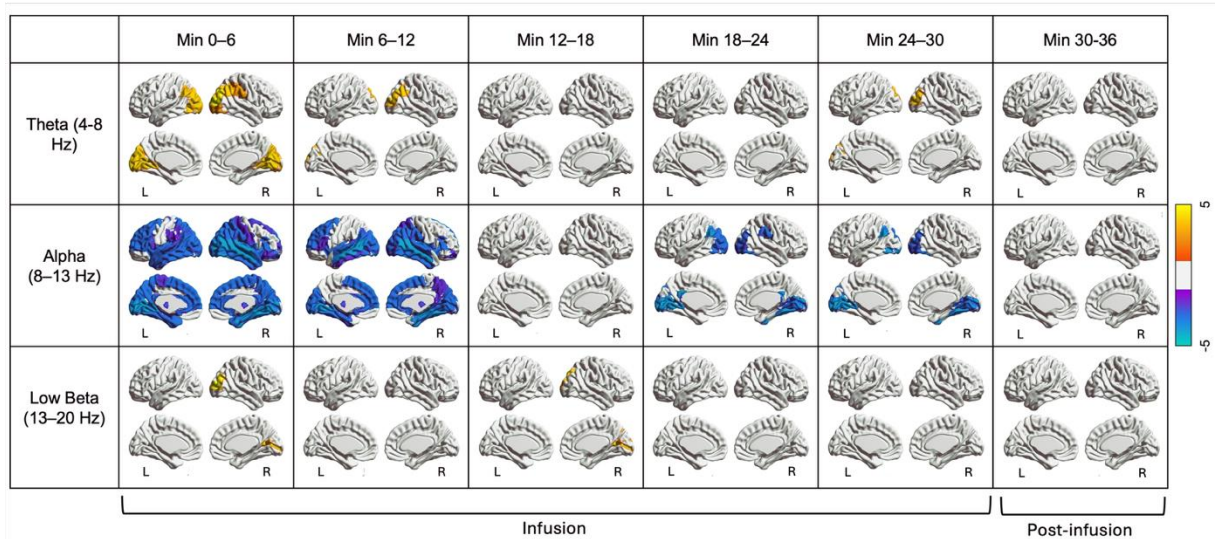


Figure 35. Source-level time-averaged spectral power (oscillatory data).

Locations of significant ($p < 0.05$, FDR corrected) changes in source-level spectral power of the oscillatory signal (after subtraction of the fractal component from the original data) plotted on a cortical surface. Contrasts represent the difference of DMT versus placebo at different timepoints during and after the infusion. Frequency bands are shown if significant differences were found (here, theta (4-8 Hz), alpha (8-13 Hz) and low beta (13-20 Hz) frequency bands). L = left, R = right.

4.3.3 LZ complexity analysis

4.3.3.1 Sensor-level time-course of LZ complexity

Figure 36 shows the average signal diversity measured by LZc for both DMT and placebo conditions over time. LZc shows a sharp increase within the first minute of DMT administration, then shows slight decreases between approximately minutes 6-24, after which it rises again,

sustaining its elevation until approximately minute 38 (8 minutes after the end of DMT administration).

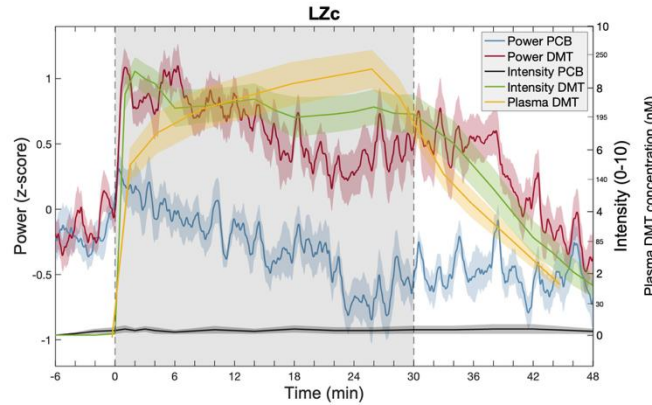


Figure 36. Average LZ complexity over time.

The data is shown for DMT (red) and placebo (blue) conditions. Average subjective intensity over time is shown in green. Values are plotted as smoothed means $\pm$ SEM.

4.3.3.2 Sensor-level time-averaged LZ complexity

LZ complexity was calculated for EEG data across DMT and placebo conditions. For this, pre-processed EEG data was segmented into 6-minute epochs, and LZc was calculated using the open-source LZ76.c code in MATLAB (Mediano et al., 2021). Grand averages of LZc were computed for all epochs under both DMT and placebo conditions, followed by baseline correction. Cluster-based permutation tests were conducted to compare LZc values between the DMT and placebo conditions. The results are visualised using topographical plots (Figure 37).

Significant increases in LZc were observed from minutes 0-6 (max. $t[17] = 7.26$, cluster $p < 0.001$) to minutes 36-42 (max. $t[16] = 5.33$, cluster $p = 0.003$) following DMT administration, compared to placebo. A first peak in LZc was observed at minutes 0-6. This was followed by a decrease in the middle infusion period, driven by frontal areas, with LZc reaching a minimum at minutes 18-24 (max. $t[16] = 4.52$, cluster $p = 0.008$). A second peak in LZc was seen at minutes 24-30 (max. $t[16] = 7.22$, cluster $p = 0.002$, all cluster corrected). No significant differences in LZc were found at minutes 42-48.

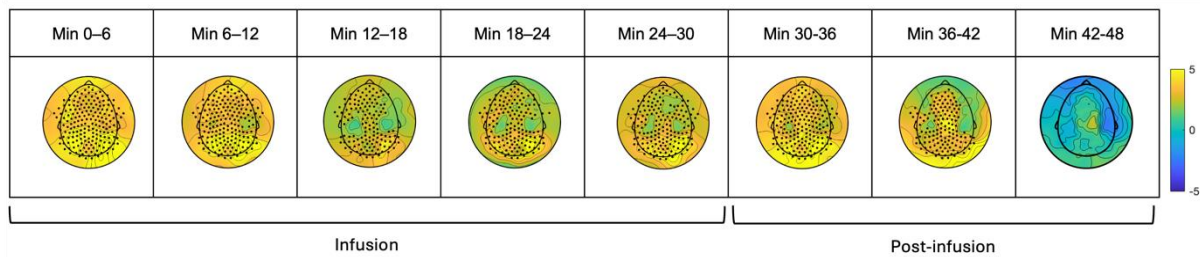


Figure 37. Sensor-level time-averaged LZc.

Topographic distributions of significant differences in LZc between DMT and placebo conditions across 6-minute epochs. T-statistic values of the t-tests between DMT and placebo conditions are represented on a colour scale, and significant differences are represented as dots corresponding to the electrode locations of significant p -values.

4.3.3.3 Post-hoc analysis of time-averaged Lempel-Ziv complexity excluding high gamma band activity

Based on previous observations of high gamma band activity driving the changes in LZ complexity following psychedelics, the above analysis was repeated with data lowpass-filtered between 1-45 Hz, to elucidate how high gamma oscillations contribute to the observed effect. Results showed smaller increases in LZc in the DMT condition compared to placebo between minutes 0-36, compared to the analysis including high-gamma oscillations, with minutes 12-24 losing significant differences between the DMT and placebo conditions. Minutes 36-42 saw a bigger increase in LZc in the DMT condition compared to placebo, compared to the analysis including high-gamma oscillations (Figure 38). Therefore, although the general direction of effects remains the same, these results point towards changes in high-gamma oscillations following DMT driving some of the observed effects.

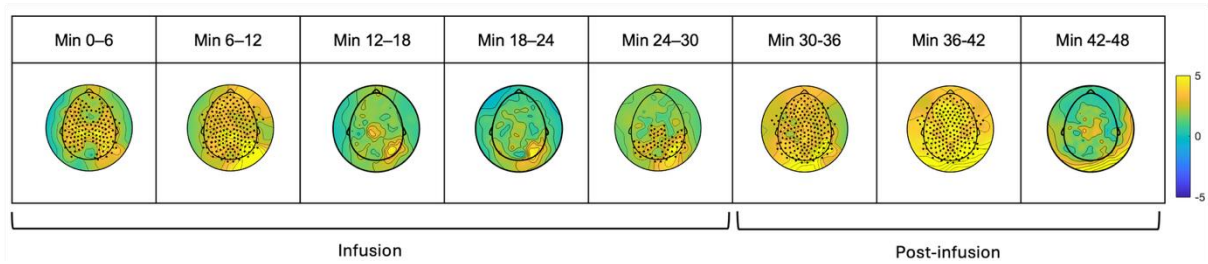


Figure 38. Sensor-level time-averaged LZ complexity computed on data lowpass-filtered between 1-45 Hz.

Topographic distributions of significant differences in LZc between DMT and placebo conditions across 6-minute epochs. T-statistic values of the t-tests between DMT and placebo conditions are represented on a colour scale, and significant differences are represented as dots corresponding to the electrode locations of significant p -values.

4.3.3.4 Source-level time-averaged LZ complexity

LZ complexity was also calculated for source-reconstructed EEG data and compared between DMT and placebo conditions. Paired-samples t-tests were used to identify significant differences in LZc between the DMT and placebo conditions across various epochs ranging from 0 to 48 minutes post-infusion. FDR correction was used to correct for multiple comparisons, and significance was set to $p < 0.05$ (Figure 39).

Significant increases in LZc were found between minutes 0-12 (mins 0-6, max. $t[17] = 38.46, p < 0.001$; mins 6-12 max. $t[17] = 6.63, p < 0.001$) and between minutes 18-36 (mins 18-24, max $t[17] = 3.58, p = 0.005$; mins 24-30, max $t[16] = 4.20, p = 0.001$; mins 30-36, max. $t[16] = 6.37, p < 0.001$, all FDR corrected), with differences being highest at the beginning of the and at the end of the infusion. Effects initially encompassed the PCC, the occipital lobe, the right fusiform gyrus, and superior parietal lobules, including the precuneus and angular gyri of the parietal lobe. During minutes 18-24, effects were reduced to only include parts of the occipital lobe.

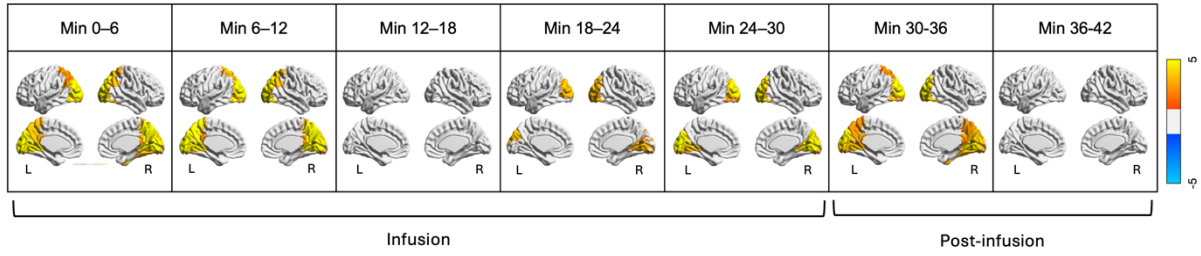


Figure 39. Source-level time-averaged LZc.

Locations of significant ($p < 0.05$, FDR corrected) source-level changes in LZc plotted on a cortical surface. Contrasts represent the difference between DMT and placebo during 6-minute epochs during and after the infusion. L = left, R = right.

4.3.4 Neuropenomenology of ‘Entities’

Statistical comparisons were performed to test the relationship between ‘entity’ experiences and spectral EEG as well as LZ complexity measures. The data were split into three conditions: 1) placebo, 2) DMT with no entities, and 3) DMT with entities and compared against each other in separate t-tests. Comparisons were performed within subjects, i.e., the placebo vs DMT no entities comparison included only participants who had given ratings of ‘No entities’ at any moment during the infusion ($n = 11$), the placebo vs DMT entities comparison included only participants who had given ratings of ‘Entities’ at any moment during the infusion ($n = 13$), and the DMT no entities vs DMT entities comparison included only participants who had given both ‘No entities’ and ‘Entities’ ratings at any point during the infusion ($n = 8$).

Results of the ‘No entities’ vs placebo comparison show a widespread reduction in alpha band power (max. $t[10] = -5.31$, cluster $p < 0.001$), as well as occipital reductions in low beta band (max. $t[10] = -5.25$, cluster $p = 0.003$) and high beta band power (max. $t[10] = -4.48$, cluster $p = 0.024$). Additionally, a strong and widespread increase in LZc was found for the ‘No entities’ condition compared to placebo (max. $t[10] = 8.94$, cluster $p < 0.001$). Comparing ‘Entities’ and placebo conditions, results show a widespread reduction in alpha band power (max. $t[12] = -4.76$, cluster $p < 0.001$), as well as occipital reductions in high beta band power (max. $t[12] = -4.04$, cluster $p = 0.018$). An increase in LZc was found for the ‘Entities’ condition compared to placebo (max. $t[12] = 8.70$, cluster $p = 0.004$). Finally, a comparison between the ‘Entities’ and ‘No entities’ conditions

revealed higher power in alpha (max. $t[7] = 2.91$, cluster $p = 0.032$) and low beta (max. $t[7] = 3.1053$, cluster $p = 0.0083$) and high beta bands (max. $t[7] = 3.92$, cluster $p = 0.048$), significant at parietal and central sensor positions. Additionally, a relative reduction in LZc in the ‘Entities’ condition compared to the ‘No entities’ conditions was found (max. $t[7] = -7.20$, cluster $p < 0.001$, all cluster corrected). Figure 40 shows the results in topographical plots of each frequency band and LZc for each comparison.

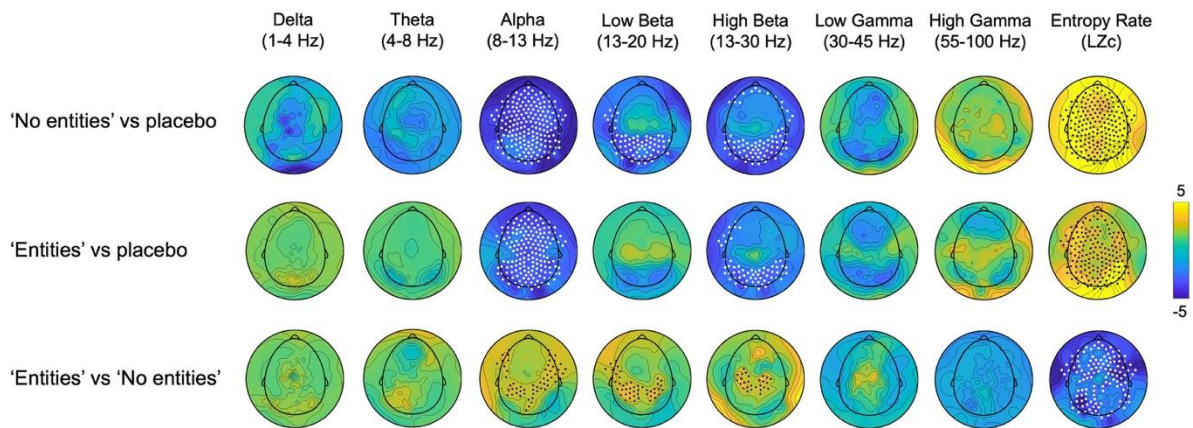


Figure 40. Neurophenomenology of ‘Entities’.

Topographical distributions of significant differences between 1) ‘No entities’ vs placebo conditions, 2) ‘Entities’ vs placebo conditions, and 3) ‘Entities’ vs ‘No entities’ conditions. These comparisons are shown in the rows, and EEG frequency bands and LZc are shown in the columns. T-statistic values of the t-tests are represented on a colour scale, and significant differences are represented as dots corresponding to the electrode locations of significant p -values after cluster correction for multiple comparison.

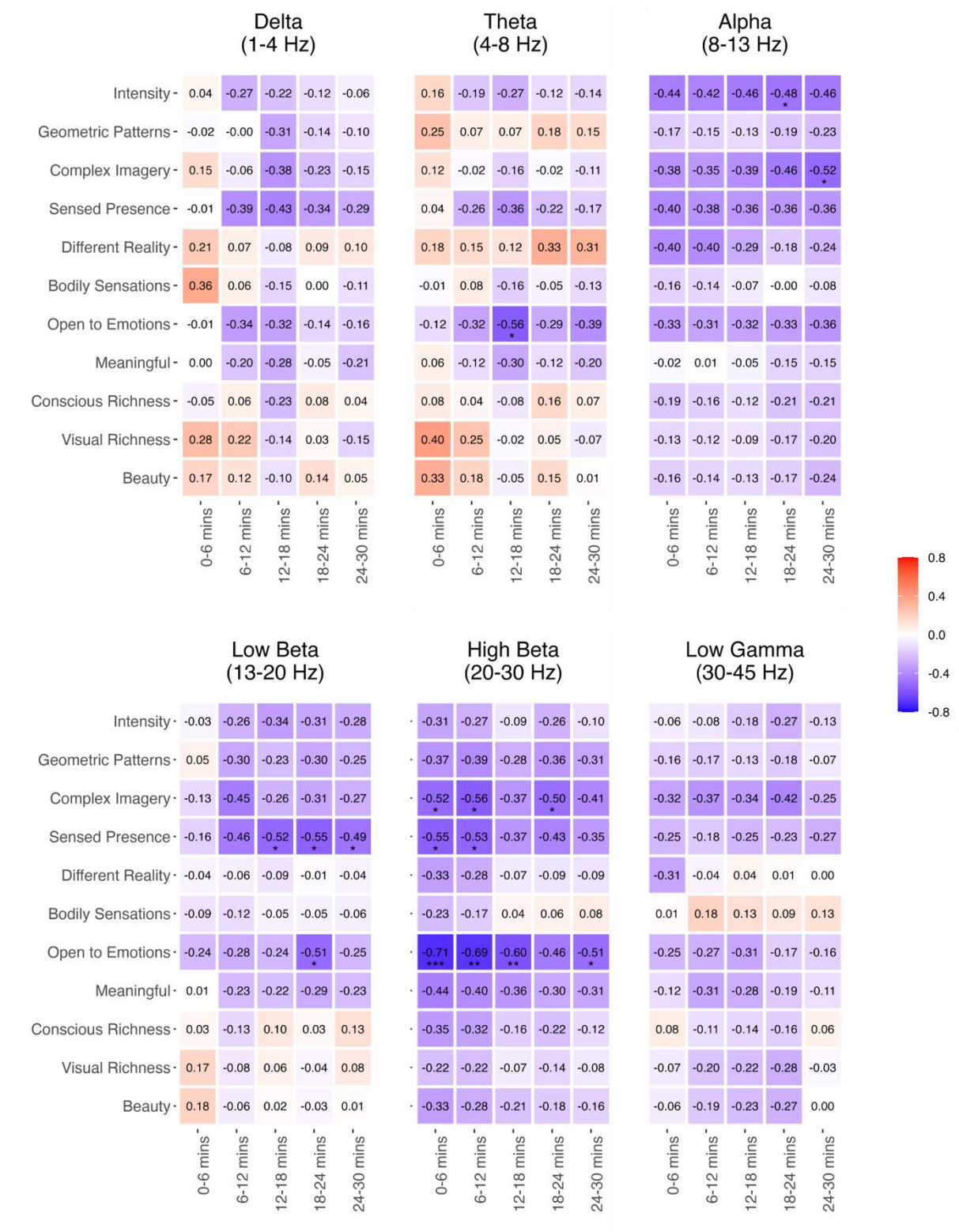
4.3.5 Psychometric correlations

4.3.5.1 Static correlations

Correlational analysis was performed using 6-minute epochs of whole-scalp averaged EEG data and selected static VAS scale items (for a detailed description of the items, see Chapter 3 – “Subjective effects and phenomenology of continuous infusions of DMT”, [section 3.2.2.1.1](#)). The following

eleven VAS items showed and average score of 70 or higher on Dose 5 and were included in the analysis: “Intensity”, “Geometric Patterns”, “Complex Imagery”, “Sensed Presence”, “Different Reality”, “Bodily Sensations”, “Open to Emotions”, “Meaningful”, “Conscious Richness”, “Visual Richness”, and “Beauty”. This resulted in a total of 440 correlations across five 6-minute epochs and eight EEG features (delta power, theta power, alpha power, low beta power, high beta power, low gamma power, high gamma power, LZc). Results showed a moderate negative correlation between alpha band power and VAS scale items ‘Intensity’, ‘Complex imagery’, ‘Sensed presence’, and ‘Open to emotions’. Additionally, there was a moderate negative correlation between alpha band power and ‘Different reality’ for the first 12 minutes of the infusion. Low beta power showed a moderate correlation with ‘Sensed presence’, which was significant before FDR correction for the later part of the infusion. High beta power showed a moderate negative correlation with ‘Complex imagery’ and ‘Sensed presence’ and a strong negative correlation with ‘Open to emotions’. These effects were significant for the first part of the infusion before FDR correction. High gamma showed a moderate positive correlation with ‘intensity’ for the first 6 minutes of infusion, significant before FDR correction. LZc showed a moderate positive correlation with ‘Intensity’ throughout the duration of the infusion. Importantly, none of these results survived FDR correction (Figure 41).

4. EEG effects of continuous IV infusions of DMT



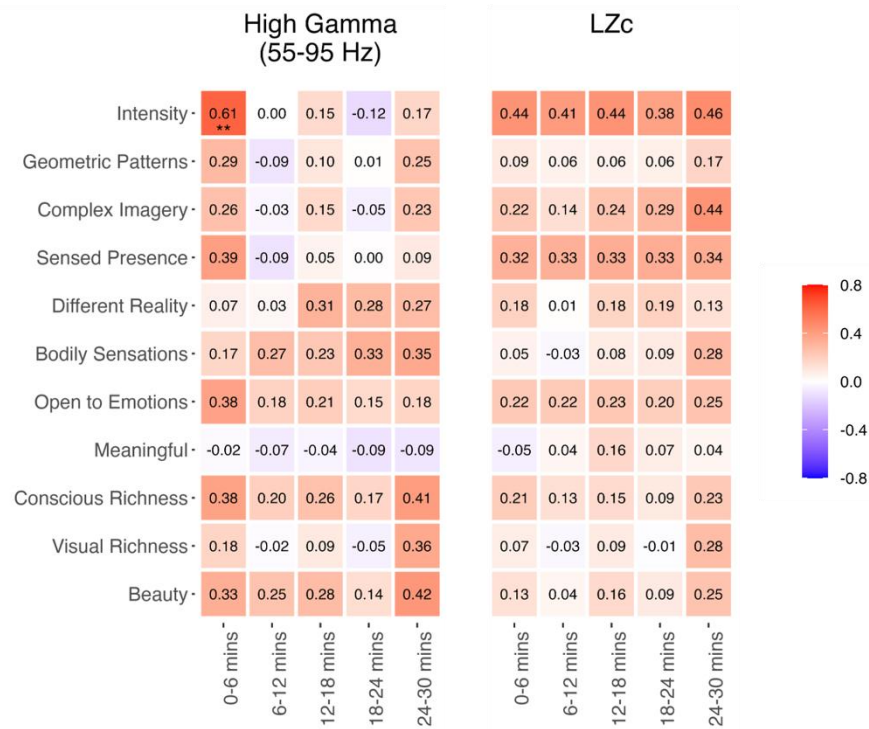


Figure 41. Correlations between EEG metrics and selected static VAS items.

Correlations of 6-minute spectral EEG and LZc epochs with selected static VAS scale items. R-values are represented on a colour scale and shown for each correlation. Significant p -values before FDR correction are shown (* = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$). Importantly, no p -values survived FDR correction.

4.3.5.2 Dynamic correlations

Dynamic correlations were performed between the dynamic VAS scale items and EEG frequency bands and LZc across time (Figure 42). A total of 19240 correlations were performed across 13 dynamic VAS scale items, eight EEG features and 185 EEG channels, grand-averaged over 18 subjects. Results show that widespread reductions in alpha band power were correlated with dynamic VAS scale items ‘Intensity’ (max. $t[17] = 8.45$, cluster $p < 0.001$), ‘Entities’ (max. $t[17] = 5.91$, cluster $p = 0.019$), ‘Visual imagery’ (max. $t[17] = 5.99$, cluster $p = 0.003$), ‘Auditory hallucinations’ (max. $t[17] = 3.75$, cluster $p = 0.039$), and ‘Ego-dissolution’ (max. $t[17] = 5.20$, cluster $p = 0.002$). Occipital and parietal alpha reductions were correlated with ‘Anxiety’ (max. $t[17] = 4.30$, cluster $p = 0.039$), ‘Bodily dissociation’ (max. $t[17] = 4.13$, cluster $p = 0.042$), ‘Emotional experience’ (max. $t[17] = 2.93$, cluster $p = 0.040$), ‘Immersion’ (max. $t[17] = 4.41$, cluster $p = 0.038$),

and ‘Richness’ (both overall, max. $t[17] = 4.28$, cluster $p = 0.044$; and visual, max. $t[17] = 5.06$, cluster $p = 0.033$). Occipital high beta reductions were correlated with ‘Intensity’ (max. $t[17] = 5.18$, cluster $p = 0.048$), while parietal increases in low gamma were correlated with ‘Metacognition’ (max. $t[17] = 4.24$, cluster $p = 0.014$). Parietal high gamma was correlated with ‘Intensity’ (max. $t[17] = 4.876$, cluster $p = 0.021$), ‘Bodily sensations’ (max. $t[17] = 3.00$, cluster $p = 0.019$), ‘Bodily dissociation’ (max. $t[17] = 5.7847$, cluster $p < 0.001$), ‘Ego dissolution’ (max. $t[17] = 5.21$, cluster $p = 0.013$), ‘Immersion’ (max. $t[17] = 6.57$, cluster $p = 0.002$), ‘Meaningfulness’ (max. $t[17] = 6.46$, cluster $p = 0.007$), and ‘Richness’ of the experience (both overall, (max. $t[17] = 5.57$, cluster $p = 0.0014$); and visual, (max. $t[17] = 5.22$, cluster $p = 0.014$), with ‘Meaningfulness’ also correlating with frontal increases in high gamma. Increases in LZc were correlated with ‘Intensity’ (max. $t[17] = 5.849$, cluster $p < 0.001$), ‘Anxiety’ (max. $t[17] = 3.99$, cluster $p = 0.040$), ‘Visual imagery’ (max. $t[17] = 4.58$, cluster $p = 0.003$), ‘Immersion’ (max. $t[17] = 3.64$, cluster $p = 0.031$), ‘Overall richness’ (max. $t[17] = 4.26$, cluster $p = 0.023$), ‘Visual richness’ (max. $t[17] = 5.47$, cluster $p = 0.002$), and ‘Ego-dissolution’ (max. $t[17] = 4.21$, cluster $p = 0.008$).

4. EEG effects of continuous IV infusions of DMT

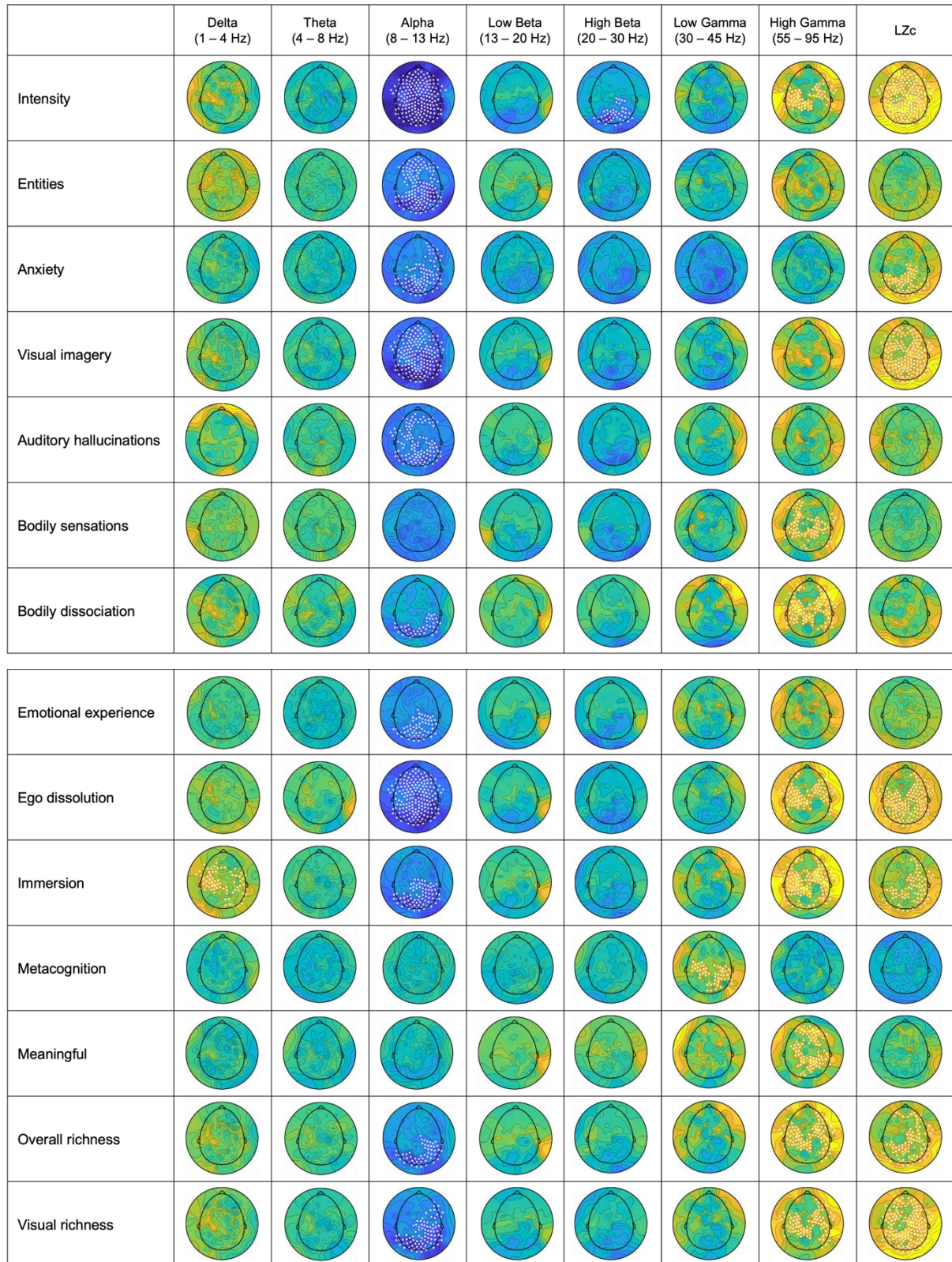


Figure 42. Correlations between EEG metrics and dynamic VAS items.

Topographic distributions of significant correlations between EEG spectral data and LZc with dynamic VAS scale items. Frequency bands are shown on the columns and VAS scale items are

displayed on the rows. R-values are represented on a colour scale, and significant correlations are represented as dots corresponding to the electrode locations of significant p-values (cluster-corrected for multiple comparisons).

4.4 Discussion

This study was the first to investigate the effects of extended administrations of DMT on resting-state EEG. Extended administration of a moderately high dose of DMT over 30 minutes was compared against the administration of a saline placebo. EEG was recorded for a baseline of 8 minutes before the beginning until 22 minutes after the end of administration. Spectral EEG activity and signal diversity were analysed on the sensor and source levels. Additionally, these measures were correlated with a range of subjective measures, both static and dynamic over time. Lastly, a neurophenomenological approach was employed to study the occurrence of ‘entity’ experiences during DMT administration.

In line with previous studies, sensor-level analysis revealed a drastic reduction in alpha band activity within one minute of the beginning of DMT administration. Decreases from peak effects are seen until approximately minute 24, at which point alpha stabilises and sustains up to minute 38. Cluster permutation t-tests showed that differences in alpha band power between DMT and placebo conditions were widespread and significant from minutes 0-6 until minutes 36-42, confirming one of the hypotheses. Source reconstruction revealed that these widespread alpha power reductions encompassed the occipital, parietal, and temporal lobes, several frontal lobe structures, the motor cortex, insula, cingulate, basal ganglia, limbic system, and thalamus. Over time, alpha reductions posteriorized to the occipital lobe, PCC, and some parietal brain areas, remaining significant until the end of infusion (minute 30).

The marked reduction in alpha band activity at the beginning of the infusion suggests a global disinhibition of cortical networks, leading to a reduction in top-down control mechanisms. This is consistent with the reported early subjective experience of “struggles”. Alpha suppression in frontal regions may reflect reduced executive control and self-monitoring, while involvement of the insula and limbic structures may underpin interoceptive and affective changes. Thalamic and basal ganglia engagement suggests transient disruptions in thalamocortical gating and sensorimotor integration. Over the duration of the infusion, alpha reductions progressively posteriorize, potentially reflecting a shift from global disruption to targeted re-engagement of frontal brain areas as time progresses.

This is in line with subjective reports of ‘acclimatisation’ and ‘navigation’ in the later infusion period, facilitated by frontal brain activity, while inhibitions in occipital, parietal and sensory areas of the brain persist, driving the sustained psychedelic effects of the infusion, including visual imagery and altered self-referential processing. These results also support the predictive processing framework of psychedelic brain action, whereby psychedelics reduce the signalling of top-down predictions, which are said to be mediated by alpha and beta oscillations and potentially generated in areas such as the prefrontal cortex, motor cortex, parietal cortex, ACC and limbic system.

Confirming a second hypothesis, the widespread reductions in alpha band power were correlated with the subjective intensity of the experience. Psychometric correlations showed additional correlations with ‘Entities’, ‘Visual imagery’, ‘Immersion’, ‘Richness’ of the experience (both conscious and visual), ‘Ego dissolution’, ‘Bodily dissociation’, and ‘Emotional experience’, suggesting the central role of alpha oscillations in the characteristic effects of DMT and other psychedelics.

In contrast to previous studies, no significant changes were observed in delta band activity following DMT administration. However, a qualitative inspection of time-series delta band activity indicates an increase in delta band power towards the second half of the infusion. After the end of DMT administration, a rebound to lower-than-baseline power is seen towards minute 38, after which the signal normalises to baseline levels. Yet, statistical analysis revealed that these qualitative trends were not significant. Nevertheless, a psychometric correlational analysis revealed a positive correlation of delta band power with the dynamic VAS item ‘Immersion’, potentially linking the immersive state induced by DMT with similar states during sleep.

In the theta band, significant decreases were found at minutes 0-6 and minutes 36-42 at occipital electrode locations. These timepoints coincide with moments during which the subjective effects of DMT began and ended, supporting the idea that theta band activity may be implied in transitions in conscious states, as seen in sleep-wake transitions (Foulkes and Vogel, 1965; Goupil and Bekinschtein, 2012; Nielsen, 2017; Siclari et al., 2014a; Siclari et al., 2014b). A visually apparent increase in theta band activity towards the second half of infusion was not statistically significant. However, after separation of the fractal ($1/f$) component from the signal, significant increases in theta oscillations were observed. This is in line with the findings of a previous study, in which the authors noted the same opposite effects for fractal and oscillatory theta power, with the separation of fractal activity revealing the effects of DMT on oscillatory brain signal (Timmermann et al., 2019). Source reconstruction showed that these increases were initially localised to the occipital lobe and parts of the parietal lobe, and later restricted to the left superior occipital gyrus and right

middle occipital gyrus. These results complement the earlier interpretation of alpha and beta power reductions using a predictive processing framework. More specifically, these theta increases could be interpreted as a bottom-up mechanism whereby occipital theta oscillations facilitate the integration of visual information in a feedforward fashion (Kienitz et al., 2020).

While most previous studies did not find any pronounced effects of DMT on beta band activity, except for slight decreases in Timmermann et al. (2019) and concurrent increases and decreases in Tagliazucchi et al. (2021), this study found pronounced effects in beta band activity following DMT administration. In both low and high beta bands, a sharp drop in power was observed for the first minute following DMT administration, although this was not sustained beyond minute 2. Low beta activity remains lower than baseline between minutes 6-10, then steadily increases until the end of DMT administration. Statistical analysis revealed that initial decreases in both low and high beta band power were significant between minutes 0-6 and 6-12. Decreases posteriorize over time, remaining significant in the high beta band until minutes 30-36. Source reconstruction revealed that initial decreases in high beta power were extensive, encompassing broad areas of the brain, but excluding the parietal lobe. Source-level beta band power reductions were not significant beyond minutes 0-6. Additionally, sensor-level results showed a concurrent increase in beta band activity at central electrode positions from minutes 6-12 to minutes 30-36, reaching significance in the lower beta band at minutes 12-18 and minutes 24-30. Similar results were obtained from the source-level analysis; however, these were not significant after FDR correction. To facilitate the interpretation of the wide-ranging effects of DMT on beta power, source-level results of the low beta band before FDR correction are shown in Figure 43. These indicate that increases in beta band activity at central electrode positions may be localised to sensorimotor areas of the brain.

After separating the fractal ($1/f$) component from the signal, widespread increases in low beta oscillatory power were observed on the sensor level. Source reconstruction revealed significant increases only for a small occipital area, including the right calcarine sulcus and right middle occipital gyrus.

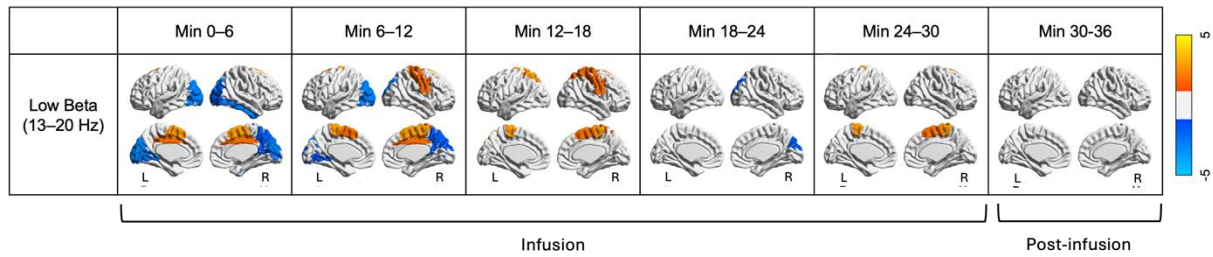


Figure 43. Source-level low beta power before FDR correction.

Locations of significant ($p < 0.05$, not corrected for multiple comparisons) source-level changes in low beta band power following DMT administration, plotted on a cortical surface. Contrasts represent the difference of DMT versus placebo at different timepoints during and after the infusion. L = left, R = right.

Psychometric correlations showed a moderate negative correlation between low beta band power and the static VAS item ‘Sensed presence’. However, this was not significant after FDR correction.

Occipital high beta band reductions were correlated with the intensity of the experience, while an association with static VAS items ‘Complex imagery’, ‘Sensed presence’ and ‘Open to emotions’ was also indicated (also not significant after FDR correction).

Together, these results suggest that DMT-induced changes in beta oscillations may mediate several distinct aspects of its effects. The initial widespread reduction in beta power may be related to the intensity of subjective effects, and the cessation of this signal may indicate a resolution of certain aspects of intensity after the initial period of infusion. Indeed, analysis of phenomenological interviews showed a common trajectory through the extended DMT experience, starting with a high occurrence of ‘struggles’ in the early infusion period, which were typically resolved in a process of acclimation, leading to a better ability to navigate the experience, and finding pleasure, insight, healing, and catharsis in the late infusion period. Consistent with this interpretation, beta oscillations have been associated with cognitive control (Ray and Cole, 1985) and self-monitoring (Engel and Fries, 2010), suggesting that an initial widespread inhibition of this signal may indicate a substantial loss of cognitive control, while its progressive return after the initial infusion period may indicate a return of cognitive control and self-monitoring. The loss of cognitive control may lead to the experience of ‘struggles’, which are typically experienced as a lack of agency, not being able to remember or implement strategies to navigate the experience, not knowing who or where

one is, and a lack of coherence of thought and narrative flow of the experience. Conversely, a return of cognitive control may facilitate the resolution of these ‘struggles’ by remembering who and where one is, how to implement strategies to navigate the experience, and improving the coherence of thought and narrative flow of the experience. As this beta power reduction is most pronounced in the initial infusion period and resolves over time, it makes sense that previous studies using inhaled or bolus IV administration of DMT did not show this effect (except for Timmermann et al., 2019). Indeed, a previous minute-by-minute analysis found reductions in beta power during the first minute post-DMT administration and an inverse association with intensity of the experience (Timmermann et al., 2023b), and time-series data from the current study shows a similar pronounced reduction in beta band power occurring in the first two minutes following the beginning of DMT infusion.

The increase in beta band activity in sensorimotor areas may be a unique signal related to the DMT-induced experience of ‘entities’. This is suggested by a (non-significant) correlation of beta power with the static VAS item ‘Sensed presence’. In support of this, a neurophenomenological analysis of ‘entities’ using ESM ratings of ‘Entities’ revealed that low and high beta band power were elevated at central electrode locations during moments of ‘entity’ experience vs moments of ‘No entities’ experience. A source-level analysis may reveal the location of these effects. Given the above results, these increases in beta band power may be suspected to be localised to sensorimotor brain areas.

In contrast to most previous studies, this study did not find significant increases in gamma band power following DMT administration. Qualitative inspection of the time-series data revealed a slow increase in low gamma power in the later infusion period, sustained until minute 32, after which the signal sharply drops to baseline levels. In the high gamma frequency band, an increase is seen from minutes 1 to 30, with a temporary dip at minutes 8-10. Conversely, statistical analysis revealed a slight but statistically significant reduction of low gamma band power for the first 12 minutes following DMT administration. A separation of the fractal component from the signal revealed additional oscillatory low gamma decreases between minutes 0-6 and 24-30. Source-level analysis showed no significant results. Increases in high gamma power were localised to peripheral electrodes (face and neck) and were not statistically significant. This suggests that any increases in high gamma power may be linked to increased muscle tension in face and neck areas. Nevertheless, psychometric correlations showed that parietal increases in low gamma were correlated with ‘Metacognition’, while increases in parietal high gamma were correlated with ‘Intensity’, ‘Bodily sensations’, ‘Bodily dissociation’, ‘Ego dissolution’, ‘Immersion’, ‘Meaningfulness’ and ‘Richness’ of

the experience, with ‘Meaningfulness’ also correlating with frontal increases in high gamma power. This potentially suggests a role of gamma oscillations in these facets of experience; however, a clear interpretation of the results is not possible, considering that increases in gamma were not seen for the main contrast. Table 15 provides a summary of all existing studies investigating the effects of DMT on spectral EEG, including previous studies and the current study.

Table 15. Previous studies investigating the effects of DMT on resting-state EEG.

Administration methods, doses, sample sizes, EEG systems, and spectral EEG results are shown.

Study	DMT and sample size	EEG system	δ	θ	α	β	γ
Acosta-Urquidi, 2015	Inhaled DMT, ca. 20-30 mg (n = 23)	19-channel EEG, 250 Hz sampling rate	↓	↑	↓		↑
Luan, 2025	Bolus IV + infusion, 20 mg + 2.3 mg/min (n = 20)	256-channel EEG, 500 Hz sampling rate		↓	↓	↑↓	↓
Pallavicini et al., 2020	Inhaled DMT, ca. 40 mg freebase (n = 35)	24-channel mobile EEG, 500 Hz sampling rate	↑		↓		↑
Tagliazucchi et al., 2021	Inhaled DMT, ca. 40 mg freebase (n = 35)	24-channel mobile EEG, 500 Hz sampling rate	↑	↑	↓	↑↓	↑
Timmermann et al., 2019	Bolus IV DMT, 7 mg, 14 mg, 18 mg, 20 mg (total n = 13)	32-channel EEG, 1000 Hz sampling rate			↓	↓	
Timmermann et al., 2023b	Bolus IV DMT, 20 mg fumarate in 10 ml saline	31-channel EEG, 5 kHz sampling rate	↑		↓		↑

Note: The study by Acosta-Urquidi (2015) is not peer-reviewed and has never obtained ethics. The analyses and results from Pallavicini et al. (2020) and Tagliazucchi et al. (2021) are based on the same sample.

Finally, in line with previous studies and confirming the last hypothesis, this study found pronounced increases in LZ complexity, starting within one minute of the beginning of DMT infusion. LZ complexity decreased from peak effects until approximately minute 24, at which point increases resumed and were sustained until minute 38. Statistical analysis showed that significant increases in LZ complexity were widespread from minutes 0-6 to minutes 6-12, then more localised to posterior electrodes from minutes 18-24 to minutes 36-42. Source reconstruction revealed that increases in LZ complexity encompassed the occipital lobe and PCC as well as some parietal brain regions during the initial and final periods of infusion, while effects at minutes 18-24 were localised to several occipital structures. Additionally, LZ complexity was positively correlated with dynamic

VAS measures of ‘Intensity’, ‘Anxiety’, ‘Visual imagery’, ‘Ego dissolution’, ‘Immersion’, ‘Overall richness’ and ‘Visual richness’. These results support the theory that psychedelics increase brain entropy, thereby exerting some of their characteristic effects (Carhart-Harris, 2018; Carhart-Harris et al., 2014). The localisation of effects indicated that increased neural signal diversity is especially expressed in networks critical for visual and self-referential processing (Schartner et al., 2017a). The trajectory from global to posterior changes mirrors the pattern seen in spectral EEG, reflecting a dynamic shift from global cortical disinhibition to targeted engagement of perceptual and self-referential networks.

Collectively, the source-localised results suggest a temporal progression of the experience, whereby DMT initially disrupts broad cortical networks involved in top-down control, integration, and sensory gating, producing early disorientation and loss of cognitive control. As the experience unfolds, neural changes become increasingly concentrated in posterior cortical regions, supporting visual, immersive, and altered self-referential aspects of the experience. This functional reorganisation is reflected across multiple frequency bands and in signal diversity, highlighting the complementary contributions of oscillatory and complexity-based dynamics to the phenomenology of DMT. [maybe rewrite last part to sound more natural]. Intriguingly, both alpha power and LZ complexity show a decrease from peak effects in the middle part of the infusion, with source-level differences between DMT and placebo losing significance during minutes 12-18, while subjective effects remain stable (see dynamic VAS scales in Chapter 3 – *“Phenomenology and subjective effects of continuous infusions of DMT”*, [section 3.3.3.3](#)). One exception is in the ‘entities’ experiences as measured through ESM, which do not show stability over time. Temporally, the reduction of alpha power and LZ complexity effects coincides with the lowest number of entity ratings, potentially suggesting that these measures are linked. This is further supported by the neurophenomenological analysis of ‘entities’ experiences, which showed increased parietal alpha and decreased LZ complexity in moments of ‘Entities’ vs moments of ‘No entities’. Therefore, experiences of entity encounters may be interpreted as a re-engagement of systems which are widely disinhibited during DMT experiences (i.e., alpha oscillations and LZ complexity), potentially contributing to the finding of some ‘signal within the noise’. This study is the first to investigate the EEG effects of extended infusions of DMT and the first using ESM for any study involving psychedelics, thereby allowing an exploration of the unique effects induced by longer DMT experiences, as opposed to previously studied short experiences using bolus IV DMT and inhaled DMT administration (Acosta-Urquidi, 2015; Pallavicini et al., 2020; Tagliazucchi et al., 2021; Timmermann et al., 2019; Timmermann et al., 2023b). A unique signal revealed by this approach is an apparent ‘settling in’

or ‘acclimation’ to the experience, characterised by a change in the spectral EEG profile after approximately 6-12 minutes of infusion, with decreases in theta, beta and low gamma band attenuating, and many effects posteriorising over the course of the infusion, thereby allowing top-down cognitive control mechanisms to resume (Bastos et al., 2012; Bastos et al., 2015; Mayer et al., 2015; Van Kerkoerle et al., 2014). Moreover, a not previously identified increase in beta power (although of note that Tagliazucchi et al. [2021] previously observed posterior beta increase), localised to sensorimotor areas, was associated with the prominent experience of a ‘sensed presence’ or ‘entities’.

This study employed a range of complimenting methods, which facilitated a stringent and informative analysis of the effects of extended infusions of DMT. Firstly, the use of an extended infusion may have uncovered effects less easily detectable with inhaled or bolus IV administration, due to the short duration of effects. This was complemented with ESM and dynamic VAS scales, allowing a correlation of subjective and brain effects over time. A neurophenomenological approach using ESM ratings of ‘Entities’ allowed a targeted examination of specific neural correlates of this particular aspect of the DMT experience. Finally, using source reconstruction and a high-density EEG system, it was possible to precisely localise any effects seen at a sensor level to potential underlying brain areas generating these effects.

The results of this study demonstrate the superiority of a neurophenomenological approach in gaining a deeper understanding of specific substates of the rich and varied psychedelic experience. While micro-phenomenological interviews may uncover common themes and structures of the experience and are valuable for generating new hypotheses, the ESM is more practical and effective in testing identified or predefined elements. It provides precise temporal information about the occurrence (or absence) of a chosen variable, thereby allowing an accurate association to co-occurring brain signals.

Importantly, while some of the observed electrophysiological changes are also observed in other altered states of consciousness (e.g., meditation, sleep, and anaesthesia), the specific combination of changes may be characteristic of psychedelics and therefore may be useful as candidate biomarkers. However, more work directly comparing across states is needed before EEG signatures can be considered specific to psychedelics or predictive of their drug effects.

The current study has several limitations. Firstly, the final sample size of $n = 18$ is small for an EEG study investigating the effects of a psychoactive substance. While the sample size was determined using a power calculation to detect an effect of Cohen’s $d = .85$ between the LZ

complexity of DMT versus placebo condition, as indicated in a previous study of IV bolus DMT (Timmermann et al., 2019), a much larger sample size is necessary to test correlations reliably. Furthermore, the infusion parameters used in this study aimed to extend the subjective effects of DMT in a stable fashion over time. While this aim was achieved, the resulting subjective data show little variance over time. To better test the relationship between subjective effects and EEG measures, future studies may use infusion parameters which introduce more variability in the effects over time.

Following the initial analyses presented here, it will be meaningful to extend the psychometric correlations and neurophenomenological analysis of ‘entities’ to the oscillatory component of the signal. Additionally, it will be valuable to perform these analyses on source-level data. Finally, a more temporally fine-grained analysis of both spectral EEG and LZ complexity measures, as well as correlations with dynamic VAS scales, may provide further insights into the trajectory of effects over time.

5. General Discussion

This thesis investigated the effects of continuous IV infusions of DMT, its tolerability and effectiveness in extending the otherwise short-lived DMT experience, and the resulting phenomenology as well as subjective and neurophysiological effects in healthy human volunteers.

DMT is not orally active, as MAO-enzymatic catabolism leads to its degradation during first-pass metabolism. Previous studies have commonly used inhaled DMT in naturalistic or survey research, while the preferred method in controlled research settings has been bolus IV administration. Inhaled and IV administrations of DMT produce psychoactive effects within seconds of administration, with peak effects reached between 2-5 minutes and the experience resolving within approximately 20 minutes. This thesis aimed to explore a novel method of DMT administration to optimise its use in research and clinical settings. The project was based on the rationale that the unique properties of DMT, which distinguish it from other classic psychedelics, make it suitable for continuous IV administration, thereby providing a psychedelic experience which is adjustable in its length and strength over time. The infusion protocol used in this thesis was based on PK parameters derived from previous bolus IV administrations of DMT. The infusion parameters were chosen to extend the peak effects of DMT over the duration of a 30-minute infusion period. For this, a bolus IV injection was paired with a slow-rate infusion over 29 minutes. Outcome variables comprised a combination of physiological measures (HR, plasma DMT concentrations), subjective measures (ESM, questionnaires and rating scales, interviews), and resting-state EEG recordings.

A detailed description of each analysis and its results has been presented in the previous chapters. This chapter will give a brief summary of the main results, their possible interpretations and implications, a comparison to other administration methods for DMT, as well as an outlook on open questions and avenues for future research.

5.1 Summary of findings

Chapter 2 focused on the tolerability of continuous IV administration of DMT and the effectiveness of the chosen dose regimens in extending the peak effects of DMT over the duration

of the infusion. Using a dose-finding protocol of five different doses of extended DMT in eleven volunteers, it was found that the continuous IV administration of DMT was psychologically and physiologically well tolerated and that the infusion parameters were effective at extending the peak psychoactive effects of DMT, achieving a steady state of intensity of drug effects over the duration of the infusion. Subjective intensity ratings were significantly different from placebo for 16 minutes following the end of infusion, and a dose-response relationship was found for all doses. Temporary increases in anxiety were seen around the start of DMT administration, suggesting some anticipatory and transitory unease but general psychological tolerability of the tested infusion protocol. HR increased by an average of approximately 30 bpm within 2-3 minutes of the beginning of infusion, with no differences in elevation between doses. HR reached baseline levels within 12 minutes of infusion, suggesting physiological tolerability of the continuous infusion. Plasma concentrations of DMT increased dose-dependently, with peak levels seen at the first plasma sampling timepoint following bolus IV injection (minute 2) and the last plasma sampling timepoint before the end of DMT infusion (minute 29). Plasma DMT concentrations were significantly different from placebo for 20 minutes after the end of infusion and fell below 1 nM within 90 minutes after the end of infusion.

Chapter 3 focused on the phenomenology and acute subjective effects of continuous IV administration of DMT. Results showed that the extended DMT experience is characterised by strong visual effects (both elementary and complex imagery), high immersion and richness (of both visual and conscious content), unusual bodily sensations, and the experience of a different reality or dimension. Participants reported heightened emotions and emotional processing, experiencing beauty, and the experience being pleasurable. This was accompanied by occurrences of mystical-type experiences. Participants experienced the presence of sentient beings in about half of the experiences and reported the overall DMT experience to be particularly ineffable. A close examination of 'entity' experiences using an ESM approach revealed that they were less predictable over time, with approximately 80% of participants reporting entity encounters at any point during the infusion. Of those, approximately 40% reported entity encounters throughout the experience, while approximately 10% only had entity experiences in the early infusion period, approximately 10% experienced them in the later infusion period, and 40% reported entity experiences sporadically throughout the infusion. Participants also reported experiencing a general sense of gratitude, and the experiences rated especially high on insight and meaningfulness. While participants reported experiencing emotional breakthroughs and ego dissolution, these occurred less often and less strongly. However, an analysis of micro-phenomenological interviews showed

that extended DMT experiences commonly progressed through three stages involving a higher occurrence of ‘struggles’ in the early infusion period, which were resolved in a process of acclimation and led to a higher occurrence of ‘fruits’ in the late infusion period. Effects generally followed a dose-response relationship, with higher doses leading to stronger experiences, rating higher on all the above-detailed effects. Although participants reported higher degrees of pleasure, beauty, insight and meaning with higher doses of extended DMT, these higher doses also led to more challenging experiences.

Chapter 4 investigated the EEG effects of a chosen moderate-to-high dose of extended DMT (20 mg + 2.27 mg/min). Results showed characteristic widespread alpha power reductions emerging within one minute of the beginning of DMT administration and lasting over the duration of the infusion, initially encompassing extensive brain areas, then posteriorising to the occipital lobe, PCC, and some parietal brain areas over the course of the infusion. Alpha reductions were correlated with the intensity of the experience and a wide range of subjective effects, including the experience of entities, visual imagery, immersion, the richness of the experience, ego dissolution, bodily dissociation, and emotional experience. Theta band power was decreased at occipital electrode positions at moments of transition into and out of the altered state of consciousness induced by the DMT infusion. Separating the fractal ($1/f$) component from the signal revealed significant increases in theta oscillations initially localised to the occipital and parietal lobes and later restricted to parts of the occipital gyrus. Reductions in low and high beta power were also observed and were most marked during the initial two minutes of infusion. Low beta decreases were significant up to minutes 6-12 and localised to the occipital lobe. Interestingly, a concurrent increase in low beta was seen in sensorimotor areas during the infusion period. Reductions in high beta power were widespread, encompassing broad areas of the brain but excluding the parietal lobes. These were correlated with the intensity of the experience. Finally, signal diversity, measured by LZ complexity, was markedly increased following DMT administration, starting within one minute of the beginning of DMT infusion and lasting until minutes 36-42. Notably, the middle of the infusion saw a decrease in LZ complexity. Increases were widespread in the early infusion period (minutes 0-12) and at minutes 30-36, while the effects in the middle-to-late infusion period were localised to several occipital brain areas. LZ complexity was positively correlated with intensity, anxiety, visual imagery, ego dissolution, immersion, and richness of the experience. A neurophenomenological analysis of the experience of ‘entities’ revealed that moments of entity experience displayed a relatively increased power in alpha and beta band power compared to moments of ‘no entity’

experience. Additionally, LZ complexity was relatively decreased compared to moments of ‘no entity’ experience.

5.2 Comparisons and interpretations

These results collectively suggest that continuous IV administration is an effective and tolerable method to extend the transient psychoactive effects of DMT. Additionally, they highlight the commonalities and differences between DMT experiences induced through different methods of administration.

Results from Chapter 2 showed the distinct effects of continuous IV infusions on the onset, trajectory and duration of the psychoactive effects of DMT. The chosen infusion parameters resulted in subjective effects beginning within one minute of administration and reaching their peak within 2 to 3 minutes, with peak effects sustaining over the duration of the infusion. The end of the infusion saw a resolution of psychoactive effects comparable to those of inhaled and bolus IV administration, with no significant differences detected between different doses of extended DMT and placebo at 16 minutes post-infusion. This suggests that continuous IV administration provides the ability to extend the psychoactive effects of DMT in a flexible fashion, depending on chosen infusion parameters. Based on the aims of research or therapy, one may adjust infusion parameters to extend the psychoactive effects further. Upon the end of administration, subjective effects resolve quickly, making DMT a convenient and controllable tool for use in research and therapy settings. Additionally, future studies may decide to exclude the use of a bolus loading dose if a slower onset of effects is desirable. This study also showed that initial HR increases, which are also seen in inhaled and bolus IV administration, resolve within 10-12 minutes of infusion, further suggesting extended DMT administration to be physiologically safe. This makes extended DMT a valuable avenue for neuroimaging studies by providing a period of immersion in the DMT state, which is not confounded by physiological artifacts. Future studies may harness this unique approach to studying the effects of DMT.

While the phenomenology and subjective effects of extended DMT experiences are largely consistent with those seen from other methods of administration, several crucial differences were identified. Comparing the results of the current study with those obtained from a bolus IV DMT study with similar doses (Timmermann, 2020), it appears that extended DMT induces comparatively lower ratings of disembodiment and feelings of unity, and higher ratings of

insightfulness and meaning compared to bolus IV DMT doses. This may suggest that feelings of disembodiment and unity occur beyond a certain threshold of intensity of the experience, more likely to be achieved by a bolus dose and less likely to be maintained by a continuous infusion. Continuous infusions, on the other hand, allow more time to progress through and process the experience, leading to more experiences of insight and meaning in the later part of the extended DMT experience. This interpretation is supported by the results of several analyses into the dynamics of the experience over time. Micro-phenomenological interview analysis revealed a common trajectory through the extended DMT experience, which involved a high occurrence of ‘struggles’ in the early infusion period, followed by a resolution of these struggles in a process of acclimation, leading to a higher occurrence of ‘fruits’ in the later infusion period. This narrative is further substantiated by ratings of several dynamic VAS scales, which showed an increase in ‘metacognition’, ‘emotional experience’ and ‘meaning’ towards the end of the infusion, with ratings of metacognition and meaning remaining elevated beyond the end of infusion and resolution of drug effects. This suggests that these processes emerge after the initial arguably overwhelming onset of DMT’s effects, supporting acclimation to and navigation of the experience, thereby facilitating experiences of insight and meaning, which remain with participants beyond the end of the DMT experience. These differences in the phenomenology and subjective effects of extended DMT compared to inhaled or bolus IV DMT suggest the potential superiority of continuous IV administration of DMT for therapy purposes. By allowing a prolonged immersion in the DMT state, a process of acclimation to its arguably intense and ineffable effects can unfold, leading to insight and meaning, which can be harnessed through complementary therapy. Given the lack of tolerance to repeated doses of DMT, one may choose to intersperse several periods of DMT immersion with segments of therapy.

Comparing the EEG effects of extended DMT to those previously found with inhaled and bolus IV administration, several commonalities and a few differences were seen. As in previous studies of inhaled and bolus IV DMT, the most pronounced signature of DMT on resting-state EEG was a widespread reduction in alpha band power and a significant increase in LZ complexity. Intriguingly, the constant rate infusion employed in this study led to a decrease from peak effects for both measures in the middle of the infusion (12-18 minutes following the beginning of administration). Decreases in theta band activity at moments of transition into and out of DMT immersion have not been seen in previous studies and may be unique to the continuous administration of DMT, where the onset and resolution of effects are extended in time, thereby allowing a more in-depth look into these moments. The implication of theta band activity in

transitions between consciousness states is in line with findings on similar processes, for example sleep onset (Foulkes and Vogel, 1965; Goupil and Bekinschtein, 2012; Nielsen, 2017; Siclari et al., 2014a; Siclari et al., 2014b). Changes in beta band activity have been seen with inhaled and bolus IV DMT administration (Tagliazucchi et al., 2021; Timmermann et al., 2019). In line with these studies, decreases in beta band activity were localised to posterior brain areas, with concurrent increases observed in somatosensory brain areas. While most previous studies found an increase in low-frequency delta band activity and high-frequency gamma band activity following DMT administration, the current study did not see these effects. However, these inconsistencies may be explained by the increased susceptibility of these frequency bands to physiological artifacts and varied data-cleaning approaches employed in different studies. Separating the fractal component from the oscillatory data revealed similar results to those seen in previous studies of bolus IV DMT (Timmermann et al., 2019; Timmermann et al., 2023b).

The current study revealed several effects which are potentially unique to the administration method and infusion protocol used. While the investigated high-dose continuous infusion produced a relatively stable plasma DMT concentration and overall subjective intensity of the experience over the duration of infusion, spectral and LZ complexity measures saw a weakening of the observed effects in the middle infusion period. Additionally, except for LZ complexity, effects posteriorised over time. This, in combination with the results on the phenomenology and subjective effects of the infusions, potentially points to an unfolding process of acclimation and drive towards homeostasis, whereby the re-engagement of frontal brain areas facilitates a settling-in and navigation of the experience to emerge in the middle and late infusion periods. Finally, by harnessing the extended effects of DMT in combination with a neurophenomenological analysis approach, the current study revealed a unique EEG signature of entity experiences within the DMT experience, characterised by increased alpha and beta band power and decreased LZ complexity compared to DMT experiences without entity experiences. This finding has relevance to our current understanding of the brain effects of psychedelics. While the richness of experience of the psychedelic state has generally been attributed to increased entropy (i.e., unpredictability) of brain activity, the current finding reveals that specific phenomenology within the psychedelic state is associated with decreased entropy and emergent signals within a state of increased disinhibition, suggesting nuance in the narrative of increased brain entropy in psychedelic states.

5.3 Limitations

The work presented in this thesis was a first exploration of continuous IV infusion as a method of DMT administration. The study was conducted on a sample of highly psychedelic-experienced, healthy volunteers. Therefore, the results cannot be generalised to the wider population or clinical populations. Additionally, due to the exploratory nature of the investigation, a fixed-order design was used, with the placebo control dose always administered during the first session. Therefore, order effects may have influenced the current results. In the dose-finding study (Chapter 2), several lower doses were only given to a few participants, and the overall sample size was small. For the EEG study (Chapter 4), the highest dose from the dose-finding study (Dose 5) was chosen and administered to an additional 15 participants for a total sample of $n = 20$. Moreover, Dose 5 employed updated infusion parameters based on the addition of the PK data from the dose-finding study to the existing data from two previous studies (Strassmann et al., 1994; Timmermann et al., 2019). Therefore, the sample used in Chapter 3 (*‘Phenomenology and subjective effects of continuous IV infusions of DMT’*) did not provide an ideal within-subjects assessment and comparisons between Dose 5 and the lower doses are flawed. Furthermore, to capture the nature of the DMT experience over time, participants were asked to rate their experience every few minutes. This continuous interruption of the experience may have interfered with and altered the unfolding of the experience. Finally, the EEG recordings obtained from the placebo sessions showed significant changes in signals over time, as participants became progressively more relaxed and sleepier during the placebo infusion and 60-minute EEG recording. To correct for this effect, for the time-averaged statistical analysis of spectral EEG and LZ complexity, the first six minutes of placebo EEG were used to compare against all epochs of DMT infusion. However, a different choice of placebo comparison may have returned different results.

5.4 Open questions & future directions

This thesis provided a first comprehensive investigation of the phenomenology and subjective, physiological and EEG effects of continuous IV administration of DMT over 30 minutes. While this study found a dose-response relationship between DMT doses and subjective intensity, an intriguing divergence between these two measures was seen over time. In particular, an increasing plasma DMT concentration was necessary to maintain stable subjective effects over time. One possible interpretation of this finding is the development of a short-term tolerance not seen in

previous studies of inhaled and bolus IV administration of DMT. Alternatively, the results may be explained by cognitive biases in the perception and evaluation of drug intensity. Contrast effects may be at play, whereby the stark contrast of change from a prior state (e.g., going from no drug effects and ordinary consciousness to the rapid onset of drug effects and change in consciousness) is perceived as more remarkable than any contents of an ongoing state (e.g., a continuing altered state of consciousness). Relatedly, an attention bias towards a new sensory experience may amplify the perception of intensity at the beginning of drug infusion. Furthermore, the initial rapid increase in plasma DMT concentration may cause more noticeable effects early in the infusion. This rapid onset may be perceived more strongly than the steady state that is reached in the late infusion period. In addition, the sudden physiological changes, including a significant increase in HR, may contribute to feelings of intensity in the initial infusion period. Future studies are needed to further understand the mechanisms involved in the divergence of plasma DMT concentrations and subjective intensity over the course of an infusion.

While the study achieved one of its primary goals of extending the peak psychoactive effects of DMT into a steady state over the duration of the infusion, inter-individual variability in dose-concentration response and dose-effects response was large. A roughly two-fold range was observed for both plasma concentrations and intensity ratings for a single dose. Although variability in dose-response of this size is not unique to DMT – similar effects are seen for anaesthetic substances administered via bolus injection (Schüttler and Ihmsen, 2000), and variances of 20-30% in plasma drug concentrations achieved using well-established infusion protocols are common (Coetzee et al., 1995), it remains relevant to determine the variables driving this variability, in order to reduce it. One way to solve issues of individual variability is with personalised dosing: Individually based PK-PD parameters could be derived from plasma concentrations acquired from an initial DMT administration, and these parameters could then be used to determine dose regimens which will be effective in inducing a stable, extended DMT experience in one individual.

Psychedelic therapy is increasingly showing transdiagnostic relevance for treating several mental health conditions (Andersen et al., 2021b; Kočárová et al., 2021). Preliminary results suggest that DMT specifically shows efficacy for treating depression, and it is currently being trialled in several phase 1 and 2 studies. Due to the short half-life and associated fast metabolism of DMT, all acute subjective effects resolve within minutes after stopping the infusion, thus making it arguably safer than prolonged psychedelic states induced by oral psilocybin or LSD. DMT is therefore an attractive alternative psychedelic intervention. Furthermore, longer infusion times can be explored using the present infusion method for therapeutic purposes. Based on our findings on the safety

and feasibility of continuous DMT administration, the author foresees a potential for continuous DMT infusions to be used in precision psychiatry, e.g., adjusting dosing parameters to suit individual cases and scenarios.

Psychedelics present an intriguing challenge in psychiatry as their psychological response is known to be highly variable and, at times, unpredictable. This unpredictability is usually accounted for by both dose and non-pharmacological or contextual variables, commonly described as (mind-) ‘set’ and ‘setting’ (Hartogsohn, 2016). The high variability of plasma DMT concentrations for a single dose in this study suggests that the subject-specific PK profile may significantly influence the psychological response as well. In the future, an approach tailored to the PK characteristics of the individual may thus be highly valuable to induce acute subjective effects that have been found to predict improvements in mental health outcomes in psychedelic experiences (Yaden and Griffiths, 2020). In this way, infusion parameters can be tailored to the specific characteristics of patient populations, treatment outcomes, and individual variables that bear relevance in psychedelic medicine, e.g., personality traits (Aday et al., 2021), genetics, and brain function (Moujaes et al., 2022). Importantly, personalised infusion parameters can be leveraged beyond attaining a stable plateau of effects. For example, longer infusion times and dynamic infusion parameters can be meaningfully employed to alter the speed of the onset and offset of effects and the occurrence of ‘rest periods’, where, e.g., subjective effects could be tapered for a period to provide a period of more sober reflection. This study is a meaningful step forward in that direction. Here, the author employed a bolus plus slow infusion protocol, but in future protocols, a more gradual onset may be favoured to allow participants to ‘acclimatise’ to the DMT state. The successful and flexible extension of DMT administration poses a significant opportunity for the application of DMT in clinical and therapeutic settings, where the length, strength and dynamics of the psychedelic experience can be adjusted according to the needs of the individual.

Extended DMT administration offers a valuable approach for investigating the dynamics of altered consciousness over time. By allowing for the flexible control of the altered state of consciousness, this approach makes it possible to link specific neural changes to the unfolding subjective experience. As such, extended DMT infusions provide a unique window into the neural mechanisms of conscious experience, offering insights into the interplay between perception, cognition, and selfhood.

This study lays the groundwork for further explorations with extended IV infusions of DMT. The extended DMT experience may be valuable for further exploring the phenomenology and neurobiology associated with this unique state of consciousness. The use of an ESM approach

combined with neurophenomenology provided the opportunity for an in-depth investigation of chosen sub-states within the broader DMT experience with high temporal precision, revealing valuable information about the potential relationship between specific phenomenology and its brain signatures. This approach promises great potential for future exploration for the study of both psychedelic phenomenology and human consciousness.

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