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Anesthesia via Dissociative Overload: A Unified Theoretical Framework Linking DMT and Ketamine Through Sigma-1 Convergence, Entropic Saturation, and Workspace Flooding

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Abstract

General anesthesia has long been understood as a unitary phenomenon driven by neural suppression — a reduction in cortical activity, entropy, and complexity that renders the brain unable to sustain conscious processing. Yet two structurally and pharmacologically distinct compounds, N,N-Dimethyltryptamine (DMT) and ketamine, produce clinical unresponsiveness while *maintaining or increasing* cortical complexity, a pattern fundamentally incompatible with the suppression paradigm. No existing theoretical framework explains how these orthogonal compounds converge on a common anesthetic mechanism that operates through informational excess rather than deprivation. Here, we propose a novel unified framework for "Anesthesia via Dissociative Overload," arguing that DMT and ketamine achieve unresponsiveness not by silencing neural activity but by saturating cortical information processing beyond the capacity for coherent external-world modeling. The framework integrates three levels of analysis: (1) *molecular convergence* on the Sigma-1 receptor (σ1R) and a prefrontal glutamate surge as shared pharmacological endpoints despite distinct primary targets (5-HT2A vs. NMDA); (2) *entropic saturation*, whereby maintained or elevated neural entropy during unresponsiveness reflects informational overload rather than a monitoring artifact; and (3) *workspace flooding*, in which mass cortical activation overwhelms the Global Neuronal Workspace's serial bottleneck, collapsing the predictive coding hierarchy and preventing coherent broadcasting of external stimuli. This framework proposes a dual taxonomy of anesthesia — Suppressive (GABAergic, entropy-reducing) versus Saturative (glutamatergic/serotonergic, entropy-preserving) — and generates six falsifiable predictions distinguishing the two modes. The Dissociative Overload model reframes general anesthesia as a family of states unified by the failure to model external reality, achievable through either information deprivation or information saturation. While the framework is empirically grounded for ketamine, its extension to DMT-induced anesthesia constitutes a central prediction awaiting direct experimental validation.

Keywords: dissociative anesthesia; N,N-dimethyltryptamine; ketamine; sigma-1 receptor; neural entropy; global neuronal workspace; consciousness

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1. Introduction

General anesthesia is among the most consequential manipulations of consciousness in clinical medicine, yet its mechanistic basis remains incompletely understood. The dominant paradigm frames anesthesia as a process of neural suppression: GABAergic agents such as propofol and sevoflurane potentiate inhibitory neurotransmission, globally reducing cortical firing rates, metabolic activity, and information processing capacity (Franks, 2008; Alkire, Hudetz, & Tononi, 2008). This suppressive framework is supported by convergent evidence from multiple information-theoretic measures. Shannon entropy, permutation entropy, and Lempel-Ziv complexity all decrease dose-dependently under GABAergic anesthetics (Viertiö-Oja et al., 2004; Schartner et al., 2015), and the Perturbational Complexity Index (PCI) — a composite measure of cortical differentiation and integration — reliably falls below the empirically validated consciousness threshold of 0.31 during propofol- and xenon-induced unresponsiveness (Casali et al., 2013; Sarasso et al., 2015). Within this paradigm, the logic of anesthesia is straightforward: reduce the brain's capacity to process information, and consciousness ceases.

Two compounds present a fundamental challenge to this framework. Ketamine, an arylcyclohexylamine that primarily antagonizes NMDA receptors, produces complete clinical unresponsiveness at anesthetic doses — yet PCI remains above 0.31, comparable to the waking state, throughout the period of unresponsiveness (Sarasso et al., 2015). Subjects emerge reporting vivid, immersive, dream-like experiences. N,N-Dimethyltryptamine (DMT), a substituted tryptamine that primarily agonizes serotonin 5-HT2A receptors, increases Lempel-Ziv complexity, signal diversity, and broadband spectral entropy relative to wakefulness at sub-anesthetic doses (Timmermann et al., 2019; Schartner et al., 2017), with preliminary evidence suggesting that high doses produce behavioral unresponsiveness accompanied by sustained cortical activation (Timmermann et al., 2023). These findings constitute what we term the *Complexity Paradox*: the coexistence of high neural complexity — at levels that, by established indices, indicate consciousness — with clinical unresponsiveness that meets the operational definition of general anesthesia.

The Complexity Paradox is not merely an anomaly of monitoring; it signals a fundamentally different route to clinical unresponsiveness. Under the suppression paradigm, anesthesia requires the brain to process *too little* information. Under ketamine and DMT, the brain appears to process *too much*. Cortical entropy is preserved or increased, near-critical dynamics are maintained (Luppi et al., 2023), and internally generated activity continues at high levels. The critical question, then, is not whether these compounds produce "real" anesthesia — they demonstrably do, by every behavioral criterion — but *how* unresponsiveness is achieved when the cortex remains maximally active.

Existing theoretical frameworks approach this question from different angles but leave the central mechanism unspecified. Gallimore (2015) speculated that high-entropy states under psychedelics might reduce integrated information (Φ) in Tononi's Integrated Information Theory, potentially producing unconsciousness, but did not propose a specific computational mechanism, did not include ketamine, and predated the critical PCI evidence from Sarasso et al. (2015). The Entropic Brain Hypothesis (Carhart-Harris, 2014; Carhart-Harris, 2018) positioned psychedelic states on an entropy continuum and acknowledged an upper bound beyond which

conscious content becomes disorganized, but did not take the explicit step of linking entropy excess to anesthesia. The REBUS model (Carhart-Harris & Friston, 2019) elegantly formalized psychedelic phenomenology through relaxed precision weighting in a predictive coding framework, but was developed for sub-anesthetic doses and does not address the transition to complete unresponsiveness. Aleksandrova and Phillips (2021) recognized pharmacological convergences between ketamine and serotonergic psychedelics, but framed their analysis around antidepressant mechanisms rather than anesthesia. The concept of "disconnected consciousness" (Sanders, Tononi, Laureys, & Sleigh, 2012) accurately *describes* the ketamine anesthetic state — consciousness present but disconnected from external reality — but does not *explain* the mechanism of disconnection.

A unified theoretical framework is therefore missing: one that explains how two structurally and pharmacologically orthogonal compounds — DMT, a tryptamine acting at 5-HT2A, and ketamine, an arylcyclohexylamine acting at NMDA receptors — converge on a common anesthetic mechanism that operates through informational excess rather than deprivation.

The present paper proposes a novel framework: *Anesthesia via Dissociative Overload*. We argue that DMT and ketamine produce clinical unresponsiveness not by silencing the cortex but by saturating cortical information processing beyond the capacity for coherent external-world modeling. The framework integrates three levels of analysis:

Level 1 — Molecular Convergence (Section 2). Despite their structural orthogonality and non-overlapping primary receptor targets, DMT and ketamine converge on two shared pharmacological endpoints: the Sigma-1 receptor (σ1R) and a massive prefrontal cortex glutamate surge. DMT achieves the glutamate surge via direct pyramidal excitation through 5-HT2A; ketamine achieves it via disinhibition of pyramidal neurons through NMDA blockade on GABAergic interneurons. Concurrent σ1R activation provides neuroprotection that renders the resulting high-excitation state sustainable. Crucially, we reframe the glutamate surge — previously discussed only as the basis of rapid antidepressant effects — as the molecular trigger for a non-suppressive anesthetic mechanism.

Level 2 — Entropic Saturation (Section 3). The convergent glutamate surge maintains or increases cortical entropy during unresponsiveness, producing the Complexity Paradox. We formalize a dual taxonomy of anesthesia: *Suppressive Anesthesia* (GABAergic, entropy-reducing, PCI < 0.31) versus *Saturative Anesthesia* (glutamatergic/serotonergic, entropy-preserving or entropy-increasing, PCI ≥ 0.31) — the latter naming the mechanism category that this framework is invoked to explain, as formalized in Section 3.4. The high entropy is not a monitoring artifact but the signature of an informationally saturated cortex in which the signal-to-noise ratio for external stimuli approaches zero.

Level 3 — Workspace Flooding (Section 4). At the computational level, the glutamate-driven mass cortical activation overwhelms the Global Neuronal Workspace's (GNW) serial winner-take-all bottleneck (Dehaene & Changeux, 2011; Mashour et al., 2020). When all representations simultaneously exceed the ignition threshold, no single representation achieves exclusive broadcasting — the workspace is flooded rather than silenced. Simultaneously, the predictive coding hierarchy collapses: DMT overloads the system from

the bottom up (an extension of REBUS to anesthetic doses), while ketamine disconnects top-down predictions and disinhibits feedforward signaling. The result is a brain that is too full for coherent external-world modeling, not too empty.

This framework proposes that general anesthesia is not a unitary phenomenon defined by neural suppression but a family of states in which the brain fails to model external reality — achievable through either information deprivation (Suppressive) or information saturation (Saturative). The two routes produce opposite neurophysiological signatures but converge on the same clinical endpoint: unresponsiveness to external stimuli. We generate six falsifiable predictions (Section 4, Table 3) that distinguish the Dissociative Overload model from the suppression paradigm, and we discuss implications for anesthetic monitoring, consciousness science, and future empirical research (Section 5).

2. Molecular Convergence — Glutamate Surge and Sigma-1 Modulation

2.1 Structural Orthogonality and Primary Targets

DMT and ketamine belong to entirely distinct chemical families. DMT (N,N-Dimethyltryptamine; $C_{12}H_{16}N_2$; MW 188.27) is a substituted indole tryptamine — a planar, bicyclic aromatic system with an ethylamine side chain bearing two methyl groups on the terminal nitrogen. It is biosynthesized endogenously from tryptophan via aromatic L-amino acid decarboxylase (AADC) and indolethylamine-N-methyltransferase (INMT) (Cozzi et al., 2011), and its structural core — the indole ring — is shared with serotonin, melatonin, and psilocybin (Barker, 2018). Ketamine ($C_{13}H_{16}ClNO$; MW 237.73) is a 2-(2-chlorophenyl)-2-(methylamino)cyclohexanone — an arylcyclohexylamine with a chiral center yielding S(+) and R(−) enantiomers, entirely synthetic and derived from phencyclidine (PCP) structure-activity optimization. The chlorinated phenyl ring and cyclohexanone core share no structural motif with the indole scaffold.

Despite this structural orthogonality, both compounds share two physicochemical properties relevant to their rapid CNS onset: high lipophilicity enabling rapid blood-brain barrier penetration (DMT: LogP ≈ 1.7; Ketamine: LogP ≈ 2.18), and a protonatable basic nitrogen (DMT: pKa ≈ 8.68; Ketamine: pKa ≈ 7.5) enabling both membrane permeability in free-base form and water solubility when protonated. Both reach peak brain concentrations within seconds to minutes of intravenous administration.

Their primary receptor targets are entirely non-overlapping. DMT acts as a high-affinity agonist at the serotonin 5-HT2A receptor (Ki = 127–462 nM; Keiser et al., 2009; Ray, 2010), with additional activity at 5-HT2C (Ki = 334–424 nM) and 5-HT1A (Ki ≈ 1,300 nM; McKenna, Repke, Lo, & Peroutka, 1990). Ketamine has no significant serotonergic binding. Conversely, ketamine acts as an uncompetitive NMDA receptor antagonist at the phencyclidine site (Ki = 300 nM for S-ketamine; Ki = 1,400 nM for R-ketamine; rat cortex, [^{3}H]MK-801 displacement; Ebert et al., 1997), while DMT has no significant glutamatergic receptor binding. Table 1 presents a comprehensive comparative receptor binding profile.

Table 1. Comparative Receptor Binding Profiles of DMT and Ketamine. Convergence rows (highlighted) indicate shared pharmacological endpoints. Reported affinities vary with species, tissue preparation, and radioligand, so values drawn from different assays are not strictly interchangeable. Sources: Fontanilla et al. (2009); Keiser et al. (2009); Ray (2010); McKenna et al. (1990); Ebert et al. (1997); Robson et al. (2012); Hustveit et al. (1995); Bunzow et al. (2001); Cozzi et al. (2009); Hirota et al. (1999); Aghajanian & Marek (1999); Moghaddam et al. (1997); Ly et al. (2018); Li et al. (2010).

Receptor/Target	DMT	Ketamine	Convergence?
5-HT2A	Ki = 127–462 nM (agonist)	No significant binding	No — DMT-specific
5-HT2C	Ki = 334–424 nM (agonist)	No significant binding	No
5-HT1A	Ki ≈ 1,300 nM (agonist)	No significant binding	No
NMDA (PCP site)	No significant binding	Ki = 300 nM (S-ket); 1,400 nM (R-ket)	No — Ketamine-specific
σ1R (Sigma-1)	Kd = 14,750 nM (agonist)	Ki ≈ 27,000 nM (R-ket); 131,000 nM (S-ket)	**Yes — Convergence**
σ2R (Sigma-2)	Not established	Ki = 26,300 nM	Unclear
TAAR1	EC_{50} ≈ 1,480 nM (agonist)	No established interaction	No — DMT-specific
SERT	Ki = 4,240 nM (substrate)	Weak at supratherapeutic doses	Marginal
VMAT2	Ki = 93,000 nM (substrate)	No established interaction	No — DMT-specific
HCN1 channels	Not established	IC_{50} = 8,500 nM	No — Ketamine-specific
Opioid (μ, κ)	Not significant	μ: Ki ≈ 28,600 nM; κ: Ki ≈ 28,200 nM	No — Ketamine-specific
PFC glutamate release	Yes — via 5-HT2A on Layer V pyramidal neurons	Yes — via NMDA blockade on GABAergic interneurons	**Yes — Convergence**
BDNF-TrkB-mTOR	Yes — via glutamate → AMPA → BDNF	Yes — via glutamate → AMPA → BDNF	**Yes — Convergence**

As Table 1 makes clear, the primary targets of DMT and ketamine are entirely non-overlapping. Convergence occurs at three points: (1) the Sigma-1 receptor, representing direct molecular convergence on a shared protein target; (2) prefrontal cortex glutamate release, representing circuit-level convergence via distinct upstream mechanisms; and (3) the downstream BDNF-TrkB-mTOR neuroplasticity cascade, representing signaling convergence. Of these, the glutamate surge is the primary mechanistic driver of the Dissociative Overload framework, while the σ1R interaction serves as a supporting convergence that enables neuroprotection during the resulting high-excitation state.

2.2 The Sigma-1 Receptor: Biology and Convergence

The Sigma-1 receptor (σ1R, gene *SIGMAR1*) is a 223-amino-acid, single-transmembrane-pass protein resident primarily at the mitochondria-associated endoplasmic reticulum membrane (MAM) — the specialized contact zone between the ER and the outer mitochondrial membrane. Crystallographic studies reveal that σ1R forms a trimeric complex, with each protomer containing a single transmembrane domain, a short N-terminal luminal segment, and a large C-terminal domain facing the ER lumen (Schmidt et al., 2016).

The canonical σ1R signaling cascade, established by Hayashi and Su (2007), proceeds through four stages. In the resting state, σ1R is bound to the ER chaperone BiP/GRP78 in an inactive complex at the MAM. Upon ligand activation — or upon ER calcium depletion — agonist binding causes σ1R to dissociate from BiP. The freed σ1R then chaperones the inositol 1,4,5-trisphosphate receptor type 3 (IP3R3) at the MAM, stabilizing IP3R3 against proteasomal degradation and ensuring sustained ER-to-mitochondrial Ca^{2+} transfer. Prolonged mitochondrial Ca^{2+} uptake enhances TCA cycle activity and ATP production. Under stress conditions, σ1R translocates throughout the ER reticular network and to the plasma membrane, where it modulates a diverse array of ion channels and receptors, including voltage-gated Na^{+} and K^{+} channels, NMDA receptors, L-type Ca^{2+} channels, and TrkB receptors (Hayashi & Su, 2007). The neuroprotective dimension of σ1R signaling — attenuation of ER stress responses, reduction of oxidative stress, and inhibition of apoptotic cascades — is well established, with σ1R knockout mice showing exacerbated neurodegeneration under ischemic stress.

DMT engages σ1R as a direct agonist. Fontanilla et al. (2009) demonstrated that DMT binds σ1R with Kd = 14.75 μM using [^{3}H](+)-pentazocine displacement, and that in σ1R knockout mice, DMT-specific behavioral effects (hyperlocomotion) were abolished while methamphetamine-induced effects were preserved — confirming σ1R-specificity. The neuroprotective arm of DMT's σ1R interaction has been independently validated: DMT increased survival of human iPSC-derived cortical neurons under severe hypoxia via σ1R, an effect abolished by σ1R siRNA (Szabo et al., 2016), and attenuated spreading depolarization and neurodegeneration in the ischemic rat brain, reversible by the σ1R antagonist NE-100 (Szabó et al., 2021).

Ketamine's σ1R interaction is enantioselective. R(−)-ketamine has approximately 5-fold higher σ1R affinity (Ki ≈ 27 μM) than S(+)-ketamine (Ki ≈ 131 μM; Hustveit, Maurset, & Øye, 1995; Robson, Elliott, Seminerio, & Matsumoto, 2012). This enantiomeric selectivity is pharmacologically significant: R-ketamine shows superior sustained antidepressant effects in rodent models despite weaker NMDA binding, leading multiple groups to propose σ1R as a key mediator of R-ketamine's distinct profile. Ma et al. (2024) provided mechanistic evidence: the σ1R antagonist BD1047 significantly weakened ketamine-induced restoration of medial prefrontal cortex pyramidal neurons, while the σ1R agonist SA4503 enhanced ketamine's sustained antidepressant effect through a σ1R → BDNF → TrkB-mTOR pathway.

Despite distinct modes of σ1R engagement and differing affinities, both DMT and ketamine activate the same downstream cascade: σ1R dissociation from BiP → IP3R3 stabilization → enhanced ER-mitochondrial Ca^{2+} transfer → BDNF-TrkB-mTOR signaling. This convergence has been recognized exclusively in the context of antidepressant mechanisms (Kadriu et al., 2019; Aleksandrova & Phillips, 2021). It has never been discussed in the context of anesthesia. We propose that σ1R serves a dual role in the Dissociative Overload framework: it contributes to the neuroplastic and neuroprotective signature that distinguishes these compounds from neurotoxic excitotoxicity, and it may facilitate the shift from integrative to self-oscillatory neuronal firing modes by modulating ion channel conductances at the plasma membrane during the high-σ1R-occupation states achieved at anesthetic doses.

An important affinity caveat must be acknowledged. DMT's σ1R affinity (Kd ≈ 15 μM) is approximately 100-fold weaker than its 5-HT2A affinity (Ki ≈ 130–460 nM). At typical

psychedelic doses, systemic plasma concentrations likely favor 5-HT2A engagement. However, two factors may enable physiologically relevant σ1R activation: DMT is actively transported into synaptic vesicles via VMAT2 (Cozzi et al., 2009), potentially achieving locally high perisynaptic concentrations; and under stress conditions, σ1R expression is upregulated, rendering the receptor more responsive to low-affinity ligands. We note this caveat explicitly: σ1R engagement by DMT at psychoactive doses remains plausible but not definitively proven.

2.3 The Glutamate Surge as Final Common Pathway

The most robust point of pharmacological convergence between DMT and ketamine is not at a single receptor but at a circuit-level outcome: both compounds trigger a massive, rapid release of glutamate in the prefrontal cortex, particularly in deep cortical layers. The pathways to this common endpoint are mechanistically distinct but converge on the same cell population — Layer V pyramidal neurons.

DMT achieves the glutamate surge through direct pyramidal excitation. 5-HT2A receptors are densely expressed on apical dendrites of Layer V pyramidal neurons in the PFC (Jakab & Goldman-Rakic, 1998). DMT binding at 5-HT2A activates Gq/11-coupled intracellular signaling, increasing pyramidal cell excitability and firing rate. Aghajanian and Marek (1999) demonstrated that serotonergic psychedelics increase spontaneous excitatory postsynaptic currents (EPSCs) in Layer V pyramidal neurons, an effect blocked by the 5-HT2A antagonist MDL-100,907.

Ketamine achieves the glutamate surge through interneuron disinhibition. NMDA receptors on fast-spiking GABAergic interneurons — particularly parvalbumin-positive basket cells — are preferentially blocked by ketamine because these interneurons maintain a relatively depolarized resting membrane potential that relieves the Mg^{2+} block, rendering their NMDA receptors tonically active (Homayoun & Moghaddam, 2007). Blocking these receptors reduces GABAergic inhibition onto pyramidal neurons, producing disinhibition that increases pyramidal firing and glutamate release. Moghaddam, Adams, Verma, and Daly (1997) demonstrated a sustained approximately 3-fold increase in PFC extracellular glutamate following subanesthetic ketamine in freely moving rats. At anesthetic doses, the glutamate surge is larger and involves broader cortical regions.

Existing literature has interpreted this convergent glutamate surge exclusively through a therapeutic lens. Aleksandrova and Phillips (2021) describe glutamate → AMPA receptor activation → BDNF release → TrkB-mTOR → synaptic plasticity as the shared mechanism underlying rapid antidepressant effects. Ly et al. (2018) extended this by demonstrating that psychedelics and ketamine promote dendritic arbor complexity, spinogenesis, and synaptogenesis through this pathway. We propose a novel reframing: the same glutamate surge that mediates neuroplasticity at sub-anesthetic doses also mediates anesthesia at higher doses — through informational saturation of cortical circuits. At sub-anesthetic concentrations, the glutamate surge is moderate and spatially constrained, enhancing signal-to-noise ratio and promoting adaptive plasticity. At anesthetic concentrations, the surge becomes overwhelming and spatially diffuse, collapsing the signal-to-noise ratio toward zero and rendering the cortex incapable of encoding coherent representations of external stimuli. The dose-response

relationship is therefore not linear but biphasic: moderate glutamate enhancement produces therapeutic effects; excessive glutamate flooding produces anesthesia. Although exact dose-response curves remain to be established, the qualitative shape of the transition can be characterized as follows. In the lower regime, the glutamate surge is regionally circumscribed and recruits a manageable population of pyramidal neurons, leaving the workspace selection process intact and producing the plasticity, antidepressant, and dissociative-experiential effects familiar from clinical and recreational use. As dose increases, the surge expands in both spatial extent and temporal density, progressively saturating workspace capacity until lateral inhibition can no longer enforce winner-take-all selection. Whether this transition is gradual or threshold-like is not settled by the present evidence. The framework anticipates a nonlinear, threshold-like transition, reflecting the all-or-nothing character of GNW ignition dynamics; this expectation is advanced not as an established finding but as a prediction formalized as P5 (Section 4.7, Table 3). The dose range over which the transition occurs likewise remains undetermined (Section 5.5, Fifth).

This reframing inverts the existing narrative: the glutamate surge is not a side effect to be managed during anesthesia but *is* the anesthetic mechanism for this compound class. The molecular-level contrast with traditional GABAergic anesthetics is stark. GABAergic agents potentiate $GABA_A$ receptor-mediated chloride currents, hyperpolarizing neurons and reducing firing rates, metabolic demand, and information processing capacity. The suppressive molecular route — enhanced inhibition → reduced firing → reduced glutamate → reduced cortical entropy — is the mirror image of the saturative molecular route — enhanced excitation → increased firing → increased glutamate → maintained or increased cortical entropy. This distinction at the molecular level provides the foundation for the dual taxonomy of anesthesia developed in Section 3. See Figure 1 below.

2.4 σ1R-Mediated Neuroprotection During High-Excitation States

A critical question arises from the preceding analysis: if DMT and ketamine produce massive glutamate surges, why do they not cause excitotoxic neuronal death? Pathological glutamate surges — such as those occurring during ischemic stroke or status epilepticus — produce calcium overload, mitochondrial dysfunction, and neuronal death through well-characterized excitotoxic cascades (Choi, 1988). The glutamate surges produced by DMT and ketamine, while potentially comparable in magnitude within the PFC, do not produce excitotoxicity in healthy individuals.

We propose that concurrent σ1R activation provides a critical component of this neuroprotective difference. The σ1R-mediated cascade — stabilization of IP3R3 at the MAM, enhanced mitochondrial Ca^{2+} buffering capacity, attenuation of ER stress through the IRE1-XBP1 and PERK-eIF2α arms of the unfolded protein response, and anti-apoptotic signaling — acts as a built-in safety mechanism that enables the brain to sustain high-excitation states without cellular damage. This is consistent with direct evidence: DMT protects neurons against hypoxic death via σ1R (Szabo et al., 2016; Szabó et al., 2021; Nardai et al., 2020), and σ1R knockout exacerbates neurodegeneration under excitotoxic stress.

This dual role of σ1R — contributing to both the pharmacological state-switch and the neuroprotective shield during high-excitation states — constitutes a key element of the Dissociative Overload framework. Without σ1R-mediated neuroprotection, the high-entropy cortical state would be self-terminating through excitotoxic damage. With it, the brain can sustain a flooded, internally active, externally disconnected state for the duration of drug action. This distinguishes Saturative Anesthesia from pathological excitotoxicity and explains its clinical safety profile.

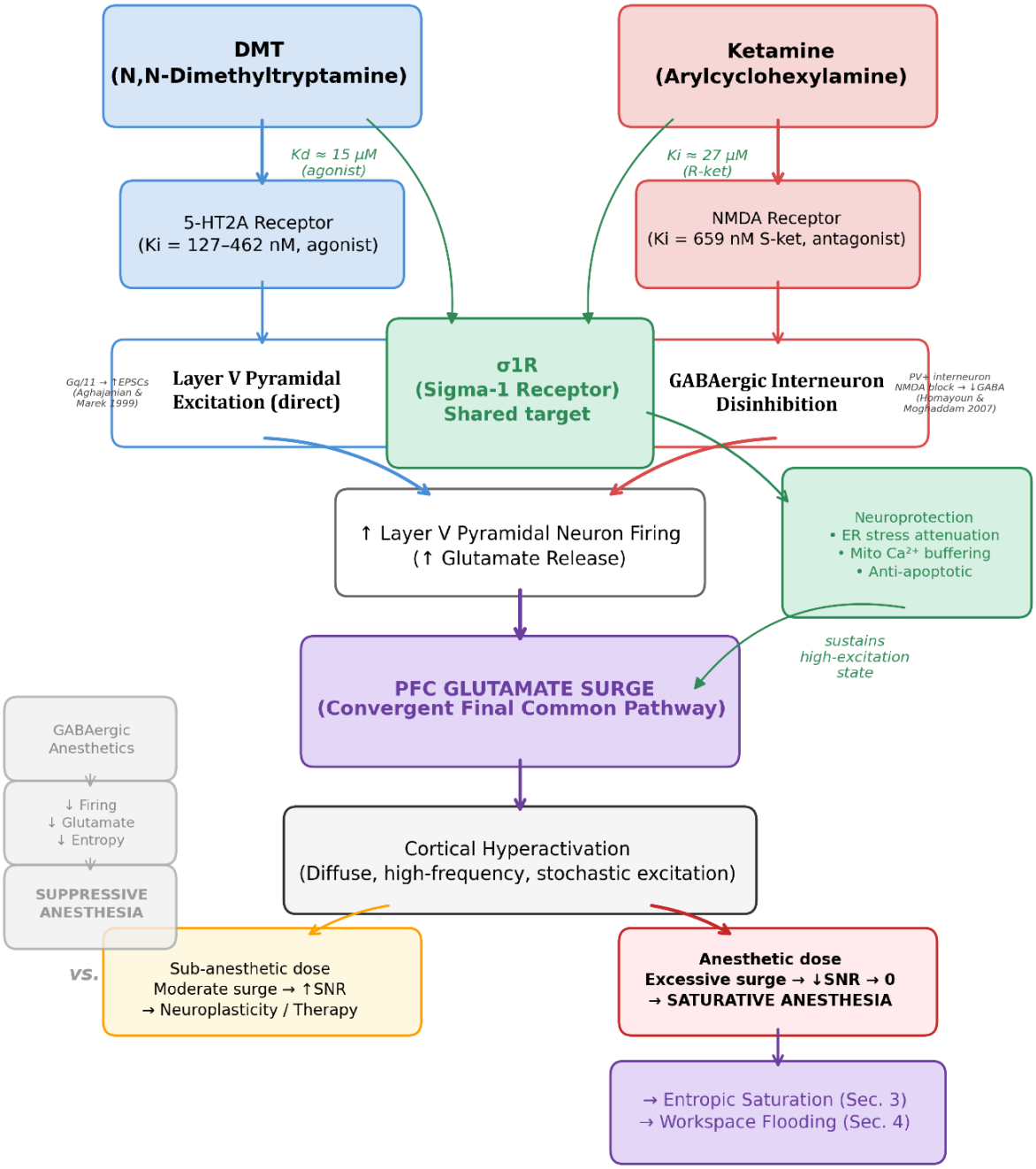


Figure 1. Convergent molecular pathways leading to prefrontal glutamate surge under DMT and ketamine. Left arrow: DMT binds 5-HT2A receptors on Layer V pyramidal neurons, directly exciting pyramidal cells and increasing glutamate release. Right arrow: Ketamine blocks NMDA receptors on GABAergic interneurons,

disinhibiting pyramidal neurons and increasing glutamate release. Both pathways converge on a common PFC glutamate surge. The Sigma-1 receptor (σ1R), engaged by both compounds, provides concurrent neuroprotection via ER stress attenuation and mitochondrial Ca^{2+} buffering, rendering the high-excitation state sustainable.

3. Entropic Saturation — The Information-Theoretic Evidence

3.1 Information-Theoretic Measures of Brain State

The claim that DMT and ketamine defy the standard anesthetic pattern requires first establishing what that standard pattern is. Multiple information-theoretic measures have been applied to characterize brain states during anesthesia, each capturing a different dimension of cortical information processing.

Shannon entropy, computed over the EEG power spectral density as $H = -\Sigma\, p(f) \log_2 p(f)$, quantifies the uniformity of frequency distribution: a flat (white noise) spectrum has maximal H, while a spectrum dominated by a single frequency has minimal H. Commercial anesthesia monitors, such as GE Healthcare's M-Entropy module, compute two operational variants — State Entropy (SE, 0.8–32 Hz) and Response Entropy (RE, 0.8–47 Hz) — that serve as real-time indices of anesthetic depth (Viertiö-Oja et al., 2004). Permutation entropy (PE) quantifies the complexity of ordinal patterns in a time series, converting successive windows of data points into rank-order permutations and computing the entropy of their distribution; PE is robust to noise and has been validated as a consciousness index (Jordan et al., 2008). Lempel-Ziv complexity (LZc) measures the algorithmic compressibility of a binarized signal: a signal with many distinct sub-patterns is "complex" (high LZc), while a repetitive signal is "simple" (low LZc). LZc has been extensively validated as a neural correlate of consciousness across wakefulness, sleep, anesthesia, and disorders of consciousness (Schartner, Seth, Noirhomme, Boly, & Bruno, 2015; Schartner et al., 2017).

The most integrative measure is the Perturbational Complexity Index (PCI), developed by Casali, Gosseries, Rosanova, Boly, and Massimini (2013). PCI measures the spatiotemporal complexity of the brain's response to a transcranial magnetic stimulation (TMS) perturbation, capturing both the differentiation (complexity of the evoked response) and integration (spatial extent of propagation) of cortical processing. A validated empirical cutoff of $PCI^* = 0.31$ reliably distinguishes conscious from unconscious states across wakefulness, locked-in syndrome, minimally conscious state, vegetative state, NREM sleep, and multiple pharmacological anesthetics (Casali et al., 2013; Comolatti et al., 2019). PCI is the only available index that operationalizes both dimensions of Tononi's Integrated Information Theory and is therefore the primary measure against which we evaluate the Complexity Paradox.

3.2 The Suppression Signature Under GABAergic Agents

Under propofol, sevoflurane, isoflurane, and other GABAergic anesthetics, all of the above measures decrease dose-dependently, forming a consistent neurophysiological signature of unconsciousness.

Under propofol, Shannon entropy decreases from approximately 90 (awake) to 30–40 (deep anesthesia) on commercial monitors (Viertiö-Oja et al., 2004). Lempel-Ziv complexity decreases

significantly from wakefulness to propofol-induced unconsciousness in both human EEG (Schartner et al., 2015) and animal models (Zhang et al., 2001). TMS-evoked responses become local, low-amplitude, and rapidly fading, and PCI drops well below 0.31 (Casali et al., 2013; Sarasso et al., 2015; Massimini et al., 2005). Under sevoflurane and isoflurane, permutation entropy decreases dose-dependently (Olofsen, Sleigh, & Dahan, 2008), and multidimensional EEG complexity measures show analogous reductions (Hudetz, Liu, & Pillay, 2015). Even xenon, a noble gas anesthetic that acts primarily through NMDA antagonism at moderate concentrations, produces PCI below 0.31 — though via a distinct mechanism: xenon evokes high-amplitude, globally spreading but stereotypical (low-complexity) responses, reflecting "integration without differentiation" (Sarasso et al., 2015).

We define *Suppressive Anesthesia* as the mechanism by which clinical unresponsiveness is achieved through global reduction of cortical information processing capacity, characterized by decreased Shannon and permutation entropy, decreased Lempel-Ziv complexity, PCI below 0.31, reduced cerebral metabolic rate, and dominant molecular action through GABAA receptor potentiation or moderate NMDA antagonism. This is the orthodox paradigm. The following subsection shows that DMT and ketamine violate every element of this definition.

3.3 The Complexity Paradox: Ketamine and DMT Defy the Pattern

The single most important empirical finding for the Dissociative Overload framework comes from Sarasso et al. (2015). In a within-subject design, healthy volunteers were rendered completely unresponsive (Ramsay Sedation Scale score 6: no response to light glabellar tap or loud auditory stimulus) under three anesthetic agents: propofol (n = 6), xenon (n = 6), and ketamine (n = 6). TMS-evoked EEG responses were recorded and PCI was computed for each condition.

Under propofol, TMS evoked local, low-amplitude, rapidly fading responses; PCI dropped well below 0.31. No subjects reported experiences upon emergence. Under xenon, TMS evoked high-amplitude, globally spreading but stereotypical responses; PCI again fell below 0.31. No subjects reported experiences. Under ketamine, TMS evoked complex, differentiated spatiotemporal activation patterns that propagated widely across the cortex; PCI remained above 0.31 — comparable to wakefulness — despite complete behavioral unresponsiveness. All six ketamine subjects reported vivid, narrative, dream-like experiences upon awakening. This dissociation between preserved cortical complexity and absent behavioral responsiveness constitutes what we have termed the Complexity Paradox.

Subsequent studies have reinforced this finding. Li and Mashour (2019) demonstrated that in rats receiving anesthetic-dose ketamine, cortical complexity initially alternated between suppression-like and high-complexity states before stabilizing at a complexity level comparable to wakefulness — in sharp contrast to propofol, which produced monotonically decreasing complexity. Brito, Li, Mashour, and Pal (2020) revealed a bandwidth-dependent nuance: ketamine reduces complexity in the high-gamma range (> 55 Hz) while preserving it in the standard clinical bandwidth (0.5–55 Hz), the frequency range captured by PCI-TMS methodology. Luppi et al. (2023) extended criticality analysis to the Sarasso dataset, showing that ketamine maintained near-critical dynamics — proximity to the phase transition between

order and disorder where information processing capacity is maximal — while propofol and xenon drove the brain away from criticality.

DMT provides complementary evidence from sub-anesthetic doses. Timmermann et al. (2019) reported significant increases in Lempel-Ziv complexity across posterior EEG channels in healthy volunteers receiving IV DMT, with the complexity increase correlating with self-reported experiential intensity. Timmermann et al. (2023) confirmed and extended these findings using simultaneous EEG-fMRI during extended IV DMT infusion: widespread increases in LZc of both EEG and fMRI signals, global increases in functional connectivity and network desegregation, compression of the principal cortical gradient (a marker of hierarchical collapse), and the highest signal diversity values yet recorded in healthy human volunteers during pharmacological perturbation.

A critical gap must be noted: formal EEG-TMS studies during DMT-induced complete unresponsiveness at "breakthrough" doses ($\geq$ 0.4 mg/kg IV) have not yet been conducted. However, the trajectory of the evidence — increasing complexity with increasing dose at sub-anesthetic levels, phenomenological overlap between DMT "breakthrough" and the ketamine "k-hole," and the shared molecular substrate described in Section 2 — supports the prediction that DMT at anesthetic-equivalent doses will produce PCI $\geq$ 0.31, replicating the Complexity Paradox documented for ketamine. This prediction, if confirmed, would provide the strongest evidence for Saturative Anesthesia as a general mechanism; if refuted, it would limit the framework to ketamine-class agents. It constitutes the most critical testable prediction of the Dissociative Overload framework (Prediction P1, Section 4).

3.4 The Dual Taxonomy: Suppressive Versus Saturative Anesthesia

The Complexity Paradox demands a reconceptualization of general anesthesia. If unresponsiveness can coexist with PCI above the consciousness threshold, then anesthesia cannot be defined solely as the suppression of cortical information processing. We propose instead that general anesthesia is a family of states in which the brain fails to model external reality, achievable through two fundamentally distinct routes.

Suppressive Anesthesia achieves this failure through information deprivation: GABAergic inhibition reduces cortical firing, glutamate signaling, and entropy below the levels required for any coherent representation — internal or external — to form. The workspace is silenced. The brain is too quiet. *Saturative Anesthesia* achieves this failure through information overload: glutamatergic excitation floods the cortex with stochastic, internally generated activity that overwhelms the brain's capacity to selectively process external stimuli. The workspace is flooded. The brain is too loud. Table 2 formalizes this distinction across thirteen neurophysiological and clinical features. A note on terminology is warranted at this point: throughout this paper, "Dissociative Overload" refers to the unified three-level framework as a whole (molecular convergence + entropic saturation + workspace flooding), while "Saturative Anesthesia" designates the specific mechanism category — the clinical-physiological state-class contrasted with Suppressive Anesthesia — that the framework is invoked to explain. The framework is therefore the explanatory apparatus; the clinical-physiological state that the mechanism category picks out is its explanandum. Three further terms recur throughout and

should be kept distinct by level of analysis. “Entropic saturation” denotes the information-theoretic signature — maintained or elevated entropy and complexity measures during unresponsiveness — and is therefore what is measured. “Workspace flooding” denotes the computational mechanism proposed to produce that signature — simultaneous supra-threshold activation defeating winner-take-all selection, developed in Section 4. “Informational saturation” denotes the functional consequence common to both levels: the signal-to-noise ratio for external stimuli approaching zero. The first is the observation, the second the proposed cause, and the third the condition the subject undergoes.

Table 2. Dual Taxonomy of Anesthesia — Suppressive Versus Saturative. Highlighted rows indicate the key entropy/complexity measures that distinguish the two modes. Sources: Integrated from Sarasso et al. (2015); Casali et al. (2013); Timmermann et al. (2019, 2023); Li & Mashour (2019); Luppi et al. (2023); Van Maldegem et al. (2025); Vohryzek et al. (2025); Hayashi & Su (2007); Fontanilla et al. (2009).

Feature	Suppressive Anesthesia	Saturative Anesthesia
Molecular target(s)	$GABA_a$ potentiation; moderate NMDA antagonism (xenon, N_2O)	5-HT2A agonism (DMT); strong NMDA antagonism (ketamine); σ1R modulation (both)
Effect on glutamate	Decreased release	Increased release (PFC surge)
Shannon/Permutation Entropy	Decreased	Maintained or increased
Lempel-Ziv Complexity	Decreased	Maintained or increased
PCI (TMS-evoked)	< 0.31 (below consciousness threshold)	≥ 0.31 (at or above consciousness threshold)
Connectome harmonics	Shifted to low-frequency (structure-locked)	Shifted to high-frequency (structure-liberated)
Criticality	Driven away from critical point	Maintained near critical point
Cerebral metabolic rate	Decreased (CMRglc ↓, $CMRO_2$ ↓)	Maintained or regionally increased
Thalamocortical dynamics	Disrupted (silenced relay)	Reconfigured (jammed or overridden relay)
Subjective reports post-emergence	None (amnesia, no experiences)	Vivid internal experiences (dreams, visions)
Proposed mechanism	Information deprivation → workspace silencing	Information saturation → workspace flooding
Prototype agents	Propofol, sevoflurane, isoflurane	Ketamine (high-dose), DMT (breakthrough dose)
σ1R involvement	Minimal	Significant (both ketamine and DMT engage σ1R)

The dual taxonomy has direct clinical implications. Current depth-of-anesthesia monitors (BIS, M-Entropy, state entropy) are calibrated to the suppressive paradigm — they equate low entropy with deep anesthesia and high entropy with wakefulness. Under ketamine, these monitors indicate “light” or “inadequate” anesthesia even when the patient is profoundly unresponsive, precisely because the saturative mechanism produces opposite entropy signatures. Awareness of this dual taxonomy is therefore essential for accurate anesthetic monitoring in clinical settings where ketamine is used as a primary anesthetic agent.

3.5 From Paradox to Mechanism: Entropy as the Overload Index

The Entropic Brain Hypothesis (Carhart-Harris, 2014; Carhart-Harris, 2018) provides the theoretical scaffolding for interpreting the entropic evidence within the Dissociative Overload framework. The original formulation positioned consciousness on a spectrum from low-entropy states (deep sleep, anesthesia, coma) through normal waking consciousness (moderate, constrained entropy) to high-entropy states (psychedelic experience). Normal waking consciousness was situated not at the top of the entropy spectrum but as a sub-critical state, ordered below the maximum entropy attainable by the brain.

The 2018 revision introduced a critical refinement: the acknowledgment that consciousness exists within both upper and lower bounds. Below a lower bound (excessive order), consciousness is lost — this corresponds to Suppressive Anesthesia. Above an upper bound (excessive disorder), conscious content becomes disorganized: individual experiences feel overwhelming, ego boundaries collapse, and the sense of self as a bounded entity dissolves. Carhart-Harris, however, stopped short of making the explicit connection that we propose here: that crossing the upper entropy bound not only alters the *quality* of consciousness but can extinguish the capacity for *external* consciousness entirely — producing a state that is clinically indistinguishable from anesthesia. This is the conceptual step that transforms the Entropic Brain Hypothesis from a theory of psychedelic experience into a theory of a new class of anesthesia.

Combining the molecular evidence from Section 2 with the entropic evidence presented here, the causal chain of Saturative Anesthesia can be articulated in full. The molecular trigger — DMT via 5-HT2A or ketamine via NMDA blockade — produces a massive glutamate surge in the PFC, with concurrent σ1R activation initiating neuroprotective cascades (Section 2). This surge hyperactivates cortical pyramidal neurons, generating diffuse, high-frequency, stochastic excitation that propagates through cortico-cortical connections. The entropic consequence is the maintenance or increase of cortical entropy measures (LZc, PE, SE), the preservation of near-critical dynamics, and the sustenance of PCI above the consciousness threshold — the Complexity Paradox. The informational consequence is saturation: the brain generates so much spontaneous activity that externally driven signals become indistinguishable from background noise, and the signal-to-noise ratio for external stimuli approaches zero. The clinical consequence is anesthesia: the subject cannot detect, encode, or respond to external stimuli while internal brain dynamics remain complex and active, generating the vivid experiences reported upon emergence. We note that this causal chain is mechanistically plausible and internally consistent but not yet empirically closed at every link; each step rests on independent evidence, but the full cascade has not been demonstrated in a single experimental paradigm.

The σ1R neuroprotection link deserves reiteration in this context. Pathological glutamate surges, such as those occurring during ischemic stroke, produce excitotoxicity and neuronal death. The glutamate surges produced by DMT and ketamine do not produce excitotoxicity in healthy individuals. Concurrent σ1R activation — stabilizing IP3R3 at the MAM, enhancing mitochondrial Ca^{2+} buffering, and attenuating ER stress — serves as the "safety valve" that makes Saturative Anesthesia biologically viable, enabling the brain to sustain a high-entropy, informationally saturated state for the duration of drug action without cellular damage. This

distinguishes the Dissociative Overload mechanism from pathological excitotoxicity and explains the clinical safety of ketamine anesthesia and high-dose DMT experiences.

To make the bridge to Section 4 explicit: PCI ≥ 0.31 documents that complex, integrated cortical activity is preserved under ketamine and predicted under DMT, but it does not by itself explain why this complex activity fails to produce conscious access to external stimuli. The workspace flooding mechanism developed in Section 4 supplies precisely this missing link — it specifies how informationally saturated cortical activity, despite remaining complex by PCI metrics, fails to model external reality because the Global Neuronal Workspace cannot select any single representation for broadcasting. That computational mechanism — workspace flooding and predictive coding collapse — is developed in Section 4.

4. Workspace Flooding — The Computational Mechanism

4.1 GNW Architecture and the Serial Bottleneck

Three candidate frameworks could in principle supply the computational level of this account: Integrated Information Theory (IIT), recurrent processing theory, and Global Neuronal Workspace (GNW) theory. We adopt GNW deliberately. The explanandum here is the failure of access to external stimuli in a cortex that remains complex and active, and GNW is the only one of the three that separates the capacity for conscious experience from the mechanism that selects content for global availability. IIT indexes the former — which is precisely why PCI remains above threshold under ketamine — but supplies no selection stage whose failure could yield unresponsiveness alongside preserved integrated information. Recurrent processing theory locates consciousness in local recurrent loops that, on the present evidence, remain intact under both compounds and therefore predicts no loss of access. Only GNW posits a capacity-limited selection stage whose overload constitutes a coherent failure mode, and it is that stage we argue is flooded. Section 5.5 (Fourth) considers what would follow were an alternative framework adopted instead.

The Global Neuronal Workspace (GNW) theory, developed by Dehaene, Kerszberg, and Changeux (1998) and comprehensively updated by Mashour, Roelfsema, Changeux, and Dehaene (2020), proposes that conscious access requires "ignition" — a sudden, nonlinear, all-or-nothing transition in which a neural representation in sensory cortex is amplified by recurrent long-range excitatory connections and broadcast globally to a distributed network of prefrontal-parietal "workspace" neurons. This ignition enables the representation to become simultaneously available to multiple cognitive systems — motor planning, memory encoding, verbal report, executive control.

Three architectural properties of the GNW are critical for the Dissociative Overload framework. First, the workspace operates under a *serial bottleneck*: it can sustain only one ignited representation at a time. Competing representations are actively suppressed through lateral inhibition, producing a winner-take-all dynamic (Dehaene & Changeux, 2011). This serial constraint is what makes conscious processing sequential — we perceive one thing at a time, even though the brain processes many things simultaneously in specialized modules. Second, ignition is a *threshold phenomenon*: a representation must reach a critical level of activation —

driven by bottom-up sensory strength, top-down attentional amplification, and contextual priming — to trigger the positive feedback loop that propels it into global broadcasting. Subthreshold representations remain unconscious. Third, the workspace is implemented by *pyramidal neurons in layers II/III and V* of prefrontal, parietal, and cingulate cortices, interconnected by long-range, predominantly glutamatergic cortico-cortical axons. The integrity and functionality of these connections is necessary for ignition.

4.2 Two Modes of Workspace Failure: Silencing Versus Flooding

GABAergic anesthetics disrupt the GNW by attacking the third property: they reduce the efficacy of long-range excitatory connections through global inhibition, preventing any representation from achieving the activation level necessary for ignition. Mashour (2013) formalized this as "cognitive unbinding" — the dissolution of functional connectivity between distant cortical regions necessary for workspace broadcasting. The result: no ignition, no broadcasting, no conscious access — unconsciousness with PCI below 0.31, reflecting a workspace that is structurally intact but functionally silenced.

We propose a third mode of workspace failure that has not been previously formalized: *workspace flooding*. When glutamate-mediated excitation (from the convergent pathway established in Section 2) simultaneously activates a massive number of representations in the workspace, the winner-take-all competition breaks down — not because no signal is strong enough to win, but because too many signals are simultaneously above threshold. The serial bottleneck cannot select a single representation for broadcasting because the lateral inhibition mechanism is overwhelmed by the number and intensity of competing activations.

Before setting out the argument, one assumption should be made explicit: that conscious selection in the GNW is implemented by a winner-take-all dynamic mediated by lateral inhibition among workspace neurons (Dehaene & Changeux, 2011). Should empirical evidence ultimately demonstrate that workspace selection is implemented by an alternative architecture — for example, parallel multi-channel broadcasting, biased-competition without strict mutual inhibition, or oscillation-gated multiplexing — the specific flooding mechanism proposed here would require corresponding refinement, though the broader information-saturation framework would remain intact.

The logical structure proceeds as follows. Premise 1 (GNW architecture): conscious access requires the workspace to select and amplify one representation at a time via winner-take-all competition. Premise 2 (glutamate surge, from Section 2): DMT and ketamine produce a massive, diffuse glutamate surge in the PFC, hyperactivating pyramidal neurons across layers II/III and V — the very neurons that constitute the workspace. Premise 3 (mass activation): this hyperactivation pushes many — potentially all — representations in the workspace above the ignition threshold simultaneously. Inference: when all representations are simultaneously above threshold, the winner-take-all competition has no winner. Every representation "ignites" but none achieves exclusive broadcasting. The workspace is in a state of indiscriminate, simultaneous activation — functionally equivalent to noise. Consequence: no coherent content is globally broadcast. External sensory representations cannot achieve the selective amplification needed to become conscious percepts because they are drowned in a sea of competing internally

generated representations. The subject is clinically anesthetic while the workspace itself remains maximally active (PCI ≥ 0.31).

This constitutes a workspace failure by saturation rather than silencing — the computational mechanism underlying the Complexity Paradox documented in Section 3. The two modes are analogous to a radio: in Suppressive Anesthesia, the radio is powered down — no signal is received. In Saturative Anesthesia, the radio receives all stations simultaneously — the result is static from which no individual station can be extracted. Both produce the same behavioral endpoint through opposite mechanisms.

4.3 Predictive Coding Collapse Under DMT and Ketamine

The brain as a predictive processing system (Rao & Ballard, 1999; Friston, 2010) maintains a generative model of the world through hierarchical Bayesian inference: higher cortical areas send top-down predictions to lower areas, while lower areas return bottom-up prediction errors — the mismatch between prediction and actual sensory input. Conscious perception emerges when this hierarchical loop stabilizes on an accurate world model, minimizing prediction errors.

DMT and ketamine break this hierarchy through mechanistically distinct but functionally convergent routes. DMT disrupts from the bottom up, through the REBUS mechanism (Carhart-Harris & Friston, 2019): 5-HT2A agonism on deep-layer pyramidal neurons reduces the precision weighting of top-down prior beliefs. When priors lose precision, bottom-up sensory prediction errors propagate upward unchecked, flooding higher processing areas with unfiltered information. Empirical support comes from Timmermann et al. (2023), who demonstrated global increases in functional connectivity, compression of the principal cortical gradient (indicating hierarchical flattening), and a shift from the canonical top-down (frontal-to-posterior, alpha-frequency) pattern of cortical traveling waves toward a bottom-up pattern — as if the cortex were processing visual input when no stimulus was present. At breakthrough doses, we propose this bottom-up overload becomes total: the prediction error signals are so numerous and high-amplitude that the brain's generative model of external reality collapses entirely, switching from modeling the external world to generating an autonomous internal reality.

Ketamine disrupts from the opposite direction — top-down disconnection combined with feedforward disinhibition. Weber et al. (2020) demonstrated that S-ketamine significantly reduced the precision-weighted mismatch negativity (MMN), an electrophysiological index of hierarchical prediction error processing — specifically impairing the model-update component while leaving initial surprise detection relatively intact. Leptourgos et al. (2023) provided the most comprehensive predictive coding account: ketamine simultaneously impairs top-down predictions via NMDA blockade on deep-layer pyramidal neurons that send feedback connections and enhances feedforward prediction errors via the glutamate surge's effect on superficial-layer neurons that send feedforward connections. This dual disruption — top-down silencing plus bottom-up amplification — renders the predictive hierarchy catastrophically non-functional at anesthetic doses.

Despite opposite entry points into the predictive hierarchy, DMT and ketamine converge on the same outcome: the complete failure of the brain's generative model of external reality. Under

DMT, the model is overwhelmed from below; under ketamine, the model is disconnected from above while simultaneously flooded from below. In both cases, external stimuli can no longer be integrated into coherent percepts because the predictive machinery that normally transforms raw sensory data into meaningful representations is non-functional. This constitutes the computational mechanism of Saturative Anesthesia.

4.4 Thalamocortical Reconfiguration

The thalamus serves as the primary relay station for sensory information reaching the cortex. In Suppressive Anesthesia, the thalamus is functionally silenced: GABAergic agents enhance thalamic reticular nucleus inhibition, producing a hypersynchronous "closed gate" that prevents sensory signals from reaching cortical areas, reflected in disrupted thalamocortical functional connectivity under propofol (Alkire et al., 2008; Boveroux et al., 2010).

Under DMT and ketamine, the thalamocortical gate is not closed — it is reconfigured. Preller et al. (2018), studying LSD (the closest pharmacological analogue to DMT with extensive fMRI data), demonstrated that serotonergic psychedelics increase thalamocortical functional connectivity, particularly between the thalamus and sensorimotor cortices. Rather than gating sensory information out, the psychedelic thalamus becomes hyperconnected, flooding the cortex with thalamic output that is likely a mixture of genuine sensory relay and internally generated thalamic activity. Under ketamine, the picture at anesthetic doses is more selective: frontoparietal connectivity is disrupted while primary sensory and some thalamocortical connections remain relatively preserved (Bonhomme et al., 2016; Höflich et al., 2015). This pattern is consistent with a "jammed gate" model: the thalamus continues to relay information, but the prefrontal-parietal workspace cannot coherently integrate it because the workspace itself is in the flooded state described above.

The distinction between a closed gate (Suppressive) and a jammed gate (Saturative) is important for the framework's internal consistency. Suppressive Anesthesia prevents information from reaching the workspace; Saturative Anesthesia allows — indeed amplifies — information reaching the workspace but prevents the workspace from coherently processing it.

4.5 Connectome Harmonic Evidence

Connectome Harmonic Decomposition (CHD), developed by Atasoy, Donnelly, and Pearson (2016), decomposes fMRI-measured brain activity into spatial eigenmodes (harmonics) of the structural connectome. Low-frequency harmonics correspond to large-scale, coarse-grained patterns that follow the brain's anatomical architecture; high-frequency harmonics correspond to fine-grained, spatially complex patterns that deviate from structural wiring.

Four key findings converge to support the Dissociative Overload framework. Atasoy et al. (2017) demonstrated that LSD shifted brain dynamics from low-frequency toward high-frequency harmonics, with increased total energy and an expanded repertoire of brain states — the brain "liberating" itself from structural constraints. We treat the LSD harmonic data as a pharmacological proxy for DMT in this analysis on three grounds: (i) both compounds are 5-HT2A receptor agonists that converge on the same primary mechanism of cortical pyramidal

excitation (Aghajanian & Marek, 1999; Nichols, 2016); (ii) both produce comparable elevations in cortical entropy and complexity measures (Schartner et al., 2017; Timmermann et al., 2023); and (iii) the proxy assumption was subsequently validated by Vohryzek et al. (2025), who confirmed directly under DMT the same high-frequency harmonic shift first reported under LSD, generalizing the finding to tryptamine psychedelics. Luppi, Vohryzek, et al. (2023) provided the critical bridging observation: the harmonic signature of loss of consciousness under propofol is the mirror image of the psychedelic signature — propofol drives brain dynamics toward low-frequency harmonics (increased structure-function coupling), while psychedelics drive toward high-frequency harmonics (decreased structure-function coupling). Most directly relevant, Van Maldegem et al. (2025) demonstrated that during ketamine-induced unresponsiveness, connectome harmonic analysis revealed a signature that aligns with the psychedelic (high-frequency expansion) pattern and misaligns with the propofol (low-frequency contraction) pattern.

This convergence provides systems-level confirmation of the dual taxonomy: Suppressive Anesthesia (propofol) locks the brain to its structural wiring, while Saturative Anesthesia (ketamine, and by extension DMT) liberates the brain from structural constraints — producing opposite harmonic signatures despite convergent clinical unresponsiveness.

4.6 The Dissociative Overload Framework: Complete Synthesis

Integrating the three levels of analysis developed across Sections 2, 3, and 4, the Dissociative Overload framework can be stated as a unified, three-level cascade.

At *Level 1 (Molecular)*, despite structural orthogonality and distinct primary receptor targets (5-HT2A for DMT; NMDA for ketamine), both compounds converge on the Sigma-1 receptor and on a massive prefrontal cortex glutamate surge — the latter achieved via pyramidal excitation (DMT) or interneuron disinhibition (ketamine). Concurrent σ1R activation provides neuroprotection that renders the high-excitation state sustainable.

At *Level 2 (Information-Theoretic)*, the glutamate surge maintains or increases cortical entropy, preserves near-critical dynamics, and sustains PCI above the consciousness threshold (≥ 0.31) — the Complexity Paradox. This directly contradicts the Suppressive paradigm's prediction that anesthesia requires entropy reduction. The high entropy is the signature of a brain that is informationally saturated: processing too much to encode any specific external signal.

At *Level 3 (Computational)*, the mass cortical activation floods the Global Neuronal Workspace, overwhelming the serial winner-take-all competition that normally selects one representation for conscious broadcasting. Simultaneously, the predictive coding hierarchy collapses — via bottom-up overload (DMT/REBUS) or top-down disconnection plus feedforward disinhibition (ketamine) — rendering the brain's generative model of external reality non-functional. Connectome harmonics shift to high-frequency, structure-liberated patterns, the mirror image of Suppressive Anesthesia. The subject is clinically anesthetic because the workspace is too full, not too empty. See Figure 2 below.

This framework proposes that general anesthesia is not a unitary phenomenon defined by neural suppression but a family of states in which the brain fails to model external reality — achievable through either information deprivation (Suppressive) or information saturation (Saturative). The two routes produce opposite neurophysiological signatures but converge on the same clinical endpoint: unresponsiveness to external stimuli.

4.7 Testable Predictions

The Dissociative Overload framework generates six falsifiable predictions, each distinguishing the overload model from the suppression model. These are summarized in Table 3 below.

Prediction P1 — the high-dose DMT PCI study — is the single most critical empirical test. If DMT at breakthrough doses produces PCI ≥ 0.31 during verified unresponsiveness, this would replicate the Complexity Paradox across a second structurally orthogonal compound class, providing strong evidence for a shared Saturative mechanism. Conversely, if PCI falls below 0.31 under high-dose DMT, this would indicate that DMT achieves anesthesia through a suppressive mechanism at high doses, undermining the universality of the framework. Predictions P2 and P3 test the causal roles of σ1R and the glutamate surge respectively, while P4–P6 test specific mechanistic predictions about harmonic signatures, dose-response dynamics, and cross-compound interactions.

Table 3. Testable Predictions of the Dissociative Overload Framework. P1 (highlighted) is the highest-priority prediction. All predictions are designed to distinguish the Overload model from the Suppression model.

#	Prediction	Experimental Design	Outcome if Overload Correct	Outcome if Suppression Correct
P1	DMT at breakthrough doses (≥ 0.4 mg/kg IV) will produce PCI ≥ 0.31 during complete unresponsiveness	High-dose IV DMT with concurrent TMS-EEG; assess PCI during verified unresponsiveness	PCI ≥ 0.31 despite unresponsiveness (Complexity Paradox replicated for DMT)	PCI < 0.31 (DMT follows suppressive pattern)
P2	σ1R antagonism will shift the ketamine/DMT anesthetic state toward a suppressive signature	Co-administer σ1R antagonist (NE-100 or BD1047) with ketamine at anesthetic dose; compare PCI, LZc, emergence behavior	σ1R antagonist reduces PCI, shifts harmonics to low-frequency, reduces dream-like emergence	σ1R antagonism has no effect on anesthetic signature
P3	Glutamate surge is necessary for the Complexity Paradox: glutamate inhibition converts Saturative to Suppressive signature	Lamotrigine pre-treatment before ketamine anesthesia; compare PCI and entropy measures	Lamotrigine reduces PCI below 0.31, reduces entropy, diminishes emergence dreams	Lamotrigine has no effect on PCI or entropy during ketamine anesthesia
P4	Connectome harmonics during high-dose DMT unresponsiveness will show high-frequency expansion, not low-frequency contraction	fMRI during extended high-dose DMT infusion with connectome harmonic decomposition	High-frequency harmonic expansion (psychedelic pattern)	Low-frequency contraction (propofol pattern)

P5	Transition from sub-anesthetic to anesthetic doses will show a nonlinear phase transition in sensory SNR	Titrate ketamine dose with repeated auditory stimuli; measure evoked response SNR across dose range	Nonlinear, threshold-like SNR collapse at dose producing unresponsiveness	Linear, gradual SNR decrease across all doses
P6	Combined sub-anesthetic DMT + ketamine will produce supra-additive effects on entropy and workspace saturation	Compare anesthetic ED_{50} of ketamine alone, DMT alone, and sub-anesthetic doses combined	Supra-additive entropy increase; PCI ≥ 0.31 maintained; anesthesia at sub-individual doses	Additive or no interaction effects

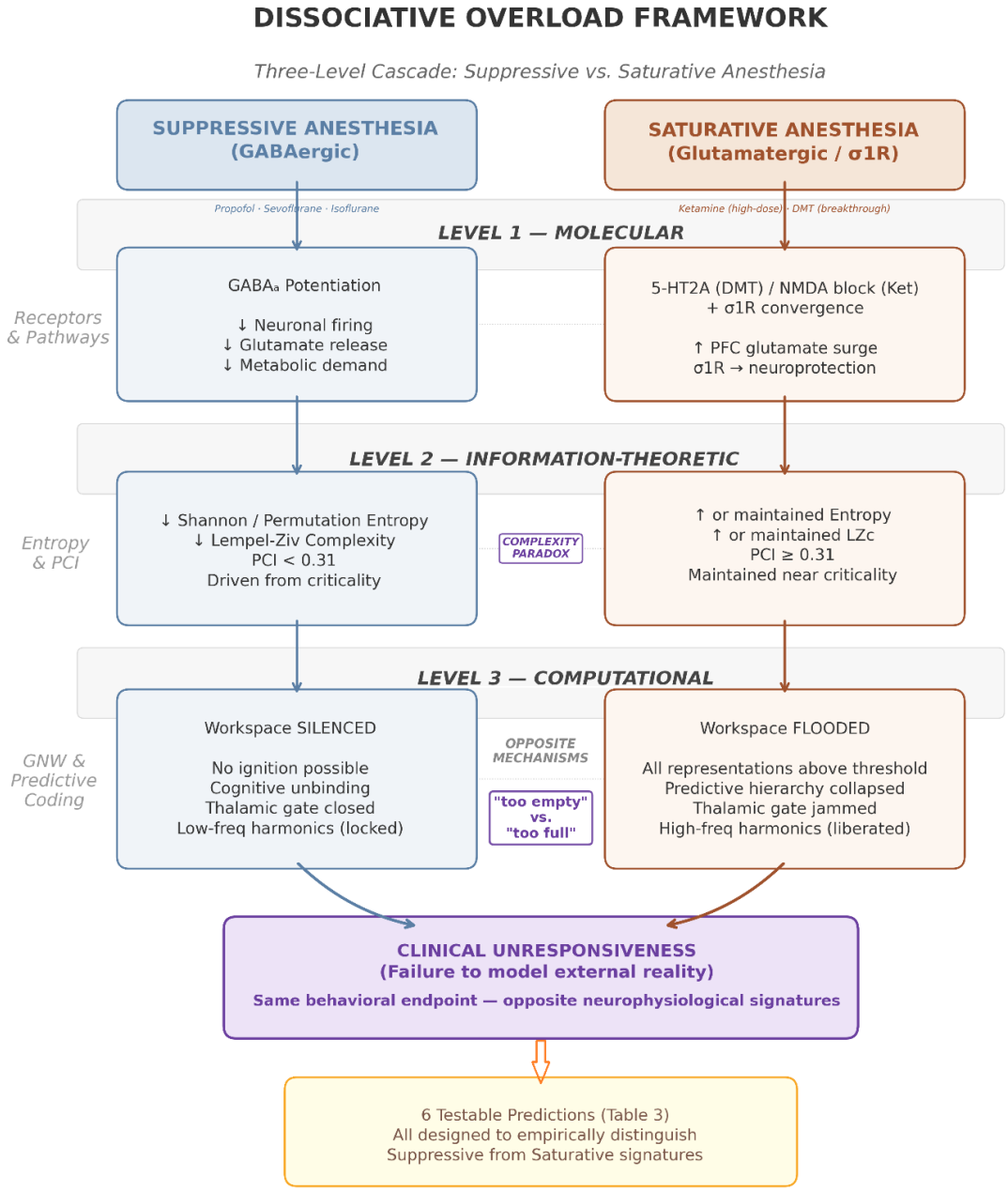


Figure 2. The Dissociative Overload framework: a three-level cascade from molecular convergence to clinical unresponsiveness. Left track: Suppressive Anesthesia (GABAergic, entropy-reducing, workspace silencing). Right

track: Saturative Anesthesia (glutamatergic/σ1R, entropy-preserving, workspace flooding). Both tracks converge on the same clinical endpoint — unresponsiveness to external stimuli — through opposite neurophysiological mechanisms.

5. Discussion

5.1 Significance of the Dual Taxonomy

The Dissociative Overload framework introduces a fundamental reconceptualization of general anesthesia. For over a century, the field has operated under the implicit assumption that anesthesia is synonymous with neural suppression — that rendering a patient unconscious requires reducing the brain's information processing capacity. This assumption is embedded in the molecular targets of nearly all approved anesthetic agents (GABAA potentiation, moderate NMDA antagonism), in the design of depth-of-anesthesia monitors (which equate low entropy with deep anesthesia), and in the theoretical frameworks used to interpret anesthetic mechanisms (cognitive unbinding, thalamocortical disruption, information complexity reduction).

The dual taxonomy proposed here — Suppressive versus Saturative Anesthesia — challenges this unitary view. If anesthesia is redefined as the brain's failure to model external reality, then this failure can be achieved through two diametrically opposite routes: information deprivation (the brain is too quiet) or information saturation (the brain is too loud). The Suppressive route silences the workspace; the Saturative route floods it. Both produce the same clinical endpoint — unresponsiveness to external stimuli — through opposite neurophysiological mechanisms, opposite entropy signatures, and opposite connectome harmonic profiles.

This reconceptualization has implications beyond pharmacology. It suggests that consciousness of external reality occupies a bounded regime — a "Goldilocks zone" of cortical entropy — and can be disrupted by departures in either direction. The lower bound has been extensively characterized; the upper bound, identified speculatively by the Entropic Brain Hypothesis (Carhart-Harris, 2014, 2018), is formalized here for the first time as a distinct anesthetic mechanism.

5.2 Clinical Implications

The most immediate clinical implication concerns anesthetic monitoring. Current commercial monitors — the Bispectral Index (BIS), M-Entropy, and Narcotrend — are calibrated exclusively to the Suppressive paradigm. They interpret high entropy as wakefulness and low entropy as adequate anesthesia. Under ketamine, these monitors produce systematically misleading readings: they indicate "light" or "inadequate" anesthesia in patients who are profoundly unresponsive, because the Saturative mechanism produces high-entropy signals that the monitors interpret as consciousness. This is not a minor calibration issue; it reflects a fundamental category error in the design assumptions of the monitoring technology. Clinicians using ketamine as a primary anesthetic agent — particularly in resource-limited settings, pediatric anesthesia, and battlefield medicine where ketamine is a preferred agent — should be aware that conventional entropy-based monitoring is unreliable in this context and that clinical assessment of responsiveness remains the gold standard.

A second clinical implication concerns the phenomenon of "awareness during surgery." Under the Suppressive paradigm, awareness is straightforwardly defined as the persistence of consciousness due to inadequate suppression. Under the Saturative paradigm, a more nuanced picture emerges: the patient under ketamine anesthesia may be intensely conscious — experiencing vivid internal realities — while being genuinely unable to perceive or respond to surgical stimuli. This is not awareness in the traditional sense (the patient is not experiencing the surgery) but represents a fundamentally different relationship between internal experience and external responsiveness than that assumed by current clinical frameworks.

5.3 Implications for Consciousness Science

The Dissociative Overload framework has implications for theories of consciousness beyond the clinical context. For Integrated Information Theory (IIT; Tononi, Boly, Massimini, & Koch, 2016), the framework poses a challenge: if PCI — the closest empirical proxy for integrated information — remains above the consciousness threshold during ketamine anesthesia, does this mean the patient is conscious? The answer appears to be yes, but conscious of internally generated content rather than external reality. This suggests that IIT's Φ may index the capacity for experience rather than the capacity for veridical perception of the external world — an important distinction that the current formulation of IIT does not clearly make.

For Global Neuronal Workspace theory, the framework introduces a novel failure mode. Previous accounts of GNW disruption focused exclusively on ignition failure — insufficient activation preventing any representation from reaching the workspace (Mashour, 2013; Dehaene & Changeux, 2011). Workspace flooding represents the complementary failure: excessive activation preventing any single representation from achieving exclusive broadcasting. This expands the GNW's explanatory scope and makes it a more complete theory of conscious access by identifying conditions under which the workspace is active yet functionally non-selective.

For predictive processing accounts, the framework extends the REBUS model (Carhart-Harris & Friston, 2019) from the psychedelic domain to the anesthetic domain. REBUS was developed to explain altered consciousness under sub-anesthetic psychedelic doses; our framework proposes that the same mechanism, scaled to higher doses, produces not merely altered but abolished external consciousness. This dose-dependent transition — from therapeutic to psychedelic to anesthetic — represents a continuous trajectory through the predictive coding framework that has not been previously articulated.

5.4 Relationship to Existing Frameworks

The Dissociative Overload framework builds upon, extends, and differentiates itself from several predecessor frameworks.

Gallimore (2015) provided the foundational insight that excessive neural entropy under psychedelics might impair consciousness, speculating that high-entropy states could reduce IIT's Φ (integrated information). Our framework differs in four respects: we propose a specific anesthetic mechanism (workspace saturation via GNW flooding) rather than merely invoking reduced Φ; we include ketamine and the σ1R convergence, which Gallimore did not address; we

build on post-2015 empirical evidence (Sarasso PCI data, connectome harmonics, REBUS, predictive coding accounts of ketamine) that was unavailable to Gallimore; and we generate specific, falsifiable predictions. We credit Gallimore for the foundational insight and position our work as the formalization and empirical grounding of this idea.

The "Disconnected Consciousness" concept (Sanders, Tononi, Laureys, & Sleigh, 2012) accurately describes the ketamine anesthetic state — consciousness present but disconnected from external reality — but does not explain the mechanism of disconnection. Our framework provides that mechanism: workspace flooding renders the brain incapable of selectively processing external stimuli, while predictive hierarchy collapse prevents the generative model of external reality from functioning. The two accounts are complementary: disconnected consciousness is the phenomenological description; Dissociative Overload is the mechanistic explanation.

REBUS (Carhart-Harris & Friston, 2019) explains the psychedelic state through relaxed beliefs and liberated prediction errors but was developed for sub-anesthetic doses and does not address the transition to anesthesia. Our framework extends REBUS to anesthetic doses by arguing that sufficient relaxation of priors produces complete external world model collapse — transitioning from altered consciousness (psychedelic experience) to abolished external consciousness (Saturative Anesthesia). We incorporate REBUS as the DMT-specific mechanism within our broader three-level framework.

5.5 Limitations

Several limitations of the present framework must be acknowledged. First, the σ1R affinity caveat: DMT's σ1R affinity (Kd ≈ 15 μM) is approximately 100-fold weaker than its 5-HT2A affinity. While local concentration effects (VMAT2-mediated vesicular accumulation) and stress-induced σ1R upregulation may enable physiologically relevant σ1R engagement, this remains plausible rather than proven. The σ1R convergence component of the framework therefore rests on firmer ground for ketamine (where enantioselective σ1R effects are well documented) than for DMT.

Second, and most critically, no formal neuroimaging studies have been conducted during DMT-induced complete unresponsiveness at breakthrough doses. The entropic evidence for DMT comes entirely from sub-anesthetic doses. While the trajectory of increasing complexity with dose and the phenomenological overlap with the ketamine "k-hole" strongly support our predictions, the framework's extension from ketamine (empirically supported by Sarasso et al., 2015) to DMT remains theoretical until Prediction P1 is tested. It should also be noted that the Sarasso et al. (2015) ketamine finding — the single most important empirical anchor for this framework — rests on a sample of six subjects; replication in a larger cohort would substantially strengthen the empirical foundation.

Third, the workspace flooding argument is theoretical. While the GNW architecture (serial bottleneck, winner-take-all competition) and the empirical evidence (glutamate surge, maintained PCI, connectome harmonics) are individually well established, the specific claim that mass activation overwhelms the winner-take-all mechanism has not been directly demonstrated.

Computational modeling of workspace dynamics under simulated glutamate flooding would strengthen this argument considerably.

Fourth, the framework is presented within the GNW theoretical framework. Alternative theories of consciousness — IIT, Higher-Order Theories, or recurrent processing theory — might generate different predictions from the same empirical data. While we have articulated implications for IIT and predictive processing, a full formulation of the Dissociative Overload mechanism within each alternative theory is beyond the scope of this paper.

Fifth, the dose-response relationship between the glutamate surge and the transition from therapeutic to psychedelic to anesthetic states remains incompletely characterized. The framework proposes a biphasic (or triphasic) dose-response curve, but the precise dose thresholds, the role of spatial diffuseness of the surge, and the kinetics of the transition remain to be empirically determined.

Sixth, the framework's redefinition of anesthesia — as the failure of external-world modeling rather than the abolition of all experience — is itself a substantive theoretical move that not all anesthesiologists will accept. Under Saturative Anesthesia, the patient may be intensely conscious of internally generated content while genuinely unable to perceive or respond to external stimuli. Whether this state should be classified as "anesthesia" or as a distinct category of dissociative unresponsiveness is a definitional question that the empirical predictions of this framework cannot resolve on their own.

5.6 Future Directions

Three priority research directions emerge from the present framework. The highest priority is the empirical test of Prediction P1: a high-dose IV DMT study with concurrent TMS-EEG, assessing PCI during verified periods of complete unresponsiveness. This study would directly test whether the Complexity Paradox generalizes beyond ketamine to a structurally orthogonal compound class that shares the molecular convergence described in Section 2. A positive result would constitute strong evidence for the Saturative mechanism; a negative result would refute the framework's universality.

Second, computational modeling of workspace dynamics under conditions of mass glutamatergic activation would provide theoretical validation for the flooding mechanism. Existing GNW computational models (Dehaene, Sergent, & Changeux, 2003) could be adapted to simulate the effects of increasing the baseline activation of workspace neurons, testing whether the winner-take-all competition indeed fails above a critical activation threshold and whether the resulting dynamics match the empirical PCI and entropy signatures.

Third, the framework provides a strong theoretical foundation for an NSF or NIH grant application targeting the "DMT–Ketamine–Anesthesia triangle" — a program of research systematically testing each prediction in Table 3 across both compound classes. Such a program would integrate molecular pharmacology (σ1R manipulation via P2), information theory (PCI and entropy measures via P1 and P3), and computational neuroscience (connectome harmonics

via P4 and dose-response modeling via P5), representing a genuinely interdisciplinary contribution to both anesthesiology and consciousness science.

6. Conclusions

General anesthesia has been understood for over a century as a unitary phenomenon — the suppression of neural activity below the threshold required for conscious experience. This paradigm, grounded in the pharmacology of GABAergic agents and validated by information-theoretic measures such as the Perturbational Complexity Index, has proven remarkably successful for the majority of clinical anesthetics. It fails, however, to account for a critical anomaly: ketamine produces complete clinical unresponsiveness while maintaining cortical complexity above the consciousness threshold (PCI ≥ 0.31; Sarasso et al., 2015), and DMT increases neural entropy dose-dependently at sub-anesthetic doses (Timmermann et al., 2019, 2023), with phenomenological evidence suggesting that breakthrough doses produce a comparable dissociative state. This Complexity Paradox — clinical anesthesia coexisting with signatures of conscious-level cortical processing — is irreconcilable with the suppression paradigm.

The Dissociative Overload framework, developed in this paper, resolves this paradox through a three-level cascade. At the molecular level, DMT and ketamine — despite structural orthogonality and non-overlapping primary receptor targets — converge on the Sigma-1 receptor and on a massive prefrontal cortex glutamate surge, the latter achieved through distinct upstream pathways (5-HT2A-mediated pyramidal excitation for DMT; NMDA-blockade-mediated interneuron disinhibition for ketamine). Concurrent σ1R activation provides neuroprotection that renders the resulting high-excitation state sustainable without excitotoxic damage. At the information-theoretic level, this glutamate surge maintains or increases cortical entropy, preserves near-critical dynamics, and sustains PCI above the consciousness threshold — producing the Complexity Paradox. At the computational level, the mass cortical activation floods the Global Neuronal Workspace, overwhelming the serial winner-take-all competition that normally selects one representation for conscious broadcasting, while simultaneously collapsing the predictive coding hierarchy — via bottom-up overload (DMT) or top-down disconnection with feedforward disinhibition (ketamine) — rendering the brain's generative model of external reality non-functional.

This framework introduces a dual taxonomy of anesthesia: Suppressive Anesthesia, in which information deprivation silences the workspace (the brain is too quiet), and Saturative Anesthesia, in which information overload floods the workspace (the brain is too loud). The two modes produce opposite neurophysiological signatures — opposite entropy trajectories, opposite connectome harmonic profiles, opposite thalamocortical configurations — yet converge on the same clinical endpoint: the brain's failure to model external reality. General anesthesia is thereby reconceptualized not as the suppression of consciousness but as the disruption of external-world modeling, achievable through either route.

The framework generates six falsifiable predictions (Table 3), each designed to empirically distinguish the overload model from the suppression model. The highest-priority prediction — that DMT at breakthrough doses will produce PCI ≥ 0.31 during verified unresponsiveness —

would, if confirmed, replicate the Complexity Paradox across a second structurally orthogonal compound class and provide strong evidence for Saturative Anesthesia as a general mechanism. The clinical, theoretical, and empirical implications of this dual taxonomy — for anesthetic monitoring, for theories of consciousness, and for the design of next-generation anesthetic agents — position the Dissociative Overload framework as a foundation for a new research program on non-canonical anesthesia.

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References

1. Aghajanian, G. K., & Marek, G. J. (1999). Serotonin and hallucinogens. Neuropsychopharmacology, 21(S1), 16S–23S. https://doi.org/10.1016/S0893-133X(98)00135-3
2. Aleksandrova, L. R., & Phillips, A. G. (2021). Neuroplasticity as a convergent mechanism of ketamine and classical psychedelics. Trends in Pharmacological Sciences, 42(11), 929–942. https://doi.org/10.1016/j.tips.2021.08.003
3. Alkire, M. T., Hudetz, A. G., & Tononi, G. (2008). Consciousness and anesthesia. Science, 322(5903), 876–880. https://doi.org/10.1126/science.1149213
4. Atasoy, S., Donnelly, I., & Pearson, J. (2016). Human brain networks function in connectome-specific harmonic waves. Nature Communications, 7, 10340. https://doi.org/10.1038/ncomms10340
5. Atasoy, S., Roseman, L., Kaelen, M., Kringelbach, M. L., Deco, G., & Carhart-Harris, R. L. (2017). Connectome-harmonic decomposition of human brain activity reveals dynamical repertoire re-organization under LSD. Scientific Reports, 7, 17661. https://doi.org/10.1038/s41598-017-17546-0
6. Barker, S. A. (2018). N,N-Dimethyltryptamine (DMT), an endogenous hallucinogen: Past, present, and future research to determine its role and function. Frontiers in Neuroscience, 12, 536. https://doi.org/10.3389/fnins.2018.00536
7. Bonhomme, V., Vanhaudenhuyse, A., Demertzi, A., Bruno, M.-A., Jaquet, O., Bahri, M. A., Plenevaux, A., Boly, M., Maquet, P., & Laureys, S. (2016). Resting-state network-specific breakdown of functional connectivity during ketamine alteration of consciousness in volunteers. Anesthesiology, 125(5), 873–888. https://doi.org/10.1097/ALN.0000000000001275
8. Boveroux, P., Vanhaudenhuyse, A., Bruno, M.-A., Noirhomme, Q., Lauwick, S., Luxen, A., Degueldre, C., Plenevaux, A., Schnakers, C., Phillips, C., Maquet, P., Laureys, S., & Boly, M. (2010). Breakdown of within- and between-network resting state functional magnetic resonance imaging connectivity during propofol-induced loss of consciousness. Anesthesiology, 113(5), 1038–1053. https://doi.org/10.1097/ALN.0b013e3181f697f5
9. Brito, M. A., Li, D., Mashour, G. A., & Pal, D. (2020). State-dependent and bandwidth-specific effects of ketamine and propofol on electroencephalographic complexity in rats. Frontiers in Systems Neuroscience, 14, 50. https://doi.org/10.3389/fnsys.2020.00050

10. Bunzow, J. R., Sonders, M. S., Arttamangkul, S., Harrison, L. M., Zhang, G., Quigley, D. I., Darland, T., Suchland, K. L., Rossi, S., Wigle, I. D., Lowe, D. G., & Grandy, D. K. (2001). Amphetamine, 3,4-methylenedioxymethamphetamine, lysergic acid diethylamide, and metabolites of the catecholamine neurotransmitters are agonists of a rat trace amine receptor. Molecular Pharmacology, 60(6), 1181–1188. https://doi.org/10.1124/mol.60.6.1181
11. Carhart-Harris, R. L. (2018). The entropic brain — revisited. Neuropharmacology, 142, 167–178. https://doi.org/10.1016/j.neuropharm.2018.03.010
12. Carhart-Harris, R. L., & Friston, K. J. (2019). REBUS and the anarchic brain: Toward a unified model of the brain action of psychedelics. Pharmacological Reviews, 71(3), 316–344. https://doi.org/10.1124/pr.118.017160
13. Carhart-Harris, R. L., Leech, R., Hellyer, P. J., Shanahan, M., Feilding, A., Tagliazucchi, E., Chialvo, D. R., & Nutt, D. J. (2014). The entropic brain: A theory of conscious states informed by neuroimaging research with psychedelic drugs. Frontiers in Human Neuroscience, 8, 20. https://doi.org/10.3389/fnhum.2014.00020
14. Casali, A. G., Gosseries, O., Rosanova, M., Boly, M., Sarasso, S., Casali, K. R., Casarotto, S., Bruno, M.-A., Laureys, S., Tononi, G., & Massimini, M. (2013). A theoretically based index of consciousness independent of sensory processing and behavior. Science Translational Medicine, 5(198), 198ra105. https://doi.org/10.1126/scitranslmed.3006294
15. Choi, D. W. (1988). Glutamate neurotoxicity and diseases of the nervous system. Neuron, 1(8), 623–634. https://doi.org/10.1016/0896-6273(88)90162-6
16. Comolatti, R., Pigorini, A., Casarotto, S., Fecchio, M., Faria, G., Sarasso, S., Rosanova, M., Gosseries, O., & Casali, A. G. (2019). A fast and general method to empirically estimate the complexity of brain responses to transcranial and intracranial stimulations. Brain Stimulation, 12(5), 1280–1289. https://doi.org/10.1016/j.brs.2019.05.013
17. Cozzi, N. V., Mavlyutov, T. A., Thompson, M. A., & Bhagwat, S. S. (2009). High-affinity uptake of sigma-1 receptor ligands by the vesicle monoamine transporter 2. *European Journal of Pharmacology*, 609(1-3), 24–29. https://doi.org/10.1016/j.ejphar.2009.03.003
18. Cozzi, N. V., Mavlyutov, T. A., Thompson, M. A., & Ruoho, A. E. (2011). Indolethylamine N-methyltransferase expression in primate nervous tissue. Journal of Chemical Neuroanatomy, 41(4), 203-213. https://doi.org/10.1016/j.jchemneu.2011.02.005
19. Dehaene, S., & Changeux, J.-P. (2011). Experimental and theoretical approaches to conscious processing. Neuron, 70(2), 200–227. https://doi.org/10.1016/j.neuron.2011.03.018
20. Dehaene, S., Kerszberg, M., & Changeux, J.-P. (1998). A neuronal model of a global workspace in effortful cognitive tasks. Proceedings of the National Academy of Sciences, 95(24), 14529–14534. https://doi.org/10.1073/pnas.95.24.14529
21. Dehaene, S., Sergent, C., & Changeux, J.-P. (2003). A neuronal network model linking subjective reports and objective physiological data during conscious perception. Proceedings of the National Academy of Sciences, 100(14), 8520–8525. https://doi.org/10.1073/pnas.1332574100
22. Ebert, B., Mikkelsen, S., Thorkildsen, C., & Borgbjerg, F. M. (1997). Norketamine, the main metabolite of ketamine, is a non-competitive NMDA receptor antagonist in the rat cortex and spinal cord. European Journal of Pharmacology, 333(1), 99–104. https://doi.org/10.1016/S0014-2999(97)01072-2
23. Fontanilla, D., Johannessen, M., Hajipour, A. R., Cozzi, N. V., Jackson, M. B., & Ruoho, A. E. (2009). The hallucinogen N,N-dimethyltryptamine (DMT) is an endogenous sigma-1 receptor regulator. Science, 323(5916), 934–937. https://doi.org/10.1126/science.1166127

24. Franks, N. P. (2008). General anaesthesia: From molecular targets to neuronal pathways of sleep and arousal. Nature Reviews Neuroscience, 9(5), 370–386. https://doi.org/10.1038/nrn2311
25. Friston, K. (2010). The free-energy principle: A unified brain theory? Nature Reviews Neuroscience, 11(2), 127–138. https://doi.org/10.1038/nrn2787
26. Gallimore, A. R. (2015). Restructuring consciousness — the psychedelic state in light of integrated information theory. Frontiers in Human Neuroscience, 9, 346. https://doi.org/10.3389/fnhum.2015.00346
27. Hayashi, T., & Su, T.-P. (2007). Sigma-1 receptor chaperones at the ER-mitochondrion interface regulate Ca^{2+} signaling and cell survival. Cell, 131(3), 596–610. https://doi.org/10.1016/j.cell.2007.08.036
28. Hirota, K., Sikand, K. S., & Lambert, D. G. (1999). Interaction of ketamine with mu2 opioid receptors in SH-SY5Y human neuroblastoma cells. Journal of Anesthesia, 13(2), 107–109. https://doi.org/10.1007/BF02484218
29. Höflich, A., Hahn, A., Küblböck, M., Kranz, G. S., Vanicek, T., Windischberger, C., Kasper, S., & Lanzenberger, R. (2015). Ketamine-induced modulation of the thalamo-cortical network in healthy volunteers as a model for schizophrenia. International Journal of Neuropsychopharmacology, 18(9), pyv040. https://doi.org/10.1093/ijnp/pyv040
30. Homayoun, H., & Moghaddam, B. (2007). NMDA receptor hypofunction produces opposite effects on prefrontal cortex interneurons and pyramidal neurons. Journal of Neuroscience, 27(43), 11496–11500. https://doi.org/10.1523/JNEUROSCI.2213-07.2007
31. Hudetz, A. G., Liu, X., & Pillay, S. (2015). Dynamic repertoire of intrinsic brain states is reduced in propofol-induced unconsciousness. Brain Connectivity, 5(1), 10–22. https://doi.org/10.1089/brain.2014.0230
32. Hustveit, O., Maurset, A., & Øye, I. (1995). Interaction of the chiral forms of ketamine with opioid, phencyclidine, sigma and muscarinic receptors. Pharmacology & Toxicology, 77(6), 355–359. https://doi.org/10.1111/j.1600-0773.1995.tb01041.x
33. Jakab, R. L., & Goldman-Rakic, P. S. (1998). 5-Hydroxytryptamine2A 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. https://doi.org/10.1073/pnas.95.2.735
34. Jordan, D., Stockmanns, G., Kochs, E. F., Pilge, S., & Schneider, G. (2008). Electroencephalographic order pattern analysis for the separation of consciousness and unconsciousness. Anesthesiology, 109(6), 1014–1022. https://doi.org/10.1097/ALN.0b013e31818d6bc1
35. Kadriu, B., Musazzi, L., Henter, I. D., Graves, M., Popoli, M., & Zarate, C. A., Jr. (2019). Glutamatergic neurotransmission: Pathway to developing novel rapid-acting antidepressant treatments. International Journal of Neuropsychopharmacology, 22(2), 119–135. https://doi.org/10.1093/ijnp/pyy094
36. Keiser, M. J., Setola, V., Irwin, J. J., Laggner, C., Abbas, A. I., Hufeisen, S. J., Jensen, N. H., Kuijer, M. B., Matos, R. C., Tran, T. B., Whaley, R., Glennon, R. A., Hert, J., Thomas, K. L. H., Edwards, D. D., Shoichet, B. K., & Roth, B. L. (2009). Predicting new molecular targets for known drugs. Nature, 462(7270), 175–181. https://doi.org/10.1038/nature08506
37. Leptourgos, P., Fortier-Davy, M., Carhart-Harris, R., & Corlett, P. R. (2023). A predictive coding account of ketamine-induced dissociative states. Neuroscience & Biobehavioral Reviews, 146, 105060. https://doi.org/10.1016/j.neubiorev.2023.105060

38. Li, D., & Mashour, G. A. (2019). Cortical dynamics during psychedelic and anesthetized states induced by ketamine. NeuroImage, 196, 32–40. https://doi.org/10.1016/j.neuroimage.2019.03.076
39. Li, N., Lee, B., Liu, R.-J., Banasr, M., Dwyer, J. M., Iwata, M., Li, X.-Y., Aghajanian, G., & Duman, R. S. (2010). mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. Science, 329(5994), 959–964. https://doi.org/10.1126/science.1190263
40. Luppi, A. I., Vohryzek, J., Kringelbach, M. L., Mediano, P. A. M., Craig, M. M., Adapa, R., Carhart-Harris, R. L., Roseman, L., Pappas, I., Peattie, A. R. D., Manktelow, A. E., Sahakian, B. J., Finoia, P., Williams, G. B., Allanson, J., Pickard, J. D., Menon, D. K., Atasoy, S., & Stamatakis, E. A. (2023). Distributed harmonic patterns of structure–function dependence orchestrate human consciousness. Communications Biology, 6, 117. https://doi.org/10.1038/s42003-023-04474-1
41. Ly, C., Greb, A. C., Cameron, L. P., Wong, J. M., Barragan, E. V., Wilson, P. C., Burbach, K. F., Soltanzadeh Zarandi, S., Sood, A., Paddy, M. R., Duim, W. C., My, L. V., & Olson, D. E. (2018). Psychedelics promote structural and functional neural plasticity. Cell Reports, 23(11), 3170–3182. https://doi.org/10.1016/j.celrep.2018.05.022
42. Ma, H., Li, J.-F., Qiao, X., Zhang, Y., Hou, X.-J., Chang, H.-X., Chen, H.-L., Zhang, Y., & Li, Y.-F. (2024). Sigma-1 receptor activation mediates the sustained antidepressant effect of ketamine in mice via increasing BDNF levels. Acta Pharmacologica Sinica, 45(4), 704–713. https://doi.org/10.1038/s41401-023-01201-8
43. Mashour, G. A. (2013). Cognitive unbinding: A neuroscientific paradigm of general anesthesia and related states of unconsciousness. Neuroscience & Biobehavioral Reviews, 37(10), 2751–2759. https://doi.org/10.1016/j.neubiorev.2013.09.009
44. Mashour, G. A., Roelfsema, P., Changeux, J.-P., & Dehaene, S. (2020). Conscious processing and the global neuronal workspace hypothesis. Neuron, 105(5), 776–798. https://doi.org/10.1016/j.neuron.2020.01.016
45. Massimini, M., Ferrarelli, F., Huber, R., Esser, S. K., Singh, H., & Tononi, G. (2005). Breakdown of cortical effective connectivity during sleep. Science, 309(5744), 2228–2232. https://doi.org/10.1126/science.1117256
46. McKenna, D. J., Repke, D. B., Lo, L., & Peroutka, S. J. (1990). Differential interactions of indolealkylamines with 5-hydroxytryptamine receptor subtypes. Neuropharmacology, 29(3), 193–198. https://doi.org/10.1016/0028-3908(90)90054-X
47. Moghaddam, B., Adams, B., Verma, A., & Daly, D. (1997). Activation of glutamatergic neurotransmission by ketamine: A novel step in the pathway from NMDA receptor blockade to dopaminergic and cognitive disruptions associated with the prefrontal cortex. Journal of Neuroscience, 17(8), 2921–2927. https://doi.org/10.1523/JNEUROSCI.17-08-02921.1997
48. Nardai, S., Laszlo, M., Szabo, A., Alpar, A., Hanics, J., Horvath, G., Abrzán, K., Varga, V. E., Körmöczi, T., Berkecz, R., Janáky, T., & Frecska, E. (2020). N,N-dimethyltryptamine reduces infarct size and improves functional recovery following transient focal brain ischemia in rats. Experimental Neurology, 327, 113245. https://doi.org/10.1016/j.expneurol.2020.113245
49. Nichols, D. E. (2016). Psychedelics. Pharmacological Reviews, 68(2), 264–355. https://doi.org/10.1124/pr.115.011478

50. Olofsen, E., Sleigh, J. W., & Dahan, A. (2008). Permutation entropy of the electroencephalogram: A measure of anaesthetic drug effect. British Journal of Anaesthesia, 101(6), 810–821. https://doi.org/10.1093/bja/aen290
51. Preller, K. H., Burt, J. B., Ji, J. L., Schleifer, C. H., Adkinson, B. D., Stämpfli, P., Seifritz, E., Repovs, G., Krystal, J. H., Murray, J. D., Vollenweider, F. X., & Anticevic, A. (2018). Changes in global and thalamic brain connectivity in LSD-induced altered states of consciousness are attributable to the 5-HT2A receptor. eLife, 7, e35082. https://doi.org/10.7554/eLife.35082
52. Rao, R. P. N., & Ballard, D. H. (1999). Predictive coding in the visual cortex: A functional interpretation of some extra-classical receptive-field effects. Nature Neuroscience, 2(1), 79–87. https://doi.org/10.1038/4580
53. Ray, T. S. (2010). Psychedelics and the human receptorome. PLOS ONE, 5(2), e9019. https://doi.org/10.1371/journal.pone.0009019
54. Robson, M. J., Elliott, M., Seminerio, M. J., & Matsumoto, R. R. (2012). Evaluation of sigma (σ) receptors in the antidepressant-like effects of ketamine in vitro and in vivo. European Neuropsychopharmacology, 22(4), 308–317. https://doi.org/10.1016/j.euroneuro.2011.09.005
55. Sanders, R. D., Tononi, G., Laureys, S., & Sleigh, J. W. (2012). Unresponsiveness ≠ unconsciousness. Anesthesiology, 116(4), 946–959. https://doi.org/10.1097/ALN.0b013e318249d0a7
56. Sarasso, S., Boly, M., Napolitani, M., Gosseries, O., Charland-Verville, V., Casarotto, S., Rosanova, M., Casali, A. G., Brichant, J. F., Boveroux, P., Rex, S., Tononi, G., Laureys, S., & Massimini, M. (2015). Consciousness and complexity during unresponsiveness induced by propofol, xenon, and ketamine. Current Biology, 25(23), 3099–3105. https://doi.org/10.1016/j.cub.2015.10.014
57. Schartner, M. M., Carhart-Harris, R. L., Barrett, A. B., Seth, A. K., & Muthukumaraswamy, S. D. (2017). Increased spontaneous MEG signal diversity for psychoactive doses of ketamine, LSD and psilocybin. Scientific Reports, 7, 46421. https://doi.org/10.1038/srep46421
58. Schartner, M. M., Seth, A. K., Noirhomme, Q., Boly, M., Bruno, M.-A., Laureys, S., & Barrett, A. B. (2015). Complexity of multi-dimensional spontaneous EEG decreases during propofol induced general anaesthesia. PLOS ONE, 10(8), e0133532. https://doi.org/10.1371/journal.pone.0133532
59. Schmidt, H. R., Zheng, S., Gurpinar, E., Koehl, A., Manglik, A., & Kruse, A. C. (2016). Crystal structure of the human σ1 receptor. Nature, 532(7600), 527–530. https://doi.org/10.1038/nature17391
60. Szabo, I., Varga, V. E., Dvoracsko, S., Farkas, A. E., Körmöczi, T., Berkecz, R., Janaky, T., & Frecska, E. (2021). N,N-Dimethyltryptamine attenuates spreading depolarization and restrains neurodegeneration by sigma-1 receptor activation in the ischemic rat brain. Neuropharmacology, 192, 108612. https://doi.org/10.1016/j.neuropharm.2021.108612
61. Szabo, A., Kovacs, A., Frecska, E., & Rajnavolgyi, E. (2016). The endogenous hallucinogen and trace amine N,N-dimethyltryptamine (DMT) displays potent protective effects against hypoxia via sigma-1 receptor activation in human primary iPSC-derived cortical neurons and microglia-like immune cells. Frontiers in Neuroscience, 10, 423. https://doi.org/10.3389/fnins.2016.00423
62. Timmermann, C., Roseman, L., Schartner, M., Milliere, R., Williams, L. T. J., Erritzoe, D., Muthukumaraswamy, S., Ashton, M., Luan, P. N., Galani, A. I., Lawrence, N. S., & Carhart-

Harris, R. L. (2019). Neural correlates of the DMT experience assessed with multivariate EEG. Scientific Reports, 9, 16324. https://doi.org/10.1038/s41598-019-51974-4
63. Timmermann, C., Roseman, L., Haridas, S., Rosas, F. E., Luan, L., Kettner, H., Martell, J., Erritzoe, D., Tagliazucchi, E., Pallavicini, C., Girn, M., Alamia, A., Leech, R., Nutt, D. J., & Carhart-Harris, R. L. (2023). Human brain effects of DMT assessed via EEG-fMRI. *Proceedings of the National Academy of Sciences*, 120(13), e2218949120. https://doi.org/10.1073/pnas.2218949120
64. Tononi, G., Boly, M., Massimini, M., & Koch, C. (2016). Integrated information theory: From consciousness to its physical substrate. Nature Reviews Neuroscience, 17(7), 450–461. https://doi.org/10.1038/nrn.2016.44
65. Van Maldegem, M., Vohryzek, J., Atasoy, S., Alnagger, N., Cardone, P., Bonhomme, V., Vanhaudenhuyse, A., Demertzi, A., Jaquet, O., Bahri, M. A., Nunez, P., Kringelbach, M. L., Stamatakis, E. A., & Luppi, A. I. (2025). Connectome harmonic decomposition tracks the presence of disconnected consciousness during ketamine-induced unresponsiveness. British Journal of Anaesthesia, 134(4), 1088–1104. https://doi.org/10.1016/j.bja.2024.12.036
66. Viertiö-Oja, H., Maja, V., Särkelä, M., Talja, P., Tenkanen, N., Tolvanen-Laakso, H., Paloheimo, M., Vakkuri, A., Yli-Hankala, A., & Jensen, E. W. (2004). Description of the Entropy algorithm as applied in the Datex-Ohmeda S/5 Entropy Module. Acta Anaesthesiologica Scandinavica, 48(2), 154–161. https://doi.org/10.1111/j.0001-5172.2004.00322.x
67. Vohryzek, J., Luppi, A. I., Atasoy, S., Deco, G., Carhart-Harris, R. L., Timmermann, C., & Kringelbach, M. L. (2025). N,N-dimethyltryptamine effects on connectome harmonics, subjective experience and comparative psychedelic experiences. Neuropsychopharmacology, 50(12), 1768–1776. https://doi.org/10.1038/s41386-025-02190-4
68. Weber, L. A., Diaconescu, A. O., Mathys, C., Schmidt, A., Kometer, M., Vollenweider, F., & Stephan, K. E. (2020). Ketamine affects prediction errors about statistical regularities: A computational single-trial analysis of the mismatch negativity. Journal of Neuroscience, 40(29), 5658–5668. https://doi.org/10.1523/JNEUROSCI.2936-19.2020
69. Zhang, X.-S., Roy, R. J., & Jensen, E. W. (2001). EEG complexity as a measure of depth of anesthesia for patients. IEEE Transactions on Biomedical Engineering, 48(12), 1424–1433. https://doi.org/10.1109/10.966601