

**Psychedelics and Music:
Characterising Changes in Hierarchy of Brain Dynamics
among the Santo Daime**



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Declaration

The work presented in this thesis was conducted between October 2021 and March 2026. Professor Morten L. Kringelbach and Professor Catherine Harmer supervised this work. I declare that the work presented is my own.

No part of this thesis has been submitted for any other degree at the University of Oxford or any other institutions. In line with the requirements of the Department of Psychiatry, Medical Sciences Division, the thesis does not exceed the 50,000 word limit.

The Santo Daime data analysed throughout Chapters 2-5 was collected prior to the start of my DPhil, by the Psychopharmacology Group at Maastricht University, Netherlands. The music paradigms utilised in the data collection were designed by Dr Christine Ahrends and Professor Morten Kringelbach at the Centre for Music in the Brain and the Centre for Eudaimonia and Human Flourishing.

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Abstract

The last few decades have been characterised by a resurgence in research and clinical interest in classic serotonergic psychedelics including N,N-dimethyltryptamine (DMT), lysergic acid diethylamide (LSD) and psilocybin, with a growing body of literature pointing to their treatment potential. Ayahuasca is a psychedelic brew commonly composed of plants carrying the psychoactive compound DMT, and beta-carbolines which enable DMT action. Ayahuasca is commonly used in indigenous ritual and syncretic religious settings, within which music plays a central role. The acute and long-term effects of psychedelics are known to be shaped by set and setting, with music being an element of the setting to which great importance has been afforded across clinical as well as ritual contexts. The Santo Daime, a religious group who incorporate the regular consumption of ayahuasca within ceremonies, are a musical doctrine. Therefore, they present a compelling case for studying the role of ayahuasca, music, and the interaction of the two in shaping brain dynamics. This thesis is the first to directly examine the role of ceremonial hymns, their presence and properties, in ayahuasca-induced changes to the functional hierarchy within the unique context of pursuing the divine.

We examine the effects of ayahuasca-ingestion across resting state and ritual-relevant music contexts on large-scale brain dynamics in an fMRI dataset of 24 members of the Santo Daime Church. By leveraging undirected dynamic approaches including harmonic decomposition and leading eigenvector decomposition as well as time-averaged and time-resolved whole-brain modelling-based trophic analysis measures of directed connectivity, we addressed three aims: 1) to examine ayahuasca-induced effects on large-scale brain dynamics and the functional hierarchy among members of the Santo Daime at rest, 2) to assess the consistency of observed effects across resting state and ritual-relevant music listening contexts, and 3) to explore the modulating role of ceremonial music’s familiarity and predictability on ayahuasca-induced effects on the functional hierarchy. This analysis should be seen in the light of the Relaxed Beliefs Under Psychedelics (REBUS) theory which proposes that psychedelics induce a flattening of the brain’s functional hierarchy.

Comparing ayahuasca to an intravenous DMT dataset serving as benchmark, in **Chapter 2** we show several consistent harmonic decomposition effects following drug administration across datasets including suppression of spatially-resolved harmonic power and contraction of latent space spread. Several differences emerged between datasets, specifically in harmonics relevant to the functional hierarchy, necessitating more direct examination of hierarchical structure. In **Chapter 3** this is done through the application of whole-brain modelling

and trophic analyses which showed significant context-independent reduction in hierarchical coherence, average trophic level reduction, and trophic level homogenisation, consistent with REBUS. In **Chapter 4** we introduce a novel state-based modelling approach through which we examine not only average hierarchy changes following ayahuasca ingestion (confirming the findings of **Chapter 3**), but also enhanced stability of this less hierarchical regime across time. Finally, **Chapter 5** leverages the within-music two-by-two factorial design of the Santo Daime dataset in exploring the effects of musical familiarity and predictability in modulating ayahuasca-induced effects on the functional hierarchy. Our results point to reduced sensitivity of hierarchy measures to musical properties following ayahuasca ingestion, aligning with REBUS and the Predictive Coding of Music Model. Further, our results indicate a unique role of the Santo Daime's own ceremonial music, as the only condition which showed a strengthening of the underlying hierarchy following ayahuasca ingestion.

Our findings extend support for the REBUS framework, by showing consistent findings following ayahuasca ingestion among long-term users both in the presence and absence of ritual relevant music listening. Importantly, our within-music results also align with a recent extension of the REBUS framework, *Altered Beliefs Under Psychedelics*. This suggests a need for expansion of REBUS to account for the complexity and variability of psychedelic-induced effects on brain dynamics and the modulating role of contextual factors such as music. This thesis characterises the first attempt to systematically examine the role of ceremonial ayahuasca consumption and music in shaping the functional hierarchy. Our work goes beyond the notion of psychedelia more broadly by exploring the nature of the interaction between ayahuasca and music in the Santo Daime's connection to the divine. These findings supporting long-standing anthropological work and theories suggesting music provides structure within the complex psychedelic state and holds a special role in connecting with God, by showing ceremonial music to uniquely enhance the brain's hierarchical structure.

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List of Abbreviations

BOLD	Blood-oxygenation level dependent
COV_τ	Time-lagged covariance
DK80	Desikan-Killiany 80 parcellation
DMT	N,N-dimethyltryptamine
EC	Effective connectivity
EEG	Electroencephalography
FC	Functional connectivity
FDR	Benjamin-Hochberg false discovery rate
FH	Functional harmonic
fMRI	Functional magnetic resonance imaging
FO	Fractional occupancy
GEC	Generative effective connectivity
HADES	Harmonic decomposition in spacetime
HCP	Human connectome project
iPC	Instantaneous phase coherence
LEiDA	Leading eigenvector dynamics analysis
LSD	Lysergic acid diethylamide
MeanTL	Mean trophic level
MEG	Magnetoencephalography
MMN	Mismatch negativity
Network: DAN	Dorsal attention network
Network: DMN	Default mode network
Network: FPN	Frontoparietal network

Network: RSN	Resting state network
Network: SMN	Somatomotor network
Network: VAN	Ventral attention network
PCM	Predictive Coding of Music
PL	Phase-locking
PMS	Probabilistic metastable substate
REBUS	Relaxed Beliefs Under Psychedelics
RO	Richness of orchestration (TL standard deviation)
SVM	Support vector machine
TC	Trophic coherence
TL	Trophic level

Chapter 1:

Introduction

1.1 Psychedelic use across time and cultures

Classic serotonergic psychedelics are psychoactive drugs with a primary mechanism of action as agonists of the 5HT_{2A} receptor, the effects of which manifest in altered states of consciousness (Nichols, 2016). These include naturally occurring tryptamines psilocybin and N,N-dimethyltryptamine (DMT), the synthetic tryptamine lysergic acid diethylamide (LSD), and the naturally occurring phenethylamine mescaline. The use of psychedelic substances stretches back thousands of years. Archaeological evidence dates use of forms of DMT as early as 2100 BC in the region that is modern-day Argentina, the use of psilocybin mushrooms is evidenced at around 6000 BC in regions of the Sahara, while the use of mescaline dates as early as 8600 BC in the area that is modern-day Peru (Samorini, 2019). Psychedelics have been used by cultures across the world, for sociocultural, religious, and healing purposes, often with music as a key element of the psychedelic experience (Dobkin de Rios, 2005; Labate et al., 2017b, 2016; Maas and Strubelt, 2003). The start of western research on psychedelics is largely associated with the psychedelic movement of the 1950s and 1960s, which was forced to a halt in the late 1960s following the reclassification of these drugs as Schedule I substances (Carhart-Harris and Goodwin, 2017; Reiff et al., 2020). We are currently in the midst of what is often referred to as ‘the psychedelic renaissance’ (Hadar et al., 2023), characterized by a resurgence in clinical (Reiff et al., 2020; Yao et al., 2024), neuroimaging, pharmacological and phenomenological research into these substances over the last three decades (McCulloch et al., 2022; Shinozuka et al., 2024). A great amount of anthropological and ethnographic work has been dedicated to understanding the traditional uses of these substances across cultures, and has been instrumental in informing contemporary research (Dobkin de Rios, 2005; George et al., 2020; Labate et al., 2017b, 2016).

1.2 Psychedelics as treatment

Classic psychedelics have been found to hold great potential for improved treatment outcomes in depression, anxiety, palliative care, post-traumatic stress disorder, obsessive compulsive disorder, substance use disorders and life-threatening disease-related anxiety and psychiatric distress (Calleja-Conde et al., 2022; Elsouri et al., 2022; Galvão-Coelho et al., 2021; Johnson, 2022; Johnson et al., 2017; Moreno et al., 2026; Muttoni et al., 2019; Reiche et al., 2018; Ross,

2018; Schimmers et al., 2022). More broadly, large-scale cross-sectional population research has associated lifetime psychedelic use with lower likelihood of psychological distress and suicidality, compared to individuals who had never taken psychedelics, adjusting for a range of covariates (Hendricks et al., 2015). In the Western clinical context psychedelics are considered as adjunct to therapy (Brennan and Belser, 2022; Carhart-Harris and Goodwin, 2017). The clinical relevance of these drugs has been reflected in national policies in countries such as Australia and Canada where the use of specific psychedelics as therapies for treatment resistant conditions is permitted (Health Canada, 2023; Therapeutic Goods Administration, 2023). The growing interest in the application of these therapies in clinical settings has been accompanied by a desire to understand the mechanisms through which psychedelics affect brain activity, as well as to ascertain the importance of the environment within which these substances are taken, with music being an environmental factor to which great importance has been attributed (Frederick S. Barrett et al., 2018; Bonny and Pahnke, 1972; Kaelen et al., 2018; O’Callaghan et al., 2020).

1.3 Set and setting: the importance of music

Set and setting are widely thought to be fundamental to shaping the acute psychedelic experience, as well as long-term outcomes following the experience (Golden et al., 2022; Haijen et al., 2018; Johnson et al., 2008). “Set” here refers to an individual’s inner state at the time of ingestion / administration (i.e. their mood and expectations), while “setting” refers to the environment (both physical and interpersonal) that they find themselves in during the psychedelic state (i.e. the ambience, the relationship with the therapist or facilitator, and notably the experience of the music being played) (Hartogsohn, 2021). Early work suggested that an “overly clinical” environment may lead to increased anxiety, and more broadly may contribute to participants having “unpleasant experiences” during the psychedelic state (Johnson et al., 2008; Strassman, 2000). A primary aim when designing the physical environment for such a session has been achieving a comfortable setting (Golden et al., 2022; Johnson et al., 2008; Noorani, 2021). Patients usually wear eye masks and listen to a curated music playlist (Garcia-Romeu and Richards, 2018).

Music has widely been agreed to be a crucial part of the setting of psychedelic experiences, with well-chosen music being thought to encourage long-term positive mental health outcomes (Kaelen, 2017; O’Callaghan et al., 2020). It has been argued to enhance meaningful and therapeutic experiences within the psychedelic state (Kaelen et al., 2018; O’Callaghan et al., 2020), and to increase the intensity of positive emotions (Kaelen et al., 2015; Zentner et al., 2008). In

a cohort of patients with treatment resistant depression undergoing psilocybin-assisted therapy, music was said to evoke therapeutically useful mental imagery (Kaelen et al., 2018). It has further been suggested to enhance the onset of mystical experiences within the psychedelic state (Kaelen et al., 2018), the occurrence of which is predictive of long-term positive outcomes (Ko et al., 2022; Schmid and Liechti, 2018). Importantly, qualitative work has shown differences in mystical experience scores, dependent on the type of music played during the session (Strickland et al., 2021). Additionally, clinicians with extensive experience of administering psychedelics within research and therapeutic settings outlined the elements of music they believed to be key in encouraging positive experiences, further supporting the therapeutic importance of music within the psychedelic state (Barrett et al., 2017). Critically, the importance attributed to music within the psychedelic state, did not originate in the modern western clinical setting.

Anthropological research characterizing the use of psychedelics and music within indigenous cultures, has been key to understanding the role of music within psychedelic rituals. The use of psychedelics and music in tandem has been recorded across cultures, including in Native Americans peyote ceremonies (Labate et al., 2016), ibogaine ceremonies of the Bwiti spiritual discipline of Gabon (Maas and Strubelt, 2003), psilocybin ceremonies of Mazatec Indians (Sabina, 2003), and most relevant to the current thesis, ayahuasca use among indigenous cultures of the Amazon and syncretic churches, commonly accompanied by songs.

1.4 Ayahuasca

Ayahuasca is a psychedelic brew, commonly made from the *Banisteriopsis caapi* vine (containing beta-carbolines) and *Psychotria viridis* (containing DMT). It has been used in rituals of Amazonian indigenous groups for a variety of purposes including diagnosis and healing of those who are unwell, solving social issues, and the gaining of insight (Frecska et al., 2016; Naranjo, 1986). The Shipibo-Konibo people of Peru, are one of the most well-documented examples of such a tradition, combining ayahuasca consumption with healing songs regarded as central to the ceremony and its intended outcomes (Gonzalez et al., 2021). Interviews with mestizo shamans in Peru highlight the importance of music in their use of ayahuasca, as the songs they sing are not only believed to have been gifted to the shamans by the spirit of the ayahuasca plant, but they are thought to have modulating effects on the psychedelic experience (Luna, 1984). These songs are thought to be able to change the strength of hallucinations, and cure specific illnesses. Dobkin de Rios and Katz, through multiple decades of anthropological fieldwork across the Peruvian Amazon, theorized that through its tone and rhythm, music acts

as a “jungle gym” of consciousness during psychedelic rituals, providing pathways for the participants’ movement through the ayahuasca-induced altered state of consciousness (Dobkin de Rios and Katz, 1975). This theory points to a functional role of ceremonial music within the psychedelic experience, suggesting that properties of the music such as its structure may play an active role in shaping the dynamics of the psychedelic state.

One-off as well as long-term, consistent ingestion of ayahuasca has been associated with a variety of positive mental health outcomes, including lower rates of anxiety (dos Santos et al., 2021), depression, (Sanches et al., 2016) and substance abuse (Barbosa et al., 2018), as well as broader improvements in mental wellbeing and cognitive flexibility (Hamill et al., 2019; Kiraga et al., 2021; Kuypers et al., 2016; Uthaug et al., 2018). Such effects have been shown to persist (van Oorsouw et al., 2022). Importantly, beyond drug effects, non-pharmacological factors (including music) have been outlined as important in ayahuasca-associated mental health improvements (Uthaug et al., 2021). For example, the therapeutic significance of shamanic ritual songs, or *icaros*, in ayahuasca ceremonies at the Addiction Rehabilitation Centro Takiwasi in Peru, were reported by patients (Graham et al., 2023).

The use of ayahuasca entered modern religious contexts through the growth of syncretic churches which incorporate the consumption of the brew into regular religious structured ceremonies (Labate et al., 2017b). Many originated in Brazil, with the three largest of these groups being the Santo Daime (the holy gift), the Uniao do Vegetal (union of the plant), and Barquinha (little boat). Two of these three groups hold music at high regard, Santo Daime and Barquinha, and value it not only as a way of verbally translating information regarding the religion, but also for its ability to allow a greater connection with God through its interaction with the brew (Dobkin de Rios, 2005; Labate et al., 2017b).

1.5 The Santo Daime Church

The Santo Daime is the oldest of the major Brazilian syncretic churches and incorporates within its beliefs and practices elements of Catholicism, European spirituality, Afro-Brazilian rituals and beliefs, as well as shamanic rituals of Amazonian indigenous peoples (Labate et al., 2017a). The Santo Daime tradition provides a compelling case study for the exploration of the interplay of music and psychedelics as music plays a fundamental and guiding role in their ayahuasca ceremonies to the extent that members often refer to the Church as a “musical doctrine” (**Figure 1.1**). The church has two major branches: the Centro de Iluminacao Crista Luz Universal (CICLU) and the Igreja do Culto Ecletico da Fuente Luz Universal (ICEFLU) (Hartogsohn, 2021). The latter has spread greatly both within Brazil and abroad and is therefore the group

referred to when the term Santo Daime is used from here onwards. The Santo Daime originated in the Amazonian state of Acre in the 1930s and has since spread to include official branches in the USA, Canada, France, Italy and the Netherlands. Santo Daime ceremonies are usually accompanied by hymns (*hinos*), which are performed by all members of the Church in unison. Therefore, these are songs that members are deeply familiar with. It is the belief of the Santo Daime that these hymns are not made by members, but rather “received” from the spirit realm which they often seek to connect with during ceremonies, making them highly meaningful (Labate et al., 2017a). Although the lyrics of these hymns may have been adapted and modified with time and voyage across countries and languages, the structure of the music itself has remained largely unchanged, consisting of songs following one of three rhythms: the march, the waltz, and the mazurka (Hartogsohn, 2021; Labate et al., 2017a). This suggests an importance of the music’s extra-verbal qualities especially as practitioners have noted being able to remember a hymn just from its melody or rhythm in the absence of remembering the words themselves (Labate et al., 2017a). Among the Santo Daime the ayahuasca brew retains critical importance in relation to the music, with many members suggesting that it is only in the presence of the ayahuasca that the true meaning of the music becomes clear (Labate et al., 2017a).



Figure 1.1 Santo Daime Ceremony. A still from a Santo Daime Ayahuasca Ceremony during which members of the Church all consume ayahuasca, and engage in making music through singing, playing instruments, and dancing. All members wear white and green uniforms and play specific roles within the ceremony. The photograph was taken by (Gold, 2008) (CC BY-NC 2.0).

1.6 The functional hierarchy

The brain is a dynamical complex system, with many interacting components that exhibit continuous nonlinear interactions across spatial and temporal scales (Breakspear, 2017). The complexity of the human brain enables dynamic integration of prior information with new information coming in from the external environment and signals from within the body (Deco et al., 2015). Brain activity is thought to constantly move between “the dual poles of segregation and integration” (Tognoli and Kelso, 2014), allowing the cognitive flexibility needed for learning (Capouskova et al., 2022). It is described as being in constant flux between varying functional brain substates, characterized by the dynamic combination of brain areas or networks providing a continuously shifting level of integration and segregation (Deco et al., 2015).

Brain activity is understood as organised in a directed hierarchy, with sensory regions, such as the primary auditory and visual cortices, providing “bottom-up” input into the system, which is progressively integrated by higher-order associative regions (Mesulam, 1998). This organization functionally enables the execution of computational goals, such as efficient segregation and integration of information, thus permitting global coordination (Meunier et al., 2010; Tognoli and Kelso, 2014; Wang et al., 2021). Seminal work by Margulies et al. (2016) provided evidence for this hierarchy by outlining a primary gradient of connectivity across the brain with integrative regions, such as the Default Mode Network (DMN), occupying one extreme of the gradient, and primary sensory and motor regions sitting at the other. They further validated this separation by showing the underlying structural connectivity to exhibit maximal distance between regions at opposite ends of the gradient. The Predictive Coding theory provides a mechanistic description of this hierarchy, proposing that rather than passive reception of new information from the environment, the brain continually generates predictions from models or priors of the world based on experience and context (Clark, 2013; Friston, 2010; Friston and Kiebel, 2009). These predictions are generated in higher-order regions and passed down the hierarchy, while incoming sensory information from lower levels is compared against these predictions, with the resulting prediction errors propagated upwards to update and refine existing model, in an effort to minimize prediction errors. The relative influence of top-down predictions and bottom-up prediction errors is determined by precision weighting of high-level priors. Precision-weighting reflects the confidence assigned to existing models, determining the influence top-down predictions have on processing relative to sensory input.

1.7 Psychedelics and the brain

The prominent theory of Relaxed Beliefs Under Psychedelics (REBUS) (**Figure 1.2**), conceptualises psychedelic action through the predictive coding framework. REBUS outlines the effects of psychedelics on the functional hierarchy through the energy landscape metaphor, such that in normal waking consciousness, and to a greater extent in psychiatric disorders such as depression, high-precision-weighting of high-level priors produces deep attractors in the brain's functional energy landscape, constraining brain activity to a limited repertoire of states, and exerting influence on the processing of sensory information coming into the system. Psychedelics are proposed to flatten this landscape, in other words flatten the functional hierarchy, resulting in a reduced precision-weighting of existing priors and more equal weighting of bottom-up sensory information (Carhart-Harris and Friston, 2019). REBUS builds on two frameworks: the free-energy principle (Friston, 2010) and the entropic brain hypothesis (Carhart-Harris et al., 2014). The free-energy principle argues that the development and survival of living things relies on the need to minimize uncertainty and avoid chaos. This argument is central to the predictive coding theory. The entropic brain hypothesis stipulates that, within a critical zone under the influence of psychedelics, there is a general increase in entropy in the brain with greater and more diverse information flow across the system. This increase in entropy of brain activity is then reflected in a richer conscious experience.

Several models of psychedelic action have been proposed, including circuit-based models such as the cortico-striato thalamo-cortical (CSTC) model (Vollenweider and Geyer, 2001; Vollenweider and Preller, 2020), emphasizing the effects of psychedelics on thalamocortical gating, and the cortico-claustro-cortical (CCC) model (Doss et al., 2022), which places focus on claustrum-based disruption of cortical activity. REBUS has emerged as an integrative framework, making predictions at the level of whole-brain hierarchical organization. The REBUS-proposed flattening of the functional hierarchy is testable through directed hierarchy measures, and is the focus of the current thesis.

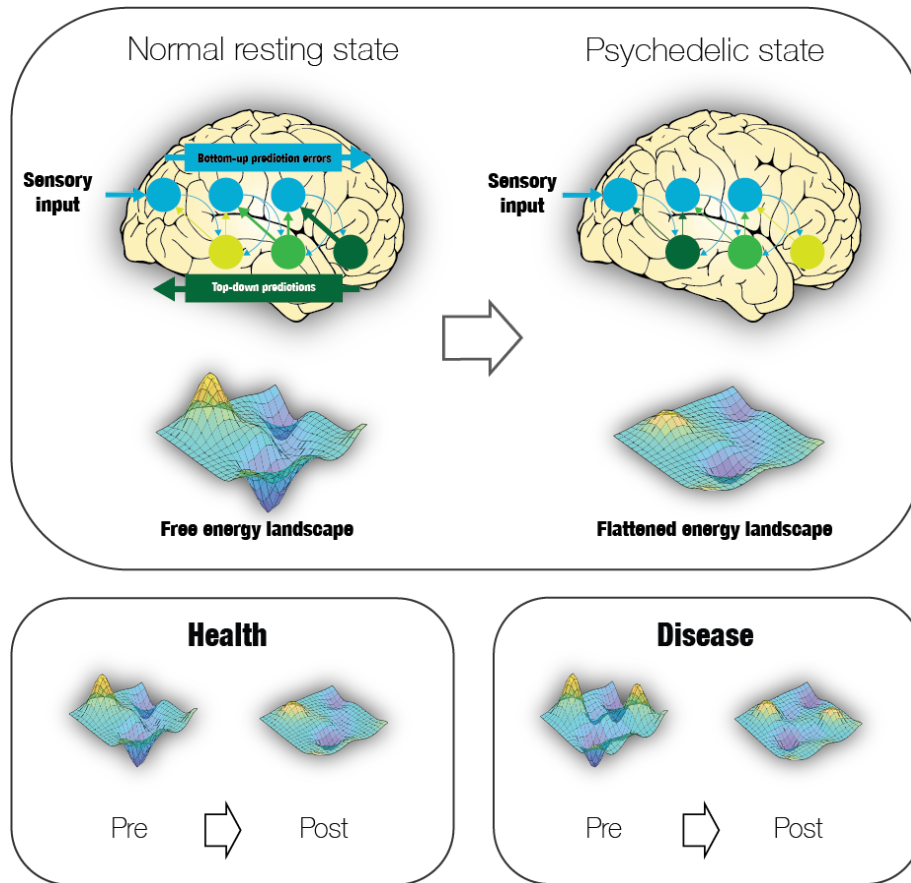


Figure 1.2 Relaxed beliefs under psychedelics (REBUS). A schematic diagram showing the psychedelic-induced flattening of the functional hierarchy, or dynamic energy landscape in the brain. The top figure shows that compared to normal wakefulness, the psychedelic state is characterized by a flatter energy landscape and more equal top-down and bottom-up influences across brain regions. The bottom panels show how the REBUS proposed mechanism manifests in health (left) and disease (right) where the resting state energy landscape is steeper (as depicted by higher peaks and deeper valleys). In both, ingestion of serotonergic psychedelics is posited to lead to a flattening of the landscape, and thus lower influence of existing models or attractor states. This figure was taken from (Jerotic et al., 2024b), adapted from (Carhart-Harris and Friston, 2019).

A growing body of neuroimaging research using undirected measures has provided evidence consistent with the predictions of REBUS. Psychedelic administration has been shown to lead to significant decoupling among brain regions higher in the functional hierarchy, alongside simultaneous increases in communication between areas lower in the functional hierarchy (Carhart-Harris et al., 2016, 2012; Tagliazucchi et al., 2016). Lord et al. (2019) showed that ingestion of psilocybin led to increased global BOLD phase coherence and movement towards a globally synchronized functional connectivity state alongside simultaneous disruption of a phase-locking pattern resembling the frontoparietal network, a network previously associated with attention-based cognitive control through top-down mechanisms (Cole and Schneider, 2007; Dosenbach et al., 2008; Xin and Lei, 2015). Further, psychedelics have been shown to expand the brain's repertoire of dynamic states (Atasoy et al., 2018a, 2017; Lord et al., 2019;

Tagliazucchi et al., 2014; Vohryzek et al., 2024b). Work examining psychedelic action through a network control theory lens, showed LSD and psilocybin to reduce control energy required for brain state transitions, and this reduction was associated with a higher frequency of state transitions (Singleton et al., 2022). Psychedelics have also been shown to increase entropy in the brain using a variety of measures (Lebedev et al., 2016; Mediano et al., 2024; Schartner et al., 2017; Timmermann et al., 2019). Girn et al (2020) extracted a principal gradient of brain connectivity spanning unimodal and transmodal regions, aligning with prior work (Margulies et al., 2016), showing LSD- and psilocybin-induced contraction of this gradient.

Approaches sensitive to the directionality of information flow have been critical in characterizing the effects of psychedelics on the functional hierarchy. EEG-based research demonstrated that DMT altered cortical travelling waves, namely suppression of backward waves and enhancement of forward waves, corresponding broadly to bottom-up and top-down waves respectively (Alamia et al., 2020). Shinozuka et al. (2025) applied directed hierarchy metrics to MEG data, showing LSD administration to result in reductions in hierarchical coherence and inhomogeneity, reflecting a psychedelic-induced flattening of the hierarchy. Deco et al. (2024) applied whole-brain modelling and trophic-coherence measures of hierarchy to fMRI data from patients with treatment resistant depression, showing psilocybin to flatten the functional hierarchy. Together, these convergent findings across imaging modalities, methodologies and psychedelic compounds, provide strong evidence for REBUS.

1.8 Ayahuasca: neuroimaging

DMT, like LSD and psilocybin is a classic serotonergic psychedelic with a primary action as a 5HT_{2A} and 5HT_{1A} agonist (Domínguez-Clavé et al., 2016). Ayahuasca, however, is a pharmacologically complex brew. Although the pharmacokinetics of DMT have been shown to align closely with the onset and development of ayahuasca's subjective effects (Riba et al., 2003), the beta-carbolines have been argued to contribute beyond MAO inhibition, with tetrahydroharmine for example, being an inhibitor of the serotonin transporter which persists in the blood stream for several hours (Domínguez-Clavé et al., 2016). Such differences, alongside the distinct temporal and phenomenological profiles of the ayahuasca-induced state compared to other forms of DMT administration (Barbosa et al., 2018; Strassman et al., 1994), necessitate the examination of ayahuasca-induced changes to brain activity specifically.

Ayahuasca-focused neuroimaging research to date spans several imaging modalities (including EEG, fMRI, SPECT, MRS, and structural MRI), examining acute and post-acute effects, in naturalistic as well as more standard research settings, among healthy drug naïve-

controls, experienced users and members of religious communities who practice regular ayahuasca use such as the Santo Daime. EEG studies have pointed to ayahuasca-induced spectral power changes, namely frequency-band-specific and time-specific changes such as alpha reductions earlier in the acute experience, and later gamma increases, alongside increased activation in temporal and frontal regions (Alves et al., 2022; Don et al., 1998; Riba et al., 2004, 2002; Schenberg et al., 2015; Silva-Costa et al., 2025; Stuckey et al., 2005). fMRI resting state research in healthy drug-naïve participants has pointed to post-acute ayahuasca-induced increases in salience network connectivity and decreases in DMN connectivity (Pasquini et al., 2020), aligning with effects observed under intravenous DMT, LSD and psilocybin (Gattuso et al., 2023; Timmermann et al., 2023). fMRI resting state studies specifically examining the effects of ayahuasca ingestion among the Santo Daime showed reduced activity of and connectivity between regions within the DMN (Palhano-Fontes et al., 2015), as well as increased network entropy and diversity (Viol et al., 2019, 2017). A more recent study examining the effects of ayahuasca ingestion among members of the Santo Daime Church examined drug-induced changes to functional connectivity (FC) profiles across subjects, using a fingerprinting approach, finding a movement towards a shared FC fingerprint across members (Mallaroni et al., 2024). Several task-based studies have been conducted outlining ayahuasca-induced increases in activation of frontal and temporal regions during a verbal fluency task among members of the Uniao do Vegetal Church (Almeida Prado et al., 2009), increased visual cortex activation during a mental imagery task among members of the Santo Daime (de Araujo et al., 2011), and dampened amygdala responses to aversive faces among experienced users more broadly (Aruda Sanchez et al., 2024). Most recently, research focusing on the posterior superior temporal sulcus, a region involved in social cognition, applied directed measures of granger causality to resting-state fMRI, showing significant ayahuasca-induced modulation of this region by early visual and motor regions (Soares 2026).

Two systematic reviews of neuroimaging literature on the effects of ayahuasca (spanning MRI, fMRI, PET and SPECT) outlined that the current evidence base is limited, and that on average studies exhibit small sample sizes and modest quality as defined by three standardized quality assessment tools (dos Santos et al., 2016; Santos et al., 2023). Further, no whole-brain directed connectivity analyses have been conducted to examine the effects of ayahuasca on the functional hierarchy.

1.9 Psychedelics and music: neuroimaging

There have been a handful of neuroscientific studies exploring the interplay of psychedelics and auditory stimuli, including music, in healthy participants. Early EEG research examining the effects of psilocybin on auditory oddball paradigms, showed N1 peak amplitude reductions compared to placebo (Umbricht et al., 2003). While later MEG work exploring the effects of LSD administration during an auditory oddball mismatch negativity paradigm (MMN) showed suppressed neural responses to novel stimuli and enhanced responses to familiar stimuli compared to placebo (Timmermann et al., 2018).

Importantly, several fMRI studies have directly examined the effects of psychedelic administration during music-listening. Kaelen et al. (2016) examined the interaction between LSD administration and music-listening on the parahippocampal cortex (PHC), previously associated with music-evoked emotion and mental imagery, finding increased connectivity between the PHC and the visual cortex as well as increased information flow from the PHC to the visual cortex when both LSD and music were present, which correlated positively with mental imagery scores. Preller et al. (2017) showed BOLD signal increases in several regions along the cortical midline following LSD administration, which were associated with enhanced perceived meaning of musical stimuli in the drug condition. Further work not only looked at the presence of music under LSD, but went a step further by using the properties of the music as regressors of interest in understanding drug-induced changes to brain activity, finding altered BOLD responses under LSD for different musical components and within distinct brain regions (Kaelen et al., 2017). Barrett et al. (2018) further examined the effect of LSD, and specifically 5HT_{2A} receptor signalling in neural response to music's time-varying tonal structures, with tonality-tracking analyses revealing 5HT_{2A} receptor signalling under LSD to alter responses in regions previously associated with higher-level auditory and musical perception and processing.

More recently research has explored the role of context in modulating psychedelic effects on brain entropy and the functional hierarchy. Using a placebo-controlled MEG dataset examining the effects of LSD on brain dynamics, Mediano et al. (2024) explored the effects of four distinct context or stimulus conditions on whole-brain complexity as measured by Lempel-Ziv. They found the greatest change in Lempel Ziv following LSD administration when participants had eyes closed with no stimulus, and progressively lower magnitude of drug-induced change across contexts in the following order: eyes closed with musical stimulus, eyes open looking at fixation, eyes open watching a silent film. Using the same dataset, further research examined

the effects of LSD administration on the functional hierarchy using three distinct measures: irreversibility, hierarchical coherence, and hierarchical inhomogeneity (Shinozuka et al., 2025). They observed a significant and consistent change across measures of hierarchy following LSD administration compared to placebo across all contexts, however, once more the relative difference in hierarchy within drug and no drug conditions varied based on context, providing evidence in support of context-dependent differences in hierarchy changes following LSD administration, and thus highlighting the need for systematic exploration of the role of context within the psychedelic state.

As evidenced by the studies outlined in the current section, the existing neuroscientific evidence for the interplay of music and psychedelics is limited and has largely focused on the effects of psychedelic ingestion on music and auditory stimulus processing, looking at specific regions and networks within the brain. With the exception of one early study which examined psilocybin (Umbricht et al., 2003), all neuroimaging research on the interplay of psychedelics and music, has focused on LSD. A recent meta-analysis showed notable differences across classic serotonergic psychedelics (LSD, psilocybin and DMT) with regard to their pharmacology, neuroimaging and phenomenology, necessitating the exploration of each drug with rigor (Shinozuka et al., 2024).

1.10 Thesis overview

Music and psychedelics have been in a constant interplay across decades and cultures, most recently emerging in modern western culture through psychedelic-assisted therapy where music is regularly used to modulate the psychedelic experience and encourage positive acute effects and long-term outcomes following the session. The regular ceremonial use of the two in tandem across syncretic churches of Brazil, particularly the Santo Daime Church, which has spread internationally (Labate et al., 2017b), provides a compelling route to examining the role of highly meaningful and familiar music within the ayahuasca-induced state. This thesis aims to systematically examine the effects of ayahuasca ingestion and ritual-relevant music listening on brain dynamics and the functional hierarchy among members of the Santo Daime Church. The following four chapters analyse an fMRI dataset of twenty-four members of the Santo Daime Church (Mallaroni et al., 2024; Ramaekers et al., 2023). The goal of this work is to characterize the effects of ayahuasca on brain dynamics and the functional hierarchy within this unique dataset of long-term users of ayahuasca within a religious, ceremonial context, and the mediating role ceremonial hymns play in these effects. To this end, the work presented in this thesis has three main aims: 1) to examine the effects of ayahuasca ingestion among the

Santo Daime on large-scale brain dynamics and the functional hierarchy at rest, 2) to assess whether observed effects are consistent across resting state and ritual-relevant music listening contexts, and 3) to explore how ceremonial music's familiarity and predictability modulated the ayahuasca-induced effects on the functional hierarchy. The following sections introduce the dataset and the preprocessing and denoising steps conducted, after which a brief overview of the approaches taken in each of the following chapters is outlined, with a more detailed introduction relevant to each methodology provided at the start of each chapter.

1.10.1 The Santo Daime dataset

The dataset was collected at Maastricht University, as part of a collaborative project between the Psychopharmacology Lab, Maastricht University; Centre for Music in the Brain, Aarhus University; and Centre for Eudaimonia and Human Flourishing, University of Oxford. Twenty-four members of the Santo Daime Church were scanned on two consecutive days. The study was conducted in accordance with the Declaration of Helsinki (1964), amended in Fortaleza, Brazil (2013), the Medical Research Involving Human Subjects Act (WMO), and was approved by the Academic Hospital and the Medical ethics committee of Maastricht University (NL70901.068.19/METC19.050).

1.10.2 Demographics

Subjects were active members of the Santo Daime Church (age: 55 ± 10 years, gender: 10 female), who had been members of the church for an average of 14 years prior to the experiment (range: 3 to 27 years) and had, on average, attended 564 ceremonies (range: 50 to 2700 ceremonies).

1.10.3 Study protocol

Participants took part in two consecutive testing days (**Figure 1.3**); day 1 was a baseline no drug condition, day 2 was the acute ayahuasca condition.

Day 1: participants filled in demographics questionnaires. Structural MRI, MRS, and fMRI scans were conducted. fMRI scans were conducted first at rest and then during a music listening paradigm, where participants listened to four hymns that systematically varied in familiarity and predictability in a two-by-two design. A more detailed description of the music paradigm

is provided in Chapter 5. Participants were instructed to keep their eyes open looking at a fixation during resting state, and to keep their eyes closed during music listening. Following scanning, participants completed questionnaires including the Ego Dissolution Inventory as well as the 5- and 11-Dimensional Altered States of Consciousness Questionnaire, among others (Ramaekers et al., 2023).

Day 2: participants consumed a personally chosen does of ayahuasca (mean: 24ml, standard deviation: 8.16 ml). The ayahuasca brew was produced and provided by the Church, containing: 0.14mg/ml DMT, 4.50 mg/ml harmine, 0.51 mg/ml harmaline, and 2.10 mg/ml tetrahydroharmine. Each participant's ayahuasca ingestion occurred within a ceremonial context organised, monitored, and facilitated by the Church. Participants drank the brew as part of a ceremony of six members, with the schedule for ingestion stratified across lab visits to allow each member to be scanned at their pharmacokinetic peak (90 minutes following administration). Participants completed the same scanning protocol as on day 1. Following the scans, blood samples were taken, and the same cognitive tests and questionnaires were completed as on day 1.

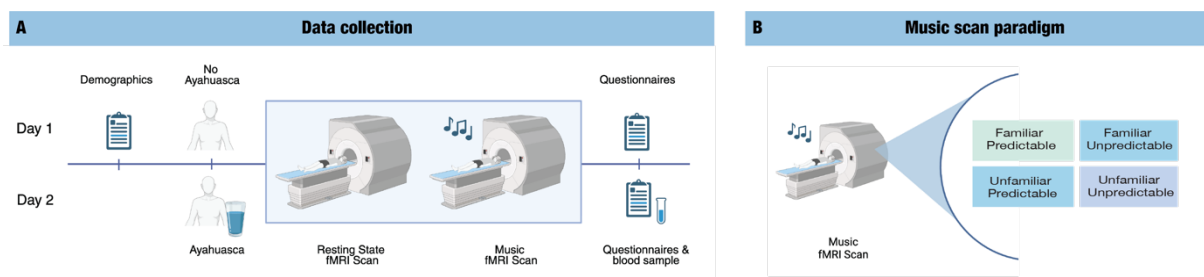


Figure 1.3 Data collection protocol for ayahuasca study with Santo Daime Church members. *A.* Data collection was carried out over two days for each participant. On the first day demographic data was collected. Structural MRI data, resting state fMRI data, as well as music listening fMRI data were collected on both days, on the first day scans were conducted with the participants no having consumed ayahuasca, on the second day the scans were conducted 90 minutes following ayahuasca ingestion. Blood samples were taken on the second day. Questionnaires were completed at the end of both scanning days. *B.* Within the music listening condition participants were played four hymns that varied in familiarity and predictability. This figure was created with BioRender.com.

1.10.4 Scanning protocol

A MAGNETOM 7T MRI scanner was used to collect structural and functional MRI scans. T1-weighted structural images were acquired 60 minutes after the ingestion of ayahuasca using a magnetisation-prepared 2 rapid acquisition gradient-echo (MP2RAGE) sequence (TR = 4500 ms, TE = 2.39 ms, TI1 = 0.90 s, TI2 = 2.75 s, flip angle 1 = 5°, flip angle 2 = 3°, voxel size =

0.9 mm isotropic, matrix size = $256 \times 256 \times 192$, phase partial Fourier = 6/8, GRAPPA = 3 with 24 reference lines, bandwidth = 250 Hz/pixel). During the fMRI scans echo planar imaging (EPI) volumes were acquired (TR = 1400ms; TE = 21ms; field of view=198 mm; flip angle = 60°; oblique acquisition orientation; interleaved slice acquisition; 72 slices; slice thickness = 1.5mm; voxel size = 1.5mm^3), followed by 5 phase encoding volumes for EPI unwarping. Fixed criteria across scans were used for shimming.

1.10.5 Preprocessing

I preprocessed the data using a combination of FSL BET and CONN preprocessing pipelines. The functional and anatomical data were skull stripped using FSL BET, a threshold of 0.2 was found to be effective and applied to all functional scans, while thresholds for anatomical scans were individually assigned (ranging from 0.1 to 0.2) to minimise removal of brain tissue. The functional data were preprocessed using the CONN functional connectivity Toolbox (version 22.a; Nieto-Castanon, 2020) implemented in MATLAB using SPM12 (revision 771; RRID:SCR_007037). The CONN Toolbox provides a widely adopted and standardised preprocessing approach, having been used in over 6000 studies (<https://web.conn-toolbox.org/>). Its default preprocessing pipeline has previously been applied effectively to studies exploring altered states of consciousness (e.g. Dai et al., 2023; Luppi et al., 2021, 2025; Varley et al., 2020).

Preprocessing followed the standard CONN pipeline. Functional images were realigned and unwrapped using SPM's realign & unwarp procedure, with scans co-registered to the first scan using a least squares approach and a six-parameter rigid body transformation. Data were resampled using b-spline interpolation to correct for head motion and magnetic susceptibility interactions. Temporal misalignment between slices was corrected following SPM slice-timing correction, applying sinc temporal interpolation to resample all BOLD timeseries to a common mid-acquisition time. Potential outlier scans were identified using the Artifact Detection Tool (ART). Framewise displacement and global BOLD signal intensity were thresholded at 0.9 mm and 5 standard deviations, respectively. For each subject, a reference BOLD image was computed by averaging all functional volumes excluding identified outliers. Functional and anatomical data were segmented into grey matter, white matter, and cerebrospinal fluid, and normalised to standard MNI space using SPM's unified segmentation and normalization algorithm with the default IXI-549 tissue probability map template. Normalised images were resampled

to 2 mm isotropic voxels. Lastly, functional data were spatially smoothed using a Gaussian kernel of 2 mm full width half maximum (FWHM).

1.10.6 Denoising

Denoising was conducted using the CONN Toolbox (version 22.a; Nieto-Castanon, 2020). functional data were denoised using the standard denoising pipeline which included the regression of potential confounding effects characterized by white matter timeseries (5 Component Based Noise Correction (CompCor) noise components), CSF timeseries (5 CompCor noise components), motion parameters and their first order derivatives (12 factors), outlier scans (below 25 factors), and linear trends (2 factors) within each functional run, followed by low-pass frequency filtering of the BOLD timeseries below 0.9 Hz. CompCor noise components within white matter and CSF were estimated by computing the average BOLD signal and the largest principal components orthogonal to motion parameters, and outlier scans within each subject's eroded segmentation masks. Data were demeaned with a narrow filter of 0.008-0.08Hz. The first and last 5 volumes were removed to reduce edge effects from filtering.

1.10.7 Analysis outline

Chapter 2 examines the effects of ayahuasca at rest on spatiotemporal brain dynamics through the application of a frequency-based undirected spatiotemporal decomposition technique termed Harmonic Decomposition in Spacetime (Vohryzek et al., 2024b), which incorporates harmonic-based decomposition (Atasoy et al., 2018a; Glomb et al., 2021) and the leading eigenvector dynamics analysis (LEiDA) framework (Cabral et al., 2017), enabling both time-averaged and dynamic features of the data to be characterised. Harmonic-based decomposition has shown consistent effects across LSD, psilocybin, and intravenous DMT among healthy participants with limited previous experience of psychedelics (Atasoy et al., 2018b; Serra et al., 2023; Vohryzek et al., 2025). To enable an initial relation of ayahuasca's effects on brain dynamics within the broader psychedelic literature, we compare results from this dataset with those of a previously analysed intravenous DMT dataset (Timmermann et al., 2019; Vohryzek et al., 2024b). This intravenous DMT dataset is chosen due to the drug being a researched Western form of DMT administration (Alamia et al., 2020; Erne et al., 2026; Pasquini et al., 2025; Piccinini et al., 2025; Timmermann et al., 2023; Vogt et al., 2023) proximal to ayahuasca. Further, the standard healthy cohort of individuals with limited prior psychedelic experience, enables an initial grounding of the effects observed in the unique case of Santo Daime members

who are regular ayahuasca consumers as compared to a more standard cohort. We examine time-averaged harmonic contribution as well as dynamic measures of fractional occupancy and lifetimes. Several harmonics have been outlined as characterising spatial patterns relevant to the functional hierarchy, including the unimodal to transmodal functional gradient of the brain, and the DMN (Glomb et al., 2021), and are thus specifically focused on during analyses. Further, we employ latent space embeddings to characterise the temporal trajectories of brain activity in functional harmonic space under the effects of ayahuasca. Importantly, these are undirected connectivity measures, which are effective in characterising spatiotemporal dynamics, however they are unable to capture the directional information flow that defines hierarchical organisation.

Undirected functional connectivity, being inherently symmetric, cannot distinguish between feedforward and feedback connections. This distinction is fundamental to hierarchical organisation. Whole-brain modelling addresses this limitation by enabling the estimation of a directed effective connectivity matrix grounded in the underlying structural connectivity of the brain, providing a biological underpinning for the observed hierarchy (Kringelbach et al., 2023). Chapters 3, 4 and 5 rely on a linearised Hopf whole-brain model of coupled Stuart-Landau oscillators constrained by the structural connectome (Ponce-Alvarez and Deco, 2024), with connection strengths iteratively adjusted until the simulated functional connectivity matches the empirical data well. This process yields a full directed, asymmetric effective connectivity. The term “generative effective connectivity” (GEC) is used to reflect that the effective connectivity is derived from a generative model of neural dynamics. Importantly, this approach operates at the whole-brain level, rather than being restricted to pre-specified regions or networks. **Supplementary Section S1.1** outlines the model, and the fitting procedure. Details of how the model was applied uniquely to each chapter are provided in each chapter’s methods and supplementary sections.

In Chapter 3 we examine the directed hierarchy through a combination of whole-brain modelling and trophic analysis measures. Trophic analyses provide key measures of trophic coherence (a global measure of how hierarchically organised the system is) and trophic levels (each region’s relative position within the hierarchy, determined by its pattern of incoming and outgoing connections) (Deco et al., 2024; MacKay et al., 2020). Prior applications of this approach to psilocybin in a clinical setting revealed a flattening of the directed hierarchy (Deco et al., 2024), motivating the examination of whether ayahuasca consumption in a ceremonial context induces similar effects. Together, these measures allow us to ask whether ayahuasca alters the

overall degree of hierarchical organisation, the central tendency and differentiation of the hierarchy, and whether observed changes are localised to specific resting state networks. We examine differences in trophic coherence prior to and following ayahuasca ingestion at rest as well as during ceremonial music listening. The average and distribution of trophic levels is compared at the whole-brain level, and average trophic level is compared within resting state networks too. To ascertain ayahuasca-induced changes to coupling strength across the brain, we further examine changes in average effective connectivity between drug conditions. This chapter examines hierarchy from a time-averaged approach, with the temporal dynamics of these measures examined in Chapter 4.

Time-averaged analyses are unable to show whether observed changes in hierarchy are temporally stable. Existing work on ayahuasca's effects on brain dynamics has largely used undirected connectivity measures (Alves et al., 2025; Mallaroni et al., 2024). In Chapter 4 we address this by combining the LEiDA methodology introduced in Chapter 2, with per-state whole-brain modelling, enabling reconstruction of subject-specific timeseries of hierarchy metrics across the scan. Through this approach we examine the temporal stability of changes to hierarchy metrics. We focus on three key measures: trophic coherence, trophic level mean and trophic level standard deviation, a measure we term *Richness of Orchestration* to capture the degree of hierarchical differentiation across brain regions. We quantify the temporal mean and standard deviation of each measure and examine ayahuasca-induced changes in each at rest and during music listening. Through a further fractional occupancy standardisation test we examine whether observed drug-induced changes are driven by changes within brain states or by shifts in state occupancy. This method provides a novel integration of dynamic state switching with Hopf whole-brain modelling.

In Chapters 3 and 4 the effects of ayahuasca ingestion on the functional hierarchy are examined both at rest and during ritual-relevant music listening, wherein we treat the music condition as a single block. However, in each scan, participants listened to four hymns that systematically varied in familiarity and predictability in a two-by-two design. These musical properties are of particular relevance given the predictive processing account of music perception, formalised in the Predictive Coding of Music (PCM) model (Vuust et al., 2022, 2009), in which familiarity and predictability shape the precision of internal prediction, and the REBUS hypothesis that psychedelics relax precision-weighting of priors (Carhart-Harris and Friston, 2019). Further, the ceremonial hymns of the Santo Daime hold deep personal and spiritual significance for Church members, who are intimately familiar with the music (Labate et al., 2017a). Chapter 5 leverages the factorial design of the music paradigm to examine how specific

musical properties modulate ayahuasca's effects on the functional hierarchy. To this end, we apply the methods introduced in Chapters 3 and 4 to the individual music conditions, examining the role of music's familiarity and predictability in moderating ayahuasca-induced changes through linear mixed modelling approaches. We examine whether ayahuasca alters the sensitivity of the functional hierarchy to musical properties, as well as the unique drug effects within each music condition. Through this analysis we provide a first step in exploring the interaction between ayahuasca ingestion and ceremonial music characteristics on the brain's functional hierarchy.

Together, the following chapters provide a systematic characterisation of ayahuasca's effects on brain dynamics and the functional hierarchy, commencing with undirected frequency-based spatiotemporal dynamics, moving towards directed hierarchy measures first using a time-averaged approach, then introducing a novel time-resolved approach, and finally examining the role of musical properties in moderating ayahuasca-induced effects. This progression from undirected to directed measures, and from static to dynamic analyses, allows us to characterise not only whether ayahuasca alters the brain's hierarchical organisation, but how such changes unfold over time, and interact with musical stimuli.

1.11 Summary

This chapter introduced the historical, cultural, and therapeutic context of psychedelic use, with particular focus on the central role of music within ayahuasca ceremonies of the Santo Daime Church. The brain's functional hierarchy was outlined alongside the REBUS model, which proposes a psychedelic-induced flattening of the hierarchy through relaxation of precision-weighting of high-level priors. The Santo Daime fMRI dataset analysed throughout this thesis was introduced, including the data collection protocol and preprocessing procedures. In Chapter 2, the effects of ayahuasca on spatiotemporal brain dynamics are examined through undirected harmonic decomposition, with comparison to an intravenous DMT dataset. Chapters 3 and 4 move towards directed measures of hierarchy through whole-brain modelling and trophic analyses, first from a time-averaged perspective and then through a novel time-resolved approach combining brain state decomposition with per-state modelling. Chapter 5 leverages the factorial design of the music paradigm to examine how familiarity and predictability of ceremonial hymns moderate ayahuasca's effects on the functional hierarchy.

Chapter 2:

Large-scale spatiotemporal dynamic changes

Abstract

Harmonic decomposition techniques have been observed to be an effective unifying tool in examining changes in frequency-based undirected spatiotemporal brain dynamics across psychedelics (including psilocybin, LSD and DMT). However, the effects of ayahuasca consumption on these dynamics, particularly within ceremonial contexts, have not previously been explored. The current chapter applies the harmonic decomposition in spacetime (HADES) framework to resting state fMRI data from members of the Santo Daime Church before ayahuasca ingestion and during the acute effects of the drug. Further, we relate observed changes under ceremonial use of ayahuasca to the more well-studied effects of intravenous DMT within a modern Western research context. To this end, drug-induced changes in time-averaged (absolute and relative power) and time-resolved (fractional occupancy, lifetimes and latent dimension spread) measures are examined. Results provide convergent evidence across datasets in suppression of absolute power of several spatially resolved functional harmonics (FHs) (notably FH9 which corresponds to the default mode network), as well as drug-induced contraction of latent space spread. However, while intravenous DMT administration showed significant changes in relative power, fractional occupancy and lifetimes of spatially resolved harmonics, these were not observed following ayahuasca ingestion among the Santo Daime. The findings of this chapter point to several consistent signatures of the psychedelic state across datasets. Nevertheless, observed differences motivate more direct examination of ayahuasca-induced changes to brain dynamics among the Santo Daime.

2.1 Introduction

The Santo Daime represent one of the few long-standing practices in which ayahuasca is used in a religious, regular, communal, and deeply ritualised manner, making it markedly different from the settings of most modern psychedelic trials (Barbosa et al., 2009; Labate and MacRae, 2016). Contemporary neuroscientific research into psychedelics in large part relies on dosing sessions taking place in a controlled, quiet room, with continuous monitoring by trained staff where participants are normally instructed to sit or lie down, wear eyeshades and listen to a curated music playlist through headphones (Johnson et al., 2008). This is an environment significantly different from that of the collective, structured and active Santo Daime ayahuasca ritual (Labate and MacRae, 2016). Despite increasing neuroscientific interest in classic psychedelics, ayahuasca remains comparatively understudied (Shinozuka et al., 2024), particularly within the naturalistic ceremonial contexts in which it is traditionally used. Yet, studies examining the effects of ayahuasca ingestion suggest positive effects on mental health, (Bouso et al., ; Osório et al., 2015; Sanches et al., 2016; Uthaug et al., 2021, 2018). This chapter explores changes in large-scale brain dynamics following ayahuasca consumption within Santo Daime ceremonies (Ramaekers et al., 2023). To relate findings to more commonly utilised psychedelic data, we explore the extent to which these align or diverge from those previously observed in participants administered intravenous DMT (Timmermann et al., 2019; Vohryzek et al., 2024b), a common form of DMT administration in Western research settings (Alamia et al., 2020; Luan et al., 2024; Pasquini et al., 2025; Piccinini et al., 2025; Timmermann et al., 2024, 2023, 2019; Vogt et al., 2023) and clinical trials (Algeron Pharmaceuticals, 2025; University Hospital, Basel, Switzerland, 2024). To this end, functional harmonic decomposition techniques, previously used in understanding the effects of classic psychedelics (LSD, psilocybin and DMT), are employed.

Just as complex sounds can be decomposed into distinct frequencies, complex brain activity can be decomposed into distinct spatial patterns that resonate with underlying brain connectivity at varying frequencies. Harmonics are the natural vibration patterns of a system. They correspond to the standing waves that emerge when a vibrating metal plate organises scattered particles, such as sand, into complex geometric patterns (Chladni, 1802). Concretely, harmonics are the eigenmodes of the graph Laplacian (Atasoy et al., 2016). Each harmonic corresponds to a specific spatial frequency (eigenvalue) and spatial pattern (eigenfunction). Eigendecomposition of the Laplace operator is a foundational mathematical framework with applications across physics, from theories of heat diffusion and wave propagation to magnetism and fluid

dynamics (Atasoy et al., 2016; Stewart, 1999), and its application to the brain enables a principled decomposition of cortical activity into frequency-specific spatial components.

Existing work on the application of harmonic decomposition to the brain has primarily relied on time-averaged analysis approaches (Atasoy et al., 2018b, 2017, 2016; Luppi et al., 2023; Vohryzek et al., 2025), capturing frequency-based spatial patterns that relate to the functional hierarchy, but neglecting their dynamics. On the other hand, dynamic approaches such as leading eigenvector decomposition analysis (LEiDA) (Cabral et al., 2017) capture spatiotemporal state switching but are not grounded in the frequency-based harmonic framework. Neither approach on its own captures how frequency-based spatial patterns evolve over time. The current chapter utilises the harmonic decomposition in spacetime (HADES) framework to examine how frequency-based spatial patterns are expressed over time (Vohryzek et al., 2024b). The following sections provide an introduction to the first applications of harmonic decomposition to the brain through connectome harmonics and the expansion of these ideas to the functional connectome through the development of functional harmonics. Further we outline the utility of dynamic analysis frameworks, specifically LEiDA, before describing HADES in more detail, as a framework which unifies functional harmonics and LEiDA enabling harmonic-based spatiotemporal decomposition of brain activity.

2.1.1 Connectome harmonics: a frequency-specific language of cortical activity

In the context of the human brain, harmonics were first applied to the structural connectome's graph Laplacian (built using both grey matter and white matter), showing the brain's natural spatial modes (Atasoy et al., 2018a, 2016). These structural connectome-derived harmonics are termed connectome harmonics. The decomposition of complex BOLD signal into these interpretable spatial modes is termed connectome harmonic decomposition. Ordered from low to high spatial frequency, harmonic modes span from large-scale coherent patterns of activity to more detailed, localised spatial patterns.

Connectome harmonics have previously been utilised in the characterisation of altered states of consciousness, including psychedelics, anaesthesia, and disorders of consciousness. Changes in conscious state, e.g. through anaesthesia or psychedelics, have been shown to affect the harmonic repertoire, or the range of connectome harmonics that the brain is using. Anaesthesia has been associated with a narrowing of the harmonic repertoire, suggesting greater reliance on low-frequency harmonics (Luppi et al., 2023). Conversely, psychedelic states have been associated with a broadening of the harmonic repertoire, suggesting the utilisation of more

higher-frequency connectome harmonics (Atasoy et al., 2018b, 2017; Vohryzek et al., 2025). This suggests an increase in diversity of brain states employed under psychedelics and a lowering of the same in anaesthesia. Such findings align with previous research showing administration of psychedelics to increase the range of dynamical states the brain utilises (Tagliazucchi et al., 2014). An overall increase in total power of all connectome harmonics was observed under the effects of LSD (Atasoy et al., 2017), psilocybin (Atasoy et al., 2018b), and DMT (Vohryzek et al., 2025). When looking at a full spectrum of 20,000 harmonics, psychedelics led to a suppression of low frequency harmonic energy, and an amplification of high frequency harmonic energy (Atasoy et al., 2018b, 2017; Vohryzek et al., 2025). The same pattern was observed in sub-anaesthetic doses of ketamine (Luppi et al., 2023). Conversely an amplification of low frequency and suppression of high frequency harmonic energy as compared to waking state were observed in states of propofol-anaesthesia and the vegetative state (Luppi et al., 2023) compared to waking state. Unlike in the case of vegetative state patients, such significant trends were not observed for patients in the minimally conscious state, a state characterised by patients' inability to respond behaviourally while exhibiting brain activity indicative of conscious awareness of the external world (Luppi et al., 2023; Owen et al., 2006). These results outline the functional relevance of connectome harmonics, exhibiting signatures of richness of experience, with psychedelic states on one end of this spectrum and anaesthesia and vegetative state on the other.

2.1.2 Functional harmonics

Building on the work of connectome harmonics, functional harmonics (FHs) were derived from the dense functional connectivity matrix (denseFC), enabling frequency-based spatial decomposition of the human brain's communication structure (Glomb et al., 2021). FHs were extracted from the group-level denseFC of 812 healthy participants from the Human Connectome Project. The resulting FHs were observed to capture varying elements of cortical organisation including topographic mapping, modularity of brain areas (Glasser et al., 2016), outline of well-known functional networks (including resting state networks (RSNs) (Yeo et al., 2011)) as well as global gradients of cortical activity, such as the separation of unimodal and multimodal brain regions (Glomb et al., 2021; Margulies et al., 2016; Mesulam, 1998). Additionally, the extent to which the resulting FHs reflected homogenous FC within parcellated regions as outlined by the HCP, was compared to four alternative functional bases: principal components, independent components, eigenvectors of the FC matrix, and eigenvectors of the adjacency matrix, with

FHs showing superior homogeneity within parcels to the first three bases, and equal to the fourth base. The first FH with eigenvalue 0 is constant, covering the whole cortex. As previously noted for connectome harmonics, increase in the corresponding eigenvalue of FHs is associated with greater segregation of the cortical surface. The first two spatially resolved, non-constant FHs show large-scale gradients spanning the whole-brain, while higher frequency FHs include more localised outlines. FH1 depicts a large-scale gradient separating the visual and somatomotor cortices, while FH2 outlines the gradient separating unimodal and multimodal regions. These gradients largely resemble the first two principal gradients outlined by Margulies et al. (2016). FH2 is particularly interesting, as this gradient is thought to reflect the functional hierarchy of the brain, with specialised unimodal sensory and motor regions sitting at one end of the gradient, or at the bottom of the hierarchy, and regions performing more complex cognitive functions, such as regions of the DMN, sitting at the top of the hierarchy. FH9, outlines much of the DMN. FHs 3 and 11 outline the somatotopic division of the body and face, FHs 4 and 8 outline retinotopy, and FHs 5 and 6 depict auditory and visual areas. Although an exact fit to known RSNs requires the convergence of multiple harmonics from across the frequency spectrum, weighted combinations of the first 11 low-frequency spatially-resolved harmonics have been found to represent the known RSNs well (Vohryzek et al., 2024d; Yeo et al., 2011). Furthermore, prior research has shown that this subset of 11 FHs and the global FH can be used to reconstruct a good portion of signal across datasets (Glomb et al., 2021; Vohryzek et al., 2024d). These results suggest the utility of FHs in decomposing brain signal in a spatially meaningful and informative manner.

2.1.3 The brain as a dynamical system

The work presented thus far highlights the utility of time-averaged harmonic decomposition in understanding a variety of brain states, by producing consistent and interpretable results. Importantly, the brain operates in a non-linear manner, showing dynamic changes across time in both tasks and rest (Huang, 2019; Snyder and Raichle, 2012). Early neuroimaging research characterised brain activity as an average across time, due largely to the constraints of available data acquisition and analysis techniques. The field has since made significant progress in incorporating dynamics, for example, by defining brain activity as a repertoire of probabilistic metastable substates (PMS), exhibiting transient arrangements across time (Cabral et al., 2017; Kringelbach and Deco, 2020). A substate is a subset of brain regions activating synchronously, while exhibiting asynchronous activity with the rest of the brain. Substates, as key components

of a system configuration, are characterized by persisting and co-existing integration and segregation across spacetime. A substate is composed of a subset of brain regions activating synchronously, while exhibiting asynchronous activity with the rest of the brain. This synchronization is due to phase synchronization between neural signals, which in consequence gives rise to correlated activity between pairs of brain regions (Fell and Axmacher, 2011). Phase synchronization refers to the point at which phases of two or more brain regions are aligned. Within the framework of the energy landscape, the system exhibits ongoing transitions between transiently stable substates, a phenomenon termed metastability. Time-averaged analysis approaches remove this temporal richness from the data.

2.1.4 Leading eigenvector dynamics analysis (LEiDA)

A growing body of literature has highlighted the importance of characterising temporal aspects of brain function, through examination of changes to substate metastability (Cabral et al., 2017; Deco et al., 2019, 2017c; Donnelly-Kehoe et al., 2019). Here we focus on one key approach to this, the Leading Eigenvector Dynamics Analysis (LEiDA) framework (Cabral et al., 2017). LEiDA characterizes PMS by extracting the leading eigenvector of the dynamic functional connectivity (dFC) matrices at each timepoint. A clustering technique, usually k-means, is then applied to all extracted leading eigenvectors, and PMSs are computed by considering the centres of the resulting clusters. The evolving dynamics of these PMSs can be characterised through measures which quantify changes in substate prevalence, such as fractional occupancy and lifetimes. Fractional occupancy refers to the probability of a substate occurring within a given timeframe (usually the duration of the scan). Lifetimes refers to the length of continuous presence of a substate. The previously published effectiveness of LEiDA in characterisation of substates in healthy participants (Cabral et al., 2017; Stark et al., 2020), and psychiatric conditions (Figuroa et al., 2019) highlights the importance of dynamics in understanding brain activity. The application of LEiDA to psychedelic research both in healthy controls (Lord et al., 2019) and clinical populations (Vohryzek et al., 2024a), consistently showed significant changes in substate fractional occupancy following drug administration, further supporting the importance of examining changes to brain state dynamics in such altered states.

2.1.5 Harmonic decomposition in spacetime

The Harmonic Decomposition in Spacetime (HADES) framework (Vohryzek et al., 2024b) characterises the brain's spatiotemporal activity in an atlas-free manner, by examining how

functional harmonics are expressed over time. Through this approach, HADES enables a dynamic perspective on functional gradients, capturing not only the spatial hierarchy of cortical organisation, but also its temporal evolution. HADES unifies FHs with the LEiDA framework, producing a dynamic state-based representation of brain activity grounded in frequency-based decomposition. Beyond standard time-averaged FH contribution, HADES quantifies how FH dominance changes across time through measures of fractional occupancy, lifetimes, and transition probabilities, capturing the dynamics of functional gradient expression. This framework has previously been applied in the analysis of psychedelic data, namely in DMT administration among healthy participants (Vohryzek et al., 2024b). Results showed significant changes in time-averaged contributions of FHs to the BOLD signal following DMT administration, as well as significant changes in time-resolved measures across several FHs. These effects were not replicated in the placebo condition. HADES has also been used to compare LSD, psilocybin, and DMT across healthy cohorts (Serra et al., 2023). Findings suggested consistent suppression of absolute (non-normalised) power of spatially resolved FHs following drug administration across drug pairs, and in some instances across all three psychedelics. These findings largely align with previous work across these drugs using connectome harmonic decomposition (Atasoy et al., 2018b, 2017; Vohryzek et al., 2025). Interestingly, time-resolved effects were less consistent across drugs (Serra et al., 2023). These results suggest that time-resolved HADES measures may reveal psychedelic-specific dynamics not present in placebo, and provide additional insights beyond time-averaged FH and connectome harmonic measures.

2.1.6 The current study

The current chapter aims to understand how ayahuasca ingestion affects large-scale brain dynamics among members of the Santo Daime tradition. Ayahuasca and intravenous DMT, although having the same primary psychoactive component, DMT, have two distinct pharmacokinetic and experiential profiles. Ayahuasca ingestion, has a slow onset (~60-120 minutes) and long duration (~4-6 hours), and is characterised by emotionally meaningful, autobiographical, and spiritual experiences (Barbosa et al., 2012). Intravenous DMT results in a rapid and intense experience, lasting up to 30 minutes, characterised by vivid geometric visual imagery and dose-dependent entity encounters (Barker, 2018; Strassman et al., 1994).

The aim of the current chapter is to examine the effects of ayahuasca ingestion among the Santo Daime on brain dynamics, through the lens of harmonic decomposition. An outline of the methodology used in this chapter is provided in **Figure 2.1**. We examine the extent to which

changes in FH expression observed following ayahuasca ingestion in this unique population align with those seen under intravenous DMT. HADES is applied to two datasets: resting-state fMRI acquired before and after ayahuasca ingestion among members of the Santo Daime (Mallaroni et al., 2024; Ramaekers et al., 2023), and resting-state fMRI acquired before and after intravenous DMT administration in healthy participants from the general population (Timmermann et al., 2023, 2019; Vohryzek et al., 2024b). The intravenous DMT dataset has previously been analysed using HADES and this work has been published (Vohryzek et al., 2024b), here these analyses are used as a comparative benchmark. The DMT data analyses are recalculated in the current chapter for consistency in statistical significance testing approaches across DMT and ayahuasca datasets, which are different to those in the published work and may result in slightly different outcomes. Both time-averaged FH contributions to the BOLD signal and time-resolved measures are applied. Given the significant differences in experience and pharmacokinetics of intravenous DMT and ayahuasca, we do not hypothesise the two datasets to produce fully aligned effects. Nevertheless, given previously observed consistencies across DMT, LSD, and psilocybin, we do hypothesise convergence in several changes, especially regarding absolute power suppression across spatially resolved harmonics. FH2 and FH9 are of particular interest as these harmonics have previously been outlined as relevant to the effects of psychedelics on the functional hierarchy (Vohryzek et al., 2024b).

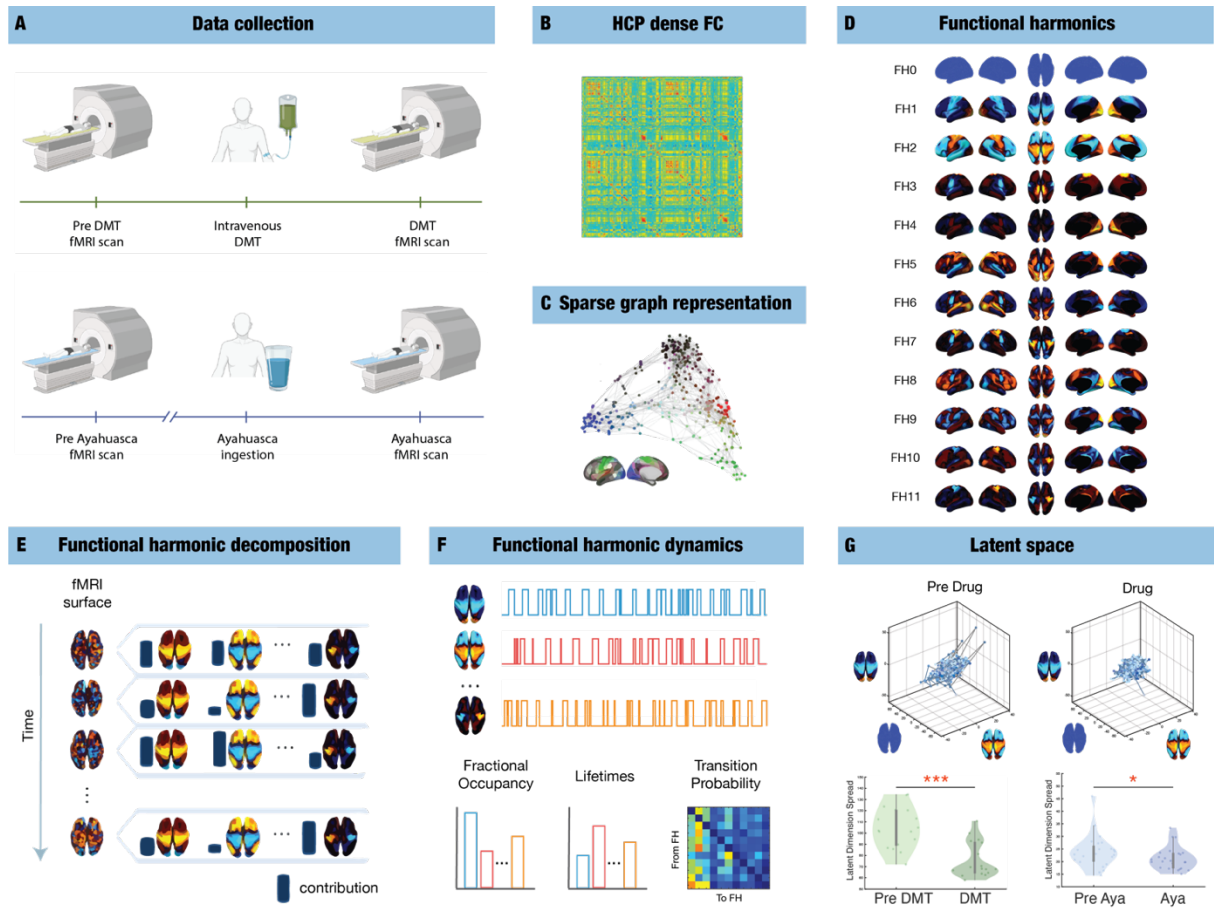


Figure 2.1 Harmonic decomposition in spacetime overview. *A.* We applied the HADES methodology to two resting state fMRI datasets. Top row: intravenous DMT trial in participants with limited prior experience of psychedelics, resting state scans taken before and after DMT administration. Bottom row: ayahuasca trial among members of the Santo Daime Church, scanned at rest 1 day before ayahuasca ceremony, and 90 minutes following ayahuasca ingestion. *B.* Functional harmonics are constructed from the dense FC matrix derived from the data of 812 subjects from the HCP S1200 release. *C.* A sparse, symmetric, binary graph representation is computed from the dense FC. *D.* Laplacian decomposition of the sparse adjacency matrix is used to derive the functional harmonics (FH), here we focus on the first 11 spatially resolved FHs, and the global FH. *E.* Individual harmonics are projected onto the surface representation of each subject's fMRI timeseries, and functional harmonic decomposition is conducted by calculating the contribution of each harmonic to the data; absolute (non-normalised) and relative (normalised) contributions are estimated for each FH. *F.* Taking a winner-takes-all approach to contribution metrics at each timepoint, dynamic measures of fractional occupancy, lifetimes, and transition probability are computed. *G.* Latent space representations are made as temporal trajectories embedded within the functional harmonic space; latent dimension spread is calculated and compared across drug conditions. This figure was adapted from Vohryzek et al. (2024b), and partially created with BioRender.com.

2.2 Methods

2.2.1 Datasets

The DMT dataset was received preprocessed, and the data collection and scanning protocols, as well as an overview of the preprocessing procedure is provided in **Supplementary Section S2.1**. The Santo Daime dataset, data collection and scanning protocols, as well as preprocessing and denoising steps are outlined in Chapter 1 sections 1.10.1 – 1.10.6. The current chapter focuses on the resting state fMRI data across drug conditions and datasets. For the current analyses, the preprocessed timeseries were projected from MNI voxel-space to HCP surface vertex space using the HCP *-volume-to-surface-mapping* command.

2.2.2 FH basis construction

FHs were derived from a high-quality group-level dense functional connectome (denseFC) constructed using data from the Human Connectome Project (HCP; WU-Minn Consortium, S1200 release of 812 subjects; available at: https://db.humanconnectome.org/data/projects/HCP_1200). This dataset was selected due to its large sample size, high resolution, standardised preprocessing, and previous use in FH analyses, ensuring both reproducibility and comparability with earlier studies (Glomb et al., 2021; Serra et al., 2023; Vohryzek et al., 2024b). The denseFC was computed as the vertex-by-vertex Pearson correlation matrix of resting-state BOLD time series (59,412 nodes), capturing the statistical coupling between every pair of vertices. To transform this dense matrix into a graph, each vertex was connected to its 300 most strongly correlated neighbours, forming a sparse, symmetric, binary adjacency matrix.

$$A(i, j) = \begin{cases} 1, & \text{if } (i, j) \in \varepsilon \\ 0, & \text{otherwise} \end{cases} \quad (2.1)$$

Where ε denotes the set of edges meeting the k-nearest neighbour criterion. Thresholding to 300 nearest neighbours preserved both global and local connectivity structures, as has been previously established (Glomb et al., 2021). From this adjacency matrix (A), a graph Laplacian was computed to describe the topology of information flow. Specifically, the degree matrix D (obtained by summing the number of connections for each vertex) was used in conjunction with A to calculate the Laplacian ($L = D - A$). The Laplacian was then normalised and symmetrised as

$$L_{(sym)} = D^{-1/2} L D^{-1/2} \quad (2.2)$$

This procedure balanced the contribution of nodes with different degrees, ensuring scale invariance. FHs were calculated as the eigenvectors of the normalised Laplacian, by solving the eigenvalue problem

$$L_{(sym)} \Psi_k(x_i) = \lambda_k \Psi_k(x_i), \forall x_i \in v \quad (2.3)$$

where each eigenvector Ψ_k corresponds to a spatial mode of synchronous activity over the cortical surface, an FH. Each eigenvector's corresponding eigenvalue λ_k represents the harmonic's spatial frequency.

2.2.3 Choice of harmonics

Aligning with prior work, the first 11 spatially resolved FHs, as well as the first (constant, global) harmonic were used in the current analyses, as was done previously (Serra et al., 2023; Vohryzek, Cabral, et al., 2024). This choice is further supported by previous work showing the first ~10 FHs to be effective in reconstructing complex fMRI signal across datasets (Glomb et al., 2021; Vohryzek, Cabral, et al., 2024).

2.2.4 FH projection onto empirical data

Once the harmonic bases were computed, they were projected onto the DMT and ayahuasca datasets, separately. For each subject, and each timepoint in each scan, the spatial BOLD activation pattern was projected onto the FH bases. The fMRI signal at each timepoint can be expressed as a weighted sum of FH contributions

$$F^S(x, t_i) = \sum_{k=1}^n \tau_k(t_i) \Psi_k(x) \quad (2.4)$$

where $\tau_k(t_i)$ quantifies how strongly the k-th FH, $\Psi_k(x)$, contributes to the BOLD signal at time t_i , computed as the inner product $\tau_k(t) = \langle F^S(x, t), \Psi_k \rangle$, yielding a set of amplitude coefficients quantifying how strongly each harmonic contributed to the overall BOLD signal at

each timepoint. This produced one amplitude timeseries per harmonic, reflecting the degree of alignment between the current spatial brain configuration and each harmonic mode at each timepoint.

2.2.5 Computing static measures

Each FH's contribution to the overall brain signal, referred to as "power", was computed. In other words, the amount of variance carried by an FH was calculated. The power of an FH at each timepoint was defined as the absolute value of its projection coefficient

$$P(\Psi_k, t) = |\tau_k(t)| \quad (2.5)$$

Absolute power is a time-averaged normalisation-free metric which computes the magnitude of the given harmonic's contribution to the overall brain activity. Higher absolute power denotes a stronger overall presence or engagement of a given FH. On the other hand, relative power denotes the proportion of total BOLD signal power attributed to a given FH, normalised across the 12 harmonics examined.

2.2.6 Computing dynamic measures

To understand the effects of drug ingestion on FH dynamics, the following metrics were computed: fractional occupancy, lifetimes, and transition probabilities. These measures are all based on the use of a winner-takes-all approach, wherein for each timepoint the FH with the greatest contribution $\tau_k(t)$ is classified as the dominant harmonic or "winner".

Fractional occupancy (FO) denoted the proportion of timepoints across the full scan that was spent with each FH as the dominant mode. In calculating FO, the number of occurrences of a given FH were summed across the full timeseries of a scan, and this number was then divided by the total number of volumes (DMT=240 volumes; Ayahuasca=500 volumes). FO for each FH is estimated independently for each scan.

To quantify changes to the stability of dominance for each FH and how this is affected by drug administration, lifetimes were calculated as the average number of consecutive timepoints an FH was dominant. A higher lifetimes score depicts a longer consecutive period spent in a given FH on average, and thus greater temporal stability of said FH.

To characterise the metastable shifts between harmonics over time, conditional transition probabilities were computed. For each subject and condition transitions between consecutive

timepoints were counted to build a transition matrix, with element (i,j) representing the number of times FH_i was followed by FH_j . Transition counts were first normalised by the total number of transitions $(T-1)$, where T is the number of timepoints, to obtain joint transition probabilities. These were divided by the probability of occurrence of each source state (FO) to obtain subject-level conditional transition probability matrices where each element depicts the $P(\text{transition to } FH_j \mid \text{currently in } FH_i)$. The resulting matrix therefore described, for each subject, how likely it was to switch from one FH to another, given the current brain state. The subject-level conditional transition matrices were averaged separately for the pre-drug and drug conditions to generate group-level representations of the FH transition landscape.

2.2.7 Latent space

The temporal trajectory of brain dynamics was further explored through a latent space analysis in which the 12 FHs (the global FH and the first 11 spatially resolved FHs) were used to create a 12-dimensional latent space. This representation captures brain dynamics as a trajectory through harmonic space, such that each timepoint is defined by the instantaneous (non-absolute) projection strength of all 12 FHs. Latent dimension spread quantifies the temporal variability of brain state trajectories within this harmonic low-dimensional space. For each FH dimension, in each scan, the standard deviation of projection strength across timepoints is calculated, defining the degree of fluctuation in projection strength along that dimension. The latent dimension spread is computed as the mean of these standard deviation across all 12 FH dimensions. This measure reflects the overall expansion or contraction of brain state trajectories within the harmonic latent space.

2.2.8 Statistical comparisons

The DMT and ayahuasca datasets originate from different studies, were collected using different scanners, procedures and scanning parameters, and were preprocessed using different preprocessing pipelines. These differences preclude direct quantitative comparisons between datasets. The DMT dataset is reanalysed to allow for complete consistency in statistical comparisons across datasets. All statistical comparisons are within-dataset only (pre- vs post-drug administration). Comparisons across datasets are only commented on qualitatively with an understanding that any observed differences may be due to the above listed differences in data collection and preprocessing approaches, and any similarities are further strengthened by their

persistence given these differences, suggesting potentially more robust signatures of the psychedelic state.

All within-dataset comparisons are conducted using Wilcoxon signed-rank non-parametric paired tests due to relatively small sample sizes (intravenous DMT: $n = 17$; ayahuasca: $n = 24$). Further, Benjamin-Hochberg False Discovery Rate (FDR) multiple comparison correction ($\alpha = 0.05$) is conducted accounting for the number of FHs within which outcomes are compared (11-12 comparisons depending on inclusion of the global FH).

2.3 Results

2.3.1 Time-averaged measures: absolute power

To assess drug-related changes in amplitude of FH projections, the significance of change in absolute power of each FH (FH0-FH11) following drug administration was examined. Wilcoxon signed-rank tests with FDR correction was conducted accounting for 12 FHs ($\alpha = 0.05$).

DMT administration in drug-naïve participants resulted in a significant reduction in absolute power across all spatially resolved harmonics (FH1-FH11) (**Figure 2.2A**). This significance was maintained after multiple comparison correction. No significant change in the global harmonic (FH0) was observed. These results are a replication of (Vohryzek et al., 2024b). Following ayahuasca ingestion among the Santo Daime, no significant change in absolute power of the global FH was observed (**Figure 2.2B**). Trends towards reductions in absolute power were observed across all spatially resolved FHs; with significant reductions observed for FH9, as well as FHs 5, 6, and 8. FHs 2 and 3 showed reductions that were significant prior to multiple comparison correction. Across datasets consistency in absolute power of the global FH was observed, alongside significant reductions in contribution of FH9 as well as FHs 5, 6, and 8 following drug administration. Full test statistics are reported in **Supplementary Table S2.1**.

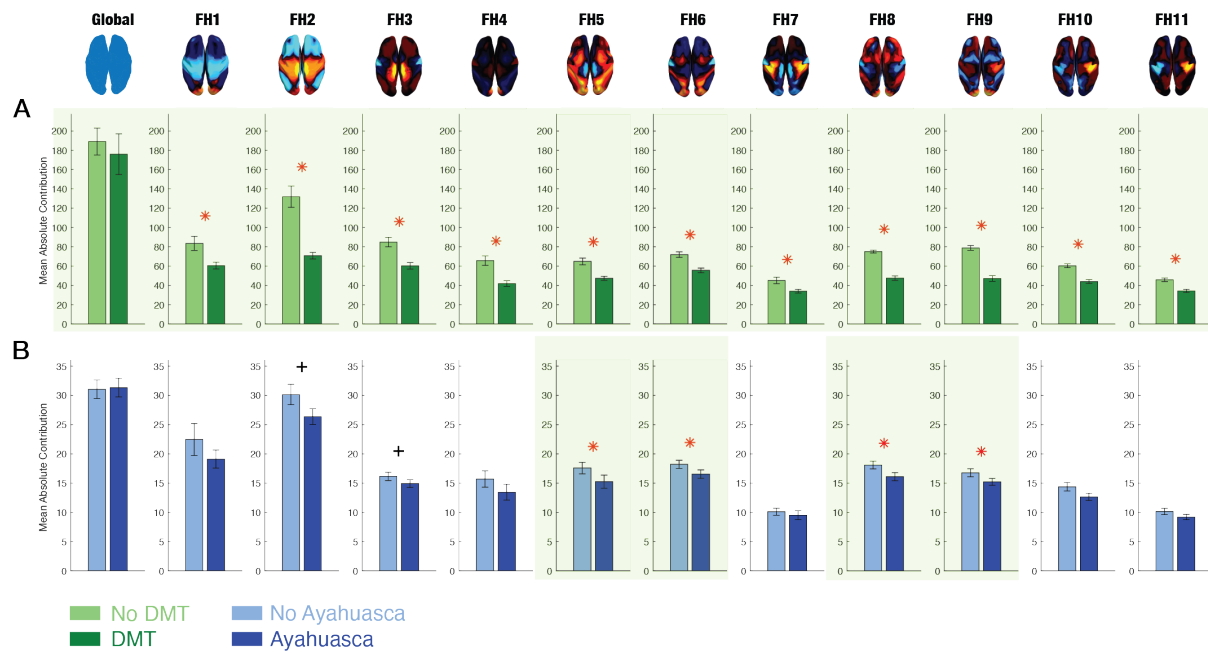


Figure 2.2 Consistencies in mean absolute contribution changes following drug administration across four harmonics. Light green: pre-intravenous DMT administration; dark green: post-intravenous DMT administration; light blue: pre-ayahuasca ingestion; dark blue: post-ayahuasca ingestion. **A.** Significant reductions in mean absolute contribution of all spatially resolved harmonics (FH1-11), alongside no significant change in global harmonic following intravenous DMT administration. **B.** Significant reductions in mean absolute contributions for FHs 5,6,8 and 9 following ayahuasca ingestion among the Santo Daime. Wilcoxon signed-rank paired test comparisons; red star: significance after FDR correction for 12 comparisons ($\alpha = 0.05$); black cross: significance before FDR correction. Error bars denote one standard deviation from mean.

2.3.2 Time-averaged measures: relative power

Changes in relative power of each FH were conducted to examine the redistribution of variance across FHs. Once more, Wilcoxon signed-rank tests were utilised for all within dataset comparisons, alongside FDR correction ($\alpha = 0.05$) for 12 FHs.

DMT administration led to a significant increase in relative power of the global harmonic following drug administration (**Figure 2.3A**). Significant reductions in relative power were observed for FHs 2, 8 and 9. FH4 observed a reduction in relative power which did not withstand multiple comparison correction. These results are a replication of (Vohryzek et al., 2024b). Ayahuasca ingestion was associated with an increase in relative power of the global harmonic, which did not withstand multiple comparison correction (**Figure 2.3B**). FH5 showed an ayahuasca-induced reduction in relative power, that was only significant prior to multiple comparison correction. No other spatially resolved harmonics were affected by ayahuasca consumption. Full test statistics are reported in **Supplementary Table S2.2**.

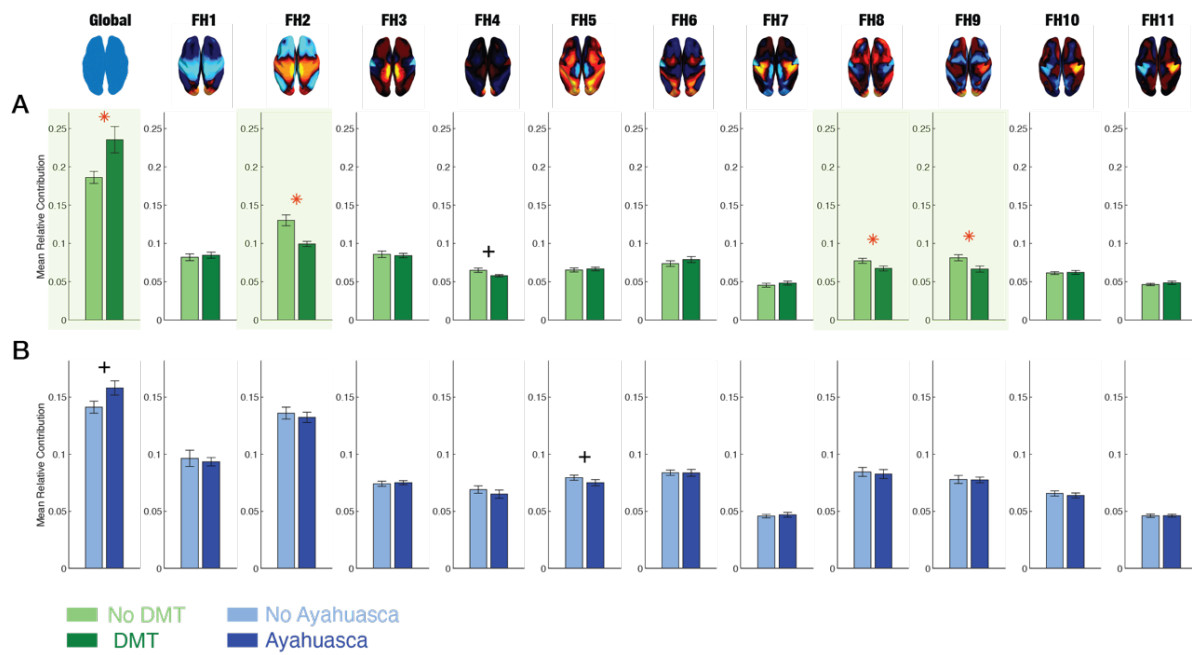


Figure 2.3 Mean relative contribution changes under intravenous DMT are not observed under ayahuasca. Light green: pre-intravenous DMT administration; dark green: post-intravenous DMT administration; light blue: pre-ayahuasca ingestion; dark blue: post-ayahuasca ingestion. **A.** Mean relative contributions showed significant reductions following DMT administration for FHs 2, 8 and 9, and significant increase for the global FH. **B.** No significant change in mean relative contributions following ayahuasca ingestion across global FH and FHs 1-11. Wilcoxon Signed-rank paired test comparisons; red star: significance after FDR correction for 12 comparisons ($\alpha = 0.05$); black cross: significance before FDR correction. Error bars denote one standard deviation from mean.

2.3.3 Time resolved: state dominance reorganisation

To examine changes in time-resolved dynamics, FO and lifetimes scores were compared pre- and post-drug administration in both the intravenous DMT and ayahuasca datasets. To align with previous work, the global FH was excluded from these analyses, to focus on time-resolved changes in spatially resolved FHs. Wilcoxon signed-rank tests are utilised alongside FDR correction accounting for 11 FHs ($\alpha = 0.05$). Intravenous DMT administration led to significant reorganisation of the FH competitive landscape across time. FO analyses showed two significant changes following FDR correction, alongside one marginal change (**Figure 2.4A & 2.4B**). Importantly, FH2 observed a significant reduction in FO following DMT administration, and FH9 exhibited a reduction of marginal significance following FDR correction ($p = 0.014$, $q = 0.051$). FH6 showed a significant increase in FO following DMT administration. Reductions in lifetimes following DMT administration were observed for FH2 and FH9, but these did not withstand multiple comparison correction. Full test statistics are reported in **Supplementary Table S2.3 & S2.4**. FO and lifetimes profiles remained largely consistent across no drug and

drug conditions (**Figure 2.4C**), with FH2 showing highest FO and lifetimes across drug conditions, and FH7 and FH11 showing lowest scores across both metrics and drug conditions.

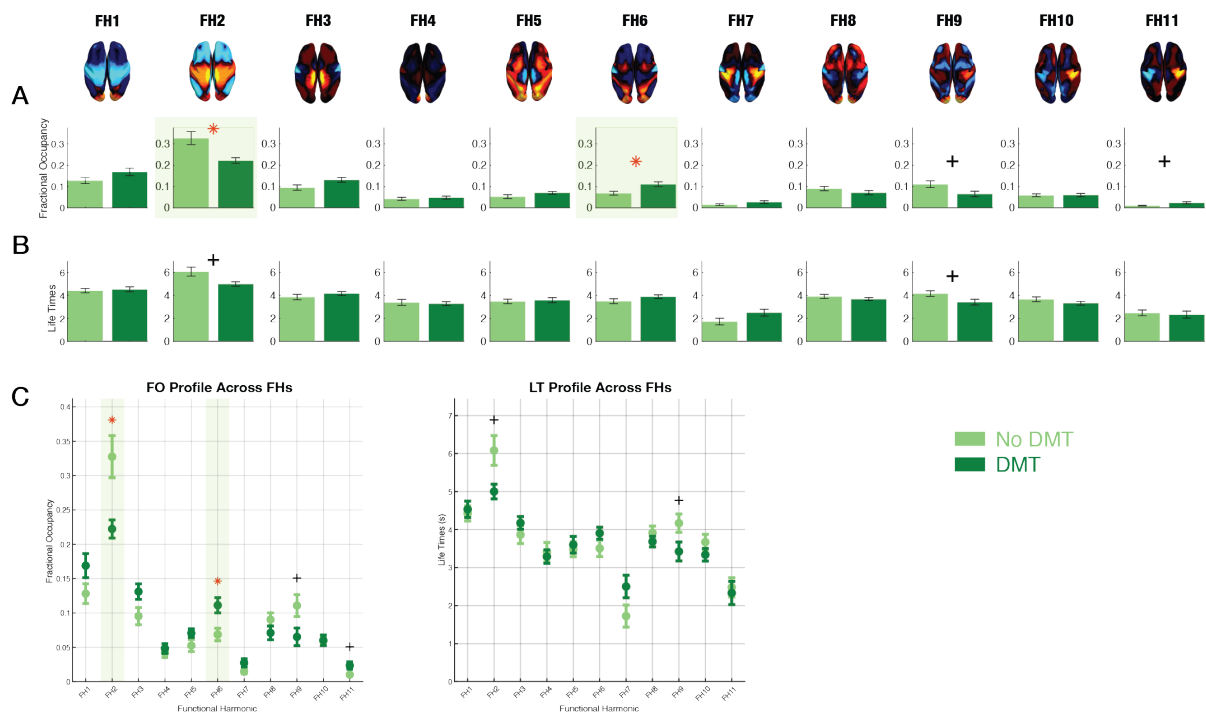


Figure 2.4 Fractional occupancy changes following intravenous DMT administration in FH2 and FH6. Light green: Pre-intravenous DMT administration; dark green: post-intravenous DMT administration. **A.** Bar plots comparing average fractional occupancy pre- and post-intravenous DMT administration for FHs 1-11, showed significant decrease for FH2 and significant increase for FH6 following DMT administration. **B.** Bar plots comparing average lifetimes pre- and post-intravenous DMT administration, showed no significant change across FHs 1-11. **C.** Fractional occupancy (left) and lifetimes (right) profiles across FHs.

Ayahwasca ingestion among the Santo Daime did not significantly change FO or lifetimes outcomes as compared to pre-drug ingestion (**Figure 2.5A & B**). Full test statistics are reported in **Supplementary Table S2.3 and S2.4**. Following on from these results, no differences are observed in distribution of FH scores across FO and lifetimes profiles (**Figure 2.5C**). As observed in the intravenous DMT dataset, FO and lifetimes profiles were characterised by highest scores for FH 2 and lowest scores for FHs 7 and 11.

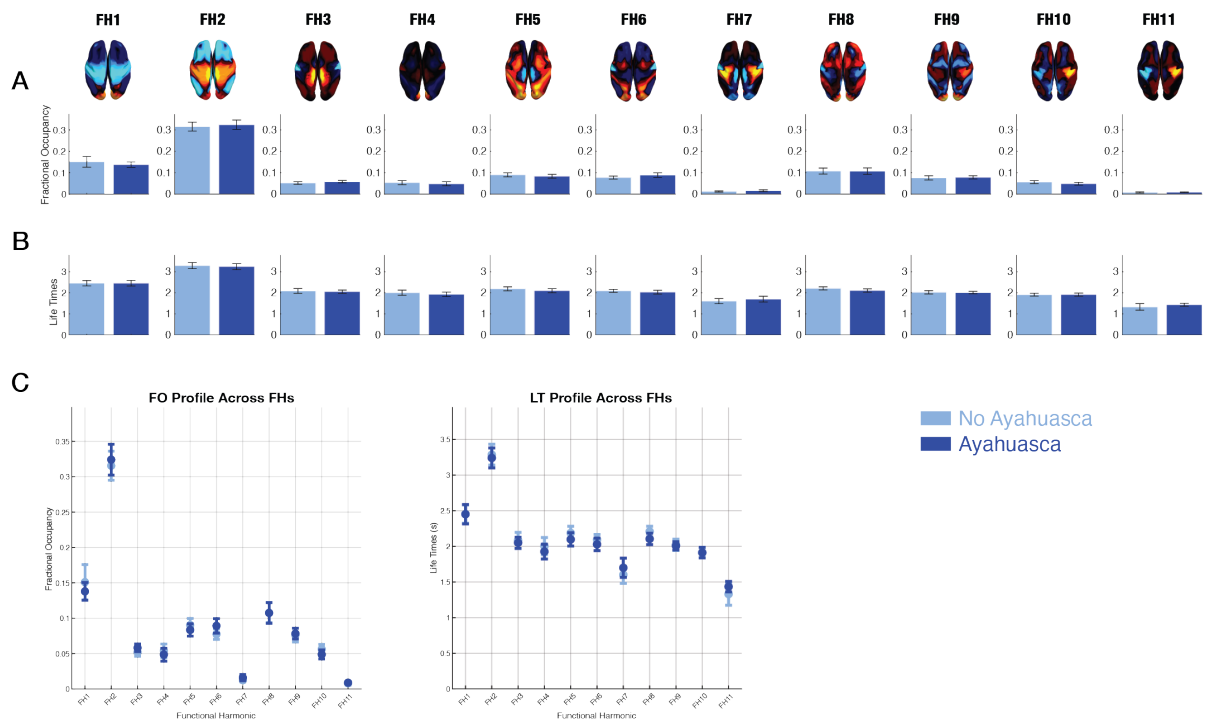


Figure 2.5 No changes in FH fractional occupancy or lifetimes following ayahuasca ingestion. Light blue: Pre-ayahuasca ingestion; dark blue: post-ayahuasca ingestion. **A.** Bar plots comparing average fractional occupancy pre- and post-ayahuasca ingestion for FHs 1-11. **B.** Bar plots comparing average lifetimes pre- and post-ayahuasca ingestion for FHs 1-11. **C.** Fractional occupancy (left) and lifetime (right) profiles across FHs.

We examined the change in conditional transition probability, or the probability of switching from dominance of FH_A to FH_B given the system currently being in FH_A , following drug administration. Following DMT ingestion, 16 changes which were significant prior to multiple comparison correction were observed. Three of these, maintained significance following FDR correction. Significant increases in transition probability from FH6 to FH5, and from FH10 to FH1 were observed, as well as a significant decrease in transition probability from FH10 to FH2 (**Figure 2.6A**). In the case of ayahuasca administration, nine significant changes in conditional transition probability were observed prior to multiple comparison correction, none of which maintained significance following FDR correction (**Figure 2.6B**). Two transitions exhibited increases in condition probability following drug administration in both DMT and ayahuasca datasets, however these did not survive multiple comparison correction. These were transition from FH3 to FH6 (DMT: $p = 0.028$; ayahuasca: $p = 0.024$) and from FH5 to FH11 (DMT: $p = 0.016$; ayahuasca: $p = 0.006$).

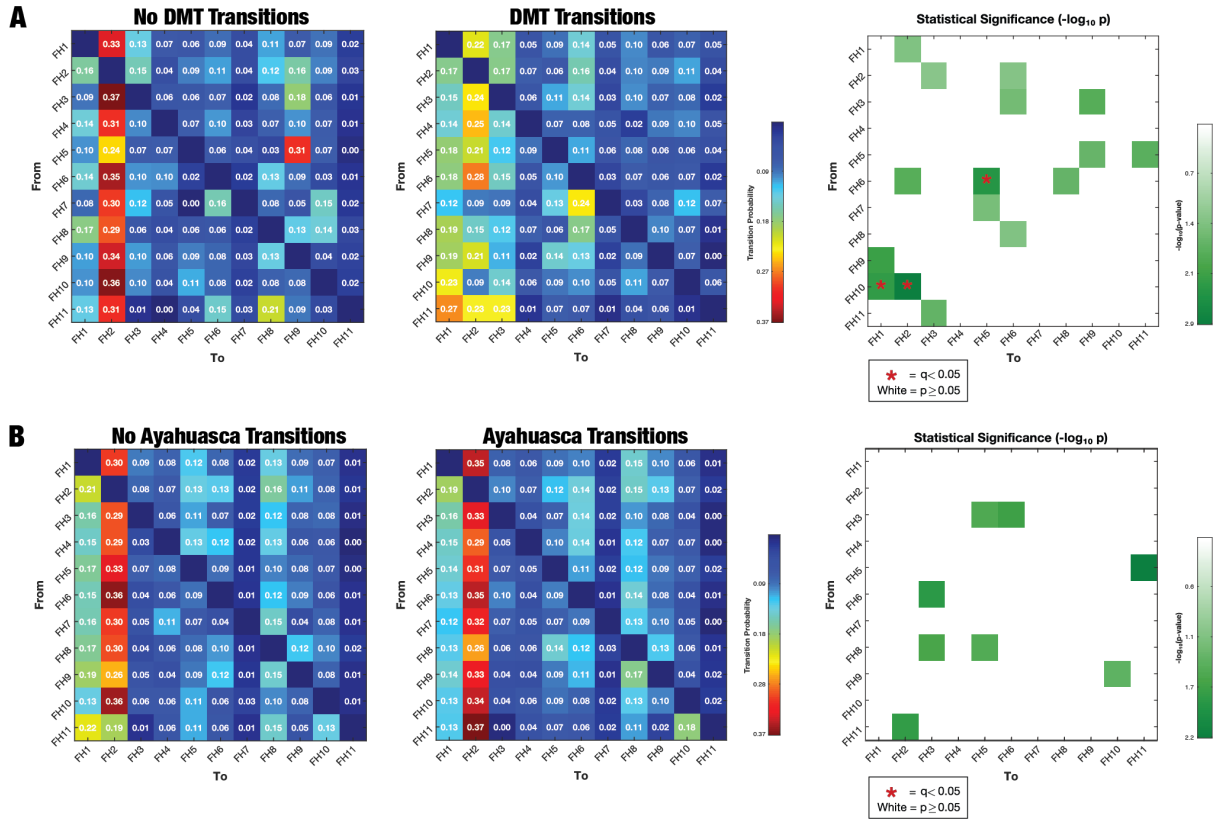


Figure 2.6 Intravenous DMT administration results in significant conditional transition probability changes, while none are significant following ayahuasca ingestion. **A.** Intravenous DMT dataset. **B.** Ayahuasca dataset. In **A** and **B**, far left and middle panels show conditional transition probability matrices for pre-drug administration and post-drug administration respectively. In each, vertical axis shows which FH was transitioned from and horizontal axis depicts which FH was transitioned to. Self-transitions (diagonal elements) are excluded. Average transition probabilities are written in each block, with warmer colours denoting higher transition probabilities, and cooler colours denoting lower transition probabilities. Far right panel in **A** and **B** shows statistical significance matrix of difference in transition probability across drug conditions (pre- versus post-drug), green squares show significance prior to FDR correction, red star signifies statistical significance following FDR. White squares denote non-significant findings prior to FDR correction.

2.3.4 Latent spread contraction

Latent space embedding of the data was carried out, using the 12FHs as latent space representations. Visual inspection of the group-averaged latent space trajectories (visualised for the first 3 FHs: the global FH, FH1 and FH2 in **Figure 2.7**) for drug-absent vs drug-present conditions suggested a contraction of the latent spread following administration of both DMT and ayahuasca. This observation was verified, and its statistical significance characterised through the measure of latent dimension spread. Significant contraction of the latent dimension spread was observed following both intravenous DMT administration (**Figure 2.7A**; $W = 153$, $Z = 3.62$, $r = 0.88$, $p < .001$) and ayahuasca ingestion (**Figure 2.7B**; $W = 224$, $Z = 2.11$, $r = 0.43$, $p = .035$).

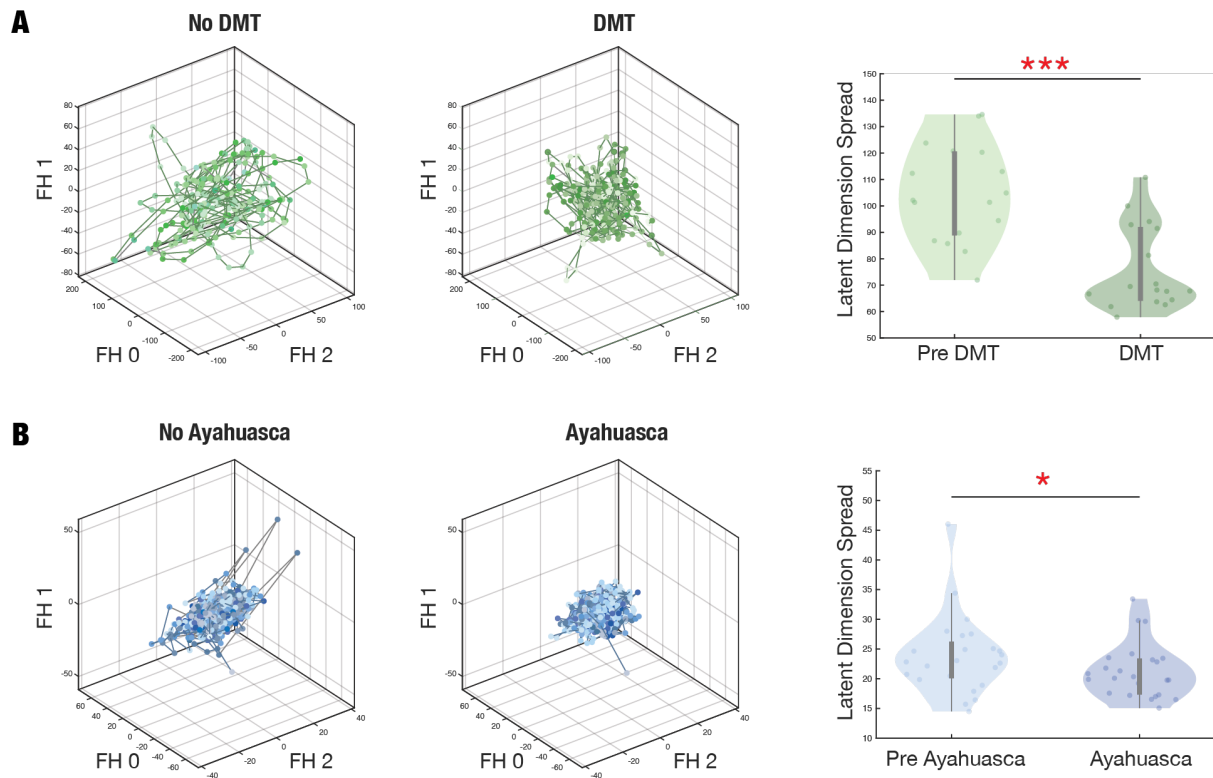


Figure 2.7 Intravenous DMT administration and ayahuasca ingestion both lead to significant latent spread contraction. Latent space representation of data using 12 FHs (first 11 spatially resolved FHs and the global FH) **A.** Mean latent space trajectories pre DMT administration (left panel) and post DMT administration (middle panel) averaged across subjects at each timepoint, visualised using the first three FHs. Right panel: violin plot showing the distribution across subjects of latent space spread comparing DMT pre- and post-administration conditions. Light green denotes the pre-drug condition and dark green denotes the post-drug condition. **B.** Mean latent space trajectories pre ayahuasca ingestion (left panel) and post ayahuasca ingestion (middle panel) averaged across subjects at each timepoint, visualised using the first three FHs. Right panel: violin plot showing the distribution of latent space spread comparing ayahuasca pre- and post-ingestion conditions. Light blue denotes the pre-drug condition and dark blue denotes the post-drug condition. Wilcoxon signed-rank paired tests used for all comparisons.

2.4 Discussion

Absolute power suppression of spatially resolved FHs was observed across both datasets. In the case of intravenous DMT, this was shown for all 11 FHs, while following ayahuasca ingestion suppression was observed for FH9, reflecting the DMN, as well as FHs 5, 6 and 8, outlining regions relevant to sensory processing. Both datasets showed maintenance of absolute power of the global FH across drug conditions. Latent space analyses showed consistent latent spread contraction of temporal trajectories within the harmonic latent space across datasets. Neither dataset exhibited significant changes to FH lifetimes following drug administration. Relative power analyses showed diverging effects across datasets, while intravenous DMT administration was characterised by increase in relative power of the global FH, alongside suppression of FHs 2, 8 and 9, ayahuasca ingestion did not result in significant changes to the relative power of any FHs. Drug-induced changes to fractional occupancy of spatially resolved harmonics were not consistent across datasets, with intravenous DMT being characterised by significant suppression of FH2 and enhancement of FH6 fractional occupancy, whereas ayahuasca ingestion showed no significant changes across FHs. Together, these results suggest common effects across datasets, as well as differences which outline the need for further exploration of the unique effects of ayahuasca within the Santo Daime ritual context.

The Entropic Brain proposes that classic psychedelics result in a shift in brain dynamics towards high-entropy states, suggesting less constrained activity, cognition, and experience (Carhart-Harris et al., 2014). The REBUS theory stipulates that this increase in entropy corresponds to a reduction in precision-weighting of higher-level priors (e.g. those associated with multimodal networks such as the DMN), and thus a flattening of the functional hierarchy (Carhart-Harris and Friston, 2019). Multimodal networks, such as the DMN, have been shown to correspond well to lower frequency FHs, both in connectome and functional harmonics (Atasoy et al., 2016; Vohryzek et al., 2024b). Across all harmonic-based psychedelic studies, a reduction in power of these low-frequency harmonics is observed, suggesting a robust effect of psychedelics on large-scale integrative brain organisation as derived through harmonic power analyses (Atasoy et al., 2018b, 2017; Luppi et al., 2023; Vohryzek et al., 2025, 2024d). Of particular relevance to the current chapter are FHs 2 and 9. FH2 delineates the gradient separating unimodal and multimodal brain regions, reflecting a hierarchy of brain function. FH9 corresponds well to the DMN, a network consistently shown to be disrupted under psychedelics (Carhart-Harris et al., 2012; Palhano-Fontes et al., 2015; Preller et al., 2018; Tagliazucchi et al., 2016). The suppression of all spatially resolved harmonics, including FH2

and FH9, paired with the maintenance of the global FH in the intravenous DMT data suggest a movement towards a more integrated global state, consistent with a flattening of the functional hierarchy. In the case of ayahuasca ingestion among the Santo Daime, the observed significant suppression of FH9 and sensory-related harmonics, as well as maintenance of absolute power of the global FH provide partial evidence for this pattern. Notably, FH2 showed a reduction in absolute power that did not survive multiple comparison correction. The overall pattern of suppression was more selective than the broad suppression of FHs observed following intravenous DMT. These differences may reflect the unique effects of ayahuasca on brain dynamics, however they may be due to factors such as dosing differences between the two datasets, the Santo Daime's regular use of ayahuasca, or differences in data collection and pre-processing protocols.

In the case of relative power, FO, and lifetimes, effects are not consistent across datasets. Results showed a significant increase in relative power of the global FH following intravenous DMT administration. FO measures showed a significant reduction following drug administration for FH2. These results suggest a movement towards global integration, and a suppression of the functional hierarchy following intravenous DMT administration. Notably, FH6, which corresponds to visual areas of the cortex, showed a significant increase in FO, suggesting a redistribution of occupancy towards this sensory-related harmonic rather than a homogenous suppression. These lower-order sensory-specific effects align with previous work showing psychedelic-induced increases in such networks, namely increased BOLD activity in the visual cortex (de Araujo et al., 2011) as well as increased bottom-up travelling waves (Alamia et al., 2020). When examining the effects of ayahuasca ingestion among the Santo Daime, results across these measures are not consistent with those observed under intravenous DMT. Although ayahuasca ingestion is associated with an increase in relative power of the global FH prior to multiple comparison correction, no significant changes are observed following multiple comparison correction in relative power, FO or lifetimes. The absence of significant ayahuasca-induced relative power changes, although significant absolute power reductions were observed for four FHs, may suggest a more uniform suppression across harmonics. In the case of DMT, given significant reductions in absolute power across spatially resolved harmonics, the observed significant reductions in relative power for FHs 2 and 9 suggest greatest suppression for these harmonics.

Although individual harmonic measures showed only partial convergence across datasets, the latent space embedding showed a consistent significant contraction of latent dimension

spread. This consistency suggests that, although differences in drug-induced changes to individual harmonic contributions and dynamics were observed, the overall spatiotemporal brain dynamics exhibited a drug-induced reduction in amplitude trajectories across datasets. This contraction of latent spread may initially appear in contradiction with the Entropic Brain hypothesis of an expansion of brain state repertoire under psychedelics (Carhart-Harris et al., 2014). However, latent spread captures the amplitude of trajectories within a fixed set of FHs, rather than a diversity of states visited. Therefore, a contraction of latent spread may occur alongside a broader repertoire if the brain visits more states at smaller amplitudes. Importantly, the latent spread measure captures the combined dynamics of all harmonics, and the relevance of this to the underlying functional hierarchy is not apparent. Therefore, the following chapters examine whether ayahuasca-induced changes in brain dynamics are reflected in changes to the functional hierarchy more directly. This is examined in both a time-averaged (Chapter 3) and dynamic (Chapter 4) manner.

The primary dataset of interest in the current chapter is the Santo Daime, a group of individuals with regular experience of ayahuasca consumption within a unique ceremonial, religious, ritualistic, and musical context. The lowest number of ayahuasca ceremonies a participating member had taken part in was 50. There is evidence, although correlative rather than causal, suggesting differences in behavioural outcomes in long-term, regular ayahuasca users compared to matched controls. These differences include: lower psychopathology rates, better performance on several cognitive tasks, and higher scores on measures of self-transcendence (Bouso et al., 2012). Additionally, differences in cortical thickness have been observed, specifically thinning in the posterior cingulate cortex (a hub of the DMN), as compared to controls (Bouso et al., 2015). Further, machine learning algorithms informed by fMRI activity patterns during an emotional processing task, were found to distinguish between long-term ayahuasca users and non-users with high accuracy (Ramos et al., 2025). Due to a lack of control sample within the Santo Daime dataset, it was not possible to directly examine the extent to which the group's unique background shaped their neural response to ayahuasca. Nevertheless, the comparison with a Western clinical DMT study was intentionally included to examine the extent to which the observed neural signatures in experienced ceremonial users aligned with those in a more well studied experimental context. These findings are an important first step in relating effects observed following psychedelic ingestion among the Santo Daime to those previously reported in the average population and a more Western clinical context.

Several key considerations must be taken into account when interpreting the findings of the present chapter. The two datasets analysed were collected independently, differing in scanners,

paradigms, and protocols. Notably, the intravenous DMT data was collected with participants instructed to keep their eyes closed, whereas in the Santo Daime dataset participants were instructed to keep their eyes open looking at a fixation cross. Prior research has shown significant effects of having eyes open compared to closed under psychedelics, with eyes closed leading to stronger effects (Mediano et al., 2024). Further, the two datasets differ not only in DMT administration route and pharmacokinetics, but also in magnitude relative to previously published work. For example, recent research has described 15mg bolus intravenous DMT as a low dose, and 25mg bolus intravenous DMT as a high dose (Vogt et al., 2023), situating the dosing of the current study as moderate. Importantly, even 15mg have been associated with very intense psychedelic effects (Vogt et al., 2023). Conversely, a systematic review of studies using ayahuasca showed DMT dosage in brew/capsule to range between 8.8 mg and 42 mg (Gable, 2007), much higher than the average dose of 3.36mg ingested in the current dataset. In conjunction, both eyes open and dosing conditions would suggest a less intense effect of ayahuasca compared to previously published work, encouraging the interpretation of observed similarities in harmonic power changes across datasets as pointing to shared and more robust features of the psychedelic experience. However, these discrepancies also make interpretation of observed differences (specifically where significant effects are observed for intravenous DMT and not for ayahuasca) more tenuous, necessitating further research using ayahuasca datasets where dosing is standardised and reflects a dose which results in moderate to strong psychedelic effects. Furthermore, the datasets were preprocessed independently, using differing preprocessing pipelines due to the ayahuasca data being preprocessed as part of this thesis while the intravenous DMT data was provided in a preprocessed form. This further supports the observed similarities in effect across datasets as a robust signature of the psychedelic state. However, the outlined differences in relative power, FO and lifetimes, are difficult to interpret meaningfully. This highlights a more general need for standardisation of data acquisition protocols and preprocessing pipelines to allow for generalisability and comparison across drugs and datasets (Linguiti et al., 2023; Shinozuka et al., 2024).

In conclusion, the application of HADES methodology to the ayahuasca and intravenous DMT datasets resulted in consistent absolute power suppression across several spatially resolved harmonics, importantly including FH9 and sensory-related FHs, partially aligning with previous work applying connectome harmonics to DMT, psilocybin, and LSD. Further, consistency in latent space contraction following drug administration was observed across datasets, suggesting a robust signature of the psychedelic state across drugs and relative doses. Importantly, several key discrepancies between the Santo Daime dataset and the intravenous DMT

dataset were observed necessitating further research into the effects of ayahuasca ingestion among the Santo Daime on the functional hierarchy more directly, as pursued in the following chapters.

2.5 Summary

The current chapter applied HADES to resting-state fMRI data from Santo Daime Church members prior to ayahuasca ingestion, and during the acute effects of the drug. An intravenous DMT dataset collected within a more standardised Western context was used as a comparative benchmark. Convergent findings across datasets included absolute power suppression of spatially resolved FHs, notably FH9 (reflecting the DMN) and sensory-related FHs, as well as significant latent-space contraction. However, relative power and fractional occupancy changes, showing suppression of hierarchy-related harmonics (FH2, FH9) were only observed in the intravenous DMT dataset. Although the observed latent space contraction confirms alterations in brain dynamics under ayahuasca, this measure does not directly capture changes to the functional hierarchy. The following chapters examine ayahuasca-induced changes to the functional hierarchy from time-averaged (Chapter 3) and time-resolved (Chapter 4) perspectives.

Chapter 3:

Time-averaged changes to functional hierarchy

Abstract

Classic serotonergic psychedelics such as DMT (ayahuasca), LSD and psilocybin are thought to flatten the brain's functional hierarchy, which is characterised by asymmetric directed interactions between regions. However, evidence of this from directed connectivity measures, which enable direct examination of this asymmetry, are limited, particularly for ayahuasca. The current chapter builds on the undirected analyses of Chapter 2, by explicitly examining changes in functional hierarchy structure and directed information flow following ayahuasca ingestion among Santo Daime members. We further expand on Chapter 2 by not only examining these effects at rest, but also during ritual-relevant music listening. To this end, Hopf whole-brain modelling-derived effective connectivity was used to compute measures of trophic coherence, trophic level central tendency and distribution, as well as average effective connectivity. SVM classifiers distinguished between drug conditions with high accuracy, when informed only by regional trophic levels. Results showed context-independent reduction in TC, TL central tendency and dispersion at the whole-brain level, as well as reductions in average TL for higher order RSNs (DMN, FPN and DAN), suggesting an ayahuasca-induced flattening of the functional hierarchy. Further, results showed context-dependent changes for average effective connectivity, and average TL for sensory networks (Visual and SMN), pointing to a moderating role of context on directed coupling and sensory network roles within the hierarchy.

3.1 Introduction

The brain exhibits a hierarchical organisation spanning multiple spatial and temporal scales, with processing spanning from primary sensory regions to higher-order associative regions (Friston, 2010; Margulies et al., 2016; Mesulam, 1998; Sporns, 2013). This functional organisation structure is thought to support key computational goals, including efficient segregation and integration, which are essential for flexible cognition and adaptive behaviour (Deco and Kringelbach, 2017; Tononi et al., 1998). Within the predictive processing framework, this hierarchical organisation provides a computational architecture for Bayesian inference, wherein higher levels generate predictions that are passed down the hierarchy, while lower levels propagate prediction errors (the discrepancy between predictions and sensory input) upward to update internal models (Bastos et al., 2012; Friston, 2010). Thus, hierarchical organisation is not merely a structural feature, but serves important computational functions. It enables large-scale coordination of neural activity, reducing metabolic costs (Bullmore and Sporns, 2012). It is proposed that psychedelic states are characterised by a relaxation of this functional hierarchy structure, through reduced precision weighting of top-down predictions, which may enhance cognitive flexibility, enabling new learning (Carhart-Harris et al., 2014; Carhart-Harris and Friston, 2019). The current chapter leverages whole-brain modelling to examine ayahuasca-induced changes in global coupling strength, hierarchical configuration, and information flow structure among members of the Santo Daime Church, in the presence and absence of the church's ritual songs, '*hinos*'.

3.1.1 *Functional hierarchy in the brain*

Efficient processing of information from the internal and external environments depends on a balance of segregation, specialised processing within local networks, and integration of information across the system (Deco and Kringelbach, 2017; Tononi et al., 1998). Individual regions and subnetworks process specific types of information with high precision, this is particularly evident in sensory cortices, with regions in the visual cortex having a primary role of detecting distinct elements of the incoming visual stimulus, and those in the auditory cortex, having a primary role of detecting different characteristics of sound for example. However, adaptive behaviour necessitates coordination and integration of these distinct processing streams into complex perception and action. The functional hierarchy allows for a balance between integration and segregation, enabling more localised subsystems to maintain rich, differentiated activity, while distinct integrative regions or hubs, provide global coordination (Meunier et al.,

2010; Tognoli and Kelso, 2014; Wang et al., 2021). It is argued that in the absence of hierarchical organisation, the system would move towards either extremes: global integration with a loss of specificity, or excessive modularity, inhibiting integration (Cohen and D’Esposito, 2016; Palma-Espinosa et al., 2025). Theoretical and empirical work suggests that hierarchical structures maximise flexibility, as metastable regimes enable efficient balance between integration and segregation (Deco et al., 2017b; Tognoli and Kelso, 2014).

3.1.2 Effective connectivity – model-free approaches

In any hierarchical system, interactions between nodes are asymmetric. This asymmetry is fundamental to defining each region’s relative position within the brain’s functional hierarchy, and governing how information is propagated and processed through the system. Standard measures of FC are undirected, providing information on the statistical correlation of activity between pairs of regions, in the absence of an understanding of directionality or causation. Effective connectivity (EC) captures the directed information flow between regions, describing the influence one region has on another (Friston, 2011). Computation of EC as understood through fMRI data, has been conducted using both model-free and model-based approaches.

Model-free approaches to estimating EC focus on identifying temporal and informational asymmetries in activity of different brain regions. Such approaches include Granger causality, through which the directionality of interactions is approximated by testing whether past activity of a region improves the prediction of another region’s future activity beyond its own past, under the assumption of linear relationships (Seth et al., 2015). Transfer entropy generalises this concept by quantifying the directed information that one region’s timeseries provides about another’s future activity, without assuming linearity (Vicente et al., 2011). Normalised directed transfer entropy (NDTE), extends these approaches by estimating, for each pair of regions, how much one region’s past activity predicts another region’s future activity, beyond what can be explained by both the target region’s past and the activity of all other brain regions (Deco et al., 2021). NDTE has previously been applied to the Human Connectome Project dataset to delineate regions of the brain composing the Global Workspace, i.e. regions sitting at the top of the brain’s functional hierarchy that integrate information from across the brain and broadcast it widely as defined by the Global Neuronal Workspace Theory (Baars, 1989; Dehaene et al., 1998; Kringelbach et al., 2023). The relevant regions were identified by determining the directed information flow between each pair of regions, and the causal importance of these

interactions was confirmed by systematically lesioning regions, *in silico*, in a whole-brain model (Deco et al., 2021).

3.1.3 Whole-brain modelling for understanding hierarchy

While model-free approaches have proven to be useful in EC estimation, EC has been proposed to “correspond to the parameter of a model that tries to explain observed dependencies” (Friston, 2011). Whole-brain modelling has shown to be effective in elucidating the mechanistic and causal underpinning of brain function. Through the fitting of structural and functional data within a whole-brain model, generative effective connectivity (GEC), i.e. the effective weighting of the anatomical connectivity, can be estimated (Kringelbach et al., 2023). GEC provides a causal mechanistic understanding of the relative influence nodes in the model exert on one another, grounded in known structural connectivity pathways. By examining how these influences vary across conditions, we can infer changes in functional hierarchy across contexts.

A whole-brain model aims to build an accurate and useful model of the brain that can be explored and manipulated to better understand how specific dynamics arise. The three major elements of a whole-brain model are: the underlying structural connectome (the location of nodes and their physical connections to one another), the functional connectome (the edges between each pair of nodes), and the local dynamics (node dynamics). A useful model of the brain relies on the inclusion of local dynamics, bound by structural connectivity and fitted to empirical functional data. Each node in the whole-brain model is typically composed of millions of neurons. Local dynamics describe estimated population-level activity of each node. These can be specified through sets of differential equations. Local dynamics can be represented using a variety of models. Here we use the Hopf model, which models brain regions and their interactions as oscillators with a Hopf bifurcation (Deco et al., 2017b; Lord et al., 2017).

3.1.4 Oscillatory dynamics and the Hopf bifurcation

Oscillatory dynamics observed in the brain, arising from groups of neurons producing rhythmic electrical activity can be directly recorded through EEG and MEG as waves in varying frequency ranges, and indirectly through measures such as fMRI. Larger-scale synchronized oscillations in the brain are thought to be key for communication between physically distant regions through phase locking (Reyner-Parra and Huguet, 2022). Many neurological diseases and psychiatric disorders have been shown to be characterized by altered oscillatory activity (Schnitzler and Gross, 2005; Sponheim et al., 2023). The modelling of such dynamics can not

only help improve understanding of the mechanisms underlying healthy brain function, but also how deviations from said dynamics may underly disease (Bosboom et al., 2006; Jafari et al., 2020; Storch et al., 2021), and altered states of consciousness, such as those induced by psychedelics (Cruzat et al., 2022; Deco et al., 2024; Jobst et al., 2021; Piccinini et al., 2025).

The Hopf bifurcation model is a local node neural mass model based on the most general expression of both oscillatory and asynchronous noise dynamics (Deco et al., 2017b). Through the Hopf model, the dynamics of each brain region are modelled as Stuart-Landau oscillators, which is the standard approach to modelling shifts between oscillatory and noisy dynamics (Kuznetsov, 2004). The inclusion of the bifurcation depicts the system sitting at the edge of criticality – the point of transition between synchronous and asynchronous dynamics. The critical value of the bifurcation parameter for the human brain is set just below 0, as the system is thought to be in a subcritical regime, whereby the oscillators remain dampened (Deco et al., 2017b). As a result of the bifurcation, a jump to a distant attractor occurs (Strogatz, 2018), which reflects the observed metastability in the human brain. The details of the model are described in **Supplementary Section S1.1**. Whole-brain Hopf models have been used in modelling EEG (Freyer et al., 2012, 2011), MEG (Deco et al., 2017a), and most commonly fMRI data (Deco et al., 2017b; Escrichs et al., 2022; Jobst et al., 2021; Saenger et al., 2017); providing generated data that fits observed empirical data well.

3.1.5 Understanding psychedelics through whole-brain modelling

Psychedelic drugs alter functional connectivity patterns, typically increasing global integration and reducing segregation (Daws et al., 2022; Tagliazucchi et al., 2016), expanding the brain's dynamic repertoire (Atasoy et al., 2017; Lord et al., 2019) and increasing entropy (Carhart-Harris et al., 2014; Lebedev et al., 2016). These changes reflect a reorganisation of the functional hierarchy, characterised by reduced dominance of higher-order networks and flattened hierarchical gradients (Carhart-Harris et al., 2016; Luppi et al., 2021), resulting in more distributed information processing and enhanced exploration of brain states (Atasoy et al., 2017; Carhart-Harris and Friston, 2019). While these model-free measures have been shown to be useful in characterising the psychedelic state, they remain descriptive. Recent computational whole-brain modelling studies provide mechanistic explanations for how these changes arise.

Several studies have applied Hopf-based whole-brain models to understand the mechanisms underlying psychedelic-induced changes to brain dynamics. Jobst et al. (2021) modelled fMRI

data from participants under LSD and placebo, using systematic *in silico* perturbation to compute the perturbative integration latency index (PILI). Under LSD, they found greater diversity of regional responses to external perturbation, as well as longer recovery times compared to placebo. These findings suggest that psychedelics shift the brain towards a weakly constrained, less hierarchical regime, in which brain dynamics are more flexible, reflecting a flatter attractor landscape. Cruzat et al. (2022) extended this approach by examining functional hierarchy changes under both LSD and psilocybin. They quantified perturbation-elicited changes, through measures of susceptibility (i.e. sensitivity to external perturbation) and information encoding capability (i.e. standard deviation of susceptibility across trials). Their results revealed lower susceptibility, alongside higher information encoding capability, reflecting an expanded repertoire of distinct states. Together these findings suggest that psychedelic administration results in a system that is locally less reactive to external perturbation, yet globally exhibits an expanded repertoire of accessible brain states and greater information encoding capacity. Vohryzek et al. (2024) extended these methods to a clinical context, modelling psilocybin therapy in treatment-resistant depression. By comparing responders and non-responders, they identified brain regions implicated in therapeutic improvement, demonstrating the translational potential of whole-brain modelling findings. These studies show that generative whole-brain modelling can reproduce observed psychedelic effects and provide mechanistic insights.

Deco et al. (2024) applied whole-brain modelling to compare the effects of psilocybin and SSRIs on the functional hierarchy in patients with treatment resistant depression. Although both treatments improved depression symptoms, the underlying mechanisms differed. SSRIs were observed to strengthen the functional hierarchy, whereas psilocybin was shown to flatten it. Hierarchical organisation was quantified using two measures derived from the GEC: trophic coherence (TC) and trophic levels. These are graph-theoretic tools originally developed and used in ecology (Levine, 1980), and later extended to directed networks more generally (MacKay et al., 2020). TC quantifies the overall hierarchical organisation of directed information flow, with higher values indicating a more organised feedforward structure. Trophic levels correspond to each brain region's position within this hierarchy, based on the directionality and strength of its connections. The dispersion of trophic levels reflects the differentiation of functional roles, with greater dispersion reflecting a more stratified hierarchy with distinct levels, while lower dispersion suggests more homogeneous regional roles and thus a flatter organisation. A recent MEG paper examining the role of LSD ingestion on the functional hierarchy used measures analogous to trophic coherence and trophic levels, observing reductions

across measures corresponding to LSD-induced flattening of the functional hierarchy (Shinozuka et al., 2025). This was observed across external sensory contexts (eyes open, eyes open with video, eyes closed, eyes closed with music).

3.1.6 Current study

The current chapter examines ayahuasca-induced changes in functional hierarchy organisation and directed coupling strength in the brain among members of the Santo Daime Church (**Figure 3.1**). We return to the importance of set and setting discussed in Chapter 1, by examining the effects of ayahuasca ingestion on the functional hierarchy across two distinct contexts: at rest and during music listening. This is of particular importance, given the musical nature of Santo Daime rituals, wherein members have reported *hinos*, or ritual songs, to be key in the ayahuasca experience (Labate et al., 2017a). To do this we apply Hopf whole-brain modelling, enabling the modelling of EC from which average EC and trophic measures are extracted.

Based on previous research showing psychedelic-induced reduction in directed functional connectivity as measured by Granger causality in MEG data (Barnett et al., 2020), we hypothesise a reduction in average directed coupling strength in the drug condition. Further, we hypothesise a reduction in trophic coherence and trophic level distribution measures, aligned with previous findings of psychedelic-induced hierarchy flattening using trophic measures (Deco et al., 2024) and analogous hierarchy metrics applied to MEG data (Shinozuka et al., 2025). Although initial work has pointed to context-independent (e.g. music absence and presence) drug effects on hierarchy measures (Shinozuka et al., 2025), music is said to play an important role within Santo Daime ceremonies (Hartogsohn, 2021; Labate et al., 2017a). Therefore, whether these effects are consistent across resting state and music listening contexts is treated as exploratory.

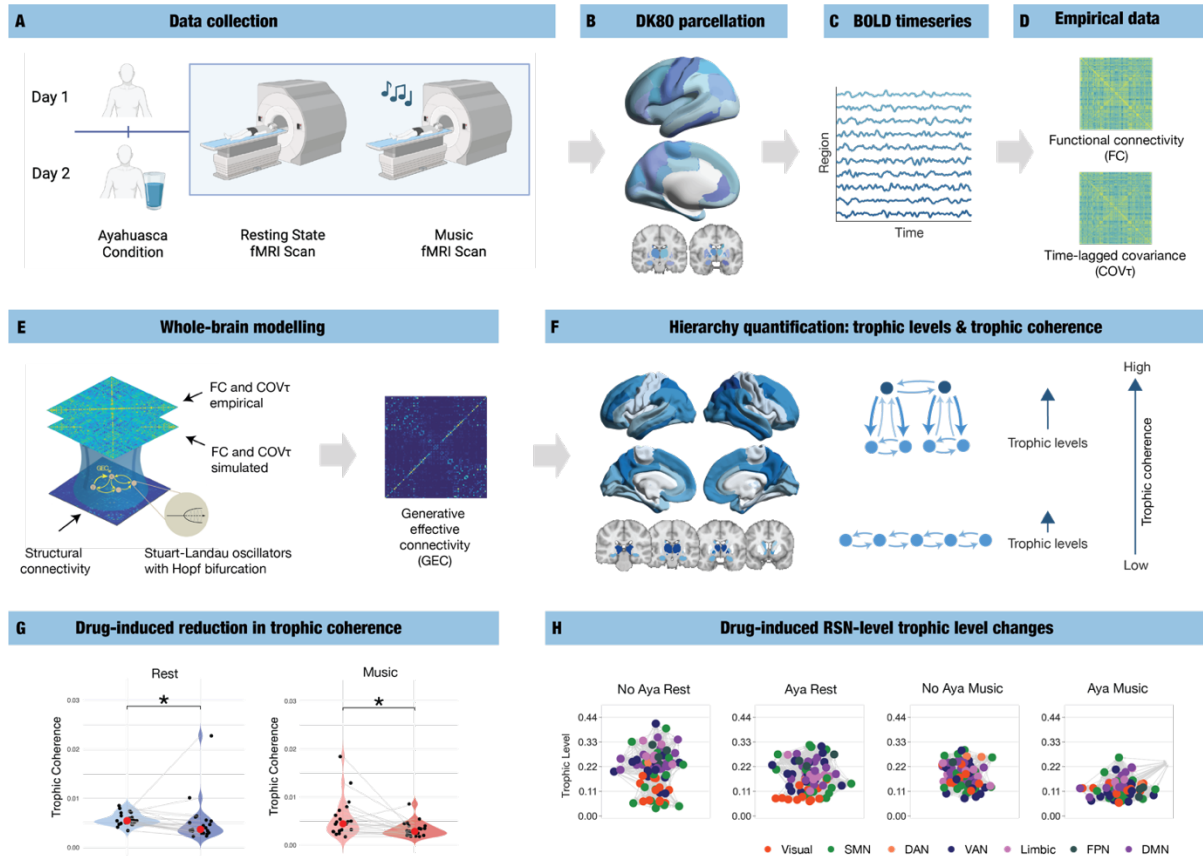


Figure 3.1 Time-averaged trophic analyses overview. *A.* We applied whole-brain modelling and trophic analyses to the Santo Daime fMRI data at rest and during music listening. *B.* Following preprocessing and denoising the data was parcellated using the DK80 parcellation. *C.* BOLD timeseries were extracted for each region, for each subject in each condition. *D.* Empirical FC and COV_τ matrices were constructed for each condition (group level) and for each subject in each condition. *E.* The FC and COV_τ matrices were used to fit a Hopf-based whole-brain model, rooted in the structural connectivity matrix, from this a generative effective connectivity (GEC) matrix was produced. The group level GEC was then used as a baseline to further optimise fitting per subject, providing subject-specific GECs. *F.* The regional trophic levels and the overall trophic coherence for each subject in each condition were computed from the condition- and subject-specific GECs. *G.* For each participant we estimate whole-brain measures of trophic coherence (shown here), average effective connectivity, and trophic level distribution metrics across the brain. *H.* RSN-level trophic level changes were computed per subject per condition to understand how these networks change their positioning within the hierarchy. This figure was partially adapted from Deco et al. (2024), and in part created with BioRender.com.

3.2 Methods

3.2.1 *Data acquisition & music paradigm*

The Santo Daime fMRI dataset described in Chapter 1 (sections 1.10.1 – 1.10.4) is analysed in the current chapter. Both resting state and music listening conditions are examined. The music listening condition is treated as a single block here, with the within-music factorial design examined in Chapter 5). Importantly, resting state scans were conducted with participants instructed to keep their eyes open looking at a fixation cross, whereas during music listening scans, they were instructed to keep their eyes closed. Therein, the current chapter explores the effects of ayahuasca ingestion across these two distinct contexts, more broadly.

3.2.2. *Participants*

Three participants were excluded due to complications, high levels of head movement, and/or increased anxiety during music listening scans. For the purposes of the current and proceeding chapters, these individuals were excluded from the resting state conditions as well. $N = 21$ participants were included in the presented analyses.

3.2.3 *fMRI data preprocessing and parcellation*

Data was preprocessed and denoised as described in Chapter 1 (sections 1.10.5 – 1.10.6). fMRI data were then parcellated using the DK80 cortical and subcortical parcellation, which is a development of the Mindboggle-modified Desikan-Killiany 62 cortical region parcellation (31 regions mirrored across hemispheres). 18 subcortical regions were added, nine regions per hemisphere: amygdala, caudate, globus pallidus external segment (GPe), globus pallidus internal segment (GPi), hippocampus, nucleus accumbens, putamen, subthalamic nucleus (STN), and thalamus. This parcellation was chosen due to previous work showing its effectiveness in balancing between spatial accuracy and computational load required for whole-brain modelling (Deco et al., 2024, 2021). Importantly, there is currently no general consensus on optimal spatial parcellation (Popovych et al., 2021). Once parcellated, the data was bandpass filtered using a frequency range of 0.008 – 0.08 Hz, and a 2nd order Butterworth filter was applied. The timeseries were detrended and demeaned, and the first and last five volumes were removed to minimise scanner artefacts.

3.2.4 Whole-brain modelling

Local dynamics of each brain region were modelled as Stuart-Landau oscillators (Kuznetsov, 2004) coupled through the structural connectome. The bifurcation parameter was set to $\alpha = -0.02$, such that the system was in a subcritical regime where oscillations are dampened and activity is driven by stochastic noise (Deco et al., 2017b). The system was approximated around its stable fixed point in a linear form, the linearised Hopf model, reducing the computational cost through the use of Jacobian operators (Ponce-Alvarez and Deco, 2024). The full mathematical description of the model and its linearisation are detailed in **Supplementary Section S1.1** and have previously been reported in (Deco et al., 2024). The following sections describe the application of this framework and the fitting procedure specific to the current analyses.

Region-specific intrinsic frequencies were determined by computing the power spectrum for each region's timeseries using the fast Fourier transform. Gaussian-smoothing (bandwidth = 0.005 Hz) was applied to the power spectrum, and the peak frequency was extracted for each region. The resulting frequencies were averaged across participants to obtain condition-specific intrinsic frequency maps used to parameterise the Hopf oscillators.

The structural connectivity matrix, used as a baseline and biological underpinning for the model was built using the Human Connectome Project high-density DTI data from 812 healthy participants (WU-Minn Consortium, S1200 release of 812 subjects; available at: https://db.humanconnectome.org/data/projects/HCP_1200). All weights of connections between pairs of regions were updated through a gradient-descent approach, to fit empirical FC and time-lagged covariance matrices. The result of the fitting was a GEC matrix for each condition. Notably, only non-zero weighted edges from the anatomical coupling matrix were updated, ensuring preservation of the underlying anatomical scaffold. The model, in its current form, does not allow for negative connections, and thus all negative connections were set to zero. A group-level optimisation was performed for each condition. These group-level GECs were then used to initialise subject-specific optimisation, in which GECs were fitted using each subject's empirical FC and time-lagged covariance. Subject-specific GECs were optimised using the same procedure as at group-level.

A pseudo-gradient descent algorithm with small learning rates ($\epsilon_{FC} = 0.0004$, $\epsilon_{COV\tau} = 0.0001$) was applied to iteratively optimise the GEC matrix. In each iteration, the resulting functional connectivity and time-lagged covariance matrices were compared to their empirical counterparts, and any discrepancies between the simulated and empirical data were used to update the model. A maximum connectivity strength of 0.2 was enforced, with the GEC matrix

rescaled to this range (0-0.2) after each iteration. Gaussian noise with $\sigma = 0.01$ was implemented into the oscillators to model stochastic fluctuations. Optimization continued for up to 5000 iterations or until the relative change in combined mean squares error (for both functional connectivity and time-lagged covariance) fell below 0.001, whichever occurred first. The Hopf model achieved good fits across all conditions. Correlations between empirical and simulated FC were on average approximately 0.71 across conditions (no ayahuasca rest: $r = 0.720 \pm 0.014$ (mean $\pm$ SEM); ayahuasca rest: $r = 0.712 \pm 0.016$; no ayahuasca music: $r = 0.720 \pm 0.015$; ayahuasca music: $r = 0.685 \pm 0.021$). Correlations between empirical and simulated time-lagged covariance were on average approximately 0.62 across conditions (no ayahuasca rest: $r = 0.635 \pm 0.014$ (mean $\pm$ SEM); ayahuasca rest: $r = 0.621 \pm 0.019$; no ayahuasca music: $r = 0.626 \pm 0.016$; ayahuasca music: $r = 0.583 \pm 0.021$).

In the fitting process we compared the output of the model with the functional correlation matrices for each condition, i.e. the normalised covariance matrices of the empirical data. To move beyond static functional connectivity patterns, the temporal directionality, or asymmetry of the underlying dynamics was incorporated. We estimated forward time-lagged covariance matrices from each participant's BOLD data. To allow direct comparison between empirical and time-lagged covariance matrices, we normalised each by dividing every matrix element by the product of the standard deviations of the corresponding pair of regions. The incorporation of directional metrics increased the model's sensitivity to non-equilibrium features of the BOLD signal and ensured that the EC was not limited to symmetric interactions. The time-lag of the covariance matrix was set at $\tau = 2$, following two complementary analyses. Pairwise cross-correlations between all regional BOLD timeseries per subject per condition, were compared across $\tau = 2$ to 5. $\tau = 2$ resulted in maximum absolute cross-correlation between pairs of regions most often, and most consistently across subjects in each condition. Further, the Hopf whole-brain model was fit at group level using $\tau = 2$ to 5 with $\tau = 2$ resulting in best fit (**Supplementary Table S3.1**). $\tau = 1$ was excluded a priori due to haemodynamic autocorrelation effects, and insufficient distinction from zero lag FC.

3.2.5 *Effective connectivity*

For each participant in each scanning condition, average EC was computed from the optimised GEC matrix. Self-connections (diagonal elements) were excluded, and the mean of all non-zero off-diagonal weights was calculated, providing a measure of average network coupling strength. Mean EC values were then compared between conditions to assess drug-dependent

changes in global network EC strength, within each context. For each subject s in each condition c , mean EC is computed as

$$\overline{EC}^{(s,c)} = \text{mean}\left(GEC_{ij}^{(s,c)} \mid i \neq j, ; GEC_{ij}^{(s,c)} \neq 0 \right) \quad (3.1)$$

3.2.6 Trophic coherence

To explore changes in the functional hierarchy structure and directed information flow following ayahuasca ingestion, measures of trophic coherence (TC) and trophic levels (TLs) were computed.

TLs provided node-specific information regarding relative regional positions in the system's information flow structure. Each participant's GEC described a weighted, directed network, wherein each node represented a brain region and each edge weight represented a direction-specific EC between two regions. The GEC matrix was transposed such that rows represented outgoing influence. For each node N in-weight and out-weight was calculated by respectively summing the columns and rows of the GEC. The in-weight represented the total incoming information to node N , whereas the out-weight corresponded to the total outgoing information from node N . The total weight of node N was defined as the sum of the in-weights and the out-weights, and the imbalance of the node as the difference between the two (total inweight – total outweight). The total weight and the imbalance were used to construct a graph Laplacian as $A = \text{diag}(u) - A - A^T$ (where A is the GEC matrix and u is the total weight) relating the imbalance to the hierarchical position of each node. For the linear system to be solvable, the first diagonal element of the Laplacian matrix ($A_{1,1}$) was set to zero, anchoring the reference point across conditions. Trophic levels were then computed by solving $Ah = v$, where v is the imbalance vector, and h is the $1 \times N$ trophic level vector. h was then shifted to ensure non-negativity as $h = h - \min(h)$, such that all scores were positive. Each region's trophic level reflected its position within the network's information flow structure, with lower scores given to regions which sent relatively more information than they received (sources) and higher levels assigned to regions which received relatively more information than they sent (sinks).

Trophic coherence (TC) is a network-wide measure of directionality and hierarchical consistency, quantifying the hierarchical organisation of the network. In a perfectly hierarchical system, any directed edge between regions i and j , would result in a trophic level difference of 1, suggesting no ambiguity in directionality. In practice this is not the case, and deviations from such a perfect directionality were measured through TC. TC was defined by first quantifying

the trophic difference, which denoted the deviation of the observed trophic distance between the two nodes from the unit step in a maximally hierarchical network. Trophic difference for a directed edge from i to j with assigned trophic levels h_i and h_j was calculated as:

$$X_{ij} = h_j - h_i - 1 \quad (3.2)$$

The variance of these trophic differences across all edges, weighted by the strength of their observed effective connections was calculated as TC, where TC approached one for maximally coherent (perfectly hierarchical) systems and decreased for systems with ambiguous or inconsistent hierarchical organisation.

$$TC = 1 - \frac{\sum_{i,j} GEC_{ij} (h_j - h_i - 1)^2}{\sum_{i,j} GEC_{ij}} \quad (3.3)$$

3.2.7 RSN-based trophic level differences

Trophic levels were derived as one value per region per subject, resulting in a 1x80 vector for each participant. To enhance interpretability of these findings, and examine network-specific changes in hierarchical organisation, changes in average trophic-level following drug ingestion across the 7 canonical RSNs (Visual, Somatomotor, Dorsal Attention, Ventral Attention, Limbic, Frontoparietal, and Default Mode) were reported (Yeo et al., 2011). Each network's trophic level was calculated as the average of individual regional trophic levels, weighted by that region's proportion of overlap with each network's parcellation. Average trophic levels were compared within networks, between ayahuasca conditions using Wilcoxon signed-rank tests with FDR correction accounting for seven comparisons (corresponding to the seven RSNs).

3.2.8 Trophic level-based support vector machine classification

To examine the reliability of trophic level differences in distinguishing between no ayahuasca and ayahuasca conditions, a support vector machine (SVM) classifier with a linear kernel was utilised. SVM classifiers are machine learning algorithms used for binary classification. They operate by finding a hyperplane which optimally separates two datasets. To ensure balanced training across groups, leave-one-subject-out (LOSO) cross-validation was implemented. In each fold, each subject's two scans (no ayahuasca and ayahuasca) were held out for testing,

and the remaining subjects were used for training. To prevent any information leakage between training and test data, within each training iteration, features were z-scored using the training data (mean and standard deviation computed across all training samples), and the same scaling parameters were applied to the test sample. A linear-kernel SVM was trained on the scaled training data and used to predict the drug state of the test sample. This procedure produced 42 independent test predictions per context (one ayahuasca absent and one ayahuasca present per subject). Overall accuracy (number of correct predictions / total number of predictions), sensitivity (proportion of correctly classified ayahuasca present samples), specificity (proportion of correctly classified ayahuasca absent samples) and balanced accuracy (mean of specificity and sensitivity) were quantified.

3.2.9 Statistical comparisons

The hierarchy measures computed in this chapter were compared between drug conditions. No clear comparisons were possible between rest and music conditions, due to differences in eye state. Specifically, the resting state scans were collected with participants instructed to keep their eyes open looking at a fixation cross, whereas during music scans participants were instructed to close their eyes. Thereby, it would not be possible to interpret whether any observed differences were due to the presence of music, or due to eye state. Several papers have outlined significant effects of eyes being open or closed during neuroimaging on brain dynamics both in psychedelic research and more broadly (Agcaoglu et al., 2019; Ingram et al., 2024; Mediano et al., 2024; Shinozuka et al., 2025). The reported results thereby look at the effect of drug within the resting state scan, and separately within the music listening conditions. Consistencies of drug effects across contexts are thought to signify robustness of psychedelic effects. Further, any differences are more broadly discussed as being associated with a change in “context”, outlining the importance of setting for the ayahuasca state.

Drug effect comparisons were conducted using the non-parametric Wilcoxon signed-rank tests due to the within-sample nature of data collection, and several conditions not meeting normality assumptions, as computed through Lilliefors tests of normality. This statistical testing approach was applied across paired comparisons for consistency.

3.2.10 Density regression for average EC and TC

As previously mentioned, the linearised Hopf model only allowed positive connections, setting all negative connections to zero and resulting in variation in density of non-zero weighted connections across participants and conditions. To control for potential confounding effects of network density on mean EC, a within-subject density regression was carried out. After confirming that density significantly predicted mean EC using a linear mixed model ($MeanEC \sim Density_c + (1|Subject)$), within-subject demeaning was performed by subtracting each subject's average density and mean EC across conditions. This was done to remove between-subject baseline differences. A common linear regression slope (β) was estimated relating density and mean EC across all subjects and conditions using ordinary least squares regression with no intercept. Density-adjusted EC residuals were calculated by subtracting the predicted EC based on each subject's density change ($\beta \times \text{centred density}$) from their centred mean EC. These residuals represent the change in EC independent of density changes. Residuals were compared between conditions using Wilcoxon signed-rank tests. Given the reliance of TC computation on edge number and weight, this procedure was replicated for observed TC values.

3.3 Results

3.3.1 Ayahuasca-induced changes in coupling strength

As a primary exploration of directed coupling within the system we examined changes in mean EC as derived from each subject's condition specific GEC. At rest, we observed a significant increase in mean EC following ayahuasca ingestion ($W = 9$, $Z = -3.68$, $r = -0.80$, $p < .001$) (**Figure 3.2A left panel**). During music listening, a significant reduction in mean EC following ayahuasca ingestion was shown ($W = 185$, $Z = 2.40$, $r = 0.52$, $p = .016$) (**Figure 3.2A right panel**). A linear mixed effects model with mean EC as the outcome, centred density as a fixed effect, and subject as a random intercept revealed that network density significantly predicted meanEC both during rest ($\beta = -0.053$, $SE = 0.009$, 95% CI $[-0.071, -0.035]$, $t(40) = -5.89$, $p < .001$) and during music listening ($\beta = -0.038$, $SE = 0.005$, 95% CI $[-0.048, -0.028]$, $t(40) = -7.96$, $p < .001$), justifying density adjustments for both comparisons. Wilcoxon signed-rank tests comparing density-adjusted ECs showed consistent effects, namely ayahuasca ingestion led to significant increase in mean EC during resting state ($W = 0$, $Z = -4.02$, $r = -0.88$, $p < .001$) and a significant decrease in mean EC during music listening ($W = 192$, $Z = 2.66$, $r = 0.58$, $p = .007$). The mean EC residual difference (ayahuasca – no ayahuasca) for the resting state and music listening conditions are visualised in **Figure 3.2B**. These results suggest differential drug effects on global coupling strength across contexts, independent of differences in network sparsity caused by model fitting.

3.3.2 Ayahuasca-induced changes in trophic coherence

A significant reduction in TC following ayahuasca ingestion was observed both while participants were at rest ($W = 189$, $Z = 2.54$, $r = 0.55$, $p = .011$) and while listening to music ($W = 186$, $Z = 2.43$, $r = 0.53$, $p = .015$) (**Figure 3.2C**). Linear mixed models confirmed that density significantly predicted TC during rest ($\beta = -0.023$, 95% CI $[-0.038, -0.008]$, $t(40) = -3.159$, $p = .003$), but not TC during music listening ($\beta = -0.0009$, 95% CI $[-0.012, 0.011]$, $t(40) = -0.153$, $p = .879$). Nevertheless, density adjustments were applied to both comparisons for methodological consistency. Wilcoxon signed-rank tests revealed significant drug-induced reductions in density-adjusted TC both during resting state ($W = 179$, $Z = 2.21$, $r = 0.48$, $p = .027$) and music listening ($W = 182$, $Z = 2.31$, $r = 0.50$, $p = .021$) (**Figure 3.2D**), consistent with results prior to density adjustment. These results suggest that ayahuasca reduced hierarchical organisation in a context-independent manner, as quantified through TC, independent of network sparsity.

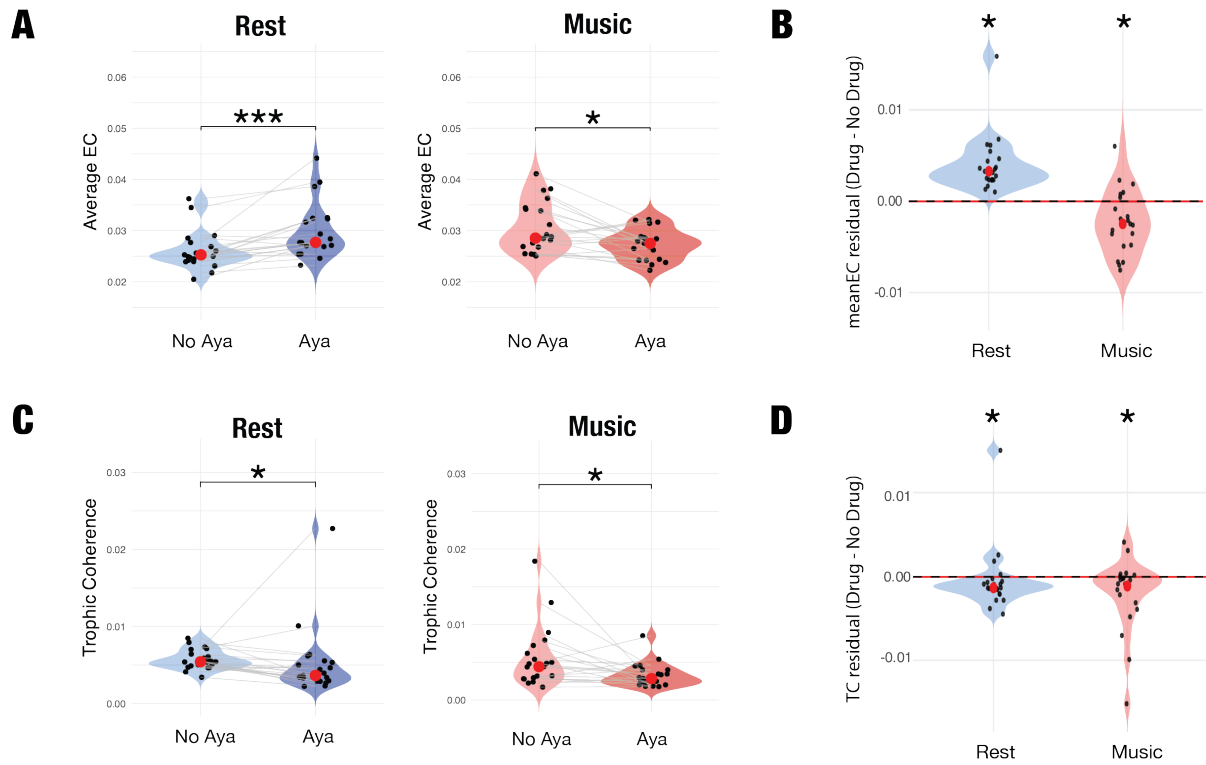


Figure 3.2 Trophic coherence measures showed context-independent ayahuasca-induced reductions, while mean EC was characterised by context-specific effects. A. Violin plots comparing non-adjusted average EC, excluding zero-weighted connections and self-connections, derived from each participant's GEC. Drug-dependent differences at rest (left) and while listening to ritual-relevant music (right). B. Violin plots of density-adjusted mean EC residuals depicting change following ayahuasca ingestion (drug – no drug). Red line denotes 0 (no change), at rest a significant increase is observed, during music listening a significant decrease is observed. C. Violin plots comparing non-adjusted TC scores pre- and post- ayahuasca during resting state scan (left) and music listening (right). D. Violin plots of density-adjusted TC residuals depicting change following ayahuasca ingestion (drug – no drug). Red line denotes 0 (no change), Across contexts a significant reduction in TC following ayahuasca ingestion. Across panels: Pre ayahuasca consumption condition marked as “No Aya”, post ayahuasca consumption condition marked as “Aya”, resting state marked as “Rest” and music listening condition marked as “Music”. Significance: * $p < .05$, ** $p < .01$, *** $p < .001$. Red dot denotes median for each conditions, black dots are per subject values.

3.3.3 Trophic levels exhibit significant context-independent redistribution following ayahuasca ingestion

Beyond the overall coherence of the network's information flow hierarchy, we examined the effects of ayahuasca ingestion on trophic level distribution. The relationship between trophic level and relative in-flow versus out-flow of information was first visualised (Figure 3.3A), providing a grounding for interpretation. Regions with higher trophic levels were consistently observed to have greater in-flow of information from the system, compared to the out-flow of information, exhibiting more sink-like behaviour. Conversely, regions with lower trophic level

scores were observed to show more source-like behaviour. The relative distribution of trophic levels was compared between drug conditions, both at rest and while listening to music. Significant reductions in median trophic level following ayahuasca ingestion were observed both during rest ($W = 185$, $Z = 2.41$, $r = 0.52$, $p = .017$) and music listening ($W = 198$, $Z = 2.86$, $r = 0.62$, $p = .004$), suggesting a movement towards more source-like and less sink-like behaviour across the brain. These shifts in average trophic level are visualised through brain renderings in **Figures 3.3B** and **3.3C**, respectively. To examine changes in distribution of trophic levels we compared the interquartile range (IQR) and median absolute deviation (MAD) across drug conditions. Both IQR ($W = 184$, $Z = 2.38$, $r = 0.52$, $p = .018$) and MAD ($W = 187$, $Z = 2.48$, $r = 0.54$, $p = .014$) were observed to be significantly reduced following ayahuasca ingestion during rest, reflecting a compression of the trophic hierarchy as well as a homogenisation of regional information flow roles. MAD was observed to be significantly reduced following ayahuasca ingestion during music listening ($W = 180$, $Z = 2.24$, $r = 0.48$, $p = .026$), however IQR reductions did not reach statistical significance ($W = 171$, $Z = 1.93$, $r = 0.42$, $p = .056$).

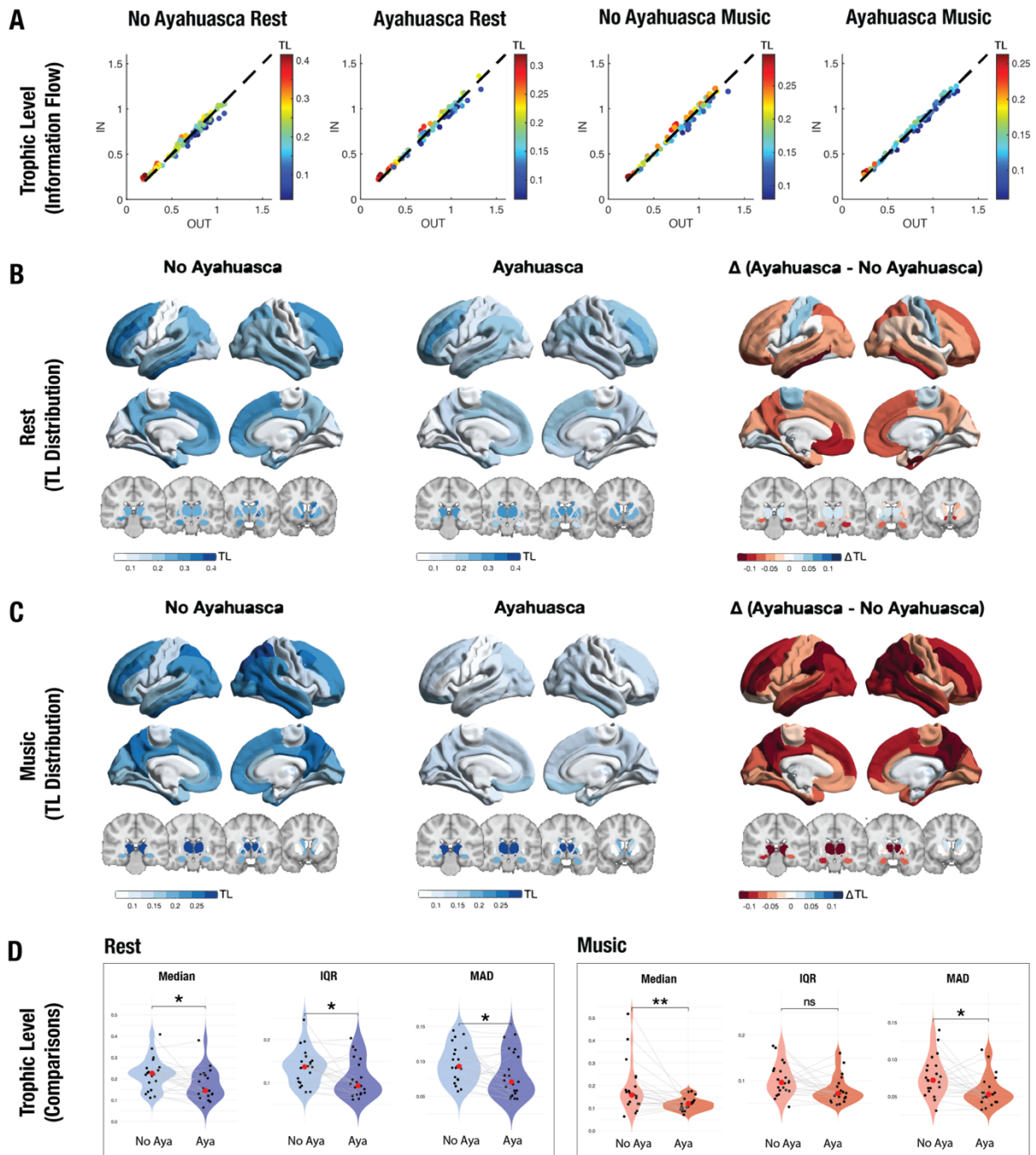


Figure 3.3 Context-independent reductions in trophic level distribution following ayahuasca ingestion. *A.* Scatter plots of average information in-flow and out-flow for each region. Colours depicting regional trophic level, warmer colours – higher trophic level, cooler colours – lower trophic level. Higher trophic levels show higher information in-flow (position in upper triangle), and lower trophic levels show higher information out-flow (position in lower triangle). *B.* Resting state eyes open: Cortical and subcortical rendering of average distribution of trophic levels across the brain in pre- (left panel) and post-ayahuasca (middle panel) conditions, as well as the difference in TL between the two (right panel). *C.* Music listening eyes closed: Cortical and subcortical rendering of average distribution of trophic levels across the brain in pre- (left panel) and post-ayahuasca (middle panel) conditions, as well as the difference in TL between the two (right panel). *D.* Statistical comparison of Median, Interquartile Range (IQR) and Median Absolute Deviation (MAD) between pre- and post-ayahuasca conditions at Rest (left panel; light blue denotes pre-ayahuasca and dark blue denotes post) and during Music Listening (right panel; light red denotes pre-ayahuasca and dark red denotes post). Significance: * $p < .05$, ** $p < .01$, *** $p < .001$.

3.3.4 Higher-level RSNs show context-independent average trophic level reductions

Further, we examined whether observed changes in trophic level persisted across resting state networks, or whether these reductions were specific to higher-order brain networks. The effects of ayahuasca ingestion on trophic level were explored across known resting state networks (RSNs) as defined by Yeo et al (2011). Regions were grouped into RSNs using a weighted approach, wherein each network's activity is a weighted linear combination of regional trophic levels. In the case of rest, five networks displayed a significant decrease in average trophic level following ayahuasca ingestion, the Visual ($W = 180$, $Z = 2.22$, $r = 0.49$, $p = .026$, $q = .044$), Dorsal Attention ($W = 185$, $Z = 2.40$, $r = 0.52$, $p = .016$, $q = .038$), Limbic ($W = 203$, $Z = 3.02$, $r = 0.66$, $p = .002$, $q = .015$), Frontoparietal ($W = 178$, $Z = 2.16$, $r = 0.47$, $p = .031$, $q = .044$), and Default Mode ($W = 198$, $Z = 2.85$, $r = 0.62$, $p = .004$, $q = .015$) networks (**Figure 3.4B**). In the case of music listening scans, significant ayahuasca-induced reductions in average trophic level were observed in four RSNs, namely Somatomotor ($W = 184$, $Z = 2.36$, $r = 0.52$, $p = .018$, $q = .042$), Dorsal Attention ($W = 219$, $Z = 3.58$, $r = 0.78$, $p < .001$, $q = .002$), Frontoparietal ($W = 214$, $Z = 3.41$, $r = 0.74$, $p = .001$, $q = .002$), and the Default Mode ($W = 181$, $Z = 2.26$, $r = 0.49$, $p = .024$, $q = .042$) networks (**Figure 3.4C**). All statistical significance of Wilcoxon signed-rank tests prior to and following FDR correction are reported in **Supplementary Table S3.2** (for resting state) and **Table S3.3** (for music listening). Across contexts, ayahuasca ingestion led to a movement towards source-like behaviour on average across multiple higher-order networks, including the Dorsal Attention, Frontoparietal, and Default Mode networks. Lower-order networks seemed to be significantly affected in a context-dependent manner, namely Visual network in the eyes open resting state condition, and Somatomotor network (encompassing many auditory processing regions) in the eyes closed music listening condition.

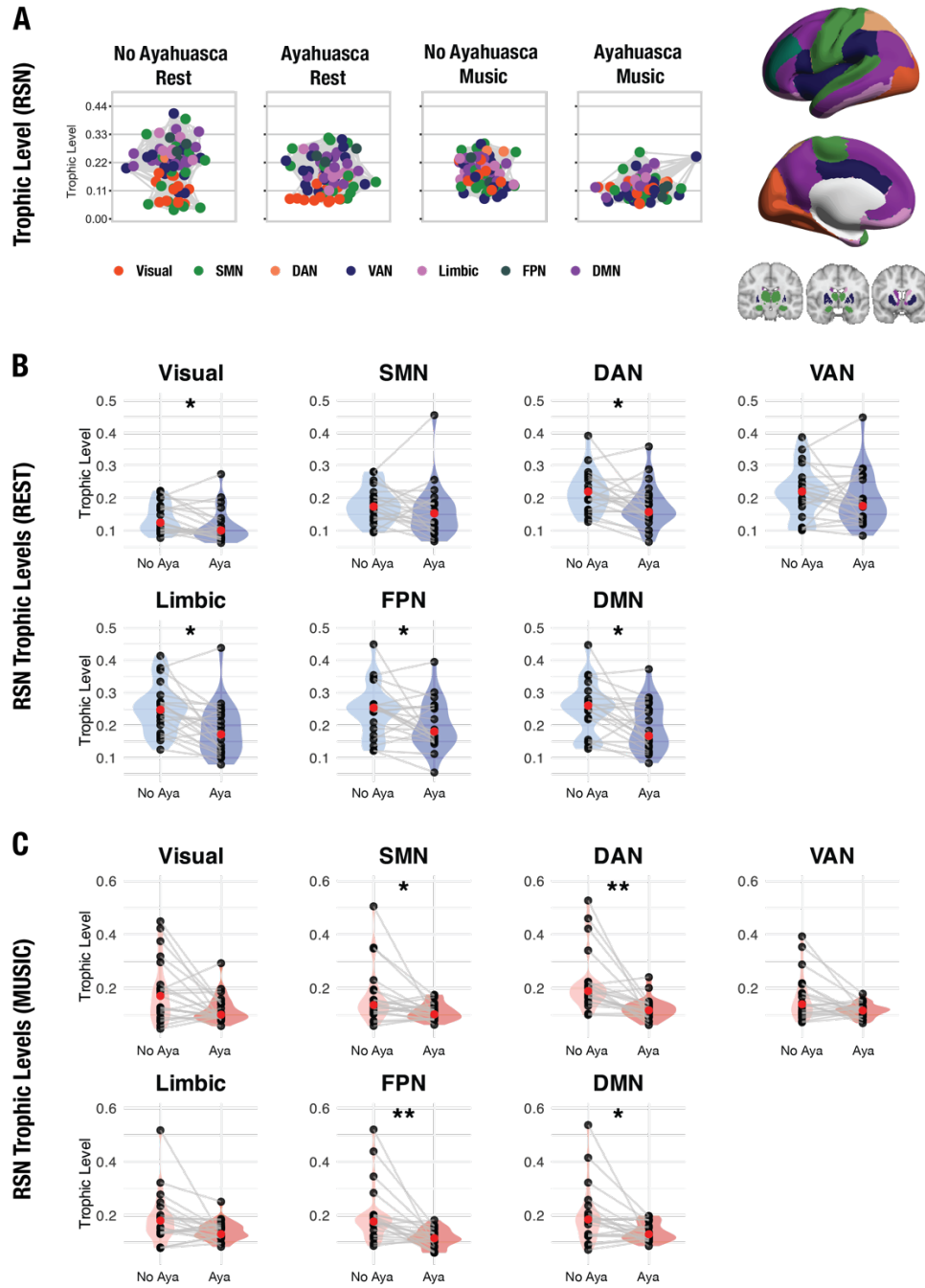


Figure 3.4 Context-independent reductions in average trophic level of higher-order RSNs following ayahuasca ingestion. RSNs are presented in the following order: Visual Network (Visual), Somatomotor Network (SMN), Dorsal Attention Network (DAN), Ventral Attention Network (VAN), Limbic Network (Limbic), Frontoparietal Network (FPN), Default Mode Network (DMN). *A.* Average trophic levels for each region grouped by RSN association through weighted contribution approach. Visualisation of relative location of networks within context of all 80 regions. Y-axis, denoting trophic is consistent across graphs. Location of nodes on x-axis is randomly generated and for visualisation purposes only. Brain rendering of all RSNs depicting cortical and subcortical region to RSN assignment. *B.* RSN-specific violin plots of TL comparisons pre-ayahuasca (light blue) and post-ayahuasca (dark blue) ingestion at rest with eyes open. *C.* RSN-specific violin plots of TL comparisons pre-ayahuasca (light red) and post-ayahuasca (dark red) ingestion during music listening with eyes closed. Significance computed using Wilcoxon Signed-rank tests and BHFD correction, accounting for seven comparisons (seven networks explored). Significance: * $p < .05$, ** $p < .01$, *** $p < .001$. Black dots: the average trophic level for each person in each condition for each RSN. Red dots: median average trophic level scores per condition per RSN.

3.3.5 Trophic level-informed SVM classifiers distinguish between drug conditions with high accuracy

As a further validation of the significant reorganisation of trophic levels following ayahuasca consumption both during rest and during music listening, SVM classifiers were used. Regional trophic levels were shown to distinguish between ayahuasca absent and ayahuasca present conditions in both resting state and music listening contexts. In the resting state (eyes-open) condition, 41 out of 42 held-out samples were correctly classified, resulting in an overall accuracy of $97.62\% \pm 10.91\%$, and a balanced accuracy of 97.62%. Accuracy in classification of data from the ayahuasca absent condition was 100%. Accuracy in classification of data from the ayahuasca present condition was 95.24%. In the music listening (eye-closed) condition, 37 out of 42 held-out samples were correctly classified, resulting in an accuracy of $88.10\% \pm 21.82\%$, and a balanced accuracy of 88.10%. Accuracy in classification of data from the ayahuasca absent condition was 85.71%, and 90.48% for the ayahuasca present condition. A permutation test with 1000 within-subject label shuffles confirmed that this performance was highly unlikely under the null hypothesis for both pairs of conditions ($p < .001$).

3.4 Discussion

The current chapter examined ayahuasca-induced effects on directed information flow and hierarchy structure through whole-brain modelling and trophic analyses. Our findings suggest flattening of the directed hierarchy of information flow following ayahuasca ingestion among Santo Daime members, across resting state and ritual-relevant music listening contexts. Our results showed context-independent ayahuasca-induced reductions in TC, and whole-brain TL central tendency and distribution, as well as context dependent changes in mean EC and RSN-based TL central tendency. Our observations provide converging evidence for psychedelic-induced flattening of the directed functional hierarchy, extending previous findings, and providing nuance by outlining context-specific effects.

Mean EC increased significantly following ayahuasca ingestion at rest, and decreased significantly during music listening. These results persisted following the removal of density-related confounds, indicating changes in edge-specific coupling strength rather than differences in connectome sparsity. Several studies have explicitly explored psychedelic-induced changes in directed connectivity, largely using dynamic causal modelling approaches. Majority of these, examined specific circuits, networks, and network interactions (Avram et al., 2024; Kraehenmann et al., 2016; Preller et al., 2019; Stoliker et al., 2024, 2023). Bedford et al (2023) examined changes in whole-brain EC following LSD administration, finding on average stronger EC under LSD, aligning with our observation following ayahuasca ingestion at rest, but not during music listening. The difference in directionality of effects across contexts in the current study suggests that ayahuasca does not uniformly alter directed coupling across the brain, but rather may modulate it in a context-dependent manner. Importantly however, the rest and music conditions differed in eye state, eyes open and eyes closed respectively. Thus, the contextual cause of the observed differences is not clear. Nevertheless, the results demonstrate that contextual factors (whether music or eye state) seem to meaningfully shape ayahuasca's effects on average directed coupling strength.

To understand the effects of ayahuasca ingestion on the functional hierarchy structure, changes in TC were examined. Significant reductions in TC were observed across both resting state and music listening contexts, with results persisting when accounting for network sparsity. These results suggest a context-independent destabilisation of hierarchical organisation following ayahuasca ingestion, aligning with prior work demonstrating lower TC scores, and thus flattening of the functional hierarchy under psilocybin (Deco et al., 2024). The Santo Daime

are a unique group who take ayahuasca in a regular, ritualised and communal setting. The consistency between the results presented in this chapter and prior literature shows reduction in TC to be a robust signature of the psychedelic state, not only across immediate contextual factors (presence of music), and psychedelic compounds, but across cultural contexts too.

Trophic coherence provides a single measure of directionality of influence across the system's hierarchy. Trophic level distribution metrics permit examination of relative changes in regional information flow roles across the system. Across contexts, significant reductions in median and MAD of trophic levels were observed following ayahuasca ingestion. The reduction in median trophic level following ayahuasca ingestion across contexts suggests a shift away from sink-like, integrative activity, towards more source-like activity across the brain. Combined with the reduced trophic level dispersion, our results indicate a movement away from sink-like activity, and a lowering of differentiation between regions that predominantly receive versus provide directed input. The observed patterns are aligned with recent evidence that LSD flattens hierarchical directed information flow (Shinozuka et al., 2025), and the REBUS framework, proposing that psychedelics expand the brain's dynamic repertoire by relaxing hierarchical constraints (Carhart-Harris and Friston, 2019). The observed restructuring in regional information-transmission roles within the system is further supported by the high accuracy of SVM classifiers in distinguishing between pre-ayahuasca and post-ayahuasca conditions, informed only by subject-specific trophic levels.

The average trophic level of each of the seven canonical RSNs was compared across drug conditions. Context-independent significant reduction in average trophic level were observed across several higher-order networks, including the DAN, FPN, and DMN. The consistency of these effects across contexts suggests this to be a general effect of ayahuasca on higher-order associative networks rather than a context-specific phenomenon. These findings are broadly consistent with evidence that psychedelics reduce the functional coherence of higher-order networks, as well as increasing their communication with the rest of the brain. Higher-order networks such as the DMN and FPN have previously been associated with reduced within-network integrity and/or increased between-network coupling under psilocybin (Carhart-Harris et al., 2012), LSD (Preller et al., 2018; Tagliazucchi et al., 2016), and ayahuasca (Palhano-Fontes et al., 2015). Importantly, TL is one measure of hierarchy organisation, and the relationship between TL and broader concepts of 'network dominance' requires further investigation, especially in the context of ayahuasca's effects on the brain's functional hierarchy, which have been underexamined thus far.

Notably the limbic network presented an exception to the context-independent drug effects observed in other higher-order networks, showing significant reductions in average trophic level during rest but not during music listening. Music has been shown to engage limbic and reward areas even in the absence of pharmacological intervention (Blood and Zatorre, 2001; Koelsch, 2014), and this ongoing engagement may interact with ayahuasca's effects on this network. However, the confound between music presence and eye state limits the conclusions that can be drawn.

Lower-order sensory RSNs showed context-specific drug effects when examining drug-induced changes in average TL. The visual network showed significant reduction in average TL during eyes open resting state, but not during eyes closed music listening. Conversely, the average TL of the SMN (which encompasses large parts of the auditory processing stream) was significantly reduced following ayahuasca ingestion during eyes closed music listening, but not during eyes open resting state. This pattern suggests that the impact of ayahuasca on sensory networks may depend on whether the relevant modality is actively engaged. A critical review by Aqil and Roseman (2023) proposed that lower-order sensory networks play an underappreciated role in shaping the psychedelic experience. Neuroimaging studies have consistently shown psychedelics to alter activity in sensory brain areas, for example LSD has been shown to increase FC between primary visual cortex and many cortical and subcortical brain regions during eyes closed resting state (Carhart-Harris et al., 2016), while ayahuasca during an eyes-closed imagery task was shown to enhance BOLD activity in the primary visual cortex to an extent “comparable in magnitude to the activation levels of natural image with the eyes open” (de Araujo et al., 2011). The findings of the current chapter add a hierarchical perspective to these observations, suggesting a context-dependent effect of psychedelics on lower-order sensory network information flow roles. Importantly, in the analyses presented in this chapter, comparisons of drug effects between contexts were not performed, due to the confound between music presence and eye state, limiting interpretations. Future work, systematically comparing these variables is needed to verify the observed context-dependent changes in lower-order networks.

In conclusion, the analyses presented in the current chapter showed ayahuasca ingestion to significantly flatten the functional hierarchy and shift average regional information-transmission roles towards more source-like activity. These effects, along with significant reductions in the TL central tendency of several higher-order networks (DMN, FPN, and DAN), were consistent across resting state eyes open and music listening eyes closed conditions. Interestingly, mean EC and average TL of lower-order sensory networks (Visual Network and SMN)

showed context-dependent drug effects, suggesting a moderating role of immediate context on specific features of directed information flow.

3.5 Summary

This chapter examined the effects of ayahuasca on the brain's functional hierarchy among members of the Santo Daime Church, across resting state and ceremonial music listening contexts. EC was modelled through Hopf whole-brain modelling and ayahuasca-induced changes in hierarchy were explored through trophic analyses. Results outlined reductions in TC, whole-brain TL central tendency and dispersion as robust markers of the psychedelic state, consistently observed across contexts. Further, context-dependent effects were observed for average EC, and while higher-order RSN average TL showed consistent effects across contexts, lower-order sensory networks showed context-specific effects that corresponded to sensory modality engagement. Our findings suggested ayahuasca-induced flattening of the functional hierarchy, with specific features of the directed connectivity and hierarchy showing context-dependent effects. Unlike the dynamic analyses of Chapter 2, the current chapter uses an established time-averaged approach to characterising psychedelic-induced changes in hierarchical structure. The following chapter extends this work by characterising time-resolved ayahuasca-induced changes in hierarchical organisation.

Chapter 4:

Time-resolved changes to functional hierarchy

Abstract

Growing evidence suggests that psychedelic states are characterised by temporally dependent reconfigurations. However, the majority of work looking at changes to brain state dynamics has used undirected or model-free approaches. This chapter builds on the exploration of changes to the functional hierarchy following ayahuasca ingestion among the Santo Daime outlined in Chapter 3, by exploring the temporal mean and stability of time-resolved changes in hierarchy measures. To this end, we introduce a novel method combining LEiDA (outlined in Chapter 2) with whole-brain modelling and trophic analyses (outlined in Chapter 3). Results confirm ayahuasca-induced flattening of the functional hierarchy across all temporal mean metrics, as observed in static analyses of Chapter 3. Further, the temporal standard deviation analyses show increased temporal stability of two hierarchy metrics (trophic coherence and mean trophic level) following ayahuasca ingestion among the Santo Daime. The standard deviation of trophic levels, here termed richness of orchestration, showed context-dependent effects in temporal standard deviation, decreasing during rest, but increasing during music listening. The findings of the current chapter point to a consistent ayahuasca-induced shift to a flattened hierarchical configuration, exhibiting stability across time, in part modulated by external stimuli.

4.1 Introduction

The acute effects of classic serotonergic psychedelics such as psilocybin, LSD, and DMT (when ingested in the form of ayahuasca) last several hours and their experiences although heterogenous can be characterised by distinct temporal phases: onset, peak, and comedown. These phases have unique phenomenological features (Brouwer et al., 2025; Riba et al., 2003), and correspond to the drugs' pharmacological profiles (Holze et al., 2024). Researchers have stressed that the psychedelic state is not one that is static or homogenous, instead emphasis has been placed on it being a dynamic process, with participants progressing through different stages across time (Masters and Houston, 2000; Preller and Vollenweider, 2018). Participants often describe sudden insights as being key (McGovern et al., 2025) with distinct events, such as mystical and breakthrough experiences, predicting long-term outcomes (Roseman et al., 2019). Given the dynamic nature of psychedelic experiences, time-averaged exploration of the underlying brain changes is likely to mask potentially meaningful aspects of temporal structure. Several studies have begun to address this gap with dynamic neuroimaging approaches.

4.1.1 Undirected dynamic neuroimaging of the psychedelic state

Many studies have examined the nature of dynamic changes in brain activity under classic serotonergic psychedelics, using a variety of undirected connectivity measures. An early study investigated effects of psilocybin administration on time-resolved BOLD signal variance using a sliding window approach, finding increased variance in the hippocampus and regions of anterior cingulate cortex (Tagliazucchi et al., 2014). Exploration of spectral properties of the signal suggested greater temporal disorganisation, pointing to greater dynamic exploration of states under psychedelics. Later research applied the LEiDA framework (introduced in Chapter 2) to identify recurrent phase-locking states, finding psilocybin administration to increase fractional occupancy of globally coherent phase-locking (PL) states, and temporal variability of global synchronisation patterns compared to placebo (Lord et al., 2019). More recent work applied LEiDA to a clinical dataset of patients with treatment-resistant depression administered psilocybin-assisted therapy, finding fractional occupancy of a globally synchronised state to significantly differentiate between responders' brain activity pre and post treatment, as well as between responders and non-responders following treatment (Vohryzek et al., 2024a). These studies point to dynamic changes in undirected brain activity during the acute psychedelic experience, as well as the potential utility of characterising these changes as markers of treatment response.

Time-specific changes in brain activity have been associated with distinct components of phenomenology during the psychedelic experience. Research examining time-varying effects of psilocybin administration in healthy volunteers observed that state-specific fractional occupancy and dwell time were associated with subjective ratings of drug intensity (Olsen et al., 2022). Similarly, a later study observed an increase in transition probability to a hyperconnected brain state under psilocybin, which was uniquely associated with ratings of oceanic boundlessness and visionary restructuralisation (Mortaheb et al., 2024). This relationship between state dynamics and phenomenology has been reported across classic psychedelics. Pasquini et al. (2025) identified a brain state characterised by hippocampal and medial parietal deactivation occurring immediately following DMT administration. They showed that deactivation of these regions was correlated with changes to sense of time, space, and self-referential processes. Research examining the effects of LSD administration on dynamic integration and segregation shifts found the effects of LSD on brain activity and subjective experience to vary across time (Luppi et al., 2021). They found ego-dissolution to be highly correlated with increased small-world organisation specifically during states of high global integration. These studies provide a more nuanced understanding of psychedelic-induced changes to brain activity and their relationship to subjective experience.

In the case of ayahuasca specifically, limited research has been conducted exploring the effects of the drug on brain dynamics. Alves et al. (2025) compared network-level effects across three timepoints (pre-dose, 2 hours post-dose, and 4 hours post-dose) through EEG, finding time-dependent network reorganisations such as shifts towards more distributed communication pathways. Although not exploring within-scan dynamics, these results point to time-dependent effects of the ayahuasca experience. More recent work used a connectome fingerprinting approach to examine static and dynamic FC patterns among members of the Santo Daime scanned at peak drug effects (Mallaroni et al., 2024). Inter-subject connectivity pattern similarity was higher under ayahuasca compared to baseline. Individual subjects remained identifiable under ayahuasca, but through different connections compared to baseline. Critically, a sliding window analysis showed these changes to be prominent at longer temporal scales. Their work showed not only that ayahuasca ingestion led to a shared functional space across members of the Santo Daime, but also that effects were timescale dependent, highlighting the importance of time-resolved approaches. Importantly, all the studies reviewed in this section relied on undirected connectivity measures.

4.1.2 Time-resolution and hierarchy

Hierarchy within a system is characterised by asymmetric interactions between nodes, which are not characterised through undirected connectivity measures. This asymmetry is fundamental to how information is propagated and processed through the system. Thus characterising information flow asymmetries is key to understanding the brain's functional hierarchy. Previous work applying both undirected coherence and directed Granger causality (GC) measures to MEG data of participants administered LSD, showed reductions in GC and increases in undirected coherence metrics under LSD as compared to placebo (Barnett et al., 2020), outlining the importance of examining directed connectivity specifically. Time-averaged directed connectivity measures applied to psychedelic neuroimaging data, both model-free and model-based, are outlined in Chapter 3. More recently, Shinozuka et al. (2025) applied directed connectivity measures of irreversibility, hierarchical coherence and hierarchical inhomogeneity as well as traditional measures of undirected FC to an MEG dataset of healthy subjects administered LSD or placebo, finding hierarchy metrics based on directed connectivity to perform better than traditional undirected measures at distinguishing between drug conditions. Hierarchy metrics pointed to an LSD-induced flattening of the functional hierarchy, providing evidence for the REBUS hypothesis (Carhart-Harris & Friston, 2019). Further, they applied network recurrence analysis with a one second sliding window to hierarchy metrics, observing a constrained repertoire of hierarchical configurations under LSD.

Model-free directed measures such as those reviewed above, including GC (Barnett et al., 2020) and irreversibility-based hierarchy metrics (Shinozuka et al., 2025), have been effectively applied to the exploration of brain dynamics in MEG and EEG data. However, their application to fMRI is often viewed as contentious due to confounds of the haemodynamic response function as well as low temporal resolution of the data (Seth et al., 2015). Whole-brain modelling, and of particular relevance to the current thesis Hopf oscillatory whole-brain modelling, has been shown to be an effective way of bypassing this issue (Deco et al., 2024; Jerotic et al., 2024a; Vohryzek et al., 2024a). Rather than estimating directionality from the temporal dependencies of the BOLD signal, it derives directed connectivity from oscillatory dynamics constrained by the underlying structural connectivity of the brain. However, it has thus far mainly been applied to entire scans, in a time-averaged manner (as was done in Chapter 3). One study has implemented time-resolution in whole-brain modelling with psychedelics by parameterising the proximity to global bifurcation using a pharmacokinetic equation, showing

transient periods within the DMT state wherein minimal perturbations can result in maximal effects across the brain (Piccinini et al., 2025).

4.1.3 Current study

Whole-brain modelling and trophic coherence measures applied in Chapter 3 showed flattening of the directed functional hierarchy following ayahuasca ingestion from a static (time-averaged) perspective. We showed consistent effects with those previously described under psilocybin (Deco et al., 2024). However, the temporal dynamics of these effects remain unknown. The current chapter introduces a novel methodology to examine state-dependent hierarchical configurations by combining the LEiDA framework and whole-brain modelling (**Figure 4.1**). Specifically, by fitting whole-brain models per LEiDA-derived state, time-resolved directed hierarchy measures are obtained. We extract three hierarchy measures per state per condition: trophic coherence (TC), reflecting how consistently information flows across hierarchical levels; mean trophic level (MeanTL), reflecting average hierarchical position and information flow role across regions; and trophic level standard deviation (termed Richness of Orchestration (RO)), reflecting differentiation of hierarchical roles within the system. Using this new framework, we calculate the temporal mean of each measure to confirm consistency with the findings of the static approach. To directly examine the temporal variability of these measures we compute temporal standard deviation for each. We hypothesise temporal mean measures to coincide with ayahuasca-induced reductions derived from static measures outlined in Chapter 3. Further, based on prior work outlining LSD-induced constraint of the repertoire of hierarchical configurations across time (Shinozuka et al., 2025), we hypothesise reductions in temporal variability of hierarchy measures under ayahuasca. Based on the findings of Chapter 3, as well as the context-independent nature of observed drug effects reported by Shinozuka et al. (2025), we hypothesise consistent drug effects across rest and music conditions.

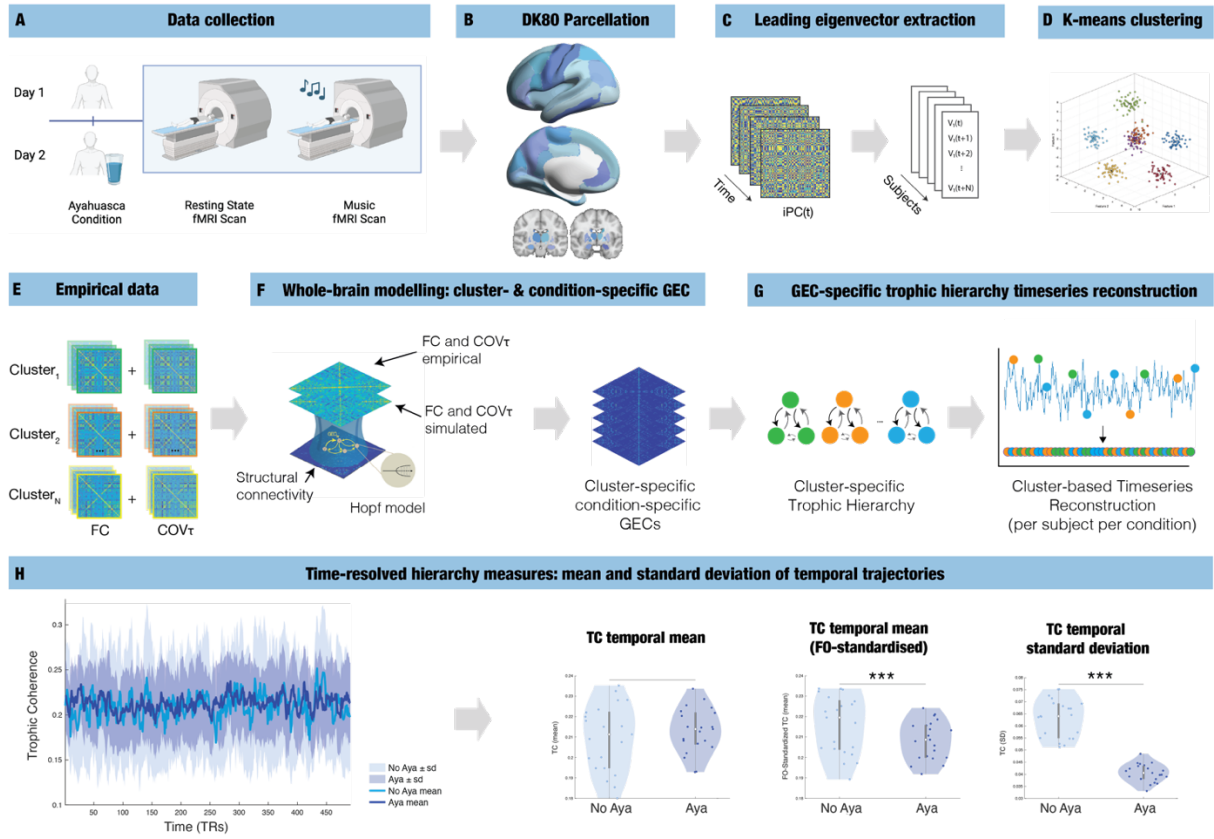


Figure 4.1 Time-resolved hierarchy analysis overview. *A.* the Santo Daime fMRI data at rest and during music listening was used. *B.* The preprocessed data was parcellated using the DK80 parcellation. *C.* Hilbert transform extracted instantaneous phase for each region, and Instantaneous phase coherence (iPC) matrices were derived per timepoint t ; from each $iPC(t)$ the leading eigenvector ($V_1(t)$) was extracted. *D.* $V_1(t)$ across the whole dataset were clustered using a k-means algorithm, through which 7 clusters (PL states) were defined. *E.* For each PL state, in each condition, a functional connectivity (FC) and a time-lagged covariance (COV τ) matrix were calculated, using BOLD data from all volumes assigned to that PL state. *F.* The linearised Hopf model, constrained by structural connectivity, was fitted to the empirical FC and COV τ matrices, resulting in cluster- and condition-specific generative effective connectivity (GEC) matrices, from which cluster- and condition-specific trophic hierarchy measures were computed. *G.* Hierarchy timeseries were constructed by assigning to each volume its corresponding PL state's hierarchy measures, enabling exploration of hierarchy dynamics. *H.* For each hierarchy measure, we computed the temporal mean, FO-standardised temporal mean, and temporal standard deviation.

4.2 Methods

4.2.1 fMRI data preprocessing, denoising & parcellation

fMRI data from 21 members of the Santo Daime Church (at rest and during ceremonial music listening) were used as described in Chapters 3. The data were preprocessed and denoised as outlined in Chapter 1 (sections 1.10.5-1.10.6). The data was parcellated using the DK80 parcellation, as described in Chapter 3. For each parcel the average BOLD signal was linearly detrended, demeaned and band-pass filtered using a 2nd order Butterworth filter (between 0.008 and 0.08 Hz). The first and last five volumes were trimmed to minimise filter edge effects.

4.2.2 Instantaneous phase coherence

The instantaneous phase of each regional BOLD signal was extracted using the Hilbert transform. At each timepoint t , an instantaneous phase coherence matrix (iPC) was computed as

$$iPC_{ij}(t) = \cos(\varphi_i(t) - \varphi_j(t)) \quad (4.1)$$

where $\varphi_i(t)$ denotes the instantaneous phase of region i at time t . This captured the degree of phase alignment between regions, ranging from 1 (perfectly in-phase) to -1 (perfectly anti-phase).

4.2.3 Leading eigenvector extraction

To define the dominant spatial pattern of phase coherence at each timepoint, the leading eigenvector (V_1) of the iPC matrix was extracted, representing each instantaneous whole-brain configuration as a signed 80-element coactivation vector, reducing the dimensionality of the data from $N(N-1)/2$ to N (Alonso Martínez et al., 2020). V_1 captures the primary mode of phase organisation across the brain, with positive and negative elements indicating regions that are in-phase (same sign) and anti-phase (opposite sign) with one another, respectively. To ensure sign consistency across timepoints and subjects, V_1 was sign-flipped such that majority of elements were negative, in line with common implementation of LEiDA (Alonso Martínez et al., 2020; Cahart et al., 2022; Panitz et al., 2025; Vohryzek et al., 2020). V_1 vectors for each volume, subject, and condition were concatenated into a single matrix for subsequent clustering. The complete analysis pipeline is visualised in **Figure 4.1**.

4.2.4 Recurrent phase-locking states

K-means clustering ($k = 7$, 10 replications, max 10,000 iterations) was used to identify recurrent spatial configurations across all volumes in the dataset. The number of clusters was determined using within-cluster Sum of Squares (WCSS) and Mean Silhouette Width, tested across $k = 2$ to 15 clusters. Silhouette analyses pointed to $k=2$ being optimal, and the WCSS Elbow Method suggested $k = 4$, as the result exhibited a steep drop between $k=2$ and $k=4$, after which the curve flattened out (**Supplementary Figure S4.1**). Low k values such as 2 and 4 capture major state separations, however they do not provide enough granularity to explore dynamic shifts. Therefore, we ran a further stability test, calculating standard deviation in silhouette scores across 10 iterations for each k between 5 and 10, finding $k=7$ to be the highest k maintaining high stability (silhouette mean $\pm$ SD: 0.1126 ± 0.0001) (**Supplementary Table S4.1**). Seven clusters were derived, hereafter referred to as phase-locking (PL) states, representing recurrent spatial configurations of whole-brain phase coherence. Minimum Euclidean distance was used to assign each timepoint to its nearest centroid, enabling PL state-based reconstruction of subject- and condition-specific timeseries.

4.2.5 Phase-locking state dynamics

The spatial profile of each of the seven PL states was characterised by comparing them with the seven canonical RSNs (Yeo et al., 2011). Every region's contribution to an RSN was defined by the proportion of overlap it had with the given network's parcellation. Each PL state's RSN profile was thus computed as the weighted average of regional phase degrees.

Given that subsequent time-resolved hierarchy measures depend on PL state fractional occupancy (FO), an initial examination of PL state dynamics was conducted. The FO and lifetimes of each PL state in each condition were computed. FO is the proportion of timepoints corresponding to each PL state across the duration of a single subject's scan per condition. Lifetime is the average number of consecutive timepoints a PL state occupied during a subject's scan per condition. Statistical comparisons were made between drug and no drug conditions (at rest and during music listening) using Wilcoxon signed-rank non-parametric paired tests. Benjamin-Hochberg False Discovery Rate (FDR) correction was applied accounting for seven comparisons (reflecting the seven PL states).

4.2.6 State-specific functional connectivity and time-lagged covariance

BOLD volumes whose V_1 was assigned to each PL state were extracted, creating PL state-specific timeseries for each condition, pooled across subjects to provide sufficient timepoints per PL state for FC and COV_τ estimation. From these, static FC (normalised by regional standard deviation) and COV_τ matrices ($\tau = 2$ TRs, normalised by regional standard deviation) were computed for each PL state within each condition.

4.2.7 Cluster-specific whole-brain Hopf modelling & trophic measure calculation

The condition- and PL state-specific FC and COV_τ matrices together with the high-resolution structural connectivity matrix described in Chapter 3, were used to iteratively fit the linearised Hopf whole-brain model. The same group-level fitting methodology as described in Chapter 3 was applied. In brief, starting from structural connectivity (normalised to maximum 0.2, and renormalised after each iteration), effective connectivity was iteratively updated through a pseudo-gradient descent algorithm over 5,000 iterations, or until the relative change in combined mean squared error fell below 0.0001. Learning rates were set at $\epsilon_{\text{FC}} = 0.0004$ and $\epsilon_{\text{COV}_\tau} = 0.005$, intrinsic noise was set at $\sigma = 0.01$, and the bifurcation parameter was $\alpha = -0.02$, reflecting a subcritical regime. Model fit was assessed using Pearson correlations between empirical and simulated FC and COV_τ matrices (**Supplementary Table S4.5**). The main modification to the fitting methodology was that the COV_τ learning rate was set to $\epsilon_{\text{COV}_\tau} = 0.005$ (compared to 0.0001 in Chapter 3). Testing across all clusters and conditions showed improved COV_τ fits (mean $r = 0.83$ ($\epsilon_{\text{COV}_\tau} = 0.005$) compared to mean $r = 0.77$ ($\epsilon_{\text{COV}_\tau} = 0.0001$), with marginal improvements in FC fit as well (mean $r = 0.85$ ($\epsilon_{\text{COV}_\tau} = 0.005$) compared to mean $r = 0.83$ ($\epsilon_{\text{COV}_\tau} = 0.0001$)).

This modelling procedure yielded a generative effective connectivity matrix (GEC) for each PL state within each condition. For each PL state in each condition, a 1×80 TL vector and a TC score were computed from the fitted GEC using the same procedures as described in Chapter 3.

4.2.8 Time-resolved hierarchy reconstruction

Hierarchy timeseries were reconstructed for each subject, enabling exploration of time-resolved changes in hierarchical configuration. For each volume, the PL state assignment (determined by minimum Euclidean distance to cluster centroids) was used to retrieve the corre-

sponding condition- and PL state-specific TL vector and TC score. This yielded, for each subject in each condition, a $N \times t$ matrix of TLs (where $N = 80$ regions, and t denotes time), and a $1 \times t$ vector of TC scores.

4.2.9 Dynamic hierarchy measures

For each PL state in each condition, three hierarchy measures were computed from the GEC: TC, mean TL across regions (here termed MeanTL), and standard deviation (SD) of TLs across regions (here termed Richness of Orchestration (RO)). These per-state values are group-level, derived from the condition- and state-specific GEC. Subject-level variability is derived from individual differences in PL state occupancy, taken from each subject's reconstructed timeseries. Using these reconstructed timeseries, for each measure, we compute the subject-specific temporal mean, or the mean across timepoints; and temporal SD, or the SD across timepoints.

4.2.10 Statistical considerations

For each metric contexts (rest and music) were examined independently. Drug conditions (no ayahuasca and ayahuasca) were statistically compared using Wilcoxon signed-rank tests. In the case of TC, within-context FDR correction was conducted accounting for two comparisons (temporal mean and standard deviation). MeanTL, and RO are statistically related measures, derived from the same TL vectors, providing two perspectives on the same distribution. To account for this interdependence, FDR correction was conducted accounting for four comparisons within each context (temporal mean and SD, as well as the two TL measures of MeanTL and RO).

4.2.11 FO-standardisation sensitivity analysis

For each subject, the temporal mean of each measure was determined by the FO of PL states, in the case of TC for example temporal mean TC is equivalent to:

$$\text{Mean TC} = \sum_{k=1}^K \text{FO}_k \times \text{TC}_k \quad (4.2)$$

Where $K = 7$, denotes the number of PL states, and FO_k and TC_k are the fractional occupancy and TC score of PL state k , respectively. Therefore, to ensure the observed effects were not FO-dependent, a sensitivity analysis was run whereby the condition specific FO for each PL state was replaced with the average FO across conditions $((FO_{NoAya} + FO_{Aya})/2)$. If both were significant, the observed effect was validated as a within-state effect. If the primary analysis was non-significant but the sensitivity analysis was significant, the effect was characterised as masked by differences in FO across conditions. If the primary analysis showed a significant difference, while the sensitivity analysis did not, this was understood as an FO-driven effect. Wilcoxon signed-rank tests were used to compare across drug conditions, as was done for primary analyses. No FDR correction was done for the sensitivity tests, as these were conducted to characterise the nature of effects observed in the primary analysis, rather than to test independent hypotheses.

This sensitivity analysis was applied to temporal means only. In the case of temporal SD, between-subject variability is entirely dependent on FO differences, and therefore FO standardisation was not applied to this measure.

4.3 Results

4.3.1 Characterisation of PL states

Seven distinct PL states were derived using k-means clustering. To gain a better understanding of these spatial configurations their correlation with the seven canonical RSNs was examined (Yeo et al., 2011). Correlation strength interpretation was based on Cohen's (1988) guidelines (large effect: $|r| \geq 0.50$; medium effect: $0.30 \leq |r| < 0.50$; small effect: $0.10 \leq |r| < 0.30$; negligible effect: $|r| < 0.10$). The resulting correlation profiles revealed distinct network signatures for each state (**Figure 4.2B**). Due to the nature of sign ambiguity of eigenvectors (V and $-V$ being equivalent), the absolute value of correlations $|r|$ reflects the strength of the spatial relationships, while the sign indicates the phase relationship. Therefore in-phase and anti-phase are relative separations between networks rather than activation vs suppression. Further, these spatial correlations are descriptive, conducted to better understand the PL states derived from the data.

Only correlations meeting the medium effect-size qualification are reported in text. A full table of correlations between each PL State and each RSN is provided in **Supplementary Table S4.2**. State 1 exhibited a strong positive correlation with the DMN ($r = 0.65$) and medium negative correlation with the SMN ($r = -0.34$), suggesting a clear separation between the two. State 2 showed strong positive correlation with SMN ($r = 0.50$), a medium positive correlation with VAN ($r = 0.40$), as well as a strong negative correlation with the DMN ($r = -0.50$). This profile indicates State 2 is characterised by coherence between sensorimotor and attention systems, as well as a clear representation and separation of the DMN. State 3 presented a medium, bordering-on-large, positive correlation with the FPN ($r = 0.49$) and a medium negative correlation with SMN ($r = -0.33$), representing areas related to higher-level processing and a clear separation between these and the SMN. State 4 demonstrated low medium correlations with the limbic network ($r = 0.36$) and FPN ($r = 0.32$). All other networks showed negligible or small correlations. Compared to all other states which showed large correlation effects for at least one network, State 4 correlations suggest a more globally integrated state. This is visible in the brain rendering of State 4 phase coherence (**Figure 4.2A**). State 5 showed a large positive correlation with VAN ($r = 0.62$) and a large negative correlation with the Visual network ($r = -0.59$). State 6 was characterised by a strong correlation with the Visual network ($r = 0.70$), as well as a strong negative correlation with VAN ($r = -0.56$), and medium negative correlation with FPN ($r = -0.33$). State 7 exhibited a strong positive correlation with the Visual network (r

= 0.67), and a large negative correlation with the DMN ($r = -0.56$), as well as medium negative correlation with FPN ($r = -0.42$).

Examination of maximum absolute correlations ($\max |r|$) showed varying degrees of network specificity across PL states. States 1, 5, 6, and 7 showed high network specificity ($\max |r|$ range: 0.62-0.71), indicating a strong association with a canonical network. States 2 ($\max |r| = 0.50$) and 3 ($\max |r| = 0.50$) exhibited moderate specificity, as their strongest correlation bordered a large effect size. State 4 showed the lowest network specificity, with its highest correlation ($\max |r| = 0.36$) showing a lower medium effect size.

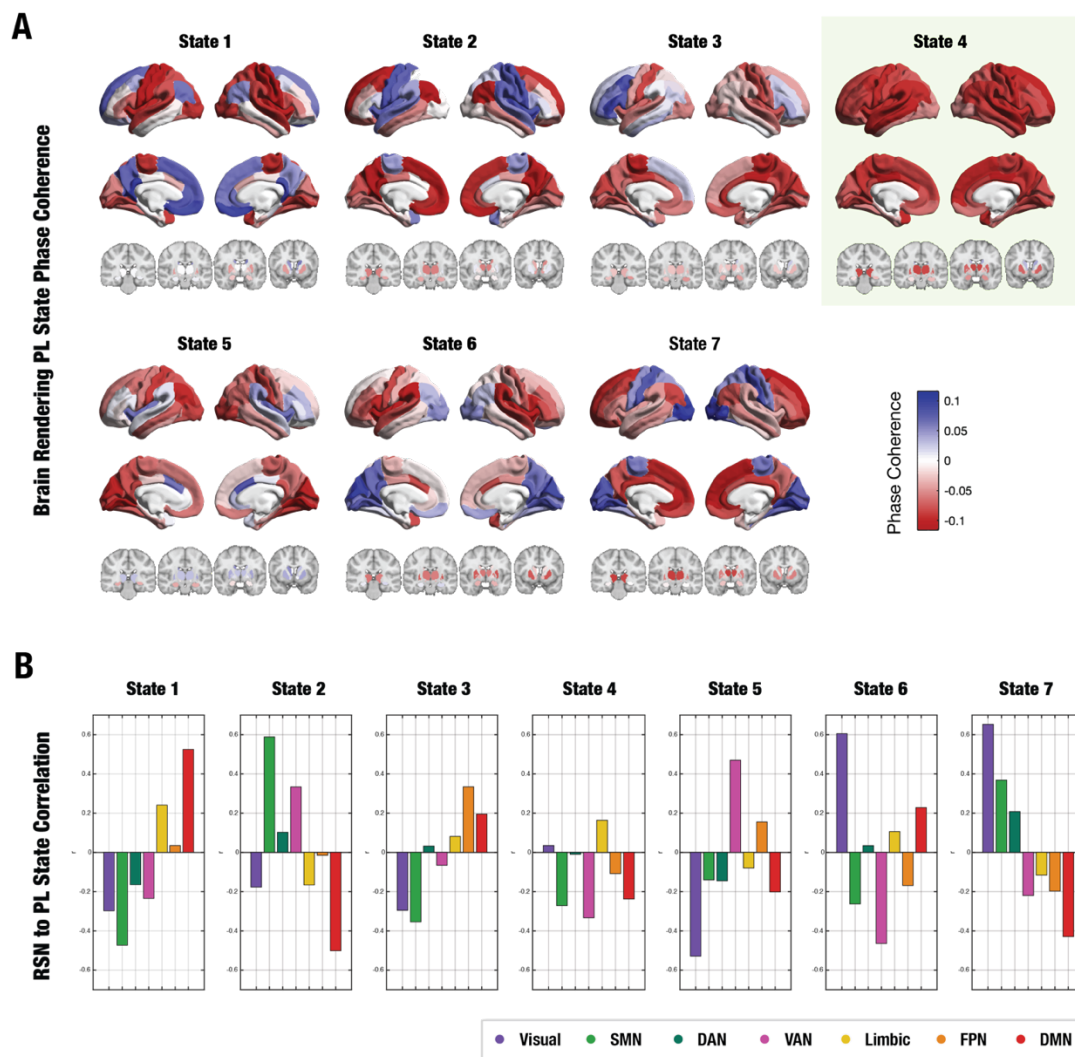


Figure 4.2 PL State 4 depicts a globally coherent state, where all regions are in-phase. **A.** Cortical and subcortical spatial rendering of phase coherence of each PL state. Blue denotes regions which are in-phase with one another, red denotes regions which are anti-phase with blue regions, but in-phase with one another. State 4 specifically denotes a synchronised in-phase state. **B.** RSN-based characterisation profile for each PL state. Spatial correlation between each state's centroid and each of seven weighted RSNs: Visual; Somatomotor (SMN); Dorsal Attention (DAN); Ventral Attention (VAN); Limbic; Frontoparietal (FPN); and Default Mode (DMN). Positive correlations ($r > 0$) denote regions which belong to that RSN having positive eigenvector values in the corresponding PL state; negative correlations ($r < 0$) outline negative eigenvector values. Regions with the same sign are in-phase with each other, while those with opposite signs are anti-phase with one another.

4.3.2 PL state fractional occupancy and lifetimes

Differences in FO and lifetimes between drug conditions were compared for each of the seven PL states using Wilcoxon signed-rank tests with FDR multiple comparison correction. Following ayahuasca ingestion at rest, a significant increase in mean lifetime of State 4, the globally integrated state, was observed ($W = 21$, $Z = -2.98$, $r = -0.65$, $p = 0.003$, $q = 0.020$) (**Figure 4.3**). State 7 showed an increase in lifetimes at rest, that was significant only prior to FDR correction ($W = 47$, $Z = -2.38$, $r = -0.52$, $p = 0.017$, $q = 0.060$). Fractional occupancy of two states showed effects that were only significant prior to FDR correction: State 4 ($W = 33.5$, $Z = -2.67$, $r = -0.58$, $p = 0.008$, $q = 0.053$) and State 2 ($W = 178$, $Z = 2.17$, $r = 0.47$, $p = 0.030$, $q = 0.104$). All non-significant comparisons are reported in **Supplementary Tables S4.3 and S4.4**.

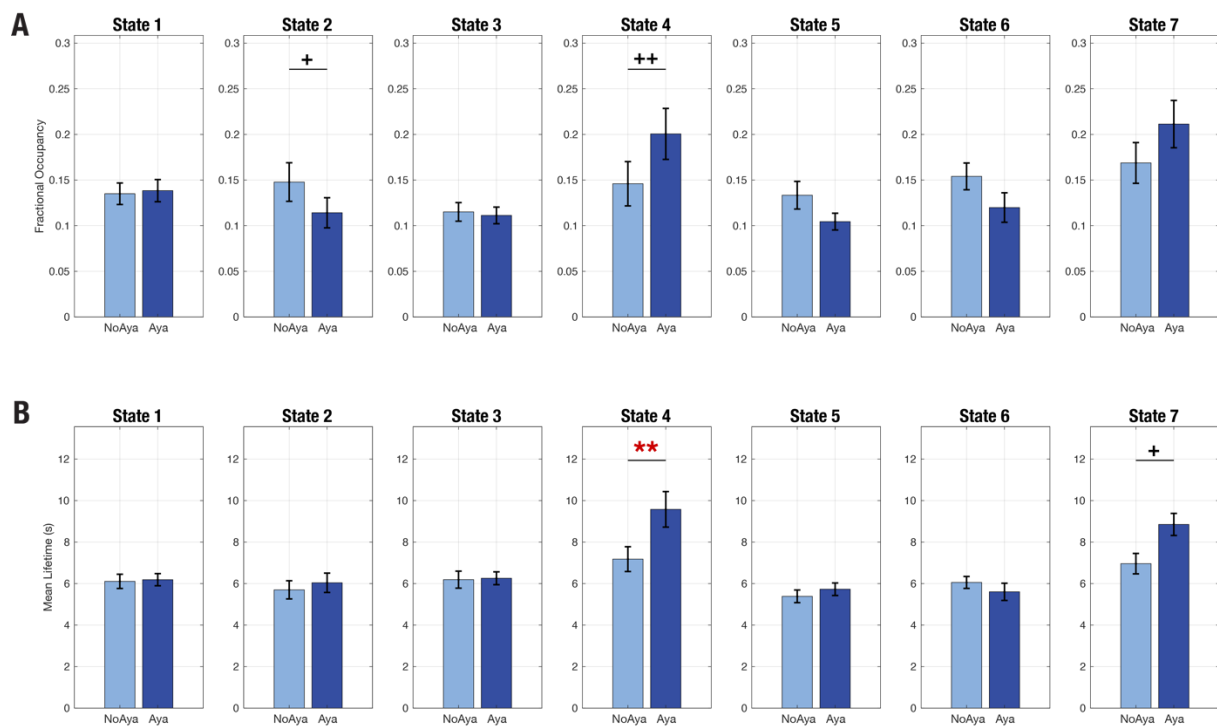


Figure 4.3 State 4 shows significantly higher mean lifetimes following ayahuasca ingestion at rest. **A.** Fractional Occupancy and **B.** Mean Lifetime changes following ayahuasca ingestion within resting state scans. Comparisons conducted using Wilcoxon signed-rank non-parametric paired samples test. Light blue: no ayahuasca; dark blue: ayahuasca. Red significance stars denote significance following FDR multiple comparison correction accounting for seven comparisons. Black significance stars denote significance prior to FDR multiple comparison correction. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

The same comparisons were conducted within the music listening context, where no significant differences in FO or lifetimes were observed between drug conditions for any of the seven PL states (**Figure 4.4**). All statistical comparisons are reported in **Supplementary Tables S4.3 and S4.4**.

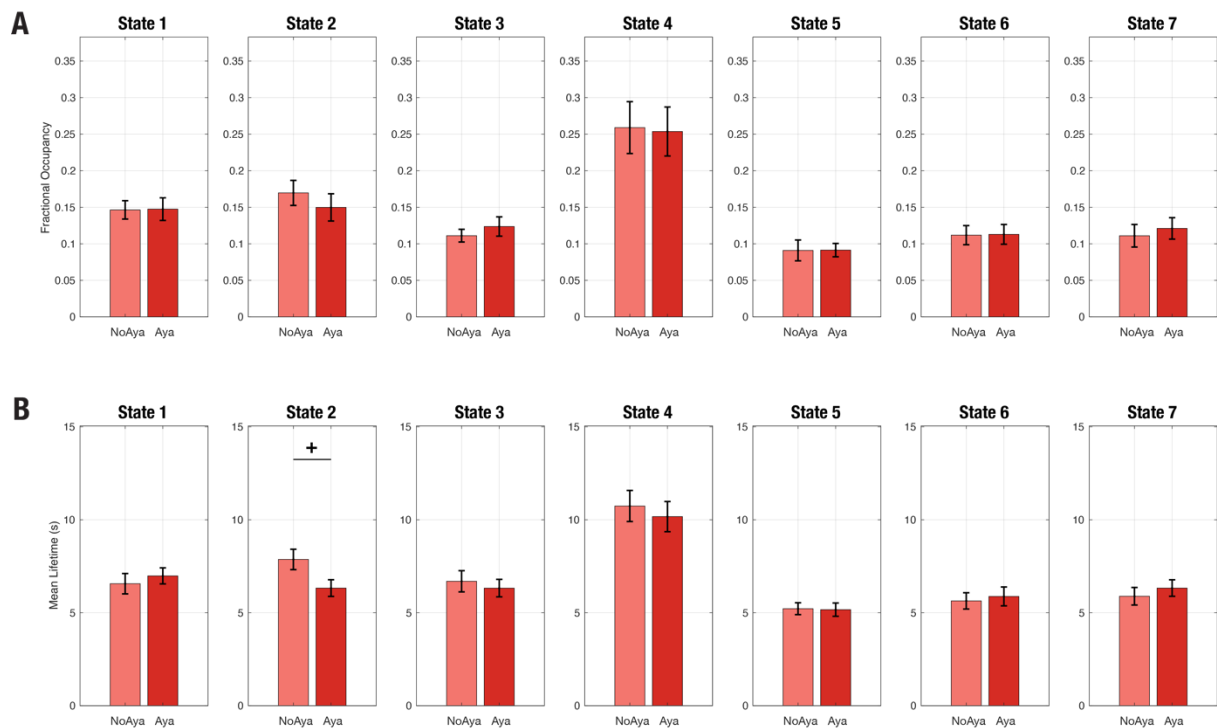


Figure 4.4 No significant changes in PL state fractional occupancy or lifetimes following ayahuasca ingestion during music listening. **A.** Fractional Occupancy and **B.** Mean Lifetime changes following ayahuasca ingestion within music listening scans. Comparisons conducted using Wilcoxon signed-rank non-parametric paired samples test. Light red: no ayahuasca; dark red: ayahuasca. Red significance stars denote significance following FDR multiple comparison correction accounting for seven comparisons. Black significance stars denote significance prior to FDR multiple comparison correction. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

4.3.3 Whole-brain model fitting

Having characterised PL state dynamics, the next step was to examine whether the same spatial configurations exhibited distinct drug-induced hierarchical metric changes. Therefore, for each cluster in each condition a Hopf whole-brain model was fit to the corresponding data achieving high fits across all conditions (FC: mean $r = 0.84$; COV τ : mean $r = 0.83$; see **Supplementary Table S4.5** for cluster- and condition-specific fit values).

4.3.4 Ayahuasca-induced reductions in average TC and TC variability

Temporal mean and SD of TC were compared between no ayahuasca and ayahuasca conditions using Wilcoxon signed-rank tests.

At rest, no significant difference in average TC was observed ($W = 77.0$, $Z = -1.34$, $r = 0.29$, $p = 0.181$, $q = 0.181$) (**Figure 4.5A**). The corresponding FO-standardised sensitivity analysis

showed a significant ayahuasca-induced reduction in temporal mean TC ($W = 22.0$, $Z = 3.67$, $r = 0.80$, $p < .001$). The discrepancy between the raw and FO-normalised outcomes suggests that the observed FO differences (**Figure 4.5A**) mask underlying within-state TC reductions following ayahuasca consumption at rest. Further, the TC temporal SD comparison showed a significant reduction in TC variability at rest ($W = 231.0$, $Z = 4.01$, $r = 0.88$, $p < 0.001$; $q < 0.001$).

In the context of music listening ayahuasca ingestion resulted in a significant reduction in temporal mean TC ($W = 221.0$, $Z = 3.67$, $r = 0.80$, $p < .001$, $q < .001$) (**Figure 4.5B**). This effect was further supported by consistent effects observed in the FO-normalised sensitivity analysis ($W = 231.0$, $Z = 4.02$, $r = 0.88$, $p < .001$), validating this as a within-state effect. Finally, TC temporal SD was found to significantly decrease following ayahuasca ingestion in the music listening condition ($W = 227$, $Z = 3.88$, $r = 0.85$, $p < .001$, $q < .001$).

These results point to ayahuasca ingestion among the Santo Daime resulting in a less hierarchical (lower temporal mean TC) and more stable (lower temporal SD of TC) functional hierarchy across resting state and music listening contexts.

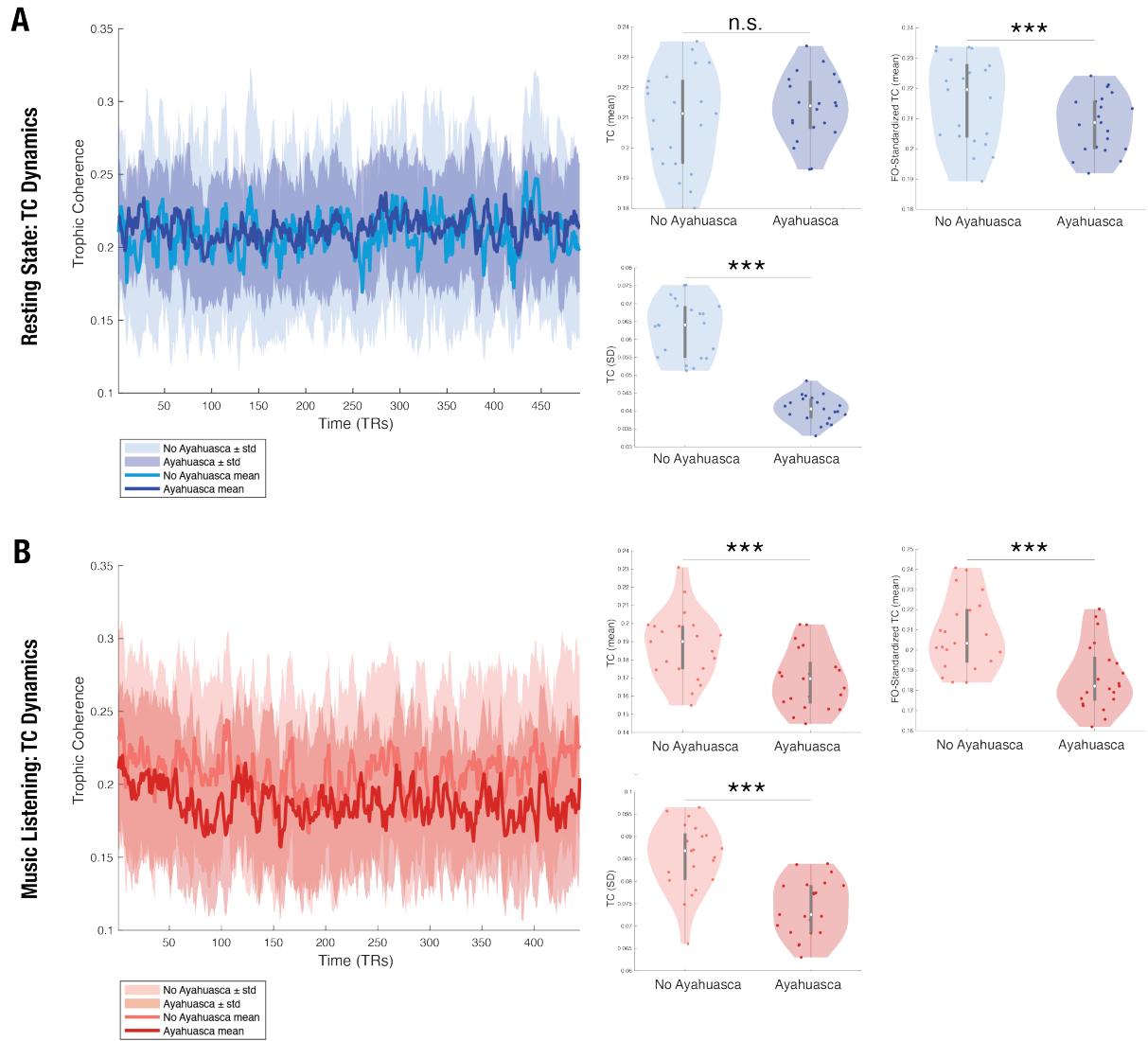


Figure 4.5 Reductions in TC temporal mean and SD following ayahuasca at rest and during music listening. TC temporal mean and standard deviation before and after ayahuasca consumption. Violin plots denote significance of change in TC mean, FO-standardised TC mean, and TC standard deviation across time following ayahuasca ingestion. **A.** Resting State Eyes Open (no ayahuasca: light blue; ayahuasca: dark blue) **B.** Music Listening Eyes Closed (no ayahuasca light red; ayahuasca: dark red). Significance presented following FDR correction accounting for two comparisons (mean and SD) within each context. FO-standardised mean sensitivity analysis is reported without FDR correction.

4.3.5 Context-independent shift towards lower and more stable average TL

Temporal mean MeanTL was significantly reduced following ayahuasca ingestion both during rest and music listening contexts (**Figure 4.6**). The corresponding FO-standardised sensitivity analyses confirmed these within-state effects across both contexts. The temporal SD of MeanTL also exhibited ayahuasca-induced significant reductions across contexts. All Wilcoxon signed-rank comparisons resulted in the maximum test statistics for 21 subjects ($W = 231$, $Z = 4.02$, $r = 0.88$, $p < .001$, $q < .001$), with all subjects showing ayahuasca-induced reductions across measures. These results were confirmed through FO-standardised temporal mean analyses ($W = 231$, $Z = 4.02$, $r = 0.88$, $p < .001$). These effects are strong and their consistency is made clear when examining per-cluster MeanTL values derived from the group-level whole-brain modelling, used to compute temporal mean and SD. Consistently lower MeanTL was observed across PL states in the post ayahuasca condition at rest (**Supplementary Table S4.7**). During music listening five of seven PL states showed lower MeanTL under ayahuasca, with the remaining two states exhibiting increases of small magnitude. The reductions in MeanTL following ayahuasca ingestion are the most robust within-state effects observed, with the reduction in MeanTL observed across brain states, contexts, and subjects. This pattern persisted across both FO-dependent and FO-standardised computations of temporal mean.

These results cumulatively suggest that ayahuasca ingestion leads to a context-independent global shift towards source-like behaviour across regions, and that this hierarchical configuration is more temporally stable under ayahuasca.

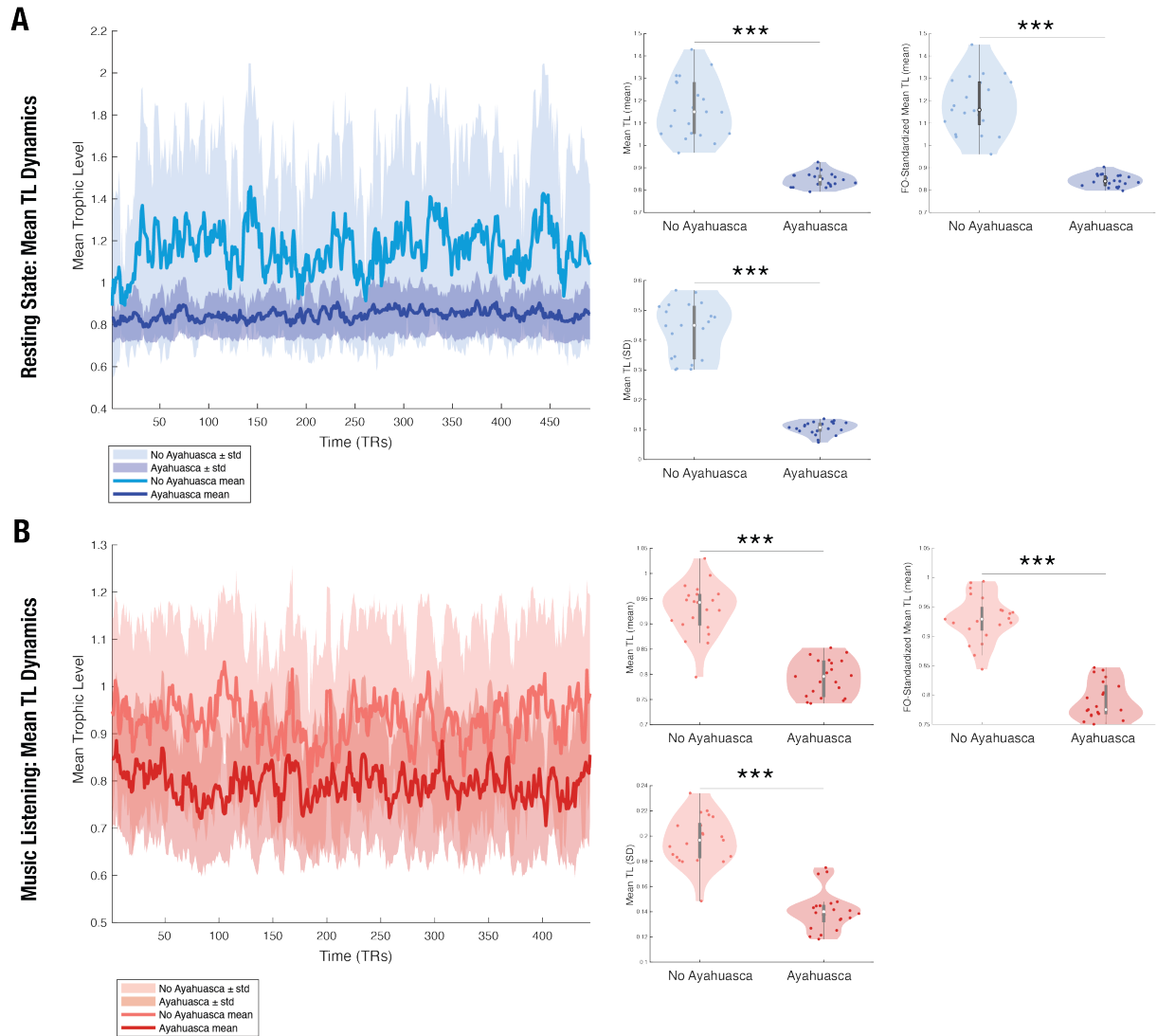


Figure 4.6 Robust context-independent reduction in MeanTL temporal mean and SD following ayahuasca ingestion. MeanTL temporal mean and standard deviation before and after ayahuasca consumption. Violin plots denote significance of change in MeanTL mean, FO-standardised MeanTL mean, and MeanTL standard deviation across time following ayahuasca ingestion. **A.** Resting State Eyes Open (no ayahuasca: light blue; ayahuasca: dark blue) **B.** Music Listening Eyes Closed (no ayahuasca: light red; ayahuasca: dark red). Significance presented following FDR correction (accounting for four comparisons within each context: temporal mean and temporal SD for both MeanTL and RO as these are mathematically interdependent). FO-standardised mean sensitivity analysis is reported without FDR correction.

4.3.6 Reduction in average RO with context-dependent effects on temporal stability

At rest, no significant reduction in temporal mean RO ($W = 136$, $Z = 0.71$, $r = 0.16$, $p = 0.476$, $q = 0.476$) (**Figure 4.7A**) was observed. However, the FO-standardised sensitivity analysis showed a significant reduction following ayahuasca ingestion ($W = 213$, $Z = 3.39$, $r = 0.74$, $p < .001$), suggesting that FO differences between conditions masked an underlying within-state reduction in RO (PL state-specific RO values are reported in **Supplementary Table S4.8**). Further, a significant reduction in temporal SD of RO ($W = 231$, $Z = 4.02$, $r = 0.88$, $p < .001$, $q < .001$) was observed, suggesting greater stability in dispersion of regional roles across time following ayahuasca ingestion.

During music listening (**Figure 4.7B**) results showed a significant reduction in temporal mean RO following ayahuasca ingestion ($W = 227$, $Z = 3.88$, $r = 0.85$, $p < .001$, $q < .001$), which was replicated through sensitivity analysis ($W = 231$, $Z = 4.02$, $r = 0.88$, $p < .001$). Further, the temporal SD of RO significantly increased under ayahuasca ($W = 55$, $Z = -2.10$, $r = 0.46$, $p = 0.036$, $q = 0.036$), suggesting more dynamic shifts in dispersion of information flow roles across the brain throughout the duration of the scan. In contrast to all other temporal SD measures, which outlined a context-independent reduction following ayahuasca ingestion, an increase in temporal RO is noted specifically within the music listening scan, suggesting a context-dependent drug effect on stability of hierarchical role dispersion.

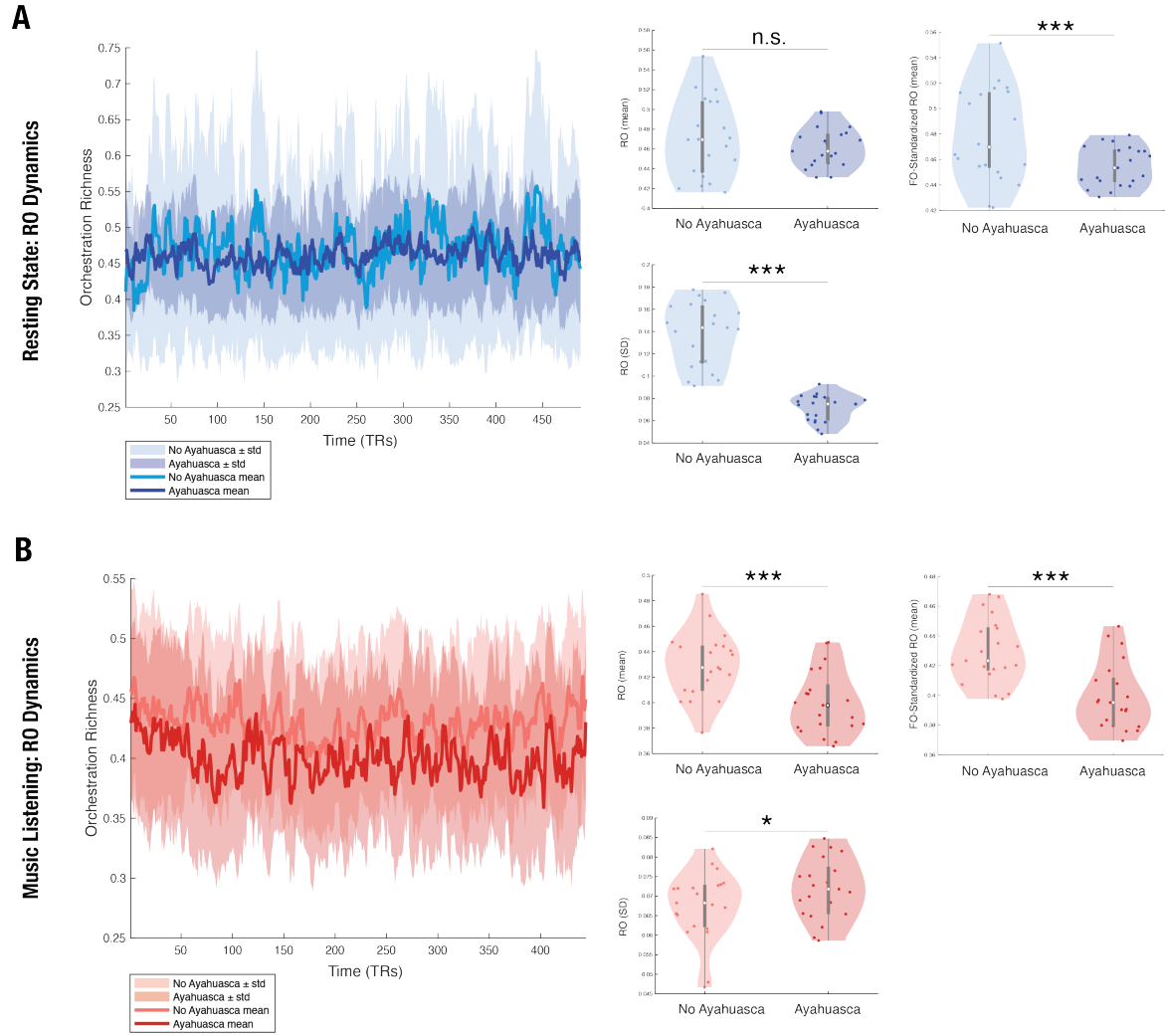


Figure 4.7 Context-dependent ayahuasca-induced effects on RO temporal stability. RO temporal mean and standard deviation before and after ayahuasca consumption. Violin plots denote significance of change in RO mean, FO-standardised RO mean, and RO standard deviation across time following ayahuasca ingestion. **A.** Resting State Eyes Open (no ayahuasca: light blue; ayahuasca: dark blue) **B.** Music Listening Eyes Closed (no ayahuasca: light red; ayahuasca: dark red). Significance presented following FDR correction (accounting for four comparisons within each context: temporal mean and temporal SD for both RO and MeanTL as these are mathematically interdependent). FO-standardised mean sensitivity analysis is reported without FDR correction.

4.4 Discussion

The current chapter introduced a novel framework combining LEiDA, whole-brain modelling, and trophic measures to quantify dynamic shifts in hierarchical organisation following ayahuasca ingestion among the Santo Daime both at rest with eyes open and during ritual-relevant music listening with eyes closed. LEiDA identified seven recurrent PL states across the dataset. These were characterised by unique spatial signatures, as seen through distinct correlation profiles with the seven canonical RSN networks (Yeo et al., 2011). State 4, specifically, was identified as a globally coherent state, and was the only state observed to have significantly longer lifetimes following ayahuasca ingestion at rest. No other states showed significant drug-induced differences in lifetimes or FO at rest, and no comparisons were significant during music listening. Based purely on undirected-connectivity examination, results would suggest a change in dynamics following ayahuasca ingestion at rest, but not during ritual-relevant music listening. Temporal mean of TC, MeanTL and RO showed significant ayahuasca-induced context-independent reductions, either directly or following FO-standardisation. These findings were accompanied by significant reductions in temporal SD of TC and MeanTL across contexts. Notably, the temporal SD of RO showed context dependence, with a significant ayahuasca-induced reduction during rest, and increase during music listening.

State 4, characterised as a globally coherent state with low network specificity, showed a significant ayahuasca-induced increase in lifetimes at rest, as well as an increase in FO that did not survive multiple comparison correction. These findings align with prior literature showing enhanced global integration under psychedelics (Dai et al., 2024; Daws et al., 2022; Luppi et al., 2021), enhanced global harmonic power (Atasoy et al., 2018b, 2017), and increased occupancy of globally coherent states (Lord et al., 2019; Mortaheb et al., 2024; Olsen et al., 2022). This effect was not observed during music listening. Supplementary analyses showed that State 4 FO and lifetimes in the no ayahuasca resting state condition were significantly lower than all other conditions, with both music conditions showing on average higher FO and lifetimes than the ayahuasca present resting state condition as well (**Supplementary Figures S4.3 and S4.4**). This suggests that music may already promote increased global coherence at a level comparable to that induced by ayahuasca. However, as rest and music conditions differed in eye state, it is not possible to determine whether these differences were driven by music presence, eye state, or a combination of the two.

Our findings broadly align with previous studies, contributing to a growing body of evidence for psychedelics disrupting the functional hierarchy. The REBUS model, through a predictive

coding framework, suggested that psychedelics reduce precision weightings of high-level priors (Carhart-Harris and Friston, 2019). Empirical studies have provided results in support of such effects. Gradient mapping techniques have outlined a principal gradient of functional connectivity separating unimodal and transmodal cortices (Haak and Beckmann, 2020; Huntenburg et al., 2018; Margulies et al., 2016), and LSD and psilocybin have been found to compress this gradient (Girn et al., 2022). From a network control theory perspective, these effects were supported by observations suggesting LSD and psilocybin reduce the control energy required for brain state transitions (Singleton et al., 2022). More recently, thermodynamic-based measures of temporal asymmetry extracted from fMRI BOLD timeseries showed that psilocybin, LSD, and DMT all lower temporal asymmetry, suggesting a reduction or collapse of directed functional hierarchy (Vohryzek et al., 2024c). Our results showed robust reductions in temporal means of TC, MeanTL and RO following ayahuasca ingestion during music listening, as well as aligned effects at rest following FO-standardisation. These findings are largely consistent with the literature and with the static results of Chapter 3, pointing to a flattening or compression of the functional hierarchy. Our approach derived dynamic hierarchy metrics from directed networks constrained by the structural connectome, providing structurally grounded evidence that ayahuasca disrupts the hierarchical organisation of brain dynamics.

Using the current time-resolved approach significant reductions in temporal mean TC, MeanTL and RO were observed, either directly or following FO-standardisation. Importantly, due to the nature of the timeseries reconstruction, time-averaged outcomes were dependent on PL state FO. Initial PL state FO analyses showed significant differences in FO of States 2 and 4 prior to multiple comparison correction during rest. Therefore, FO-standardised sensitivity analyses accompanied each temporal mean comparison to disentangle FO-based contributions from within-state changes. During music listening robust ayahuasca-induced reductions in temporal mean TC, MeanTL and RO were observed, and further supported by concurrent findings in the sensitivity analyses. Specifically, we observed a shift towards a more hierarchically disorganised regime, a movement of central tendency of information-flow roles towards more source-like activity on average, as well as a compression of information-flow role dispersion across the system. During eyes open resting state a significant reduction in temporal mean MeanTL was observed, aligning with drug effects during eyes closed ceremonial music listening. Importantly, initial comparison across drug states showed no significant change in temporal mean TC or RO following ayahuasca ingestion. However, FO-standardised sensitivity analyses showed significant reductions across both metrics, showing that ayahuasca ingestion at rest lowered hierarchical coherence and compressed information-flow roles when controlling

for state occupancy differences. Resting state results point to within-state reductions across measures, with FO-based attenuation observed for two of the three measures. This may be due to eyes open conditions being reported to exhibit smaller psychedelic-induced effects on brain activity as compared to eyes closed (Mediano et al., 2024), due to the importance of music within the Santo Daime ayahuasca ceremony (Aldridge and Fachner, 2006; Labate et al., 2017b), or more broadly due to external stimuli playing a significant moderating role in how hierarchy is expressed dynamically (Kringelbach et al., 2023). However, these context-dependent effects need to be more systematically explored in future datasets specifically looking at eye state and music presence within the psychedelic context separately.

To assess temporal stability of changes in hierarchical coherence and information flow, the temporal SD of each hierarchy measure was calculated. Across contexts we observed a reduction in SD of TC and mean TL following ayahuasca ingestion. This suggests that the brain, although entering more hierarchically flattened information flow configurations, exhibits higher temporal stability, rather than dynamically oscillating between distinct hierarchical configurations. At first glance, these results may seem to sit in contradiction with prior research using undirected measures which pointed to psychedelics leading to a wider repertoire of connectivity states (Atasoy et al., 2018b, 2017; Lord et al., 2019; Tagliazucchi et al., 2014). However, this may outline a key distinction between the effects of psychedelic administration on dynamics of undirected and directed connectivity. Namely, the brain dynamically shifts between a wider array of spatial patterns, while maintaining a more stable less hierarchical directed information transfer regime. Prior work has outlined the differential effects of psychedelics on directed and undirected connectivity outcomes (Barnett et al., 2020). Furthermore, our findings align with existing literature examining temporal irreversibility in MEG data under LSD which showed not only lower irreversibility in LSD state compared to placebo, but also a higher recurrence rate of observed irreversibility states, suggesting the hierarchical structure to be more temporally constrained under LSD as compared to placebo (Shinozuka et al., 2025). More recent work examined changes in temporal asymmetry in fMRI BOLD data, showing psilocybin, LSD, and DMT administration to not only lead to significant reductions in temporal asymmetry or irreversibility, but also a contraction of observed patterns of temporal asymmetry variation across time (Vohryzek et al., 2024c).

Notably, when looking at temporal stability of RO, we observed a reduction in standard deviation across time following ayahuasca ingestion at rest, and an increase during music listening. Such findings point to context-dependent effects of ayahuasca ingestion on temporal

stability of regional information flow dispersion. This may be due to music providing a temporal structure that interacts with ayahuasca's effects on hierarchical role differentiation, in a manner distinct from that at rest. However, within the current dataset, it is not possible to distinguish whether this is due to eye state or music presence.

The analyses presented in the current chapter are a novel approach to characterising time-resolved biologically grounded changes in directed information transfer and hierarchical configuration as derived through a combination of LEiDA, whole-brain modelling and trophic analysis. Each PL-state's condition-specific timeseries was fit to a Hopf whole-brain model which correlated to the observed data's FC and COV τ well. The high fit can in part be explained by the nature of k-means clustering, grouping similar activity patterns together. However, important limitations need to be acknowledged. This methodology relies on a subset of seven PL states derived from k-means clustering of the whole dataset, with trophic coherence measures extracted from the GEC modelled using condition- and PL state-specific FC and time-lagged covariance computed from the fMRI volumes assigned to each PL state. Thus, individual differences in hierarchy measures are estimated from group-level hierarchy metrics, and are PL-state occupancy dependent. The FO-standardisation sensitivity analysis addresses this, but does not fully resolve it. Future work should look to conduct subject-specific dynamic whole-brain modelling, and trophic measure extraction, enabling examination of subject-specific changes in such dynamics. However, computing dynamic directed connectivity measures remains a methodological challenge in the field, particularly when analysing fMRI data, where common model-free approaches such as Granger causality face well-established limitations (Seth et al., 2015). Further, although our approach addresses the inference-based limitations of applying existing methods such as Granger causality to fMRI, the low temporal resolution of the data remains an issue in capturing potential dynamical shifts in hierarchical configuration. Higher temporal resolution neuroimaging such as MEG, combined with methodological developments, may enable more precise subject-specific exploration of such dynamics. Coupled oscillator models have been applied to MEG data (Cabral et al., 2014; Deco et al., 2017a), and model-free directed measures have shown time lags below the temporal resolution of fMRI to be key in characterising differences between psychedelic states and placebo (Shinozuka et al., 2025).

In conclusion, the current chapter presents a novel approach to exploration of ayahuasca-induced dynamic hierarchy changes across contexts, through the incorporation of LEiDA, Hopf whole-brain modelling and trophic analyses. We reproduce significant context-independent ayahuasca-induced reductions in temporal mean of trophic measures, reflecting flattening and

compression of the functional hierarchy, aligning with the findings of Chapter 3 and prior literature. Further, we show that ayahuasca ingestion leads to greater temporal stability of two of these measures: TC and mean TL. This suggests that the hierarchical information flow structure underpinning brain activity not only moves to a flatter directed connectivity regime, characterised by more source-like activity on average, but also becomes more stable across time. Importantly, the temporal SD of RO was observed to be affected differently across contexts, decreasing during rest, and increasing while listening to music. This context-dependent reversal highlights the role of external stimuli in modulating how psychedelics affect the brain's hierarchy, necessitating further investigation.

4.5 Summary

The current chapter examined time-resolved changes in hierarchical configuration following ayahuasca ingestion among members of the Santo Daime Church at rest and during music listening. For this purpose, we introduced a novel method combining LEiDA, whole-brain modelling and trophic coherence analyses, enabling a state-based estimation of hierarchy measures (TC, MeanTL and RO). Temporal mean results confirmed the static hierarchy findings of Chapter 3, supporting ayahuasca-induced flattening of the functional hierarchy. Temporal SD analyses revealed greater stability of TC and MeanTL under ayahuasca, suggesting the system settled into this flatter hierarchical configuration across time. Crucially, the temporal SD of RO shifted in a context-dependent manner following ayahuasca ingestion, decreasing at rest (as was observed for TC and MeanTL), but increasing during music listening. The current chapter examined the music condition as one stimulus, however, as was alluded to in Chapter 3 and explored in the following chapter, the music listening condition was characterised by distinct musical pieces which may have driven the increased RO variability, warranting a more detailed exploration of changes to hierarchy within these music conditions.

Chapter 5:

The interplay of ayahuasca and music

Abstract

Music is a central component of psychedelic rituals across indigenous and religious contexts, as well as in modern psychedelic-assisted therapy. Yet, how musical properties affect the brain's hierarchy under psychedelics has not been studied. This chapter decomposes the music listening condition presented in Chapters 3 and 4 into four distinct sub-conditions varying in familiarity (familiar and unfamiliar) and predictability (predictable and unpredictable) in a two-by-two design. Time-resolved analyses (introduced in Chapter 4) identified several key interactions across hierarchy metrics. Temporal mean TC and RO measures showed reduced sensitivity to musical properties under ayahuasca compared to the no ayahuasca condition, consistent with the REBUS prediction. Importantly, MeanTL showed a redirection of sensitivity to musical characteristics, rather than a reduction. Further, temporal mean TC and RO showed unique drug effects for the Church's own unmanipulated music, pointing to a unique role of ceremonial music in shaping brain dynamics under ayahuasca, aligning with existing qualitative literature on the importance of music within Santo Daime rituals. Time-averaged analyses (introduced in Chapter 3) showed no significant effects, highlighting the importance of dynamic approaches. This is the first study to systematically examine effects of distinct musical properties within the psychedelic experience on the brain's functional hierarchy.

5.1 Introduction

The effects of psychedelics are widely known to be shaped not only by pharmacology and dosage, but also to depend on the internal state of the individual (set) and the environment within which the substance is consumed and experienced (setting) (Carhart-Harris et al., 2018). Many different elements of the setting are thought to shape the psychedelic experience including physical comfort, relationship with the therapist, facilitator, or guide, lighting, and music (Johnson et al., 2008; Kaelen et al., 2018; Noorani, 2021; Villiger, 2025). Of these, music has been afforded great importance across indigenous (Aldridge and Fachner, 2006; Labate et al., 2017b) and religious psychedelic practices such as those of the Santo Daime (Hartogsohn, 2021), as well as within modern clinical psychedelic-assisted therapy (Kaelen et al., 2018; MacLeod et al., 2025).

Despite the longstanding importance attributed to music in shaping psychedelic experiences, relatively little is known about how specific characteristics of music during a psychedelic state affect brain dynamics, and particularly, the brain's hierarchical organisation shown to be altered under psychedelics (e.g. Atasoy et al., 2018; Carhart-Harris et al., 2016; Deco et al., 2024; Luppi et al., 2021). Chapter 3 and 4 of this thesis examined the effects of ayahuasca ingestion at rest and during music listening on the brain's hierarchical organisation, showing consistent reduction in hierarchical coherence, as quantified through trophic coherence, as well as functional role central tendency (trophic level mean) and dispersion (trophic level standard deviation). The current chapter delves into the importance of musical familiarity and predictability within the ayahuasca experience of the Santo Daime.

5.1.1 Music Perception as Predictive Processing

Music perception is seen as a process of hierarchical predictive coding (Friston, 2005; Friston et al., 2009; Vuust et al., 2022), a Bayesian process through which the brain aims to minimise prediction error (i.e. the difference between bottom-up sensory inputs and top-down predictions). Therein, music perception is thought to depend on both the structure of music as well as the listener's expectations. The Predictive Coding of Music (PCM) model extends this view by accounting for the influence of biological, cultural, and contextual factors that impact the internal models from which predictions are generated (Vuust et al., 2022; Vuust and Frith, 2008). Complementary work showed that these internal models are built and developed through statistical learning and cultural experiences (Pearce, 2018). This points to the importance of prior experience and notably familiarity of a stimulus or stimulus type in perception. Greater

familiarity with a piece of music or music genre would suggest greater precision of predictions and thus stronger precision-weighted prediction errors (Vuust et al., 2018). Improved precision weighting is associated with greater knowledge or experience, for example, when comparing musicians and non-musicians, musicians were more accurate in identifying deviant tones, and exhibited stronger neural error response to deviants (Quiroga-Martinez et al., 2020; Vuust et al., 2009). Thus, predictive brain mechanisms underlying music perception seem to depend on precision of priors, which would be enhanced by listener's familiarity with the music (Vuust et al., 2022). In the context of this thesis, the hymns of the Santo Daime, sung repeatedly across ceremonies, are very familiar and deeply meaningful to members of the Church (Labate et al., 2017a). Additionally, prior work has shown that the amplitude of early neural response to deviant tones was dependent on the predictability of the musical piece, showing weaker responses in less predictable stimuli, independent of listener expertise (Garrido et al., 2013; Quiroga-Martinez et al., 2020).

If, as the REBUS model proposes, psychedelics relax the precision weighting of high-level priors within the functional hierarchy (Carhart-Harris and Friston, 2019), then during the acute effects of psychedelics, the system could be hypothesised to be less sensitive to the predictability of incoming musical stimuli, as the hierarchy through which predictions and prediction errors are propagated is compromised. Although the REBUS model posits psychedelic-induced relaxation of top-down prediction precision weighting (Carhart-Harris and Friston, 2019), this disruption may be mediated by strongly held priors encoded through factors such as familiarity of the music. However, no work has examined the interplay of psychedelics and musical familiarity and/or predictability thus far.

5.1.2 Music and Psychedelics: Neuroimaging Evidence

Several neuroimaging studies have explored how psychedelics, specifically LSD, alter brain activity during music listening. LSD significantly attenuated neural responses to music in brain regions associated with auditory, self-referential, and emotion processing, with effects blocked by the 5-HT_{2A} antagonist ketanserin (Frederick S Barrett et al., 2018). LSD enhanced the perceived meaningfulness of music, with corresponding increases in BOLD activation in regions associated with music listening (Preller et al., 2017). Dynamical analyses showed LSD and music in combination to alter FC dynamics in a specific task-positive network (Adamska and Finc, 2023). Kaelen et al. (2016), showed that interaction between LSD and music increased effective connectivity from parahippocampal cortex to visual cortex. Timmermann et al.

(2018), using an auditory oddball paradigm, demonstrated that LSD modulated feedback and feedforward connectivity within the auditory system, with reductions in neural adaptation to repeated stimuli and a dampened response to novel deviants in the stimulus, providing support for the theory of reduced sensitivity to surprising or unpredictable stimuli following flattening of functional hierarchy under psychedelics. Importantly, these studies take a unidirectional approach, focusing on how LSD affects music perception and associated brain activity, not discussing how music may mediate brain dynamics underpinning the psychedelic state.

Two studies, analysing the same MEG dataset, examined how systematic variations in context (eyes state and auditory/visual stimulus presence) mediated LSD-induced effects. Whole-brain entropy (Mediano et al., 2024) and functional hierarchy measures (Shinozuka et al., 2025) under LSD were observed to be significantly different from placebo across contexts. Mediano et al (2024) showed that although across contexts LSD induced significant increases in entropy, placebo condition entropy values were distinct across contexts, and resulted in differential drug effects. These findings suggest a context-dependent effect size mediation of psychedelic-induced brain entropy increases. Shinozuka et al., (2025) examined LSD-induced changes in hierarchy using model-free measures of irreversibility, coherence, and inhomogeneity. Across contexts, LSD significantly reduced all three measures. However, in the placebo condition, scores across hierarchy measures were significantly higher in the music condition compared to the video condition suggesting an effect of stimulus type or eye state on hierarchy measures, with these effects largely being lost under LSD. Their findings suggest psychedelic-induced reductions in sensitivity of hierarchical measures, and thus brain activity, to distinct types of external stimuli.

To the best of our knowledge, all neuroimaging studies examining the acute relationship between psychedelics and music thus far have focused on LSD. Moreover, none of these studies applied whole-brain modelling.

5.1.3 Music Within the Santo Daime Church

The Santo Daime Church is a syncretic religion, in which ayahuasca consumption is performed within highly structured ceremonies (Hartogsohn, 2021). The Santo Daime tradition includes distinct ceremonies some of which are silent and meditative, and others during which collective singing of hymns (*hinos*) is central to the experience (Shanon, 2002). We focus on those within which music is regarded as essential. Decades of anthropological research on the Santo Daime culminated in an understanding that “[hymns] are the main conductors of religious ritual ...

without music, there is no ritual” (Labate, Loures de Assis, et al., 2017, p. 103). Hymns are described as providing both temporal structure and spiritual guidance (Hartogsohn, 2021). Further, these hymns are regarded as sacred, believed to be received from the divine rather than composed by senior members of the Church (Labate et al., 2017a). Among the Santo Daime the relationship between the ayahuasca brew and the music is crucial, with members suggesting that it is only in the presence of the ayahuasca that the true meaning of the songs becomes clear. Members are deeply familiar with the hymns of their Church, and their relationship to the music is well captured by the quote “hymns are recorded in the heart” (Labate, Loures de Assis, et al., 2017, p. 106). The well-established familiarity and importance of ceremonial hymns attributed by church members, makes them a strong candidate for exploring the relationship between music and psychedelics from a predictive processing perspective.

5.1.4 The Current Study

Findings from Chapters 3 and 4 showed ayahuasca-induced modulation of hierarchical brain organisation among the Santo Daime, both at rest and while listening to music. Time-averaged and time-resolved whole-brain modelling and trophic coherence analyses showed significant reductions in hierarchy measures, outlining a flattening of the functional hierarchy independent of context and drug state. The current chapter extends this work by decomposing the music listening periods, into four distinct music conditions varying in familiarity (Familiar and Unfamiliar) and predictability (Predictable and Unpredictable) (**Figure 5.1**). Time-averaged and time-resolved whole-brain modelling and trophic analyses (from Chapters 3 and 4 respectively) are applied to directly test the effects of specific musical properties on changes to hierarchical brain organisation following ayahuasca ingestion among the Santo Daime. Informed by prior work utilising model-free hierarchy metrics in examining LSD-induced changes across contexts (Shinozuka et al., 2025), we hypothesise a reduction in sensitivity of hierarchy measures to music characteristics following ayahuasca ingestion. Further, experiential reports and prior research suggest that personally or ceremonially meaningful music plays a fundamental role within the psychedelic experience, both by anchoring the person to reality and enhancing the experience (Dobkin de Rios and Katz, 1975; Hartogsohn, 2021; Kaelen et al., 2018). Therefore, we hypothesise a unique drug effect within the Familiar Predictable music condition, as this represents the Church’s own unmanipulated hymns, though the direction of this effect is not

specified a priori. This study is the first to systematically vary musical properties within a psychedelic neuroimaging paradigm, as well as the first to examine ayahuasca-induced changes to whole-brain directed hierarchical organisation in this context.

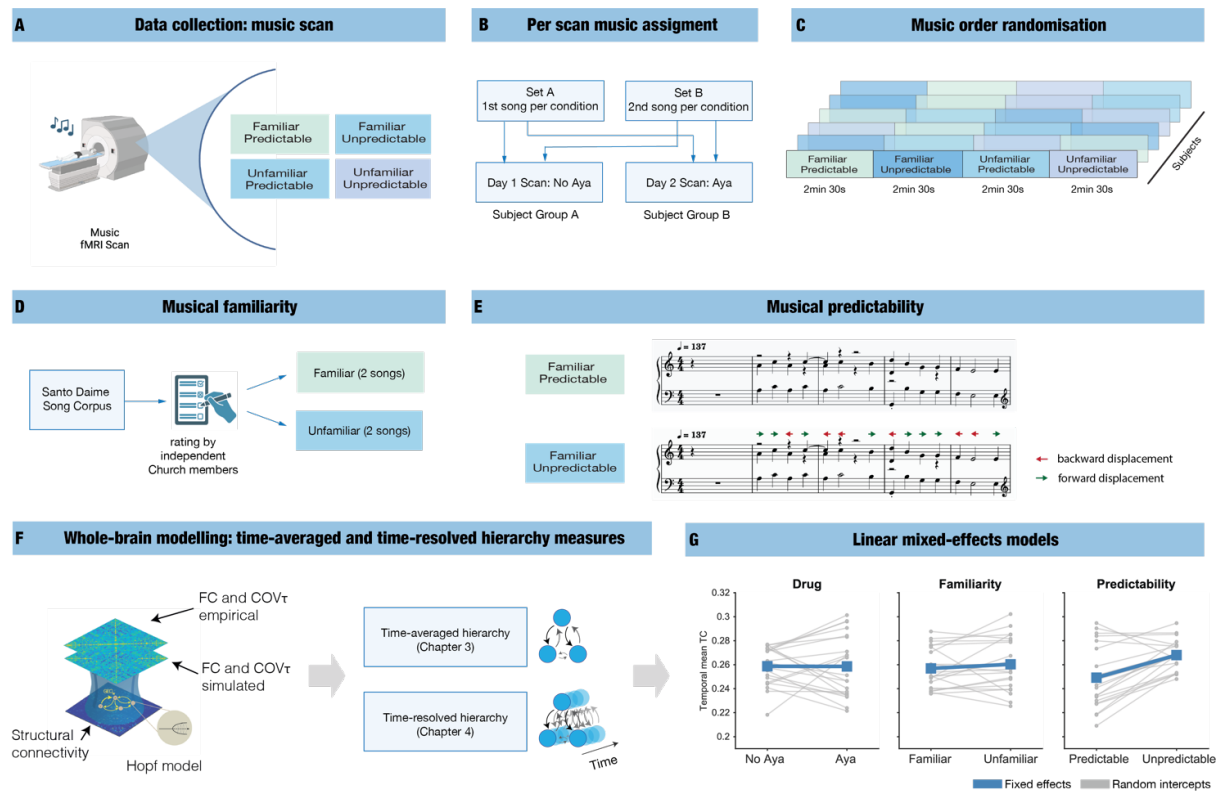


Figure 5.1 Music paradigm and hierarchy analysis pipeline overview. **A.** During the music listening scans participants listened to four musical pieces across four categories: Familiar Predictable, Familiar Unpredictable, Unfamiliar Predictable, and Unfamiliar Unpredictable. **B.** Participants were split into counterbalanced groups such that one group listened to one set of four songs (one from each category) on day 1, and another set on day 2, with the order of sets switched between the groups. **C.** During each scan the order of the four songs was randomised across participants. **D.** Musical familiarity was rated independently by a separate group of Church members, providing two songs for the familiar condition, and two for the unfamiliar condition. **E.** The original songs made up the predictable group, the unpredictable version of each song was adding random temporal shifts in note onset of up to ± 1000 ticks (1 tick = $1/240$ th of 16th note). **F.** Time-averaged (Chapter 3) and time-resolved (Chapter 4) whole-brain modelling and trophic analyses pipelines were applied to the eight music x drug conditions. **G.** Linear mixed models were used to examine the interaction between drug presence, musical familiarity and musical predictability on each of the measures. This figure was in part created with BioRender.com.

5.2 Methods

5.2.1 *The Music Paradigm*

The Santo Daime dataset reported on throughout this thesis is examined in the current chapter. On both scanning days (Day 1: no ayahuasca; Day 2: following ayahuasca ingestion), participants completed a resting state scan followed by a music listening paradigm. The current chapter focuses on the music listening paradigm. On each day, participants listened to four songs that varied in predictability and familiarity in a two-by-two design (conditions: familiar predictable, familiar unpredictable, unfamiliar predictable, and unfamiliar unpredictable). Eight songs were prepared to avoid exposure effects across scanning days. Four songs were extracted from the Santo Daime Church's corpus of songs, rated by an independent subset of church members as either familiar (two songs) or unfamiliar (two songs) to this branch of the Church. Each song had a predictable version (original) and an unpredictable version. The unpredictable version of each song was created by adding random non-quantised temporal shifts in onset of up to ± 1000 ticks (1 tick = $1/240^{\text{th}}$ of 16^{th} note) to each note in the melody. The onset randomization was applied once to the piano melody and then replicated for the guitar (at two octaves: the same octave as the piano and one octave above). The tambourine was kept at steady 8^{ths}. All songs were in C-major, 4/4 time, 137 BPM (the most common median tempo identified through MIR-analysis of the Santo Daime song database). The eight songs were split into two sets (A and B) each containing one song per condition. Participants were divided into two counterbalanced groups: one listened to set A on Day 1, and set B on Day 2; the other in reverse order. The order of songs within each set was randomised across participants. The music paradigm was designed and developed by Dr. Christine Ahrends, Prof Peter Vuust and Prof. Morten Kringelbach.

5.2.2 *Preprocessing and Parcellation*

The preprocessing and denoising of the data is described in Chapter 2. Data were parcellated using the DK80 parcellation as described in Chapters 3. Song onset times were extracted automatically from E-Prime logs. These were used to segment the fMRI time-series into the four music condition blocks per scanning session. As noted in Chapter 4, three participants were excluded from analysis as they did not complete the music-listening scan. The remaining 21 participants are included in the analysis.

5.2.3 Time-averaged analysis

Whole-brain modelling for the time-averaged analysis was largely consistent with methods outlined in Chapter 3. The majority of modelling parameters were kept the same, given the data is a sub-division of that examined in previous chapters. The structural connectivity matrix was built using the Human Connectome Project high-density DTI data from 812 healthy participants (WU-Minn Consortium, S1200 release of 812 subjects; available at: https://db.human-connectome.org/data/projects/HCP_1200). Consistent parameters included: the bifurcation parameter $\alpha = -0.02$, the gaussian noise $\sigma = 0.01$, and the time-lag parameter $\tau = 2$. The strength of edgewise connections in the GEC matrix was normalised to a range of 0-0.2 following each iteration. FC and COV τ learning rates were optimised through a parameter sweep to improve model fit. Learning rates of $\epsilon_{FC} = 0.002$ and $\epsilon_{COV\tau} = 0.001$ were chosen as they resulted in improved Pearson correlations between empirical and simulated matrices for both FC (~0.07 improvement) and COV τ (~0.09 improvement) compared to those used in Chapter 3. Iterations were increased to 15,000 to allow convergence. Following fitting, the GEC was thresholded at 0.015 to reduce noise, in line with Chapter 3. Per condition Pearson correlations between empirical and simulated FC and COV τ are reported in **Supplementary Table S5.1**.

Three hierarchy measures were derived from the GEC: trophic coherence (TC), quantifying the hierarchical consistency in the network; mean trophic level (TL (mean)), capturing the central tendency of information flow roles across the network; and SD of trophic levels (TL (SD)), reflecting differentiation of hierarchical information flow roles across the network.

5.2.4 Time-resolved analysis

For the time-resolved analysis, the approach outlined in Chapter 4 was largely replicated. Seven recurrent phase-locking (PL) states were identified in Chapter 4. These were derived from the entire dataset; from all subjects across all four main conditions (No Ayahuasca Rest, Ayahuasca Rest, No Ayahuasca Music, Ayahuasca Music). Rather than deriving new centroids from the within-music conditions specifically, the same seven PL states were utilised. This was done for several reasons: 1) the within-music conditions examined here are sub-divisions of the music sessions analysed in Chapter 4, 2) the use of the same PL states enables direct comparison with results of Chapter 4, and 3) the within-music conditions have shorter timeseries, and thus extracting new PL states from this subset would reduce the reliability of k-means clustering outcomes.

Nevertheless, the 7 PL states were extracted from both the music and rest data; as such, validation checks were carried out to ensure they appropriately represented the within-music conditions. Mean Euclidean distance from each timepoint's leading eigenvector to its assigned cluster centroid was computed per subject per condition, and these distances were compared to those observed for the four main conditions originally used to derive the centroids. No substantial differences were observed between the original four conditions (range of group means: 0.811-0.838) and the within-music conditions examined here (range of group means: 0.810-0.835). Importantly as inter-subject variability is reliant on cluster fractional occupancy, fractional occupancy was computed per state per condition. Comparisons were made within each cluster across all eight conditions, with none surviving multiple comparison correction (**Supplementary Figure S5.1**).

5.2.5 Per-cluster model fitting

For each of the seven PL states, state- and condition-specific FC and COV τ matrices were derived. The same whole-brain modelling approach was applied as in Chapter 4, with consistent parameters: $\alpha = -0.02$, $\sigma = 0.01$, $\varepsilon_{FC} = 0.0004$, $\varepsilon_{COV\tau} = 0.005$. The same structural connectome as in the time-averaged analysis was used. With the structural connectome as a starting point, the weights of effective connections were iteratively updated through a pseudo-gradient descent procedure with 5,000 iterations. The effective connectivity matrix was normalised to a range of 0-0.2 following each iteration. This procedure yielded a simulated FC and COV τ for each PL state in each condition. Across conditions and clusters, a good fit to the empirical data was achieved (mean Pearson r : FC = 0.760 ± 0.076 ; COV τ = 0.750 ± 0.064). A breakdown of per condition fits is reported in **Supplementary Table S5.4**. A trophic coherence score and a trophic level vector (one value per region) were computed for each PL state in each condition using the resulting GEC, as outlined in Chapter 4.

5.2.6 Time-resolved hierarchy metrics

For each subject in each condition, hierarchy timeseries were constructed by replacing each volume from the original timeseries with the corresponding PL state- and condition-specific TC score and TL vector, resulting in a subject-specific temporal trajectory of brain hierarchy. As outlined in Chapter 4, six measures were derived from the hierarchy timeseries. We derived three hierarchy measures from the state- and condition-specific GEC: TC, MeanTL (the mean TL across regions), and RO (the standard deviation of TLs across regions). For each of these

metrics, the temporal mean and temporal SD were computed per subject per condition, as described in Chapter 4. Temporal mean results are reported in the main text. Temporal SD results are reported in **Supplementary Section S5.3**.

5.2.7 Statistical analysis

To account for the full 2x2x2 factorial design (Drug x Familiarity x Predictability), a linear mixed-effects model (LMM) was fit to each dependent variable (DV; hierarchy measure) as (DV ~ Drug × Familiarity × Predictability +(1|Subject)). The Subject random intercept was included to account for the repeated measures design. Primary tests were Type III ANOVAs with Satterthwaite degrees of freedom. Sum coding was used to ensure that any observed main effects reflected deviation from the grand mean rather than a specific pre-assigned reference. The models were run using the lme4 (v1.1-35) and lmerTest (v3.1-3) packages in R (v4.4.2).

To disentangle observed significant effects and interactions, follow-up analyses took two distinct forms. The first examined drug condition contrasts within each music condition. Estimated marginal means (EMMs) derived from the LMM were used to compute the drug contrast (No Ayahuasca – Ayahuasca) within each of the four music conditions. FDR multiple comparison correction was applied accounting for four contrasts per hierarchy measure. Effect sizes were computed as Cohen’s d with 95% confidence intervals. Secondly, to examine the main Type III ANOVA test results from a complementary perspective, repeated measures ANOVAs were conducted separately for the No Ayahuasca and Ayahuasca conditions to understand how music’s familiarity and predictability affected hierarchy measures within each drug condition.

5.2.8 Diagnostics and non-parametric sensitivity analysis

The analyses presented here are parametric, assuming normality of residuals. Normality assessment of the residuals was conducted for each LMM using Shapiro-Wilk tests. Regarding the time-averaged analyses, all three hierarchy measures showed significant violations of normality assumptions (**Supplementary Table S5.2**). In the time-resolved analyses, the three temporal SD hierarchy measures violated the normality assumption, while the three temporal mean measures passed the Shapiro-Wilk test (**Supplementary Table S5.5**). Notably, two temporal mean measures passed only marginally (RO and MeanTL). Therefore, non-parametric sensitivity analyses were conducted for all Type III ANOVAs and follow-up repeated-measures ANOVAs. The Aligned Rank Transform (ART) ANOVA (Wobbrock et al., 2011) was used as a non-parametric alternative. ART was implemented via the ARTool package (Kay et al.,

2025). The pattern of significant and non-significant effects was compared across parametric and non-parametric analyses. Only the time-resolved temporal mean TC measure showed discrepancies for effects near the significance threshold. The observed alignment in significant effects across measures suggests that the parametric LMM results reported in text, are robust to violations of the normality assumption. A detailed breakdown of non-parametric results for each measure is outlined in **Supplementary Tables S5.6-S5.9**.

5.3 Results

5.3.1 Time-averaged analysis

Time-averaged analyses, in line with that of Chapter 3, extracted three hierarchy measures: TC, TL (mean) and TL (SD). Three independent LMMs were fit, one per hierarchy measures as the DV. No significant effects of Drug, Familiarity, or Predictability were observed for any measure (**Table 5.1**). No interactions reached significance.

Table 5.1 LMM Type III ANOVA results for time-averaged hierarchy measures show no significant effects or interactions. Three separate models were conducted for trophic coherence (TC, mean trophic level (TL (mean)) and standard deviation of trophic levels (TL (SD))). The resulting F-values, p-values, and partial eta-squared (η^2p) effect sizes are reported for each effect and interaction. Fam = Familiarity, Pred = Predictability.

Effect	TC			TL (mean)			TL (SD)		
	F(1,140)	p	η^2p	F(1,140)	p	η^2p	F(1,140)	p	η^2p
Drug	0.444	.506	.003	0.563	.454	.004	0.003	.954	<.001
Familiarity	2.455	.119	.017	0.346	.557	.002	0.396	.530	.003
Predictability	0.703	.403	.005	0.147	.702	.001	1.616	.206	.011
Drug x Fam	0.017	.896	<.001	0.224	.637	.002	1.066	.304	.008
Drug x Pred	0.012	.913	<.001	0.025	.874	<.001	0.123	.727	.001
Fam x Pred	0.005	.942	<.001	0.017	.896	<.001	0.084	.773	.001
Drug x Fam x Pred	0.613	.435	.004	1.655	.200	.012	0.866	.354	.006

5.3.2 Time-resolved analysis: TC (temporal mean)

An LMM was first fit to temporal mean TC, examining changes to edge-level hierarchical coherence across the brain. The Type III ANOVA showed a significant main effect of Predictability, alongside significant Drug x Predictability and Familiarity x Predictability interactions (**Table 5.2**). The three-way Drug x Familiarity x Predictability interaction was marginal. All other effects and interactions were non-significant. Non-parametric ART ANOVA confirmed all significant effects and additionally reached significance for the three-way interaction ($p = .013$).

Table 5.2 Type III ANOVA results of temporal mean TC. *F*-statistics, *p*-values, and partial eta-squared (η^2p) effect sizes are reported for each effect.

Effect	F	Df ₁	Df ₂	p	η^2p
Drug	0.00	1	140	.970	<.001
Familiarity	0.70	1	140	.404	.005
Predictability	20.80	1	140	<.001	.129
Drug x Familiarity	1.51	1	140	.221	.011
Drug x Predictability	6.20	1	140	.014	.042
Familiarity x Predictability	23.41	1	140	<.001	.143
Drug x Familiarity x Predictability	3.89	1	140	.051	.027

EMM contrasts were computed within each of the music conditions (**Figure 5.2B**). Only the Familiar Predictable music condition showed a significant drug effect (estimate = -0.023, $t(140) = -2.83$, $q = .022$, $d = -0.87$, 95% CI [-1.49, -0.26]), indicating higher Mean TC under Ayahuasca. No other music conditions reached significance: Familiar Unpredictable (estimate = 0.013, $t(140) = 1.63$, $q = .209$, $d = 0.50$, 95% CI [-0.10, 1.11]), Unfamiliar Predictable (estimate = 0.003, $t(140) = 0.37$, $q = .708$, $d = 0.12$, 95% CI [-0.49, 0.72]), and Unfamiliar Unpredictable (estimate = 0.007, $t(140) = 0.89$, $q = .497$, $d = 0.28$, 95% CI [-0.33, 0.88]), suggesting an ayahuasca-induced increase in TC specific to the hymns church members know well.

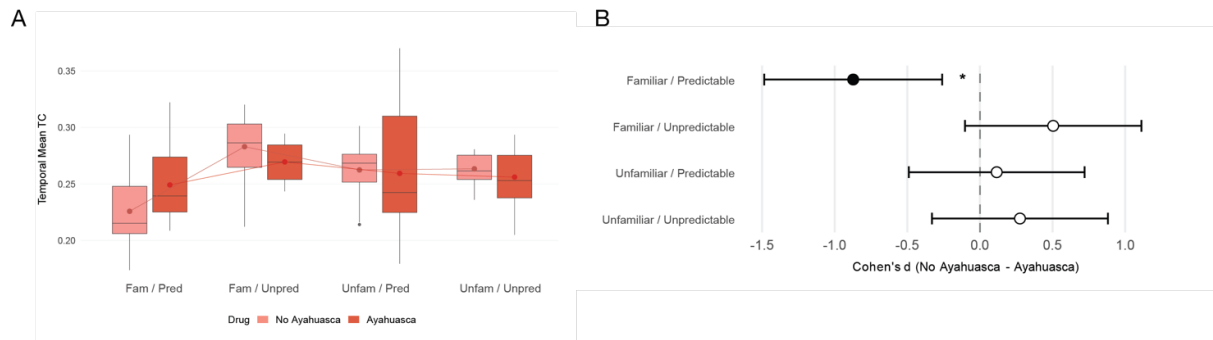


Figure 5.2 Ayahuasca-induced increase in temporal mean TC during Familiar Predictable music listening. **A.** Boxplot of distribution of temporal mean TC per condition. Colour separation between drug conditions No Ayahuasca (light red) and Ayahuasca (dark red). Lines connect group means (dots) across music conditions within each drug condition. For each group lower and upper limits of the box represent 25th and 75th percentiles, respectively, and line in between is the median. **B.** Forest plot of LMM-derived EMM contrasts (No Ayahuasca – Ayahuasca) within each music condition. Dot demarcates Cohen's *d*, with lines indicating 95% confidence intervals. Filled dots represent FDR-corrected significance. Empty dots show no significant drug effect. . * $p < .05$, ** $p < .01$, *** $p < .001$.

Within-drug two-way repeated-measures follow-up ANOVAs were run to further clarify the nature of the observed interactions (**Table 5.3**). During No Ayahuasca music listening, the main effect of Predictability and the Familiarity x Predictability interaction were both highly significant. There was no significant main effect of Familiarity. These results indicate sensitivity to musical properties in the no ayahuasca condition. Following ayahuasca ingestion, no effects or interactions reached significance. These results suggest that ayahuasca ingestion reduced the sensitivity of the hierarchical coherence of the brain to music's familiarity and predictability as quantified through temporal mean TC.

Table 5.3 Temporal mean TC within-drug two-way repeated-measures ANOVA results. Analysis conducted separately for No Ayahuasca and Ayahuasca conditions. *F*-statistics, *p*-values, and partial eta-squared (η^2p) effect sizes are reported.

Effect	No Ayahuasca			Ayahuasca		
	F(1,60)	p	η^2p	F(1,60)	p	η^2p
Familiarity	3.45	.068	.054	0.07	.797	.001
Predictability	40.16	<.001	.401	1.85	.179	.030
Familiarity x Predictability	37.46	<.001	.384	3.54	.065	.056

5.3.3 Time-resolved analysis: RO (temporal mean)

An LMM was fit to the temporal mean RO, characterising changes to standard deviation of trophic levels, or regional information flow roles, across the brain. Type III ANOVA revealed significant main effects of Drug and Predictability as well as all two-way interactions (Drug x Familiarity, Drug x Predictability, and Familiarity x Predictability) (**Table 5.4**). The Familiarity x Predictability interaction, although significant, was near the threshold. The three-way interaction was highly significant. No significant main effect of Familiarity was observed.

Table 5.4 Type III ANOVA results for temporal mean RO. F-statistics, p-values, and partial eta-squared (η^2p) effect sizes are reported for each effect.

Effect	F	Df ₁	Df ₂	p	η^2p
Drug	18.36	1	140	<.001	.116
Familiarity	0.13	1	140	.719	<.001
Predictability	8.00	1	140	.005	.054
Drug x Familiarity	40.83	1	140	<.001	.226
Drug x Predictability	10.03	1	140	.002	.067
Familiarity x Predictability	4.00	1	140	.047	.028
Drug x Familiarity x Predictability	63.40	1	140	<.001	.312

The EMM contrasts showed music-condition specific drug effects (**Figure 5.3B**). During Familiar Predictable music listening, temporal mean RO was significantly higher under Ayahuasca (estimate = -0.043, $t(140) = -6.61$, $q < .001$, $d = -2.04$, 95% CI [-2.69, -1.40]). All other music conditions showed effects in the opposite direction, namely significantly lower temporal mean RO under Ayahuasca: Familiar Unpredictable (estimate = 0.029, $t(140) = 4.51$, $q < .001$, $d = 1.39$, 95% CI [0.77, 2.02]), Unfamiliar Predictable (estimate = 0.050, $t(140) = 7.74$, $q < .001$, $d = 2.39$, 95% CI [1.73, 3.05]), and Unfamiliar Unpredictable (estimate = 0.019, $t(140) = 2.94$, $q = .004$, $d = 0.91$, 95% CI [0.29, 1.52]).

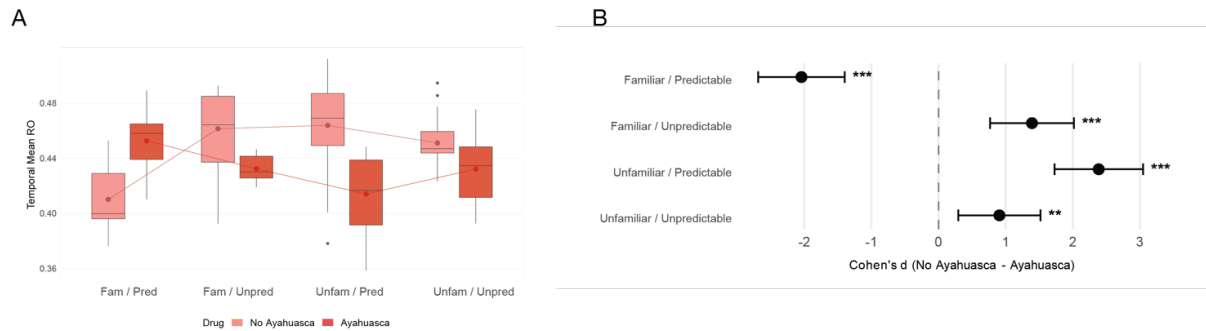


Figure 5.3 Temporal mean RO ayahuasca-induced increase during Familiar Predictable music listening. **A.** Boxplot of distribution of temporal mean RO per condition. Colour separation between drug conditions No Ayahuasca (light red) and Ayahuasca (dark red). Lines connect group means (dots) across music conditions within each drug condition. Lower and upper limits of the box represent 25th and 75th percentiles, respectively, and line in between is the median. **B.** Forest plot of LMM-derived EMM contrasts (No Ayahuasca – Ayahuasca) within each music condition. Dot demarcates Cohen's d, with lines indicating 95% confidence intervals. Filled dots represent FDR-corrected significance. Empty dots show no significant drug effect. * $p < .05$, ** $p < .01$, *** $p < .001$.

Within-drug follow-up ANOVAs showed ayahuasca-specific loss of sensitivity to music's predictability. In the No Ayahuasca condition, all effects were significant (**Table 5.5**). Following ayahuasca ingestion, no main effect of Predictability was observed. The main effect of Familiarity remained significant, with the effect size largely unchanged. The Familiarity x Predictability interaction was significant with a lower effect size than in the No Ayahuasca condition.

Table 5.5 Temporal mean RO within-drug two-way repeated-measures ANOVA. Analysis conducted separately for No Ayahuasca and Ayahuasca conditions. *F*-statistics, *p*-values, and partial eta-squared (η^2p) effect sizes are reported.

Effect	No Ayahuasca			Ayahuasca		
	F(1,60)	p	η^2p	F(1,60)	p	η^2p
Familiarity	22.55	<.001	.273	21.79	<.001	.266
Predictability	17.79	<.001	.229	0.07	.795	.001
Familiarity x Predictability	49.12	<.001	.450	21.30	<.001	.262

5.3.4 Time-resolved analysis: MeanTL (temporal mean)

Finally, an LMM was fit to temporal mean MeanTL, examining changes to central tendency of information flow roles across the brain. The Type III ANOVA revealed significant main effects of Familiarity and Predictability, as well as significant Drug x Familiarity, Drug x Predictability, and Familiarity x Predictability interactions (**Table 5.6**). The main effect of Drug was non-significant, as was the three-way interaction.

Table 5.6 Type III ANOVA results of LMM for temporal mean MeanTL. *F-statistics, p-values, and partial eta-squared (η^2p) effect sizes are reported for each effect.*

Effect	F	Df ₁	Df ₂	p	η^2p
Drug	0.00	1	140	.994	<.001
Familiarity	5.95	1	140	.016	.041
Predictability	7.67	1	140	.006	.052
Drug x Familiarity	46.14	1	140	<.001	.248
Drug x Predictability	23.37	1	140	<.001	.143
Familiarity x Predictability	11.89	1	140	<.001	.078
Drug x Familiarity x Predictability	1.43	1	140	.233	.010

EMM contrasts showed distinct effects of ayahuasca in two music conditions (**Figure 5.4B**). The Unfamiliar Predictable music condition showed significantly lower temporal mean MeanTL under ayahuasca (estimate = 0.113, $t(140) = 6.41$, $q < .001$, $d = 1.98$, 95% CI [1.33, 2.62]), whereas during Familiar Unpredictable music listening significantly higher MeanTL was observed under Ayahuasca (estimate = -0.092, $t(140) = -5.22$, $q < .001$, $d = -1.61$, 95% CI [-2.24, -0.98]). The Familiar Predictable EMM contrast was non-significant (estimate = -0.028, $t(140) = -1.58$, $q = .155$, $d = -0.49$, 95% CI [-1.10, 0.12]), as was the Unfamiliar Unpredictable contrast (estimate = 0.007, $t(140) = 0.38$, $q = .706$, $d = 0.12$, 95% CI [-0.49, 0.73]).

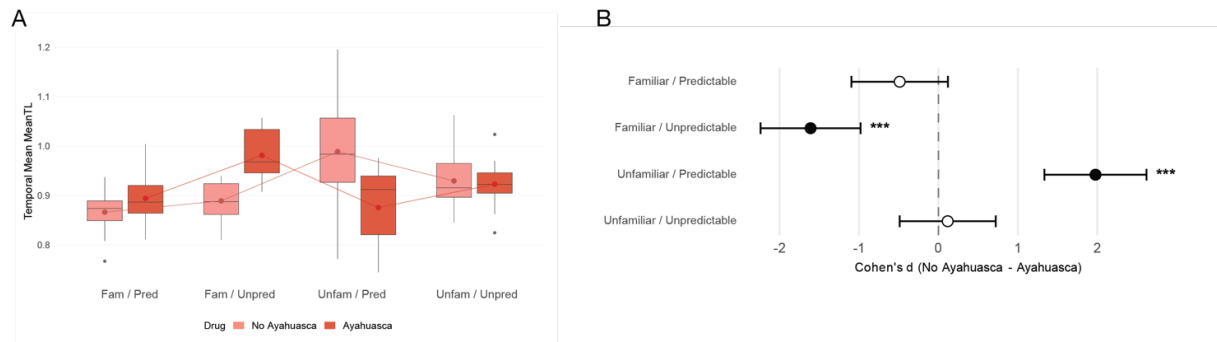


Figure 5.4 Music-dependent drug effects on temporal mean MeanTL. **A.** Boxplot of distribution of temporal mean MeanTL per condition. Colour separation between drug conditions No Ayahuasca (light red) and Ayahuasca (dark red). Lines connect group means (dots) across music conditions within each drug condition. Lower and upper limits of the box represent 25th and 75th percentiles, respectively, and line in between is the median. **B.** Forest plot of LMM-derived EMM contrasts (No Ayahuasca – Ayahuasca) within each music condition. Dot demarcates Cohen's d, with lines indicating 95% confidence intervals. Filled dots represent FDR-corrected significance. Empty dots show no significant drug effect. * $p < .05$, ** $p < .01$, *** $p < .001$.

Within-drug follow-up ANOVAs were conducted. The No Ayahuasca condition showed a highly significant main effect of Familiarity, and a significant Familiarity x Predictability interaction (**Table 5.7**). There was no significant main effect of Predictability. Following ayahuasca ingestion, the pattern changed. The main effect of Predictability became highly significant. The main effect of Familiarity was significant, although with a lower effect size than seen in the No Ayahuasca condition. The Familiarity x Predictability interaction was no longer significant. These results suggest ayahuasca-induced alterations in which musical properties affect MeanTL. Namely, Predictability, which was non-significant in the No Ayahuasca condition, became highly significant and showed the highest effect size in the Ayahuasca condition.

Table 5.7 Temporal mean MeanTL within-drug two-way repeated-measures ANOVA. Analysis conducted separately for No Ayahuasca and Ayahuasca conditions. F-statistics, p-values, and partial eta-squared (η^2p) effect sizes are reported.

Effect	No Ayahuasca			Ayahuasca		
	F(1,60)	p	η^2p	F(1,60)	p	η^2p
Familiarity	35.91	<.001	.374	13.59	<.001	.185
Predictability	1.79	.185	.029	41.47	<.001	.409
Familiarity x Predictability	9.09	.004	.132	3.63	.061	.057

5.4 Discussion

The current chapter examined how ceremonial music's familiarity and predictability moderated ayahuasca-induced effects on the brain's hierarchical organisation among members of the Santo Daime Church. To this end, we applied the whole-brain modelling-based time-averaged and time-resolved hierarchy analyses introduced in Chapters 3 and 4, respectively. Time-resolved analyses captured significant interactions between musical characteristics and ayahuasca effects. Temporal mean TC and RO measures showed reductions in sensitivity to music's characteristics following ayahuasca ingestion, alongside unique drug effects while listening to Familiar Predictable music, which corresponded to the Church's own music. MeanTL findings diverged from this pattern, showing reorganisation of susceptibility to musical characteristics following ayahuasca ingestion, rather than an attenuation or loss of effects. Time-averaged analyses showed no significant effects or interactions, further highlighting the importance of dynamics in understanding the psychedelic state. The following sections discuss these findings in relation to the broader literature examining the interplay of psychedelics and music.

Methodologically, the findings presented here highlight the importance of temporal dynamics in understanding brain activity. Whereas time-averaged analyses revealed no significant effects of drug or musical characteristics on hierarchy measures, time-resolved analyses showed key interactions between drug and music conditions. As shown in **Supplementary Table S4.6-S4.8**, PL states were associated with distinct drug effects on TC, MeanTL and RO, some showed increases following ayahuasca ingestion, while others showed inverse trends. The time-averaged analyses lose this detail. Psychedelics have been shown to affect brain dynamics (Lord et al., 2019; Luppi et al., 2021; Tagliazucchi et al., 2014) and the discrepancies between the time-averaged and time-resolved analyses presented in the current chapter further highlight the need to include temporal resolution in the future. The following sections discuss the time-resolved findings.

TC, as an edge-level measure of global hierarchical organisation, showed a complete loss of sensitivity to characteristics of the music following ayahuasca ingestion. Where significant main effects of musical familiarity, predictability and the interaction were observed in the absence of ayahuasca, no significant effects were seen following ayahuasca ingestion. Therein, following ayahuasca ingestion the consistency of directional information flow across the brain was no longer responsive to music's familiarity and predictability. Reduced sensitivity to characteristics of musical stimuli sits well with the REBUS model, aligning with the concept of

psychedelics flattening the functional hierarchy and reducing the precision-weighting of priors (Carhart-Harris and Friston, 2019). This loss of sensitivity to musical stimuli may be a contributing factor to the observed loss of temporal standard deviation of TC following ayahuasca ingestion across the music scan reported in Chapter 4. Importantly, EMM drug contrasts showed a significant drug effect only within the Familiar Predictable music condition, which was the unmanipulated form of the Church’s ceremonial music which the participants knew well. The Unfamiliar Predictable condition did not show the same effects, which suggests that this effect is truly unique to the music Santo Daime members know well. Upon visual inspection of **Figure 5.2A**, the No Ayahuasca Familiar Music condition exhibits the lowest TC across music and drug conditions, potentially pointing to the Santo Daime’s own music having a unique effect outside the ayahuasca state in shaping the brain’s hierarchy. Future work should look into this effect more explicitly, directly comparing no music to the Church’s ceremonial music. Further, future work should compare ceremonial music to personally meaningful and familiar music (outside the ceremonial context) to better understand whether observed effects are due to the ceremonial music being familiar and predictable, or whether there is something specific about the ceremonial music that is unique within the ayahuasca experience.

RO is a node-level measure of hierarchical position spread across the brain. We observe a loss of the main effect of predictability following ayahuasca ingestion. This, once more aligns with the proposed predictive-coding-based mechanism of psychedelic-action, namely reduced precision-weighting of priors, which are necessary for differential brain responses to predictable versus unpredictable stimuli (Vuust et al., 2022). However, the main effect of familiarity is preserved, suggesting that there is not a complete loss of response to music’s characteristics, and that familiarity of music still plays an important role in the dispersion of information flow roles within the brain’s hierarchy, even under ayahuasca. Findings suggesting a reorganisation rather than complete dissolution of the functional hierarchy. When looking at EMM drug contrasts, we see clear distinction between the Church’s own music (Familiar Predictable) where we see a significant increase in RO following ayahuasca ingestion, and all other music conditions, where a significant decrease is observed. The observed increase in hierarchy measures while listening to the Familiar Predictable hymns may reflect a unique role of the Church’s ceremonial music in providing structure during the psychedelic experience. A seminal anthropological theory of the role of music within psychedelic rituals, based largely on ayahuasca rituals, describes music as a “Jungle Gym” within the psychedelic state, providing structure in an otherwise chaotic experience (de Rios & Katz, 1975).

Time-resolved temporal mean TC and RO measures both showed a reduction in sensitivity to musical characteristics following ayahuasca ingestion. These measures reflect how hierarchical the network's organisation is from two complementary perspectives. The observed reductions in TC and RO responsiveness to changes in predictability following ayahuasca ingestion confirm our primary hypothesis of an ayahuasca induced flattening of the functional hierarchy reflecting attenuation of responses to unpredictable stimuli, which are posited to depend on the precision-weighting of high-level priors (Carhart-Harris and Friston, 2019; Vuust et al., 2022). Further, the unique drug effects within the Familiar Predictable music condition across these measures, aligns well with qualitative work describing the unique importance of the ceremonial music in the experience of the ayahuasca (Hartogsohn, 2021; Labate et al., 2017a).

Although TC and RO show largely consistent effects, MeanTL depicts a different pattern. MeanTL captures a qualitatively different aspect of brain organisation to that characterised by TC and RO. It does not explicitly look at how hierarchical the system is, but rather where on average regions sit within the hierarchy in terms of their information flow roles, namely, whether they are more sink-like or source-like. A shift in MeanTL can be observed without accompanying changes in how differentiated or coherent the hierarchical organisation of the system is. MeanTL findings show a redirection of sensitivity to characteristics of musical stimuli rather than a complete loss. Results suggest that while MeanTL was most susceptible to changes in familiarity prior to ayahuasca, following ayahuasca ingestion this measure became more sensitive to changes in predictability of the music. This goes against the hypothesised reduction in sensitivity to predictability under ayahuasca. When looking at drug contrasts, we see significant changes only in music conditions where one factor was manipulated, and the observed pattern of these changes is non-intuitive. These results are difficult to interpret with the available data, the collection of larger datasets would permit region-specific examination of changes in TL to better understand the mechanisms underlying these effects.

Our results provide an interesting tension with REBUS, which proposes a general relaxation of priors. Familiar ceremonial music may invoke strong priors which are resistant to this relaxation, or may play a unique functional role within the experience. Further, the unique drug effects in TC and RO observed in the Familiar Predictable music condition point to a potential interaction between set and setting, whereby the participants' prior relationship with the music may determine its role within the ayahuasca experience. Further, research is needed to explore this interpretation. Nevertheless, the unique effects of familiar ceremonial music, support the commonly stated intuition among clinicians and facilitators, that choice of music matters within psychedelic experiences (Barrett et al., 2017). The discrepancy in effects observed for MeanTL

compared to TC and RO, suggest that although the hierarchy's responsiveness to characteristic of music does reduce, the average information flow roles of regions shift responding differentially to musical stimuli with sensitivity moving away from differences in familiarity, towards differences in predictability. Importantly, our results are based on observed changes in modelled effective connectivity, and any references to perception, cognition, and/or phenomenology are an effort to contextualise our findings in the wider literature, as these factors were not available and thus not analysed within the current work.

To the best of our knowledge, this study is the first to systematically examine effects of musical familiarity and predictability on functional hierarchy following psychedelic consumption. Nevertheless, the current study has several key limitations which need to be acknowledged and which necessitate future work to support and validate the observed effects. Each condition comprised only 25% of the original music listening scan per-subject (approximately 2.5 minutes of scanning each). Future work should aim to collect richer within-music data. This would enable improved whole-brain modelling (including potential subject-specific dynamic modelling approaches), and thus greater accuracy in time-resolved analyses. Further, the nature of the predictability manipulation in the current study design was such that each note could not be predicted from the last. However, recent work has pointed to the importance of building prediction before prediction is violated in music perception (Vuust et al., 2018). Therein, future unpredictable music stimuli should be developed such that they build and then break expectations, providing a more accurate examination of how unpredictability in music may affect brain dynamics under psychedelics. Finally, rich phenomenological or cognitive data specific to the music conditions was not collected. Incorporation of continuous phenomenological techniques such as Temporal Experience Tracing (Jachs et al., 2022), or neurophenomenological approaches that systematically bridge first-person accounts with neurobiological data (Berkovich-Ohana et al., 2020), alongside continuous physiological measures (Rosas et al., 2023) would be essential to relating observed changes in brain dynamics to the psychedelic experience more meaningfully.

5.5 Summary

The music listening condition of the Santo Daime fMRI data was decomposed into its original Familiarity x Predictability design. Whole-brain modelling-based time-averaged and time-resolved hierarchy measures introduced in Chapters 3 and 4 respectively were applied to disentangle the effects of ayahuasca during listening to music characterised by distinct properties.

Time-resolved analyses outlined key effects and interactions, whereas time-averaged analyses showed none, further highlighting the importance of temporal resolution and dynamic approaches to understanding psychedelic-induced changes in the brain. Temporal mean TC and RO showed reduced sensitivity to musical properties under ayahuasca, with TC showing the strongest effects, while MeanTL showed a redirection of sensitivity rather than a loss. These results suggest the relationship between the brain's hierarchy and musical properties is not uniformly diminished within the psychedelic state, but partially reorganised in a manner specific to the properties of the music. Importantly, TC and RO showed unique drug effects in the Familiar Predictable music, the Church's own music. Our results demonstrate an interaction between ayahuasca and the properties of the music in affecting the directed hierarchy, supporting extensive qualitative research on the importance of music within the psychedelic state.

Chapter 6:

General discussion and conclusions

Across cultures, psychedelics are used in combination with music for a variety of purposes from celebration and social cohesion, to physical and mental healing (Dobkin de Rios, 2005; Efthimiou et al., 2024; Labate et al., 2017a, 2016; Maas and Strubelt, 2003). A compelling case for the examination of the effects of the interplay between psychedelics and music is found in the Santo Daime, a syncretic religious group whose ceremonies centre around the communal ingestion of ayahuasca, wherein music plays a central role. In light of the REBUS theory, this thesis addressed three main aims: 1) we examined the effects of ayahuasca ingestion among the Santo Daime on large-scale brain dynamics and the functional hierarchy at rest, 2) we assessed whether observed effects were consistent across resting state and ritual-relevant music listening contexts, and 3) we explored how ceremonial music's familiarity and predictability modulated the ayahuasca-induced effects on the functional hierarchy. Using a combination of HADES, LEiDA, whole-brain modelling, and trophic analyses, we were able to show context-independent ayahuasca-induced flattening of the functional hierarchy, as well as context-dependent effects in, for example, lower-order sensory networks. Our analyses further showed that the Church's own ceremonial music had unique effects on the functional hierarchy. The following sections provide a synthesis of our findings, as well as a discussion of key implications and considerations for future studies.

6.1 Ayahuasca flattens the functional hierarchy

The REBUS model (Carhart-Harris and Friston, 2019) predicts that psychedelics flatten the brain's functional hierarchy by relaxing precision-weighting of high-level priors. We tested this prediction through progressively more direct measures of hierarchy, and further explored the temporal stability of such changes.

Our first study (**Chapter 1**) applied functional harmonic decomposition to the resting state fMRI data of the Santo Daime prior to and following ayahuasca ingestion, using an intravenous DMT dataset as a comparative benchmark. Results revealed convergent effects across datasets. Latent space embedding of all 11 spatially resolved harmonics and the global harmonic demonstrated significant latent spread contraction following drug ingestion, reflecting a psychedelic-induced reduction of trajectory amplitudes within the pre-assigned harmonic space. In other words, under ayahuasca and intravenous DMT, brain activity was less dominated by coherent large-amplitude expressions of specific harmonic spatial patterns. The observed contraction

aligns with the flattened energy landscape framework proposed by REBUS and can be further interpreted through Singleton et al.'s (2022) findings of psychedelic-induced control energy reductions. Within a flatter energy landscape, the brain transitions between a broader repertoire of states more easily (Atasoy et al., 2017; Lord et al., 2019; Tagliazucchi et al., 2014), with transitions requiring less deviation in activity, resulting in more diverse dynamics but at lower amplitudes.

Mean absolute power suppression of several spatially resolved FHs, with preservation of the global harmonic was observed across datasets. Notably, FH9 (outlining the DMN) was suppressed in both datasets, aligning with prior literature pointing to reduction in DMN intra-network coherence under psychedelics (Carhart-Harris et al., 2016, 2012; Madsen et al., 2021; Palhano-Fontes et al., 2015). However, FH2 (outlining the unimodal-transmodal gradient most directly related to hierarchy; Margulies et al., 2016)) was significantly affected under intravenous DMT but not following ayahuasca consumption. DMT showed more robust effects overall, including relative power redistribution through FH2 and FH9 suppression alongside increase in global harmonic expression, and FH2 fractional occupancy suppression. Ayahuasca showed more selective effects, showing significant alterations in a subset of harmonics only for mean absolute power, although trends towards significance were observed across several measures in line with those outlined for intravenous DMT (including suppression in absolute power of FH2 and FH3 as well as relative power increase in the global harmonic, all significant prior to multiple comparison correction). These differences may be due to several factors including long-term regular use of ayahuasca among Santo Daime members compared to the intravenous DMT cohort, relatively higher doses of DMT in the intravenous DMT study (Gable, 2007; Vogt et al., 2023), as well as differences in eye state across the datasets (eyes closed at rest in the intravenous DMT data, and open looking at a fixation in the Santo Daime dataset). The observed consistent changes in brain dynamics point to potentially robust markers of the psychedelic state co-occurring across dosing, experience, eye state, and cultural backgrounds (Vohryzek et al., 2024; Serra et al., 2023), whereas inconsistencies motivated more direct examination of ayahuasca-induced changes to the functional hierarchy.

Our whole-brain modelling and trophic analyses provided the first examination of ayahuasca-induced changes to the brain's directed hierarchy (**Chapter 3**). Context-independent ayahuasca-induced reductions were observed in TC, TL median, and TL MAD, reflecting loss of hierarchical structure, a shift towards more source-like activity, and compression of hierarchical position differentiation, respectively. Findings were confirmed in **Chapter 4** where our time-resolved approach outlined temporal mean reductions in TC, MeanTL, and RO across

resting state and music listening contexts. These findings align with and extend previous research revealing TC reductions following psilocybin-assisted psychotherapy for depression (Deco et al., 2024). Network-level analyses revealed context-independent reductions in average trophic level of several higher-order associative networks (DAN, FPN, DMN), consistent with REBUS's prediction that transmodal networks at the top of the hierarchy lose their dominant positions of influence (Carhart-Harris and Friston, 2019; Gattuso et al., 2023). This further aligns with evidence that LSD and psilocybin flatten the unimodal-transmodal gradient in the brain, and that this flattening is in part driven by reduced functional differentiation of networks at the transmodal end of the gradient (Girn et al., 2022). SVM classification using trophic level vectors alone achieved high accuracy in distinguishing drug conditions both at rest and during music listening, further supporting a clear reorganisation of the functional hierarchy under ayahuasca. These findings, in combination with the drug-induced latent-space contraction revealed in **Chapter 2**, support ayahuasca-induced flattening of the functional hierarchy.

In **Chapter 4**, we introduced a novel methodological integration of the LEiDA framework and whole-brain modelling, through per-state whole-brain modelling and trophic analyses, which extended the findings of **Chapter 3**. Temporal SD reductions in TC and MeanTL (and RO at rest) revealed that the flattened hierarchy was not a transient perturbation but rather a more sustained regime over the course of the acute ayahuasca scans, such that under ayahuasca the brain settles into a more stable, less hierarchical regime, with more source-like average activity across regions. This is consistent with prior work showing LSD to constrain hierarchical structure variability to a smaller set of dynamics (Shinozuka et al., 2025). These findings are further corroborated by reduced sensitivity of temporal mean TC to changes in musical properties outlined in (**Chapter 5**), reflecting an ayahuasca-induced shift towards a more stable hierarchical structure that is less responsive to changes in external stimuli. In the case of temporal SD of RO, an increase in temporal SD during music listening, motivated examination of how specific musical properties modulate drug-induced changes to the functional hierarchy (**Chapter 5**).

One mechanistically coherent account, offered by network control theory, says that the flattening of the functional hierarchy is directly relevant for the psychedelic-induced expanded repertoire of states (Lord et al., 2019; Tagliazucchi et al., 2014), and increased frequency of state transitions derived through undirected measures (Olsen et al., 2022; Singleton et al., 2022). Prior work modelling the effects of LSD and psilocybin using receptor-density maps showed drug-induced flattening of the control energy landscape across compounds, whereby less energy was required for transitions between states (Singleton et al., 2022). Further work

showed that within-level transitions in a hierarchy are energetically less expensive than between-level transitions, therefore hierarchy flattening should result in lower energy expenditure, given lower inter-level movement, predicting the psychedelic-induced state repertoire expansion. The evidence of hierarchical flattening provided through reductions in TC and TL distribution measures in **Chapters 3** and **4**, alongside latent-spread contraction reported in **Chapter 2** provide convergent evidence for this account.

6.2 Ayahuasca: A unique psychedelic?

Our results align with prior work showing significant hierarchy flattening as characterised by directed connectivity measures in psilocybin (Deco et al., 2024) and LSD (Shinozuka et al., 2025). Importantly, this convergence is meaningful given recent work challenging the assumption that findings across classic serotonergic psychedelics are inter-generalisable. A comprehensive meta-analysis across DMT (including ayahuasca), LSD, and psilocybin (Shinozuka et al., 2024) demonstrated that these three compounds produce significantly different profiles across phenomenology, pharmacology, and neuroimaging, with nonlinear relationships observed across the three levels. For example, fMRI studies on ayahuasca and DMT (pooled in the meta-analysis due to the low number of studies on either individually) showed no significant change in limbic network FC with other brain regions, unlike LSD which showed significant increases in FC between the limbic network and both the visual network and the FPN. Further, the ayahuasca and DMT group was the only one to show reductions in FC between the visual network and both the SMN and FPN. Thereby, presenting a unique FC profile. Pharmacological comparisons showed that although DMT, LSD and psilocin presented largely consistent receptor affinities across 5-HT_{2A}, 5-HT_{2C} and D₂, significant differences in relative activity at the inositol phosphate formation pathway were observed between drugs. The meta-analysis further outlined that DMT may uniquely bind to sigma-1 receptors. The inter-drug differences outlined in the meta-analysis make apparent the need to systematically examine the effects of each psychedelic on brain activity and the functional hierarchy, as findings from one compound should not be assumed to generalise to others.

Ayahuasca specifically is pharmacologically complex, as it is composed of a mixture of DMT and beta-carbolines (harmine, harmaline, and tetrahydroharmine) whose roles have been shown to extend beyond MAO inhibition. Each of these harmala alkaloids has been characterised as having unique psychotropic effects (Ruffell et al., 2023), as well as moderate affinity to 5-HT_{2A} (Glennon et al., 2000). Further, there is evidence that at high doses, these alkaloids may have hallucinogenic effects (Ruffell et al., 2023). Therefore, the consistency in findings

between this thesis and prior work on psilocybin and LSD, and even other forms of DMT administration go beyond replication, extending observed changes in large-scale brain dynamics and directed hierarchy flattening as signatures of the psychedelic state to a compound whose pharmacological, and neural profiles diverge from other classic psychedelics.

The primary ingredient of ayahuasca across South American cultures which use it in ceremonies and treatment is the *Banisteriopsis caapi* vine which contains beta-carbolines, with many but not all iterations incorporating the DMT-containing *psychotria viridis* (Nižnanský et al., 2022). The recent change in legal status of ayahuasca consumption in the Netherlands (where the dataset analysed in this thesis was collected) provides an exciting future route for examining the unique role of DMT-containing ayahuasca on brain dynamics. Ayahuasca ingestion for any purpose, including religious ceremonies, was prohibited in the Netherlands in 2018, causing many of the Churches which incorporate its use in divine ritual to transition to the use of *Psilohuasca*, made through the combination of *Baanisteriopsis caapi* and *sclerotia* (psilocybin-containing magic mushrooms) (Talin, 2024).

6.3 Context-dependent effects of ayahuasca ingestion

While our analyses largely showed ayahuasca-induced hierarchical flattening (TC, TL distribution) to be context-independent, some measures were differentially affected across resting state and music listening conditions, opening doors for future research. Mean EC (**Chapter 3**) showed opposing drug effects across contexts, namely increasing at rest and decreasing during music listening. Results from Bedford et al. (2023) corroborate the resting state findings, showing increase in EC under LSD at rest. Reductions in directed connectivity during music listening have been shown within reward and fronto-temporo-parietal networks using stochastic dynamic causal modelling and granger causality approaches, independent of psychedelic or alternative pharmacological interventions (Brodal et al., 2017; Burunat et al., 2024). This suggests that music on its own may potentially shift the brain towards a lower EC, however this research examined EC changes within specific pre-selected networks, rather than at the whole-brain level. Future work should aim to examine the role of ritual music listening in the presence and absence of psychedelic intervention on whole-brain changes in EC, to ascertain the role of music in coupling strength changes.

Context-dependence of ayahuasca-induced effects was further observed at the network level (**Chapter 3**), where lower-order sensory RSNs showed differential average TL reductions across rest and music listening conditions, with effects seemingly depending on the sensory

modality employed during scanning. The visual network was affected at rest (where participants were instructed to keep their eyes open looking at a fixation) but not during music (where participants were instructed to keep their eyes closed). Conversely, the somatomotor network (encompassing large parts of the auditory processing system) was affected during music listening, in the presence of auditory stimuli, but not at rest. This specificity points to a key role of context in how ayahuasca shapes activity of lower-level sensory networks, and relates to the previously proposed need for greater focus on the role of bottom-up activity within REBUS, and the potential causal roles these networks may have on the brain's directed hierarchy (Aqil and Roseman, 2023). Interestingly, although many higher-order networks showed context-independent effects, the limbic network, also a higher-order network, showed significant change only at rest, this was posited to potentially reflect an interaction between ayahuasca and the known engagement of limbic and reward regions during music listening, even in the absence of pharmacological intervention (Blood and Zatorre, 2001; Koelsch, 2014; Lerner et al., 2009). Further, the deeply meaningful, and potentially emotionally arousing nature of the ceremonial music used in this study may have contributed to the unique observation pertaining to the limbic network, necessitating future systematic exploration into the effects of meaningful music on the limbic network within the psychedelic state. Importantly, the confound between music presence and eye state limits interpretation of any between-context comparisons, necessitating a more detailed characterisation of how changes in eye state and music presence, separately, shape brain activity prior to and during the psychedelic state in future data collection.

Chapter 4 revealed further context-dependent effects, outlining a globally coherent PL state, which showed significantly greater mean lifetimes under ayahuasca at rest but not during music. A movement towards a more globally coherent state has been outlined in prior psychedelic neuroimaging research (Atasoy et al., 2017; Lord et al., 2019; Luppi et al., 2021; Tagliazucchi et al., 2014). Our supplementary analyses suggested that music listening, irrespective of drug presence, promotes significantly higher FO and lifetimes of this globally coherent state than the no ayahuasca resting state condition. This converges with recent evidence that listening to certain types of music in the absence of pharmacological intervention shifts the brain towards a more globally integrated state (Papadaki et al., 2025). Notably, in **Chapter 4** the temporal mean hierarchy metrics of TC and RO during rest reached significance only after FO-standardisation, reflecting within-state hierarchy reductions masked by drug-induced changes in state occupancy. This masking was not observed during music, where effects were significant both prior to and following FO-standardisation, as no significant differences in state-specific FO were observed between drug conditions. This may reflect music providing an

external anchor across drug conditions, constraining state dynamics, and enabling more straightforward interpretation of underlying hierarchical configurations.

6.4 Interplay between ayahuasca, music and its properties

The within-music analyses conducted in **Chapter 5** provided a strong demonstration that static approaches miss effects captured by dynamic methods. While time-averaged hierarchy measures showed no significant effects, time-resolved analyses of the same data revealed significant interactions between drug presence and musical familiarity and predictability. Ayahuasca-induced changes in per-state hierarchy values shifted in non-constant directions across PL states (**Supplementary Tables S4.6-S4.8**). Time-averaging nullifies such bidirectional effects, while time-resolved analyses preserve the state-specific variation.

Temporal mean TC, lost sensitivity to the main effects of musical predictability and the familiarity x predictability interaction following ayahuasca ingestion. This aligns with both REBUS (Carhart-Harris and Friston, 2019) and the PCM framework (Vuust et al., 2022, 2018), as differential brain responses to predictable versus unpredictable stimuli depend on precision-weighting of predictions, drug-induced relaxation of the functional hierarchy on which this precision-weighting depends, would inhibit differential processing of these musical properties. Temporal mean RO similarly lost its predictability main effect under ayahuasca, with the main effect of familiarity preserved, suggesting familiarity-related processing persists in shaping the dispersion of information flow roles even during the acute effects of ayahuasca. Thereby, the heterogeneity of regional positions within the hierarchy seems to lose sensitivity to the moment-to-moment temporal structure of the stimulus, while retaining sensitivity to familiarity of the music, potentially reflecting higher-level, more culturally or experientially grounded predictions. Psychedelic-induced reductions in responsiveness to unpredictable stimuli have been reported in ERP studies where reductions in responses to deviant stimuli under psilocybin have been reported in the tactile domain through observed reduction in the mismatch negativity response (Duerler et al., 2021) and the auditory domain where reduced amplitude of the P300 was observed (Bravermanová et al., 2018).

Temporal MeanTL showed a redirection of sensitivity rather than a loss, with a shift from being primarily driven by familiarity prior to ayahuasca ingestion, to being primarily driven by predictability under ayahuasca. Notably, the MeanTL measure captured where regions sit on average in the hierarchy. This is a qualitatively different measure from TC and RO, which capture the hierarchy's coherence and heterogeneity, therefore more directly reflecting structure. This dissociation between the findings of TC and RO on the one hand and those of

MeanTL on the other suggest the relationship between the brain's hierarchy and musical properties to not be uniformly diminished under ayahuasca. While the structure of the underlying hierarchy (as quantified through RO) appears to remain partially modulated by higher-order priors relating to musical familiarity, the central tendency of regional information flow roles across the brain (quantified through MeanTL) becomes more responsive to lower-order features of predictability. The observed redirection in MeanTL sensitivity represents a movement from a listener-specific property of the music (how familiar it is to the participant) to a stimulus-based one (how predictable the music is), potentially as a consequence of hierarchical flattening enabling stimulus-based features to have greater influence on regional activity, and thus shift the system's central tendency. The relationship between psychedelic-administration and responsiveness to external stimuli has not previously been explored from the perspective of changes to functional hierarchy, however research on the effects of psychedelics on facial emotion responsivity have outlined the effects to be more complex than a general reduction in sensitivity. Several studies have outlined reductions in reactivity to fearful or negative faces alongside increased recognition or a lack of change in responsiveness to happy or positive faces (Kometer et al., 2012; Mueller et al., 2017), as well as functional connectivity changes in response to fearful and neutral faces, but not happy ones (Mertens et al., 2020). Although not relating to functional hierarchy directly, this work does point to the relationship between drug and stimulus and their resulting effects on brain activity not being stimulus-ambivalent nor reflecting a simple linear reduction in sensitivity.

6.5 Insights into the unique role of ceremonial music

The Church's own ceremonial hymns (the Familiar Predictable condition) stood out as the only music condition where ayahuasca increased temporal mean TC and RO, standing in contrast to the general ayahuasca-induced hierarchical flattening pattern observed throughout the thesis. Deeply familiar ceremonial music seems to interact with the psychedelic state in a qualitatively distinct way, enhancing hierarchical structure where in the presence of other music it is observed to be homogenised (RO) or maintained (TC), aligning with qualitative work on the unique importance of ceremonial music within the ayahuasca experience (Hartogsohn, 2021; Labate et al., 2017a). The unique effects of ayahuasca during the Familiar Predictable music condition provide the first directed-connectivity evidence consistent with the seminal "Jungle Gym of Consciousness" theory of the role of music within the ayahuasca-induced state (Dobkin de Rios and Katz, 1975). The ceremonial hymns seem to uniquely enhance the brain's directed hierarchical structure under ayahuasca.

The recently proposed Altered Beliefs Under Psychedelics (ALBUS) framework (Safron et al., 2025) offers one theoretical account that is well-placed to interpret the unique effects observed in the presence of the Church's own music. ALBUS proposes that 5-HT_{2A} agonism induced by serotonergic psychedelics can produce both relaxation of beliefs (REBUS) and strengthening of beliefs (Strengthened Beliefs Under Psychedelics, SEBUS), and that these may co-occur at different hierarchical levels of representation within the same psychedelic experience. Dose, set, setting and the nature of the priors engaged are argued to jointly determine whether the balance shifts towards REBUS or SEBUS. Within this framework, the "enhanced meaning-making" within psychedelic experiences was identified as a clear actualization of SEBUS. Safron et al. outline that the perceived vividness of experience under psychedelics which is suggested to reflect greater precision of sensory information, may equally reflect enhanced precision and thus vividness of expectations through SEBUS. Viewed through this lens, the thesis findings display both effects described by ALBUS, as the general hierarchical flattening observed across conditions is consistent with REBUS, while the selective strengthening of directed hierarchy during ceremonial music listening is broadly consistent with SEBUS. Further, the ceremonial hymns within the Santo Daime tradition are uniquely placed here, as they are not only familiar to members of the Church but also critically imbued with religious meaning. The hymns are thought to be received from the divine rather than created by Church members, and function as the primary vehicle for transmission of the doctrine (Hartogsohn, 2021). The following section considers existing evidence and discourse on religious experience through the predictive coding lens, as the basis for understanding how regular ritual practice may shape the strength of priors evoked by listening to ceremonial music during the ayahuasca state.

6.6 Implications for the predictive coding of religious experience

The observed unique role of ceremonial music in shaping the functional hierarchy under ayahuasca necessitates consideration of the fact that the ceremonial music is part of a complex ceremony and reflects and embodies a set of strong religious beliefs. Therefore, in this section I outline existing evidence on the role of religion, and ritual in shaping priors, and speculate on how the ceremonial music's role within the ayahuasca state may be understood as a tether to the rich religious context it sits at the heart of.

A limited but growing body of literature has examined religious experiences through the lens of predictive processing (Andersen et al., 2019; Schjoedt and Andersen, 2017; van Elk and Aleman, 2017). Prior work has proposed that regular religious contexts may result in strong priors, constraining one's interpretation of incoming information (van Elk and Aleman, 2017).

Interestingly, not only the content, but also the sensory modality of hallucinations has been proposed to be determined by the specific religious background of the individual (Cassaniti and Luhrmann, 2014). Xygalatas (2025) developed these ideas further, by proposing that it is the continued practice of ritual itself which provides an active inference mechanism, as the enactment of rituals grounds abstract religious concepts through embodied action, thereby strengthening the associated priors. They suggest that the perceived value of ritual actions is often closely associated with their cost or difficulty. Santo Daime ceremonies are physically and mentally strenuous undertakings, referred to as *works* (*trabalhos*; Hartogsohn, 2021), and may thereby contribute to the strengthening of relevant religious or ceremonial priors. Dupuis (2021) proposed that psychedelics induce a “hyper-suggestible state”, within which cultural and religious priors, and the embodiment of these through ritual (of which music is a central component), provide a scaffold for not only how the experience is interpreted, but also what is experienced, aligning with the Jungle Gym of Consciousness Theory (Dobkin de Rios and Katz, 1975). The findings presented in this thesis provide initial empirical support for such effects, through observations of general hierarchy flattening in line with REBUS, alongside enhancement of hierarchy under conditions where ayahuasca ingestion is accompanied by ceremonial music listening, through which the experience is anchored to its regular religious context.

The ceremony is a densely structured ritual environment including collective ayahuasca ingestion, coproduction of music, wearing of a uniform or *farda*, assigned placement based on gender and seniority, specified geometric organisation of the group, and a shared spiritual intention (Hartogsohn, 2021; Labate et al., 2017b, 2017a). The collective nature of these events is an important element of ayahuasca ceremonies, amplifying the "socialisation of hallucinations", or shaping of psychedelic experience through social interactions (Dupuis, 2021). The psychosocial aspects of collective psychedelic experience have been argued to be essential to psychedelic ceremonies (Kettner et al., 2021; Rose, 2025), and prior work has pointed to music specifically bridging between participants within ayahuasca ceremonies (Roseman et al., 2021). Beyond the environment, the set of Santo Daime members is also unique, with members having a shared divine purpose when participating in ceremonies, and the ayahuasca brew itself being adorned with divine significance, as is made apparent by the name of the religion, *Santo Daime*, (in translation ‘sacred give-me’) referring to the brew as a sacred gift (Hartogsohn, 2021). Drinking the brew is thought of as drinking the blood of Christ and has been spoken of as “divine being transformed into liquid”. The calendar of ceremonies has been said to enhance

the perceived importance of ceremonies, further shaping the set of members entering the ayahuasca ceremony. From an active inference perspective, the preparation for and enactment of ceremonies functions as a mechanism for enhancing participants' priors (Xygalatas, 2025). The Santo Daime ayahuasca ceremonies are complex and multifaceted, importantly for the current thesis, their symbolism is largely carried in the content of their hymns (Hartogsohn, 2021), thus listening to the music may provide a bridge to the Santo Daime's usual context of ayahuasca ingestion, namely in seeking God.

6.7 Clinical relevance for the unique role of music within psychedelic states

The unique effects of familiar predictable music as well as the differential effects between ayahuasca-induced changes at rest and during music listening add to a growing body of literature examining the role of music, and importantly different types of music on the psychedelic experience. This has implications for psychedelic-assisted psychotherapy. As outlined in Chapter 1, well-chosen music has been argued to encourage therapeutically useful emotions, mental imagery and a sense of safety during the acute psychedelic experience (Kaelen et al., 2018), as well as positive long-term mental health outcomes (Kaelen, 2017; O'Callaghan et al., 2020). Music choice has also been associated with differences in mystical experience scores during sessions (Strickland et al., 2021), and patients' prior experiences of the music played have been found to predict psychedelic experience quality (Kaelen, 2017). Following psychedelic-assisted therapy patients outlined a preference for personalisation of musical playlists (Noorani et al., 2018). The findings presented in this thesis suggest that ceremonially meaningful, familiar music interacts with the psychedelic state in a qualitatively different way from other forms of music. Importantly, the strong priors relating to religion and ceremony among the Santo Daime, limit the immediate generalisability of our findings. Caution should be exercised in any attempts to directly apply music from such a unique context to individuals with no priors relating to the wider culture within which these hymns play a key role. Future research would need to compare the effects of more broadly utilised music playlists developed for psychedelic therapy, personally curated music playlists based on individual perceptions of musical familiarity and meaning, and ceremonial music within the psychedelic state. Effects on brain dynamics as well as the experience and clinical outcomes should be examined in tandem, to enable a more holistic understanding of the role of music in shaping the psychedelic state. Such work would provide further discernment in whether the observed differential effects of the Familiar Predictable music condition in the current thesis are dependent simply on familiarity, or whether

the strongly embedded ritual and belief context underlying this music is truly driving these effects.

6.8 The relevance of directed hierarchy measures in testing REBUS

Predictive processing accounts of brain function describe brain activity as a hierarchically organised generative model, in which higher levels produce predictions about activity of lower levels, and regions comprising lower levels transmit prediction errors back upwards through the hierarchy, with these interactions mediated through precision-weighting (Clark, 2013; Friston, 2010, 2005). This hierarchical organisation has been mapped onto specific laminar architecture in the cortex, within which feedforward and feedback information is carried in distinct cortical layers (Bastos et al., 2012; Felleman and Van Essen, 1991). The REBUS framework relies on this architecture (Carhart-Harris and Friston, 2019). Importantly, directly measuring precision weighting from non-invasive neuroimaging is not currently possible as precision parameters are not neural activity, but rather they are parameter values which inform how the system weights different signals, and thus how much influence signals carry. Extracting these parameters from BOLD or other non-invasive neuroimaging signals is an inverse problem with many-to-one mapping, as different combinations of parameters could result in the same signal output (Shinozuka, 2024). REBUS outlines that the reduced precision-weighting or influence of high-level priors, results in a flattening of the hierarchy. Our trophic analyses provide direct evidence of this hierarchical flattening through context-independent reductions in hierarchical coherence, homogenisation of information flow roles across the directed hierarchy, as well as a global movement towards more source-like activity on average.

Rajpal et al. (2022) developed a Bayesian state-space model which was used to examine the relationship between LSD-induced changes in brain activity (derived from MEG) and modelled changes in precision-weighting. Their model was composed of two levels within which the high-level variable generated top-down predictions about low-level activity, and the low-level variable generated prediction errors, and precision parameters defined the precision of the prior as well as of the bottom-up sensory information. By reducing the precision of high-level priors, through the addition of noise, explicitly aligning with the proposal of REBUS, they observed increased Lempel-Ziv complexity, and importantly decreased directed transfer entropy, aligning with observed LSD-induced changes. Transfer entropy is a measure of time-directed information transfer (Barnett et al., 2009), and has previously been effective in showing ayahuasca-induced reductions in top-down and increases in bottom-up directed information flow in EEG data (Alonso et al., 2015). The undirected Lempel-Ziv measure was not able to discriminate

between the effects of LSD administration and the difference in brain dynamics of patients with schizophrenia compared to matched controls (Rajpal et al., 2022). On the other hand, transfer entropy clearly dissociated these groups showing LSD-induced reductions and schizophrenia-based increases, with the modelled reduction of precision weighting of priors uniquely reflecting the LSD state, further highlighting the importance of directed measures in testing REBUS.

6.9 The contribution of dynamics to understanding hierarchy

The combination of LEiDA, whole-brain modelling and trophic analyses introduced in **Chapter 4** represents, to the best of our knowledge, the first incorporation of state-based dynamics into whole-brain model-based directed hierarchy quantification. The value of the novel state-based approach is clearly demonstrated by the findings of **Chapter 5**, where time-averaged hierarchy analyses showed no significant effects of drug or music properties, whereas time-resolved state-based analyses revealed extensive interactions across conditions. Further, FO and lifetimes of undirected PL states outlined in **Chapter 4** showed significant ayahuasca-induced effects at rest but not during music listening. However, the incorporation of whole-brain modelling and trophic analyses revealed significant ayahuasca-induced differences in hierarchical structure during music listening as well. Thus, the novel approach represents a methodological development from two complementary perspectives: it extends undirected dynamic measures (LEiDA) by incorporating them within a directed hierarchy modelling and analysis framework, and it extends static hierarchy analyses by resolving them across dynamic brain states. This framework can be applied to any research where hypotheses concern changes to directed hierarchy dynamics, these could include research on meditation, sleep, disorders of consciousness, and other pharmacological interventions. An important future direction is the development of subject-specific time-resolved whole-brain modelling, which would enable individual differences in hierarchical dynamics to be captured more accurately, rather than being estimated from subject-specific state trajectories in group- and state-level models.

6.10 Methodological considerations and future directions

The potential of observed context-independent reductions in trophic measures reflecting decisions relating to the modelling procedures from which effective connectivity and directed hierarchy measures are derived must be considered. Firstly, findings may reflect increased noise in the data following ayahuasca ingestion, which would impact GEC estimation, and thus lead to changes in resulting hierarchy measures not necessarily reflective of a true hierarchical re-

organisation. However, across conditions, whole-brain models achieved high fit quality, suggesting that differences in GEC-derived hierarchy measures reflecting random noise in the acute ayahuasca data is unlikely. The entropic brain hypothesis does posit enhanced complexity in neural activity under psychedelics, however this increased complexity is viewed as meaningful and non-random, as psychedelic states are characterised by enhanced entropy in specific aspects of brain activity such as increased repertoire of functional connectivity states (Carhart-Harris et al., 2014). Secondly, the Hopf whole-brain models used throughout **Chapters 3-5** apply a single fixed bifurcation parameter value across all conditions, as modelling the relationship between drug pharmacokinetics and proximity to the bifurcation was not a focus of this work. Prior whole-brain modelling research has shown intravenous DMT administration to shift this parameter closer to the bifurcation point compared to baseline (Piccinini et al., 2025), and if ayahuasca produces a similar shift, the fixed value may provide a more accurate fit to the pre-ayahuasca state, potentially introducing systematic differences in the resulting hierarchy measures. The consistency of findings across **Chapter 3** and **4**, where the modelling differed in approach to data modelling, namely subject- (**Chapter 3**) compared to state-specific (**Chapter 4**) modelling as well as in fitting procedure parameters, provides grounding for the validity of our findings, while not eliminating the need for future work to incorporate ayahuasca's pharmacokinetic profile in modelling. Third, our findings, as is a general facet of neuroimaging analyses, may be parcellation dependent. The DK80 parcellation applied throughout **Chapters 3-5**, is a development of the DK62 parcellation namely in the inclusion of subcortical structures. Prior work has demonstrated the effectiveness of the DK80 parcellation, in balancing spatial accuracy and the computational demands of whole-brain modelling (Deco et al., 2024, 2021), providing a solid grounding for its use in this thesis. Nevertheless, future work should systematically examine the effects of different parcellations on whole-brain modelling fit quality and resulting findings.

The GEC, derived through whole-brain modelling, provides a causal mechanistic understanding of the relative influence nodes within the model exert on one another. This mechanistic understanding is provided through the local dynamics incorporated into the model, in this case specifically each pair of nodes being modelled as coupled Stuart-Landau oscillators. Further, the model provides a biological underpinning to the observed changes in dynamics, as connections are restricted only to those which are present in the underlying structural connectome. Structural connectivity data (such as diffusion tensor imaging (DTI), diffusion magnetic resonance imaging (dMRI) or high angular resolution diffusion imaging (HARDI)) is often difficult to acquire, with many whole-brain modelling studies relying on what are considered to

be standardised averaged representations of structural data from high-resolution high-density DTI such as that provided by the HCP, as was used in this thesis. Importantly, this choice is most directly translatable when conducting analyses on data from healthy adult controls, as the available connectomes most accurately reflect this group. Prior research applying whole-brain modelling techniques to patients who had experienced strokes, showed that the inclusion of patient-specific lesion masks improved the model's accuracy (Idesis et al., 2022). As noted previously, research on long-term ayahuasca users showed structural differences in gray matter compared to matched controls, specifically thicker corpus callosum (Simonsson et al., 2022) and thinner posterior cingulate cortex (Bouso et al., 2015). Therefore, future work should aim to collect and incorporate DTI data from Santo Daime members, enhancing accuracy in the underlying structural connectome through which effective connectivity is derived. Although this inclusion would enhance the biological accuracy of future models, the within-subject design of the current dataset removes the potential for the structural connectome used biasing findings.

Majority of generative models of brain activity rooted in the structural connectome, including the Hopf model used in **Chapters 3-5**, assume connections between regions to be positive, such that if two regions are connected, an increase in the activity of one increases the activity of the other. This assumption has persisted in part due to structural connectivity methods such as DTI only producing positive connectivity patterns (Luppi et al., 2026; Tanner et al., 2024). However, work published in March this year examined the effects of permitting the inclusion of negative connections in Hopf whole-brain model fitting across humans, macaques and mice, showing improved fit quality across species (Luppi et al., 2026). Importantly, their approach did not impose negative connections, but rather enabled their inclusion only if they improved the fit of the model. Across species they observed the resulting optimised GEC to include approximately 25-40% negative connections, which are currently not accounted for by the positive only GECs produced by models such as the one applied in this thesis. Further, they showed that the model which included negative connections produced dynamics which exhibited greater synergy, metastability, and importantly more structured hierarchical information flow. The improved fits following negative connection inclusion across species provide an exciting future avenue for whole-brain modelling, with the potential to produce more accurate models of brain dynamics, but do not invalidate existing whole-brain modelling findings which have relied on the positive-only approach, especially when high fit quality is achieved.

6.11 Conclusion

This thesis presents a systematic exploration of how ceremonial ayahuasca consumption and music shape the functional hierarchy in 24 members of the Santo Daime Church. We took a predictive processing perspective, examining our findings in light of the REBUS framework. Through a combination of undirected dynamic measures including harmonic decomposition and LEiDA, as well as whole-brain modelling-based trophic analyses of directed connectivity we demonstrated a largely context-independent flattening of the functional hierarchy under ayahuasca, providing support for REBUS within a unique dataset of long-term users to whom consumption of the psychedelic brew sits at the heart of a musical religious doctrine. Our novel method combining LEiDA with per-state whole-brain modelling and trophic analyses, revealed that the functional hierarchy is not only flattened, but this flattened regime is more temporally stable under ayahuasca, exhibiting reduced sensitivity to changes in musical stimuli. The Santo Daime's own ceremonial music was uniquely associated with a clear strengthening of hierarchy under ayahuasca, suggesting a specific role of this music in shaping the brain's functional hierarchy during ceremonies. These findings provide the first empirical evidence for the unique role of ceremonial music in the Santo Daime's ayahuasca-induced pursuit of the divine, described in anthropological work for decades. Our findings encourage future research to examine the relationships between hierarchy, psychedelics, music and religion, and our novel methodology provides an exciting future avenue for exploring state-based transition in the configuration of functional hierarchy.

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Supplementary

Section S1.1 Whole-brain modelling

Large-scale brain dynamics were described as a network of N coupled neural oscillators ($N = 80$ brain regions in the Desikan-Killiany 80 parcellation). Local dynamics of each region were modelled as a Stuart-Landau oscillator, corresponding to the normal form of a Hopf bifurcation, a formulation that has been regularly applied to modelling shifts between oscillatory and noise-driven brain dynamics (Kuznetsov, 2004). In this approach, whole-brain dynamics are modelled through the coupling of Stuart-Landau oscillators' local dynamics through the connectivity matrix C , as follows:

$$\frac{dz_j}{dt} = (a_j + i\omega_j)z_j - |z_j|^2 z_j + \sum_{k=1}^N C_{jk}(z_k - z_j) + \eta_j \quad (\text{S1.1})$$

Each oscillator in region j is described as a complex variable z_j denoting the state ($z_j = x_j + iy_j$), where the real part x_j corresponds to the simulated fMRI BOLD signal. Each node's bifurcation parameter a_j defines the dynamical regime of the oscillator, such that when $a_j < 0$, local dynamics present a stable spiral point, whereby oscillations are dampened and activity is driven by added Gaussian noise η_j . The intrinsic frequency $f_j = \omega_j/(2\pi)$ of each region lies in the 0.008-0.08Hz band and was derived from the empirical data as the mean peak frequency of each region's narrowband BOLD power spectrum, averaged across participants (Deco et al., 2017b).

When fitting whole-brain neuroimaging dynamics, the bifurcation parameter a_j is set to be slightly negative, but close to zero, previously estimated at $a_j = -0.02$ (Deco et al., 2017b). Placing the system in a *subcritical* regime, where the fixed point z_j is stable and oscillations are driven by noise (reflecting a system of dampened oscillators amplified by stochastic input). At this operating point, the nonlinear term ($|z_j|^2 z_j$) becomes negligible and the dynamics can be linearised, such that the FC can be solved for analytically (Ponce-Alvarez and Deco, 2024). It is this linearised form of the model which is applied throughout the current thesis. The FC between all region pairs is approximated using a linear noise approximation. Therefore, the dynamical system outlined in **Equation S1.2** can be expressed in vector format:

$$\frac{d\mathbf{z}}{dt} = (\mathbf{a} - \mathbf{S} + i\boldsymbol{\omega}) \odot \mathbf{z} - (\mathbf{z} \odot \bar{\mathbf{z}})\mathbf{z} + \mathbf{C}\mathbf{z} + \boldsymbol{\eta} \quad (\text{S1.2})$$

where $\mathbf{z} = [z_1, \dots, z_N]^T$, $\mathbf{a} = [a_1, \dots, a_N]^T$, $\boldsymbol{\omega} = [\omega_1, \dots, \omega_N]^T$, $\boldsymbol{\eta} = [\eta_1, \dots, \eta_N]^T$ are vectors collecting the complex state variable, bifurcation parameter, intrinsic frequency, and noise of each node, respectively. $\mathbf{S} = [S_1, \dots, S_N]^T$ is the vector of node strength, where $S_j = \sum_k C_{jk}$ is the total incoming coupling strength of node j . $[\]^T$ represent the transpose of each vector, $\odot$ is the Hadamard (element-wise) product, and $\bar{\mathbf{z}}$ is the complex conjugate of $\mathbf{z}$. Neglecting the higher-order term $(\mathbf{z} \odot \bar{\mathbf{z}})\mathbf{z}$ and separating real and imaginary parts, enables the description of the linear fluctuations around the fixed point $\mathbf{z}=0$ by a stochastic linear (Langevin) equation:

$$\frac{d}{dt}\delta\mathbf{u} = \mathbf{J}\delta\mathbf{u} + \boldsymbol{\eta} \quad (\text{S1.3})$$

Here $\delta\mathbf{u} = [\delta x, \delta y]^T = [\delta x_1, \dots, \delta x_N, \delta y_1, \dots, \delta y_N]^T$ is the 2N-dimensional vector of fluctuations in the real and imaginary state variables, and $\mathbf{J}$ is the 2N x 2N Jacobian evaluated at the fixed point, with block structure:

$$\mathbf{J} = \begin{bmatrix} \mathbf{J}_{xx} & \mathbf{J}_{xy} \\ \mathbf{J}_{yx} & \mathbf{J}_{yy} \end{bmatrix} \quad (\text{S1.4})$$

The $N \times N$ blocks are defined as $\mathbf{J}_{xx} = \mathbf{J}_{yy} = \text{diag}(\mathbf{a} - \mathbf{S}) + \mathbf{C}$ and $\mathbf{J}_{xy} = -\mathbf{J}_{yx} = \text{diag}(\boldsymbol{\omega})$, where $\text{diag}(\mathbf{v})$ denotes a diagonal matrix with the vector $\mathbf{v}$ on its diagonal.

The stationary covariance matrix $\mathbf{K} = \langle \delta\mathbf{u} \delta\mathbf{u}^T \rangle$ can be obtained analytically. Writing **Equation S1.3** in differential form, $d\delta\mathbf{u} = \mathbf{J} \delta\mathbf{u} dt + d\mathbf{W}$, where $d\mathbf{W}$ is a 2N-dimensional Wiener process with covariance $\langle d\mathbf{W} d\mathbf{W}^T \rangle = \mathbf{Q} dt$ and $\mathbf{Q} = \sigma^2 \mathbf{I}_{(2N)}$ is the noise covariance matrix ($\sigma = 0.01$), the stationary covariances satisfy the Lyapunov equation (Ponce-Alvarez and Deco, 2024):

$$\mathbf{J}\mathbf{K} + \mathbf{K}\mathbf{J}^T + \mathbf{Q} = 0 \quad (\text{S1.5})$$

Simulated functional connectivity FC^{sim} was derived from the first N rows and columns of $\mathbf{K}$, corresponding to covariances among the real parts of the dynamics (i.e., the simulated fMRI BOLD signal), normalised to Pearson correlations:

$$FC_{jk}^{sim} = \frac{K_{jk}}{\sqrt{K_{jj}K_{kk}}} \quad (S1.6)$$

In addition to the zero-lag FC, the model was fitted to the empirical time-lagged covariance at lag τ , capturing how the activity of one region at time t predicts the activity of another at time $t + \tau$. The time-lagged covariance is obtained by propagating K forward in time through the Jacobian:

$$K^\tau = e^{J\tau} K \quad (S1.7)$$

The normalised time-lagged covariance was computed analogously to FC:

$$COV_{\tau,jk}^{sim} = \frac{K_{jk}^\tau}{\sqrt{K_{jj}K_{kk}}} \quad (S1.8)$$

We estimated an $N \times N$ matrix of directed GEC weights C_{jk}^{GEC} by iteratively adjusting individual connection strengths to minimise the discrepancy between empirical and simulated statistics, following the methods outlined in (Deco et al., 2024, 2018). The GEC matrix was initialised from the structural connectome $C^{(SC)}$, built using the Human Connectome Project high-density DTI data (WU-Minn Consortium, S1200 released of 812 subjects; available at: https://db.humanconnectome.org/data/projects/HCP_1200), normalised to $[0, C_{max}]$, where $C_{max} = 0.2$:

$$C_{jk}^{GEC}(0) = C_{jk}^{SC} / \max(C^{SC}) \cdot C_{max} \quad (S1.9)$$

At each iteration n , the forward model (**Equations S1.5–S1.8**) was evaluated and each connection weight was updated in proportion to the mismatch between empirical and simulated statistics:

$$C_{jk}^{GEC}(n+1) = C_{jk}^{GEC}(n) + \varepsilon_{FC}(FC_{jk}^{emp} - FC_{jk}^{sim}) + \varepsilon_{COV\tau}(COV_{\tau,jk}^{emp} - COV_{\tau,jk}^{sim}) \quad (S1.10)$$

where ε_{FC} and $\varepsilon_{COV\tau}$ are the learning rates. Updates were constrained to connections with non-zero structural connectivity $C_{(jk)}^{(SC)} > 0$ or interhemispheric homotopic pairs, with non-negativity enforced ($C_{(jk)}^{(GEC)} \leftarrow \max(C_{(jk)}^{(GEC)}, 0)$) and the matrix renormalised to $[0, C_{(max)}]$ after each iteration. The optimisation minimised the total mean squared error between empirical and simulated FC and time-lagged covariance and was terminated when the relative improvement fell below a threshold (assessed every 100 iterations), the error increased, or a maximum number of iterations was reached. The specific values of ε_{FC} and $\varepsilon_{COV\tau}$, the improvement threshold, and the maximum iterations differed between analyses and are reported in each chapter.

Goodness of fit was assessed as the Pearson correlation between the lower-triangular elements of the empirical and simulated matrices, computed separately for FC and time-lagged covariance.

Section S2.1 DMT dataset

The intravenous DMT fMRI data was collected at Imperial College Research Facility, under a Home Office license for research with Schedule 1 drugs. The study was approved by the National Research Ethics Committee London-Brent and the Health Research Authority; it was conducted in accordance with the revised Declaration of Helsinki (2000) guidelines, the International Committee on Harmonization Good Clinical Practices guidelines, and the National Health Service Research Governance Framework.

Study protocol

The single-blind, placebo-controlled study recruited 25 participants. They were scanned on two days (two weeks apart), with the order of DMT and placebo administration randomised. The current study analyses the pre and post DMT administration fMRI data. A bolus dose of 20mg DMT (in fumarate form dissolved in 10ml of sterile saline) was injected over 30 seconds, and then flushed with 10ml of saline over 15 seconds. Resting state scans were conducted before administration and during the acute effects of DMT (after administration). Each scan lasted eight minutes. Participants were instructed to lie in the scanner with their eyes closed. Following the scanning sessions, subjective assessments were carried out. 20 participants completed the study, of which three were excluded due to excessive head motion during the DMT recording, thus 17 were included in analyses. For further details on the data collection protocol please refer to (Timmermann et al., 2023, 2019; Vohryzek et al., 2024b).

Scanning protocol

Structural and functional MRI scans acquisition was conducted using a 3T scanner (Siemens Magnetom Verio Syngo MR 12). T1-weighted structural scans were acquired. The following parameters were used with a T2-weighted echo planar sequence: TR = 2000 ms; TE = 30 ms; acquisition time = 28.06 mins, flip angle = 80°; voxel size = 3x3x3 mm³ and 35 slices (0mm interslice distance).

Preprocessing

The data was received preprocessed using a previously developed fMRI-prep preprocessing pipeline. In brief, the following preprocessing steps were taken: 1. Despiking, 2. Slice-timing correction, 3. Motion correction, 4. Brain extraction, 5. Rigid body registration to structural scans, 6. Non-linear registration to 2mm MNI space, 7. Motion-correction scrubbing, 8. Spatial

smoothing of 6mm (FWHM), 9. Bandpass filtering into frequency range 0.01-0.08Hz, 10. Linear and quadratic detrending, 11. Regression of 9 nuisance regressors (3 translations, 3 rotations, and 3 anatomical signals) (Vohryzek et al., 2024b).

Section S2.2 HADES test statistics

Table S2.1 Mean absolute contribution: Wilcoxon signed-rank test statistics. Comparing no drug and drug conditions across the global FH and 11 spatially resolved FHs. Left panel: Intravenous DMT dataset. Right panel: Ayahuasca dataset. Statistics reported: W = signed-rank test statistic, Z = normal approximation of test statistic, p = uncorrected p -value, q = FDR corrected p -value (accounting for 12 FHs).

FH	Intravenous DMT				Ayahuasca			
	W	Z	p	q	W	Z	p	q
Global	98	1.02	.309	.309	131	-0.54	.587	.587
1	125	2.30	.022	.024	176	0.74	.458	.499
2	153	3.62	<.001	.001	221	2.03	.043	.089
3	142	3.10	.002	.003	220	2.00	.046	.089
4	148	3.38	<.001	.001	217	1.91	.056	.089
5	147	3.34	<.001	.001	250	2.86	.004	.026
6	151	3.53	<.001	.001	250	2.86	.004	.026
7	128	2.44	.015	.018	204	1.54	.123	.147
8	153	3.62	<.001	.001	239	2.54	.011	.044
9	153	3.62	<.001	.001	234	2.40	.016	.049
10	150	3.48	<.001	.001	216	1.89	.059	.089
11	144	3.20	.001	.002	205	1.57	.116	.147

Table S2.2 Mean relative contribution: Wilcoxon signed-rank test statistics. Comparing no drug and drug conditions across the global FH and 11 spatially resolved FHs. Left panel: intravenous DMT dataset. Right panel: ayahuasca dataset. Statistics reported: W = signed-rank test statistic, Z = normal approximation of test statistic, p = uncorrected p -value, q = FDR corrected p -value (accounting for 12 FHs).

FH	Intravenous DMT				Ayahuasca			
	W	Z	p	q	W	Z	p	q
Global	10	-3.15	.002	.010	52	-2.80	.005	.061
1	62	-0.69	.492	.591	140	-0.29	.775	.909
2	145	3.24	.001	.010	178	0.80	.424	.726
3	86	0.45	.653	.712	119	-0.89	.376	.726
4	119	2.01	.044	.106	203	1.51	.130	.520
5	62	-0.69	.492	.591	230	2.29	.022	.134
6	49	-1.30	.193	.386	178	0.80	.424	.726
7	56	-0.97	.332	.498	118	-0.91	.361	.726
8	128	2.44	.015	.044	154	0.11	.909	.909
9	134	2.72	.006	.026	146	-0.11	.909	.909
10	69	-0.36	.723	.723	172	0.63	.530	.794
11	54	-1.07	.287	.492	136	-0.40	.689	.909

Table S2.3 Fractional occupancy: Wilcoxon signed-rank test statistics. Comparing no drug and drug conditions across 11 spatially resolved FHs. Left panel: intravenous DMT dataset. Right panel: ayahuasca dataset. Statistics reported: W = signed-rank test statistic, Z = normal approximation of test statistic, p = uncorrected p -value, q = FDR corrected p -value (accounting for 11 FHs). Z values are not available in cases where there is a zero difference between no drug and drug conditions within participants resulting in an effective sample size below 15, such that the MATLAB signrank function computes the p -value from the exact distribution, not the normal approximation.

FH	Intravenous DMT				Ayahuasca			
	W	Z	p	q	W	Z	p	q
1	42	-1.63	.102	.141	146	-0.11	.909	.909
2	141	3.05	.002	.025	141	-0.26	.797	.877
3	36	-1.92	.055	.113	116.5	-0.96	.338	.754
4	63.5	-0.62	.538	.592	161	0.70	.484	.754
5	38.5	-1.80	.072	.113	167.5	0.50	.617	.754
6	14	-2.80	.005	.028	108.5	-0.90	.369	.754
7	32	-1.87	.062	.113	98	-1.22	.222	.754
8	108.5	1.52	.129	.158	130.5	-0.56	.577	.754
9	128.5	2.46	.014	.051	116.5	-0.65	.513	.754
10	57	—	.879	.879	157.5	1.01	.314	.754
11	34	-2.02	.044	.113	75	-1.92	.055	.600

Table S2.4 Mean lifetimes: Wilcoxon signed-rank test statistics. Comparing no drug and drug conditions across 11 spatially resolved FHs. Left panel: intravenous DMT dataset. Right panel: ayahuasca dataset. Statistics reported: W = signed-rank test statistic, Z = normal approximation of test statistic, p = uncorrected p -value, q = FDR corrected p -value (accounting for 11 FHs). Z values are not available in cases where there is a zero difference between no drug and drug conditions within participants resulting in an effective sample size below 15, such that the MATLAB signrank function computes the p -value from the exact distribution, not the normal approximation.

FH	Intravenous DMT				Ayahuasca			
	W	Z	p	q	W	Z	p	q
1	63.5	-0.62	.538	.658	145	-0.14	.886	.951
2	133	2.67	.007	.082	173	0.66	.511	.951
3	58.5	-0.85	.394	.658	141	-0.26	.797	.951
4	82	0.26	.795	.795	162	0.73	.465	.951
5	63	-0.64	.523	.658	166	0.46	.648	.951
6	43	-1.59	.113	.310	164	0.40	.689	.951
7	26	—	.101	.310	37	—	.575	.951
8	93	0.78	.435	.658	175	0.71	.475	.951
9	108	2.07	.039	.212	140	0.06	.951	.951
10	98	1.02	.309	.658	135	-0.09	.927	.951
11	60	—	.659	.725	21	—	.555	.951

Section S3.1 Time-averaged hierarchy tables

Table S3.1 Tau optimisation model fitting. Combined model fit: mean of Pearson correlations between empirical and simulated FC and COV τ matrices. Highest fit is achieved at $\tau = 2$ across all conditions.

Condition	$\tau = 2$	$\tau = 3$	$\tau = 4$	$\tau = 5$
No Ayahuasca Rest	0.7666	0.7449	0.7067	0.5380
Ayahuasca Rest	0.6893	0.6547	0.6045	0.5330
No Ayahuasca Music	0.7066	0.6845	0.6481	0.5813
Ayahuasca Music	0.6165	0.5765	0.5207	0.4346
Mean	0.6948	0.6652	0.6200	0.5217

Table S3.2 Resting state: Differences in average trophic level of each canonical RSN (Yeo et al. 2011) following ayahuasca ingestion within resting state scans. Statistical significance of Wilcoxon Signed-rank Tests prior to and following FDR correction. Average trophic level is derived as mean trophic level across regions comprising RSN, weighted by proportion of region accounted for within given RSN. Resting state networks: Vis (Visual Network), SMN (Somatomor Network), DAN (Dorsal Attention Network), VAN (Ventral Attention Network), Lim (Limbic Network), FPN (Frontoparietal Network), and DMN (Default Mode Network).

RSN	Median (pre)	Median (post)	W	Z	r	p	q
Vis	0.125	0.101	180	2.224	0.485	0.026	0.044
SMN	0.174	0.153	154	1.321	0.288	0.187	0.198
DAN	0.220	0.157	185	2.398	0.523	0.016	0.038
VAN	0.220	0.176	153	1.286	0.281	0.198	0.198
Lim	0.248	0.172	203	3.024	0.660	0.002	0.015
FPN	0.254	0.181	178	2.155	0.470	0.031	0.044
DMN	0.261	0.168	198	2.850	0.622	0.004	0.015

Table S3.3 Music Listening: Differences in average trophic level of each canonical RSN (Yeo et al. 2011) following aya-huasca ingestion within music listening scans. Statistical significance of Wilcoxon Signed-rank Tests prior to and following FDR correction. Average trophic level is derived as mean trophic level across regions comprising RSN, weighted by proportion of region accounted for within given RSN. Resting state networks: *Vis* (Visual Network), *SMN* (Somatomor Network), *DAN* (Dorsal Attention Network), *VAN* (Ventral Attention Network), *Lim* (Limbic Network), *FPN* (Frontoparietal Network), and *DMN* (Default Mode Network).

RSN	Median (No Aya)	Median (Aya)	W	Z	r	p	q
Visual	0.171	0.101	168	1.807	0.394	0.071	0.071
SMN	0.137	0.102	184	2.364	0.516	0.018	0.042
DAN	0.189	0.117	219	3.580	0.781	0.000	0.002
VAN	0.140	0.117	172	1.946	0.425	0.052	0.060
Limbic	0.180	0.130	175	2.051	0.447	0.040	0.056
FPN	0.177	0.115	214	3.406	0.743	0.001	0.002
DMN	0.185	0.130	181	2.259	0.493	0.024	0.042

Section S3.2 Time-averaged hierarchy figures

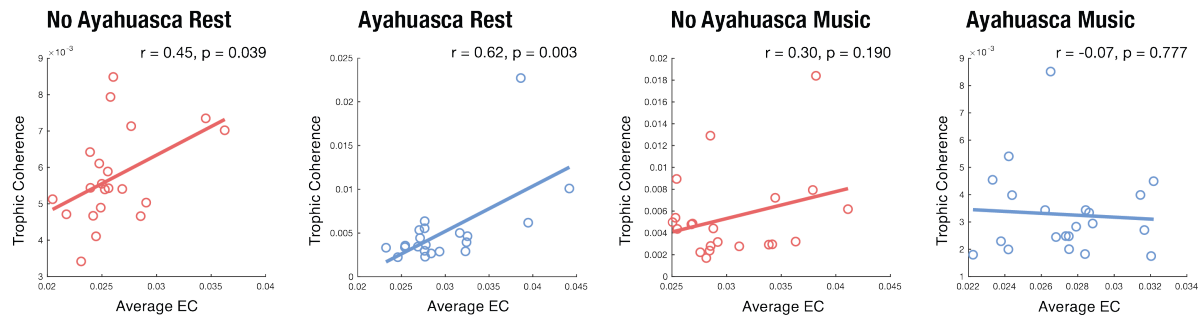


Figure S3.1 Scatter plot depicting results of Spearman correlation between average EC and TC for each of the main conditions. Each participant's scores are depicted by a circle, correlation coefficient (r) and statistical significance (p) are outlined in the top right corner of each graph. We observe significant positive correlation between average EC and TC in resting state ayahuasca conditions. No significant correlation is observed between average EC and TC during music listening scans.

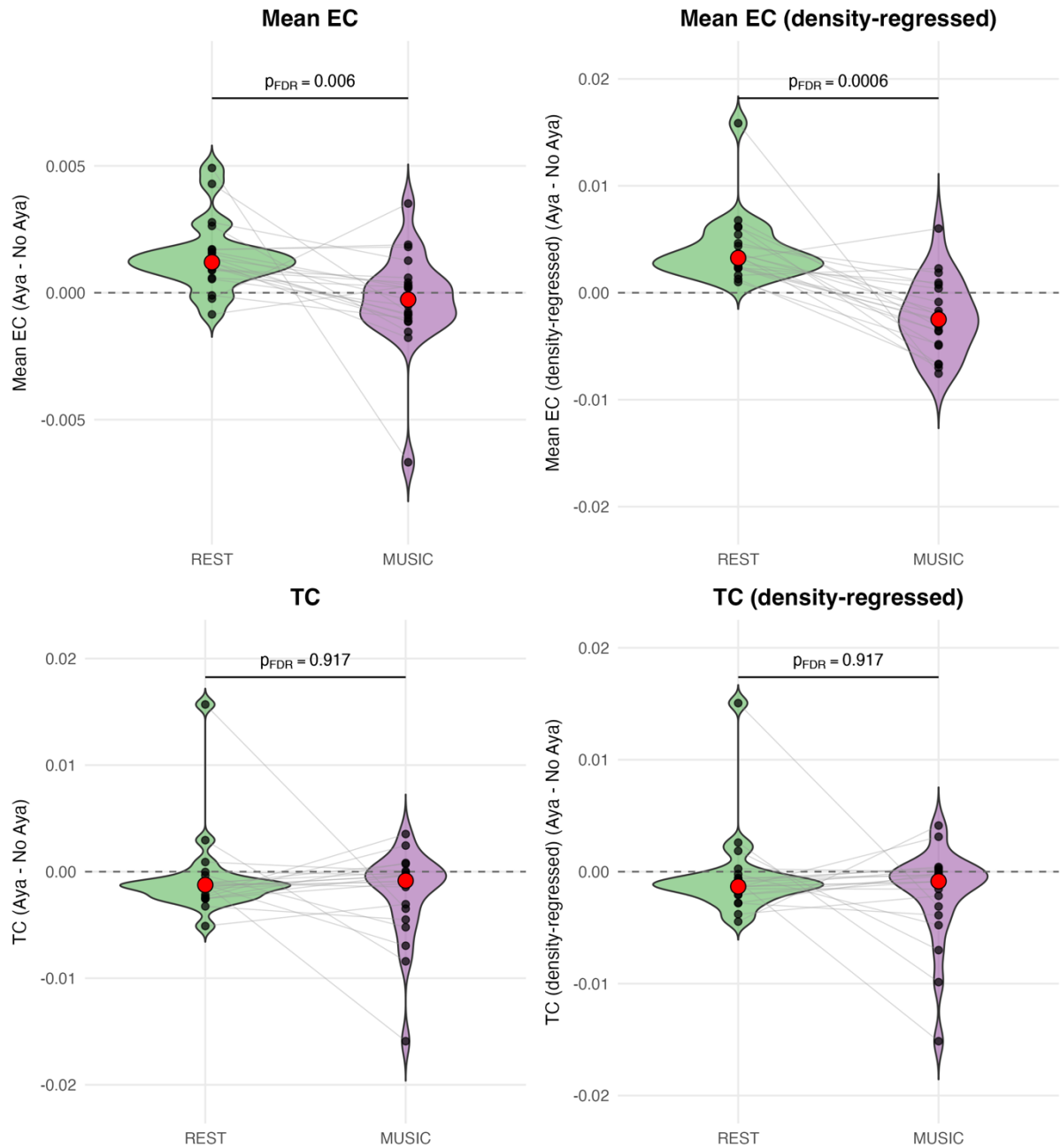


Figure S3.2 Drug x Context Interactions on Average EC and TC. To test whether ayahuasca induced changes in hierarchy measures differed between contexts (resting state eyes open and music listening eyes closed), difference-of-difference interactions were computed for each measure. For each subject, within each context, the change score (Δ = Ayahuasca – No Ayahuasca) was computed. The interaction score was computed as $\Delta_{rest} - \Delta_{music}$. A one-sample Wilcoxon signed-rank test compared the interaction score to zero. Dashed black lines show point of no change between drug conditions, with scores above this line showing measures to have increased under ayahuasca, and scores below showing measures to have decreased under ayahuasca. Green violins represent resting state Δ and purple violins represent music listening Δ . FDR multiple comparison correction is conducted, accounting for all four comparisons. A. Average EC comparison, showing a significant interaction ($W = 201$, $Z = 2.957$, $r = 0.645$, $q = 0.006$). B. Average EC comparison (density-regressed), showing significant interaction ($W = 225$, $Z = 3.789$, $r = 0.827$, $q = 0.0006$). C. TC comparison, showing no significant interaction effect ($W = 112$, $Z = -0.104$, $r = -0.023$, $q = 0.917$). D. TC comparison (density-regressed), showing no significant interaction effect ($W = 106$, $Z = -0.313$, $r = -0.068$, $q = 0.917$).

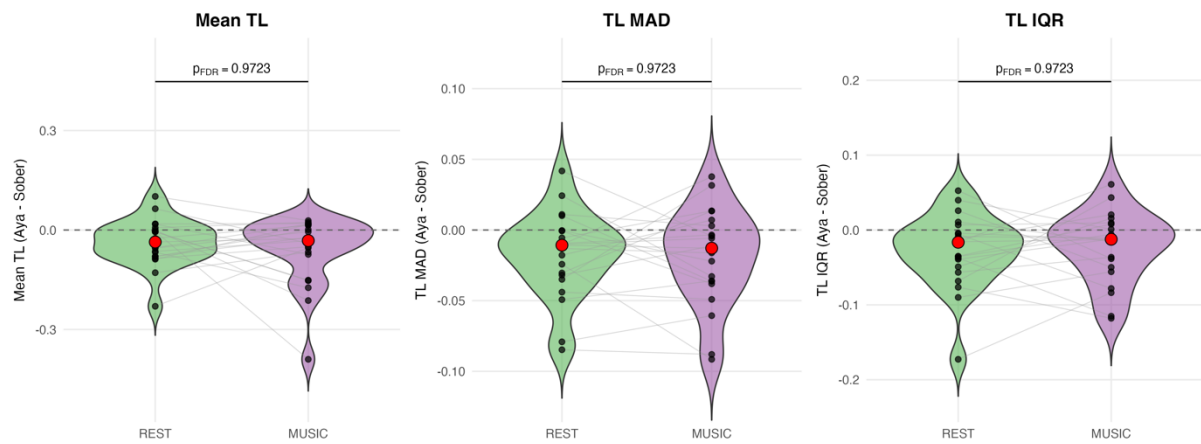


Figure S3.3 Drug x Context Interaction across TL measures. To test whether the effects of ayahuasca on average TL and distribution of TL significantly varied across contexts we computed difference-of-difference comparisons. For each subject, within each context, the change score (Δ = Ayahuasca – No Ayahuasca) was computed. The interaction score was computed as $\Delta_{\text{Rest}} - \Delta_{\text{Music}}$. A one-sample Wilcoxon signed-rank test compared the interaction score to zero. Dashed black lines show point of no change between drug conditions, with scores above this line showing measures to have increased under ayahuasca, and scores below showing measures to have decreased under ayahuasca. Green violins represent resting state Δ and purple violins represent music listening Δ . FDR multiple comparison correction is conducted accounting for all three comparisons. A. Mean TL comparison, showing no significant interaction effect ($W = 130$, $Z = -0.104$, $r = -0.023$, $q = 0.972$). B. TL median absolute deviation (MAD) comparison, showing no significant interaction effect ($W = 117$, $Z = 0.035$, $r = 0.008$, $q = 0.972$). C. TL interquartile range (IQR) comparison, showing no significant interaction effect ($W = 103$, $Z = -0.417$, $r = -0.091$, $q = 0.972$).

Section S4.1 Cluster optimisation

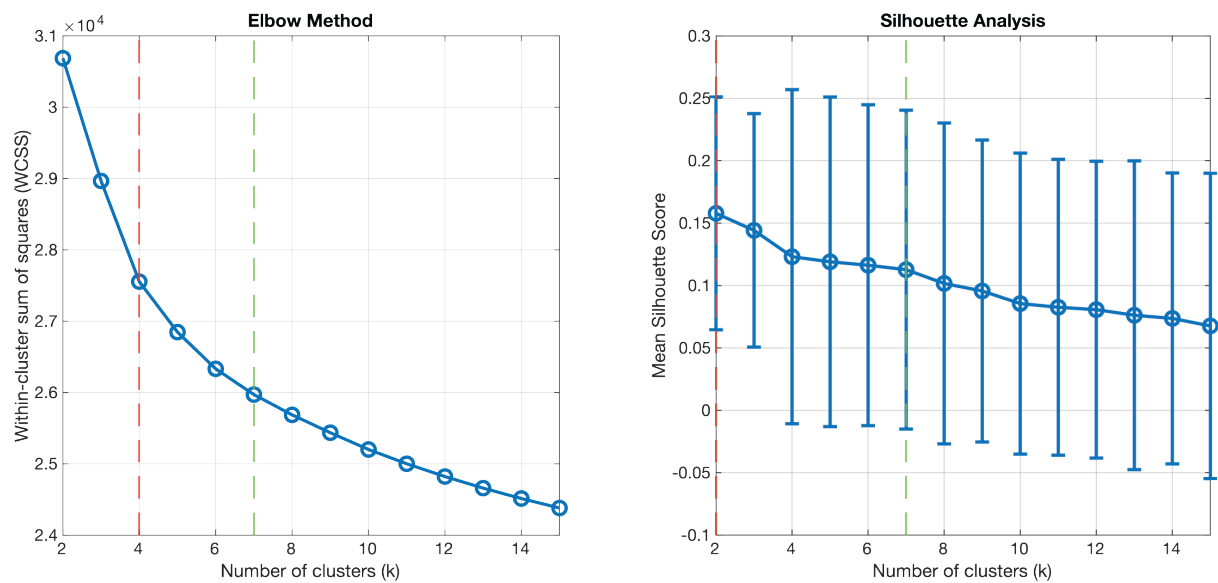


Figure S4.1 Cluster Optimisation Analysis. A. WCSS Elbow Method computed the sum of squares Euclidian distance from every timepoint to cluster it is assigned to. Optimal k (red line) shows point of maximum curve, after which distance from cluster stops significantly decreasing the sum of squares Euclidian distance. Green line denotes chosen cluster B. Silhouette Analysis computes for each timepoint, its relative proximity to points in its own cluster compared to points in the closest non-self cluster. Here the mean and standard deviation across all timepoints is plotted for each number of clusters. Red line denotes the recommended cluster. Green line denotes chosen cluster.

Table S4.1 Cluster Optimisation Stability Analysis. K-mean clustering is run 10 times for each k value (k = 5-9). The mean silhouette score is computed for each run. Here we present the mean across runs and SD across the ten runs, characterising the stability of silhouette scores across runs. Low standard deviation shows clustering converging to consistent values, and therefore marks stability. K = 7 shows equal or improved stability compared to k = 5 or 6. K = 8 or 9 shows an increase in standard deviation, suggesting a reduction in cluster stability once more than 7 clusters are used.

Number of Clusters (k)	Silhouette Mean	Silhouette SD
5	0.1191	0.0002
6	0.1163	0.0001
7	0.1126	0.0001
8	0.1025	0.0017
9	0.1008	0.0043

Section 4.2 PL state characterisation

Table S4.2 PL State correlation with canonical resting state networks (RSNs) (Yeo et al., 2011). Spatial correlation between each PL state's centroid (k-means clustering derived 80-dimensional V_1) and each of seven weighted RSN templates. The current table provides the correlation coefficient (r) for each cluster centroid and RSN pair.

Resting State Networks							
State	Visual	SMN	DAN	VAN	Limbic	FPN	DMN
1	-0.247	-0.344	-0.120	-0.246	0.269	0.074	0.653
2	-0.247	0.497	0.068	0.395	-0.167	-0.022	-0.496
3	-0.305	-0.327	0.152	0.043	0.063	0.493	0.236
4	0.072	-0.026	-0.165	-0.148	0.360	-0.317	0.060
5	-0.592	0.002	-0.253	0.618	0.006	0.285	0.070
6	0.705	-0.269	0.017	-0.559	0.102	-0.332	0.109
7	0.667	0.264	0.145	-0.237	-0.098	-0.420	-0.557

Table S4.3 Fractional Occupancy (FO) comparisons between No Ayahuasca and Ayahuasca drug conditions for each PL state, within rest and music listening contexts. Wilcoxon signed-rank tests were used for all comparisons, with following statistics reported: W , Z , r (effect size; $r = Z/\sqrt{N}$), p (prior to FDR correction), q (significance post FDR correction accounting for seven comparisons within each context). No comparisons survived FDR correction.

State	Rest					Music				
	W	Z	r	p	q	W	Z	r	p	q
1	83	-0.48	-0.11	0.629	0.734	116	0.02	0.00	0.986	0.986
2	178	2.17	0.47	0.030	0.104	142.5	0.94	0.20	0.348	0.986
3	122.5	0.24	0.05	0.808	0.808	94	-0.41	-0.09	0.681	0.986
4	33.5	-2.67	-0.58	0.008	0.053	102.5	0.30	0.07	0.763	0.986
5	152.2	1.29	0.28	0.198	0.278	100	-0.19	-0.04	0.852	0.986
6	167	1.79	0.39	0.073	0.128	114	-0.05	-0.01	0.958	0.986
7	62.5	-1.84	-0.40	0.065	0.128	95.5	-0.70	-0.15	0.487	0.986

Table S4.4 Lifetimes comparisons between No Ayahuasca and Ayahuasca drug conditions for each PL state, within rest and music listening contexts. Wilcoxon signed-rank tests were used for all comparisons, with following statistics reported: W , Z , r (effect size; $r = Z/\sqrt{N}$), p (prior to FDR correction), q (significance post FDR correction accounting for seven comparisons within each context). Only state 4, during rest, showed significant difference between drug conditions following FDR correction.

State	Rest					Music				
	W	Z	r	p	q	W	Z	r	p	q
1	92	-0.49	-0.11	0.627	0.639	79	-0.97	-0.21	0.332	0.774
2	95	-0.71	-0.16	0.476	0.639	177	2.14	0.47	0.033	0.228
3	102	-0.47	-0.10	0.639	0.639	125	0.33	0.07	0.741	0.865
4	21	-2.98	-0.65	0.003	0.020	145	1.03	0.22	0.305	0.774
5	85	-1.06	-0.23	0.289	0.639	119	0.12	0.03	0.903	0.903
6	137	0.75	0.16	0.455	0.639	102	-0.47	-0.10	0.639	0.865
7	47	-2.38	-0.52	0.017	0.060	98	-0.61	-0.13	0.543	0.865

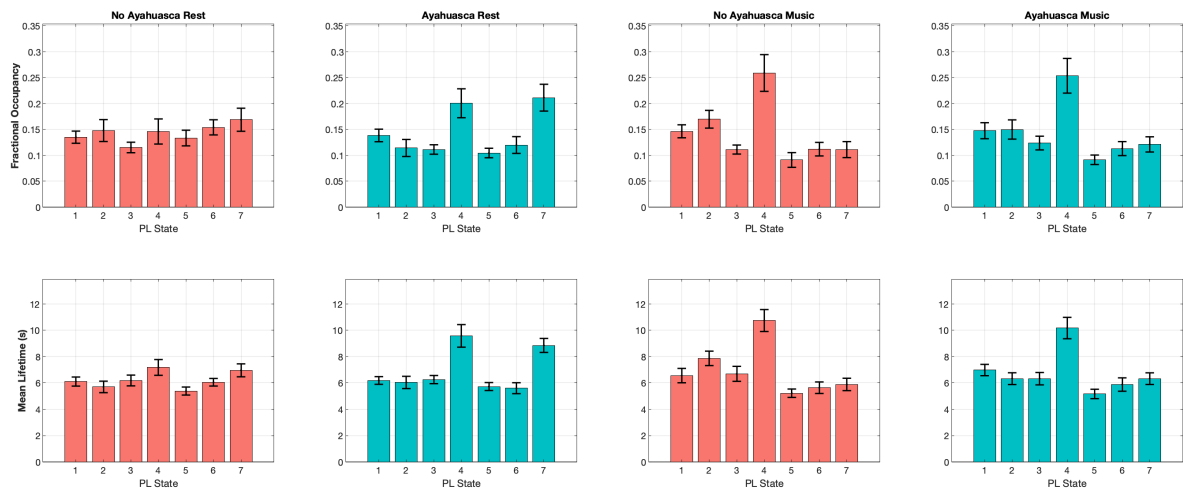


Figure S4.2 PL State Fraction Occupancy and Lifetime profiles within Resting State No Ayahuasca, Resting State Ayahuasca, Music Listening No Ayahuasca, and Music Listening Ayahuasca conditions.

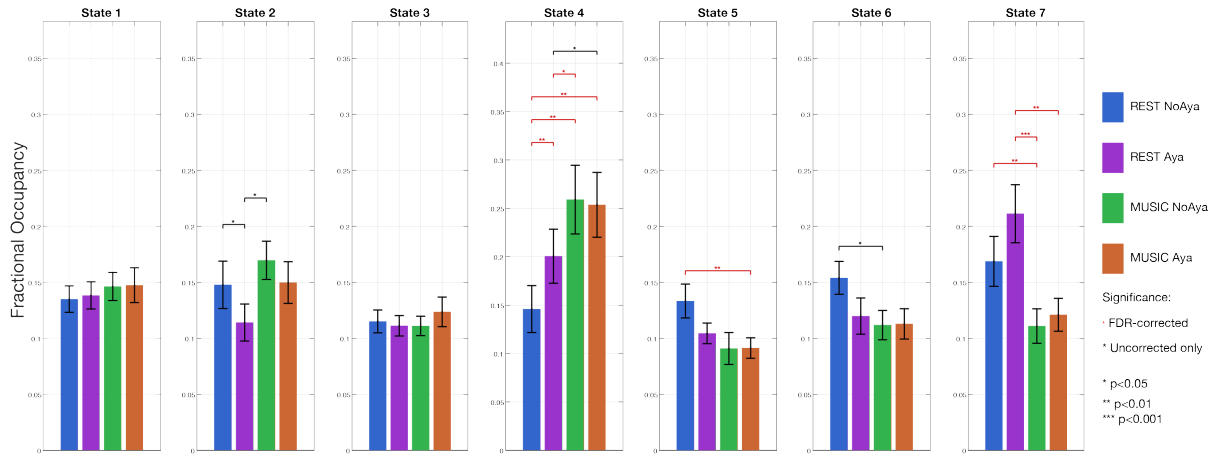


Figure S4.3 Fractional Occupancy of PL States Comparison Across Drug and Context Conditions. Wilcoxon signed-rank tests used to compare fractional occupancy of each PL State between drug and context conditions. FDR correction was done within each state, accounting for all six pairwise comparisons. Comparisons surviving FDR correction are marked using red asterisk, observed statistical significance which does not withstand FDR correction is marked with black asterisk. Notably there is increased fractional occupancy of State 4 (characterised by near global phase alignment) in resting state ayahuasca, music listening no ayahuasca and music listening ayahuasca conditions compared to resting state no ayahuasca. Across contexts we cannot determine whether observed differences are due to music presence or eye state, and are visualised here for completeness.

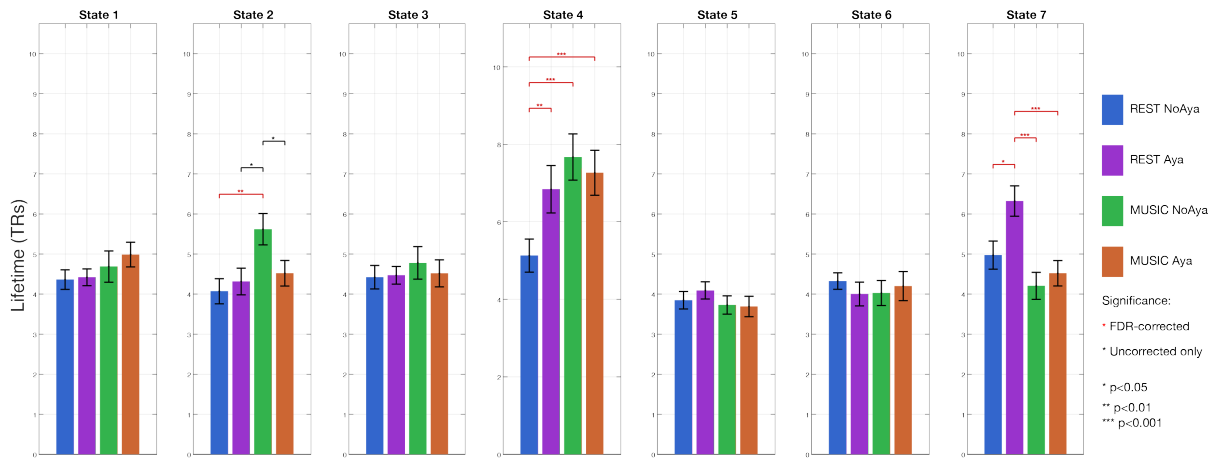


Figure S4.4 Lifetimes of PL States Comparison Across Drug and Context Conditions. Wilcoxon signed-rank tests used to compare lifetimes of each PL State between drug and context conditions. FDR correction was done within each state, accounting for all six pairwise comparisons. Comparisons surviving FDR correction are marked using red asterisk, differences which do not withstand FDR correction are marked with black asterisk. Notably there is increased lifetimes of State 4 (characterised by near global phase alignment) in resting state ayahuasca, music listening no ayahuasca and music listening ayahuasca conditions compared to resting state no ayahuasca. Across contexts we cannot determine whether observed differences are due to music presence or eye state, and are visualised here for completeness.

Section 4.3 Time-resolved whole-brain modelling and hierarchy measures

Table S4.5 Cluster- and Condition-Specific Pearson correlations between empirical and whole-brain modelling derived simulated FC and COV τ matrices. Outcomes show very good fits of over 0.8 across FC and COV τ in all conditions and clusters.

State	FC (Rest)		FC (Music)		COV τ (Rest)		COV τ (Music)	
	No Aya	Aya	No Aya	Aya	No Aya	Aya	No Aya	Aya
1	0.818	0.834	0.815	0.815	0.799	0.812	0.829	0.802
2	0.824	0.815	0.825	0.802	0.807	0.795	0.819	0.777
3	0.817	0.849	0.835	0.841	0.802	0.835	0.824	0.833
4	0.922	0.932	0.920	0.924	0.907	0.925	0.911	0.903
5	0.830	0.817	0.812	0.833	0.827	0.791	0.802	0.816
6	0.855	0.865	0.854	0.845	0.852	0.842	0.843	0.816
7	0.838	0.861	0.873	0.860	0.810	0.843	0.849	0.851

Table S4.6 Cluster- and Condition-Specific Trophic Coherence, derived from Whole-brain Modelling generated effective connectivity estimates. Δ is computed as (Ayahuasca – No Ayahuasca) per context per cluster, such that positive deltas indicate a cluster and context specific increase in TC under ayahuasca, while negative Δ shows a decrease in TC. These measures are descriptive, and reported to add context to observed shifts in hierarchy across time following ayahuasca ingestion.

State	TC (Rest)			TC (Music)		
	No Aya	Aya	Δ	No Aya	Aya	Δ
1	0.235	0.210	-0.025	0.176	0.139	-0.037
2	0.133	0.157	+0.024	0.126	0.110	-0.016
3	0.159	0.208	+0.049	0.133	0.189	+0.056
4	0.253	0.243	-0.009	0.295	0.265	-0.029
5	0.146	0.160	+0.013	0.171	0.194	+0.023
6	0.189	0.169	-0.020	0.221	0.146	-0.074
7	0.323	0.271	-0.052	0.263	0.209	-0.054

Table S4.7 Cluster- and Condition-Specific MeanTL, derived from Whole-brain Modelling generated effective connectivity estimates. Δ is computed as (Ayahuasca – No Ayahuasca) per context per cluster, such that positive deltas indicate a cluster and context specific increase in MeanTL under ayahuasca, while negative Δ shows a decrease in MeanTL. These measures are descriptive, and reported to add context to observed shifts in hierarchy across time following ayahuasca ingestion.

State	MeanTL (Rest)			MeanTL (Music)		
	No Aya	Aya	Δ	No Aya	Aya	Δ
1	1.357	0.836	-0.522	0.884	0.639	-0.244
2	0.973	0.832	-0.141	0.730	0.644	-0.086
3	0.821	0.790	-0.031	0.708	0.791	+0.084
4	0.753	0.751	-0.003	1.079	0.917	-0.162
5	0.925	0.783	-0.142	0.611	0.692	+0.080
6	0.990	0.777	-0.213	1.233	0.706	-0.526
7	2.110	1.056	-1.053	1.113	1.063	-0.050

Table S4.8 Cluster- and Condition-Specific Richness of Orchestration (RO), derived from Whole-brain Modelling generated effective connectivity estimates. Δ is computed as (Ayahuasca – No Ayahuasca) per context per cluster, such that positive deltas indicate a cluster and context specific increase in RO under ayahuasca, while negative Δ shows a decrease in RO. These measures are descriptive, and reported to add context to observed shifts in hierarchy across time following ayahuasca ingestion.

State	RO (Rest)			RO (Music)		
	No Aya	Aya	Δ	No Aya	Aya	Δ
1	0.528	0.438	-0.090	0.445	0.307	-0.138
2	0.348	0.414	+0.066	0.350	0.320	-0.030
3	0.372	0.465	+0.093	0.360	0.415	+0.055
4	0.409	0.477	+0.068	0.532	0.508	-0.024
5	0.349	0.364	+0.014	0.338	0.371	+0.032
6	0.442	0.370	-0.071	0.411	0.348	-0.063
7	0.767	0.585	-0.182	0.455	0.440	-0.015

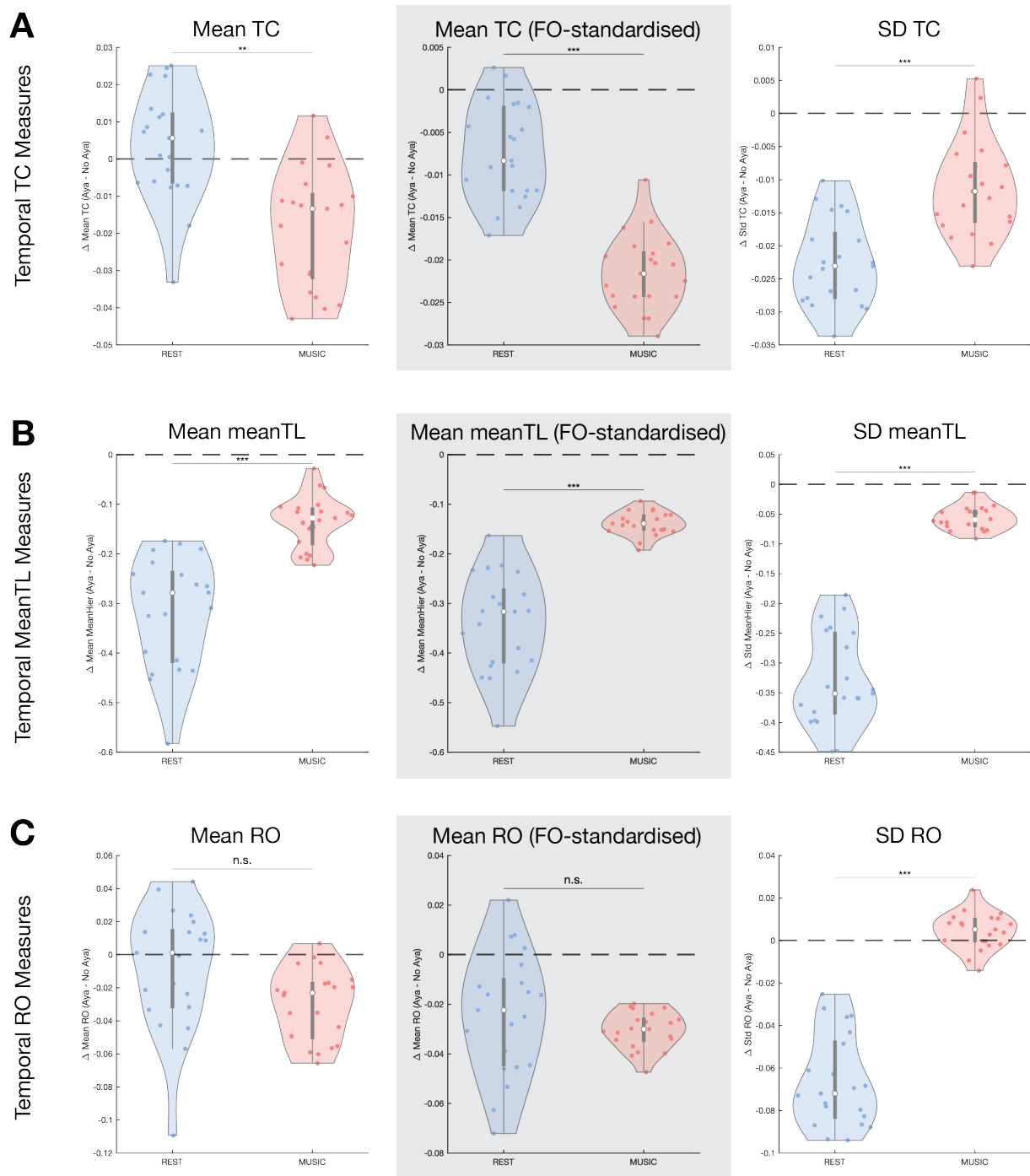


Figure S4.5 Drug x Context interactions across hierarchy measures. To test whether ayahuasca induced changes in hierarchy measures differed between contexts (resting state eyes open and music listening eyes closed), difference-of-difference interactions were explored. For each measure's temporal average and standard deviation, within each context, the change score (Ayahuasca – No Ayahuasca) was computed. Wilcoxon signed-rank tests were conducted comparing within measure change scores between contexts. Dashed black lines show point of no change between drug conditions, with scores above this line showing measures increased under ayahuasca, and scores below showing measures decreased under ayahuasca. Blue violins represent resting state Δ and red violins represent music listening Δ . For each measure we compute this statistical difference for the temporal mean (column 1), FO-standardised temporal mean sensitivity test (column 2) and temporal standard deviation (column 3). **A.** TC comparisons, with FDR accounting for two comparisons for temporal mean and standard deviation. TC Results: Temporal mean TC shows opposing effects of ayahuasca ingestion across contexts, an ayahuasca-

induced increase at rest, and a reduction during music listening. FO-standardised sensitivity analyses show ayahuasca to lead to within-state reductions in TC across contexts, such that the observed significant difference is in magnitude rather than direction of drug-induced effects between the two contexts. Temporal stability of TC is observed to be decreased under ayahuasca with a significant difference in magnitude of effects. **B.** Mean TL comparisons, with FDR accounting for four comparisons (as mean TL and RO are statistically dependent on each other). FO-standardised temporal mean outputs are sensitivity tests that help decompose whether observed effects are true within-state effects, or FO-dependent, therein no additional multiple comparison correction is conducted on these. MeanTL Results: MeanTL outcomes show consistent reductions across temporal mean and standard deviation measures following ayahuasca ingestion, with all measures showing significant difference between contexts which seem to be magnitude dependent, specifically resting state reductions in MeanTL are of much larger magnitude as compared to while listening to music. **C.** RO comparisons, with FDR correction accounting for four comparisons, aligned with mean TL. RO Results: temporal mean of RO shows no significant difference in effects of ayahuasca across contexts, prior to or following FO-standardisation. Temporal stability of this measure shows significant difference, and importantly opposing effects following ayahuasca ingestion, with ayahuasca ingestion leading to lower RO temporal SD outcomes at rest, and higher RO temporal SD outcomes during music listening. These analyses are provided for completeness, however due to multiple independent variables (music presence and eye state) we are not able to decompose the cause of any observed differences, and therefore ask readers to interpret with caution. Further, any consistent findings show robust effects of ayahuasca ingestion across distinct contexts.

Section S5.1 Time-averaged within-music

Table S5.1 Time-averaged analysis: Per condition pearson correlation between whole-brain modelling derived simulated FC and COV τ matrices and empirical FC and COV τ matrices, averaged across subjects. Reported as mean $\pm$ SD.

Drug Condition	Music Condition	FC r	COV τ r
No Ayahuasca	Familiar Predictable	0.761 $\pm$ 0.067	0.673 $\pm$ 0.071
Ayahuasca	Familiar Predictable	0.727 $\pm$ 0.055	0.633 $\pm$ 0.057
No Ayahuasca	Familiar Unpredictable	0.738 $\pm$ 0.051	0.652 $\pm$ 0.058
Ayahuasca	Familiar Unpredictable	0.750 $\pm$ 0.043	0.643 $\pm$ 0.054
No Ayahuasca	Unfamiliar Predictable	0.736 $\pm$ 0.039	0.635 $\pm$ 0.056
Ayahuasca	Unfamiliar Predictable	0.739 $\pm$ 0.039	0.639 $\pm$ 0.030
No Ayahuasca	Unfamiliar Unpredictable	0.753 $\pm$ 0.051	0.662 $\pm$ 0.065
Ayahuasca	Unfamiliar Unpredictable	0.737 $\pm$ 0.034	0.639 $\pm$ 0.048

Table S5.2 Time-averaged analysis: Shapiro-Wilk LMM residuals normality assessment and singularity warning summary table. All three hierarchy metrics failed the normality test. None presented a singularity warning during LMM fitting. TC = Trophic coherence; TL (mean) = mean trophic level; TL (SD) = standard deviation of trophic level.

Dependent Variable	Shapiro-Wilk	P-value	Normal distribution	Distribution	Singularity warning
TC	0.919	< .001	Fail		No
TL (mean)	0.945	< .001	Fail		No
TL (SD)	0.904	< .001	Fail		No

Table S5.3 Time-averaged analysis: Non-parametric ART ANOVA results. F(1,140) values and p-values are reported. No significant effects or interaction are observed across measures.

Effect	TC		TL (mean)		TL (SD)	
	F	p	F	p	F	p
Drug	0.602	0.439	0.022	0.883	0.841	0.361
Familiarity	3.539	0.062	0.609	0.437	1.288	0.258
Predictability	0.660	0.418	0.008	0.927	0.649	0.422
Drug x Fam	0.422	0.517	0.166	0.684	0.260	0.611
Drug x Pred	0.677	0.412	0.208	0.649	0.365	0.547
Fam x Pred	0.011	0.916	0.008	0.927	0.054	0.817
Drug x Fam x Pred	1.194	0.276	3.472	0.065	1.902	0.170

Section S5.2 Time-resolved within-music

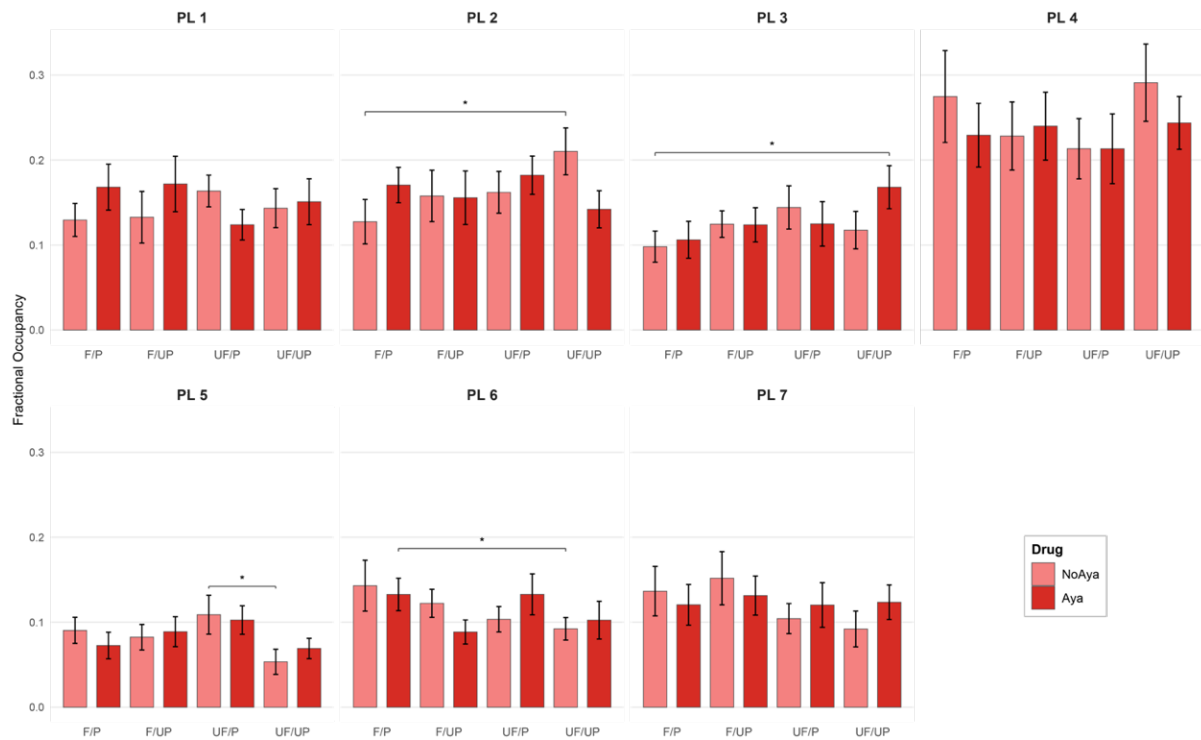


Figure S5.1 Fractional occupancy differences of each PL state across drug and music conditions. Comparisons conducted using Wilcoxon Signed-rank non-parametric paired samples tests. Black stars denote significance prior to FDR multiple comparison correction accounting for 28 within-PL comparisons. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. Light red = No Ayahuasca; dark red = ayahuasca; on x axis: F/P = Familiar Predictable; F/UP = Familiar Unpredictable; UF/P = Unfamiliar Predictable; UF/UP = Unfamiliar Unpredictable music.

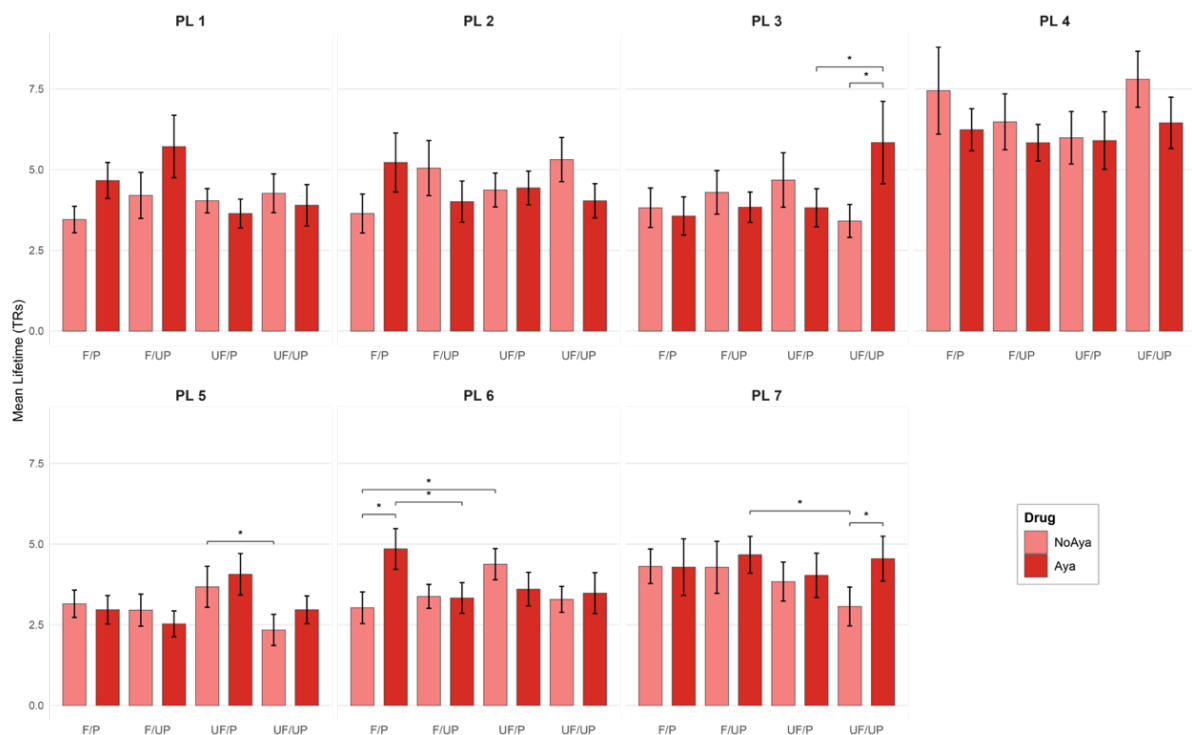


Figure S5.2 Lifetime differences of each PL state across drug and music conditions. Comparisons conducted using Wilcoxon Signed-rank non-parametric paired samples tests. Black stars denote significance prior to FDR multiple comparison correction accounting for 28 within-PL comparisons. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. Light red = No Ayahuasca; dark red = ayahuasca; on x axis: F/P = Familiar Predictable; F/UP = Familiar Unpredictable; UF/P = Unfamiliar Predictable; UF/UP = Unfamiliar Unpredictable music.

Table S5.4 Time-resolved analysis: Whole-brain model FC and COV τ fit. Per condition Pearson correlation between whole-brain modelling derived simulated FC and COV τ matrices and empirical FC and COV τ matrices, averaged across clusters. Reported as mean $\pm$ SD.

Drug Condition	Music Condition	FC r	COV τ r
No Ayahuasca	Familiar Predictable	0.758 $\pm$ 0.089	0.760 $\pm$ 0.077
Ayahuasca	Familiar Predictable	0.731 $\pm$ 0.085	0.726 $\pm$ 0.078
No Ayahuasca	Familiar Unpredictable	0.774 $\pm$ 0.061	0.771 $\pm$ 0.064
Ayahuasca	Familiar Unpredictable	0.787 $\pm$ 0.045	0.762 $\pm$ 0.040
No Ayahuasca	Unfamiliar Predictable	0.768 $\pm$ 0.047	0.753 $\pm$ 0.046
Ayahuasca	Unfamiliar Predictable	0.771 $\pm$ 0.069	0.758 $\pm$ 0.051
No Ayahuasca	Unfamiliar Unpredictable	0.748 $\pm$ 0.108	0.746 $\pm$ 0.080
Ayahuasca	Unfamiliar Unpredictable	0.746 $\pm$ 0.107	0.742 $\pm$ 0.086

Table S5.5 Time-resolved analysis: Shapiro-Wilk LMM residuals normality assessment and singularity warning summary table. All temporal SD measures failed the normality test, and two of three temporal mean measures passed marginally. TC = trophic coherence, MeanTL = mean trophic level, RO = standard deviation of trophic level; mean = mean across time; SD = standard deviation across time.

Dependent Variable	W	p	Normality ($\alpha = 0.05$)	Singular fit
TC (mean)	0.984	.052	Marginal Pass	No
MeanTL (mean)	0.991	0.323	Pass	No
RO (mean)	0.984	0.051	Marginal Pass	No
TC (SD)	0.956	<.001	Fail	No
MeanTL (SD)	0.948	<.001	Fail	Yes
RO(SD)	0.964	<.001	Fail	Yes

Table S5.6 Non-parametric Aligned Rank Transform (ART) ANOVA results across temporal means of hierarchy measures.
The non-parametric sensitivity analysis for the primary Type III ANOVA, 2x2x2 (Drug x Familiarity x Predictability) factorial design with Subject as random intercept. F-values and p-values are reported. Notations: Fam = Familiarity; Pred = Predictability.

Measure	TC (mean)		MeanTL (mean)		RO (mean)	
Effect	F(1,140)	p	F(1,140)	p	F(1,140)	p
Drug	0.42	.520	0.00	.949	21.39	< .001
Familiarity	0.90	.345	5.70	.018	0.28	.600
Predictability	29.28	< .001	6.63	.011	6.22	.014
Drug x Fam	2.18	.142	48.40	< .001	38.82	< .001
Drug x Pred	5.29	.023	25.75	< .001	10.25	.002
Fam x Pred	29.45	< .001	13.06	< .001	6.70	.011
Drug x Fam x Pred	6.35	.013	1.38	.241	71.54	< .001

Table S5.7 Aligned Rank Transform (ART) ANOVA results across temporal standard deviation of hierarchy measures. The non-parametric sensitivity analysis for the primary Type III ANOVA, 2x2x2 (Drug x Familiarity x Predictability) factorial design with Subject as random intercept. F-values and p-values are reported. Notations: Fam = Familiarity; Pred = Predictability..

Measure	TC (SD)		MeanTL (SD)		RO (SD)	
Effect	F(1,140)	p	F(1,140)	p	F(1,140)	p
Drug	70.37	< .001	16.82	< .001	17.21	< .001
Familiarity	3.69	.057	154.53	< .001	87.25	< .001
Predictability	64.30	< .001	50.39	< .001	13.54	< .001
Drug x Fam	75.79	< .001	60.61	< .001	5.38	.022
Drug x Pred	9.48	.002	37.05	< .001	3.64	.058
Fam x Pred	2.03	.156	8.02	.005	6.78	.010
Drug x Fam x Pred	0.55	.458	18.55	< .001	178.71	< .001

Table S5.8 Within-drug follow up Aligned Rank Transform (ART) ANOVA results across temporal mean hierarchy measures. Results of within-drug 2x2 (Familiarity x Predictability) ART ANOVAs conducted within each drug condition (No Ayahuasca: left, and Ayahuasca: right) for TC (mean), MeanTL (mean), and RO (mean).

		No Ayahuasca		Ayahuasca	
	Effect	F(1,60)	p	F(1,160)	p
TC (mean)	Familiarity	2.96	.091	0.28	.598
	Predictability	45.64	< .001	4.53	.037
	Fam x Pred	43.98	< .001	4.00	.050
MeanTL (mean)	Familiarity	48.87	< .001	10.64	.002
	Predictability	2.40	.127	37.80	< .001
	Fam x Pred	12.85	< .001	2.98	.089
RO (mean)	Familiarity	22.72	< .001	17.06	< .001
	Predictability	17.34	< .001	0.22	.639
	Fam x Pred	53.84	< .001	19.54	< .001

Table S5.9 Within-drug follow up Aligned Rank Transform (ART) ANOVA results across temporal standard deviation of hierarchy measures. ART was applied as non-parametric sensitivity test for primary parametric within-drug LMM Type III ANOVAs. The table reports the outcomes of two separate 2x2 (Familiarity x Predictability) ART ANOVAs conducted within each drug condition (No Ayahuasca and Ayahuasca) for TC (SD), MeanTL (SD), and RO (SD).

		No Ayahuasca		Ayahuasca	
	Effect	F(1,60)	p	F(1,160)	P
TC (SD)	Familiarity	51.66	< .001	39.76	< .001
	Predictability	25.22	< .001	36.95	< .001
	Fam x Pred	4.82	.032	0.34	.561
MeanTL (SD)	Familiarity	72.92	< .001	20.40	< .001
	Predictability	44.72	< .001	0.75	.390
	Fam x Pred	17.65	< .001	1.66	.203
RO (SD)	Familiarity	17.86	< .001	121.39	< .001
	Predictability	1.27	.265	19.47	< .001
	Fam x Pred	46.94	< .001	142.54	< .001

Section S5.3 Temporal standard deviation primary analyses

The same analyses were conducted for temporal standard deviation of each measure as were done for temporal mean. However, synthesising findings across six measures proved to be outside the reasonable scope of this thesis. A summary of primary findings of the temporal standard deviation analyses is provided below.

TC (temporal SD)

An LMM was fit to the temporal SD of TC. The resulting Type III ANOVA showed significant main effects of Drug and Predictability. No significant main effect of Familiarity was observed. The Drug x Familiarity and Drug x Predictability interactions were significant. The Familiarity x Predictability interaction was non-significant, as was the three-way interaction.

Table S5.10 Type III ANOVA results of temporal SD TC. F-statistics, p-values, and partial eta-squared (η^2p) effect sizes are reported for each effect.

Effect	F	Df ₁	Df ₂	p	η^2p
Drug	63.80	1	140	<.001	.313
Familiarity	2.88	1	140	.092	.020
Predictability	51.38	1	140	<.001	.268
Drug x Familiarity	64.28	1	140	<.001	.315
Drug x Predictability	6.13	1	140	.015	.042
Familiarity x Predictability	1.92	1	140	.168	.014
Drug x Familiarity x Predictability	0.78	1	140	.380	.006

EMM drug contrasts showed significant ayahuasca-induced increases in temporal SD of TC for both unfamiliar music conditions: Unfamiliar Predictable (estimate = -0.043, $t(140) = -8.80$, $q < .001$, $d = -2.72$, 95% CI [-3.39, -2.04]) and Unfamiliar Unpredictable (estimate = -0.035, $t(140) = -7.21$, $< .001$, $d = -2.22$, 95% CI [-2.87, -1.57]). Neither Familiar condition showed a significant drug effect: Familiar Predictable (estimate = -0.008, $t(140) = -1.66$, $q = .098$, $d = -0.51$, 95% CI [-1.12, 0.10]) and Familiar Unpredictable (estimate = 0.008, $t(140) = 1.69$, $q = .098$, $d = 0.52$, 95% CI [-0.09, 1.13]).

Follow-up within-drug two-way repeated-measures ANOVAs were conducted. Within the No Ayahuasca condition, all main effects and interactions were significant. Within the Ayahuasca condition, significant main effects of Familiarity and Predictability were observed.

However, the Familiarity x Predictability interaction was no longer significant, reflecting an attenuation in sensitivity of TC temporal stability to musical stimuli under ayahuasca.

Table S5.11 Temporal SD TC within-drug two-way repeated-measures ANOVA results. Conducted separately for No Ayahuasca and Ayahuasca conditions. F-statistics, p-values, and partial eta-squared (η^2p) effect sizes are reported.

Effect	No Ayahuasca			Ayahuasca		
	F(1,60)	p	η^2p	F(1,60)	p	η^2p
Familiarity	38.86	<.001	.393	37.39	<.001	.384
Predictability	21.42	<.001	.263	36.83	<.001	.380
Familiarity x Predictability	5.00	.032	.077	0.10	.561	.002

RO (temporal SD)

The LMM model fit to temporal SD of RO produced a singular fit (the random intercept variance was estimated at zero, suggesting minimal inter-subject variability). Outcomes of Type III ANOVA showed significant main effects of Drug, Familiarity, and Predictability. The Drug x Familiarity, Drug x Predictability and three-way interactions were significant. Only the Drug x Predictability interaction was not significant.

Table S5.12 Type III ANOVA results of temporal SD RO. F-statistics, p-values, and partial eta-squared (η^2p) effect sizes are reported for each effect.

Effect	F	Df ₁	Df ₂	p	η^2p
Drug	13.91	1	160	<.001	.080
Familiarity	79.31	1	160	<.001	.331
Predictability	13.00	1	160	<.001	.075
Drug x Familiarity	6.52	1	160	.012	.039
Drug x Predictability	2.95	1	160	.088	.018
Familiarity x Predictability	5.30	1	160	.023	.032
Drug x Familiarity x Predictability	157.17	1	160	<.001	.496

Within-music EMM drug contrasts showed varying effects. During Familiar Predictable music listening, RO variability significantly increased following ayahuasca ingestion ($t(140) = -3.99$, $q < .001$, $d = -1.23$, 95% CI [-1.85, -0.61]), as was the case during Unfamiliar Unpredictable music listening ($t(140) = -4.82$, $q < .001$, $d = -1.49$, 95% CI [-2.11, -0.86]). Conversely, the Unfamiliar Predictable music condition showed a significant reduction in temporal standard

deviation of RO following ayahuasca ingestion ($t(140) = 6.00$, $q < .001$, $d = 1.85$, 95% CI [1.21, 2.49]), as did the Familiar Unpredictable music condition ($t(140) = 10.27$, $q < .001$, $d = 3.17$, 95% CI [2.47, 3.87]).

Follow up within-drug two-way repeated-measures ANOVAs produced singular fits. The No Ayahuasca condition showed a significant main effect of Familiarity, and a significant Familiarity x Predictability interaction. The main effect of Predictability was non-significant. In the Ayahuasca condition all three effects were highly significant with larger effects than observed in the ayahuasca absent ANOVA, pointing to an increase in susceptibility of RO temporal variability to musical characteristics following ayahuasca ingestion.

Table S5.13 Temporal SD RO within-drug two-way repeated-measures ANOVA results. Conducted separately for No Ayahuasca and Ayahuasca conditions. F-statistics, p-values, and partial eta-squared (η^2p) effect sizes are reported.

Effect	No Ayahuasca			Ayahuasca		
	F(1,80)	p	η^2p	F(1,80)	p	η^2p
Familiarity	15.77	<.001	.165	91.06	<.001	.532
Predictability	1.39	.241	.017	19.65	<.001	.197
Familiarity x Predictability	40.94	<.001	.339	152.70	<.001	.656

Mean TL (temporal SD)

The LMM model produced a singular fit. The Type III ANOVA showed all main effects and interactions to be significant.

Table S5.14 Type III ANOVA results of temporal SD MeanTL. F-statistics, p-values, and partial eta-squared (η^2p) effect sizes are reported for each effect.

Effect	F	Df ₁	Df ₂	p	η^2p
Drug	8.70	1	160	.004	.052
Familiarity	119.20	1	160	<.001	.427
Predictability	33.73	1	160	<.001	.174
Drug x Familiarity	41.23	1	160	<.001	.205
Drug x Predictability	25.66	1	160	<.001	.138
Familiarity x Predictability	5.85	1	160	.017	.035
Drug x Familiarity x Predictability	12.48	1	160	<.001	.072

Follow up EMM drug contrasts revealed two significant conditions. Unfamiliar Predictable music listening was characterised by significantly lower temporal SD of MeanTL under ayahuasca ($t(140) = 8.98$, $q < .001$, $d = 2.77$), whereas the Familiar Unpredictable condition showed the opposite pattern ($t(140) = -2.50$, $q = .027$, $d = -0.77$). No significant drug effects were observed within the Familiar Predictable ($t(140) = -0.97$, $q = .446$, $d = -0.30$) nor the Unfamiliar Unpredictable ($t(140) = 0.39$, $q = .700$, $d = 0.12$) conditions.

Within-drug ANOVAs were applied. The No Ayahuasca condition showed significant main effects of Familiarity, Predictability and the Familiarity x Predictability interaction. Following ayahuasca ingestion, only the main effect of Familiarity persisted, with a reduced effect size. The main effect of Predictability was non-significant as was the Familiarity x Predictability interaction, pointing to a reduction in sensitivity of this measure to changes in musical characteristics following ayahuasca ingestion.

Table S5.15 Temporal SD MeanTL within-drug two-way repeated-measures ANOVA results. Conducted separately for No Ayahuasca and Ayahuasca conditions. F-statistics, p-values, and partial eta-squared (η^2p) effect sizes are reported.

Effect	No Ayahuasca			Ayahuasca		
	F(1,80)	p	η^2p	F(1,80)	p	η^2p
Familiarity	95.49	<.001	.544	23.74	<.001	.229
Predictability	37.56	<.001	.319	0.65	.424	.008
Familiarity x Predictability	11.25	.001	.123	1.46	.231	.018