Title page:

Title:

Brain substates induced by DMT relate to sympathetic output and meaningfulness of the experience

Abbreviated title:

Brain activity substates under DMT

Author names:

Lorenzo Pasquini[1]*, Alexander J. Simon[2], Courtney L. Gallen[1], Hannes Kettner[1,3], Leor Roseman[3,4], Adam Gazzaley[1, 5,6], Robin L. Carhart-Harris[1,3,5], Christopher Timmermann[3]*

Author affiliations:

[1]Department of Neurology, Neuroscape, University of California, San Francisco, CA 94158

[2]Interdepartmental Neuroscience Program, Yale University, New Haven, CT 06511

[3]Division of Psychiatry, Department of Brain Sciences, Centre for Psychedelic Research, Imperial College London, W12 0NN London, UK

[4]Department of Psychology, University of Exeter, UK

[5]Department of Psychiatry, University of California, San Francisco, CA 94158

[6]Department of Physiology, University of California, San Francisco, CA 94158

***Corresponding authors:**

Lorenzo Pasquini: lorenzo.pasquini@ucsf.edu

Christopher Timmermann: c.timmermann-slater15@imperial.ac.uk

Length: Number of pages: 43**;** Figures: 4; Tables: 1; words Abstract: 243; Significance Statement: 113; Introduction: 647; Discussion: 1488.

Conflict of interest: LP is a scientific advisor for AWEAR LLC.

Contributions: L.P. and C.T. conceived the study. R.L.C-H, L.R., H.K. and C.T. acquired the data. L.P. designed and developed the methodologies. L.P., C.T., and A.J.S. analyzed the data. L.P. and C.T. wrote the paper. L.P., A.G., C.L.G., C.T., R.L.C-H. interpreted the findings. All authors revised the paper and provided critical feedback.

Acknowledgements: This work was supported by the following agencies: L.P.: K99-AG065457 (NIA), R00AG065457 (NIA), and philanthropic support from David Dolby and the Dolby family.

Abstract:

N,N-Dimethyltryptamine (DMT) is a serotonergic psychedelic, known to rapidly induce short-lasting alterations in conscious experience, characterized by a profound and immersive sense of physical transcendence alongside rich and vivid auditory distortions and visual imagery. Multimodal neuroimaging data paired with dynamic analysis techniques offer a valuable approach for identifying unique signatures of brain activity – and linked autonomic physiology – naturally unfolding during the altered state of consciousness induced by DMT. We leveraged simultaneous fMRI and EKG data acquired in 14 healthy volunteers prior to, during, and after intravenous administration of DMT, and, separately, placebo. EKG data was used to derive continuous heart rate; fMRI data was preprocessed to derive individual dynamic activity matrices, reflecting the similarity of brain activity in time, and community detection algorithms were applied on these matrices to identify brain activity substates. We identified a brain substate occurring immediately after DMT injection, characterized by increased superior temporal lobe activity, and hippocampal and medial parietal deactivations under DMT. Superior temporal lobe hyperactivity correlated with the intensity of the auditory distortions, while hippocampus and medial parietal cortex hypoactivity correlated with scores of meaningfulness of the experience. During this first post-injection substate, increased heart rate under DMT correlated negatively with the meaningfulness of the experience and positively with hippocampus/medial parietal deactivation. These results suggest a chain of influence linking sympathetic regulation to hippocampal and medial parietal deactivations under DMT, which combined may contribute to positive mental health outcomes related to self-referential processing following psychedelic administration.

Significance Statement:

Human subjective experience entails an interaction between bodily awareness and higher-level self-referential processes. DMT is a fast-acting psychedelic that induces intense and short-lasting disruptions in subjective experience. We applied dynamic analysis techniques and graph theoretical approaches to multimodal fMRI/EKG data from a pharmacological study in healthy volunteers. We show that DMT injection is followed by a brain substate characterized by superior temporal lope hyperactivity, related to auditory distortions, and medial parietal and hippocampal hypoactivity, related to meaningfulness of the psychedelic experience. These deactivations were also related to lower increases in heart rate under DMT, suggesting that sympathetic regulation and medial parietal/hippocampal deactivations are an important component of the DMT-induced altered state of consciousness.

Introduction:

Bodily self-awareness (Damasio and Damasio, 2022) is thought to result from the integration of visceral and autonomic bodily functions into a distributed brain network supporting homeostasis, interoception, and emotions (Critchley and Harrison, 2013), encompassing a set of subcortical and cortical structures including the insula, anterior cingulate cortex, and ventral striatum (Seeley et al., 2007). On the other hand, one's sense of identity rooted in autobiographic memories, often referred to as the "narrative self" (Gallagher, 2000), has been demonstrated to rely on a distributed brain network spanning midline parietal and medial temporal structures, including the precuneus, posterior cingulate cortex, and hippocampi (Northoff and Bermpohl, 2004). These regions are collectively known to be a core component of the default mode network (DMN) (Raichle et al., 2001), a large-scale brain system associated with self-referential processes such as autobiographical memories, mind wandering, and future planning (Buckner and DiNicola, 2019). Crucially, insight into the neural underpinning of one's sense of self has been catalyzed via the timely re-introduction of psychedelic substances in human neuroscience research (Vollenweider and Kometer, 2010; Carhart-Harris et al., 2012; McCulloch et al., 2022).

N,N-Dimethyltryptamine (DMT) is a serotonergic psychedelic (Nichols, 2016) known to rapidly induce an intense but short-lasting altered state of consciousness (Strassman, 1995; Vogt et al., 2023), characterized by a sense of transcendence of physical bounds and intense sensory immersion – including vivid and elaborate visual imagery, and in about half of cases, a sense of being in the presence of other sentient entities (Lawrence et al., 2022; Timmermann et al., 2023b). The subjective effects of

DMT, when administered intravenously at high doses, arise within seconds of the injection, and rapidly progress into an altered state of consciousness characterized by deep and profound immersion (Timmermann et al., 2019). This state typically lasts several minutes, and gradually attenuates as participants regain normal waking consciousness approximately 20 min following the injection (Timmermann et al., 2023b). Due to its fast dynamics and profound subjective effects, DMT has been recognized as a powerful tool to explore the neurophenomenology and neural underpinning of consciousness (Timmermann et al., 2023a).

As with other serotonergic psychedelics, the altered state of consciousness induced by DMT is usually accompanied by changes in autonomic and central nervous system physiology (Strassman and Qualls, 1994; Carbonaro and Gatch, 2016; Alamia et al., 2020). DMT often triggers transient increases in sympathetic tone as measured through continuous heart rate, which normalize as the effects of the drug dissipates (Strassman and Qualls, 1994). Further, recent studies have found interesting associations between altered cardiac activity and the psychedelic experience (Rosas et al., 2023). Studies leveraging resting-state functional magnetic resonance imaging (rs-fMRI), a method used to measure the synchronicity of spontaneous activity across distant brain regions (Smith et al., 2009), have shown that DMT results in global hyperconnectivity, collapsed hierarchical organization, and reduced intra-network integrity, particularly among core regions of the DMN (Timmermann et al., 2023b). Further, dynamic analyses have revealed that rs-fMRI-based global connectivity peak in the first 4-6 minutes after the injection, corresponding to the highest intensity ratings of subjective effects under DMT (Timmermann et al., 2023b). These findings highlight the

dynamic character of DMT and raise further questions about whether distinguishable physiological substates could be identified across the natural progression of a psychedelic experience under DMT. Novel dynamic analysis methods allow for the identification of functional substates occurring during the duration of an entire scan (Deco et al., 2008; Calhoun et al., 2014; Lurie et al., 2020). Dynamic analysis approaches could hence play an invaluable contribution to the identification of distinguishable signatures of brain activity – and linked autonomic physiology – naturally emerging and dissolving under the fast action of DMT.

Here, we applied dynamic analysis methods combined with graph theoretical techniques to rs-fMRI and electrocardiogram (EKG) data acquired in a pharmacological study with 14 healthy volunteers, to assess the natural evolution of autonomic physiology and brain activation substates during the administration of DMT.

Materials and Methods:

Study sample. This study involved secondary analyses of fMRI and EKG data acquired in 14 healthy volunteers (4 females; age [mean, SD, range] in years = 34.1, 8.8, 23-53) in the context of a single-blind, placebo-controlled, counter-balanced study assessing the effects of DMT on brain function (Timmermann et al., 2023b). Primary exclusion criteria included: <18 years of age, MRI contraindications, absence of experience with a psychedelic, an adverse reaction to a psychedelic, history of psychiatric or physical illness rendering unsuitable for participation (i.e., diabetes, epilepsy, or heart disease), family history of psychotic disorder, or excessive use of alcohol or drugs of abuse. All participants provided written informed consent for

participation in the study. This study was approved by the National Research Ethics Committee London—Brent and the Health Research Authority and was conducted under the guidelines of the revised Declaration of Helsinki (2000), the International Committee on Harmonization Good Clinical Practices guidelines, and the National Health Service Research Governance Framework. Imperial College London sponsored the research, which was conducted under a Home Office license for research with Schedule 1 drugs.

Study design. 20 enrolled participants visited the Imperial College Clinical Imaging Facility and completed two visits separated by two weeks. At each visit, participants were tested for drugs of abuse and completed two sessions: a “resting state” and a “ratings” session. For the “resting state” session, participants were placed in an MRI scanner after an MRI-compatible electroencephalography (EEG) cap was placed on their scalp. The acquired EEG data was analyzed in previous work, and we did not further analyze this data since it was outside the scope of the current study. While being scanned, participants received intravenous administration of either placebo (10 mL of sterile saline) or 20 mg DMT (in fumarate form dissolved in 10 mL of sterile saline) —injected over 30 s, and then flushed with 10 mL of saline over 15 s — in a counter-balanced order (half of the participants received placebo and the other half received DMT for this session). Rs-fMRI data acquisition lasted 28 min in total, with DMT/placebo being administered at the end of the 8th min. While participants laid in the scanner with their eyes closed, EKG activity was simultaneously recorded through sensors available in the MRI compatible electroencephalography cap. At the end of the scanning session, participants were interviewed and completed questionnaires

designed to assess the subjective effects experienced during the scan. This was followed by a second “ratings” session on the same day and consisted of the same procedure as the initial session, except on this occasion participants received DMT (if they received placebo on the “resting state” session) or placebo (if they received DMT on the “resting state” session), and were audio cued to verbally rate the subjective intensity of drug effects every minute in real time while in the scanner. A second visit consisted of the same procedure as the first visit, however the order of DMT/placebo administration was reversed for each of the sessions. Here we report findings only for the “resting state” session.

End of scanning surveys. Approximatively 30 min after participants completed the scanning session and regained normal waking consciousness, they were asked to rate on several items describing the psychedelic experience using visual analogue scales (ratings ranged from 0-1, in incremental steps of 0.01). 25 items were presented sequentially, which assessed aspects of the psychedelic experience related to drug intensity, primary sensory distortion (including auditory hallucinations), feelings of disembodiment and dissociation, and self-referential processes (primarily ego-dissolution and meaningfulness of the experience) (Timmermann et al., 2023b) . Ratings for theses scales were acquired for both the DMT and placebo conditions.

Neuroimaging and EKG data acquisition. Functional images were acquired in a 3T MRI scanner (Siemens Magnetom Verio syngo MR B17) using a 12-channel head coil compatible with EEG acquisition using a T2*-weighted blood-oxygen-level-dependent (BOLD) sensitive gradient echo planar imaging sequence [repetition time (TR) = 2000ms, echo time (TE) = 30 ms, acquisition time (TA) = 28.06 mins, flip angle

(FA) = 80°, voxel size = 3.0 × 3.0 × 3.0mm3, 35 slices, interslice distance = 0 mm]. Whole-brain T1-weighted structural images were also acquired. EKG channels were used to acquire continuous heart rate by using an MR-compatible 32-channel EEG cap (BrainCap MR; BrainProducts GmbH, Munich, Germany), and an MRI-compatible BrainAmp MR amplifier (BrainProducts, Munich, Germany), sampled at 5 kHz and with a hardware 250 Hz low-pass filter. EKG-MRI clock synchronization was ensured using the Brain Products SyncBox hardware. For more details, see parent paper (Timmermann et al., 2023b).

Neuroimaging and EKG data preprocessing. Details on MRI data preprocessing can be found on previous published work (Carhart-Harris et al., 2016) and in the parent paper (Timmermann et al., 2023b). Briefly, preprocessing leveraged standard AFNI (https://afni.nimh.nih.gov/), FSL (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki), and in house code to perform rs-fMRI data despiking, slice time correction, functional registration for motion correction, anatomical brain extraction, rigid body registration of functional scans to anatomical scans, and nonlinear registration to a 2 mm Montreal Neurological Institute brain template. Additional preprocessing steps included rs-fMRI data scrubbing using an framewise head-displacement threshold of 0.4 mm followed by linear interpolation using the mean of the surrounding volumes, spatial smoothing with a 6 mm full width at half maximum kernel, band-pass filtering between 0.01 and 0.08 Hz, linear and quadratic detrending, and regression of nine motion-related and three anatomical nuisance regressors (Timmermann et al., 2023b). Participants with >20% of scrubbed volumes based on a frame-wise displacement threshold of 0.4 mm were discarded from group analyses, resulting in the final sample of 14 participants analyzed

in this study. Simultaneously acquired EKG data was preprocessed using the *hrvanalysis* module in Python (https://www.python.org/) to derive continuous heart rate estimates based on the RR-intervals (Pasquini et al., 2022).

Neuroimaging data analysis. Voxel-level brain activity estimates derived from rs-fMRI data were reduced by obtaining the average activity from 100 areas in the Schaefer atlas (Schaefer et al., 2018) and 12 subcortical areas derived from the automated anatomical atlas (AAL) (Tzourio-Mazoyer et al., 2002). Pearson's correlation was used to derive individual time-resolved brain activity similarity matrices, by, e.g., correlating the activity of all nodes at time point one with the activity of all nodes at time point two. This procedure resulted in matrices reflecting the homogeneity of brain activity during the entire duration of the scanning session (Kringelbach and Deco, 2020), estimated once for the DMT and once for the placebo conditions (**Figure 1A-B**). Group-averaged time-resolved brain activity similarity matrices derived once under DMT and once under placebo were then subtracted, and these subtraction matrices were used to identify portions of the rs-fMRI scan with more similar brain activity under DMT versus placebo (**Figure 1C**). This subtraction matrix was iteratively thresholded for absolute Pearson's correlation values ranging from 0.20 to 0.30, in incremental steps of 0.01 (**Figure 1D** and **Table 1**). For each of these thresholded matrices, the Louvain community detection algorithm, as implemented in the publicly available Brain Connectivity Toolbox (https://sites.google.com/site/bctnet/)(Rubinov and Sporns, 2010), was then used to identify brain activity similarity modules within the duration of the entire scan (**Figure 1E**). Community detection was run using the default resolution parameter G = 1 and an asymmetric treatment of negative weights. This procedure

resulted in community affiliation vectors, assigning each functional volume to one of the identified brain activity similarity modules. We then used these vectors to quantify which brain activity similarity modules were occupied for at least 10% of the entire scan duration by dividing the occurrence of that brain activity similarity module by the total duration of the rs-fMRI scan. We also used X^2 tests to quantify which brain activity similarity modules were significantly more occupied either during the pre- or the post-injection periods ($p < 0.05$). Both analyses helped identify a subset of brain activity similarity modules that were sufficiently occupied during the duration of the entire rs-fMRI scan and at the same time differentially occupied when comparing the pre- to the post-injection periods (**Figure 1F**). These selected vectors where then used to derive mean brain activation maps for each participant, and were also entered in a general linear model, using individual nodal activity time series as dependent variables, to derive nodal β-maps reflecting individual brain activation associated with each brain activity similarity module.

Statistical Analyses. Individual nodal β-maps of brain activity similarity modules were compared across the placebo and DMT conditions using paired *t*-tests (false discovery rate [FDR] adjusted $p < 0.05$). This procedure helped identify a brain activity similarity module showing significant differences across the DMT and placebo conditions, which emerged immediately after DMT injection and lasted for several minutes. Nodes of this brain activity similarity module displaying either hyperactivity or hypoactivity in the DMT condition were identified. Identified nodes were then used as mask to derive averaged levels of activity from the individual β-maps. Identified nodes were also used on the preprocessed rs-fMRI volumes to estimate averaged BOLD

activity time series of these regions for the duration of the entire rs-fMRI scan. Individual estimates of nodal hyperactivity or hypoactivity under DMT were correlated with change scores (DMT minus placebo) in auditory perception, ego dissolution, and meaningfulness of the experience using Pearson's correlation coefficients ($p < 0.05$). These scales were selected post-hoc and the selection process was influenced by the neuroanatomy of functional changes identified when comparing substate activity maps across the DMT and placebo conditions. A more detailed rationale for the choice of these scales is provided later in the results section. Ratings of subjective experience scales were compared across the DMT and placebo conditions using paired *t*-tests ($p < 0.005$). Individual heart rate was averaged during the occurrence of the previously mentioned post-injection brain activity similarity module and compared across the placebo and DMT conditions using paired *t*-tests ($p < 0.05$). Changes in heart rate were compared to nodal activity changes and to change score in meaningfulness of the experience using Pearson's correlation coefficients ($p < 0.05$). A median split was finally used to separate participants into individuals showing low-to-moderate heart rate increase or high heart rate increase during specific brain activity similarity modules emerging under DMT.

Code availability. Code for deriving brain activity similarity modules is available on GitHub (https://github.com/lollopasquini). Maps of brain substates are available on NeuroVault (https://neurovault.org/) (Gorgolewski et al., 2015).

Results:

Dynamic brain activity substates under DMT and placebo. In this study, we explored the dynamic emergence of brain substates following DMT and placebo administration by capitalizing on neuroimaging data from a pharmacological study conducted in 14 healthy volunteers (Timmermann et al., 2023b). We applied community detection algorithms to the group-averaged subtraction (DMT minus placebo) matrix of time-resolved activity similarity (**Figure 1A-C**), to identify temporal modules of homogenous brain activity differentiating the DMT from the placebo condition. This approach was optimized for several Pearson's correlation thresholds applied to the group-mean subtraction time-resolved activity similarity matrix (**Table 2**) to identify a maximum amount of temporal modules of brain activity, here forth referred to as "brain activity substates", which: (*i*) differentiated the DMT from the placebo condition, (*ii*) were sufficiently occupied during the duration of the entire scan, and (*iii*) were differentially occupied when comparing the pre- and post-injection periods (**Figure 1 D-F**). Three major brain activation substates were identified that met these conditions (**Figure 2**). The first identified brain activation substate predominantly occurred before the injection of DMT/placebo and towards the end of the scanning session (State 2; **Figure 1E**), accounting for 34% (2.7 min) of the pre-injection scanning period and 10% (2.0 min) of the post-injection scanning period **(Figure 1D**). It was characterized by orbitofrontal activations under both DMT and placebo (**Figure 2A-B**), while subcortical as well as medial and lateral parietal activations were identified only under DMT (**Figure 2B**). This substate was also characterized by widespread deactivation of primary sensory areas under both DMT and placebo. A second primary brain activation substate emerged shortly after the injection of DMT/placebo (State 4; **Figure 1E**) which accounted for 6%

(0.5 min) of the pre-injection scanning period and 19% (3.8 min) of the post-injection scanning period **(Figure 1D**). This substate was characterized by widespread activations of primary sensory and cingulo-opercular brain regions under both the DMT and placebo conditions (**Figure 2C-D**), while deactivations where mainly observed in prefrontal areas under both DMT and placebo and within medial parietal cortices under DMT. A third substate was identified (State 5; **Figure 1E**), which occurred immediately after the first post-injection State 4 and occupied 6% (0.5 min) of the pre-injection scanning period and 18% (3.6 min) of the post-injection scanning period **(Figure 1D**). State 5 displayed overall high resemblance to the previous substate (**Figure 2E-F**), showing primary sensory and cingulo-opercular activations as well as prefrontal and medial parietal deactivations under DMT and placebo, yet displayed marked temporopolar activations compared to previous substates.

Post-injection brain substate activations and deactivations under DMT. We then used linear regression models to estimate individual activation maps for each of the brain substates and compared these maps across the DMT and placebo conditions. Only the first post-injection substate (State 4) showed significant differences in brain activity when comparing regional activation levels across the DMT and placebo conditions (FDR adjusted $p < 0.05$). Specifically, it displayed increased right superior temporal lobe activity under DMT, while deactivations under drug were found in the left hippocampus and in bilateral medial parietal areas overlapping with the precuneus and posterior cingulate cortices (**Figure 3A**). Crucially, mean frame-wise head displacement, a common confounder in rs-fMRI analyses, did not significantly correlate with right superior temporal lobe activity ($R(12) = 0.00$, $p = 0.99$) nor with left hippocampal and

medial parietal deactivations (R(*12*) = 0.28, *p* = 0.32). To further evaluate the dynamics of activity changes under DMT, raw BOLD activity time series were averaged across voxels of State 4 regions displaying hyperactivity/hypoactivity under DMT. Raw activity time series were subtracted across the DMT and placebo conditions and plotted, showing sustained medial parietal and hippocampal deactivations and superior temporal lobe hyperactivations immediately after the injection of DMT (**Figure 3B**).

We next explored the association between regional hypoactivity/hyperactivity changes under DMT and change scores of scales reflecting the quality of the psychedelic experience, which were assessed after the end of the scanning session. Given that the superior temporal lobe plays a prominent role in auditory perception (Howard et al., 2000), we first explored the association between State 4 hyperactivations under DMT with change scores of altered auditory perception, which were significantly higher under DMT when compared to placebo (*t(13)* = 3.42; *p* = 0.005). Increased activation in the right superior temporal lobe correlated positively with the intensity of the auditory distortion (**Figure 3C**, R(*12*) = 0.57, *p* = 0.03). We next assessed the link between hippocampal/medial parietal deactivations and change scores of ego-dissolution and meaningfulness of the experience, given the crucial role that these regions play in self-referential processes, including the narrative self, autobiographical memories, and constructing meaning (Northoff and Bermpohl, 2004; Buckner and DiNicola, 2019). Both scores of ego-dissolution (*t(13)* = 9.17; *p* < 0.0001) and meaningfulness of the experience (*t(13)* = 7.96; *p* < 0.0001, respectively) were rated significantly higher under DMT than placebo. While hippocampus/medial parietal cortex deactivations did not correlate with ego-dissolution scores (R*(12)* = 0.28, *p* =

0.34), we found a negative correlation between brain deactivation and change scores of meaningfulness of the experience (**Figure 3D**, R(*12*) = -0.61, *p* = 0.02). Overall, these findings suggest marked brain activity changes in the first four minutes of DMT administration, characterized by superior temporal hyperactivity related to altered acoustic perception and hippocampus/medial parietal deactivations linked to the attribution of meaning as normal waking consciousness is regained.

Heart rate changes under DMT relate to regional brain deactivations and meaningfulness of the experience. Since autonomic bodily functions are key factors contributing to one's sense of self (Damasio and Damasio, 2022), we proceeded to investigate changes in heart rate – a marker of sympathetic activity of the autonomic nervous system (Critchley and Harrison, 2013) – during the administration of DMT. We focused our analyses on heart rate changes occurring during the first post-injection substate, since State 4 was the only one showing significant differences in brain activity when comparing the DMT and placebo conditions. During the first post-injection substate, heart rate was significantly increased during DMT when compared to placebo (**Figure 4A**, *t(13)* = 2.68 , *p* = 0.02). DMT-related heart rate increases during State 4 showed a negative, albeit not-significant, correlation with change scores of the meaningfulness of the experience (**Figure 4B**, R(*12*) = -0.51, *p* = 0.06) and a significant positive correlation with State 4 hippocampus/medial parietal deactivations under DMT (**Figure 4C**, R(*12*) = -0.56, *p* = 0.04). We then used a median split to separate participants into individuals showing low-to-moderate heart rate increases or high heart rate increases on DMT for the duration of State 4. Continuous heart rate time series from the DMT and placebo conditions were subtracted to estimate continuous heart rate

change time series for the duration of the entire scan. Group-averaged subtraction heart rate time series were plotted separately for individuals showing low and high heart rate changes (**Figure 4D**). These plots revealed sustained heart rate increases post-DMT injection in participants showing high heart rate changes during State 4, while individuals with low heart rate changes during State 4 showed overall stable heart rate across the duration of the entire scan. In line with previous work, our findings corroborate that the peak DMT experience is characterized by increases sympathetic output (Strassman and Qualls, 1994). Yet, lower heart rate changes are linked to a more positive psychedelic experience and stronger deactivations of brain regions related to self-referential functions.

Discussion:

To date, most efforts exploring acute brain changes during psychedelic administration have relied on metrics that capture the topology of node-to-node functional connectivity changes estimated for the duration of the entire scanning time (McCulloch et al., 2022). Yet, there is little understanding for how these functional connectivity patterns may relate to relative BOLD signal changes, as indexed via e.g., task-based fMRI (Smith et al., 2009). Further, there is an increased recognition that the brain displays highly dynamic properties, which underlie the emergence of complex behaviors (Calhoun et al., 2014; Cabral et al., 2017; Saggar et al., 2022). Here, we took advantage of the intrinsic dynamics of a rapidly acting psychedelic, DMT, and paired this with data-driven analytical approaches combining dynamic analyses (Kringelbach and Deco, 2020) and graph theoretical techniques (Rubinov and Sporns, 2010).

By comparing the DMT to the placebo condition, this analytical approach allowed us to identify sequential brain activation/deactivation substates naturally unfolding with the administration of DMT. A primary brain substate was identified before the injection of DMT, characterized by activation of DMN areas when compared to the rest of the scan, as expected for a resting-state condition (Buckner and DiNicola, 2019). The presence of this substate at the beginning of the scanning session may reflect normal waking consciousness anchored by normal DMN functioning, relative to brain substates and consciousness changes emerging under DMT. This DMN-based substate also occurred towards the end of the scanning session, likely reflecting the recovery from the psychedelic state back to the normal or “default” mode of waking consciousness (Raichle et al., 2001).

Two brain activity substates were identified corresponding to the post-DMT injection phase of the timeseries. The first brain substate emerged immediately after injection and lasted for several minutes. This substate was characterized by increased activity in regions subserving sensory, attentional, and interoceptive functions (Dosenbach et al., 2007; Critchley and Harrison, 2013), while deactivations were particularly prominent in medial parietal and medial temporal areas. A final brain substate was identified which temporally succeeded the previously described substate, displaying marked anterior temporal pole hyperactivity, possibly related to the attribution of semantic meaning (Younes and Gorno-Tempini, 2021). This is consistent with previous phenomenological analysis showing a recovery of higher-level qualities of cognition after the peak DMT experience has subsided (Timmermann et al., 2019). Statistical comparisons of the brain activation maps between the DMT and the placebo

conditions, confirmed significant changes for the first post-injection DMT brain substate, by revealing superior temporal lobe hyperactivity and medial parietal/hippocampal hypoactivity under DMT.

Our chosen statistical threshold prevented us from finding more widespread activity changes when comparing brain substates across DMT and placebo, possibly due to the relatively small study sample. Furthermore, psychedelic experiences are highly subjective and heterogenous (Prugger et al., 2022), with factors such as the participant's mindset, the cultural and social background, as well as the set-and-setting of a session heavily influencing the perceptions, emotions, and insights elicited in different individuals (Hartogsohn, 2017; Carhart-Harris et al., 2018). This intrinsic heterogeneity may represent a challenge for the reliable identification of brain substates occurring during a psychedelic experience. Yet, medial parietal and hippocampal deactivations during peak effects may represent a signature activity pattern common to most psychedelics (Carhart-Harris et al., 2014; Tagliazucchi et al., 2014). Future work repeatedly assessing the same participant (Poldrack et al., 2015; Gratton et al., 2018; Siegel et al., 2023) across different days and dosing protocols may shed light on the inter- and intra-individual neural variability of psychedelic experiences.

When relating activity changes in brain substates following the injection of DMT to phenomenological scores acquired after the psychedelic experience, our analyses revealed that right superior temporal lobe hyperactivity correlated with the intensity of auditory distortions. The superior temporal lobe is a key component of the auditory cortex and plays a critical role in hearing, speech, and language (Howard et al., 2000). Smaller volume in this area has been related to auditory hallucinations in schizophrenia

(Barta et al., 1990) and its activity has been associated with the emergence of false auditory perceptions (Moseley et al., 2014). Overall, our findings may relate to previous reports showing increased functional connectivity of primary sensory areas, including auditory cortices, under the acute administration of DMT and other psychedelics (Tagliazucchi et al., 2016; Timmermann et al., 2023b). While hyperactivity was related to altered auditory perception, hypoactivity was related to the attribution of meaning to the psychedelic experience. Deactivations were circumscribed to the medial parietal cortices, including the posterior cingulate and precuneus, as well as to the left hippocampus. These regions are key components of the DMN, a brain system which has been repeatedly associated with narrative self-referential functions (Yeshurun et al., 2021). Diminished functional integrity of the DMN, in particularly of the posterior cingulate and the precuneus, was initially shown under psilocybin (Carhart-Harris et al., 2012), and has been since confirmed under LSD (Carhart-Harris et al., 2016), ayahuasca (Palhano-Fontes et al., 2015), and DMT (Timmermann et al., 2023b). Specifically, psilocybin has been shown to induce reduced cerebral blood flow and BOLD activity in medial parietal areas (Carhart-Harris et al., 2012), in line with the DMT-induced midline parietal deactivations found in our study. Recent human intracranial electrophysiological studies have revealed that posteromedial cortical rhythms play a crucial role in sustaining self-referential functions as proven by both pathological seizure-based (Lyu et al., 2023) and ketamine-induced dissociations (Vesuna et al., 2020). When considering the role of hippocampal deactivations, previous rs-fMRI studies found that psychedelics induce a decrease in the amplitude of spontaneous BOLD signal fluctuations within the parahippocampal gyri and induce an uncoupling

between the hippocampus/parahippocampus and other DMN regions (Carhart-Harris et al., 2014). Further, spontaneous connectivity changes within the hippocampus, parahippocampus, and medial parietal regions have been found to relate to the so-called “ego-dissolving” experience of psychedelics (Lebedev et al., 2015; Carhart-Harris et al., 2016). Potentially consistent with our present findings with DMT, a recent spectroscopy study found lower levels of glutamate metabolism in the hippocampus under psilocybin to be correlated with its ego-dissolving properties (Mason et al., 2020).

These findings collectively point towards the relevance of medial temporal lobe structures for the maintenance of normal waking consciousness and the ordinary sense of self that accompanies it. We found deactivation of the hippocampus to be correlated with the experiences of meaningfulness occurring under DMT, in line with the well-known relationship between the hippocampus, consciousness, and self-related processes (Northoff and Bermpohl, 2004; Carhart-Harris and Friston, 2010; Buckner and DiNicola, 2019). Alternatively, it is plausible that the degree to which an experience is considered meaningful depends on how much it perturbs novelty coding brain structures, in line with the notion that the anterior hippocampus plays a crucial role in novelty detection (Kumaran and Maguire, 2009). Further studies are required to test the relationship between meaningfulness of an experience and medial parietal/hippocampal activity patterns naturally unfolding under psychedelic administration.

Corroborating previous work on DMT and related psychedelics (Strassman and Qualls, 1994), our study revealed that the early-to-peak phase of the DMT experience is accompanied by increased heart rate, a common indicator of heightened sympathetic tone (Critchley and Harrison, 2013). Yet, participants with the highest heart rate

increases under DMT showed weaker hippocampal/medial parietal deactivations. Crucially, mean heart rate assessed during the peak DMT effects was further used to differentiate participants showing either sustained increased or normal heart rate after DMT injection. Our findings are in line with human intracranial electrophysiological studies showing that medial parietal areas, including the anterior precuneus, are causally involved in the processing of the bodily sense of self (Lyu et al., 2023).

Successful regulation of the sympathetic nervous system may be mechanistically linked to midline parietal and temporal deactivation patterns (Beissner et al., 2013) underlying altered embodied experiences commonly induced by psychedelics, including ego dissolution (Carhart-Harris et al., 2012; Muthukumaraswamy et al., 2013; Lebedev et al., 2015) and self-dissociation (Lyu et al., 2023). Furthermore, those with the more modest heart rate increases were those who rated highest for the “meaningfulness” of the experience. Overall, our findings suggests that sympathetic regulation is a fundamental mechanism relevant to the emergence of neural activity patterns underlying meaningful psychedelic experiences. Intuitively, our findings can be linked to cognitive frameworks commonly used in the psychedelic field, often indicated by terms such as “acceptance”, “letting-go”, or “surrender”, which have been shown to be key mediators of improved well-being following assisted psychedelic therapy (Roseman et al., 2018; Wolff et al., 2020; Yaden and Griffiths, 2021). The parasympathetic and sympathetic systems play a crucial role in shaping human emotions and social behavior (Critchley and Harrison, 2013) through direct and indirect neural pathways underlying interoceptive processes and the homeostatic control of internal bodily states (Critchley and Harrison, 2013; Damasio and Damasio, 2022). We hope that our findings will

stimulate future clinical studies elucidating the role of autonomic changes in predicting outcomes following psychedelic therapy, as well as multimodal neuroscience studies exploring the dynamic integration of bodily signals within specific brain circuits under acute psychedelic administration.

References:

Alamia A, Timmermann C, VanRullen R, Carhart-Harris RL (2020) DMT alters cortical travelling waves. Elife 9:1–16.

Barta PE, Pearlson GD, Powers RE, Richards SS, Tune LE (1990) Auditory hallucinations and smaller superior temporal gyral volume in schizophrenia. American Journal of Psychiatry 147:1457–1462 Available at: https://doi.org/10.1176/ajp.147.11.1457.

Beissner F, Meissner K, Bär K-J, Napadow V (2013) The Autonomic Brain: An Activation Likelihood Estimation Meta-Analysis for Central Processing of Autonomic Function. The Journal of Neuroscience 33:10503 Available at: http://www.jneurosci.org/content/33/25/10503.abstract.

Buckner RL, DiNicola LM (2019) The brain's default network: updated anatomy, physiology and evolving insights. Nat Rev Neurosci Available at: http://www.ncbi.nlm.nih.gov/pubmed/31492945.

Cabral J, Kringelbach ML, Deco G (2017) Functional connectivity dynamically evolves on multiple time-scales over a static structural connectome: Models and mechanisms. Neuroimage 160:84–96 Available at: http://dx.doi.org/10.1016/j.neuroimage.2017.03.045.

Calhoun VD, Miller R, Pearlson G, Adali T (2014) The Chronnectome: Time-Varying Connectivity Networks as the Next Frontier in fMRI Data Discovery. Neuron 84:262–274.

Carbonaro TM, Gatch MB (2016) Neuropharmacology of N,N-dimethyltryptamine. Brain Res Bull 126:74–88 Available at: https://www.sciencedirect.com/science/article/pii/S0361923016300909.

Carhart-Harris R, Leech R, Hellyer P, Shanahan M, Feilding A, Tagliazucchi E, Chialvo D, Nutt D (2014) The entropic brain: a theory of conscious states informed by neuroimaging research with psychedelic drugs. Front Hum Neurosci 8 Available at: https://www.frontiersin.org/articles/10.3389/fnhum.2014.00020.

Carhart-Harris RL et al. (2016) Neural correlates of the LSD experience revealed by multimodal neuroimaging. Proceedings of the National Academy of Sciences 113:4853–4858 Available at: https://www.pnas.org/doi/abs/10.1073/pnas.1518377113.

Carhart-Harris RL, Erritzoe D, Williams T, Stone JM, Reed LJ, Colasanti A, Tyacke RJ, Leech R, Malizia AL, Murphy K, Hobden P, Evans J, Feilding A, Wise RG, Nutt DJ (2012) Neural correlates of the psychedelic state as determined by fMRI studies with psilocybin. Proc Natl Acad Sci U S A 109:2138–2143.

Carhart-Harris RL, Friston KJ (2010) The default-mode, ego-functions and free-energy: a neurobiological account of Freudian ideas. Brain 133:1265–1283 Available at: https://doi.org/10.1093/brain/awq010.

Carhart-Harris RL, Roseman L, Haijen E, Erritzoe D, Watts R, Branchi I, Kaelen M (2018) Psychedelics and the essential importance of context. Journal of

Psychopharmacology 32:725–731 Available at: https://doi.org/10.1177/0269881118754710.

Critchley HD, Harrison NA (2013) Visceral Influences on Brain and Behavior. Neuron 77:624–638 Available at: http://dx.doi.org/10.1016/j.neuron.2013.02.008.

Damasio A, Damasio H (2022) Homeostatic feelings and the biology of consciousness. Brain 145:2231–2235 Available at: https://doi.org/10.1093/brain/awac194.

Deco G, Jirsa VK, Robinson PA, Breakspear M, Friston K (2008) The Dynamic Brain: From Spiking Neurons to Neural Masses and Cortical Fields. PLoS Comput Biol 4:1–35.

Dosenbach NUF, Fair DA, Miezin FM, Cohen AL, Wenger KK, Dosenbach RAT, Fox MD, Snyder AZ, Vincent JL, Raichle ME, Schlaggar BL, Petersen SE (2007) Distinct brain networks for adaptive and stable task control in humans. Proceedings of the National Academy of Sciences 104:11073–11078.

Gallagher S (2000) Philosophical conceptions of the self: implications for cognitive science. Trends Cogn Sci 4:14–21 Available at: https://www.sciencedirect.com/science/article/pii/S1364661399014175.

Gorgolewski KJ, Varoquaux G, Rivera G, Schwarz Y, Ghosh SS, Maumet C, Sochat V V, Nichols TE, Poldrack RA, Poline JB, Yarkoni T, Margulies DS (2015) NeuroVault.Org: A web-based repository for collecting and sharing unthresholded statistical maps of the human brain. Front Neuroinform 9:1–9.

Gratton C, Laumann TO, Nielsen AN, Greene DJ, Gordon EM, Gilmore AW, Nelson SM, Coalson RS, Snyder AZ, Schlaggar BL, Dosenbach NUF, Petersen SE (2018)

Functional Brain Networks Are Dominated by Stable Group and Individual Factors, Not Cognitive or Daily Variation. Neuron:439–452.

Hartogsohn I (2017) Constructing drug effects: A history of set and setting. Drug Sci Policy Law 3:2050324516683325 Available at: https://doi.org/10.1177/2050324516683325.

Howard MA, Volkov IO, Mirsky R, Garell PC, Noh MD, Granner M, Damasio H, Steinschneider M, Reale RA, Hind JE, Brugge JF (2000) Auditory cortex on the human posterior superior temporal gyrus. Journal of Comparative Neurology 416:79–92 Available at: https://onlinelibrary.wiley.com/doi/abs/10.1002/%28SICI%291096-9861%2820000103%29416%3A1%3C79%3A%3AAID-CNE6%3E3.0.CO%3B2-2.

Kringelbach ML, Deco G (2020) Brain States and Transitions : Insights from Computational Neuroscience. CellReports 32:108128 Available at: https://doi.org/10.1016/j.celrep.2020.108128.

Kumaran D, Maguire EA (2009) Novelty signals: a window into hippocampal information processing. Trends Cogn Sci 13:47–54 Available at: https://doi.org/10.1016/j.tics.2008.11.004.

Lawrence DW, Carhart-Harris R, Griffiths R, Timmermann C (2022) Phenomenology and content of the inhaled N, N-dimethyltryptamine (N, N-DMT) experience. Sci Rep 12:8562 Available at: https://doi.org/10.1038/s41598-022-11999-8.

Lebedev A V, Lövdén M, Rosenthal G, Feilding A, Nutt DJ, Carhart-Harris RL (2015) Finding the self by losing the self: Neural correlates of ego-dissolution under

psilocybin. Hum Brain Mapp 36:3137–3153 Available at: https://onlinelibrary.wiley.com/doi/abs/10.1002/hbm.22833.

Lurie DJ et al. (2020) Questions and controversies in the study of time-varying functional connectivity in resting fMRI. Network Neuroscience 4:30–69.

Lyu D, Stieger JR, Xin C, Deisseroth K, Lyu D, Stieger JR, Xin C, Ma E, Lusk Z, Aparicio MK (2023) Case Study Causal evidence for the processing of bodily self in the anterior precuneus Case Study Causal evidence for the processing of bodily self in the anterior precuneus. Neuron:1–11 Available at: https://doi.org/10.1016/j.neuron.2023.05.013.

Mason NL, Kuypers KPC, Müller F, Reckweg J, Tse DHY, Toennes SW, Hutten NRPW, Jansen JFA, Stiers P, Feilding A, Ramaekers JG (2020) Me, myself, bye: regional alterations in glutamate and the experience of ego dissolution with psilocybin. Neuropsychopharmacology 45:2003–2011 Available at: https://doi.org/10.1038/s41386-020-0718-8.

McCulloch DE-W, Knudsen GM, Barrett FS, Doss MK, Carhart-Harris RL, Rosas FE, Deco G, Kringelbach ML, Preller KH, Ramaekers JG, Mason NL, Müller F, Fisher PM (2022) Psychedelic resting-state neuroimaging: A review and perspective on balancing replication and novel analyses. Neurosci Biobehav Rev 138:104689 Available at: https://doi.org/10.1016/j.neubiorev.2022.104689.

Moseley P, Fernyhough C, Ellison A (2014) The role of the superior temporal lobe in auditory false perceptions: A transcranial direct current stimulation study. Neuropsychologia 62:202–208 Available at: https://www.sciencedirect.com/science/article/pii/S0028393214002607.

Muthukumaraswamy SD, Carhart-Harris RL, Moran RJ, Brookes MJ, Williams TM, Errtizoe D, Sessa B, Papadopoulos A, Bolstridge M, Singh KD, Feilding A, Friston KJ, Nutt DJ (2013) Broadband Cortical Desynchronization Underlies the Human Psychedelic State. The Journal of Neuroscience 33:15171 Available at: http://www.jneurosci.org/content/33/38/15171.abstract.

Nichols DE (2016) Psychedelics. Pharmacol Rev 68:264–355.

Northoff G, Bermpohl F (2004) Cortical midline structures and the self. Trends Cogn Sci 8:102–107 Available at: https://www.sciencedirect.com/science/article/pii/S136466130400021X.

Palhano-Fontes F, Andrade KC, Tofoli LF, Santos AC, Crippa JSE, Hallak JEC, Ribeiro S, de Araujo DB (2015) The Psychedelic State Induced by Ayahuasca Modulates the Activity and Connectivity of the Default Mode Network. PLoS One 10:1–13 Available at: https://doi.org/10.1371/journal.pone.0118143.

Pasquini L, Noohi F, Veziris CR, Kosik EL, Holley SR, Lee A, Brown JA, Roy ARK, Chow TE, Allen I, Rosen HJ, Kramer JH, Miller BL, Saggar M, Seeley WW, Sturm VE (2022) Dynamic autonomic nervous system states arise during emotions and manifest in basal physiology. Psychophysiology:1–19.

Poldrack RA et al. (2015) Long-term neural and physiological phenotyping of a single human. Nat Commun 6:8885 Available at: http://www.nature.com/ncomms/2015/151209/ncomms9885/full/ncomms9885.html.

Prugger J, Derdiyok E, Dinkelacker J, Costines C, Schmidt TT (2022) The Altered States Database: Psychometric data from a systematic literature review. Sci Data 9:720 Available at: https://doi.org/10.1038/s41597-022-01822-4.

Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL (2001) A default mode of brain function. Proceedings of the National Academy of Sciences 98:676 LP – 682 Available at: http://www.pnas.org/content/98/2/676.abstract.

Rosas FE, Mediano PAM, Timmermann C, Luppi AI, Candia-Rivera D, Abbasi-Asl R, Gazzaley A, Kringelbach ML, Muthukumaraswamy S, Bor D, Garfinkel S, Carhart-Harris RL (2023) The entropic heart: Tracking the psychedelic state via heart rate dynamics. bioRxiv:2023.11.07.566008 Available at: http://biorxiv.org/content/early/2023/11/09/2023.11.07.566008.abstract.

Roseman L, Nutt DJ, Carhart-Harris RL (2018) Quality of Acute Psychedelic Experience Predicts Therapeutic Efficacy of Psilocybin for Treatment-Resistant Depression. Front Pharmacol 8 Available at: https://www.frontiersin.org/articles/10.3389/fphar.2017.00974.

Rubinov M, Sporns O (2010) Complex network measures of brain connectivity: Uses and interpretations. Neuroimage 52:1059–1069 Available at: http://dx.doi.org/10.1016/j.neuroimage.2009.10.003.

Saggar M, Shine JM, Liégeois R, Dosenbach NUF, Fair D (2022) Precision dynamical mapping using topological data analysis reveals a hub-like transition state at rest. Nat Commun 13.

Schaefer A, Kong R, Gordon EM, Laumann TO, Zuo X-N, Holmes AJ, Eickhoff SB, Yeo BTT (2018) Local-Global Parcellation of the Human Cerebral Cortex from Intrinsic Functional Connectivity MRI. Cerebral Cortex 28:3095–3114 Available at: https://doi.org/10.1093/cercor/bhx179.

Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, Reiss AL, Greicius MD (2007) Dissociable intrinsic connectivity networks for salience processing and executive control. J Neurosci 27:2349–2356 Available at: http://www.ncbi.nlm.nih.gov/pubmed/17329432.

Siegel JS et al. (2023) Psilocybin desynchronizes brain networks. medRxiv:2023.08.22.23294131 Available at: http://medrxiv.org/content/early/2023/08/24/2023.08.22.23294131.abstract.

Smith SM, Fox PT, Miller KL, Glahn DC, Fox PM, Mackay CE, Filippini N, Watkins KE, Toro R, Laird AR, Beckmann CF (2009) Correspondence of the brain's functional architecture during activation and rest. Proc Natl Acad Sci U S A 106:13040–13045 Available at: http://www.ncbi.nlm.nih.gov/pubmed/19620724.

Strassman RJ (1995) Human psychopharmacology of N,N-dimethyltryptamine. Behavioural Brain Research 73:121–124 Available at: https://www.sciencedirect.com/science/article/pii/0166432896000812.

Strassman RJ, Qualls CR (1994) Dose-Response Study of N,N-Dimethyltryptamine in Humans: I. Neuroendocrine, Autonomic, and Cardiovascular Effects. Arch Gen Psychiatry 51:85–97 Available at: https://doi.org/10.1001/archpsyc.1994.03950020009001.

Tagliazucchi E, Carhart-Harris R, Leech R, Nutt D, Chialvo DR (2014) Enhanced repertoire of brain dynamical states during the psychedelic experience. Hum Brain Mapp 35:5442–5456 Available at: https://doi.org/10.1002/hbm.22562.

Tagliazucchi E, Roseman L, Kaelen M, Orban C, Muthukumaraswamy SD, Murphy K, Laufs H, Leech R, McGonigle J, Crossley N, Bullmore E, Williams T, Bolstridge M,

Feilding A, Nutt DJ, Carhart-Harris R (2016) Increased Global Functional Connectivity Correlates with LSD-Induced Ego Dissolution. Current Biology 26:1043–1050 Available at: http://dx.doi.org/10.1016/j.cub.2016.02.010.

Timmermann C, Bauer PR, Gosseries O, Vanhaudenhuyse A, Vollenweider F, Laureys S, Singer T, Antonova E, Lutz A (2023a) A neurophenomenological approach to non-ordinary states of consciousness: hypnosis, meditation, and psychedelics. Trends Cogn Sci 27:139–159 Available at: https://www.sciencedirect.com/science/article/pii/S1364661322002911.

Timmermann C, Roseman L, Haridas S, Rosas FE, Luan L, Kettner H, Martell J, Erritzoe D, Tagliazucchi E, Pallavicini C, Girn M, Alamia A, Leech R, Nutt DJ, Carhart-harris RL (2023b) Human brain effects of DMT assessed via EEG-fMRI. Proceedings of the National Academy of Sciences 120:2023 Available at: http://www.pnas.org/lookup/suppl/doi:10.1073/pnas.2216830120/-/DCSupplemental.https://doi.org/10.1073/pnas.2216830120.

Timmermann C, Roseman L, Schartner M, Milliere R, Williams LTJ, Erritzoe D, Muthukumaraswamy S, Ashton M, Bendrioua A, Kaur O, Turton S, Nour MM, Day CM, Leech R, Nutt DJ, Carhart-Harris RL (2019) Neural correlates of the DMT experience assessed with multivariate EEG. Sci Rep 9:16324 Available at: https://doi.org/10.1038/s41598-019-51974-4.

Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, Mazoyer B, Joliot M (2002) Automated Anatomical Labeling of Activations in SPM Using a Macroscopic Anatomical Parcellation of the MNI MRI Single-Subject Brain.

Neuroimage 15:273–289 Available at: https://www.sciencedirect.com/science/article/pii/S1053811901909784.

Vesuna S, Kauvar I V, Richman E, Gore F, Oskotsky T, Sava-segal C, Luo L, Malenka RC, Henderson JM, Nuyujukian P (2020) Deep posteromedial cortical rhythm in dissociation. Nature Available at: http://dx.doi.org/10.1038/s41586-020-2731-9.

Vogt SB, Ley L, Erne L, Straumann I, Becker AM, Klaiber A, Holze F, Vandersmissen A, Mueller L, Duthaler U, Rudin D, Luethi D, Varghese N, Eckert A, Liechti ME (2023) Acute effects of intravenous DMT in a randomized placebo-controlled study in healthy participants. Transl Psychiatry 13:172 Available at: https://doi.org/10.1038/s41398-023-02477-4.

Vollenweider FX, Kometer M (2010) The neurobiology of psychedelic drugs: Implications for the treatment of mood disorders. Nat Rev Neurosci 11:642–651 Available at: http://dx.doi.org/10.1038/nrn2884.

Wolff M, Evens R, Mertens LJ, Koslowski M, Betzler F, Gründer G, Jungaberle H (2020) Learning to Let Go: A Cognitive-Behavioral Model of How Psychedelic Therapy Promotes Acceptance. Front Psychiatry 11 Available at: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.00005.

Yaden DB, Griffiths RR (2021) The Subjective Effects of Psychedelics Are Necessary for Their Enduring Therapeutic Effects. ACS Pharmacol Transl Sci 4:568–572 Available at: https://doi.org/10.1021/acsptsci.0c00194.

Yeshurun Y, Nguyen M, Hasson U (2021) The default mode network: where the idiosyncratic self meets the shared social world. Nat Rev Neurosci Available at: http://dx.doi.org/10.1038/s41583-020-00420-w.

Younes K, Gorno-Tempini ML (2021) Right temporal lobe and socioemotional semantics: semantic behavioural variant frontotemporal dementia. Brain 145(11)4080-4096. Available at: https://doi.org/10.1093/brain/awac217

Figures, Legends, and Tables:

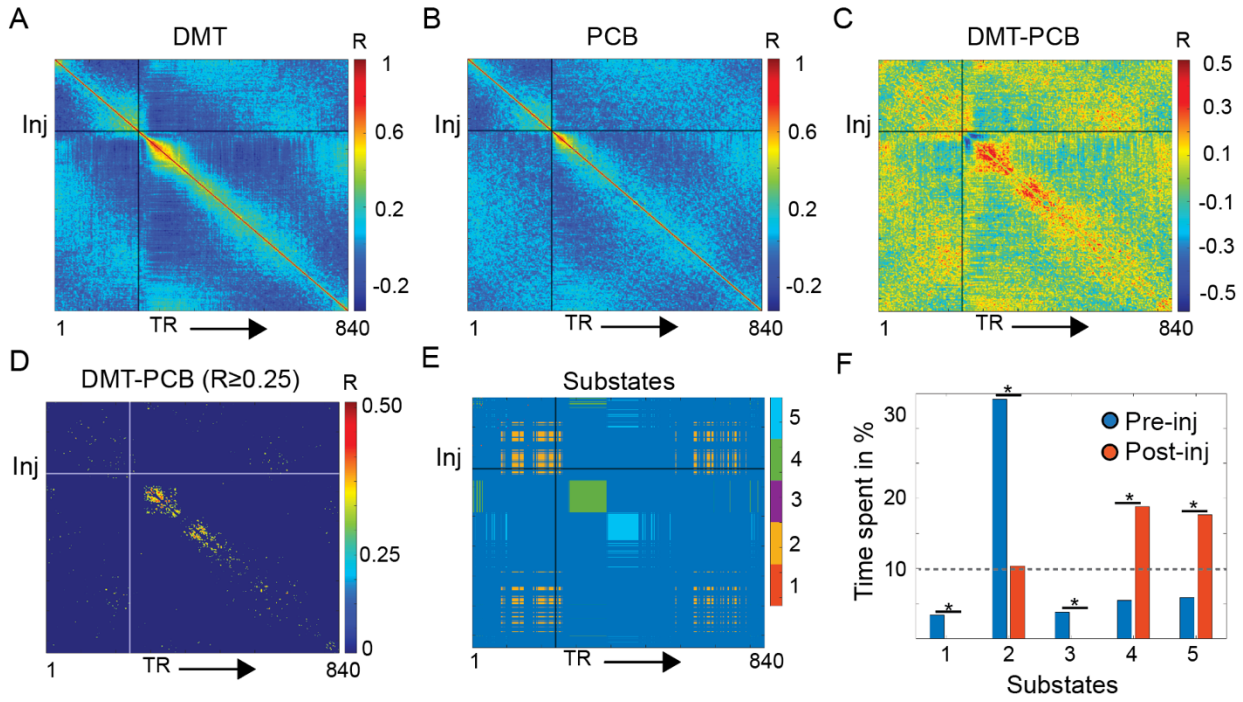

Figure 1. Analysis pipeline and metrics. Group-mean continuous brain activity similarity matrix, reflecting the homogeneity of brain activity in time during the DMT (**A**) condition and the placebo (PCB; **B**) conditions. (**C**) Mean subtraction matrix reflecting how continuous brain activity similarity varies across the DMT and placebo conditions. Warm colors reflect higher similarity of brain activity during the DMT condition. (**D**) The subtraction matrix was thresholded for similarity values maximizing the identification of brain activation substates occurring either during the pre-injection or post-injection phase (Pearson's correlation values R ≥ 0.25) using an unsupervised community detection algorithm. This community detection algorithm identified five brain activation substates differentiating the DMT from the placebo condition (**E**). (**F**) These five substates were occupied at significant higher rates either during the pre- or post-injection periods, but only three out of these five substates were occupied for more that

10% of the duration of the entire scanning time. Following analyses focused on these three activation substates: State 2, 4, and 5. DMT = N,N-Dimethyltryptamine; Inj = timepoint of injection, indicated by continuous vertical and horizontal lines; TR = fMRI volume acquired at each repetition time. *$p < 0.05$

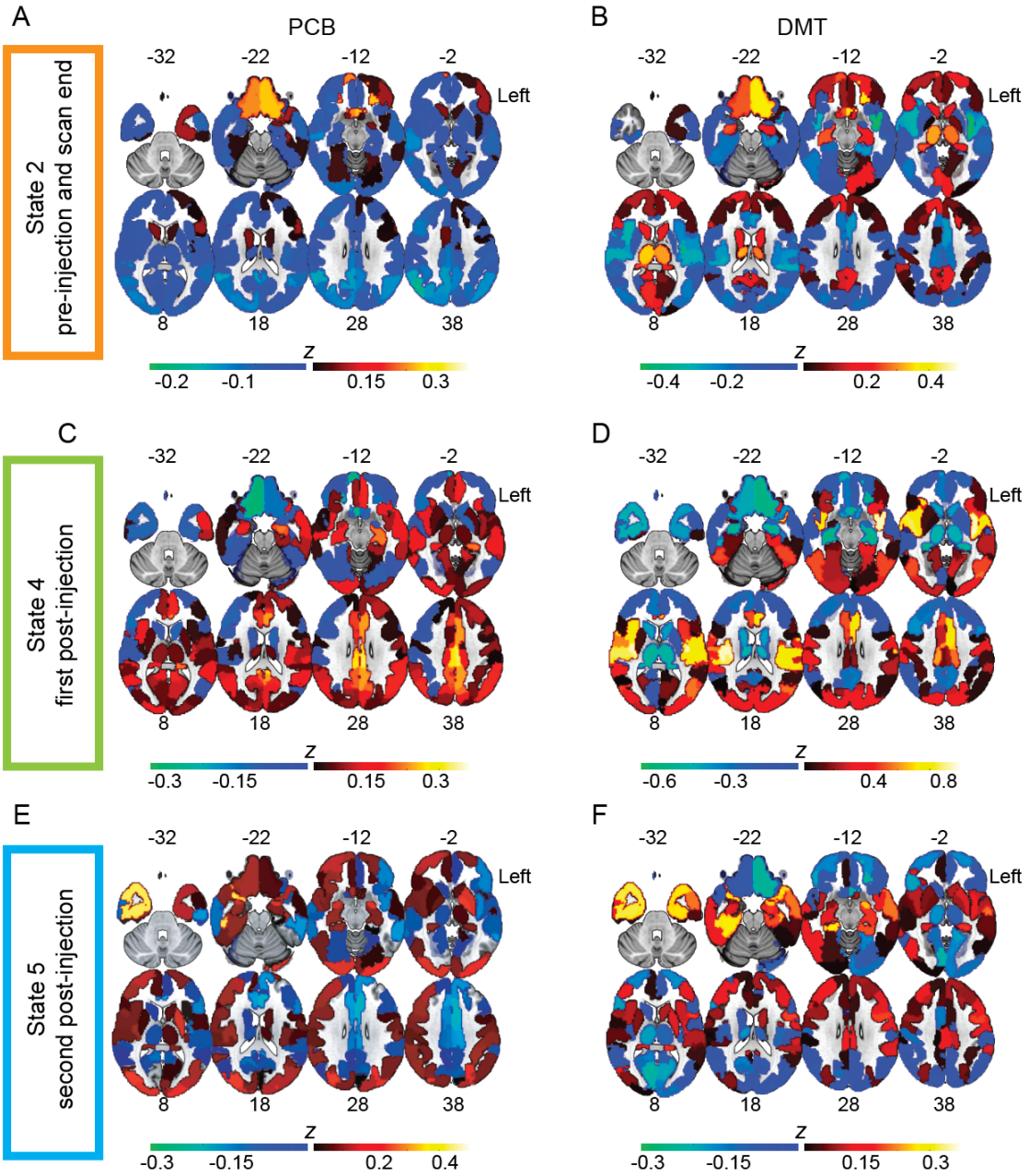

Figure 2. Maps of brain activation substates. Mean activation maps (z-scores) of brain substates, reflecting relative hyperactivity (warm colors) or hypoactivity (cold colors) when compared to the rest of the scan, shown once for placebo (PCB, on the left) and once for DMT (on the right). Mean activity of State 2, which occurred before

injection and towards the end of the scan, once for placebo (**A**) and once for DMT (**B**). The length of this substate before injection was 2.7 min, after injection 2.0 min. Mean brain activity of State 4, occurring immediately after injection, once for placebo (**C**) and once for DMT (**D**). The length of this substate post-injection was 3.8 min. Mean activity of State 5, the second post-injection substate, once under placebo (**E**) and once under DMT (**F**). The length of this substate post-injection was 3.6 min. The left hemisphere is shown on the right side.

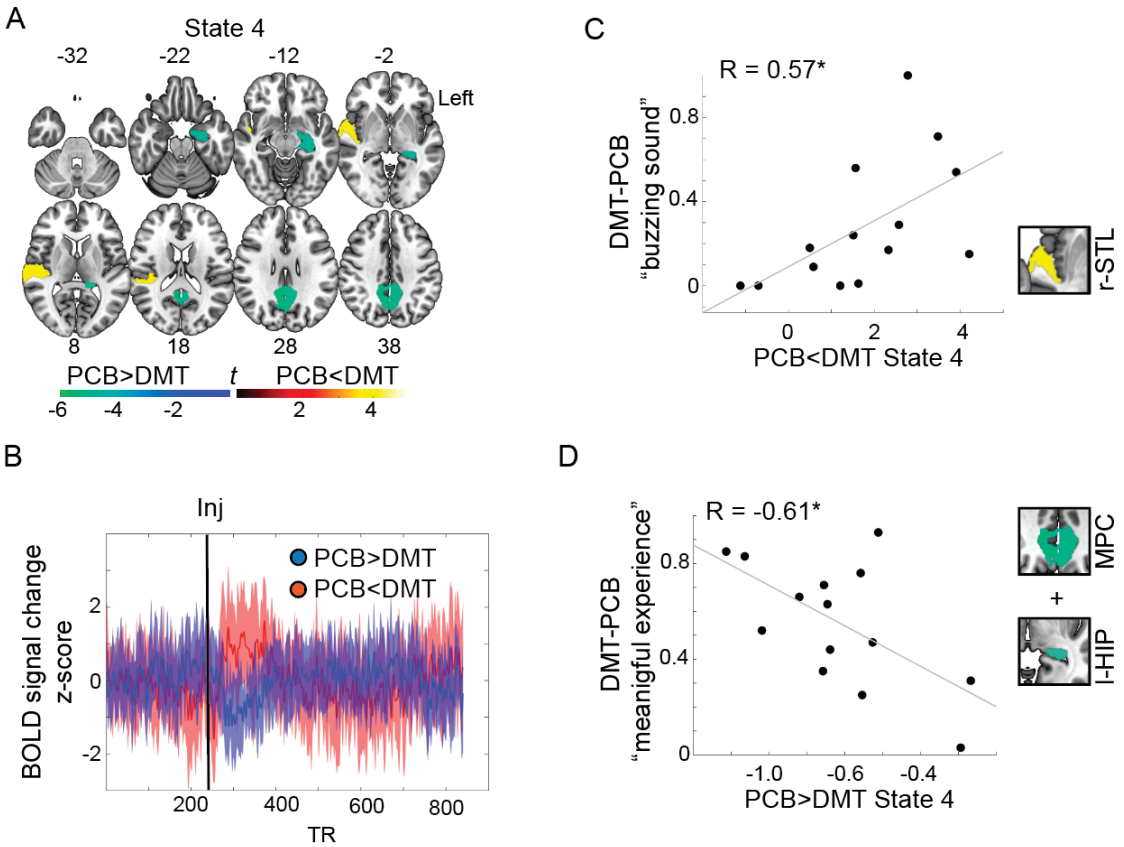

Figure 3. Substate hypoactivity and hyperactivity under DMT. (**A**) Hyperactivity (warm colors) and hypoactivity (cold colors) in the first post-injection substate (State 4) under DMT when compared to placebo. Findings are FDR adjusted $p < 0.05$; color bar indicates associated *t*-values. (**B**) Increased mean activity of the right superior temporal lobe (red line) and decreases in hippocampus/medial parietal activity (blue line) following DMT injection. (**C**). Hyperactivity of the superior temporal lope during State 4 under DMT correlates with auditory distortion experienced under the effects of the drug. (**D**) Hypoactivity of the hippocampus/medial parietal cortex in State 4 under DMT correlates with meaningfulness of the experience under the effects of the drug. Regions-of-interest used to derive activity changes are shown to the right of panels **C**

and **D**. l-HIP = left hippocampus; MPC = medial parietal cortex; r-STL = right superior temporal lobe. *$p < 0.05$

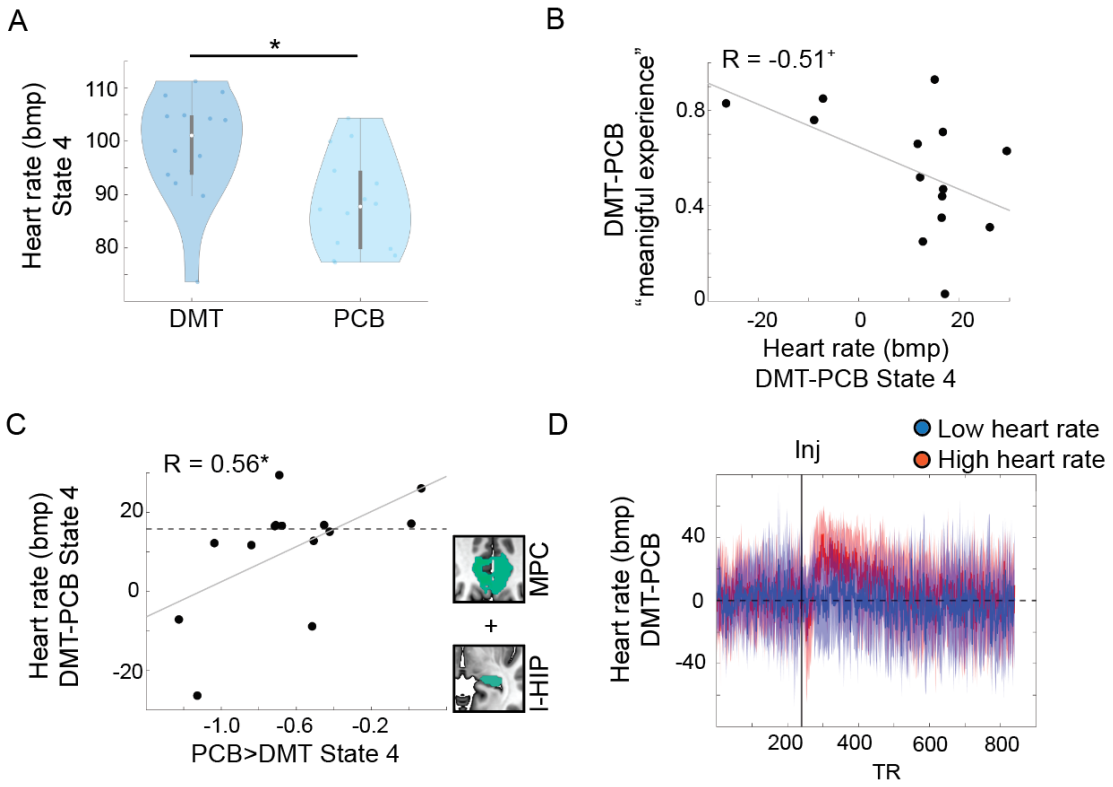

Figure 4. The lower heartrate under DMT, the stronger hippocampus and medial parietal deactivations. (**A**) Increased heartrate during the first post-injection activation substate (State 4) under DMT when compared to placebo. (**B**) The higher heart rate under the first post-injection DMT substate, the less meaningful the psychedelic experience. (**C**) The lower the heart rate under the first post-injection DMT substate, the stronger hippocampus and medial parietal deactivations under the same substate. Dashed horizontal line separates participants with high heart rate during the first post-injection DMT state from participants with lower heart rate based on a median split. Regions-of-interest used to derive activity decreases under DMT are shown to the right of panel **C** (l-HIP = left hippocampus; MPC = medial parietal cortex). (**D**) Continuous heart rate for participants with high heart rate (in red) and low heart rate (in blue) during the first post-injection DMT substate. Note the marked fluctuations and sustained

increases in heart rate following the injection among participants with higher median heart rate during State 4. Bpm = beats per minute. $^{+}p < 0.1$; $^{*}p < 0.05$

R threshold	0.20	0.21	0.22	0.23	0.24	0.25	0.26	0.27	0.28	0.29	0.30
***Mean X^2* statistics**	33.0	24.3	16.5	19.8	31.6	31.1	25.2	28.2	17.4	17.5	23.3
# of substates	2	2	4	4	4	5	6	4	6	6	3

Table 1. Optimal threshold for brain activity substate identification. The mean continuous brain activity similarity subtraction matrix was thresholded for Pearson's correlation values ranging from R = 0.20-0.30, in incremental steps of 0.01. Each of these thresholds yielded a distinct amount of brain activation substates (# of substates) differentially occupied before and after the injection (mean X^2 statistics). The R threshold of 0.25 was chosen since it maximized the number of brain activation substates separately occupied either during the pre- or post-injection periods.