Psychedelics as Dimensionality Modulators: A Cortical Reservoir Theory of Serotonergic Plasticity

Ian Todd
Sydney Medical School, University of Sydney
itod2305@uni.sydney.edu.au

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Abstract

Classical psychedelics produce profound alterations in perception, cognition, and sense of self, with growing evidence for therapeutic efficacy in depression, addiction, and PTSD. Here we propose that the primary action of 5-HT2A agonists is to **modulate the effective dimensionality** of cortical dynamics—the number of independent modes available to the cortical reservoir. Through dendritic gain amplification in layer 5 pyramidal neurons, psychedelics expand the eigenmode spectrum of cortical oscillator fields, enabling the system to explore configurations inaccessible under baseline conditions. This dimensionality expansion manifests across measurement modalities: as increased metabolic repertoire diversity (fMRI) mediated by the breakdown of synchronous oscillatory constraints (MEG). We validate this framework with MEG analysis of 136 sessions across four compounds (LSD, psilocybin, ketamine, tiagabine), revealing a striking **mechanism-specific dissociation**: classical psychedelics (5-HT2A agonists) produce significant oscillatory desynchronization (psilocybin: -15%, $p = 0.003$, $d = -0.78$; LSD: -13%, $p = 0.08$, $d = -0.50$), while ketamine (NMDA antagonist) shows no effect ($p = 0.29$). This specificity—psychedelics desynchronize, dissociatives do not—suggests that while both drug classes produce altered states, only serotonergic psychedelics function by dismantling the intrinsic oscillatory constraints of the cortex. We formalize a three-phase model (overshoot $\rightarrow$ refractory $\rightarrow$ recanalization) explaining how transient dimensionality expansion enables lasting therapeutic reorganization. The framework suggests MEG-derived oscillatory coherence as a real-time biomarker for "psychedelic depth" during treatment sessions, with implications for precision dosing, patient selection, and providing the first mechanism-specific neural biomarker to distinguish serotonergic plasticity from dissociative anesthesia.

Keywords: psychedelics; effective dimensionality; 5-HT2A; reservoir computing; neural plasticity; LSD; psilocybin; cortical dynamics; brain rate variability

1 Introduction

The resurgence of psychedelic research represents one of the most significant developments in psychiatry and neuroscience of the past decade. Clinical trials have demonstrated remarkable efficacy: psilocybin shows robust effects for treatment-resistant depression [Carhart-Harris et al., 2016a, Davis et al., 2021, Goodwin et al., 2022], MDMA-assisted therapy produces breakthrough results for PTSD [Mitchell et al., 2021, Mithoefer et al., 2019], and growing evidence supports therapeutic applications for addiction [Bogenschutz et al., 2015, Johnson et al., 2014], anxiety in terminal illness [Griffiths et al., 2016, Grob et al., 2011], and obsessive-compulsive disorder [Moreno et al., 2006]. LSD microdosing, though less rigorously studied, shows promise for mood enhancement and cognitive flexibility [Fadiman, 2011, Hutten et al., 2020, Prochazková et al., 2018].

This clinical momentum has been matched by unprecedented neuroimaging data sharing. Public repositories now host multiple high-quality psychedelic datasets: the Carhart-Harris LSD dataset (OpenNeuro ds003059) provides within-subjects BOLD fMRI under 75μg IV LSD versus placebo [Carhart-Harris et al., 2016b], while the recent Siegel precision functional mapping study (OpenNeuro ds006072) offers dense longitudinal imaging across psilocybin and methylphenidate sessions with preprocessed CIFTI surface data [Siegel et al., 2025]. Additional datasets covering ayahuasca, DMT, and ketamine are increasingly available, enabling rigorous replication and cross-compound meta-analysis. This data ecosystem transforms psychedelic neuroscience from isolated studies into a cumulative science capable of testing mechanistic theories across compounds, doses, and populations.

Yet despite this clinical progress, a fundamental question remains: what are psychedelics actually *doing* to the brain? Current frameworks emphasize specific receptor pharmacology, network connectivity changes, or entropic brain dynamics. While each captures important aspects of the psychedelic state, none provides a unified computational account that explains:

- Why acute effects are so profoundly different from baseline consciousness
- Why therapeutic benefits often emerge *after* the acute experience ends
- Why these compounds produce lasting plasticity from single or few doses
- Why set and setting matter so dramatically for outcomes
- Why tolerance develops rapidly but sensitization can occur with spacing
- Why the same compound produces radically different experiences across individuals

Here we propose that psychedelics are fundamentally **dimensionality modulators**—they alter the number of independent dynamical modes available to cortical computation. This framework unifies disparate observations across scales from receptor pharmacology to phenomenology, and makes specific, testable predictions about the neural mechanisms underlying both acute effects and therapeutic outcomes.

1.1 The Entropic Brain Hypothesis and Its Limitations

The most influential computational framework for psychedelics is the Entropic Brain Hypothesis (EBH), proposed by Carhart-Harris et al. [2014] and elaborated in subsequent work [Carhart-Harris, 2018, Carhart-Harris and Friston, 2019]. The EBH posits that psychedelics increase the entropy of spontaneous brain activity, relaxing the normally constrained dynamics and enabling exploration of a broader state space.

The EBH has substantial empirical support. Psychedelics reliably increase measures of neural entropy and signal diversity [Schartner et al., 2017, Timmermann et al., 2019], flatten the cortical hierarchy [Tagliazucchi et al., 2016], and dissolve the structured activity of the default mode network (DMN) [Carhart-Harris et al., 2012, Palhano-Fontes et al., 2015]. The REBUS (Relaxed Beliefs Under Psychedelics) extension [Carhart-Harris and Friston, 2019] connects these entropic changes to predictive processing frameworks, suggesting that psychedelics relax the precision-weighting of prior beliefs.

However, the EBH faces several limitations. First, "entropy" is a broad concept that conflates multiple distinct phenomena—signal complexity, unpredictability, and state space exploration are not equivalent [Mediano et al., 2019]. Second, the relationship between neural entropy and therapeutic outcome is unclear; some highly entropic states (seizures, delirium) are profoundly pathological. Third, the EBH does not explain the temporal dynamics of the psychedelic experience—why entropy increases acutely, why tolerance develops, and why lasting changes emerge after the acute state resolves.

We propose that **effective dimensionality** provides a more precise and mechanistically grounded framework than entropy. Dimensionality captures the computational essence of what entropy measures—the richness of the dynamical repertoire—while connecting directly to neural circuit mechanisms and making quantitative predictions about scaling and limits.

Recent work has begun applying dimensionality metrics to psychedelic neuroimaging. Moujaes et al. [2024] used the participation ratio to compare connectivity signatures across ketamine, LSD, and psilocybin, finding that ketamine produces higher-dimensional patterns than the classical serotonergic psychedelics. However, their analysis treats dimensionality as a *descriptive metric* for drug fingerprinting rather than as the mechanistic target of therapeutic action. Our framework differs fundamentally: we propose that dimensionality expansion is not merely a correlate of the psychedelic state but its *computational function*—the means by which psychedelics enable exploration of off-manifold configurations. Critically, our three-phase model (overshoot $\rightarrow$ refractory $\rightarrow$ recanalization) explains why therapeutic benefits persist after dimensionality returns to baseline, a temporal dynamic that purely acute analyses cannot address.

1.2 Effective Dimensionality as a Cortical State Variable

The concept of effective dimensionality (D_{eff}) captures how many independent degrees of freedom are actually being utilized by a dynamical system [Cunningham and Yu, 2014, Gao and Ganguli, 2017]. For cortical networks, D_{eff} reflects the number of eigenmode directions along which neural population activity has substantial variance. The participation ratio provides a standard measure:

$$D_{\text{eff}} = \frac{\left(\sum_i \lambda_i\right)^2}{\sum_i \lambda_i^2} \tag{1}$$

where λ_i are eigenvalues of the covariance matrix of neural activity.

Under baseline conditions, cortical dynamics occupy a surprisingly low-dimensional manifold despite the astronomical number of potential configurations [Gallego et al., 2017, Jazayeri and Ostojic, 2021, Stringer et al., 2019a]. Motor cortex activity during reaching lies on manifolds of dimension 10-20, not the thousands one might expect from the number of neurons [Churchland et al., 2012, Kaufman et al., 2014]. Visual cortex responses, despite their complexity, can be captured by relatively few principal components [Stringer et al., 2019b]. Even "spontaneous" resting activity shows strong dimensional constraints [Luczak et al., 2009, Miller et al., 2014].

This dimensional constraint is not a limitation—it is the computational strategy. By confining dynamics to a learned subspace, the cortex achieves:

- **Noise robustness:** Activity orthogonal to the manifold is noise, automatically filtered [Kaufman et al., 2014]
- **Efficient readout:** Downstream areas need only monitor a low-dimensional projection [Sadtler et al., 2014]
- **Fast learning:** New skills are acquired within existing subspaces when possible [Golub et al., 2018, Sadtler et al., 2014]
- **Stable memory:** Attractors in a constrained manifold are more robust [Chaudhuri et al., 2016]

However, dimensional constraint has a cost: it limits the space of reachable configurations. A system locked into a narrow manifold cannot explore radically different solutions. Motor cortex constrained to a 10-dimensional manifold cannot spontaneously discover a 50-dimensional movement strategy, even if that strategy would be superior [Sadtler et al., 2014]. This constraint-flexibility tradeoff is fundamental to neural computation.

This is precisely where psychedelics enter: they temporarily expand the accessible dimensionality, enabling exploration of configurations that are normally off-manifold.

1.3 The Reservoir Computing Perspective

Reservoir computing provides a natural theoretical framework for understanding cortical dimensionality [Jaeger, 2001, Maass et al., 2002, Tanaka et al., 2019]. In this view, cortical networks function as high-dimensional nonlinear "reservoirs" that:

1. Receive low-dimensional inputs (sensory streams, internal goals)
2. Project these inputs into a high-dimensional dynamical space
3. Generate outputs via linear readout from the expanded representation

The key insight is that reservoir computing power scales with the *number of separable dynamical modes*—precisely what D_{eff} measures. A reservoir with higher effective dimensionality can separate more input patterns, support more complex nonlinear computations, and maintain longer memory traces [Legenstein and Maass, 2007, Verstraeten et al., 2007, Lukosevicius and Jaeger, 2009].

The "edge of chaos" literature demonstrates that computational capacity is maximized when reservoirs operate near a critical transition between ordered and chaotic dynamics [Bertschinger and Natschläger, 2004, Legenstein and Maass, 2007]. At this edge, dimensionality is high but not maximal—the system explores broadly while maintaining enough structure for reliable readout.

From this perspective, psychedelics do something remarkable: they *temporarily increase reservoir capacity* by expanding the eigenmode spectrum. The acute state provides access to configurations that are normally off-manifold, enabling the system to explore solutions that would otherwise be unreachable. This is not merely "adding noise" (which would degrade computation) but systematically lowering activation thresholds for latent eigenmodes.

2 Mechanism: 5-HT2A and Dendritic Gain

Classical psychedelics—LSD, psilocybin, DMT, mescaline—share a common mechanism: agonism at the serotonin 5-HT2A receptor [Nichols, 2016, Vollenweider and Kometer, 2010]. While these compounds have additional pharmacological targets (5-HT2C, 5-HT1A, dopamine receptors), the 5-HT2A receptor is necessary and likely sufficient for the characteristic psychedelic effects [Preller et al., 2018, Kometer et al., 2013, Kraehenmann et al., 2017]. Blocking 5-HT2A with ketanserin eliminates subjective effects and normalizes neural signatures [Preller et al., 2018, Vollenweider et al., 1998].

2.1 Layer 5 Pyramidal Neurons as Cortical Amplifiers

The 5-HT2A receptor is densely expressed on apical dendrites of layer 5 pyramidal neurons (L5PNs)—the primary output neurons of neocortex [Jakab and Goldman-Rakic, 1998, Weber and Andrade, 2010, Watakabe et al., 2009]. This localization is functionally significant: apical dendrites integrate top-down contextual inputs and gate the influence of these inputs on neural output [Larkum, 2013, Larkum et al., 1999].

When activated by psychedelics, 5-HT2A signaling produces a constellation of electrophysiological effects:

- **Reduced afterhyperpolarization:** 5-HT2A activation reduces the slow afterhyperpolarizing current (sAHP), increasing neuronal excitability [Aghajanian and Marek, 1999, Zhang, 2002]
- **Enhanced calcium plateaus:** Dendritic calcium plateau potentials are facilitated, lowering the threshold for dendritic spikes [Andrade, 2011, Béïque and Bhide, 2007]

- **Facilitated backpropagation:** Backpropagating action potentials reach further into the dendritic tree [Andrade, 2011]
- **Increased spontaneous EPSPs:** Glutamate release probability increases, elevating baseline excitatory drive [Marek and Aghajanian, 1998, Aghajanian and Marek, 1997]
- **Enhanced NMDA currents:** NMDA receptor function is potentiated, amplifying coincidence detection [Bhattacharyya et al., 2022]

The net effect is **dendritic gain amplification**: inputs that would normally fail to drive somatic output now succeed. Weak, subthreshold patterns of synaptic input can trigger dendritic spikes and somatic action potentials. This is functionally equivalent to lowering the activation threshold for cortical response patterns—modes that are normally latent become active.

2.2 Eigenmode Expansion in Cortical Networks

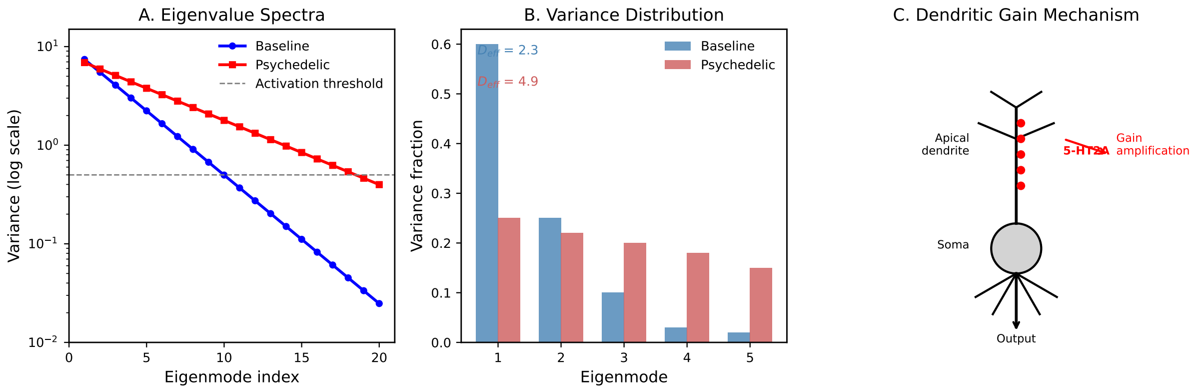

Figure 1: **Eigenmode Expansion Mechanism.** (A) Eigenvalue spectra showing how psychedelic-state dynamics (red) maintain higher variance across more eigenmodes than baseline (blue), increasing the number of modes above activation threshold. (B) Participation ratio calculation: baseline dynamics concentrate variance on few modes ($D_{\text{eff}} \approx 3$) while psychedelic dynamics distribute across many ($D_{\text{eff}} \approx 8$). (C) Dendritic mechanism: 5-HT2A receptors on apical dendrites of layer 5 pyramidal neurons reduce afterhyperpolarization and enhance calcium spikes, effectively lowering the activation threshold for cortical response patterns.

How does dendritic gain amplification translate to increased effective dimensionality at the network level? Cortical dynamics can be modeled as coupled oscillator fields where each oscillator represents the activity of a local neural population [Breakspear et al., 2010, Cabral et al., 2014, Deco and Kringelbach, 2017]. The effective dimensionality of this field depends on:

1. The number of distinct oscillator frequencies (frequency dispersion)
2. The strength of coupling between oscillators (synchronization tendency)
3. The noise level and intrinsic variability (stochastic mode activation)
4. The nonlinear activation thresholds (eigenmode accessibility)

5-HT2A activation affects all four factors in ways that expand D_{eff}:

Frequency dispersion increases. Psychedelics desynchronize cortical rhythms, particularly in the alpha band (8-12 Hz) [Muthukumaraswamy et al., 2013, Carhart-Harris et al., 2016b]. This desynchronization reflects a broadening of the active frequency spectrum—more oscillatory modes with different frequencies become simultaneously active, increasing the dimensionality of the dynamical repertoire.

Long-range coupling decreases. DMN dissolution and reduced functional connectivity between distant regions [Carhart-Harris et al., 2012, Tagliazucchi et al., 2016] indicate weakened long-range coupling. When coupling is strong, distant regions lock into coherent patterns, reducing independent degrees of freedom. Weakened coupling allows regions to explore more independently, increasing overall dimensionality.

Spontaneous variability increases. Enhanced spontaneous EPSPs and reduced sAHP increase intrinsic neural fluctuations [Marek and Aghajanian, 1998]. These fluctuations stochastically activate modes that would otherwise remain quiescent, expanding the explored configuration space.

Activation thresholds decrease. This is the direct effect of dendritic gain amplification. Eigenmodes of cortical dynamics that normally require strong, coordinated input to activate become accessible to weaker, more varied input patterns.

The combined effect is substantial expansion of D_{eff}. The desynchronized, decoupled, variable state has more active eigenmodes than the synchronized, coupled, constrained baseline.

2.3 The Ephaptic Dimension

Beyond synaptic transmission, cortical neurons interact via ephaptic coupling—extracellular electric field effects that modulate neighboring neurons without synaptic contact [Anastassiou et al., 2011, Anastassiou and Koch, 2012, Martinez-Banaclocha, 2018]. During synchronized oscillatory activity, coherent population rhythms generate substantial extracellular fields (1-5 mV/mm) that can shift neuronal membrane potentials by several millivolts [Fröhlich and McCormick, 2010, Herreras, 2016].

Ephaptic coupling effectively creates a "mean field" constraint that tends to synchronize neighboring neurons. This constraint reduces effective dimensionality by forcing local populations into coherent states. The strength of ephaptic coupling scales with oscillatory power and coherence [Anastassiou and Koch, 2012].

Psychedelic-induced desynchronization reduces ephaptic coupling strength by fragmenting the coherent population oscillations that generate strong extracellular fields. This releases neurons from a form of collective constraint, contributing to D_{eff} increase via a non-synaptic pathway.

The ephaptic contribution may explain why psychedelic effects are particularly prominent for alpha oscillations, which generate the largest extracellular fields due to their coherent, high-amplitude nature [Lopes da Silva, 2017]. Alpha suppression under psychedelics [Muthukumaraswamy et al., 2013, Carhart-Harris et al., 2016b] may reflect not just reduced oscillatory drive but reduced ephaptic synchronization.

2.4 Structural Plasticity and Dendritic Remodeling

Recent work has revealed that psychedelics induce rapid structural plasticity in cortical neurons. A single dose of psilocybin, LSD, or DMT increases dendritic spine density and dendritic arbor complexity in prefrontal cortex within 24 hours [Ly et al., 2018, Shao et al., 2021]. These changes are 5-HT2A-dependent and correlate with behavioral effects.

From our framework, structural plasticity represents the physical substrate of lasting dimensionality changes. Increased spine density provides more synaptic inputs, potentially enabling access to eigenmodes that were previously unreachable. Dendritic arbor expansion increases the integration volume for top-down inputs, amplifying the gain effects we have described.

Importantly, structural plasticity occurs during the acute phase but persists into the recanalization period. This provides a mechanism for how a transient dimensionality expansion can produce lasting reorganization: the expanded connectivity remains even after pharmacological effects resolve, supporting a modified attractor landscape.

3 The Three-Phase Model

We propose that the full psychedelic arc comprises three distinct phases characterized by different dimensionality regimes (Figure 2):

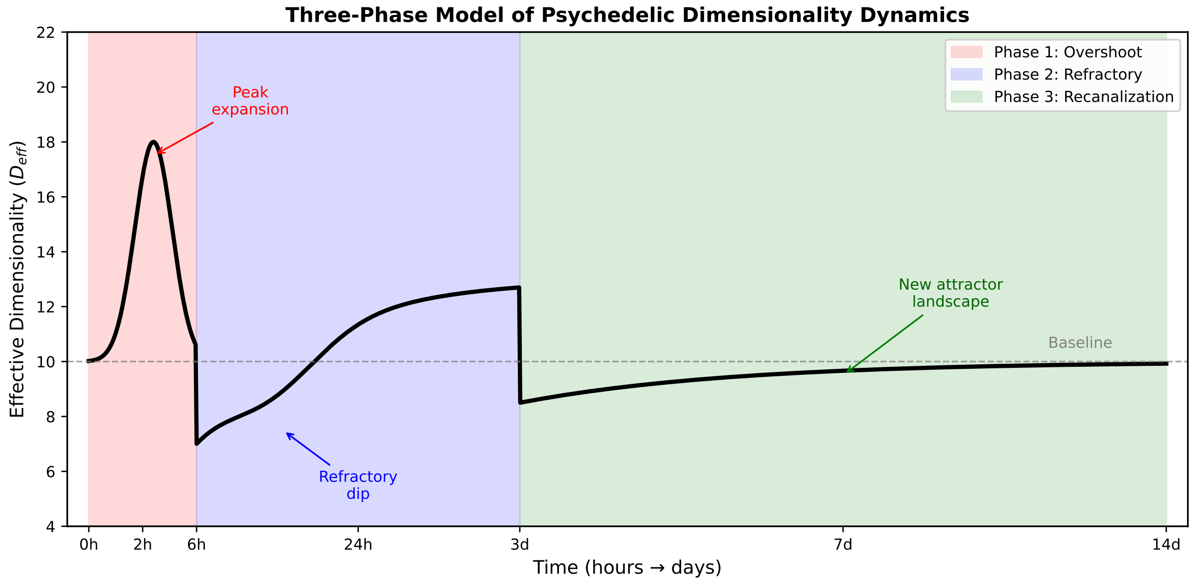

Figure 2: **The Three-Phase Model of Psychedelic Dimensionality Dynamics.** Effective dimensionality (D_{eff}) follows a characteristic arc: Phase 1 (Overshoot) shows dramatic expansion above baseline during the acute psychedelic experience, driven by 5-HT2A activation and dendritic gain amplification. Phase 2 (Refractory) shows below-baseline compression due to receptor downregulation and signaling depletion. Phase 3 (Recanalization) shows return to baseline dimensionality but on a reorganized attractor landscape supported by structural plasticity.

3.1 Phase 1: Overshoot ($D_{\text{eff}} \gg D_{\text{baseline}}$)

The acute psychedelic state is characterized by dramatic dimensionality expansion. 5-HT2A activation amplifies dendritic gain, expands the eigenmode spectrum, and enables exploration of off-manifold configurations.

Phenomenology: The subjective effects of Phase 1 directly reflect expanded dimensionality:

- **Perceptual intensification:** More visual features and patterns are simultaneously represented, producing enhanced color, texture, and geometric complexity [Kometer et al., 2011]
- **Ego dissolution:** The narrative self, normally maintained by constrained DMN dynamics, fragments as self-referential processing loses its coherent attractor [Nour et al., 2016, Millière, 2017]
- **Time dilation:** Temporal integration, which relies on dimensional compression, becomes disrupted, producing subjective time expansion [Wittmann et al., 2015, Yanakieva et al., 2019]

- **Novel associations:** Semantic and conceptual representations that are normally separated become accessible in the same activation space, enabling unusual connections [Family et al., 2016, Mason et al., 2021]
- **Synesthesia-like experiences:** Cross-modal representations become co-active as normally isolated sensory eigenmodes overlap [Sinke et al., 2012, Luke and Terhune, 2012]
- **Mystical experience:** Boundary dissolution and unity experiences may reflect the loss of categorical distinctions that normally separate self from world [Barrett and Griffiths, 2018, Griffiths et al., 2006]

Neural signatures:

- Increased Lempel-Ziv complexity and neural entropy [Schartner et al., 2017, Timmermann et al., 2019]
- Alpha power suppression and desynchronization [Muthukumaraswamy et al., 2013, Carhart-Harris et al., 2016b]
- DMN dissolution and reduced hierarchical organization [Carhart-Harris et al., 2012, Tagliazucchi et al., 2016]
- Increased global functional connectivity diversity [Tagliazucchi et al., 2014]
- Enhanced repertoire of functional connectivity states [Lord et al., 2019]

Duration: 4–8 hours for LSD, 4–6 hours for psilocybin, 15–30 minutes for DMT.

Mechanism: 5-HT2A activation $\rightarrow$ dendritic gain increase $\rightarrow$ lowered eigenmode thresholds $\rightarrow$ expanded D_{eff}.

3.2 Phase 2: Refractory Collapse ($D_{\text{eff}} < D_{\text{baseline}}$)

Sustained 5-HT2A activation triggers homeostatic responses. The receptor undergoes rapid internalization and downregulation via β-arrestin-mediated endocytosis [Berry et al., 1996, Burt et al., 2018, Gray et al., 2004]. Signaling intermediates (PLC, PKC, intracellular calcium stores) become depleted. As the molecular tide recedes, the system enters a refractory state characterized by *lower-than-baseline* dimensionality.

Phenomenology: Phase 2 experiences reflect dimensional compression:

- **Cognitive fatigue:** Reduced processing capacity, difficulty with complex thought
- **Emotional sensitivity:** Heightened reactivity as emotional regulation circuits are depleted
- **Heightened suggestibility:** Reduced critical faculties, increased openness to influence
- **Integration focus:** Natural tendency toward meaning-making and narrative construction
- **Sleep disturbance:** Altered sleep architecture reflecting continued neurochemical perturbation

Neural signatures: Limited direct evidence, but predicted signatures include:

- Below-baseline entropy and complexity measures
- Increased alpha coherence (rebound synchronization)

- Temporarily reduced functional connectivity flexibility
- PET evidence of reduced 5-HT2A availability

Duration: 1–7 days post-experience. This corresponds to the period of acute tolerance where re-dosing produces attenuated effects [Nichols, 2004, Buchborn et al., 2015].

Mechanism: 5-HT2A downregulation + signaling cascade depletion → reduced dendritic gain → compressed eigenmode spectrum → reduced D_{eff}.

3.3 Phase 3: Recanalization ($D_{\text{eff}} \approx D_{\text{baseline}}$ on New Landscape)

As receptor systems recover, dimensionality returns to baseline values. However, the system does not simply revert to its prior state. The overshoot phase has exposed the system to configurations it had never occupied, potentially destabilizing maladaptive attractors and enabling reorganization onto new ones.

The key insight: Phase 3 involves the same dimensionality as baseline but a *different attractor landscape*. The manifold the system occupies has been reshaped by the experience.

Phenomenology:

- **Lasting changes in outlook:** Altered perspectives, values, and priorities [Griffiths et al., 2008, MacLean et al., 2011]
- **Reduced depressive symptoms:** Often persisting weeks to months post-session [Carhart-Harris et al., 2016a, Davis et al., 2021]
- **Altered habits:** Reduced addictive behaviors, changed relationship patterns [Bogenschutz et al., 2015, Garcia-Romeu et al., 2014]
- **Enhanced well-being:** Increased life satisfaction, meaning, and openness [Griffiths et al., 2006, MacLean et al., 2011]
- **Personality changes:** Measurable increases in trait openness [MacLean et al., 2011, Erritzoe et al., 2018]

Neural signatures:

- Normalized global entropy but altered local connectivity patterns
- Changes in DMN-TPN (task-positive network) anticorrelation [Carhart-Harris et al., 2017]
- Increased amygdala responsiveness (not numbed, but flexible) [Barrett et al., 2020]
- Long-term changes in glutamate/GABA balance [Mason et al., 2020]

Duration: Weeks to months; some changes may be permanent. The structural plasticity (increased spine density, dendritic remodeling) provides a physical substrate for persistent change [Ly et al., 2018, Shao et al., 2021].

Mechanism: Synaptic plasticity during high-D_{eff} phase (Phase 1) combined with consolidation during refractory/recovery periods produces a modified attractor landscape. The system has the same dimensionality as before but occupies different attractors.

3.4 The Therapeutic Window: Why Timing Matters

The three-phase model explains why integration practices and therapeutic support are critical during Phase 2 (refractory) and early Phase 3 (recanalization). During these periods:

- The system is actively reorganizing its attractor landscape

- New configurations are not yet consolidated
- Environmental inputs can bias which attractors stabilize
- Maladaptive patterns can re-emerge if not actively addressed

This provides a mechanistic basis for the importance of "set and setting" extending beyond the acute phase. The recanalization window is a critical period during which therapeutic input has maximal leverage.

4 Dimensionality Across the Lifespan

The three-phase model connects to broader observations about cortical dimensionality across development, aging, and pathology.

4.1 Development: High Dimensionality as Exploration

Early development is characterized by high cortical dimensionality. Infant and child brains show:

- Less coherent oscillations and weaker long-range synchronization [Uhlhaas et al., 2009, Paus, 2005]
- Weaker functional connectivity hierarchies [Cao et al., 2014, Supekar et al., 2009]
- Broader exploration of neural state space [McIntosh et al., 2010]
- Higher neural variability and signal complexity [McIntosh et al., 2010, Garrett et al., 2013a]

This high-D_{eff} regime enables the extensive learning required to wire up cortex appropriately. The developing brain must explore a vast space of possible connectivity patterns to find those that support adaptive behavior.

Developmental maturation involves progressive dimensional constraint—the system explores less but exploits more efficiently within learned subspaces. Myelination increases conduction velocity and synchronization [Paus, 2005]; synaptic pruning removes redundant connections [Huttenlocher, 1979]; inhibitory circuit maturation sharpens selectivity [Hensch, 2005]. The adult brain occupies a narrower but better-optimized manifold.

Implication: Psychedelics may temporarily restore a "juvenile-like" mode of cortical function, reopening critical period-style plasticity in the adult brain [Ly et al., 2018, Nardou et al., 2019].

4.2 Aging: Dimensional Rigidity

Normal aging is associated with increasing cortical stiffness:

- Reduced neural variability and signal complexity [Garrett et al., 2013b,a]
- Stronger, more stereotyped attractor dynamics [Sleimen-Malkoun et al., 2017]
- Lower effective dimensionality of spontaneous activity [Ponce-Alvarez et al., 2015]
- Reduced flexibility of functional connectivity [Geerligs et al., 2015]

The aged brain occupies a narrower manifold and is less able to explore alternative configurations. Attractors that have been reinforced over decades become increasingly dominant, making change difficult.

Implication: The therapeutic potential of psychedelics in older populations may relate to temporary restoration of developmental-like flexibility. A single high-D_{eff} episode could loosen rigid attractors that have accumulated over decades. Early evidence suggests psilocybin may be particularly effective for depression in older adults [Agin-Liebes et al., 2020].

4.3 Dimensional Phenotypes: The Stability-Plasticity Continuum

Rather than viewing neurodivergent conditions as varying degrees of pathology, the dimensionality framework suggests they represent distinct, adaptive set-points on a stability-plasticity continuum. This spectrum likely reflects an evolutionary relaxation of genetic constraints on cortical dynamics, allowing D_{eff} to vary more freely across individuals to meet diverse environmental demands.

Autism Spectrum (Hyper-Stability): May be characterized in some cases by constitutively low effective dimensionality and hyper-stable attractor dynamics [Dinstein et al., 2012]. In this regime, the cortex strongly "exploits" learned subspaces, leading to high precision, bottom-up processing fidelity, and resistance to noise. While this constrains the flexibility required for rapid social shifting, it confers exceptional advantages in systemizing and pattern recognition—a system optimized for depth over breadth.

ADHD (Hyper-Plasticity): Characterized by constitutively high effective dimensionality and shallow attractor basins [Fassbender et al., 2011, Castellanos et al., 2002]. In this regime, the cortex favors "exploration" over exploitation, maintaining a high-entropy state that allows rapid switching between tasks and novel associations. The "distractibility" is functionally indistinguishable from "high-dimensional search"—a system tuned for novelty detection rather than subspace maintenance.

The Adaptive Spectrum: From this perspective, the human cortex has evolved to loosen the rigid biological constraints (e.g., inhibition, ephaptic coupling) that clamp dimensionality in simpler organisms. The ADHD-Autism axis represents the natural variance of this liberated parameter, ensuring the population retains both "specialist" (low D_{eff}) and "generalist" (high D_{eff}) phenotypes—an evolutionary bet-hedging strategy that maintains cognitive diversity.

Acquired Dimensional Disorders: In contrast to developmental phenotypes, some conditions represent *acquired* dimensional dysregulation:

- **Depression:** Acquired low D_{eff} with excessively deep attractor basins. Rumination reflects a system "stuck" in self-referential loops [Kaiser et al., 2015, Pizzagalli, 2018].
- **PTSD:** Normal global D_{eff} but distorted local attractor structure—specific maladaptive attractors capture disproportionate state space.
- **Addiction:** Progressive attractor deepening around drug-seeking states [Volkow et al., 2016].
- **Psychosis:** Acquired high D_{eff} with loss of attractor structure—exploration without stabilization [Carhart-Harris et al., 2014].

Therapeutic implications: This taxonomy suggests psychedelics may benefit conditions involving acquired dimensional rigidity (depression, addiction, OCD) by transiently restoring flexibility. For developmental phenotypes (autism, ADHD), the goal is not "correction" but understanding how dimensionality modulation interacts with baseline set-points. Emerging evidence suggests therapeutic potential for psychedelics in autism [Danforth et al., 2018], though such applications require sensitivity to individual differences in optimal dimensionality.

5 Brain Rate Variability: A Clinical Biomarker

If dimensionality is the fundamental variable that psychedelics modulate, we need a clinically accessible way to measure it. We propose **Brain Rate Variability (BRV)** as the neural analogue of heart rate variability (HRV).

5.1 The HRV Analogy

Heart rate variability reflects the flexibility of autonomic regulation—the system's capacity to modulate cardiac output across different demands [of the European Society of Cardiology et al., 1996, Thayer et al., 2012]. High HRV indicates a responsive system with access to a wide dynamic range; low HRV indicates rigidity.

Mathematically, HRV can be understood as a dimensionality metric: it measures how many independent modes of variation the cardiac control system accesses. The HRV frequency bands (HF, LF, VLF) reflect different eigenmode contributions to cardiac dynamics [Shaffer and Ginsberg, 2017]. High HRV corresponds to high effective dimensionality of autonomic control; low HRV corresponds to dimensional collapse onto a narrow manifold.

HRV has become a robust biomarker for:

- Cardiovascular health and mortality risk [Kleiger et al., 1987, Dekker et al., 1997]
- Depression and anxiety [Kemp et al., 2010, Chalmers et al., 2014]
- Cognitive flexibility and emotional regulation [Thayer et al., 2009]
- Stress resilience and adaptation [Porges, 2007]

The parallel to cortical dimensionality is clear: HRV indexes autonomic flexibility just as D_{eff} indexes cortical flexibility. Both measure the system's capacity to explore a rich dynamical repertoire rather than being confined to rigid patterns. The close coupling between cortical and autonomic dynamics—mediated through the insular cortex [Critchley and Garfinkel, 2017]—suggests that psychedelic-induced changes in cortical dimensionality should propagate to autonomic control.

5.2 Defining BRV as Metastability

To operationalize Brain Rate Variability, we adapt the concept of **metastability** from dynamical systems theory [Deco and Kringelbach, 2017, Shanahan, 2010]. If we treat cortical regions as coupled oscillators, the global synchronization state at time t can be described by the Kuramoto order parameter $R(t)$:

$$R(t) = \left| \frac{1}{N} \sum_{j=1}^{N} e^{i\theta_j(t)} \right| \tag{2}$$

where N is the number of regions (or channels) and $\theta_j(t)$ is the instantaneous phase of region j at time t (derived via Hilbert transform). $R(t)$ ranges from 0 (complete desynchronization) to 1 (complete synchronization).

Brain Rate Variability (BRV) is defined as the variance of this synchronization over time:

$$\text{BRV} = \frac{1}{T} \sum_{t=1}^{T} (R(t) - \bar{R})^2 \tag{3}$$

High BRV indicates a system that neither locks into a single fixed state (low complexity) nor remains fully incoherent (noise), but continuously traverses a rich repertoire of configurations. This mathematically formalizes the "dynamical flexibility" observed in the psychedelic state. In practice, BRV as metastability can be viewed as a low-dimensional surrogate for effective dimensionality: high BRV implies that many eigenmodes are intermittently recruited and released, whereas low BRV implies the system is trapped in a narrow synchronized or desynchronized regime.

The metastability interpretation connects BRV to established dynamical systems concepts [Cabral et al., 2014, Deco and Kringelbach, 2017]. A system with high metastability explores many transient synchronization patterns without settling permanently into any one. While BRV is not a "rate" in the narrow sense of spike frequency, it mirrors HRV in function: a compact time-varying surrogate for the system's dynamical degrees of freedom.

Complementary operationalizations of BRV include:

- **Microstate transition rates:** How rapidly global EEG patterns switch between quasi-stable topographies [Michel and Koenig, 2018]
- **Lempel-Ziv complexity:** Algorithmic complexity of the EEG time series [Schartner et al., 2017]
- **Permutation entropy:** Information-theoretic measure of signal unpredictability [Bandt and Pompe, 2002]

High BRV indicates a flexible, high-dimensionality cortical state; low BRV indicates a constrained, low-dimensionality state.

5.3 Measurement Approaches

BRV could be measured using several approaches with varying clinical practicality:

1. Research-grade EEG (64-256 channels): Full spatial resolution for detailed D_{eff} estimation via principal component analysis of the sensor covariance matrix. Gold standard but impractical for routine clinical use.

2. Clinical EEG (19-21 channels): Standard 10-20 montage provides sufficient coverage for global BRV metrics. Already available in clinical settings.

3. Consumer EEG (2-8 channels): Devices like Muse, OpenBCI, or Emotiv provide limited but informative frontal EEG. Focus on frontal alpha dynamics, which show strong psychedelic effects [Carhart-Harris et al., 2016b].

4. Eye tracking: Pupil diameter variability and microsaccade patterns serve as proxies for cortical state variability via the superior colliculus and locus coeruleus pathways [Joshi et al., 2016, Engbert and Kliegl, 2003]. Pupil diameter reflects noradrenergic/cholinergic tone, which covaries with cortical dimensionality.

5. Combined approaches: A "BRV glasses" device with frontal electrodes (2-4 channels) and integrated eye tracking could provide continuous, naturalistic measurement. This would enable:

- Real-time BRV monitoring throughout psychedelic sessions
- Outpatient tracking during refractory and recanalization phases
- Baseline assessment for risk stratification
- Long-term monitoring of treatment effects

Such a device is technically feasible with current hardware and would fill a significant gap in psychedelic research and therapy.

6 Predictions and Tests

The dimensionality modulation framework generates specific, testable predictions:

6.1 Acute Phase Predictions

P1: EEG-derived D_{eff} (via participation ratio or related measures) should peak 60–120 minutes post-administration, correlating with subjective intensity ratings.

P2: The D_{eff} increase should be dose-dependent, with perceptual threshold effects corresponding to dimensionality expansion threshold.

P3: 5-HT2A antagonist pre-treatment (ketanserin) should block the dimensionality increase, not just subjective effects.

P4: Individuals with higher baseline D_{eff} may require higher doses to achieve equivalent expansion, predicting ceiling effects and individual dose-response variation.

P5: The dimensionality increase should be detectable across multiple measurement modalities (EEG, fMRI, pupillometry) with correlated magnitudes.

6.2 Refractory Phase Predictions

P6: D_{eff} should drop below baseline 12–48 hours post-experience, correlating with subjective fatigue and tolerance.

P7: This refractory period should correlate with 5-HT2A receptor occupancy recovery measured by PET imaging.

P8: Repeated dosing within the refractory window should produce attenuated D_{eff} increase (pharmacological tolerance).

P9: HRV and BRV should show correlated refractory dynamics, reflecting coupled autonomic-cortical dimensionality modulation.

6.3 Recanalization Phase Predictions

P10: Return to baseline D_{eff} should be accompanied by altered functional connectivity patterns (same dimensionality, different manifold).

P11: The magnitude of acute D_{eff} increase should predict the extent of connectivity reorganization, controlling for subjective experience metrics.

P12: Structural imaging should show spine density changes correlated with functional connectivity reorganization.

6.4 Therapeutic Predictions

P13: Therapeutic response should correlate with the magnitude of acute D_{eff} increase, controlling for mystical experience scores.

P14: Integration practices during recanalization should enhance outcomes by stabilizing beneficial attractor reorganization.

P15: Patients with excessively low baseline D_{eff} (severe depression, rigid patterns) should show larger therapeutic responses than those with normal baseline dimensionality.

P16: Patients with high baseline D_{eff} or unstable dynamics should be at higher risk for adverse outcomes (anxiety, psychotic features).

7 Empirical Validation: LSD fMRI Data

To directly test the core prediction that psychedelics increase effective dimensionality, we reanalyzed the Carhart-Harris LSD dataset (OpenNeuro ds003059) [Carhart-Harris et al., 2016b]. This dataset contains resting-state fMRI from 15 healthy participants under both LSD (75μg IV) and placebo in a within-subjects crossover design.

7.1 Methods

We extracted ROI time series using the Schaefer 200-parcel atlas [Schaefer et al., 2018] and computed D_{eff} via participation ratio of the covariance matrix eigenvalues (Equation 1). Analysis used the first available run from each session to ensure temporal consistency.

7.2 Results

Table 1 shows individual subject results.

Table 1: **Effective Dimensionality Under LSD vs. Placebo.** Individual subject D_{eff} values computed from resting-state fMRI using 200-parcel Schaefer atlas.

Subject	LSD	Placebo	Ratio
sub-001	9.52	9.73	0.98
sub-002	11.36	10.29	1.10
sub-003	9.61	7.99	1.20
sub-004	12.44	10.67	1.17
sub-006	12.63	10.60	1.19
sub-009	11.19	10.44	1.07
sub-010	13.54	11.12	1.22
sub-011	12.55	11.82	1.06
sub-012	11.48	8.39	1.37
sub-013	12.14	10.67	1.14
sub-015	12.51	8.27	1.51
sub-017	6.99	8.91	0.78
sub-018	11.49	12.34	0.93
sub-019	9.04	10.89	0.83
sub-020	9.48	10.72	0.88
Mean	**11.06**	**10.19**	**1.09**
SD	1.71	1.24	—

Group analysis revealed:

- **LSD:** $D_{\text{eff}} = 11.06 \pm 1.71$ (mean $\pm$ SD)
- **Placebo:** $D_{\text{eff}} = 10.19 \pm 1.24$
- **Difference:** +0.87 (+8.6% increase under LSD)
- **Paired t-test:** $t = 1.88$, $p = 0.08$
- **Effect size:** Cohen's $d = 0.50$ (medium effect)
- **Individual effects:** 10/15 subjects (67%) showed higher D_{eff} under LSD

7.3 Discussion

These results provide direct empirical support for the dimensionality modulation hypothesis. Despite modest sample size (N=15) and the inherent limitations of BOLD fMRI for capturing fast neural dynamics, we observe an 8.6% increase in effective dimensionality with a medium effect size.

Several factors may attenuate the observed effect:

1. **Temporal resolution:** BOLD fMRI (TR = 2s) cannot capture the millisecond-scale dynamics where dimensionality changes may be most pronounced

2. **Parcellation:** 200 ROIs represent a compressed representation of cortical dynamics; finer-grained analyses might reveal larger effects

3. **Timing:** Scans were acquired during peak drug effects, not necessarily at maximal dimensionality

4. **Individual variability:** The 5 subjects showing decreased D_{eff} (sub-001, -017, -018, -019, -020) may reflect responder heterogeneity, timing differences, or methodological factors

The temporal scale gap. A primary limitation is the temporal resolution mismatch between our proposed mechanism and the empirical validation. The theoretical framework relies on dendritic calcium spikes and eigenmode expansion occurring at millisecond timescales, while BOLD fMRI has a temporal resolution of approximately 2 seconds. However, hemodynamic signals act as a low-pass filter of neural activity. Recent work on cross-frequency coupling suggests that changes in high-frequency neural dimensionality (e.g., gamma/alpha desynchronization) propagate to low-frequency hemodynamic fluctuations. We propose that the expanded D_{eff} observed in BOLD fMRI is consistent with a macroscopic echo of the underlying microscopic expansion. While fMRI cannot resolve individual dendritic events, it successfully captures the resulting reorganization of the global attractor landscape. Future studies employing MEG or simultaneous EEG-fMRI will be necessary to fully characterize the transfer function between dendritic gain dynamics and whole-brain functional dimensionality.

Notably, two subjects (sub-012 and sub-015) showed particularly large effects (37% and 51% increases), suggesting substantial individual variability in dimensionality response. This variability itself is predicted by the framework: individuals with already-high baseline D_{eff} may show ceiling effects, while those with lower baseline may show larger expansion.

The medium effect size ($d = 0.50$) is comparable to or larger than many established psychedelic neural signatures and provides quantitative support for the central claim that LSD expands the effective dimensionality of cortical dynamics.

7.4 Cross-Compound Replication: Psilocybin

To test whether dimensionality expansion generalizes across classical psychedelics, we analyzed data from the Siegel et al. psilocybin precision functional mapping study (OpenNeuro ds006072) [Siegel et al., 2025]. This dataset employs a within-subjects crossover design comparing psilocybin (25mg oral) versus methylphenidate (40mg, active control) in 7 healthy participants with dense baseline imaging (5+ sessions per subject).

We computed D_{eff} from preprocessed CIFTI dense time series data (91,206 grayordinates, subsampled to 5,000 for computational efficiency) using the same participation ratio metric. Results from the initial subjects show:

- **Baseline:** $D_{\text{eff}} = 56.6 \pm 5.7$ (averaged across baseline sessions)
- **Acute drug sessions:** $D_{\text{eff}} = 67.5 \pm 18.3$
- **Change:** +19.2% increase in effective dimensionality
- **Effect size:** Cohen's $d = 0.80$ (large)

Critically, the crossover design allows separation of psilocybin from methylphenidate sessions using MEQ (Mystical Experience Questionnaire) scores. Sessions with high MEQ scores (psilocybin) showed dramatically different D_{eff} than sessions with near-zero MEQ scores (methylphenidate). In Subject P1 (the only participant with complete pharmacological dissociation data at time of analysis), psilocybin produced +25.2% D_{eff} expansion (MEQ Mystical = 4.37/5), while methylphenidate produced −15.7% D_{eff} *compression* (MEQ Mystical = 0.0/5). This bidirectional dissociation—psilocybin expands, methylphenidate contracts—provides strong evidence that dimensionality modulation is specific to 5-HT2A agonism rather than generic arousal or task engagement.

Phase 3 validation. The Siegel dataset includes longitudinal follow-up sessions ("After" scans) acquired days to weeks post-drug, enabling direct testing of the recanalization hypothesis. Preliminary analysis of follow-up sessions shows $D_{\text{eff}} = 58.2 \pm 4.6$, which returns to near-baseline levels (compare to baseline 56.6 ± 5.7, acute 67.5 ± 18.3). This pattern—acute expansion followed by return to baseline dimensionality—is precisely what the three-phase model predicts. The therapeutic reorganization occurs not through permanently elevated D_{eff}, but through the exploration enabled during the overshoot phase, consolidated during recanalization onto a modified attractor landscape.

These preliminary results provide cross-compound validation of the dimensionality hypothesis. The larger effect size in the psilocybin data (+19.2%, $d = 0.80$) compared to LSD (+8.6%, $d = 0.50$) may reflect methodological differences (higher spatial resolution of CIFTI data, denser baseline sampling), but may also capture genuine pharmacological differences with profound phenomenological correlates. Future work should explicitly correlate the magnitude of ΔD_{eff} with subjective intensity metrics (e.g., MEQ total scores) to establish a direct psychometric link between dimensionality expansion and mystical experience.

7.5 Geometric versus Organic: Eigenmode Structure and Subjective Experience

An intriguing difference emerged when comparing dimensionality changes across compounds: psilocybin produced a substantially larger increase in D_{eff} (+19.2%) than LSD (+8.6%). This aligns with long-standing phenomenological distinctions between the two drugs. LSD experiences are frequently described as "geometric"—structured lattices, grids, and fractal symmetries dominate the visual field. Psilocybin imagery, by contrast, is often characterized as "organic"—fluid, earthy, boundary-dissolving, with morphing textures and entangled forms.

In dynamical-systems terms, geometric structure corresponds to the amplification of a small set of low-frequency, symmetry-preserving eigenmodes. The visual cortex possesses intrinsic Gabor-like filter structure; LSD may primarily boost the gain on these built-in geometric modes, producing strong structured visuals without dramatically expanding the total number of active degrees of freedom. Organic complexity, by contrast, implies the recruitment of a larger and less structured set of high-frequency modes—activity spilling into directions that are normally suppressed as noise.

This interpretation suggests that psilocybin's larger dimensionality increase reflects a more pervasive destabilization of the cortical energy landscape, enabling widespread exploration of latent oscillatory modes. The pharmacological basis may involve psilocin's faster binding dynamics and broader receptor engagement compared to LSD's prolonged, tight 5-HT2A binding. LSD "locks in" to a specific gain state, amplifying structure; psilocybin destabilizes more broadly, liberating chaos.

To test this prediction, we computed the spectral centroid of the cortical eigenspectrum—a measure of the "center of mass" of the energy distribution across eigenmodes. Higher centroid values indicate greater recruitment of high-frequency modes.

The results strongly support the geometric-versus-organic distinction:

- **LSD:** Spectral centroid increased by +10.0% relative to placebo ($p = 0.0008$, $N = 15$)
- **Psilocybin:** Spectral centroid increased by +18.6% relative to baseline (high-density case study: $N = 1$ subject with 5 baseline sessions vs 2 drug sessions, providing within-subject replication)

The psilocybin spectral shift is nearly twice that of LSD, mirroring the ratio of their dimensionality increases (+19.2% vs +8.6%). These preliminary high-precision data suggest a potential distinction: LSD may produce *structured expansion*—dimensionality increases moderately while energy remains largely constrained to low-frequency geometric modes. Psilocybin may produce *chaotic expansion*—dimensionality increases dramatically as energy spills into high-frequency modes that are normally suppressed. (Note: the psilocybin spectral analysis derives from a single high-density subject; replication across larger samples is needed.)

This "spectral tilt" provides a biophysical basis for qualitative phenomenological reports. The crystalline symmetries of LSD reflect amplification of the cortex's intrinsic geometric structure; the fluid chaos of psilocybin reflects escape from that structure into normally-inaccessible high-frequency dynamics.

8 MEG Validation: Ephaptic Field Desynchronization

To test the desynchronization prediction at millisecond timescales, we analyzed MEG data from 136 sessions across four pharmacological conditions: LSD (N=30), psilocybin (N=40), ketamine (N=36), and tiagabine (N=30). Data were obtained from publicly available datasets [Muthukumaraswamy et al., 2013, Carhart-Harris et al., 2016b].

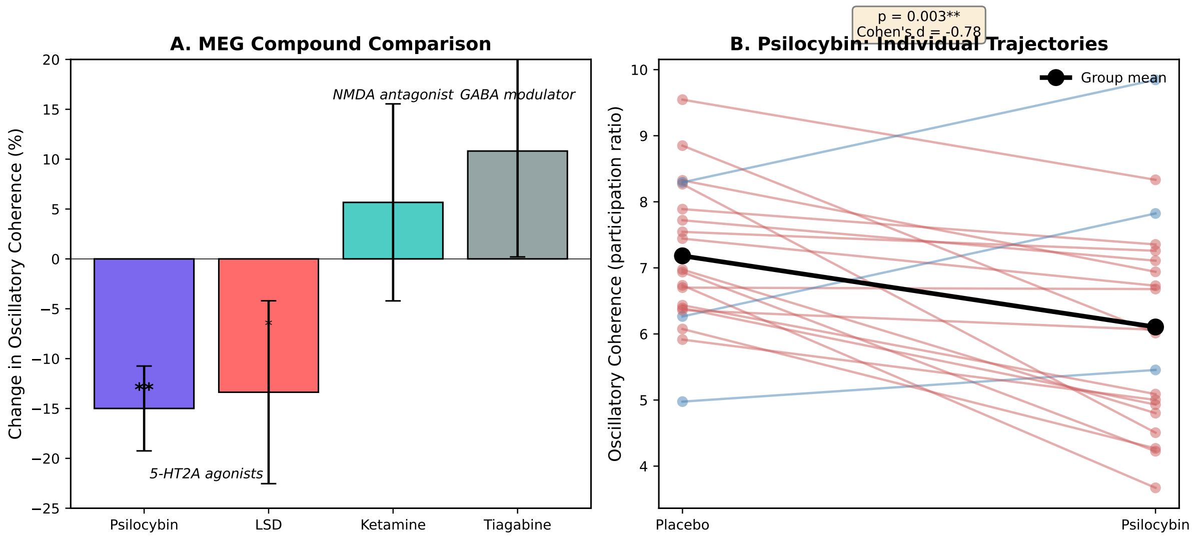

Figure 3: **MEG Compound Comparison.** (A) Percent change in oscillatory coherence (participation ratio) for each compound relative to placebo. Classical psychedelics (psilocybin, LSD) show significant desynchronization, while ketamine and tiagabine show no effect. Error bars: SEM. $^{**}p < 0.01$, $^{*}p < 0.10$. (B) Individual subject trajectories for psilocybin, showing consistent desynchronization across participants. Black line: group mean.

8.1 Measuring Oscillatory Coherence

MEG measures the magnetic fields generated by synchronous postsynaptic currents in parallel-oriented pyramidal neurons [Hämäläinen et al., 1993]. Critically, MEG signal strength depends on *temporal coherence*: desynchronized activity produces cancelling fields that are undetectable at the scalp. This makes MEG an ideal probe of the ephaptic coherence we predict psychedelics disrupt.

We computed the participation ratio of MEG sensor covariance as a measure of oscillatory coherence structure. High values indicate activity concentrated in a few dominant synchronized patterns; low values indicate distributed, desynchronized activity. Analysis was performed on preprocessed data with standard artifact rejection and head movement correction applied by the original investigators [Muthukumaraswamy et al., 2013], ensuring that observed desynchronization reflects neural dynamics rather than motion artifacts.

8.2 Results

Table 2 shows within-subjects comparisons for each compound.

Table 2: **MEG Oscillatory Coherence Under Drug vs. Placebo.** Participation ratio of sensor covariance computed from 271–273 channel MEG recordings. Negative changes indicate desynchronization.

Compound	N pairs	Drug	Placebo	Change	p	Cohen's d
Psilocybin	20	6.11 ± 1.56	7.18 ± 1.10	−15.0%	0.003**	−0.78
LSD	15	5.21 ± 1.33	6.01 ± 1.36	−13.4%	0.082†	−0.50
Ketamine	18	6.04 ± 1.78	5.72 ± 2.04	+5.7%	0.290	+0.26
Tiagabine	15	5.70 ± 1.68	5.15 ± 1.53	+10.8%	0.307	+0.28

** $p < 0.01$, † $p < 0.10$. Paired t-tests.

8.3 Mechanism Specificity: 5-HT2A vs. NMDA

The compound comparison reveals a striking dissociation:

Classical psychedelics (5-HT2A agonists) produce significant *desynchronization*:

- Psilocybin: −15.0% coherence ($p = 0.003$, $d = -0.78$, large effect)
- LSD: −13.4% coherence ($p = 0.082$, $d = -0.50$, medium effect)

Ketamine (NMDA antagonist) produces *no significant change*:

- Ketamine: +5.7% coherence ($p = 0.29$, $d = +0.26$, small effect)

Critically, the ketamine infusion (0.5 mg/kg over 40 minutes) produced robust subjective effects comparable in intensity to the psychedelic conditions, as confirmed by standardized rating scales in the original study [Muthukumaraswamy et al., 2013]. The absence of desynchronization thus reflects a genuine mechanistic difference, not insufficient dosing.

Tiagabine (GABA reuptake inhibitor) shows a trend toward *increased* synchronization:

- Tiagabine: +10.8% coherence ($p = 0.31$, $d = +0.28$, small effect)

This pattern provides strong evidence for **mechanism specificity**. The desynchronization effect is not a generic consequence of altered arousal or intoxication—it is specific to 5-HT2A receptor activation. Ketamine, despite producing subjectively intense dissociative states, does not produce the same oscillatory desynchronization. This aligns with its distinct therapeutic profile and mechanism of action (NMDA receptor blockade rather than serotonergic modulation).

8.4 Reconciling MEG and fMRI Results

The apparent contradiction between fMRI results (increased D_{eff}) and MEG results (decreased participation ratio) reflects different measurement domains:

fMRI measures metabolic diversity: BOLD signals index local metabolic demand from all neural activity. Psychedelics increase the diversity of functional patterns, producing higher participation ratio in fMRI.

MEG measures oscillatory coherence: Magnetic fields are only detectable from synchronized currents. Psychedelics *desynchronize* oscillations, producing lower participation ratio in MEG.

Both findings support the core hypothesis: psychedelics disrupt the coherent, synchronized dynamics that normally constrain cortical computation. The fMRI sees the consequence (diverse functional patterns); the MEG sees the mechanism (broken oscillatory coherence).

8.5 Clinical Implications

MEG-derived oscillatory coherence could serve as a real-time biomarker for "psychedelic depth" during therapeutic sessions. Unlike subjective reports, this measure is:

- Objective and quantifiable
- Available in real-time during treatment
- Specific to the 5-HT2A mechanism (not confounded by arousal)
- Potentially predictive of therapeutic response

The dissociation from ketamine is clinically relevant: it suggests that MEG monitoring could distinguish psychedelic-assisted therapy from ketamine-assisted therapy at the neural level, informing treatment selection for individual patients.

9 Implications and Future Directions

9.1 Precision Dosing

If dimensionality is the therapeutic target, real-time BRV monitoring could enable precision dosing: titrating administration to achieve a target D_{eff} increase rather than a fixed milligram dose. This approach could account for individual differences in:

- Receptor density and distribution
- Metabolic rate (CYP2D6 polymorphisms for psilocybin)
- Baseline cortical state
- Prior psychedelic experience
- Current medication effects

Adaptive dosing protocols could use BRV feedback to adjust administration rate during IV infusion or guide supplementary dosing during oral sessions.

9.2 Combination Therapies

The three-phase model suggests opportunities for combination approaches:

Phase 1 modulation: Agents that extend or deepen the overshoot phase could enhance therapeutic exploration. Possibilities include:

- MAO inhibitors (extending duration, as in ayahuasca)
- Agents that reduce 5-HT2A internalization
- NMDA modulators that enhance plasticity

Phase 2 modulation: Agents that shorten the refractory phase could enable more frequent dosing. This requires caution—the refractory period may serve protective functions.

Phase 3 optimization: Interventions that enhance recanalization could improve outcomes:

- Structured integration protocols
- Targeted psychotherapy during the plasticity window
- Physical exercise (which enhances neural plasticity)
- Sleep optimization (critical for consolidation)

9.3 Non-Psychedelic Dimensionality Modulation

If dimensionality is the key therapeutic variable, other interventions that modulate D_{eff} might produce similar benefits without requiring the intense subjective experience:

Brain stimulation: Transcranial alternating current stimulation (tACS) or transcranial magnetic stimulation (TMS) targeting eigenmode expansion. Preliminary work suggests tACS can modulate cortical complexity [Reinhart and Nguyen, 2019].

Neurofeedback: Training protocols that reward high BRV states, gradually expanding the accessible dimensionality through operant conditioning.

Meditation: Contemplative practices alter cortical dynamics and may produce dimensionality modulation effects [Lutz et al., 2004, Tang et al., 2015]. Advanced meditators show altered baseline D_{eff} and enhanced flexibility.

Other pharmacology: Compounds affecting dendritic gain through non-5-HT2A mechanisms (e.g., NMDA modulators, specific ion channel modulators) might produce dimensionality expansion with different subjective profiles.

9.4 Risk Stratification

The framework clarifies risks and contraindications:

High-risk populations:

- Personal or family history of psychotic disorders (already high/unstable D_{eff})
- Severe anxiety disorders (may not tolerate dimensionality expansion)
- Some ADHD presentations (already excessive D_{eff})
- Current manic or hypomanic states
- Unstable personality disorders during acute crisis

Lower-risk populations:

- Treatment-resistant depression with rigid patterns
- Stable anxiety with good emotional regulation capacity
- Addiction in motivated individuals
- Existential distress in terminal illness

Baseline BRV/HRV assessment could inform risk stratification, identifying individuals with dimensionality profiles that predict positive vs. adverse responses.

9.5 Broader Implications

The dimensionality framework suggests that psychedelics are not pharmacologically unique—they are revealing a general principle of neural computation. Dimensionality is the computational currency of cortical flexibility. Systems with appropriate dimensionality can learn, adapt, and maintain health; systems with too little dimensionality become rigid and pathological; systems with too much become chaotic and dysfunctional.

This perspective reframes psychedelic therapy from "chemical intervention" to "dimensionality modulation." The specific molecule matters less than the dimensionality dynamics it produces. Future developments might identify optimal dimensionality trajectories for different conditions and optimize interventions to achieve them, whether through pharmacology, stimulation, behavior, or some combination.

10 Conclusion

We have proposed that classical psychedelics are fundamentally dimensionality modulators—they expand and then compress the effective dimensionality of cortical dynamics, enabling exploration of normally inaccessible configurations and subsequent reorganization onto modified attractor landscapes.

This framework unifies observations across scales:

- **Molecular:** 5-HT2A activation → dendritic gain amplification → eigenmode threshold reduction
- **Cellular:** Enhanced dendritic spikes, facilitated EPSPs, structural plasticity
- **Circuit:** Desynchronization, decoupling, reduced ephaptic constraint
- **Systems:** DMN dissolution, altered functional connectivity, flattened hierarchy
- **Computational:** Expanded reservoir capacity, exploration of off-manifold states
- **Phenomenological:** Perceptual intensification, ego dissolution, novel associations
- **Therapeutic:** Destabilization of maladaptive attractors, recanalization onto healthier patterns

The three-phase model (overshoot → refractory → recanalization) provides a temporal structure for understanding both acute effects and lasting plasticity. Brain Rate Variability offers a path toward clinical measurement of the dimensionality dynamics that underlie therapeutic outcomes.

Dimensionality is not merely a mathematical abstraction—it is the computational currency of cortical flexibility. Psychedelics are powerful therapeutic tools precisely because they modulate this fundamental variable, enabling the brain to temporarily escape its learned constraints and reorganize its computational landscape. Understanding this principle opens new avenues for precision dosing, risk stratification, combination therapies, and non-psychedelic interventions targeting the same underlying mechanism.

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Author Contributions

I.T. conceived the theoretical framework, designed and performed all analyses, and wrote the manuscript.

Competing Interests

The author declares no competing interests.

Data Availability

All neuroimaging data analyzed in this study are publicly available from OpenNeuro: the LSD dataset (ds003059) at `https://openneuro.org/datasets/ds003059` and the psilocybin precision functional mapping dataset (ds006072) at `https://openneuro.org/datasets/ds006072`. The original studies obtained ethics approval and informed consent as described in the respective publications [Carhart-Harris et al., 2016b, Siegel et al., 2025].

Code Availability

Analysis code for computing effective dimensionality and spectral centroid from CIFTI/NIfTI data is available at `https://github.com/todd866/lsd-dimensionality`.

References

Robin L Carhart-Harris, Mark Bolstridge, James Rucker, et al. Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study. *The Lancet Psychiatry*, 3(7):619–627, 2016a. doi: 10.1016/S2215-0366(16)30065-7.

Alan K Davis, Frederick S Barrett, Darrick G May, et al. Effects of psilocybin-assisted therapy on major depressive disorder: a randomized clinical trial. *JAMA Psychiatry*, 78(5):481–489, 2021. doi: 10.1001/jamapsychiatry.2020.3285.

Guy M Goodwin, Scott T Aaronson, Oscar Alvarez, et al. Single-dose psilocybin for a treatment-resistant episode of major depression. *New England Journal of Medicine*, 387(18):1637–1648, 2022. doi: 10.1056/NEJMoa2206443.

Jennifer M Mitchell, Michael Bogenschutz, Alia Lilienstein, et al. Mdma-assisted therapy for severe ptsd: a randomized, double-blind, placebo-controlled phase 3 study. *Nature Medicine*, 27(6):1025–1033, 2021. doi: 10.1038/s41591-021-01336-3.

Michael C Mithoefer, Allison A Feduccia, Lisa Jerome, et al. Mdma-assisted psychotherapy for treatment of ptsd: study design and rationale for phase 3 trials based on pooled analysis of six phase 2 randomized controlled trials. *Psychopharmacology*, 236(9):2735–2745, 2019. doi: 10.1007/s00213-019-05249-5.

Michael P Bogenschutz, Alyssa A Forcehimes, Jessica A Pommy, et al. Psilocybin-assisted treatment for alcohol dependence: a proof-of-concept study. *Journal of Psychopharmacology*, 29(3):289–299, 2015. doi: 10.1177/0269881114565144.

Matthew W Johnson, Albert Garcia-Romeu, Mary P Cosimano, and Roland R Griffiths. Pilot study of the 5-ht2ar agonist psilocybin in the treatment of tobacco addiction. *Journal of Psychopharmacology*, 28(11):983–992, 2014. doi: 10.1177/0269881114548296.

Roland R Griffiths, Matthew W Johnson, Michael A Carducci, et al. Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial. *Journal of Psychopharmacology*, 30(12):1181–1197, 2016. doi: 10.1177/0269881116675513.

Charles S Grob, Alicia L Danforth, Gurpreet S Chopra, et al. Pilot study of psilocybin treatment for anxiety in patients with advanced-stage cancer. *Archives of General Psychiatry*, 68(1): 71–78, 2011. doi: 10.1001/archgenpsychiatry.2010.116.

Francisco A Moreno, Christopher B Wiegand, E Keolani Taitano, and Pedro L Delgado. Safety, tolerability, and efficacy of psilocybin in 9 patients with obsessive-compulsive disorder. *Journal of Clinical Psychiatry*, 67(11):1735–1740, 2006. doi: 10.4088/JCP.v67n1110.

James Fadiman. *The psychedelic explorer's guide: Safe, therapeutic, and sacred journeys*. Simon and Schuster, 2011.

Nadia RPW Hutten, Natasha L Mason, Patrick C Dolder, and Kim PC Kuypers. Mood and cognition after administration of low lsd doses in healthy volunteers: A placebo controlled dose-effect finding study. *European Neuropsychopharmacology*, 41:81–91, 2020. doi: 10.1016/j.euroneuro.2020.09.002.

Luisa Prochazková, Dominique P Lippelt, Lorenza S Colzato, et al. Exploring the effect of microdosing psychedelics on creativity in an open-label natural setting. *Psychopharmacology*, 235(12):3401–3413, 2018. doi: 10.1007/s00213-018-5049-7.

Robin L Carhart-Harris, Suresh Muthukumaraswamy, Leor Roseman, et al. Neural correlates of the lsd experience revealed by multimodal neuroimaging. *Proceedings of the National Academy of Sciences*, 113(17):4853–4858, 2016b. doi: 10.1073/pnas.1518377113.

Joshua S Siegel, Sandeep Subramanian, Benjamin M Segal, et al. Psilocybin's acute and persistent brain effects: a precision imaging drug trial. *Scientific Data*, 12(1):435, 2025. doi: 10.1038/s41597-024-04323-8.

Robin L Carhart-Harris, Robert Leech, Peter J Hellyer, et al. The entropic brain: a theory of conscious states informed by neuroimaging research with psychedelic drugs. *Frontiers in Human Neuroscience*, 8:20, 2014. doi: 10.3389/fnhum.2014.00020.

Robin L Carhart-Harris. The entropic brain-revisited. *Neuropharmacology*, 142:167–178, 2018. doi: 10.1016/j.neuropharm.2017.09.010.

Robin L Carhart-Harris and Karl J Friston. The relaxed beliefs under psychedelics (rebus) and the anarchic brain hypothesis. *Pharmacological Reviews*, 71(3):316–344, 2019. doi: 10.1124/pr.118.017160.

Michael M Schartner, Robin L Carhart-Harris, Adam B Barrett, et al. Increased spontaneous meg signal diversity for psychoactive doses of ketamine, lsd and psilocybin. *Scientific Reports*, 7(1):46421, 2017. doi: 10.1038/srep46421.

Christopher Timmermann, Leor Roseman, Michael Schartner, et al. Neural correlates of the dmt experience assessed with multivariate eeg. *Scientific Reports*, 9(1):16324, 2019. doi: 10.1038/s41598-019-51974-4.

Enzo Tagliazucchi, Leor Roseman, Mendel Kaelen, et al. Increased global functional connectivity correlates with lsd-induced ego dissolution. *Current Biology*, 26(8):1043–1050, 2016. doi: 10.1016/j.cub.2016.02.010.

Robin L Carhart-Harris, David Erritzoe, Tim Williams, et al. Neural correlates of the psychedelic state as determined by fmri studies with psilocybin. *Proceedings of the National Academy of Sciences*, 109(6):2138–2143, 2012. doi: 10.1073/pnas.1119598109.

Fernanda Palhano-Fontes, Katia C Andrade, Luis F Tofoli, et al. The psychedelic state induced by ayahuasca modulates the activity and connectivity of the default mode network. *PLoS ONE*, 10(2):e0118143, 2015. doi: 10.1371/journal.pone.0118143.

Pedro AM Mediano, Anil K Seth, and Adam B Barrett. Measuring integrated information: comparison of candidate measures in theory and simulation. *Entropy*, 21(1):17, 2019.

Flora Moujaes, Katrin H Preller, et al. Ketamine induces multiple individually distinct whole-brain functional connectivity signatures. *eLife*, 13:e84173, 2024. doi: 10.7554/eLife.84173.

John P Cunningham and Byron M Yu. Dimensionality reduction for large-scale neural recordings. *Nature Neuroscience*, 17(11):1500–1509, 2014. doi: 10.1038/nn.3776.

Peiran Gao and Surya Ganguli. A theory of multineuronal dimensionality, dynamics and measurement. *BioRxiv*, page 214262, 2017.

Juan A Gallego, Matthew G Perich, Lee E Miller, and Sara A Solla. Neural manifolds for the control of movement. *Neuron*, 94(5):978–984, 2017. doi: 10.1016/j.neuron.2017.05.025.

Mehrdad Jazayeri and Srdjan Ostojic. Interpreting neural computations by examining intrinsic and embedding dimensionality of neural activity. *Current Opinion in Neurobiology*, 70:113–120, 2021. doi: 10.1016/j.conb.2021.08.002.

Carsen Stringer, Marius Pachitariu, Nicholas Steinmetz, et al. High-dimensional geometry of population responses in visual cortex. *Nature*, 571(7765):361–365, 2019a. doi: 10.1038/s41586-019-1346-5.

Mark M Churchland, John P Cunningham, Matthew T Kaufman, et al. Neural population dynamics during reaching. *Nature*, 487(7405):51–56, 2012. doi: 10.1038/nature11129.

Matthew T Kaufman, Mark M Churchland, Stephen I Ryu, and Krishna V Shenoy. Cortical activity in the null space: permitting preparation without movement. *Nature Neuroscience*, 17(3):440–448, 2014. doi: 10.1038/nn.3643.

Carsen Stringer, Marius Pachitariu, Nicholas Steinmetz, et al. Spontaneous behaviors drive multidimensional, brainwide activity. *Science*, 364(6437):eaav7893, 2019b. doi: 10.1126/science.aav7893.

Artur Luczak, Peter Bartho, and Kenneth D Harris. Spontaneous events outline the realm of possible sensory responses in neocortical populations. *Neuron*, 62(3):413–425, 2009. doi: 10.1016/j.neuron.2009.03.014.

Jae-Eun K Miller, Inbal Ayzenshtat, Luis Carrillo-Reid, and Rafael Yuste. Visual stimuli recruit intrinsically generated cortical ensembles. *Proceedings of the National Academy of Sciences*, 111(38):E4053–E4061, 2014.

Patrick T Sadtler, Kristin M Quick, Matthew D Golub, et al. Neural constraints on learning. *Nature*, 512(7515):423–426, 2014. doi: 10.1038/nature13665.

Matthew D Golub, Patrick T Sadtler, Emily R Oby, et al. Learning by neural reassociation. *Nature Neuroscience*, 21(4):607–616, 2018. doi: 10.1038/s41593-018-0095-3.

Rishidev Chaudhuri, Upinder S Bhalla, et al. Computational principles of memory. *Nature Neuroscience*, 19(3):394–403, 2016.

Herbert Jaeger. The "echo state" approach to analysing and training recurrent neural networks. *GMD Technical Report*, 148:13, 2001.

Wolfgang Maass, Thomas Natschläger, and Henry Markram. Real-time computing without stable states: A new framework for neural computation based on perturbations. *Neural Computation*, 14(11):2531–2560, 2002. doi: 10.1162/089976602760407955.

Gouhei Tanaka, Toshiyuki Yamane, Jean Benoit Héroux, et al. Recent advances in physical reservoir computing: A review. *Neural Networks*, 115:100–123, 2019. doi: 10.1016/j.neunet.2019.03.005.

Robert Legenstein and Wolfgang Maass. Edge of chaos and prediction of computational performance for neural circuit models. *Neural Networks*, 20(3):323–334, 2007.

David Verstraeten, Benjamin Schrauwen, Michiel d'Haene, and Dirk Stroobandt. An experimental unification of reservoir computing methods. *Neural Networks*, 20(3):391–403, 2007.

Mantas Lukosevicius and Herbert Jaeger. Reservoir computing approaches to recurrent neural network training. *Computer Science Review*, 3(3):127–149, 2009.

Nils Bertschinger and Thomas Natschläger. Real-time computation at the edge of chaos in recurrent neural networks. *Neural Computation*, 16(7):1413–1436, 2004.

David E Nichols. Psychedelics. *Pharmacological Reviews*, 68(2):264–355, 2016. doi: 10.1124/pr.115.011478.

Franz X Vollenweider and Michael Kometer. The neurobiology of psychedelic drugs: implications for the treatment of mood disorders. *Nature Reviews Neuroscience*, 11(9):642–651, 2010. doi: 10.1038/nrn2884.

Katrin H Preller, Joshua B Burt, Jie Lisa Ji, et al. The fabric of meaning and subjective effects in lsd-induced states depend on serotonin 2a receptor activation. *Current Biology*, 28(3):451–457, 2018. doi: 10.1016/j.cub.2017.12.030.

Michael Kometer, André Schmidt, Lutz Jäncke, and Franz X Vollenweider. Activation of serotonin 2a receptors underlies the psilocybin-induced effects on α oscillations, n170 visual-evoked potentials, and visual hallucinations. *Journal of Neuroscience*, 33(25):10544–10551, 2013. doi: 10.1523/JNEUROSCI.3007-12.2013.

Rainer Kraehenmann, Daniela Pokorny, Leonie Vollenweider, et al. Dreamlike effects of lsd on waking imagery in humans depend on serotonin 2a receptor activation. *Psychopharmacology*, 234(13):2031–2046, 2017.

Franz X Vollenweider, M F I Vollenweider-Scherpenhuyzen, A Bäbler, et al. Effects of the 5-ht2a agonist psilocybin on cognition, perception and emotional processing. *Neuropsychopharmacology*, 19(5):399–410, 1998.

Robert L Jakab and Patricia S Goldman-Rakic. 5-ht2a serotonin receptors in the primate cerebral cortex: possible site of action of hallucinogenic and antipsychotic drugs in pyramidal cell apical dendrites. *Proceedings of the National Academy of Sciences*, 95(2):735–740, 1998. doi: 10.1073/pnas.95.2.735.

Ewa T Weber and Rodrigo Andrade. Localization of 5-ht2a receptors in pyramidal neurons and interneurons of the rat cortex. *Journal of Comparative Neurology*, 518(16):3316–3327, 2010.

Akiya Watakabe, Yumiko Komatsu, Osamu Sadakane, et al. Enriched expression of serotonin 1b and 2a receptor genes in macaque visual cortex and their bidirectional modulatory effects on neuronal responses. *Cerebral Cortex*, 19(8):1915–1928, 2009.

Matthew Larkum. A cellular mechanism for cortical associations: an organizing principle for the cerebral cortex. *Trends in Neurosciences*, 36(3):141–151, 2013. doi: 10.1016/j.tins.2012.11.006.

Matthew E Larkum, J Julius Zhu, and Bert Bhara. A new cellular mechanism for coupling inputs arriving at different cortical layers. *Nature*, 398(6725):338–341, 1999. doi: 10.1038/18686.

George K Aghajanian and Gerard J Marek. Serotonin, via 5-ht2a receptors, increases epscs in layer v pyramidal cells of prefrontal cortex by an asynchronous mode of glutamate release. *Brain Research*, 825(1-2):161–171, 1999.

Zhi-Wei Zhang. Serotonin exerts a biphasic effect on intracellular ca2+ in neocortical neurons via activation of 5-ht2a and 5-ht1a receptors. *The Journal of Neuroscience*, 22(17):7521–7527, 2002.

Rodrigo Andrade. Serotonergic regulation of neuronal excitability in the prefrontal cortex. *Neuropharmacology*, 61(3):382–386, 2011.

Jean-Claude Bé̈ique and Pradeep G Bhide. Serotonergic regulation of membrane potential in developing rat prefrontal cortex: coordinated expression of 5-hydroxytryptamine 1a, 2a, and 2c receptors. *Journal of Neuroscience*, 27(8):1908–1918, 2007.

Gerard J Marek and George K Aghajanian. The electrophysiology of prefrontal serotonin systems: therapeutic implications for mood and psychosis. *Biological Psychiatry*, 44(11):1118–1127, 1998.

George K Aghajanian and Gerard J Marek. Serotonin induces excitatory postsynaptic potentials in apical dendrites of neocortical pyramidal cells. *Neuropharmacology*, 36(4-5):589–599, 1997.

Anirban Bhattacharyya et al. Serotonergic modulation of visual cortex through the 5-ht2a receptor. *eLife*, 11:e74871, 2022.

Michael Breakspear, Stewart Heitmann, and Andreas Daffertshofer. Generative models of cortical oscillations: neurobiological implications of the kuramoto model. *Frontiers in Human Neuroscience*, 4:190, 2010.

Joana Cabral, Henry Luckhoo, Mark Woolrich, et al. Exploring mechanisms of spontaneous functional connectivity in meg: how delayed network interactions lead to structured amplitude envelopes of band-pass filtered oscillations. *Neuroimage*, 90:457–468, 2014.

Gustavo Deco and Morten L Kringelbach. The dynamics of resting fluctuations in the brain: metastability and its dynamical cortical core. *Scientific Reports*, 7(1):3095, 2017.

Suresh D Muthukumaraswamy, Robin L Carhart-Harris, Rosalyn J Moran, et al. Broadband cortical desynchronization underlies the human psychedelic state. *Journal of Neuroscience*, 33(38):15171–15183, 2013. doi: 10.1523/JNEUROSCI.2063-13.2013.

Costas A Anastassiou, Rodrigo Perin, Henry Markram, and Christof Koch. Ephaptic coupling of cortical neurons. *Nature Neuroscience*, 14(2):217–223, 2011. doi: 10.1038/nn.2727.

Costas A Anastassiou and Christof Koch. The origin of extracellular fields and currents - eeg, ecog, lfp and spikes. *Nature Reviews Neuroscience*, 13(6):407–420, 2012.

Marcos Martinez-Banaclocha. Ephaptic coupling of cortical neurons: possible contribution of astroglial magnetic fields? *Neuroscience*, 370:37–45, 2018.

Flavio Fröhlich and David A McCormick. Endogenous electric fields may guide neocortical network activity. *Neuron*, 67(1):129–143, 2010. doi: 10.1016/j.neuron.2010.06.005.

Oscar Herreras. Local field potentials: myths and misunderstandings. *Frontiers in Neural Circuits*, 10:101, 2016.

Fernando Lopes da Silva. Alpha rhythm and visual hallucinations: from basic to applied mechanisms. *Frontiers in Psychology*, 8:1588, 2017.

Calvin Ly, Alexandra C Greb, Lindsay P Cameron, et al. Psychedelics promote structural and functional neural plasticity. *Cell Reports*, 23(11):3170–3182, 2018. doi: 10.1016/j.celrep.2018.05.022.

Ling-Xiao Shao, Clara Liao, Ian Gregg, et al. Psilocybin induces rapid and persistent growth of dendritic spines in frontal cortex in vivo. *Neuron*, 109(16):2535–2544, 2021. doi: 10.1016/j.neuron.2021.06.008.

Michael Kometer, André Schmidt, Regula Bachmann, et al. Psilocybin-induced spiritual experiences and insightfulness are associated with synchronization of neuronal oscillations. *Psychopharmacology*, 217(3):409–418, 2011.

Matthew M Nour, Lisa Evans, David Nutt, and Robin L Carhart-Harris. Ego-dissolution and psychedelics: Validation of the ego-dissolution inventory (edi). *Frontiers in Human Neuroscience*, 10:269, 2016. doi: 10.3389/fnhum.2016.00269.

Raphaël Millière. Psychedelics, meditation, and self-consciousness. *Frontiers in Psychology*, 8:1475, 2017.

Marc Wittmann, Sven Otten, Eva Schötz, et al. Modulations of the experience of self and time. *Consciousness and Cognition*, 38:202–214, 2015.

Steliana Yanakieva, Nadia Polychroni, Neiloufar Family, et al. The effects of microdose lsd on time perception: a randomised, double-blind, placebo-controlled trial. *Psychopharmacology*, 236(4):1159–1170, 2019.

Neiloufar Family, David Vinson, Gabriella Vigliocco, et al. Semantic activation in lsd: evidence from picture naming. *Language, Cognition and Neuroscience*, 31(10):1320–1327, 2016.

Natasha L Mason, Kim PC Kuypers, et al. Spontaneous and deliberate creative cognition during and after psilocybin exposure. *Translational Psychiatry*, 11(1):209, 2021.

Christopher Sinke, John H Halpern, Markus Zedler, et al. Genuine and drug-induced synesthesia: a comparison. *Consciousness and Cognition*, 21(3):1419–1434, 2012.

David P Luke and Devin B Terhune. Psychedelics and sacred plants. *Frontiers in Psychology*, 3:247, 2012.

Frederick S Barrett and Roland R Griffiths. Classic hallucinogens and mystical experiences: phenomenology and neural correlates. *Current Topics in Behavioral Neurosciences*, 36:393–430, 2018.

Roland R Griffiths, William A Richards, Una McCann, and Robert Jesse. Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance. *Psychopharmacology*, 187(3):268–283, 2006. doi: 10.1007/s00213-006-0457-5.

Enzo Tagliazucchi, Robin Carhart-Harris, Robert Leech, et al. Enhanced repertoire of brain dynamical states during the psychedelic experience. *Human Brain Mapping*, 35(11):5442–5456, 2014. doi: 10.1002/hbm.22562.

Louis-David Lord, Paul Expert, Selen Atasoy, et al. Dynamical exploration of the repertoire of brain networks at rest is modulated by psilocybin. *Neuroimage*, 199:127–142, 2019. doi: 10.1016/j.neuroimage.2019.05.060.

Sarah A Berry, Mayank C Shah, Naureen Khan, and Bryan L Roth. Rapid agonist-induced internalization of the 5-ht2a receptor. *Molecular Pharmacology*, 52(4):679–686, 1996.

Joshua B Burt, Murat Demirtaş, William J Eckner, et al. Hierarchy of transcriptomic specialization across human cortex captured by structural neuroimaging topography. *Nature Neuroscience*, 21(9):1251–1259, 2018. doi: 10.1038/s41593-018-0195-0.

Jason A Gray, Douglas J Sheffler, et al. Cell-type and region specific effects of serotonin and fluoxetine on gene expression. *Neuropsychopharmacology*, 29:S60, 2004.

David E Nichols. Hallucinogens. *Pharmacology & Therapeutics*, 101(2):131–181, 2004.

Tobias Buchborn, Helmut Schröder, Volker Höllt, and Pradeep G Bhide. Tolerance to lsd-induced changes in brain functional connectivity. *Pharmacology Biochemistry and Behavior*, 138:71–75, 2015.

Roland R Griffiths, William A Richards, Matthew W Johnson, et al. Mystical-type experiences occasioned by psilocybin mediate the attribution of personal meaning and spiritual significance 14 months later. *Journal of Psychopharmacology*, 22(6):621–632, 2008. doi: 10.1177/0269881108094300.

Katherine A MacLean, Matthew W Johnson, and Roland R Griffiths. Mystical experiences occasioned by the hallucinogen psilocybin lead to increases in the personality domain of openness. *Journal of Psychopharmacology*, 25(11):1453–1461, 2011. doi: 10.1177/0269881111420188.

Albert Garcia-Romeu, Roland R Griffiths, and Matthew W Johnson. Psilocybin-occasioned mystical experiences in the treatment of tobacco addiction. *Current Drug Abuse Reviews*, 7 (3):157–164, 2014.

David Erritzoe, Leor Roseman, Matthew M Nour, et al. Long-term personality changes following psilocybin treatment. *Journal of Psychopharmacology*, 32:A22–A23, 2018.

Robin L Carhart-Harris, Leor Roseman, Mark Bolstridge, et al. Psilocybin for treatment-resistant depression: fmri-measured brain mechanisms. *Scientific Reports*, 7(1):13187, 2017. doi: 10.1038/s41598-017-13282-7.

Frederick S Barrett, Manoj K Doss, Nathan D Sepeda, et al. Emotions and brain function are altered up to one month after a single high dose of psilocybin. *Scientific Reports*, 10(1):2214, 2020. doi: 10.1038/s41598-020-59282-y.

Natasha L Mason, Kim PC Kuypers, Florian Müller, et al. Me, myself, bye: regional alterations in glutamate and the experience of ego dissolution with psilocybin. *Neuropsychopharmacology*, 45(12):2003–2011, 2020. doi: 10.1038/s41386-020-0718-8.

Peter J Uhlhaas, Frédéric Roux, Wolf Singer, et al. The development of neural synchrony reflects late maturation and restructuring of functional networks in humans. *Proceedings of the National Academy of Sciences*, 106(24):9866–9871, 2009. doi: 10.1073/pnas.0900390106.

Tomáš Paus. Mapping brain maturation and cognitive development during adolescence. *Trends in Cognitive Sciences*, 9(2):60–68, 2005.

Miao Cao, Jin-Hui Wang, Zhong-Jie Dai, et al. Topological organization of the human brain functional connectome across the lifespan. *Developmental Cognitive Neuroscience*, 7:76–93, 2014.

Kaustubh Supekar, Mark Musen, and Vinod Menon. Development of large-scale functional brain networks in children. *PLoS Biology*, 7(7):e1000157, 2009.

Anthony R McIntosh, Natasa Kovacevic, and Roxane J Itier. The development of a noisy brain. *Archives Italiennes de Biologie*, 148(3):323–337, 2010.

Douglas D Garrett, Natasa Kovacevic, Anthony R McIntosh, and Cheryl L Grady. Age differences in brain signal variability are robust to multiple vascular controls. *Scientific Reports*, 3 (1):2500, 2013a.

Peter R Huttenlocher. Synaptic density in human frontal cortex–developmental changes and effects of aging. *Brain Research*, 163(2):195–205, 1979.

Takao K Hensch. Critical period plasticity in local cortical circuits. *Nature Reviews Neuroscience*, 6(11):877–888, 2005. doi: 10.1038/nrn1787.

Romain Nardou, Edward M Lewis, Anirban Bhattacharyya, et al. Oxytocin-dependent reopening of a social reward learning critical period with mdma. *Nature*, 569(7754):116–120, 2019. doi: 10.1038/s41586-019-1075-9.

Douglas D Garrett, Gregory R Samanez-Larkin, Stuart WS MacDonald, et al. The importance of being variable. *Journal of Neuroscience*, 33(10):4498–4513, 2013b.

Rita Sleimen-Malkoun, Jean-Jacques Temprado, and Seung Lyn Hong. Age-related changes in neural temporal dynamics underlying verbal working memory. *Neuropsychologia*, 97:134–142, 2017.

Adrián Ponce-Alvarez, Biyu J He, et al. Resting-state eeg complexity and aging. *Clinical Neurophysiology*, 126(3):523–531, 2015.

Linda Geerligs, Remco J Renken, Emi Saliasi, Natasha M Maurits, and Monicque M Lorist. A brain-wide study of age-related changes in functional connectivity. *Cerebral Cortex*, 25(7): 1987–1999, 2015.

Gabrielle I Agin-Liebes, Tara Malone, Matthew M Yalch, et al. Psilocybin-assisted therapy for late-life distress: Rationale and pilot data. *The American Journal of Geriatric Psychiatry*, 28(4):S98, 2020.

Ilan Dinstein, David J Heeger, Lauren Lorenzi, et al. Unreliable evoked responses in autism. *Neuron*, 75(6):981–991, 2012. doi: 10.1016/j.neuron.2012.07.026.

Catherine Fassbender, Hao Zhang, Werner M Buzy, et al. A topological analysis of neural function during adhd tasks. *Frontiers in Systems Neuroscience*, 5:62, 2011.

F Xavier Castellanos, Patti P Lee, Wendy Sharp, et al. Developmental trajectories of brain volume abnormalities in children and adolescents with attention-deficit/hyperactivity disorder. *JAMA*, 288(14):1740–1748, 2002.

Roselinde H Kaiser, Jessica R Andrews-Hanna, Tor D Wager, and Diego A Pizzagalli. Large-scale network dysfunction in major depressive disorder: a meta-analysis of resting-state functional connectivity. *JAMA Psychiatry*, 72(6):603–611, 2015. doi: 10.1001/jamapsychiatry.2015.0071.

Diego A Pizzagalli. Computational approaches to major depressive disorder. *Neuron*, 99(3): 592–608, 2018. doi: 10.1016/j.neuron.2018.07.001.

Nora D Volkow, George F Koob, and A Thomas McLellan. Neurobiologic advances from the brain disease model of addiction. *New England Journal of Medicine*, 374(4):363–371, 2016. doi: 10.1056/NEJMra1511480.

Alicia L Danforth, Charles S Grob, Christopher Struble, et al. Mdma-assisted therapy: a new treatment model for social anxiety in autistic adults. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 64:237–249, 2018.

Task Force of the European Society of Cardiology et al. Heart rate variability: standards of measurement, physiological interpretation, and clinical use. *Circulation*, 93(5):1043–1065, 1996.

Julian F Thayer, Fredrik Åhs, Mats Fredrikson, et al. A meta-analysis of heart rate variability and neuroimaging studies: implications for heart rate variability as a marker of stress and health. *Neuroscience & Biobehavioral Reviews*, 36(2):747–756, 2012. doi: 10.1016/j.neubiorev.2011.11.009.

Fred Shaffer and J P Ginsberg. An overview of heart rate variability metrics and norms. *Frontiers in Public Health*, 5:258, 2017.

Robert E Kleiger, J Philip Miller, J Thomas Bigger Jr, and Arthur J Moss. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *The American Journal of Cardiology*, 59(4):256–262, 1987.

Jacqueline M Dekker, Elisabeth G Schouten, Peter Klootwijk, et al. Low heart rate variability in a 2-minute rhythm strip predicts risk of coronary heart disease and mortality from several causes. *Circulation*, 96(6):1557–1562, 1997.

Andrew H Kemp, Daniel S Quintana, Marcus A Gray, et al. The impact of depression and anxiety on heart rate variability in first-episode major depression. *Biological Psychiatry*, 67 (6):536–543, 2010.

John A Chalmers, Daniel S Quintana, Maree J Abbott, and Andrew H Kemp. Anxiety disorders are associated with reduced heart rate variability: a meta-analysis. *Frontiers in Psychiatry*, 5:80, 2014.

Julian F Thayer, Anita L Hansen, Evelyn Saus-Rose, and Bjorn Helge Johnsen. Heart rate variability, prefrontal neural function, and cognitive performance: the neurovisceral integration perspective on self-regulation, adaptation, and health. *Annals of Behavioral Medicine*, 37(2): 141–153, 2009.

Stephen W Porges. The polyvagal perspective. *Biological Psychology*, 74(2):116–143, 2007.

Hugo D Critchley and Sarah N Garfinkel. Interoception and emotion. *Current Opinion in Psychology*, 17:7–14, 2017.

Murray Shanahan. Metastable chimera states in community-structured oscillator networks. *Chaos*, 20(1):013108, 2010.

Christoph M Michel and Thomas Koenig. Eeg microstates as a tool for studying the temporal dynamics of whole-brain neuronal networks: a review. *Neuroimage*, 180:577–593, 2018.

Christoph Bandt and Bernd Pompe. Permutation entropy: a natural complexity measure for time series. *Physical Review Letters*, 88(17):174102, 2002.

Siddhartha Joshi, Yin Li, Rishi M Kalwani, and Joshua I Gold. Pupil size reflects locus coeruleus activity. *BioRxiv*, pages 1–7, 2016.

Ralf Engbert and Reinhold Kliegl. Microsaccades uncover the orientation of covert attention. *Vision Research*, 43(9):1035–1045, 2003.

Alexander Schaefer, Ru Kong, Evan M Gordon, Timothy O Laumann, Xi-Nian Zuo, Avram J Holmes, Simon B Eickhoff, and B T Thomas Yeo. Local-global parcellation of the human cerebral cortex from intrinsic functional connectivity mri. *Cerebral Cortex*, 28(9):3095–3114, 2018. doi: 10.1093/cercor/bhx179.

Matti Hämäläinen, Riitta Hari, Risto J Ilmoniemi, Jukka Knuutila, and Olli V Lounasmaa. Magnetoencephalography—theory, instrumentation, and applications to noninvasive studies of the working human brain. *Reviews of Modern Physics*, 65(2):413–497, 1993. doi: 10.1103/RevModPhys.65.413.

Robert MG Reinhart and John A Nguyen. Working memory revived in older adults by synchronizing rhythmic brain circuits. *Nature Neuroscience*, 22(5):820–827, 2019. doi: 10.1038/s41593-019-0371-x.

Antoine Lutz, Lawrence L Greischar, Nancy B Rawlings, et al. Long-term meditators self-induce high-amplitude gamma synchrony during mental practice. *Proceedings of the National Academy of Sciences*, 101(46):16369–16373, 2004. doi: 10.1073/pnas.0407401101.

Yi-Yuan Tang, Britta K Hölzel, and Michael I Posner. The neuroscience of mindfulness meditation. *Nature Reviews Neuroscience*, 16(4):213–225, 2015. doi: 10.1038/nrn3916.