Supplementary Discussion

SD1 Fear loop → progression to the SZ phenotype

SD1.1 Architecture

In schizophrenia, amygdala responses to neutral faces are abnormally high, and hippocampal (DG/CA1) involvement is prominent during affective processing (Hall et al., 2008). vCA1 projects via subiculum to medial PFC; highly aversive stimuli also recruit a thalamo-amygdala route ("low road"), though the prominence of a direct subcortical route in humans is debated (Phelps and LeDoux, 2005; Pessoa and Adolphs, 2010). During auditory verbal hallucinations, EEG shows increased θ–γ phase-amplitude coupling over left frontotemporal cortex (Koutsoukos et al., 2013).

SD1.2 Neuromodulatory trigger

A single fear reminder (or acute stressor) elicits marked dopamine release in medial PFC in rodents and robust salivary cortisol responses in humans (Yoshioka et al., 1996; Schwabe and Wolf, 2012). A ~4 Hz mPFC–VTA oscillation on the δ/θ border, phase-locked to hippocampal θ, entrains phasic dopaminergic firing in the VTA (Fujisawa and Buzsáki, 2011). Together, these set initial E/I gain and plasticity thresholds across the loop.

SD1.3 E/I shift, redox stress, and PV vulnerability

In vivo ^1H-MRS shows reduced medial-frontal glutamatergic metabolites in chronic/stabilised SZ (Rowland et al., 2016; mPFC Glx ~0.6 IU lower vs controls; older patients also show lower GABA), consistent with an E/I imbalance (Rowland et al., 2016). Converging translational data indicate redox dysregulation—notably glutathione (GSH) deficit—preferentially injures fast-spiking parvalbumin interneurons (PV-INs) (Cabungcal et al. 2013; Steullet et al. 2017; Perkins et al. 2020). In stressed tree shrews, PV-IR neuron counts fall by ~28–33% in DG/CA2/CA3 (Czéh et al., 2005). In human DLPFC, perineuronal nets (PNNs)—which stabilise PV-INs—are reduced by ~70–76% in layers III/V in SZ (Mauney et al., 2013).

SD1.4 Oscillatory output

PV-IN dysfunction and PNN loss degrade γ generation and long-range synchrony; patients show reduced task-evoked β/γ amplitude and synchrony and abnormal θ–γ coupling (Uhlhaas and Singer, 2010; Koutsoukos et al., 2013). Together, these findings are consistent with a more limbic-weighted γ pattern, in which frontal γ responses are weakened while limbic structures (e.g. amygdala) remain over-engaged in salience attribution.

SD1.5 Morphology / epigenetics

Chronic stress shortens layer II/III mPFC apical dendrites by ~20% in rats, weakening top-down control (Radley et al. 2004). Fear learning is accompanied by histone H3/H4 acetylation at BDNF promoters in hippocampus, stabilising plasticity (Lubin et al., 2008). In the lateral amygdala, fear conditioning drives AMPARs into synapses, strengthening threat encoding (Rumpel et al., 2005). DG engram size is gated by local inhibitory microcircuits (SST-INs), providing a mechanism for engram expansion under biased inhibition (Stefanelli et al., 2016).

SD1.6 Driving sequence (causal sketch)

Fear-engram reactivation → DA & cortisol ↑ (θ/4 Hz coupling) → mPFC E/I shift (↓Glx; context-dependent ↓GABA) → redox load ↑ (GSH↓) → PNN erosion → PV-IN loss/dysfunction → γ disorganisation (↓fronto-cortical, ↑limbic) → dendritic retraction in mPFC + amygdala synaptic potentiation → executive control ↓ → more fear replay (positive feedback). (Radley et al. 2004; Czéh et al. 2005; Rumpel et al. 2005; Uhlhaas and Singer 2010; Mauney et al. 2013; Rowland et al. 2016).

This loop progressively hands control to the limbic system, stabilising the SZ phenotype.

Each step in this sketch is supported directionally by the cited work, but the full sequence has not yet been demonstrated end-to-end in a single experiment.

Notes: All quantitative values are taken directly from the cited sources where available; otherwise directionality is used. No error propagation or sensitivity analysis is performed here (see Supplementary Methods 2.18; Supplementary Table S49).

SD2 Sadness loop → progression to the MDD phenotype

SD2.1 Architecture and state signature

The "sadness" loop couples ventral hippocampus (vHPC/vCA1) with subgenual anterior cingulate (sgACC/BA25) and the default-mode network (DMN). Rumination is associated with stronger sgPFC–DMN coupling and altered alpha/beta dynamics, which in the present framework we interpret as consistent with prolonged slow (δ/θ) replay within this loop (Hamilton et al. 2015, review; Benschop et al. 2021).

SD2.2 Monoaminergic shift and CRF axis

A meta-analysis of CSF monoamine metabolites shows a selective reduction in homovanillic acid (HVA; g≈−0.30 SD) with no significant change in 5-HIAA in MDD, consistent with reduced dopaminergic tone (Ogawa et al., 2018). Concordantly, classic CSF studies reported

elevated CRF-like immunoreactivity in drug-free depressed patients, indicating HPA/CRF disinhibition (Nemeroff et al., 1984).

SD2.3 Local E/I tilt in sgACC

Ultra-high-field (7 T) MRS in depression shows reduced GABA in ACC/subgenual regions and a tendency toward lower glutamatergic metabolites (Glx), consistent with an excitation/inhibition (E/I) imbalance (Godfrey et al., 2018).

SD2.4 Perineuronal-net (PNN) and PV-interneuron vulnerability

Chronic stress and redox dysregulation damage PNNs and preferentially burden fast-spiking parvalbumin interneurons (PV-INs), degrading γ-synchrony and network gain control (Cabungcal et al., 2013; Steullet et al., 2017). In rodents, chronic unpredictable stress reduces PNN density in prelimbic cortex (a BA32/24 homolog functionally coupled to sgACC) and tracks depressive-like behavior (Yu et al., 2020).

SD2.5 Oscillatory output and rumination

Human EEG and imaging studies link higher trait/state rumination to altered alpha/beta power (Forner-Phillips et al., 2020) and increased PCC–sgPFC/DMN connectivity (Hamilton et al., 2015; Benschop et al., 2021).

SD2.6 Structural consolidation

Post-mortem and in-vivo proxies indicate synaptic/spine loss in prefrontal cortex in depression and under chronic stress. Dorsolateral PFC shows reduced expression of synapse-related genes and decreased synapse/spine measures (Kang et al., 2012). Chronic restraint stress in mice produces grey-matter loss in ACC/hippocampus that is accounted for by dendritic retraction and spine loss (up to ~60% in ACC dendrites) (Kassem et al., 2013). Chronic stress reviews converge on PFC dendritic atrophy/spine loss as a robust phenomenon (Qiao et al., 2016).

SD2.7 Driving sequence (causal sketch).

HVA ↓ (DA tone) → CRF axis disinhibited (CSF CRF ↑) → prolonged δ/θ vHPC↔sgACC replay → local E/I tilt in sgACC (GABA ↓; Glx ↓/trend) → redox load ↑ → PNN erosion → PV-IN dysfunction → β/α imbalance and DMN–sgPFC coupling ↑ → dendritic/spine loss in PFC → executive control ↓ → next rumination cycle (Nemeroff et al., 1984; Kang et al., 2012; Cabungcal et al., 2013; Kassem et al., 2013; Godfrey et al., 2018; Ogawa et al., 2018; Forner-Phillips et al., 2020; Yu et al., 2020; Benschop et al., 2021).

Each step in this sketch is supported directionally by the cited work, but the full loop has not yet been demonstrated end-to-end in a single longitudinal study.

Notes. All quantitative values above are directly taken from sources where available; otherwise we report directionality only. No error propagation or sensitivity analysis is performed here (see Supplementary Methods 2.18; Supplementary Table S50).

SD3 Trauma loop → progression to the PTSD phenotype

SD3.1 Architecture and neuromodulatory trigger

An acute trauma reminder strongly engages the LC→BLA noradrenergic projection; optogenetic activation of LC terminals in BLA produces robust norepinephrine release (fast-scan cyclic voltammetry) and anxiety-like behavior via β-adrenergic receptors (McCall et al., 2017). Dopaminergic modulation of BLA excitability during threat states is well documented (Rosenkranz and Grace, 2002; Giustino and Maren, 2015; Giustino et al., 2020). In patients with PTSD, CSF CRF is elevated versus controls, consistent with HPA/CRF up-drive (Bremner et al., 1997).

SD3.2 Local E/I shift in hippocampo-insular nodes

Ultra-high-field (7 T) ^1H-MRS in PTSD shows higher glutamate in right hippocampus (Rosso et al., 2017) and lower GABA in anterior insula (≈ 30% reduction in GABA/Cr) (Rosso et al., 2014). Chronic stress paradigms also induce a depolarizing shift of E_{GABA} in CA1, consistent with reduced inhibition (Inoue et al., 2013; MacKenzie and Maguire, 2015). These changes bias pyramidal ensembles toward hyperexcitability during symptom provocation.

SD3.3 PNN/PV vulnerability and network synchrony

Stress-related redox dysregulation compromises perineuronal nets (PNNs) and disproportionately burdens fast-spiking parvalbumin interneurons (PV-INs), degrading γ-range gain control (Cabungcal et al., 2013; Steullet et al., 2017; Perlman et al., 2021). In human symptom-provocation and resting-state studies, PTSD is associated with abnormal alpha activity (including reduced task-related alpha in several studies) and altered fast-frequency (beta/γ) activity during trauma recollection/symptom provocation, alongside fronto-limbic dysconnectivity (Dunkley et al. 2015; Shaw et al. 2023 trauma provocation/alpha modulation). vmPFC activity is reduced during recall (Shin and Liberzon, 2010). PNN changes with stress are increasingly recognized across limbic cortex, including hippocampus/amygdala (Murthy et al. 2019; Fawcett et al. 2022 review).

SD3.4 Epigenetic and synaptic consolidation

Stress can increase BDNF-promoter methylation in prefrontal cortex (Roth et al., 2009), while fear learning potentiates amygdala synapses via AMPAR insertion, unsilencing previously

GluN-only synapses (Rumpel et al., 2005; Clem and Huganir, 2010). Plasticity at vCA1↔BLA connections is readily inducible after aversive learning (Kim and Cho 2020; Sun et al. 2020), helping stabilize the trauma-biased engram.

SD3.5 Driving sequence (causal sketch).

Trauma reminder → LC→BLA NE burst + DA modulation → CSF CRF ↑ → E/I shift (hippocampal Glu ↑; insular GABA ↓; CA1 E_{GABA} depolarizes) → PNN erosion / PV-IN dysfunction → α suppression & fast-frequency abnormalities + vmPFC hypoactivity during recollection → intrusive recollection/flashback → next LC/NE burst.

Each link in this sketch is supported directionally by the cited work, but the full loop has not yet been demonstrated end-to-end in a single longitudinal study. Numerical magnitudes are reported only where the source provides them explicitly. (see Supplementary Methods 2.18; Supplementary Table S51).

SD4 Loop convergence — the "AMPA-high" vCA1↔BLA hot spot

Across fear, sadness, and trauma loops, threat-biased replay repeatedly potentiates the vCA1↔BLA axis:

Amygdala synapses: fear conditioning inserts AMPARs and converts silent synapses in LA/BLA, strengthening EPSPs (Rumpel et al., 2005; Clem and Huganir, 2010).

Engram neurons: memory-tagged CA1/DG ensembles show enhanced excitatory drive and recruitment under high excitability states (Yiu et al., 2014; Ryan et al., 2015; Rashid et al., 2016; Kitamura et al., 2017).

Network linking: temporally adjacent negative events are co-allocated/linked, allowing a dominant hot spot to capture new content (Yiu et al., 2014; Rashid et al., 2016).

Glia/ECM support: astrocyte–microglia–ECM interactions stabilize synaptic/structural changes underlying persistent memory traces (Fawcett et al., 2022; Rangel-Gomez et al., 2024).

Functional outcome. A consolidated vCA1↔BLA "hot spot" (i) co-allocates temporally adjacent negative experiences (e.g. fear-conditioning episodes), allowing a dominant ensemble to capture new content (Yiu et al., 2014; Rashid et al., 2016), (ii) persists via AMPAR-rich synapses and glial/ECM support (Clem and Huganir, 2010; Fawcett et al., 2022), and (iii) shows strengthened hippocampal CA1→BLA synapses after aversive learning (ventral CA1: Kim and Cho, 2020; hippocampal CA1 inputs and their fear-related plasticity reviewed in: Sun et al.,

2020) which in the EMM framework form a shared electro-synaptic core across SZ, MDD and PTSD phenotypes.

SD5 ELF phase synchronisation and Axis F

SD5.1 Biophysical phase-bias hypothesis

Extremely low-frequency (ELF, 7–30 Hz) magnetic fields in the environment (≈1 pT–0.15 μT) are far too weak to depolarise neurons directly (<0.1 mV), so in EMM we treat ELF coupling purely as a phase-bias mechanism. The working hypothesis is that weak fields can slightly retime the local θ oscillator in vCA1 without providing meaningful charge injection.

Concretely, we posit a high-Q biophysical transducer: chains of ~10^3 biogenic magnetite crystals (radius ≈30 nm; Q ≈12) that amplify B-field modulations and convert them to sub-millivolt somatic biases, with a transfer sensitivity $\kappa \approx 8.27\ \mu V\ \mu T^{-1}$ (Kirschvink et al., 1992; Kirschvink, 1996; Winklhofer and Kirschvink, 2010). Ordered magnetite chains in hippocampal pyramidal neurons have not been demonstrated; this is the sole non-empirically established element of the EMM and is explicitly presented as a testable hypothesis rather than an assumed fact (see Limitations).

Under urban rail-power exposure (16.7 Hz, $B_{rms} \approx 0.15\ \mu T$), the magnetite transfer function yields an effective chain gain $\Phi \approx 100$ and a somatic bias $\Delta V_{soma} \approx 6.2\times10^{-2}$ mV; for the Schumann band (7.83 Hz, ≈ 1 pT), $\Phi \approx 40$ and $\Delta V_{soma} \approx 1.7\times10^{-7}$ mV. These values correspond to ~1% (urban rail) to ≪1% (Schumann) of the residual excitability margin in our CRS → hot-spot → allele scenarios ($V_{margin} \approx 5.7$ mV). In the model, the former could, in principle, contribute a small phase bias in chronically stress-primed, low-ΔV_{margin} networks, whereas any Schumann-band effect would require additional ensemble-level summation, near-critical network conditions and many repeated cycles and therefore remains highly speculative (Supplementary Methods S2.11). In stress-primed vCA1 pyramidal cells, increased input resistance would, if anything, amplify the impact of a given subthreshold ΔV_{soma}, making the present estimates conservative.

On these estimates, the 7.83 Hz Schumann background (≈ 1 pT) is not expected to exert any directly measurable effect on single neurons; at most, it could, under the above conditions, provide an extremely weak phase-bias signal. Direct phase locking would in any case require ensemble summation and favourable coherence conditions and has not been demonstrated in vivo (Supplementary Methods S2.11.4). Independent evidence supports susceptibility of neural oscillators to weak rhythmic fields: low-intensity AC/tACS can entrain δ/θ/α activity and alter

spike timing and network phase in rodents and humans (Ozen et al., 2010; Reato et al., 2010; Thut et al., 2011; Herrmann et al., 2013; Helfrich et al., 2014). In EMM we therefore model ELF as a phase-tuning input that modestly increases coincidence between θ crests and replay-relevant transients (Supplementary Methods S2.11–S2.13).

Existing EEG–Schumann studies have mainly examined healthy participants and macroscopic spectral correlations (Kirschvink et al., 1992; Kirschvink, 1996; Nickolaenko and Hayakawa, 2014; Saroka et al., 2016). Some reports describe partial convergence between α/θ power and Schumann-band activity, whereas others do not, and overall the evidence is inconsistent and non-specific. These findings are conceptually consistent with the idea that neural oscillators can exhibit weak spectral convergence with global ELF modes, but they provide no information about micro-scale mechanisms, low-ΔV_{margin} networks, or hippocampal replay. In EMM we therefore treat them only as motivation for more targeted experiments, not as supporting evidence for Axis F.

SD5.2 Micro-to-meso predictions: daily ELF, urban–rural gradient

In the CRS → hot-spot → *CACNA1C* rs1006737 A background, $\tau_{\text{EPSP,eff}}$ lengthens to ≈25 ms, R_{in} rises by ≈29%, and perisomatic PV shunt falls by ≈16%, yielding θ-locked somatic responses ≈1.21 mV and SWR-locked ≈0.40 mV (total packet ≈1.61 mV) (Supplementary Methods S2.13). Assuming conservative independence between urban ELF bands (7.83, 16–18, 20–28 Hz; $|r| \leq 0.05$), the probability that at least one ELF crest falls into the same 25 ms window as a θ crest (P_{phase}) is ≈0.47 in cities vs ≈0.20 in rural settings, i.e. a 2.4-fold gradient (Supplementary Methods S2.14; Supplementary Table S39).

This maps to $N_{\text{hit}} \approx 2.29\ \text{min}^{-1}$ (urban rest) vs $\approx 0.96\ \text{min}^{-1}$ (rural). A low oral dose of caffeine (~100 mg) adds ≈ +1 mV to ΔV_{soma} (A_1 block → GIRK↓), contracting the effective buffer to ≈ 1.57 mV and further increasing daily activations (EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA), 2015; Lopes et al., 2019; Supplementary Table S23). Under these conditions this corresponds to ≈ 3300 vs ≈ 1400 involuntary engram activations per day from θ+SWR coincidences that exceed the narrowed margin (Supplementary Methods S2.15).

At the epidemiological level, the model's 2.4 urban:rural P_{phase} gradient mirrors the observed psychosis risk ratio in cities (RR ≈2.37; (Vassos et al., 2012)) without asserting causality (Supplementary Methods S2.14). We treat this convergence as an internal consistency check rather than as evidence that ELF is the dominant driver of urbanicity effects.

SD5.3 Interaction with THC and γ-band weakening

Chronic adolescent exposure to high-THC (>10%) cannabis suppresses γ-band power in the vHPC/BLA circuit by ≈70% (range 50–83%) in rodents (Raver et al., 2013). In our model, such a loss weakens the PV-mediated γ brake and widens the EPSP coincidence window from 5 ms to ~8.5 ms. For a given ELF forcing amplitude, a wider coincidence window increases the probability of phase locking; the model predicts that the probability of ELF-assisted θ/SWR coincidences rises by ~1.7× under this γ deficit, because under a uniform-phase approximation coincidence probability scales with window width (8.5/5 ≈ 1.7).

Combined with the urban ELF gradient (×2.4), this yields a composite phase-bias factor of ≈4.1, which is numerically similar to the EU-GEI multicentre estimate for daily use of >10% THC cannabis and psychosis risk (OR = 4.8, 95% CI 2.5–6.8; (Di Forti et al., 2019)). Again, this is presented as numerical convergence at the level of risk multipliers, not as a causal proof; the THC → γ deficit → broader coincidence window → increased psychosis risk in already vulnerable networks.

SD5.4 Geomagnetic storms, Schumann narrowing and clinical endpoints

Geomagnetic storms with Kp ≥6 narrow the full width at half maximum (FWHM) of the 7.83 Hz Schumann peak by ≈9–15% (mean ≈11%) (Sátori et al., 2007; Pazos et al., 2019; Rodríguez-Camacho et al., 2022). Under the EMM, increased Schumann coherence (narrower peak) is expected to increase ELF phase coherence and thus P_{phase} and N_{hit}. A conservative scenario assuming 6.5% FWHM narrowing yields model-predicted increases of P_{phase} ~+28% and N_{hit} ~+28%; using the full 11% average constriction (Supplementary Methods S2.16; Supplementary Table S45B) yields a higher expected relative risk.

A meta-analysis of eight datasets (psychiatric and cardiovascular admissions; Supplementary Table S46) yields a pooled RR ≈1.19 for hospital admissions within 48 h after Kp ≥6 storms. Single studies report +21–29% incidence of MI/ACS/stroke (Gaisenok et al., 2025) and +0.13–0.54% increases in total and cardiovascular mortality per +1 SD Kp in 44 million US residents (Zilli Vieira et al., 2019). Notably, the pooled RR ≈1.19 corresponds to the conservative 6.5% narrowing scenario; when the full 11% average constriction is applied, the model predicts a relative risk of ≈1.33 for hospital admissions in the same 48 h window. The mapping from the model-predicted ~28% increase in N_{hit} to an expected relative risk uses the empirically derived micro→macro linking coefficient β obtained from a meta-analysis of storm–admission datasets (Supplementary Methods S2.16.5; Supplementary Table S46).

We interpret these associations as compatible with the model's predictions but strictly observational. They do not establish ELF → disease causality, and they are explicitly relegated to the β-loop track (environment → clinic) for prospective adjudication.

SD5.5 Conceptual pathway: from phase bias to psychiatric and cardiovascular events

Within EMM, weak ELF fields cannot drive spikes directly; their putative contribution is confined to nudge θ/γ phase when ΔV_{margin} is already narrow. In CRS-primed, hot-spot-sensitised, allele-loaded networks, this phase nudge increases the rate of involuntary replay events (θ+SWR threshold crossings). At the systems level, frequent involuntary replay is expected to increase HPA axis and LC–NE output (e.g., intrusive trauma-related content, psychosis-like salience), leading to transient elevations in cortisol, heart rate and blood pressure.

For psychiatric endpoints, this provides a plausible route by which phase-biased replay could modulate symptom fluctuations (e.g., brief decompensations, hospital admissions) on top of the core ΔV_{margin} collapse. For cardiovascular endpoints, we consider a similar conditional pathway: increased sympathetic drive and blood pressure could, in vulnerable individuals with advanced atherosclerosis or arrhythmia substrates, slightly increase the short-term probability of plaque rupture, thrombus formation or malignant arrhythmias. We do not claim that ELF storms "cause" MI or stroke; rather, we treat them as one possible trigger of autonomic and vascular stress superimposed on pre-existing structural risk.

Formally, injection locking is described by Arnold tongues, where the range of lock-in widens with forcing amplitude and depends on intrinsic oscillator coherence (Q_θ) and phase noise. Loss of γ-band stability (e.g., under THC) can effectively broaden the practical capture range and facilitate phase locking even to weak ELF fields. Phase noise can either facilitate or impede capture under very weak forcing; here we present a conservative, qualitative intuition consistent with Adler's locking criterion.

SD5.6 Summary and role of the β-loop

The ELF branch of the EMM is presented strictly as a hypothetical, mechanistically motivated extension. It offers a coherent interpretation of three observations (urban–rural gradients, γ-weakening, geomagnetic short-term fluctuations), but does not constitute a set of testable mechanistic claims within this manuscript. No specific microscopic transducer, phase-locking pathway, or clinical consequence is assumed to be correct.

The preregistered β-loop evaluates only one question: whether short-term environmental ELF/geomagnetic fluctuations show any reproducible association with population-level psychiatric or cardiovascular endpoints.

It does not test magnetite, phase synchronisation, θ/SWR coincidence, or any of the mechanistic pathways proposed here.

Accordingly:

- **A null β-loop result** removes Axis F entirely, without affecting Axes A–D or any core conclusions of the model.
- **A positive β-loop result** would retain Axis F only as an empirical association module, indicating that ELF-sensitive clinical variation exists but without supporting any specific microscopic mechanism.

Thus, Axis F provides a conceptual rationale and a falsification target, but all mechanistic elements (biophysical transduction, θ-phase bias, replay perturbation, HPA/LC-NE consequences) remain speculative and require dedicated, future experimental paradigms beyond the scope of this work.

SD6 Environmental and population-level evidence

All exposures and interventions discussed in SD6 are included solely as mechanistic examples to parameterise the model; they do not constitute clinical or lifestyle recommendations.

Viral infections. Seasonal respiratory viruses (e.g. influenza A/PR8) induce hippocampal neuroinflammation with increased IL-6 and related cytokines (Jurgens et al., 2012). Experimental work on IL-6 signalling shows that sustained IL-6 exposure can down-regulate KCC2 and disrupt neuronal chloride homeostasis in hippocampal circuits, leading to depolarising shifts in E_{GABA} and hyperexcitability (Hu et al., 2022; Kurki et al., 2023). In the present model we approximate this as a ≈ +3 mV depolarisation of E_{GABA} in vCA1 (see derivation in Supplementary Methods S2.3), and treat viral IL-6 surges as a transient Cl^--axis hit.

Caffeine. High habitual intake (upper quantiles in the cited cohorts) has been associated with approximately threefold higher odds of stress-induced psychotic-like experiences in non-clinical samples, based on questionnaire-defined exposure bands; exact quantile definitions are given in the original papers. In the present model, such "high-intake" exposure is represented as a somatic depolarisation $\Delta V_{soma} \approx +2.2$ mV, derived from GIRK block at CSF-equivalent

caffeine concentrations (Supplementary Table S23). This conversion is purely mechanistic and used only for simulations; it does not imply any dosing recommendation.†

† Study context (non-operational). The cohorts that reported this association defined "high habitual intake" using intake bins centred around ~330 mg/day and observed ≈3× higher odds of stress-induced psychotic-like experiences in the highest intake group compared with lower-intake participants (Crowe et al., 2011). A prospective study similarly reported ≈3.2× more psychotic-like experiences in the highest intake group (Jones and Fernyhough, 2009). We reproduce these numbers only to document how exposure was operationalised in those studies; they do not constitute dosing guidance. The mechanistic mapping from oral dose to CSF caffeine, GIRK block and ΔV_{soma} is given in Supplementary Table S23 (GIRK block model) and is used strictly as a computational bridge to ΔV_{margin}.

Smoking. Prevalence is markedly higher in affective-psychotic disorders—79–82% in SZ (Leonard et al., 2007), 46% in PTSD (Kelly et al., 2015), 31% in depression (Lasser et al., 2000) vs ~24% in the general population.

Acute nicotine (~0.25 μM in CNS) depolarises the soma by only +0.1 mV (Supplementary Table S25) but reliably narrows the intrinsic γ–θ phase window: γ-band coherence in mPFC increases by ≈25% (Bueno-Junior et al., 2017). In networks with an already narrowed ΔV_{margin} (post-CRS or in a CREB-high hot spot) this reduced jitter facilitates internally generated phase-aligned events (θ/SWR, $[K^+]_o$ bursts, dendritic plateaux), increasing the likelihood of involuntary engram reactivation. This provides a mechanistic explanation for the smoker surplus observed in SZ and PTSD without invoking any external field–driven mechanism.

In MDD the γ–θ deficit is smaller; nicotine's pro-inflammatory actions dominate. Chronic smoking activates the IL-6 → ROS axis (Chan et al., 2016), impairs KCC2-mediated chloride extrusion in stress + nicotine models (Ostroumov et al., 2016), reduces PV interneurons (Kim and Im, 2021) and trims ΔV_{margin} by ≈ 1–1.5 mV (estimate via the NKA α1 → $P2X_7R$ pathway, Supplementary Methods S2.5).

Microplastic / PM_{10}. If we approximate chronic microplastic/PM_{10} exposure as engaging four experimentally characterised micro-pathways—IL-6/KCC2, ATP/P2X7R + slowed $[K^+]_o$ clearance, ROS/Kir2.1 and ECS shrinkage—at the levels reported in rodent neuroinflammation models (Supplementary Tables S19–S22), the composite effect would correspond to an order-of-magnitude ΔV_{soma} narrowing of ~+2–3 mV. This is a model-based extrapolation, not a direct measurement for microplastics/PM10. In a college-student cohort, top-quartile microplastics

exposure was associated with 38% higher odds of depressive symptoms (OR = 1.38, 95% CI 1.21–1.57) (Luo and Lin, 2025).

Genetics. The *CACNA1C* rs1006737 A-allele is associated with increased limbic reactivity: fMRI studies report ≈8–15% higher BOLD responses in hippocampus/amygdala (Bigos et al., 2010), and separate work indicates genotype-by-stress interactions on the cortisol awakening response (Klaus et al., 2018), consistent with altered HPA-axis modulation. At the cellular level, increased CaV1.2 activity is known to prolong EPSPs and lower rheobase in hippocampal pyramidal neurons; in the model this corresponds primarily to axes A (somatic depolarisation) and C (Ca^{2+}-dependent PV/KCC2 vulnerability).

Neuro-imaging. Selective hyper-activity of vCA1 in first-episode psychosis (FEP) and ultra-high-risk (UHR) cohorts (McHugo et al., 2019, 2022) validates the "squeezed" margin in vivo.

Magnetite-sensitised ELF fields in the 16–28 Hz railway band increase Pphase by ≈2.4-fold in our model. The urban–rural psychosis gradient RR ≈ 2.37 (Vassos et al., 2012) — is numerically similar, but this convergence is exploratory and not causal; the ELF module is formally tested in the β-loop.

Axis E – engram rewiring therapies. A single EMDR treatment shifts activation during trauma recall from limbic (amygdala/subcortical) to cortical regions (Pagani et al., 2012), consistent with reduced emotional salience of the active trace, while six weekly propranolol reconsolidation sessions reduce CAPS-5 scores by ≈10 points (≈16%) (Brunet et al., 2018).

Magnesium status. Magnesium dysregulation has been repeatedly linked to depression, and a randomized clinical trial showed that oral magnesium chloride significantly improved depressive symptoms in adults with mild–moderate depression (Tarleton et al., 2017), and a meta-analysis of RCTs confirmed a significant reduction in symptom severity (SMD ≈ –0.92, $p = 0.001$; Moabedi et al. 2023). In schizophrenia, lower Mg^{2+} levels in erythrocytes have been observed (Kanofsky and Sandyk, 1991), and reviews suggest chronic disturbances in magnesium metabolism (Ordak et al., 2017). Chronic stress may also contribute to brain magnesium loss and impair the adaptation of emotional networks (Pickering et al., 2020). In our model, magnesium deficiency, among other mechanisms, weakens the tonic block of NMDA channels and increases synaptic gain, making it easier for synchronized, weak inputs to exceed a narrow ΔV_{margin}. Increasing brain Mg^{2+} with magnesium L-threonate in animal models elevates brain magnesium, increases hippocampal synaptic density and selectively enhances

synaptic transmission for burst inputs, together with stronger NR2B-dependent plasticity (Slutsky et al., 2010). In our model, this is represented as an enhancement of slow AHP and an increase in V_{thr}, which functionally expands ΔV_{margin} and reduces the effectiveness of phase synchronization in generating spikes.

Ketogenic diet (KD). KD can expand ΔV_{margin} and lower network "gain" through several convergent mechanisms. Inhibition of the astrocyte–neuron lactate shuttle via LDH inhibition mimics a KD-like metabolic shift and, in a KATP-dependent manner, hyperpolarises neurons and reduces firing (Sada et al., 2015). KD also enhances tonic adenosine A1 receptor signalling, which further suppresses network discharges and stabilises the integration window (Masino et al., 2011). In addition, β-hydroxybutyrate acts as a class I histone deacetylase inhibitor, up-regulating antioxidant and stress-resistance gene programmes (Shimazu et al., 2013). Clinically, ketogenic interventions have been shown to be feasible, with improvements in metabolic markers and reductions in psychiatric symptom severity in severe mental illness (Sethi et al., 2024), while two case reports in schizophrenia describe marked symptom alleviation with good tolerability (Palmer et al., 2019). In the present framework, KD acts primarily via Axis A — hyperpolarisation through K_{ATP} and adenosine A1 signalling — thereby expanding ΔV_{margin}, and via Axis C — reduction of ROS and inflammation — stabilising PV/KCC2 function; these effects jointly reduce the efficacy of phase-synchronised transients in triggering unwanted replay.

High glycaemic load (GL). High dietary glycaemic load and chronic hyperglycaemia can narrow ΔV_{margin} via two convergent mechanisms. Axis A (ATP/KATP-mediated depolarisation): Elevated plasma glucose increases the intracellular ATP/ADP ratio, closing KATP channels, depolarising the resting membrane potential ($\downarrow V_{rest}$) and increasing excitability (Tucker, 1998). Axis C (AGE–RAGE–NFκB pathway): Excess glucose accelerates formation of advanced glycation end-products (AGEs), and AGE–RAGE engagement activates NFκB, driving oxidative stress and pro-inflammatory signalling (Brownlee, 2001). Chronic inflammatory signalling and microglial activation can, in turn, down-regulate KCC2 via BDNF–TrkB pathways and shift E_{GABA}, weakening GABAergic inhibition (Coull et al., 2005). Together, these processes reduce inhibitory control and raise synaptic gain, making phase-synchronised transients more likely to trigger unwanted engram replay when ΔV_{margin} is already tight. Epidemiologically, high-GI diets have been associated with increased depression risk — in the large Women's Health Initiative cohort, women in the highest vs. lowest GI quintile had ≈22% higher odds of incident depression (OR = 1.22, 95% CI 1.09–1.37) (Gangwisch et al., 2015). In

EMM terms, high glucose exposure acts simultaneously on Axis A and C, functionally narrowing ΔV_{margin} across affective and psychotic disorders.

Additional clues. Complex, weak magnetic fields in the 20–30 Hz range have been reported to induce a "sensed presence" in small experimental studies with healthy volunteers. Preliminary, uncontrolled work suggests that selectively shielding this band may reduce symptom scores in some participants; replication and controlled trials are required.‡

‡ **Study-context (non-operational).** The published experiments used weak, band-limited exposures and high-permeability shielding targeting 20–30 Hz in very small samples (e.g., Cook & Persinger, 1997; Van Moorselaar et al. 2017). Reported figures (e.g., sub-μT field strengths, ~35 dB attenuation) are reproduced solely to document how those prototypes were implemented and are not technical or clinical guidance. See the cited papers for instrumentation and procedures.

SD7 Convergence of single-vector interventions and why monotherapies—even high-tech ones—fade

Although the pharmacological classes and delivery techniques differ, each intervention listed below (see Table SD1/SD2) enlarges the vCA1 excitability margin via one predominant model vector:

- **Axis A** – ionic buffer (hyperpolarise V_{rest} or raise V_{thr})
- **Axis B** – Cl^- reset (drive E_{GABA} more negative)
- **Axis C** – PV/KCC2 & redox (restore perisomatic inhibition, quench ROS)
- **Axis D** – oscillatory gating (narrow the γ/θ integration window)

Table SD1 Representative clinical interventions that widen the vCA1 margin

#	Intervention (class)	Clinical effect (example metric)	Mechanism in our model — how the margin widens	Key reference
1	Silexan (5-HT_{1A} agonist, Ca^{2+} channel block)	Hamilton Anxiety Rating Scale ↓ ≈ 60% (subsyndromal anxiety, 10 weeks)	↓ Ca^{2+} influx via VDCC inhibition + engagement of 5-HT1A-linked K^+ currents → stabilisation / mild hyperpolarisation of V_{rest} (Axis A)	(Kasper et al., 2010)
2	Magnesium L-threonate	Novel-object recognition ↑ 18% (aged mice, 4 weeks)	↑ brain Mg^{2+} → modulation of NMDA receptor gating and spike after-potentials, effectively increasing the depolarisation needed for spike initiation (Axis A)	(Slutsky et al., 2010)

3	N-acetylcysteine	Meta-analyses report small but statistically significant improvements in PANSS total and negative symptoms, and modest reductions in depressive symptoms in mood disorders.	↑ GSH → ↓ oxidative / cytokine stress (incl. IL-6) + ↑ EAAT2/GLT-1; in the model this indirectly preserves KCC2/PV function and reduces excitotoxic drive (Axis C)	(Yolland et al., 2020; Peng et al., 2024)
4	ω-3 EPA	Meta-analyses report small improvements on depressive rating scales (MADRS/HDRS), consistent with a modest antidepressant augmentation effect.	Membrane incorporation → modulation of glutamatergic receptor/ion-channel function and pro-inflammatory mediators, operationalised here as a mild reduction in effective excitatory gain / EPSP summation (Axis B/C)	(Mocking et al., 2016)

Note: No dose or timing information is shown. Interventions are listed as mechanistic classes used to parameterise the model. See cited studies for exact experimental protocols.

Most current treatments target only one axis:

A (ionic buffer), B (Cl^- reset), C (PV/KCC2 & redox) or D (oscillatory gating). A single-vector stimulus briefly widens the buffer, but the remaining axes stay constricted. Within days the network compensates (KCC2 de-phosphorylation, PV-IN loss, ROS rise), flattening the clinical benefit.

Table SD2 Typical single-vector interventions – clinical data and mechanistic rationale

#	Intervention (dose / duration, class)	Model axis	Short biophysical effect (in our model)	Clinical trajectory (≈)	Main source
1	Memantine – non-competitive NMDA blocker	A	↓ Ca^{2+} entry via NMDA; Mg^{2+} block at ≈ −50 mV ⇒ V_{rest} more negative, sAHP ↑	Clinically meaningful improvements in BPRS total and negative-symptom scores over 12 weeks as add-on to clozapine in TR schizophrenia (vs placebo).	(De Lucena et al., 2009)
2	Bumetanide – NKCC1 antagonist	B	Expected hyperpolarising shift of E_{GABA} via NKCC1 block (Axis B)	In a 13-week double-blind RCT in acute schizophrenia, low-dose bumetanide did not significantly outperform placebo on psychotic symptom scales (no	(Rahmanzadeh et al., 2017)

				robust monotherapy benefit).	
3	N-acetylcysteine/ GLT-1 modulator	C	↑ brain GSH → ↓ oxidative / cytokine stress; preclinical data support ↑ EAAT2/GLT-1. In the model this indirectly preserves KCC2/PV-IN function and reduces excitotoxic drive (Axis C).	Meta-analyses report small improvements in PANSS total and negative symptoms after ≥ 24 weeks of adjunctive treatment; benefits appear contingent on ongoing treatment.	(Zheng et al., 2018; Yolland et al., 2020)
4	Esketamine – NMDA modulator	C + D	Transient NMDA modulation increasing synaptic plasticity and altering γ/θ activity (operationalised as a narrowed effective γ window and altered threshold dynamics; Axes C + D).	In phase 3 TRD trials, roughly half to two-thirds of patients achieve an acute response, with about one-quarter to one-third maintaining remission over several months of optimisation/maintenance under continued treatment.	(Daly et al., 2018)
5	Clozapine – atypical antipsychotic	D	Broad receptor profile (incl. D2/5-HT2A) reducing aberrant dopaminergic gain and restoring fronto-limbic gating (Axis D).	Systematic reviews suggest ≈ 40% of TRS patients achieve clinically meaningful response on clozapine, with roughly one-third reaching symptomatic remission during long-term treatment.	(Siskind et al., 2017)

A monotherapy opens only one "valve"; the network rapidly re-tightens the others.

Note: No dose or timing information is shown. Interventions are listed as mechanistic classes used to parameterise the model. See cited studies for exact experimental protocols.

SD8 Four-Axis Reset (FAR) — a multi-vector strategy

The FAR framework operationalises EMM predictions by testing whether the self-reinforcing loop ΔV_{margin} collapse → spontaneous replay → further collapse can be attenuated by concurrently engaging the four primary axes of excitability control (A–D) within the vCA1–BLA–mPFC circuit.

Auxiliary axes (E,F) address secondary contributors—consolidated engrams (E) and, contingent on independent evidence, external ELF phase entrainment (F).

Table SD3 Axes A–F of the FAR programme

Axis	Biophysical / network goal	Mechanistic target	Illustrative interventions *
A — Ionic buffer	Hyperpolarize V_{rest}, stabilise spike initiation	↓ Ca^{2+} influx, ↑ Mg^{2+} block NMDA, ↑ outward K^+	$MgSO_4$ i.v. · magnesium L-threonate · taurine/glycine · propranolol (HVA Ca^{2+}) · memantine
B — Cl^- reset	Shift E_{GABA} back toward ≈ −70 mV	NKCC1↓, KCC2↑, ATPase↑	Torasemide · bumetanide · CLP257 (KCC2 potentiator) · sarcosine
C — PV/PNN & oxidative protection	Restore perisomatic inhibition, protect KCC2/ATPase from ROS/cytokines	↓ IL-6/TNF-α, ↓ ROS, preserve PNN	Sulforaphane · NAC + GSH · omega-3 · minocycline · riluzole/lamotrigine · ketamine (BDNF window)
D — Oscillatory entrainment	Narrow/organise γ/θ timing, reduce EPSP summation window	↑ γ synchrony, ↑ feedforward inhibition	GENUS (40 Hz sensory) · 40 Hz tACS · iTBS 40 Hz · deep TMS (sgACC)
E — Engram rewiring (optional)	Reduce pathological replay probability	↓ hippocampal–mPFC replay transfer	CBT-exposure timing · sleep timing · prazosin · propranolol memory reconsolidation
F — Electromagnetic shielding / gating (conditional)	Reduce external field-driven entrainment (only if β-loop module is empirically supported)	↓ ELF propagation to vCA1	Magnetic shielding · head-mounted μ-metal · coil orientation

* Interventions are illustrative; not all are approved or clinically validated.

Axis F is strictly experimental and would only be considered if the β-loop submodule (external ELF sensitivity) is independently confirmed; it is not required for the core EMM or for any multi-axis interventions (A–E). Notably, Axis D (40 Hz γ entrainment) may already counteract ELF-driven phase locking by strengthening intrinsic γ generators, reducing their susceptibility to external phase capture, and effectively narrowing the Arnold tongue. Stabilised γ-phase dynamics broaden the permissible jitter range within the θ–γ–SWR timing cascade, thereby lowering the probability that transient network events align within the replay window. In the EMM framework this directly reduces spontaneous replay in low-ΔV_{margin} states, even without modifying ionic or inflammatory axes.

SD8.1 Single-vector approaches

Targeting a single axis improves one term of the excitability equation while the other three channels stay open. The margin expands only modestly, so typical network transients (θ peak, SWR, brief K^+ bursts) still cross threshold, reactivate the engram and gradually erase the clinical gain.

SD8.2 Synergy of the four primary axes

1. **A + B** Drive V_{rest} more negative and pull E_{GABA} back, enlarging the ionic buffer.
2. **C** Restores the PV "brake", phosphorylates KCC2, suppresses excess ROS.
3. **D** Narrows the γ/θ integration window and stabilises phase.

Together these forces raise ΔV_{margin} beyond the replay threshold.

SD8.3 Role of the auxiliary axes

- **E** (CBT exposure / EMDR / propranolol) extinguishes existing hot spots, reducing involuntary activations.
- **E+** refers to protocols that pair transient plasticity windows (e.g., ketamine) with structured neuromodulation (iTBS / tVNS; Supplementary Table S52).
- **F** is considered only if external ELF sensitivity is independently confirmed (Supplementary Table S53; S58).

A positive β-loop (Supplementary Table S53) would indicate a small but detectable association between ELF fluctuations and clinical endpoints at the population level. In this framework, such a signal is sufficient to justify keeping axis F available as an experimental module within FAR, but it does **not** by itself establish the hypothesised phase-locking mechanism or any specific biophysical transduction pathway (e.g. magnetite). These would require dedicated biophysical and MEG/EEG studies.

Table SD4 Phenotype-specific overlays

Phenotype	Dominant stressor	Pharmacological add-on	Preferred entrainment
Schizophrenia	DA ↑ + cortisol ↑	Clozapine / cariprazine + glutamate-stabiliser	γ 40 Hz + iTBS left DLPFC
Treatment-resistant MDD	CRF ↑ / 5 HT ↓	SSRI/SNRI + antalarmin or mifepristone	θ 2 Hz frontal + α 10 Hz occipital
PTSD	NE ↑ ± DA	Prazosin + propranolol	θ 2 Hz + deep TMS (sgACC) 1 Hz

Phenotype overlays are hypothesis-generating only and do not represent clinical guidance.

SD9 Dual-track validation — from environment to biomarkers (β-loop + biomarker track; pilot/RCT II).

All operational parameters (dosing ranges, device settings, duty cycles) will be pre-specified in a Statistical Analysis Plan (SAP) at trial registration and kept within established safety envelopes; falsification relies on sign- and threshold-defined endpoints, not on specific dosing recipes.

To keep EMM falsifiable we will test it in parallel on two independent tracks.

- β-loop (environment → clinic) adjudicates the existence and clinical relevance of the ELF/magnetite module (Axis F).
- Biomarker track (vCA1 margin validation) adjudicates whether Axes A–D produce a measurable pro-buffer shift in vivo with today's non-invasive markers.

Table SD5 Proposed falsification models

Track	Boundary question	Positive result	Consequence
β-loop (environment → clinic)	Do real-world fluctuations of ELF 7–30 Hz (esp. 7.83 Hz ΔFWHM and amplitude) precede day-to-day changes in hospitalisations with ICD-10 F and I codes?	$\beta_{ELF} \neq 0$ at both macro- and micro-scales with the same sign; pooled Bayesian estimate (hierarchical model) excludes 0 after adjustment for weather/season/smog and multiple-testing control.	Axis F stays (if positive) or is removed (if negative).
Pilot RCT "A–D ± E/E+"	Does simultaneous A–D achieve the pre-specified primary endpoint with supportive secondary movement in HRV?	Primary: on-scalp MEG γ-burst ↓ ≥ 35% in vCA1-derived sources ($p < 0.05$). Key secondary: HRV rMSSD ≥ +5 ms ($p < 0.05$). Exploratory: ^{23}Na-MRI direction-only; PET-KCC2 if available (not gating).	GO → RCT II if the primary is met; GO+ if primary+secondary are both met. Failure of the primary = NO-GO, trigger rescue pathway per SD9.4

Failure on either track falsifies the corresponding branch of the model.

SD9.1 β-loop — three-step causal test (18–24 mo)

Table SD6 Falsification criteria for the environment-to-clinical beta loop (β-loop)

Phase	Goal & metric	Data / method	Success criterion
0 – retrospective	"Crash test": does the daily peak of a geomagnetic storm (Kp ≥ 6 or ΔFWHM 7.83 Hz ≥ 2 SD) precede a rise in admissions with ICD-10 F (psychiatric) and I (cardiovascular) codes?	ΔFWHM from Schumann Resonance Network (SRN); admissions WHO/HCUP; GAM with splines for DOY, DOW, Tmax, RH; pre-registered model spec	95% CI $\beta_{macro} \neq 0$ (BH-FDR controlled across lags/regions)
1 – prospective	Do day-to-day changes in the 7.83 Hz peak (ΔFWHM, Hz) and/or amplitude (A_{rms}, pT) predict admissions?	1–300 Hz magnetometer ≤ 1 pT RMS; DLNM with meteorology/smog covariates	β_{micro} significant ($p < 0.05$) with the same sign as β_{macro}
2 – Bayesian hierarchy	Does β_{pooled} remain ≠ 0 after removing season / weather / smog?	Two-level model (countries/cities); prior N(0, 1); convergence $\hat{R} < 1.1$† (Gelman & Rubin, 1992)	95% CrI for β_{pooled} excludes 0
3 – 48 h alert *	Can K_p, ΔFWHM, weather predict admissions?	GBM (XGBoost) or LSTM	ROC AUC ≥ 0.80

*Phase 3 is exploratory and does not inform falsification, but demonstrates potential clinical utility.

† Gelman–Rubin convergence diagnostic; $\hat{R} < 1.1 \Rightarrow$ chain convergence.

SD9.2 vCA1-margin validation (≈ 24 mo horizon)

This track evaluates whether engaging the four primary axes (A–D) produces a measurable pro-buffer shift in vivo, as predicted by EMM.

Interventions are defined at the mechanistic class level (Table SD3) and selected per local feasibility; falsification relies on pre-specified electrophysiological and autonomic endpoints, not on specific compounds or device settings.

Table SD7 Step-wise falsification — from cultures to RCT II

Phase	Key question → metric	Protocol (abridged)	Pass / fail criterion	Est. time *
0 in vitro	Does A+B widen ΔE_{GABA} in a KCC2-deficient system?	vCA1 cultures ± shKCC2; 4 arms (– / A / B / A+B); perforated patch or Cl^- sensor	$\Delta E_{GABA} \uparrow \geq 1.5$ mV or ≥ 25% rescue (A+B)	6 weeks
0b in vivo†	Does the effect persist after chronic stress? → ΔV_{margin}	CRS mice + KD KCC2; veh / A / A+B; ≥ 60 neurons, perforated patch ex vivo	$\Delta V_{margin} > 0$ in ≥ 70% of cells	8–10 weeks
1 pilot	Do A–D ± E shift MEG/HRV in humans?	30 participants (10 SZ / 10 MDD / 10 PTSD); axes A–D delivered using locally approved mechanistic classes; on-scalp MEG (vCA1 source); 5-min ECG HRV	Primary: MEG γ-burst ↓ ≥ 35% ($p<0.05$) Secondary: rMSSD ≥ +5 ms	7–8 mo
2 RCT II	Is the effect durable vs standard care?	1:1 A–D ± E/E+ vs SC+sham; MMRM	MCID: MADRS ≥ 6 pt or PANSS ≥ 15% or CAPS-5 ≥ 10 pt	12–16 mo

* From phase start; total ≈ 24 mo

† Phase 0b only if 0 in vitro hits its primary endpoint.

Notes:

– HRV is analysed as a secondary, supportive biomarker due to its sensitivity to caffeine/nicotine and other lifestyle factors; MEG γ-burst reduction remains the primary ΔV_{margin} endpoint.

– HRV sensitivity (caffeine/nicotine) is handled per stratification/exclusion rules (Table S57).

– Operational parameters will be defined in the SAP at trial registration

SD9.3 Primary decision rule (pilot → RCT II)

Decision rule.

- GO → RCT II: Primary endpoint met — on-scalp MEG γ-burst ↓ ≥ 35% ($p < 0.05$).
- GO+ (strong signal): Primary and key secondary — rMSSD ≥ +5 ms ($p < 0.05$). Failure to meet the HRV secondary endpoint does not falsify the model, as HRV is not required for ΔV_{margin} validation and is expected to show higher variability due to autonomic and lifestyle modulation.
- NO-GO: Primary not met → trigger rescue pathway (SD9.4).
- Exploratory reads: ^{23}Na MRI (if available) direction only; PET KCC2 (if available) is not gating.

Table SD8 Estimating ΔV_{margin} gain (pilot vs remission)

Network marker (ROI vCA1)	Pilot threshold	Contribution to ΔV_{margin}	Projected remission range	Key refs
PET KCC2 (SUVR)	+15% (exploratory; tracer-dependent)	≈ +2.2 mV	+30–35% → +4.3 – +5.0 mV	(Medina et al., 2014; Keramidis et al., 2023) (Tab. S54)
MEG γ-burst	–35%	≈ +1.0 mV	–60% → +1.7–2.0 mV	sym. NEURON_gamma_gain.hoc; (Kim and Johnston 2015; Malik and Johnston 2017) (Tab. S55)
HRV rMSSD	+5 ms	≈ +0.4 mV*	+10 ms → +0.8 mV	(Thayer et al., 2012; Rowland et al., 2016; Shaffer and Ginsberg, 2017) (Tab. S56)

* Current operational sum (no PET): ≈ +1.4 mV (MEG ≈ +1.0; HRV ≈ +0.4). With PET-KCC2 available, a minimum measurable ≈ +3.6 mV becomes feasible; second-generation tracers (PET-PV, PET-Kir4.1) are expected to add ≈ +1.5–2 mV. HRV is caffeine/nicotine-sensitive and remains auxiliary (Supplementary Table S57).

SD9.4 Excitability buffer — conceptual thresholds, escalation, role of hot spots

With today's operational markers (MEG + HRV), we can conservatively account for ≈ +1.4 mV (pilot) of the buffer directly. This suffices for falsification (MEG primary), but not yet for a full 7–9 mV "remission meter", which depends on second-generation tracers (ionic MRI upgrades, PET-KCC2/Kir4.1/PV).

Table SD9 Excitability buffer tiers (with PET-KCC2)

Stable V_{margin}	Clinical meaning	Algorithm
≥ 7 mV (observable with PET-KCC2 / 2nd-gen tracers; ≈ 9 mV full)	Ca^{2+} plateau ≈ 5 mV + common triggers cannot cross threshold	Axis D + Axis E as long-term hygiene; A/B/C tapered off where feasible
5 – 7 mV	Remission; strong stress may cause replay	Maintain full Axis D; gradual taper of A/B/C; Axis E in low-intensity maintenance (e.g., CBT/EMDR)
3 – 5 mV	Network stable, but coincident transients → incidental replay	Full A–D + weekly E; <5 mV at 8 weeks → E^+ (ketamine-facilitated extinction; see Table S52); if β-loop (+), consider

		Rescue F (μ-metal attenuation; Table S58)
< 3 mV	Vulnerability zone — replay ↻ stress → ROS → KCC2↓	Full A–D + E; escalate to E^+ if <3 mV persists; Axis F if β-loop (+)

Monitoring. MEG γ-burst and rMSSD every 4 weeks; PET-KCC2 where available.

Note on individual variability.

Throughout this work we treat $\Delta V_{margin} \approx 5$ mV as an operational "vulnerability threshold" rather than a hard biophysical transition. This value is anchored in the amplitude of routinely occurring depolarising micro-events in CA1 pyramidal neurons: somatic equivalents of dendritic plateau potentials and composite θ–γ/SWR packets commonly reach 5–8 mV in the literature. The lower bound of this range (~5 mV) is therefore a conservative estimate of the smallest robust transients that can trigger spikes when the residual margin is sufficiently narrow. Above ~7–8 mV such events typically remain subthreshold; below ~5 mV at least one major class of routine transients (dendritic plateaux, $[K^+]_o$ micro-events, clustered EPSPs) will cross threshold in a non-trivial fraction of cells.

Importantly, these thresholds are not expected to be neuron-invariant or person-invariant. ΔV_{margin} integrates multiple cell-intrinsic and circuit-level factors — input resistance, dendritic architecture, AIS geometry, PV/PNN integrity, and especially the strength of γ-band perisomatic inhibition. Individuals with exceptionally strong γ-mediated shunting, for example, may effectively "clip" the somatic impact of the same dendritic plateau, resulting in a higher practical safety margin (e.g., 9–12 mV rather than 7–9 mV). Conversely, individuals with reduced PV/PNN protection, mild KCC2 down-regulation, or elevated R_{in} may enter the vulnerability regime at higher nominal margins.

For these reasons, the 3–5–7–9 mV tiers in Table SD9 should be interpreted as heuristic, population-level guideposts, designed to anchor the operational logic of the FAR programme (A–D ± E) and its biomarker endpoints. They do not imply a universal numerical boundary for remission or relapse across all individuals. Future higher-resolution markers (e.g., PET–KCC2/Kir4.1/PV combined with on-scalp MEG) will allow these thresholds to be personalised at the circuit level.

Rescue pathway.

- **E^+:** brief ELF-shielded session timed to a plasticity window (per SAP; DSMB oversight; details Table S52).

- **F (contingent):** temporary, high-attenuation ELF shielding (μ-metal enclosure or active cancellation) only if the β-loop is positive and E^+ is insufficient. Parameters are pre-specified in the protocol supplement (research only; not clinical guidance; details Table S58).

RCT III (contingent). If RCT II (A–D ± E) misses the MCID *and* the β-loop is positive, we will test the same protocol under high-attenuation ELF shielding in continuous mode; exact attenuation bands and duty cycles are pre-specified (research only). RCT III is conceived as a pre-specified, dedicated falsification test for the ELF/Axis F branch; if it is negative despite a positive β-loop, no further protocol variants will be pursued within EMM.

Falsification cascade (SZ / MDD / PTSD).

1. No progression in any marker → STOP (futility).
2. Partial signal → add E^+; if β-loop (+) → add Rescue F.
3. Failure after Rescue F → "narrow margin → disease" hypothesis rejected.

The programme is conceptual; recruitment has not begun. Cost-effectiveness modelling is deferred. The full protocol (randomisation, DSMB, MedDRA 25.1) will be submitted to the ethics board and preregistered at ClinicalTrials.gov.

SD10 Regional Ignition Sites Beyond Ventral CA1 and a Unified Downstream ΔV_{margin} Cascade

The EMM framework proposes that, in schizophrenia, major depression and PTSD, the critical drop of the excitability margin (ΔV_{margin}) below ≈5 mV initiates in ventral CA1, where emotional-memory assemblies interface with amygdala-bound output channels. However, across other neuropsychiatric and neurodevelopmental phenotypes, the same biophysical threshold may be crossed first in different network hubs. These "regional ignition sites'' would determine where margin collapse begins, while the downstream consequences of such collapse follow a largely conserved trajectory across conditions.

SD10.1 Candidate Regional Ignition Sites Across Phenotypes

Convergent electrophysiological signatures, oscillatory motifs and patch-clamp data suggest that early ΔV_{margin} breach may occur in the following circuits:

- **Temporal lobe epilepsy (TLE), Dravet, SCN8A EIEE, KCNQ2 EE.**

Recurrent glutamatergic bursting and channelopathy-driven hyperexcitability point to early collapse in CA3 or dorsal CA1 pyramidal fields, often spreading to entorhinal cortex before ventral CA1 is recruited.

- **ADHD.**

  Noradrenergic and dopaminergic hypofunction, together with an increased θ/β ratio, implicate instability in prefrontal–locus-coeruleus (PFC–LC) circuits, with later hippocampal involvement.

- **High-functioning autism / Asperger.**

  Chronic sensory overload and 5-HT/OXT deficits suggest E/I imbalance in temporo-parietal association cortex and dorsal hippocampal CA2/CA3, aligning with characteristic γ-coherence deficits.

- **Chronic migraine.**

  Cortical spreading depolarisation combined with CGRP/TRP signalling implies initial ΔV_{margin} breach in primary visual cortex (V1) and adjacent occipital areas, preceding limbic engagement.

- **OCD / Tourette spectrum.**

  CSTC "error-loop'' overdrive produces β–γ bursts that appear to precede hippocampal replay recruitment, placing ignition in cortico-striato-thalamo-cortical networks.

- **Addictions.**

  Cue-induced craving activates nucleus accumbens ↔ vCA1 loops; the earliest ΔV_{margin} collapse may arise in NAc medium-spiny neurons with rapid hippocampal co-activation.

- **Alzheimer's disease / MCI.**

  Aβ-driven ROS and IL-1β elevation likely breach ΔV_{margin} in entorhinal cortex and dorsal hippocampus first, consistent with early navigation and memory-mapping deficits.

- **Multiple sclerosis with epilepsy.**

  Chronic IL-6/TNFα exposure and Kir4.1 dysfunction suggest ignition in dorsal CA1/CA3 and peri-hippocampal cortex, sometimes extending into neocortical layer V during epileptiform γ bursts.

- **Bipolar disorder / mania.**

  Repeated dopamine surges and strong cortical Glu drive implicate medial prefrontal–hippocampal projections as early candidates for runaway excitability.

- **Parkinson's disease (cognitive subtype).**

  Combined DA depletion and cholinergic dysregulation implicate fronto-hippocampal θ–γ coupling nodes—especially dorsolateral PFC—as initial points of ΔV_{margin} failure.

These proposed ignition sites are inferred from EEG/MEG oscillatory motifs, in-vivo firing patterns and available cellular markers. They remain hypotheses requiring direct testing via laminar LFP, region-specific perforated-patch recordings, and source-resolved MEG.

SD10.2 Why Diverse Triggers Converge on the Same Biophysical Mechanism

Despite heterogeneity in clinical triggers, symptom clusters and anatomical loci, all phenotypes in Supplementary Table S61 share a set of pathophysiological pressures—neuromodulatory, metabolic and inflammatory—that converge on the same downstream mechanism: progressive narrowing of the excitability margin (ΔV_{margin}).

Across disorders, chronic triggers initiate a common sequence:

1. Sustained microglial activation and cytokine load (IL-6, TNF-α, IL-1β), often triggered by stress, Aβ, seizures, or chronic neuromodulatory insult.
2. ATP depletion and energy failure, leading to ↓ Na^+/K^+-ATPase function.
3. Homeostatic disruption of Cl^- transport, characterised by ↓ KCC2 with compensatory ↑ NKCC1.
4. Intracellular Cl^- accumulation, producing depolarised V_{rest}, lowered V_{thr}, and a net narrowing of ΔV_{margin}.
5. PV interneuron and perineuronal net vulnerability due to oxidative/metabolic stress.
6. γ desynchronisation and impaired inhibitory control within hippocampal–amygdala or CSTC loops.
7. Increased probability of spontaneous replay, promoting recurrent sensory/emotional activation.
8. Self-reinforcing stress/cytokine loops, locking circuits into rigid attractor states.

Regardless of where ΔV_{margin} collapse begins—PFC, CA3, NAc, V1, CSTC, or entorhinal cortex—the downstream cascade is structurally conserved, aligning distinct clinical trajectories with a single biophysical principle.

SD10.3 Exemplary ignition-site–specific cascades (post-ΔV_{margin} collapse)

For each candidate ignition site in Table S61, we propose a simplified, phenotype-linked cascade that unfolds after the local excitability margin has fallen below the critical ΔV_{margin} threshold. These sequences are schematic and reconstructed from convergent but separate literatures; they are intended as mechanistic hypotheses and not as experimentally verified end-to-end pathways.

- **vCA1 (SZ / MDD / PTSD).**

  Cortisol → microglial M1 polarisation → IL-6 / TNF-α ↑ → ROS ↑ → KCC2↓ & NKCC1↑ + ATP↓ → Na^+/K^+-ATPase↓ → PV-interneuron dysfunction → γ-band desynchronisation.

- **dCA1 / CA3 (TLE / MS with epilepsy).**

  Glu↑ during recurrent seizures → dendritic plateau Ca^{2+} events → ROS ↑ → Na^+/K^+-ATPase stress → depolarising loops → PNN loss and PV vulnerability → epileptiform γ / fast-ripple activity.

- **mPFC / ACC (bipolar disorder, OCD, Tourette).**

  Repeated DA + Glu surges → CaMKII / PKC activation → Nav1.6 and AIS phosphorylation → V_{thr}↓ with pyramidal disinhibition → persistent β–γ bursts in CSTC and mPFC loops.

- **LC–PFC circuits (ADHD / hyperarousal phenotypes).**

  Noradrenergic dysregulation (α_2A↓ / $\alpha_1\beta$↑) → cAMP / PKA / PKC ↑ → HCN channel up-regulation and KCNQ (M-current) down-regulation → θ/β imbalance and progressive ΔV_{margin} narrowing in fronto-hippocampal networks.

- **CA2 / temporo-parietal junction (autism spectrum).**

  5-HT↓ and OXT↓ → E/I shift in CA2 / TPJ → KCC2↓ and impaired perisomatic inhibition → reduced γ-coherence in social-cognitive assemblies.

- **Entorhinal cortex → dorsal hippocampus (Alzheimer's disease / MCI).**

Aβ accumulation → ROS ↑ → PNN breakdown → PV cell loss → γ desynchronisation and unstable grid–place coupling in EC–dHPC loops.

- **Primary visual cortex V1 (migraine with aura).**

  Recurrent Glu / K^+ surges → propagating Ca^{2+} waves → Na^+/K^+-ATPase stress + ROS ↑ → wave-front instability (cortical spreading depolarisation) and local ΔV_{margin} collapse.

- **Nucleus accumbens (addictions).**

  DA + Glu co-release during cue exposure → CP-AMPAR insertion ↑ → replay locking of drug-linked engrams → PV inhibition↓ → craving reinforcement and narrow-margin salience bursts.

- **DLPFC ↔ hippocampus (Parkinson's disease, cognitive subtype).**

  Cholinergic dysregulation → PV desynchronisation in DLPFC and hippocampus → loss of γ-coupling and fragmented replay sequences → executive and memory-navigation deficits.

These ignition-site–specific sketches make explicit how local biochemistry and receptor pharmacology can shape the immediate consequences of ΔV_{margin} collapse in different circuits, while remaining embedded within a shared downstream architecture.

At a more abstract level, the regional cascades condense to a common backbone:

Chronic trigger → microglial / cytokine activation → ATP↓ → Na^+/K^+-ATPase↓ + KCC2↓ + NKCC1↑ → $[Cl^-]_i$ accumulation → V_{rest}↑ + V_{thr}↓ → ΔV_{margin} collapse → PNN/PV vulnerability → γ desynchronisation → dysregulated replay → symptom stabilisation / circuit rigidity.

Together with Supplementary Table S61, this section is meant to provide a worked-out hypothesis space for future laminar LFP, source-resolved MEG and patch-clamp studies: once an ignition site and local cascade are empirically confirmed or refuted, the same ΔV_{margin} framework can be refined for each phenotype.

SD10.4 Implications

If validated, the EMM predicts that many neuropsychiatric and neurodevelopmental conditions are not distinguished by whether ΔV_{margin} collapses, but by where the collapse begins and which neuromodulatory cascade becomes dominant thereafter. The ΔV_{margin} threshold may therefore

represent a transdiagnostic stability constraint, while regional ignition sites govern the outward clinical phenotype.

These hypotheses, although grounded in convergent evidence, require dedicated testing via invasive recordings, oscillatory biomarkers and region-specific mV-level measurements across disorders.