The GABAergic Gateway: A Chemist's Hypothesis for Psychedelic Mechanisms

J. D. Rolfes

Department Theory & Praxis, Albert Hofmann Institute for Physiochemical Sustainability, Albert-Schweitzer-Str. 22, D-32602 Vlotho, Germany.

AUTHOR PERSPECTIVE

As a PhD chemist with expertise in psychedelic pharmacology, I approach this question from a pharmacokinetic and receptor-binding perspective. This cross-disciplinary synthesis is intended to stimulate discussion and collaboration among neuroscientists, psychiatrists, and pharmacologists. While I bring deep understanding of drug-receptor interactions and pharmacokinetics, the neuroscientific details proposed here (MRS methodologies, TMS-EEG protocols, GABAergic circuit mechanisms) represent a chemist's interpretation of the literature and should be critically evaluated by systems neuroscience experts.

I welcome collaborations to test these hypotheses empirically.

Contact: jd.rolfes@a-h.institute

Core Thesis:

This paper proposes that GABAergic circuit modulation is a necessary – but not sufficient – systems-level gate, with potential contributions from thalamocortical (TRN) circuitry, that may convert transient 5-HT2A activation into acute phenomenology and sustained plasticity.

Abstract

Background: Psychedelic-assisted therapies show promise for MDD, PTSD, and addiction, yet mechanisms are often framed as 5-HT2A-centric, despite evidence of GABAergic pathology in these conditions.

Hypothesis (Author Perspective): As a chemist examining psychedelic pharmacology, I propose that inhibitory-circuit modulation acts as a necessary systems-level gate converting transient 5-HT2A activation into acute phenomenology and sustained plasticity.

Evidence: (i) Provisional 1H-MRS indicates coordinated mPFC GABA-glutamate recalibration (GABA+ denotes macromolecule-containing edited signal; interpretation requires harmonized pipelines); (ii) critical-period reopening (2 days-4 weeks) outlasts receptor occupancy, implicating downstream gating; (iii) target disorders show robust GABAergic deficits.

Predictions: This framework suggests ΔGABA+ should couple to network and gamma changes; post-acute GABA_A positive allosteric modulation (PAM) potentiation should truncate plasticity windows; baseline GABA+ may stratify response.

Implications: This perspective suggests treating GABA as a potential gate, not the origin, and encourages integrating 7T MRS, PET, TMS-EEG, and pharmacological challenges.

Disconfirmers: The hypothesis would be challenged by an absence of ΔGABA+-network coupling; failure of post-acute GABA_A PAMS to truncate plasticity windows; or no prognostic value of baseline GABA+ after harmonized analysis.

Note: This hypothesis paper presents a cross-disciplinary perspective intended to stimulate neuroscience research. Empirical validation by systems neuroscience experts is required.

1. The Serotonin Blind Spot

This paper treats excitatory-inhibitory (E/I) gating as a potentially compound-general mechanism, while acknowledging class-specific entry points (5-HT2A vs NMDAR vs monoamine release). While this paper uses psilocybin as a primary exemplar, the hypothesis may also apply to ketamine. However, the MRS evidence for ketamine's GABAergic effects is mixed, with studies showing increases, decreases, or no change in GABA+ (Singh et al., 2021; Rowland et al., 2005); thus, the E/I gating mechanism might be achieved differently (e.g., via direct NMDAR blockade on interneurons) even if the functional outcome is similar.

Yet the conditions psychedelics treat—MDD, PTSD, addiction—all exhibit profound GABAergic deficits: reduced cortical GABA concentrations (-20-50%) (Schür et al., 2016), decreased GAD67 expression (Gabbay et al., 2012; Luscher et al., 2011), and altered GABA_A receptor subunit composition (Hasler et al., 2007; Fogaça & Duman, 2019; Huang et al., 2023; Sarawagi et al., 2021).

This creates an apparent mechanistic paradox: if psychedelics operate primarily through 5-HT2A activation, why do they appear effective at treating disorders characterized by GABAergic—not serotonergic—deficits? Early head-to-head and indirect comparisons suggest overlapping effect sizes at prespecified timepoints; longer-term comparative effectiveness remains unresolved (Goodwin et al., 2022; Carhart-Harris et al., 2021; Davis et al., 2021). The Gateway Hypothesis proposed here aims to resolve this by repositioning GABA as a potential central mediator.

A counterargument holds that 5-HT2A activation on GABAergic interneurons represents the sole mechanism. However, this hierarchical model may not explain: (1) why psychedelics with similar 5-HT2A affinity produce vastly different plasticity window durations (Nardou et al., 2023), (2) why baseline GABA deficits might predict clinical response better than serotonin measures (speculative but testable), (3) why GABAergic drugs like fluoxetine can independently reopen plasticity windows (Maya Vetencourt et al., 2008), or (4) why other GABAergic drugs (e.g., benzodiazepines) do not produce lasting antidepressant effects, suggesting that while GABAergic

modulation appears necessary, it may not be sufficient in isolation to produce durable antidepressant effects.

Acknowledging Gaps: This paper focuses on the cortical GABAergic gate but acknowledges other critical, under-explored hubs, including thalamocortical gating (thalamus/TRN) and non-neuronal players (astrocytic GABA, microglial PNN remodeling, MMPs) which could be complementary to this hypothesis.

2. Mechanistic Evidence: Three Converging Lines

Three independent lines of evidence converge to suggest GABAergic circuits may be central rather than peripheral to psychedelic action:

A. Acute Neurochemical Reorganization

Provisional MRS evidence: Early studies using 1H-MRS (MEGA-PRESS) suggest psilocybin may alter mPFC "GABA+" (a composite signal including macromolecules) (Mason et al., 2020). "GABA+" is used here to denote macromolecule-containing edited signal. Interpretations depend on voxel tissue-fraction correction, macromolecule suppression, and motion QC. A harmonized meta-analysis with standardized pipelines (Osprey/LCModel versions, TE/TR, water scaling) is needed to confirm these findings (see Table 1).

Electrophysiological signatures: Psychedelics robustly modulate gamma-band activity (30-80 Hz) (Muthukumaraswamy et al., 2013; Carhart-Harris et al., 2012), a proxy biomarker for, but not definitive proof of, GABAergic interneuron engagement, as comprehensively reviewed by Hatzipantelis et al. (2024). Gamma is treated here as a proxy of PV/SST engagement; TMS-EEG SICI (GABA_A) and LICI (GABA_B) may provide closer inhibitory assays (Table 2). Recent neurovascular coupling studies further suggest that psychedelic-induced alterations in GABA-mediated circuits might create measurable changes in hemodynamic-neuronal relationships (Padawer-Curry et al., 2025).

5-HT2A localization & Cell-Type Specificity: These receptors densely populate both layer V pyramidal neurons AND GABAergic interneurons (Martin & Nichols, 2016; Willins et al., 1997; López-Giménez & González-Maeso, 2018; Schmitz et al., 2025; De Filippo, 2024). Recent work suggests a possible sequence: lasting antidepressant effects may be dependent on 5-HT2A activation on pyramidal cells (Michaiel et al., 2024; Urban et al., 2023; Cao et al., 2023), which then likely recruits interneuron-mediated network gating to enact the plasticity program.

Intracellular Mechanisms: Psychedelics promote neuroplasticity by activating 5-HT2A receptors located inside the neuron, initiating distinct downstream signaling cascades (Vargas et al., 2023). This is an emerging mechanism that may be complementary to the network-level gateway model.

Thalamocortical Gating: Given dense GABAergic inhibition within the thalamic reticular nucleus (TRN), thalamocortical gating is a plausible upstream contributor to cortical E/I recalibration; incorporating thalamic ROIs into MEG-fMRI DCM could

help adjudicate cortico- vs thalamocentric pathways. The TRN is treated here as a complementary parallel pathway requiring separate validation; the cortical GABAergic gate remains the primary focus for Hypotheses 1-3.

B. Critical Period Plasticity Reopening

Landmark finding: Multiple psychedelics reopen social reward learning critical periods in mice (Nardou et al., 2023). Critically, these reopening durations (2 days-4 weeks) outlast receptor occupancy, implicating downstream reorganization (Dölen, 2024). This temporal mismatch suggests durability may be driven by combined effects of structural plasticity (Ly et al., 2018), PNN remodeling, astrocytic signaling, and transcriptional programs (e.g., BDNF/mTOR), with GABA gating as a possible proximal brake.

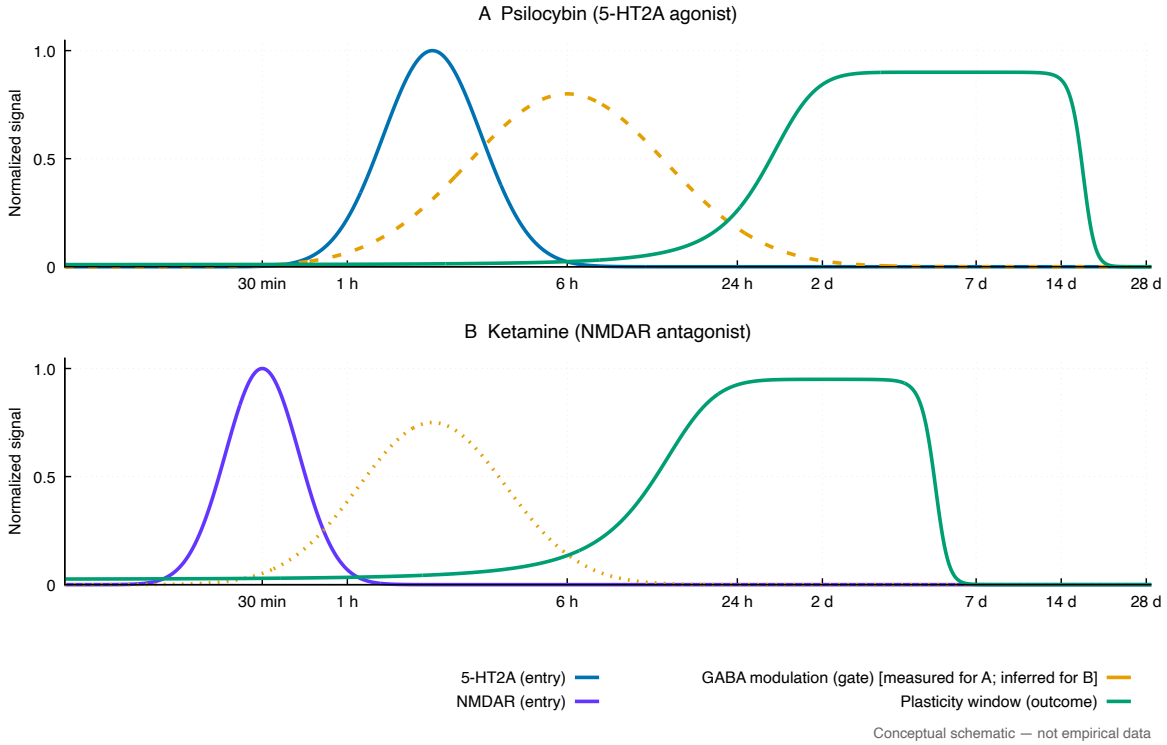

Figure 1. Temporal dissociation between receptor occupancy and sustained plasticity suggests GABAergic gating mechanism. Schematic (non-quantitative) curves illustrate pharmacologic entry phases (5-HT2A/NMDAR; blue/purpl), GABAergic gating (orange), and plasticity windows (green). Time axis is logarithmic to span hours–days–weeks. **(A) Psilocybin:** 5-HT2A receptor occupancy (blue) peaks at 2h and returns to baseline by 8h, consistent with psilocin pharmacokinetics (half-life 2-3h) (Madsen et al., 2019; Holze et al., 2022). GABAergic circuit modulation (orange) peaks at ~6h based on provisional MRS measurements (Mason et al., 2020) and normalizes by 48h. The plasticity window (green) opens around 6h and remains elevated through 14+ days, supported by sustained dendritic spine density and structural synaptic changes (Ly et al., 2018; Nardou et al., 2023). **(B) Ketamine:** NMDAR occupancy (purple) peaks at 30 min and returns to baseline by 2h (Zanos et al., 2018). GABAergic modulation (orange) peaks at ~2h with faster kinetics than psilocybin, inferred from NMDAR blockade on GABAergic interneurons (Fogaça & Duman, 2019). The plasticity window (green) sustains 5-7 days, consistent with clinical antidepressant duration (Murrough et al., 2013; Ma et al., 2023). **Core hypothesis:** Both compounds demonstrate Entry → Gate → Outcome temporal sequence, suggesting compound-general GABAergic gating with class-specific entry points (Calder & Hasler, 2023). **Line style conventions:** Solid lines represent timing supported by pharmacokinetic/PET data; dashed (psilocybin) indicates MRS-measured but interpretation-complex GABA signal; dotted (ketamine) indicates mechanistic inference

requiring direct validation. ΔGABA+ reflects MRS-measured concentration changes; the hypothesized functional mechanism is GABAergic disinhibition (reduced inhibitory tone) (De Gregorio et al., 2021).

Pharmacological Precedent: This mechanism was first demonstrated with MDMA, which reopens a critical period for social reward learning in mice (Nardou et al., 2019).

GABAergic gating mechanism: Critical period closure in visual and social systems is mediated by maturation of GABAergic circuits, particularly parvalbumin+ interneurons and perineuronal nets (PNNs) (Pizzorusso et al., 2002). Psychedelics may act as proximal gates by modulating PNNs or extracellular matrix enzymes (MMPs) to temporarily reverse these GABAergic brakes (Hensch, 2005; Fagiolini & Hensch, 2000; Takesian & Hensch, 2013). The 2025 Beretta et al. review provides emerging evidence that psychedelics may specifically target these GABA-dependent closure mechanisms through coordinated serotonin-GABA signaling (Beretta et al., 2025).

Proposed Causal Chain: I propose an explicit causal chain: acute 5-HT2A activation leads to cortical disinhibition (0-6h), which reduces the activity of key interneuron populations (e.g., PV+). This reduction in activity may, in turn, trigger enzymatic remodeling of their surrounding perineuronal nets (PNNs) via matrix metalloproteinases (MMPs), effectively "unlocking" the circuit and enabling the sustained critical period reopening (48h-7d).

Translation to psychiatry: The critical period framework, proposed as a specific model for psychedelic-assisted psychotherapy (Gul & Niehaus, 2021) and supported by systematic reviews on neuroplasticity (de Vos et al., 2021), suggests psychedelics create temporary windows of enhanced neuroplasticity, during which therapeutic "reprogramming" may become possible—analogous to how fluoxetine reopens visual cortex plasticity via GABAergic modulation (Maya Vetencourt et al., 2008).

Non-Neuronal Mechanisms: Astrocytic GABA (tonic inhibition via α_5/δ subunits), microglial PNN remodeling, and MMP activity likely shape window duration even when initiation is pyramidal 5-HT2A-dependent.

C. Therapeutic Target Alignment

The deficit-correction model: Depression shows 20-50% reductions in cortical GABA, decreased GAD67, and parvalbumin interneuron density loss. PTSD exhibits altered GABAergic function in hippocampus and PFC (Luscher et al., 2011; Fogaça & Duman, 2019; Meyerhoff et al., 2014; Rosso et al., 2014; Schür et al., 2016).

Psychedelic action: By modulating GABAergic interneuron activity and reopening plasticity windows, psychedelics may restore deficient inhibitory tone while simultaneously enabling experience-dependent circuit rewiring (De Gregorio et al., 2021; Calder & Hasler, 2023).

Compound & Disorder Heterogeneity: This paper considers E/I gating as potentially compound-general but entry-point-specific (5-HT2A vs NMDAR vs monoamine release) and phenotype-specific across MDD, PTSD, and SUD; predictions could be stratified accordingly.

3. The GABAergic Gateway Hypothesis

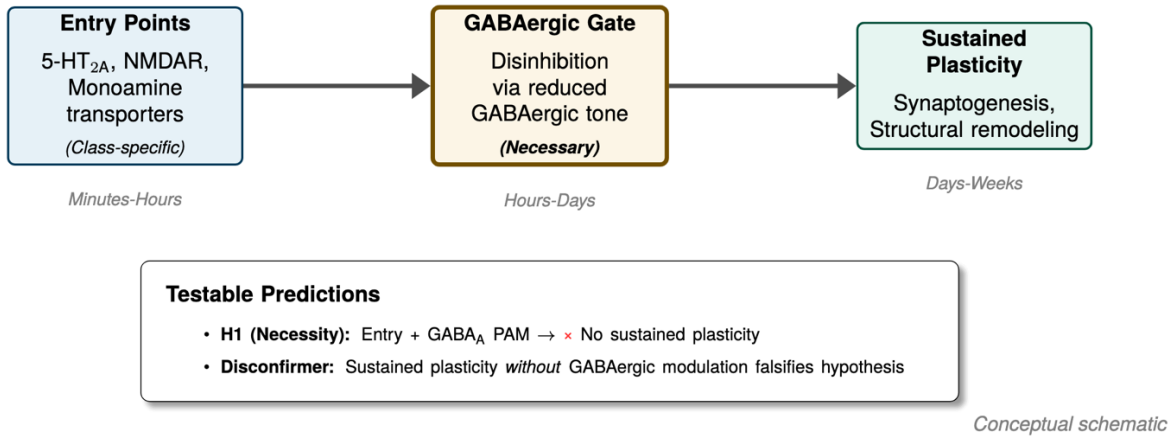

Figure 2. The GABAergic Gateway Hypothesis: compound-general gating mechanism with class-specific entry points. The model proposes three sequential stages: **(1) Entry Points**—class-specific receptor activation (e.g., 5-HT_2A for psilocybin, NMDAR for ketamine, monoamine transporters for MDMA) (Vollenweider & Preller, 2020); **(2) GABAergic Gate**—common disinhibition mechanism via reduced GABAergic tone on pyramidal neurons, marked as **necessary** for sustained effects (De Gregorio et al., 2021; Calder & Hasler, 2023); and **(3) Sustained Plasticity**—synaptogenesis and structural remodeling lasting days to weeks (Ly et al., 2018; Nardou et al., 2023). **Testable prediction (H1):** Co-administration of entry point activation with GABAA positive allosteric modulator (PAM) at 6h should block sustained plasticity despite intact receptor occupancy by counteracting the necessary disinhibition (Hypothesis 2). **Disconfirmer:** Demonstration of sustained plasticity without GABAergic circuit modulation would falsify the necessity claim. Time annotations (minutes-hours, hours-days, days-weeks) correspond to temporal phases in Figure 1. Conceptual schematic illustrates the hypothesis framework requiring empirical validation.

Hypothesis 1: Network Reorganization (Test-Ready)

It is proposed that ΔGABA_mPFC (macromolecule-suppressed 7T MEGA-PRESS; water-scaled) predicts Δeffective connectivity (spectral DCM) and ΔMEG gamma 30-80 Hz, beyond ΔGlu and subjective intensity. A potential preregistered partial-R^2 target could be ≥ .05.

- **Assays:** 7T MEGA-PRESS (macromolecule-suppressed), concurrent MEG-fMRI, spectral DCM.
- **Disconfirmers:** No ΔGABA+-network coupling or gamma changes fully explained by arousal proxies.

Hypothesis 2: Plasticity Window Opening (Test-Ready)

Administering a GABA_A PAM 6-8 h post-dose (to minimize psychotherapy/acute-state confounds), with propranolol as a non-GABA anxiolytic control and a timing arm (PAM at +24 h), might shorten TMS PAS aftereffects and reduce Day-14 extinction retention vs controls. An δ-pref agonist might show > γ_2-pref PAM in truncation magnitude.

- **Assays:** Paired-associative stimulation (TMS), motor learning, fear-extinction retention; clinical scales at 2-6 weeks.

- **Bidirectionality test:** A δ-subunit-preferring agonist (e.g., gaboxadol) or GAT-1 inhibitor (e.g., tiagabine) could modulate the window's duration.
- **Null result:** A null result (i.e., the PAM has no effect on the plasticity window) would challenge this hypothesis, suggesting the GABAergic gate is merely permissive, not necessary, and would require reframing.

Hypothesis 3: Individual Response Prediction (Test-Ready)

Baseline GABA+ z-score may predict peak intensity, early AEs, and 4-8 week response (multilevel models, site random intercepts); genetics (GAD1/GABRA1/5) could enter as interaction terms.

- **Confounders:** Would require pre-specifying covariates (sex hormones, circadian, caffeine, nicotine, recent alcohol, benzodiazepines, antiepileptics).
- **Genetics sub-study:** GAD1/GABRA1/5 variants might moderate dose-response.

4. Research Agenda

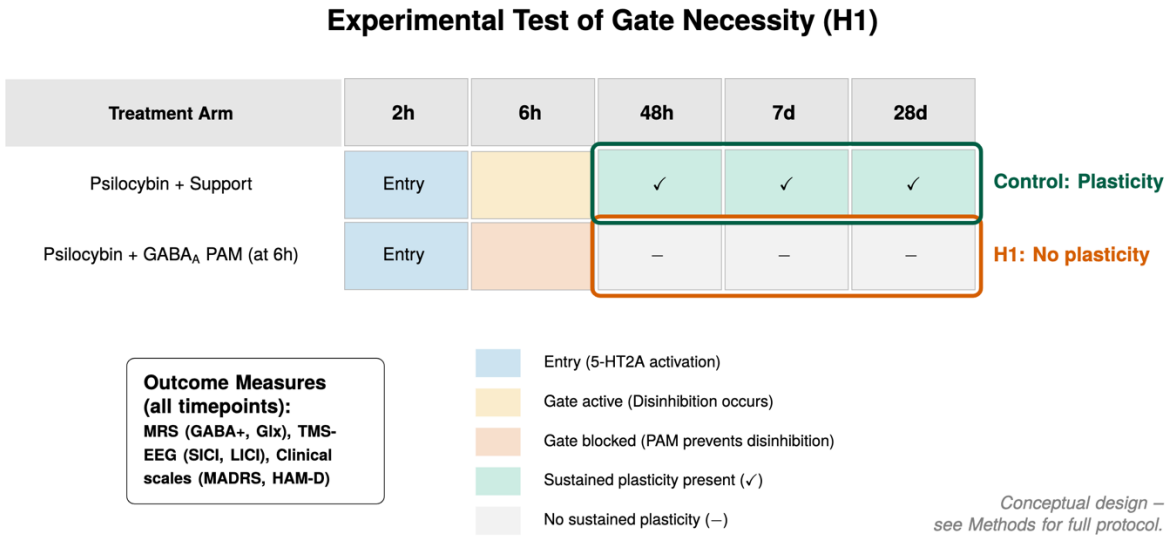

Figure 3. Experimental design for testing GABAergic gate necessity (H1). Two-arm comparison tests the prediction that blocking the GABAergic gate prevents sustained plasticity despite intact entry point activation. **Active arm** (psilocybin + psychotherapy support) shows predicted temporal sequence matching Figure 1: entry activation at 2h (5-HT2A receptor occupancy), GABAergic gating (disinhibition) at 6h, and sustained plasticity markers emerging at 48h and persisting through 7d and 28d (green, ✓) (Ly et al., 2018; Nardou et al., 2023). **Gate-blocked arm** (psilocybin + GABAA positive allosteric modulator administered at 6h) shows entry activation but PAM-mediated enhancement of GABAergic inhibition counteracts the necessary disinhibition, predicted to prevent plasticity window opening (gray, –). Outcome measures include MRS for GABA+/Glx quantification, TMS-EEG for cortical excitability (SICI, LICI), and clinical scales (MADRS, HAM-D) collected at all timepoints per Hypothesis 2 protocol. **Critical prediction:** Plasticity markers should diverge between arms by 48h, when the active arm shows open plasticity window while blocked arm shows closure. **Disconfirmer:** If sustained plasticity emerges in the gate-blocked arm (48h–28d), H1 (gate necessity) is falsified (De Gregorio et al., 2021; Calder & Hasler, 2023). Timeline corresponds to Figure 1 temporal dynamics. Full protocol including additional control arms (placebo, microdose) detailed in Methods.

Methodological Rigor & Multimodal Imaging

- **Pre-register Pipelines:** Harmonize MRS quantification (Osprey/LCModel params), motion thresholds, tissue-fraction correction, outlier policy; commit to code release.
- **Power:** A potential power target: detectable partial-$R^2 \geq .05$ for ΔGABA+ Δconnectivity at $\alpha = .05$, $1\text{-}\beta = .80$ implies $n \approx 84$/arm (multisite, random intercepts).
- **TMS-EEG Suite:** Add SICI (GABA_A), LICI (GABA_B), and SAI (cholinergic) measures pre/acute/post to map the full inhibitory trajectory.
- **Multimodal Imaging:** Combine MRS with PET ligands (e.g., [11C]flumazenil for GABA_A sites (Gunn et al., 1997), [11C]UCB-J for synaptic density (Nabulsi et al., 2016)) and myelin-sensitive MRI (MT, qT1) to disambiguate E/I shifts from synaptogenesis; PET kinetic modeling (e.g., SRTM vs 2TCM) should be preregistered.
- **Timing Grid:** Standardize assessments at 0h, 6h, 48h, Day 7, Day 14, Day 28.
- **Controls:** Include psychological support-only and microdose + full-support arms to separate expectancy and therapeutic alliance from physiology.

Technical innovation needed: Current MRS methodology cannot resolve GABA concentrations in hippocampus or amygdala—regions critical to trauma processing and emotional regulation. Next-generation ultra-high-field MRS (7T+) will be essential.

Ethics & Safety: Benzodiazepine arms would need to include sedation monitoring, memory assessments, and therapist-blinding checks to separate neural from psychotherapeutic engagement effects and incorporate a therapist-engagement checklist to quantify session-level confounding.

Table 1: Proposed MRS Harmonization Checklist (for Meta-Analysis)

Parameter	Specification	Rationale
Field Strength	3T/7T	Report field; 7T preferred for SNR
Sequence	MEGA-PRESS (TE/TR)	Report all sequence parameters
MM Suppression	Y/N; method (e.g., symmetric editing, ON-OFF); report basis set	Critical for interpreting "GABA+"
Voxel	Size (cc), Location	Report MNI coordinates
Tissue Fraction	GM/WM/CSF %	Correct signal for tissue composition
Scaling	Water / Cr	Water-scaled (mmol/kg) preferred
Software	Osprey / LCModel (version)	Report quantification pipeline
Motion QC	Threshold (e.g., <2mm)	Pre-specify motion exclusion criteria
Effect Size	Hedges' g	95% CI

Table 2: Assay Glossary for Testing the Gateway Hypothesis

Claim	Assay	Target	Expected Direction	Disconfirmer	Timing
Acute Inhibition	TMS-EEG: SICI	GABA_A	↑ or ↓ (complex)	No change vs. placebo	Acute (0-8 h)
Acute Inhibition	TMS-EEG: LICI	GABA_B	↑ or ↓ (complex)	No change vs. placebo	Acute (0-8 h)
GABA Function	1H-MRS: GABA+	GABA+ pool	↑ (provisional)	No change; or no coupling	Acute (0-8 h)
Synaptic Density	PET: [^{11}C]UCB-J	SV2A	UCB-J	-	Post-acute
GABA Receptor	PET: [^{11}C]flumazenil	GABA_A-BZD site	flumazenil	-	Acute/Post
Network State	MEG/EEG: Gamma	PV/SST networks	↑ (acute)	No coupling to GABA+	Acute (0-8 h)
Connectivity	fMRI: Spectral DCM	E/I parameters	↑ Excitatory	Model fit not improved	Acute (0-8 h)

Near-term (1-3 years)

- Retrospective analysis of existing MRS datasets correlating baseline GABA with therapeutic outcomes (Mason et al., 2020).
- Biomarker validation: EEG gamma-band biomarker validation in clinical trials already underway (Hatzipantelis et al., 2024).
- Genetic associations using existing biobanks (e.g., GAD1/GABRA variants) (Luscher et al., 2011; Fogaça & Duman, 2019).

Long-term (3-5+ years)

- Prospective Neuroimaging: Combined MRS/fMRI studies during acute psychedelic states to map region-specific GABA/glutamate dynamics (Mason et al., 2020).
- Pharmacological dissection: Co-administration studies with GABAergic modulators (e.g., benzodiazepines, neurosteroids) to test causal role (Sjöstedt et al., 2021).
- Integration optimization: Define optimal "therapeutic windows" post-dosing based on compound-specific critical period reopening durations (Nardou et al., 2023).

5. Discussion and Conclusion

This hypothesis paper aims to challenge the 5-HT2A-centric model of psychedelic action by synthesizing evidence that positions inhibitory circuits as a potential central, necessary but not sufficient mechanistic hub. The central thesis—the GABAergic Gateway Hypothesis—proposes that the modulation of specific GABAergic interneuron populations may be the critical systems-level gate that translates acute serotonergic

activation into both the characteristic phenomenological state and, most importantly, the sustained windows of therapeutic neuroplasticity.

This framework may help resolve the apparent paradox of why "serotonergic" drugs appear effective at treating "GABAergic" pathologies. Furthermore, it provides a compelling explanation for the temporal mismatch between acute receptor kinetics and long-lasting therapeutic change—a gap that hierarchical serotonergic models may fail to explain. This view also complements existing network-level theories like the REBUS model (Carhart-Harris & Friston, 2019).

This hypothesis must also address an apparent paradox in the evidence: the "GABA+" signal measured by MRS (Mason et al., 2020) provisionally increases, while the hypothesized functional mechanism is a disinhibition (a decrease in inhibitory tone). This might be explained by: (1) a compartmental shift, where reduced synaptic GABA release leads to accumulation in the extrasynaptic space, increasing the total MRS-visible pool, or (2) the MRS signal reflecting a metabolic uncoupling, where total GABA concentration is disconnected from the rate of synaptic release.

It is important to acknowledge the limitations of the current data. Much of the human evidence remains correlational. This hypothesis will be challenged if: (1) no reproducible link is found between ΔGABA+ and network changes; (2) GABA_A PAMs administered post-acute fail to shorten the plasticity window; or (3) strong responders show normal baseline GABA+ once site effects are controlled. Causal studies, particularly the pharmacological challenge and genetic association studies proposed in the research agenda, are now required to falsify or refine these hypotheses.

The clinical implications of this paradigm shift could be significant. If baseline GABAergic tone is a key predictor of response, it could become a foundational biomarker for personalized psychedelic medicine. Understanding the GABA-gated nature of the plasticity window might also allow for the optimization of psychotherapy, timing interventions to coincide with periods of maximal neural receptivity.

In conclusion, this paper proposes that GABA may act as the systems gate, not the origin. 5-HT2A (and other entry points like NMDAR) may light the fuse; it is hypothesized that interneuron-centered network control could set the shape and duration of change. The program is testable with multimodal physiology and targeted pharmacology.

Call for Collaboration

The author welcomes collaborations with systems neuroscientists, psychiatrists, and pharmacologists to test the hypotheses presented in this paper empirically.

Acknowledgements

Large language model tools (Claude/Anthropic, ChatGPT/OpenAI, Gemini/Google, and Perplexity AI) were used to assist with literature search, reference verification,

figure creation, and manuscript editing. All content was critically evaluated, verified against primary sources, and edited by the author, who retains full responsibility for the work's accuracy and integrity.

Conflict of Interest Statement

The author declares no competing financial or personal interests. This research received no specific grant funding from any agency in the public, commercial, or not-for-profit sectors.

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