
Supplementary information

Psychedelics align brain activity with context

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Psychedelics Align Brain Activity with Context

Supplementary Information

Devon Stoliker¹, Leonardo Novelli¹, Moein Khajehnejad¹, Mana Biabani¹, Matthew D. Greaves¹, Tamrin Barta¹, Martin Williams², Sidhant Chopra^{3,4}, Olivier Bazin⁵, Otto Simonsson⁶, Richard Chambers⁷, Frederick Barrett⁸, Gustavo Deco⁹, Katrin H. Preller¹⁰, Robin Carhart-Harris^{11,12}, Anil Seth^{13,14}, Suresh Sundram¹⁵, Gary F. Egan^{1,16}, Adeel Razi^{1,16, 17}

¹Turner Institute for Brain and Mental Health, School of Psychological Sciences, Monash University, Australia.

²School of Health Sciences, Swinburne University of Technology, Hawthorn, VIC 3122, Australia.

³Orygen, The University of Melbourne, Parkville, Australia.

⁴Centre for Youth Mental Health, The University of Melbourne, Australia.

⁵British Association of Mindfulness-based Approaches (BAMBA) Listed Teacher, Oxford, UK.

⁶Department of Neurobiology, Care Sciences and Society, Karolinska Institute, Sweden.

⁷Monash Centre for Consciousness and Contemplative Studies, Monash University, Melbourne, Australia.

⁸Department of Psychiatry and Behavioral Sciences, Center for Psychedelic and Consciousness Research, Johns Hopkins University School of Medicine, Baltimore, MD, USA.

⁹Center for Brain and Cognition, Theoretical and Computational Group, Universitat Pompeu Fabra/ICREA, Barcelona, Spain.

¹⁰Department of Adult Psychiatry and Psychotherapy, Psychiatric University Clinic Zurich and University of Zurich, Switzerland.

¹¹Centre for Psychedelic Research, Department of Brain Sciences, Imperial College, London, London, UK.

¹²Psychedelics Division, Neuroscape, University of California, San Francisco, USA.

¹³Sussex Centre for Consciousness Science, Department of Informatics, University of Sussex, Brighton, UK.

¹⁴Program on Brain, Mind, and Consciousness, Canadian Institute for Advanced Research, Toronto, Canada.

¹⁵Department of Psychiatry, School of Clinical Sciences, Monash University, Clayton, VIC 3168, Australia.

¹⁶Monash Biomedical Imaging, Monash University, Australia.

¹⁷CIFAR Azrieli Global Scholars Program, Toronto, Canada.

Correspondence to: devon.stoliker@monash.edu; adeel.razi@monash.edu

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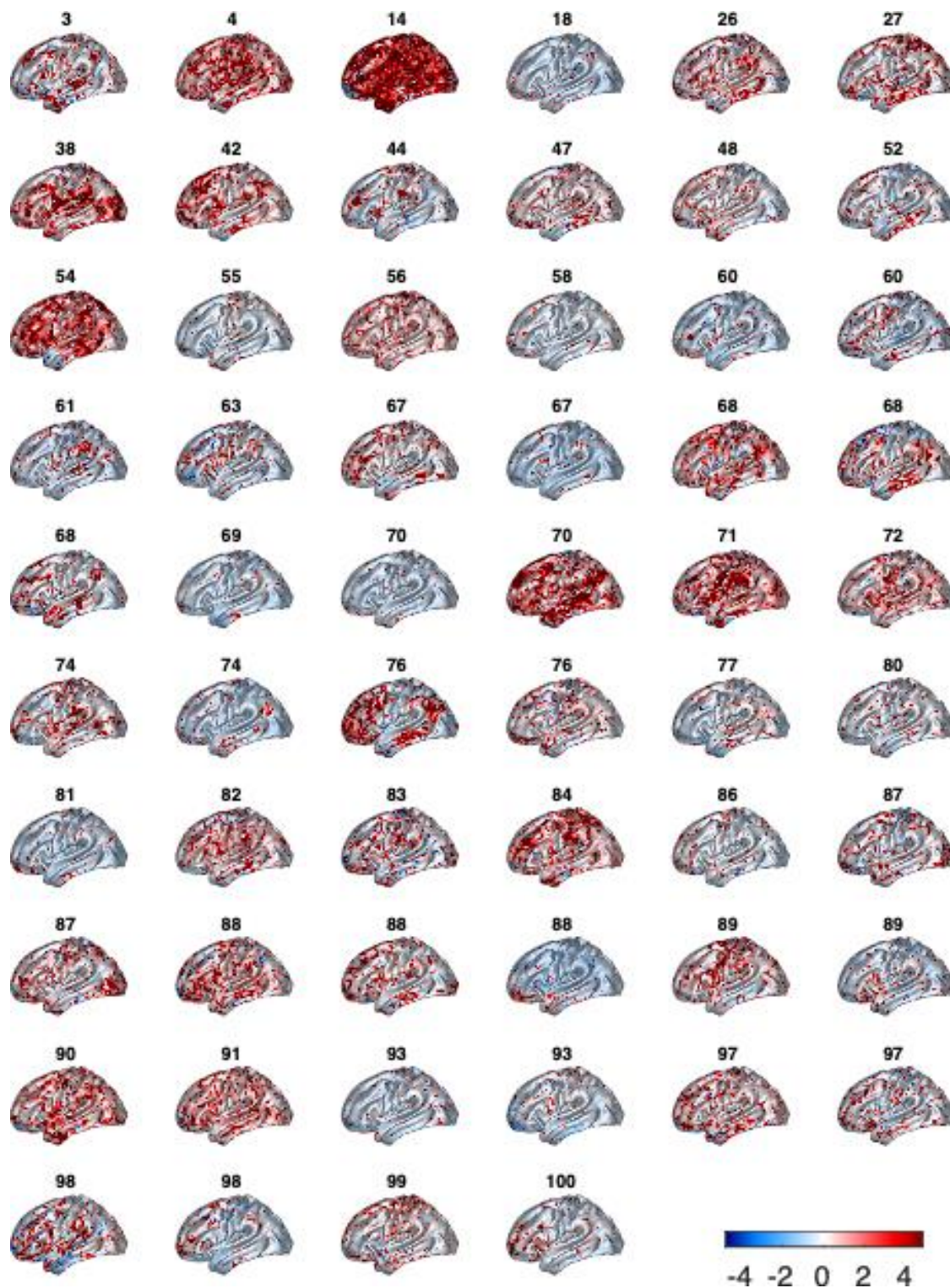
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Supplement to Psilocybin redistributes cortical GFC

Per-subject GFC change maps in the resting-state condition (Supplementary Fig. 1) show that group-level GFC differences coexist with substantial individual variability.

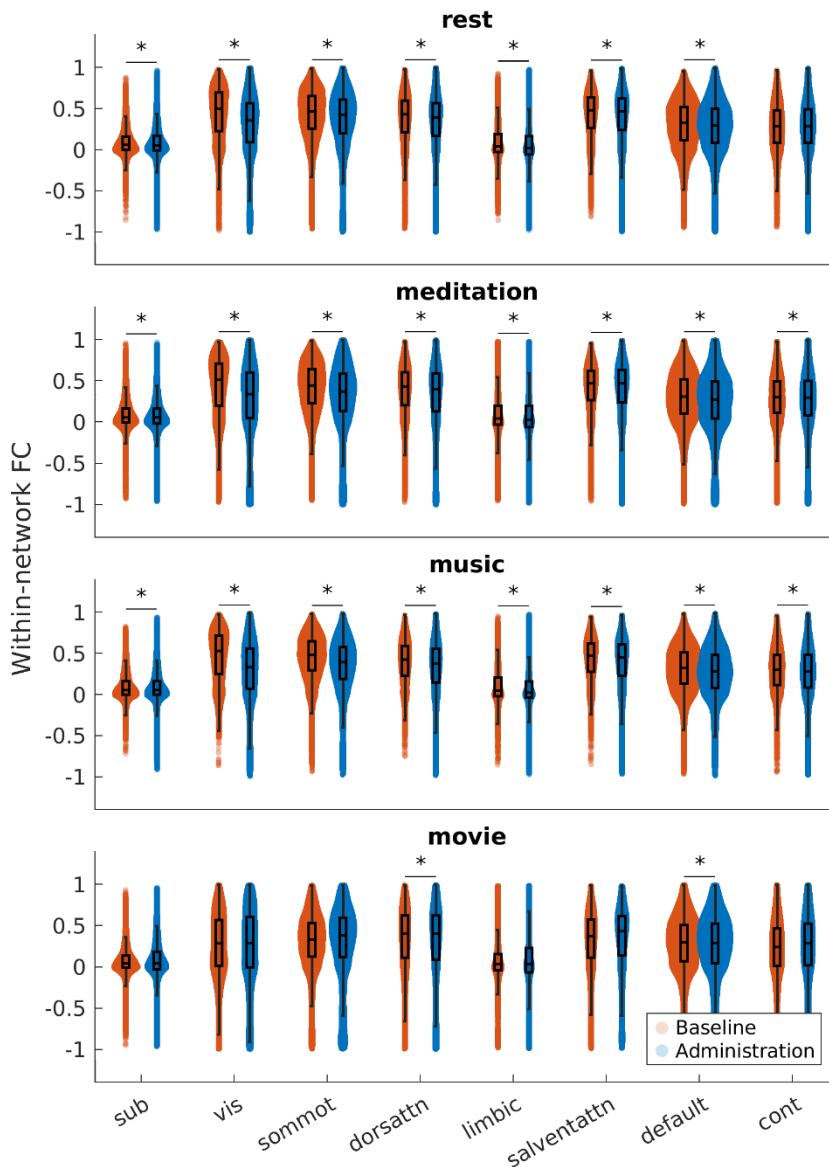


Supplementary Fig. 1. Per-subject variability in GFC change under psilocybin (resting-state condition). Despite the statistically significant group differences, GFC is highly variable across subjects, even when the

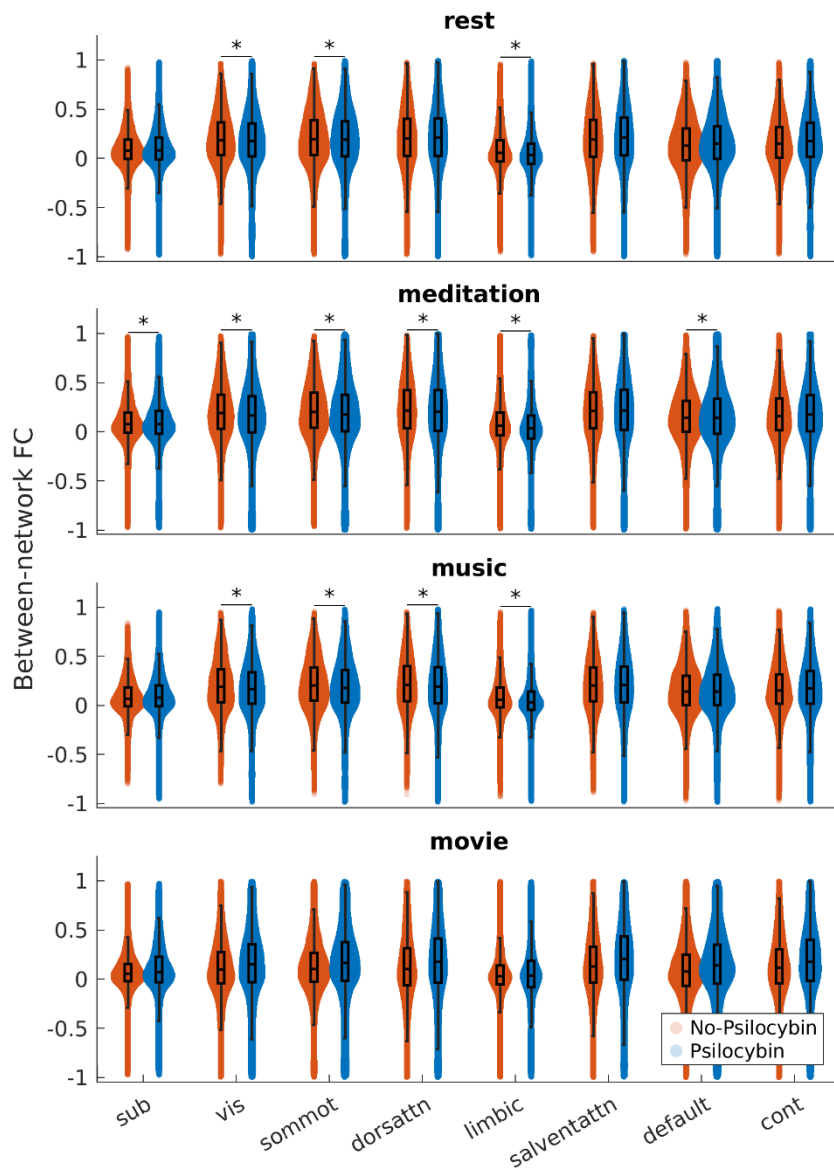
subjective effects measured via the Mystical Experience Questionnaire (MEQ30) are similar. Here, the subjects are sorted by MEQ30 values and the individual GFC percentage difference maps (psilocybin minus baseline, divided by baseline) are shown for the resting-state condition.

Supplement to Decreased functional modularity

Within-network (Supplementary Fig. 2) and between-network (Supplementary Fig. 3) functional connectivity changes under psilocybin are shown per resting-state network.



Supplementary Fig. 2. Psilocybin reduces functional connectivity within most networks during the eyes-closed conditions: resting-state, meditation, and music. Conversely, during the movie, the within-network functional connectivity only decreases in the dorsal attention network and the default-mode network (DMN). Each swarm chart and box plot indicates the average functional connectivity between one network and the rest of the brain. Each star symbol indicates a significant decrease based on the Mann-Whitney U-test ($\alpha = 0.00625$ to correct for multiple comparisons across eight resting-state networks). $N=59$ participants. Number of within-network FC values: sub ($n=60416$), vis ($n=130331$), sommot ($n=191691$), dorsattn ($n=68204$), limbic ($n=23600$), salventattn ($n=68204$), default ($n=272816$), cont ($n=94400$).



Supplementary Fig. 3. Psilocybin reduces functional connectivity between specific networks (visual, somato-motor, limbic) and the rest of the brain during the eyes-closed conditions. Conversely, during the movie, the functional connectivity increases between most networks. Each swarm chart and box plot indicates the average functional connectivity between one network and the rest of the brain. Each star symbol indicates a significant decrease based on the Mann-Whitney U-test ($\alpha = 0.00625$ to correct for multiple comparisons across eight resting-state networks). $N=59$ participants. Number of between-network FC values: sub ($n=566400$), vis ($n=790305$), sommot ($n=924825$), dorsattn ($n=597788$), limbic ($n=368160$), salventattn ($n=597788$), default ($n=1059168$), cont ($n=689120$).

Mindset measure

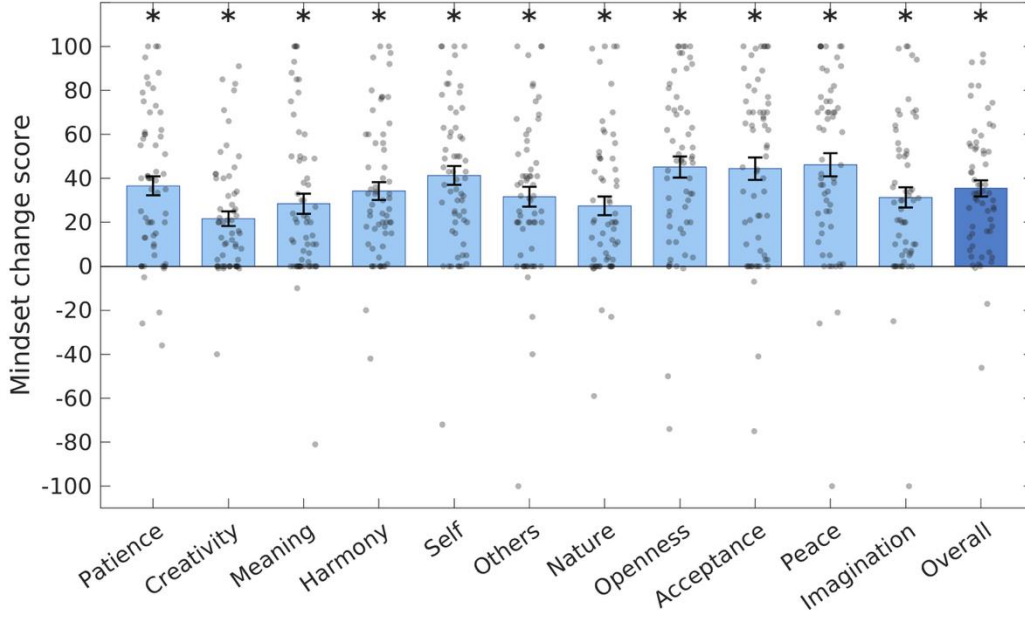
We used a custom-made, unvalidated Likert scale to measure mindset (psychological) change the day after psilocybin, measuring 11 qualities on a scale from -100 to +100. The average scores across these 11 qualities were used as a mindset score. The term *mindset* here denotes a composite of perceived psychological change across these dimensions. Group-level results, summarised in Supplementary Table 1 and Supplementary Fig. 4, are reported below.

Survey Question:

“Please remark on the mindset qualities that you notice have changed since the psilocybin experience. Please note: The scale of this measure is -100 to +100. Any score below 0 means you experienced a negative change for the item after psilocybin. A middle score of 0 means no change. Any score above 0 means a positive change for the item after psilocybin.”

Dimension	n	Mean ± SEM	t	Cohen’s d	Bonferroni-corrected p
Patience	61	36.60 ± 4.32	8.47	1.08	9.3×10^{-11}
Creativity	61	21.65 ± 3.33	6.51	0.83	2.1×10^{-7}
Meaning	61	28.42 ± 4.57	6.21	0.80	6.5×10^{-7}
Harmony	61	34.20 ± 4.05	8.44	1.08	1.0×10^{-10}
Self	61	41.34 ± 4.26	9.70	1.24	8.1×10^{-13}
Others	61	31.64 ± 4.53	6.99	0.89	3.1×10^{-8}
Nature	61	27.48 ± 4.25	6.46	0.83	2.5×10^{-7}
Openness	61	45.14 ± 4.79	9.42	1.21	2.3×10^{-12}
Acceptance	61	44.39 ± 5.10	8.70	1.11	3.8×10^{-11}
Peace	59	46.18 ± 5.27	8.77	1.14	3.8×10^{-11}
Imagination	59	31.31 ± 4.60	6.80	0.89	7.5×10^{-8}
Overall	61	35.40 ± 3.66	9.68	1.24	8.8×10^{-13}

Supplementary Table 1. One-sample tests of perceived mindset change one day after psilocybin. Two-sided one-sample t-tests against H_0 : mean = 0; $df = n - 1$; Cohen’s d = mean / standard deviation; p-values Bonferroni-corrected across the 12 tests (all corrected $p < 0.000001$). Overall = per-participant mean across available dimensions.



Supplementary Fig. 4. Average mindset cores across different dimensions. Mean change scores ($\pm$ SEM) on a -100 (large negative change) to +100 (large positive change) scale, where 0 indicates no perceived change. Bars: light blue = individual dimensions; deep blue = overall composite (per-participant mean across available dimensions). Grey dots show individual participants (jittered horizontally for visibility). The highest scores are observed in Peace, Openness, and Acceptance, while Creativity and Nature have the lowest averages. $n = 59$ for Peace and Imagination; $n = 61$ for Patience, Creativity, Meaning, Harmony, Self, Others, Nature, Openness, Acceptance and Overall. Two-sided one-sample t-tests against H_0 : mean = 0. All 12 tests remained significant after Bonferroni correction (all corrected $p < 0.000001$).

Supplement to Network perturbation analysis

For the network perturbation analysis described in Methods, we defined a formal attribution framework to quantify each functional network’s contribution to context-aligned trajectory organisation under psilocybin.

Let s index subjects ($s = 1, \dots, S$) and k index functional networks ($k = 1, \dots, K$). The total improvement in SVM classification accuracy from baseline to psilocybin is:

$$G^{(s)} = Acc_{admin}^{(s)} - Acc_{baseline}^{(s)}$$

The contribution of network k is measured as the accuracy drop under baseline substitution of that network:

$$\Delta Acc_k^{(s)} = Acc_{admin}^{(s)} - Acc_{admin \text{ with } k \rightarrow baseline}^{(s)}$$

Normalised weights, retaining only positive contributions:

$$w_k^{(s)} = \frac{\max(\Delta Acc_k^{(s)}, 0)}{\sum_{j=1}^K \max(\Delta Acc_j^{(s)}, 0)}$$

Each network's attributed contribution:

$$Contrib_k^{(s)} = w_k^{(s)} \times G^{(s)}$$

guaranteeing that:

$$\sum_{k=1}^K Contrib_k^{(s)} = G^{(s)}$$

For visualisation (Main Fig. 3h), contributions were expressed as percentages of the total gain:

$$Contribution\%_k^{(s)} = \frac{Contrib_k^{(s)}}{G^{(s)}} \times 100$$

This additive decomposition ensures that each network's contribution is expressed relative to the total psilocybin-induced accuracy gain, allowing direct comparison across networks and participants. For the per-condition decomposition, recall was defined as the diagonal of the row-normalised confusion matrix for each condition, and Δ recall was computed as $\text{recall}(\text{psilocybin}) - \text{recall}(\text{substituted})$ for each network and condition.

Per-condition decomposition of network contributions

The per-condition decomposition revealed that Default Mode and Visual networks showed the largest Δ recall across all four conditions, with graded modulation across contexts rather than condition-specific dissociation (Extended Data Fig. 7b).

Rest showed the strongest overall dependence on individual network substitutions (Visual: Δ recall = +0.15; Default Mode: +0.14), consistent with the absence of an external stimulus scaffold allowing internally generated dynamics, particularly within Default Mode and Visual systems, to dominate trajectory organisation.

Movie viewing showed strong Visual network contributions (Δ recall = +0.13), consistent with the dominant role of visual processing during the eyes-open condition.

Music listening consistently showed the weakest dependence on any single network's substitution (largest single contribution: Default Mode, Δ recall = +0.06), despite exhibiting strong overall clustering quality (silhouette scores: $\Delta s = 0.515$, $p < 0.0001$; Main Fig. 3d). This indicates that the trajectory organisation for music is robust but draws on a more distributed set of neural resources. We note two factors that may contribute to this pattern. First, this condition involved a substantially longer, continuously evolving auditory stimulus (11:24 min vs. 6–8 min for other conditions), which is likely to increase temporal heterogeneity in BOLD trajectories under psilocybin. Second, auditory processing regions are not represented as a dedicated network in the Schaefer cortical parcellation, meaning that condition-specific contributions from auditory systems may be distributed across multiple network labels. We therefore interpret the attenuated per-network effects for music as a consequence of the richer temporal structure and parcellation coverage of this condition,

consistent with context-dependent alignment mediated by a broader coalition of systems rather than a few dominant networks.

Taken together, the per-condition decomposition confirms that the anatomical anchoring identified in the aggregate analysis (Default Mode and Visual dominance) generalises across contexts, while the graded variation across conditions is consistent with context-dependent modulation of a common organisational motif.

Condition-order considerations

The fixed within-modality sequence was chosen for safety and experiential coherence. We note that: (i) the movie condition was reversed across modalities (last in fMRI, first in EEG) and separated by a 20–40 minute setup break; (ii) head-motion indices showed no monotonic rise across scan sequences (Extended Data Fig. 2b); (iii) inter-individual post-dose pharmacokinetic-pharmacodynamic timing variability (Brown et al., 2017; Hasler et al., 2004; Otto et al., 2025) means the scan order does not correspond to a common exposure phase across participants; (iv) each scan lasted 6–11 minutes, limiting carry-over effects; (v) structured CEBRA clustering was already evident during rest (the first scan sequence), before cumulative sequence effects could accrue; and (vi) a mixed-effects model with silhouette $\sim$ scan index + (1 | participant) showed no linear trend with scan order ($\beta = 0.046$, SE = 0.041, $p = 0.258$); the typical silhouette profile across conditions was non-monotonic (Movie $\approx$ Meditation > Rest > Music), and network modularity followed an independent non-monotonic pattern (rest > music > movie > meditation), neither consistent with progressive order effects. Together with the absence of sequence-aligned signatures in the ML embeddings (Main Fig. 2 and Main Fig. 3) and cross-modal replication of reduced differentiation between eyes-open and eyes-closed (Main Fig. 1 and Main Fig. 6), these factors mitigate the risk that fixed order explains the main results (i.e., the ML findings and the eyes-open vs eyes-closed convergence).

While these analyses argue against fixed-order or pharmacokinetic effects as drivers of the CEBRA clustering, complete exclusion of subtle temporal contributions would require a counterbalanced design.

Residual order influence cannot be excluded for fine-grained comparisons among the eyes-closed conditions analysed with conventional metrics. Because these scans were presented in a specific order, progressing from low- to high-stimulus (rest $\rightarrow$ meditation $\rightarrow$ music), subtle sequence effects (potentially state-dependent under psilocybin, and longer-timescale context drift) could contribute to their relative differences. Accordingly, eyes-closed comparisons are reported descriptively.

EEG timing

Our EEG session sampled the late-peak/early-offset portion of the acute response. Human PK/PD data indicate that, after oral dosing, plasma psilocin T_{max} typically occurs at $\sim$ 2–3 h ($\approx$ 90–150 min) with inter-individual variability, and concentrations remain elevated for

several hours; subjective intensity closely tracks psilocin levels and neocortical 5-HT_{2A} engagement across this window (Holze et al., 2022; Ley et al., 2023; Madsen et al., 2019). Consistent with this coupling, psilocybin-induced changes in large-scale network integrity/segregation have been characterised over multiple hours post-dose, indicating robust central effects throughout our EEG interval (Madsen et al., 2021). Evidence that EEG timing is within the acute state is additionally demonstrated by consistency between our findings and canonical electrophysiological signatures observed in established EEG/MEG psychedelic research—most notably broadband desynchronisation with pronounced parieto-occipital alpha reductions and increased neural signal diversity/entropy (Muthukumaraswamy et al., 2013; Scharfner et al., 2017; Timmermann et al., 2023).

Day-after qualitative self-reports on psilocybin experiences

The following tables are drawn from semi-structured self-report questionnaires collected from participants the day after psilocybin. Key excerpts from participant reports are structured by the specific questions under which they were collected. Responses that appear in the main text are marked with an asterisk (*). Column headings and verbatim questions are listed above each table in brackets.

Emotional Responses During MRI (EXP.MRIEMOTIONS – “During the MRI my emotions were...”)

Theme	Raw Participant Report
Wave-like Sensory Immersion in MRI*	<i>“Honestly I can’t even explain. I remember preparing and [names omitted] organising me for the MRI and lying down, then within minutes the sounds of the machine were creating a wave of music that was so beautiful, so intense. It was building from a couple of sounds, then louder and louder until it was an inevitable wave of sound that crashed through me. I don’t know how to describe it other than to say I lost all sense of self, and I became at one with all my surroundings.”</i>
Melding with the Environment (MRI)*	<i>“I melded with the MRI machine, floor, walls, air. It was like nothing existed except for me, or me as part of something bigger.”</i>
Loss of Self & Integration into Surroundings (MRI)*	<i>“I lost all sense of self, and I became at one with all my surroundings. I melted into everything else around me and became part of a larger, bigger thing. I saw myself as part of a bigger network of things.”</i>

Visual and Perceptual Alterations (EXP.VISUALPT1, EXP.VISUALPT2 – “Did you have an altered visual experience? If yes, please describe your visual experience and note where you were.”)

Theme	Raw Participant Report
Seamless Transitions Between Eyes-Closed & Eyes-Open	<i>“Switching from eyes closed to eyes open and vice versa... visual experience with eyes closed was of being in an open ‘sky’ area... merging seamlessly into the EEG environment when opening my eyes.”</i>
Perceptual Expansion	<i>“I saw my inner monologue (maybe all of language?) as a floating double helix that I could bend at will.”</i>

Music, Synaesthesia, and Multisensory Integration (EXP.MUSIC, EXP.SYNAESTHESIA – “Did you experience synaesthesia? If yes, please describe your experience.”)

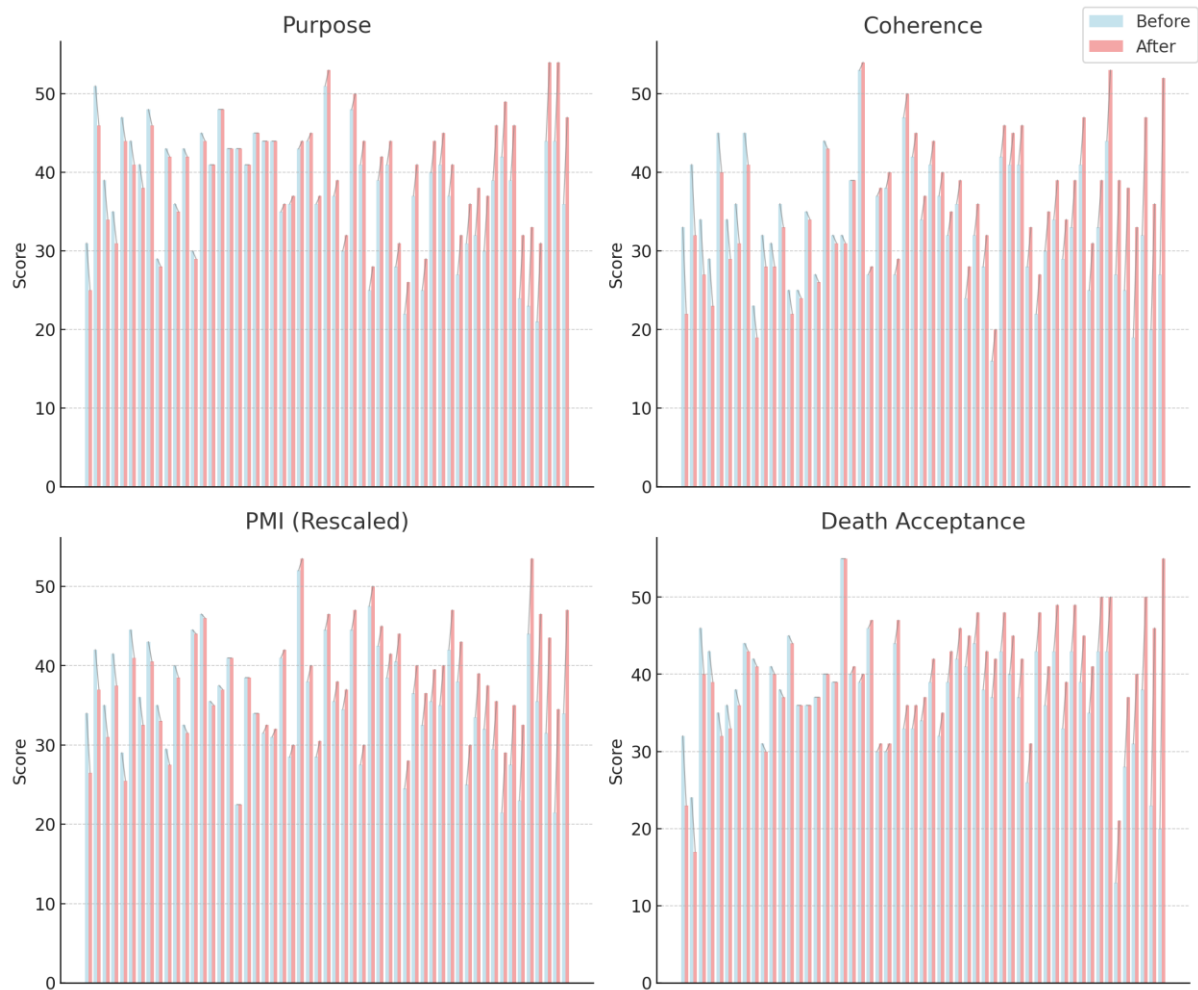
Theme	Raw Participant Report
Music as a Guide to the Experience	<i>“Became the landscape of my experience - I stopped being able to distinguish between myself, the music, the evolving patterns.”</i>
Auditory-Induced Imagery	<i>“The music influenced what I saw. It wasn’t necessarily like a visual representation of the music, but it was more like the music was the landscape.”</i>
Rhythmic Synchronisation	<i>“Visual hallucinations were in rhythm/sync with the music, as the music changed, so would what I was seeing.”</i>
MRI-Induced Visual Patterns	<i>“The sound of the MRI created incredibly real visual imagery – rolling waves of gold and silver like an ocean of watered steel with fine detailed Thai motifs.”</i>

Meaning, Self-Dissolution, and Psychological Insights (EXP.FINDMEANING, EXP.MOSTMEANINGPT1, EXP.INTEREST – “Did you find meaning in your experience? If yes, please describe how.” / “What aspects of the experience were most interesting or important to you?”)

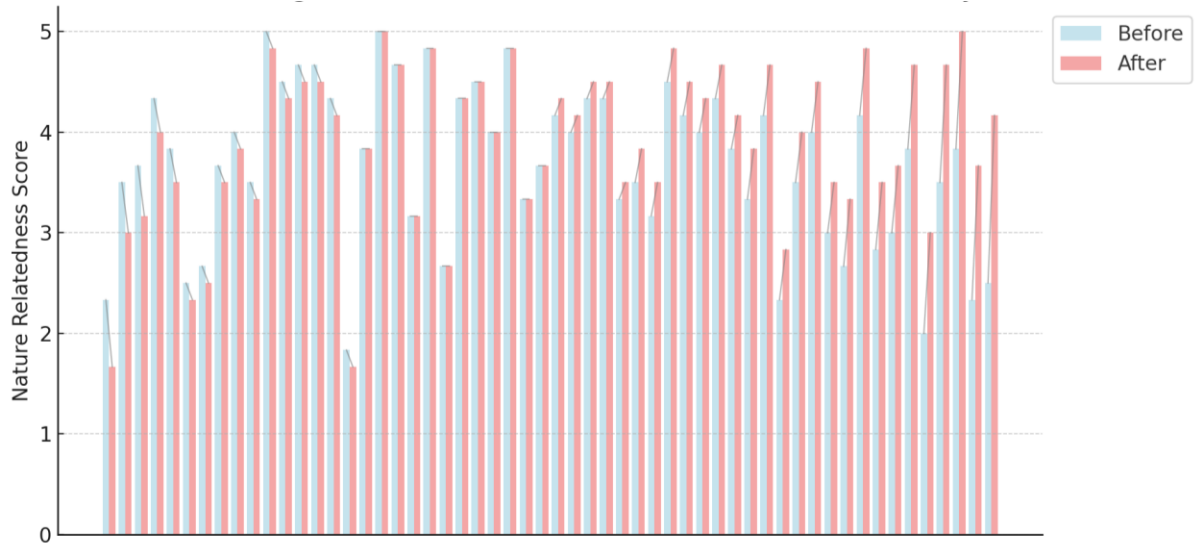
Theme	Raw Participant Report
Altered Sense of Self & Narrative	<i>“The fact that I lost the narrative of myself and ended up just kind of vibing makes me realise how much of who I think I am is just a story that I am telling myself.”</i>
Life Perspective & Acceptance	<i>“I now see I was not in total control of my life... I now feel grateful for this life and want to cherish my time better.”</i>
Reduced Attachment to Stressors	<i>“The meaning that I derived most from the experience was realising the little stressors in life that often keep me in my head and ruminating became insignificant and no longer held me hostage.”</i>
Profound Self-Dissolution in MRI	<i>“Definitely the MRI because I completely lost all sense of self, of body, of being. And I legitimately felt that I existed only in consciousness.”</i>
Loss of Plot and Self During EEG*	<i>“During the EEG, everything blended into the colours/patterns/landscape... I lost any form of language and couldn’t hold a thought. I lost the plot of who I was, where I was, if I was even here, what was happening.”</i>
Ego Dissolution & Profound Experience (MRI)*	<i>“The MRI, that experience of what I now know is ego dissolution, and not existing, is one of the most peaceful and profound things I could ever experience.”</i>

Supplement to Structure of psychedelic phenomenology

Group-level changes in Life Attitudes (Supplementary Fig. 5) and Nature Relatedness (Supplementary Fig. 6) are accompanied by substantial individual variability.



Supplementary Fig. 5. Individual variability in changes in Life Attitudes (LAP-R) dimensions before and one month after psilocybin (n = 55). Each panel displays individual participant changes for Purpose, Coherence, Personal Meaning Index (PMI) (Purpose + Coherence), and Death Acceptance. Participants are sorted by change magnitude, from largest decrease to largest increase. Each participant has two bars: blue (before psilocybin) and red (after psilocybin), with gray linking lines indicating the change for each individual. Personal Meaning was rescaled by dividing the score by 2. At the group level, paired t-tests revealed statistically significant improvements: Purpose: $t(54) = -3.87$, $p = 0.0003$, $d = 0.52$ (moderate effect). Coherence: $t(54) = -2.81$, $p = 0.0069$, $d = 0.38$ (small-to-moderate effect). Personal Meaning (Purpose + Coherence): $t(54) = -3.77$, $p = 0.0004$, $d = 0.51$ (moderate effect). Death Acceptance: $t(54) = -3.66$, $p = 0.0006$, $d = 0.49$ (moderate effect). These results indicate group-level increases in all four dimensions of interest post-psilocybin, while also highlighting substantial individual variability in response patterns. Some participants showed large increases, while others exhibited minimal or negative changes. The linking lines emphasize heterogeneity in individual responses, demonstrating that while the overall effect is positive, not all participants experience the same degree of change.



Supplementary Fig. 6. Individual variability in changes in Nature Relatedness before and one month after psilocybin (n = 56). Participants are sorted by change magnitude, from largest decrease to largest increase. Each participant has two bars: blue (before psilocybin) and red (after psilocybin), with grey linking lines indicating the change for each individual. At the group level, paired t-tests revealed statistically significant improvements $t(55) = -3.37$, $p = 0.0014$, $d = 0.26$ (small effect).

Spectral Dynamic Causal Modelling

Dynamic causal modelling (DCM) is a Bayesian framework that infers the directed (causal) connectivity among neuronal systems – referred to as effective connectivity. We used spectral DCM for resting-state fMRI, which is based on a generative model of the cross-spectra of BOLD signals. A stochastic component, i.e. endogenous fluctuations, is used to model resting-state activity in the absence of external stimuli. Mathematically, we can express the stochastic generative model using two equations: the neuronal state equation,

$$\dot{x}(t) = Ax(t) + v(t), \quad (S1)$$

and the observation equation, which is a region-dependent nonlinear mapping from the hidden physiological states in (S1) to the observed BOLD activity:

$$y(t) = h(x(t), \varphi) + e(t), \quad (S2)$$

where $\dot{x}(t)$ is the rate of change of the neuronal states $x(t)$, A is the effective connectivity, $v(t)$ are the endogenous fluctuations, and $e(t)$ is the measurement or observation noise. In the observation equation, φ are the unknown parameters of the (haemodynamic) response function for each brain region. Spectral DCM simplifies the generative model by replacing the original timeseries with their second-order statistics (i.e., cross spectra). Instead of estimating time varying hidden states, it estimates their covariance, which is time invariant. The spectrum of the neuronal fluctuations, $v(t)$, is parameterised as a power-law, motivated

from previous work on neuronal activity (Beggs & Plenz, 2003; Shin & Kim, 2006; Stam & de Bruin, 2004) – as follows:

$$\begin{aligned} g_v(\omega, \theta) &= \alpha_v \omega^{-\beta_v} \\ g_e(\omega, \theta) &= \alpha_e \omega^{-\beta_e} \end{aligned} \tag{S3}$$

Here, $\{\alpha, \beta\} \subset \theta$ are the parameters controlling the amplitudes and exponents of the spectral density of the neural fluctuations. The parameterisation of endogenous fluctuations means that the states are no longer probabilistic; hence the inversion scheme is significantly simpler, requiring estimation of only the parameters (and hyperparameters) of the model.

Variational Laplace was used to infer the parameters of the model in (S1), (S2) and (S3), from the observed signal $y(t)$. The description of the Bayesian model inversion procedures based on variational Laplace can be found elsewhere for the interested readers (Friston et al., 2007; Friston et al., 2003; A. Razi & K. Friston, 2016).

Parametric Empirical Bayes

Empirical Bayes refers to the Bayesian inversion or fitting of hierarchical models. In hierarchical models, constraints on the posterior density over model parameters at any given level are provided by the level above. These constraints are called empirical priors because they are informed by empirical data. We recently introduced a second-level or between-subjects model over parameters, which represents how individual (within-subject) connections derive from the subjects' group membership (Friston et al., 2016) – based on parametric empirical Bayes (PEB). Mathematically, for DCM studies with N subjects and M parameters per DCM, we have a hierarchical model, where the responses of the i -th subject and the distribution of the parameters over subjects can be modeled as:

$$y_i = \Gamma_i^{(1)}(\theta^{(1)}) + \varepsilon_i^{(1)} \tag{S4}$$

$$\theta^{(1)} = \Gamma^{(2)}(\theta^{(2)}) + \varepsilon^{(2)}$$

$$\theta^{(2)} = \eta + \varepsilon^{(3)}$$

where, y_i is the BOLD time series from i -th subject and $\Gamma_i^{(1)}$ is a nonlinear mapping from the parameters of a model to the predicted response y for e.g. as shown in Eq. S1 above. $\varepsilon_i^{(1)}$ is observation noise (equivalent to $e(t)$ in Eq. S2). In this hierarchical form, *empirical priors* encoding second (between-subject) level effects place constraints on subject-specific parameters. The second level would be a linear model where the random effects are parameterised in terms of their precision:

$$\Gamma^{(2)}(\theta^{(2)}) = (X \otimes W)\beta$$

where, $\beta \subset \theta$ are group means or effects encoded by a design matrix with between X and within-subject W parts. The between-subject part encodes differences among subjects or

covariates such as age, while the within-subject part specifies mixtures of parameters that show random effects. We assume that the first column of the design matrix is a constant term, modelling group means and the second column encodes group differences.

Self-connections

While effective connectivity matrices are traditionally plotted with log-scaled diagonal elements, in Main Fig. 5, the diagonal elements are transformed via an exponential function ($-1/2 * \exp(x)$) that reverses the log-scaling. This ensures that all the connections (diagonals and off-diagonals) are presented using the same units (Hz), and facilitates the interpretation of changes in self-connection values: a positive change means that a region becomes more responsive to inputs; a negative change means that it becomes less responsive to inputs. Note, the self-connections displayed in Supplementary Tables 2-5 are in the traditional log-scale.

Supplement to Context directs hippocampus-DMN coupling

Connectivity patterns shown in Main Fig. 5; per-condition posterior expectations with credible intervals are reported in Supplementary Tables 2-5 (Bayesian model averaging; connections with posterior probability > 0.99 shown).

Dynamic causal modelling (DCM) (Friston et al., 2003; Friston et al., 2014; A. Razi & K. J. Friston, 2016) revealed context-dependent changes in effective connectivity from baseline (no-psilocybin) to psilocybin administration between the anterior hippocampus (aHip) and nodes of the core Default Mode Network (DMN).

Connectivity patterns varied significantly depending on experimental conditions, with left inferior parietal cortex (IPC_L) consistently inhibiting the right anterior hippocampus (aHip_R) across the conditions but not at rest. During the resting state, excitation from the posterior cingulate cortex (PCC) to the aHip_R and inhibition from the medial prefrontal cortex (mPFC) to the aHip_R were observed, alongside inhibition from the left anterior hippocampus (aHip_L) to the IPC_L. These connections suggest a regulatory mechanism, with the PCC driving hippocampal activations, the mPFC attenuating them, and the aHip_L suppressing parietal engagement, potentially tuning self, evaluative and context-related contributions of these regions' integration with memory. During meditation, bilateral inferior parietal cortex (IPC_L and IPC_R) inhibited bilateral anterior hippocampi (aHip_L and aHip_R), suggesting a regulatory role that may inhibit processes involved in memory retrieval and self-related thinking. Under music conditions, inhibition from the aHip_R to the aHip_L was observed, which may alter interhemispheric coordination of memory representations through asymmetric dampening of hippocampal connectivity. The strongest connectivity changes were elicited during eyes-open movie stimuli, where inhibition from the IPC_L, IPC_R, and mPFC to the hippocampi and intra-cortical excitation predominated, in response to a shift toward externally driven visual processing. Excitation from the aHip_L to the mPFC, IPC_R, and IPC_L during this condition may indicate heightened integration of narrative memory with evaluative processes, potentially reflecting a redistribution of influence in this network from higher-order regions to subcortical-driven memory integration.

Overall, eyes-open movie watching produced a more complex pattern of connectivity changes relative to the predominantly decrease-biased patterns observed in eyes-closed states, demonstrating that aHip–DMN connectivity is sensitive to context.

Together, these results demonstrate acute, context-dependent reconfiguration of directed aHip–DMN coupling under psilocybin. The dynamic nature of these connectivity changes highlights how psilocybin supports neural adaptability, providing a temporal window for context-dependent neural reorganisation (Calder & Hasler, 2023). These directed connectivity changes offer mechanistic insights that bridge preclinical and post-psilocybin imaging evidence of hippocampal plasticity in humans with acute mechanisms, illustrating how psychological and sensory context (i.e., set and setting) modulate brain function at the circuit level.

These findings extend preclinical and post-administration imaging evidence, highlighting a potential role for the aHip–DMN circuit in psychedelic-induced plasticity (Shao et al., 2021; Siegel et al., 2024; Vaidya et al., 1997) and suggest that structuring a sensory and cognitive environment can shape neural activity and may be used to guide behavioural outcomes. This avenue of research can advance precision psychiatry, along with the examination of the longitudinal behavioural effects of specific connectivity changes in culturally diverse healthy and clinical populations; however, it currently remains underexplored.

These circuit-level changes also complement broader eyes-open vs eyes-closed patterns across analyses, linking circuit-level dynamics to broader transformations—fMRI (global functional connectivity [GFC] and BOLD signal variability [SD]) and EEG (spectral power and Lempel–Ziv complexity [LZC])—while providing directional estimates that complement the ML embeddings (Main Fig. 2 and Main Fig. 3) and the broader cross-modal pattern (Main Fig. 1 and Main Fig. 6).

Supplementary Table 2. Rest Effective Connectivity Change

From	To	Posterior expectation	Credible interval
aHip_L	IPC_L	-0.14	(-0.216,-0.063)
IPC_L	PCC	0.13	(0.014,0.238)
IPC_L	IPC_R	0.1	(0.040,0.160)
mPFC	aHip_R	-0.09	(-0.137,-0.046)
PCC	aHip_R	0.12	(0.078,0.167)
PCC	PCC	0.35	(0.203,0.499)
IPC_R	PCC	0.17	(0.045,0.286)

Supplementary Table 3. Meditation Effective Connectivity Change

From	To	Posterior expectation	Credible interval
aHip_L	IPC_R	0.15	(0.058,0.251)
IPC_L	aHip_L	-0.09	(-0.147,-0.037)
IPC_L	IPC_L	0.26	(0.123,0.395)
IPC_L	aHip_R	-0.1	(-0.189,-0.017)
aHip_R	IPC_R	-0.13	(-0.201,-0.065)
IPC_R	aHip_L	-0.19	(-0.245,-0.135)
IPC_R	IPC_R	0.14	(0.041,0.238)

Supplementary Table 4. Music Effective Connectivity Change

From	To	Posterior expectation	Credible interval
IPC_L	aHip_R	-0.1	(-0.154,-0.045)
mPFC	mPFC	0.17	(0.056,0.275)
PCC	mPFC	0.13	(0.080,0.175)
aHip_R	aHip_L	-0.21	(-0.311,-0.100)
aHip_R	IPC_R	-0.13	(-0.203,-0.064)
IPC_R	mPFC	-0.16	(-0.235,-0.082)

Supplementary Table 5. Movie Viewing Effective Connectivity Change

From	To	Posterior expectation	Credible interval
aHip_L	IPC_L	0.14	(0.020,0.249)
aHip_L	mPFC	0.13	(0.032,0.235)
aHip_L	IPC_R	0.11	(0.021,0.203)
IPC_L	mPFC	-0.09	(-0.150,-0.026)
IPC_L	aHip_R	-0.14	(-0.205,-0.066)
mPFC	IPC_L	0.16	(0.086,0.239)
mPFC	PCC	0.11	(0.034,0.178)
mPFC	aHip_R	-0.13	(-0.189,-0.077)
PCC	IPC_R	0.15	(0.055,0.238)
IPC_R	aHip_L	-0.19	(-0.259,-0.124)
IPC_R	PCC	-0.13	(-0.235,-0.017)
IPC_R	IPC_R	0.34	(0.211,0.460)

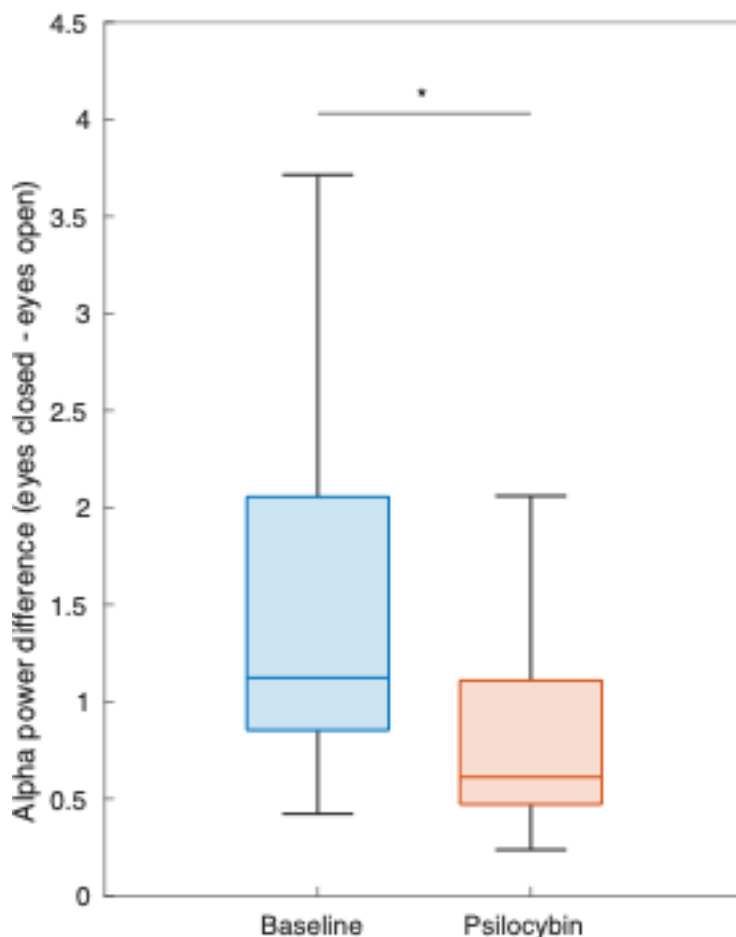
Effective connectivity changes across different scan conditions (rest, meditation, music, and movie watching) for between region connections (Supplementary Tables 2-5). Brain regions include the left anterior hippocampus (aHip_L), right anterior hippocampus (aHip_R), left inferior parietal cortex (IPC_L), right inferior parietal cortex (IPC_R), medial prefrontal cortex (mPFC), and posterior cingulate cortex (PCC). The model was specified as fully connected, allowing all possible directed interactions between regions. Effect sizes (posterior expectations) are presented in Hz. These estimates represent group-level posterior means derived via Bayesian model averaging, highlighting context-dependent modulation of connectivity patterns. Results demonstrate differential changes in aHipp-DMN connectivity across conditions, reinforcing the influence of context on psilocybin-induced network dynamics. Connections with a posterior probability >0.99 are reported, indicating very strong evidence. Self-connections displayed in tables are log-scaled. Self-connections in Main Fig. 5 are not log-scaled.

Note on model space

Multiple valid operationalisations of the DMN exist (e.g., PCC-centric, precuneus-centric, or combined posterior-midline schemes) (Andrews-Hanna et al., 2010; Thomas Yeo et al., 2011; Utevsky et al., 2014). We selected the posterior cingulate cortex (PCC) as the posterior-midline DMN node to align with our focus on changes to self-related cognition across sensory and cognitive contexts. The PCC is implicated in psychedelic neuroimaging (Carhart-Harris et al., 2012; Muthukumaraswamy et al., 2013; Smigielski et al., 2019) and this choice is in line with our prior work, including psychedelic and DCM/DMN studies (Stoliker et al., 2023, 2024) (Preller et al., 2019; Zhou et al., 2018). Given causal evidence implicating the anterior precuneus in bodily-self processing (Lyu et al., 2023), we flag an expanded model variant including an explicit precuneus node as a future, hypothesis-driven extension for studies of the bodily sense of self under psychedelics.

Supplement to Context modulates power and complexity

The eyes-closed vs eyes-open alpha-power difference contracted under psilocybin (Supplementary Fig. 7).



Supplementary Fig. 7. Convergence of eyes-closed and eyes-open alpha power under psilocybin. The alpha power difference between eyes-closed and eyes-open conditions decreased by 48% after psilocybin administration ($n=192$ resulting from 64 channels pooled across three power differences: rest minus movie, meditation minus movie, music minus movie, Cohen's $d = -0.79$, Mann-Whitney U-test right-tailed p -value $< 10^{-19}$). The boxes indicate the median and quartiles, and the whisker length is 1.5 times the interquartile range.

Vigilance considerations

Because psilocybin is an arousing state, the reduced separation between eyes-closed and eyes-open conditions might be interpreted as heightened arousal during eyes-closed conditions under psilocybin, relative to comparatively drowsy eyes-closed scans at baseline, rather than as context-driven reorganisation. Two electrophysiological signatures argue against this. First, baseline eyes-closed alpha was robust (Main Fig. 6b,c): a large baseline eyes-closed versus eyes-open alpha difference can only arise when eyes-closed alpha is strong, the signature of alert relaxed wakefulness, whereas drowsiness would have attenuated

this rhythm and narrowed, rather than widened, the baseline gap. The premise that baseline eyes-closed scans were drowsy is therefore not supported by the data. Second, signal complexity was highest during eyes-closed conditions under psilocybin (Main Fig. 6d) —the reverse of the reduction that sleep and drowsiness reliably produce—indicating an aroused, complex eyes-closed state rather than a quiescent one. These signatures derive from the separately acquired EEG session, recorded later in the day when fatigue would be more, not less, likely, which strengthens rather than weakens the inference. These features make a purely arousal-driven account of the convergence improbable. However, without explicit vigilance monitoring, a partial arousal contribution cannot be formally excluded.

Screening disclosures of serotonergic psychedelic exposures

While our screening excluded any serotonergic psychedelic use with subjective effects within the past 6 months (to avoid subacute carryover/tolerance and expectancy reinforcement) and acted as an explicit lower bound threshold for exclusion, in practice, we were able to recruit a sample meeting our operational definition of “psychedelic-naïve”, meaning no prior serotonergic psychedelic experience *with subjective effects*. Supplementary Table 6 lists the 3 occurrences of nominal or remote serotonergic psychedelic exposures in our sample of 65 subjects.

Study ID	Timing	Self-Report
PC-026	2017	“Psilocybin, twice, microdose. No effects noticed.”
PC-029	1998	“Psilocybin, twice, unspecified dose. Minimal/No recollection of subjective effects.”
PC-225	> 6 months pre-screening	“Psilocybin, once, microdose. No effects noticed.”

Supplementary Table 6. Table of screening disclosures of nominal/remote serotonergic psychedelic exposures (n = 3; ≈4.6% of total sample).

Expectancy considerations

At moderate–high psychedelic doses, effective blinding is difficult to achieve in practice because distinctive subjective effects make allocation easy to infer (Gasser et al., 2014; Holze et al., 2022; Holze et al., 2023; Studerus et al., 2011; Szigeti & Heifets, 2024), and suitable active placebos are lacking, with participants often discerning allocation when active placebos are used (Bogenschutz et al., 2022; Muthukumaraswamy et al., 2021). Several further features make it doubtful that expectancy accounts for our main findings: (i) large

separations in reported subjective effects between active-dose and placebo arms in both oral clinical-dose and intravenous designs (Bogenschutz et al., 2022; Muthukumaraswamy et al., 2013), including 20 mg oral psilocybin (Ley et al., 2023), which is comparable to our 19 mg dose and shows very low placebo subjective scores; dose–response and time-dependent evidence across designs further corroborates pharmacological dominance over expectancy (Hirschfeld et al., 2023; Hirschfeld & Schmidt, 2021; Muthukumaraswamy et al., 2013; Preller et al., 2020); (ii) pharmacokinetic–pharmacodynamic coupling between psilocin exposure, receptor engagement, and time-varying neural dynamics (M. K. Madsen et al., 2019; Olsen et al., 2022; Preller et al., 2018; Preller et al., 2020); and (iii) condition-separated ML embeddings appear only when subjective effects are strong (high MEQ) and are absent at baseline/low-MEQ. Consistent with this, a published re-analysis of a head-to-head double-blind RCT found that pre-trial expectancy significantly predicted outcomes in the escitalopram arm but not in the psilocybin arm (Szigeti et al., 2024). Although expectancy is empirically difficult to eliminate in psychedelic trials, the subjective-response-dependent emergence of structured embeddings, their absence at baseline or with low subjective effects, and the replicated convergence between eyes-open and eyes-closed conditions across modalities despite reversed order collectively make expectancy an implausible primary driver of our main results.

Biological interpretability of the latent spaces derived from machine-learning analyses

Our machine learning analyses, while agnostic to underlying neurochemistry, allow biologically grounded interpretations of functional brain reorganisation under psilocybin. CEBRA embeddings capture temporally structured, condition-sensitive trajectories of multiregional activity within individuals, revealing neural states that scale with the quality of subjective experience. TAVRNN complements this by modelling time-evolving changes in brain network topology, capturing both increased within-network cohesion and enhanced cross-network integration across conditions.

To quantify within-network cohesion in the TAVRNN embedding space, we computed the mean Euclidean distance between all pairs of ROIs belonging to the same functional network, for each condition and participant. These distances were then averaged separately across participants with the highest (top 5) and lowest (bottom 5) MEQ scores. Across all four conditions, within-network distances were lower in high-MEQ participants than in low-MEQ participants, as reflected by the heatmap diagonals in Extended Data Fig. 8. This indicates that ROIs within the same network cluster more compactly in the learned embedding space under stronger subjective effects. The consistency of this pattern across rest, meditation, music, and movie confirms that psilocybin-enhanced within-network cohesion is not condition-specific but reflects a broad reorganisation that scales with subjective intensity. This pattern is reported descriptively as convergent support for the formally tested CEBRA findings (Main Fig. 3d), where silhouette scores confirmed statistically significant differences in clustering quality between high- and low-MEQ groups across all four conditions.

These low-dimensional embeddings do not measure anatomy or causal directionality. Instead, they reflect how cortical activity reorganises over time in response to psilocybin-dependent subjective effects and context, and reveal behaviourally relevant structure in the temporal

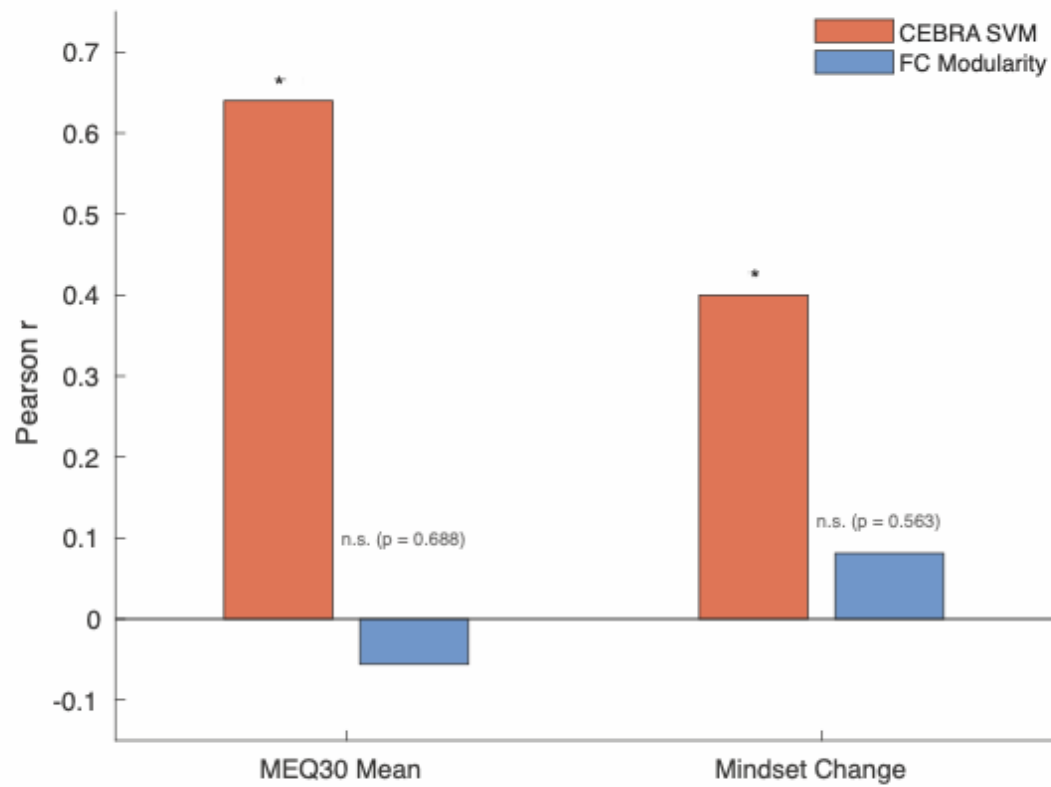
organisation of whole-brain activity. The biological inference is therefore about the organisation of distributed network dynamics under psilocybin linked to subjective experience.

Conventional and ML metric complementarity

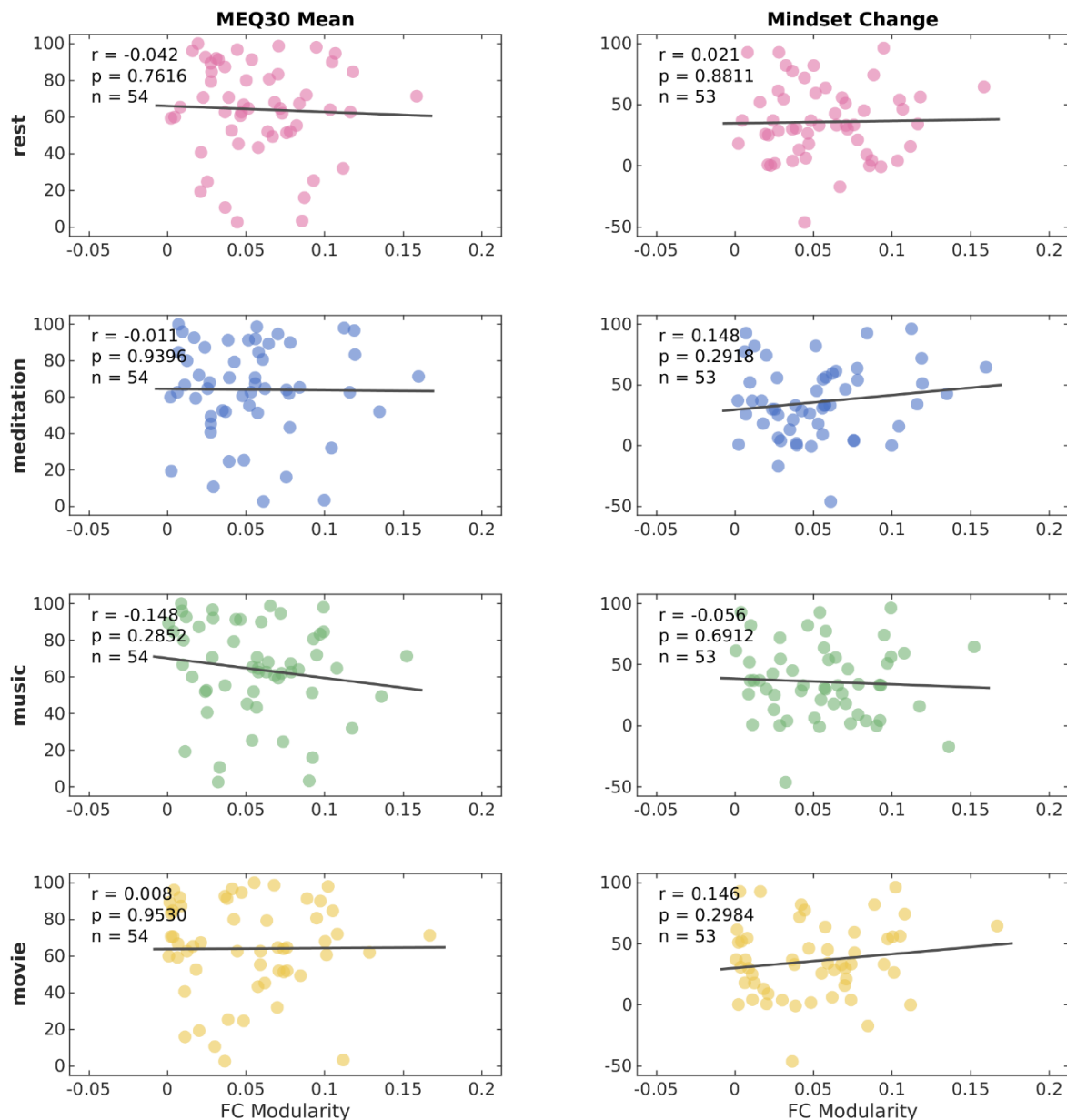
Our analytic strategy combined conventional methods (e.g., SD, GFC, parcel FC, modularity, DCM), which quantify amplitude fluctuations, global integration–segregation balance, and directed interactions. These approaches typically characterise macrodose psychedelic states as exhibiting increased signal variance and reduced modular organisation (Carhart-Harris et al., 2016; Daws et al., 2022; Tagliazucchi et al., 2014). In parallel, we applied ML-based embeddings (CEBRA, TAVRNN) that recover latent temporal and regional structure within these high-variance dynamics, and that scale meaningfully with subjective effects.

Whereas traditional metrics primarily index amplitude, variance, and network coupling, ML embeddings capture the high-dimensional temporal geometry of brain state trajectories. These approaches thus probe complementary features of brain activity. Accordingly, differences in apparent similarity—such as high similarity between eyes-closed scans (rest, meditation, music) in traditional metrics versus their condition-separability in ML embeddings, may be expected rather than contradictory.

This complementarity extends to brain–behaviour prediction: per-subject functional modularity under psilocybin was not associated with MEQ30 mean or next-day mindset change in any condition, whereas CEBRA classification accuracy predicted both outcomes (Supplementary Fig. 8; per-condition scatter plots in Supplementary Fig. 9).



Supplementary Fig. 8. Comparison of CEBRA SVM and functional modularity correlations with behavioural outcomes. Functional modularity values were averaged across all four conditions to match the CEBRA analysis, which concatenates all conditions. CEBRA SVM classification accuracy correlated with MEQ30 mean ($r = 0.64$, $p < 10^{-6}$) and mindset change ($r = 0.40$, $p < 0.01$), whereas averaged functional modularity did not (n.s.; exact p values shown; two-tailed Pearson; $n = 53-54$). Per-condition scatter plots are shown below.



Supplementary Fig. 9. Per-condition scatter plots of functional modularity vs behavioural outcomes. Per-subject functional modularity (psilocybin session) plotted against MEQ30 mean (left column, $n = 54$) and next-day mindset change (right column, $n = 53$) for each condition (rows: rest, meditation, music, movie). Pearson r , uncorrected p , and n are annotated in each panel. Black lines indicate least-squares regression fits. No correlation was significant (two-tailed Pearson correlations, Bonferroni-corrected across 8 tests, $\alpha = 0.0063$; confirmed with Spearman rank correlations).

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