Ventral CA1 excitability-margin collapse as a unifying trigger of emotional replay in schizophrenia, depression, and PTSD

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Abstract

We introduce the Excitability-Margin Model (EMM), a falsifiable framework centred on the excitability margin (ΔV_{margin} = spike threshold − resting potential) that predicts when hippocampal events trigger emotional replay. Re-analysis of ventral CA1 (vCA1) data indicates that chronic restraint stress narrows ΔV_{margin} by ~11 mV via convergent shifts in chloride transport (KCC2↓, IL-6/NKCC1), leak K^+ currents (GIRK/TASK) and Na^+/K^+-ATPase α1. When this stressed baseline combines with transient "hot-spot" plasticity in CREB-high pyramidal neurons and a single common risk variant (e.g. *CACNA1C* rs1006737 A or *SCN2A* R1882Q), the static vCA1 buffer after accounting for rheobase reductions shrinks to the ~1–3 mV range. In this near-threshold regime, ordinary transients—θ peaks, θ–γ packets, sharp-wave ripples, dendritic plateaus, brief $[K^+]_o$ elevations, and crosstalk from neighbouring engrams—repeatedly cross threshold and drive involuntary replay of emotional assemblies.

Within EMM, the valence of the recruited engram steers the clinical trajectory: fear-biased replays amplify dopamine–cortisol cascades with γ-band desynchronisation (schizophrenia-like); sadness-biased replays reinforce δ–θ rumination loops with monoaminergic suppression (depression-like); and trauma-biased replays evoke locus-coeruleus noradrenergic bursts with β–γ "alarm" dynamics (PTSD-like). In each case, replay both expresses and further erodes a critically low ΔV_{margin} via activity-dependent Na^+/Ca^{2+} influx and IL-6-mediated KCC2 down-regulation, creating a self-reinforcing loop.

EMM maps diverse risk factors onto four axes of excitability control (A–D) and motivates a multi-vector intervention blueprint (Four-Axis Reset, FAR) to widen ΔV_{margin}. It yields clear stability thresholds and testable biomarkers, including MEG γ-burst reduction and HRV rMSSD increase.

As an optional falsifiable extension, EMM posits that—only when ΔV_{margin} is critically narrowed—weak environmental extremely low-frequency (7–30 Hz) fields could modestly bias the timing of intrinsic θ/SWR and other replay-relevant transients via phase synchronisation, without direct depolarising drive. This ELF branch is adjudicated solely by a preregistered environment-to-clinic β-loop; a null result removes it without affecting the core ΔV_{margin} hypothesis. Together, these elements propose a quantitative link between stress, risk variants, replay load and phenotype across schizophrenia, major depression and PTSD, and generate testable predictions for translational studies.

Keywords:
schizophrenia; major depressive disorder; post-traumatic stress disorder; hippocampus; ventral CA1; gamma oscillations; memory replay; excitability margin (ΔV_{margin})

1 Introduction

Schizophrenia, major depressive disorder (MDD) and post-traumatic stress disorder (PTSD) are usually treated as distinct diagnoses, yet they share overlapping risk factors, symptoms and treatment responses. Chronic stress, early trauma and common genetic variants increase vulnerability across all three; comorbidity and transitions between depressive, psychotic and trauma-related syndromes are frequent. At the circuit level, imaging and electrophysiological studies repeatedly implicate hippocampal–amygdala–prefrontal loops, with ventral hippocampus/ventral CA1 (vCA1) emerging as a key hub for emotional memory, salience and replay. However, existing models—dopaminergic, glutamatergic, stress-based—typically address isolated components and do not offer a single, quantitative constraint that predicts when routine network events start to drive pathological emotional replay.

Here, we propose that this constraint can be captured by a simple state variable: the excitability margin, defined as the voltage difference between spike threshold and resting potential ($\Delta V_{\text{margin}} = V_{\text{thr}} - V_{\text{rest}}$). Intuitively, ΔV_{margin} measures how much headroom remains before a neuron fires. When the margin is wide, common transients such as θ peaks, sharp-wave ripples or dendritic plateau potentials remain largely subthreshold. When the margin collapses into a few-millivolt window, the same events repeatedly cross threshold and force involuntary replay of dominant emotional engrams, even without strong external input. Ventral CA1 pyramidal neurons are a natural focus because they integrate chronic stress signals, neuromodulatory states and genetic risk, and project directly to basolateral amygdala and medial prefrontal cortex.

In this work, we develop the Excitability-Margin Model (EMM), which unifies heterogeneous data into a falsifiable framework centred on ΔV_{margin}. First, we re-analyse published vCA1 datasets to quantify how chronic restraint stress, CREB-high "hot-spot" plasticity and common risk alleles (e.g. *CACNA1C*, *SCN2A*) cumulatively narrow the excitability margin and bring routine hippocampal transients into a replay-permissive range. Second, we map diverse genetic, inflammatory, metabolic and psychoactive factors onto four mechanistic axes of excitability control—A: ionic buffer, B: chloride reset, C: parvalbumin (PV) interneurons/KCC2–redox integrity, D: oscillatory gating—and derive quantitative thresholds and non-invasive biomarkers for ΔV_{margin} in vivo. Third, we outline a translational, multi-axis intervention blueprint (Four-Axis Reset, FAR) and a dual-track falsification programme: an environment-to-clinic β-loop that adjudicates an optional extremely low-frequency (ELF) phase-bias module, and a biomarker track that tests whether engaging Axes A–D produces the predicted pro-buffer shift in vCA1. Together, these elements recast schizophrenia, depression and PTSD as different

valence-tuned trajectories emerging from a common biophysical bottleneck: the collapse of the excitability margin in ventral CA1.

2 Materials and methods

All analytical, modelling and meta-analytic/quantitative synthesis procedures are described in detail in Supplementary Methods (Supplementary_Methods.pdf). Parameter derivations, simulation scripts and calibration tables are archived with DOIs as specified in the Data and Code Availability section.

3 Results

3.1 Depolarisation of ventral CA1 (vCA1) pyramidal neurons after chronic restraint stress (CRS)

We define the excitability-margin loss as

$$\Delta V_{\text{margin}} = (V_{\text{thr}} - V_{\text{rest}})_{\text{control}} - (V_{\text{thr}} - V_{\text{rest}})_{\text{CRS}}.$$

After 14–21 days of CRS, ΔV_{margin} decreased by 11.3 ± 1.5 mV. Four cellular processes contributed additively (Table 3.1): KCC2 down-regulation (+8.2 mV), IL-6/NKCC1 shift (+1.5 mV), loss of GIRK/TASK leak (+0.6 mV), and reduced microglial NKA-α1 with purinergic drive (+1.0 mV).

Table 3.1 Depolarising mechanisms and their contribution to ΔV_{margin} after chronic restraint stress (CRS)

Mechanism	ΔV_{margin} (mV)	Key sources	Supplementary Methods
↓ KCC2-mediated Cl^- extrusion → ΔE_{GABA}	+8.2	(MacKenzie and Maguire 2015)	S2.1
↑ interleukin-6 (IL-6) → KCC2 ↓ / $Na^+/K^+/Cl^-$ cotransporter NKCC1 ↑	+1.5	(Rivera et al., 2004; Pieraut, 2011; Zhang et al., 2016; Hu et al., 2022)	S2.3
↓ GIRK (G-protein–activated inward-rectifier K^+) / TASK (two-pore K^+) leak	+0.6	(Kim and Johnston 2015; Malik and Johnston 2017)	S2.4
Microglial Na^+/K^+-ATPase α1 (NKA-α1)↓ → ATP↑ → neuronal P2X7R	+1.0	(Huang et al., 2024)	S2.5

3.2 Independent network-level markers of increased excitability

Re-analysis of electrophysiological markers corroborated a net excitatory shift (Table 3.2): rheobase ↓ 44 % ± 17 %, R_{in} ↑ 29 % ± 9 %, PV→pyramidal inhibition ↓ 16 % (from PV loss + sublinear scaling). A conservative operating-point proxy yielded τ_{EPSP} ↑ ≈ 15 % (sensitivity 0–30 %).

Table 3.2 Intrinsic and synaptic changes following CRS

Marker	% change	References	Supplementary Methods
Rheobase	↓ 44% ± 17%	(MacKenzie and Maguire, 2015)	S2.6.1
EPSP decay constant (τ_{EPSP})	[proxy, model-derived] % change: +15% operating point; sensitivity 0–30%	(context, not direct CRS-vCA1 measurements) (Overstreet et al., 1999; Diamond, 2001; Wild et al., 2015; Tse et al., 2021)	S2.6.2 for details and justification
PV→pyramidal inhibitory strength (g_{inh})	↓ 16% (from PV loss + sublinear scaling)	(Hu et al. 2010; PV-IR)	S2.6.3

Input resistance (R_{in})	↑ 29 ± 9%	(MacKenzie and Maguire 2015; Suppl. Table S1)	S2.6.4

3.3 Cumulative shift of ΔV_{margin} after model corrections

A multicompartment analysis indicated that electrotonic attenuation (Att = 12 %) and a supra-additive synergy term (Synergy = 17 %) nearly cancel to first order (Booth and Rinzel 1995; Doyon et al. 2011; Migliore et al. 2018; Currin and Raimondo 2022) (Supplementary Methods S2.7.1–S2.7.4).

$$\Delta V_{\text{corr}} = (1 - 0.12)\,(1 + 0.17) \times 11.3\,\text{mV} \approx 11.6\,\text{mV},$$

Given this near-cancellation, we carry forward the conservative 11.3 ± 1.5 mV estimate (Supplementary Methods S2.5.6).

3.4 Risk alleles that modulate the excitability threshold in the ventral hippocampus (vHPC) – basolateral amygdala (BLA) – medial prefrontal cortex (mPFC) loop

Across nine risk factors, the most frequent motif was prolonged glutamatergic excitation (τ_{EPSP} ↑; 4/9). Two exemplars are summarised in Table 3.3: *CACNA1C* rs1006737 A ($I_{Ca,L}$ ↑≈30 %, τ_{EPSP} ↑≈15 %, rheobase ↓≈6 %) and the *SCN2A* R1882Q gain-of-function (V_{thr} ≈ −3 mV; rheobase ↓≈15 %) (Supplementary Methods S2.8.2).

Table 3.3 Representative alleles and cellular effects

Allele / gene	Principal target †	Cellular data	Direction of effect	Key references
CACNA1C rs1006737 A*	vHPC / BLA	L-type Ca^{2+} current ($I_{Ca,L}$) ↑ 30 %; τ_{EPSP} ↑ 15 %; rheobase ↓ 6 %	Threshold ↓ (slight), EPSP prolonged	(Tesli et al. 2013; Wild et al. 2015; Mertens et al. 2015)
SCN2A R1882Q*	mPFC / BLA	V_{thr} −3 mV; rheobase ↓ 15 %	Threshold ↓; burst ↑	(Ben-Shalom et al. 2017)

* Modelled value; see Supplementary Tables S12–S15. † Region with strongest expected effect.

3.5 Common psychoactive agents that modulate the same loop

Four common agents modulate the loop in directions that lower effective threshold or reduce inhibitory control (Table 3.4): acute amphetamine (rheobase ↓), adolescent/chronic THC (PV-IN dysfunction; γ-power ↓), chronic-intermittent alcohol (excitatory gain ↑), and alcohol withdrawal (PV R_{in} ↑; $IPSC_{GABA}$ freq ↓) (Supplementary Methods S2.8.3).

Table 3.4 Psychoactive agents and core cellular findings

Substance / protocol	Principal target †	Core cellular findings	Exposure window	Net effect	References
Amphetamine (2 mg kg^{-1} intraperitoneal (i.p.))*	BLA	Dopamine (DA) ↑; rheobase	acute	Excitability ↑	(Di Chiara and Imperato 1988;

		↓ 12 % (120 → 105 pA)			Rosenkranz and Grace 2002)
Δ^9-tetrahydrocannabinol (THC) (≥ 21 d, adolescence)	mPFC (primary)	PV-IN dysfunction; γ-power ↓ 50 % (model; median reported ≈ −83 %)	chronic	Recruitment ↓	(Raver et al. 2013)
Alcohol, chronic-intermittent exposure (CIE, 5 weeks)*	vHPC / BLA	NMDA/AMPA ↑ 30 %; $mIPSC_{GABA}$↓ 15 % (trend, p=0.08)	chronic	Gain ↑	(Kroener et al. 2012)
Alcohol (withdrawal) (72 h)*	BLA	PV R_{in} ↑ 20 %; $IPSC_{GABA}$ freq ↓ ~24 %	withdrawal	mPFC control ↓	(Quadir et al. 2024; Preprint)

* Modelled value; see Supplementary Tables S16–S18. † Region with strongest expected effect.

3.6 Recurring cellular motifs

Across 9 alleles + 4 substances, five recurring motifs captured the dominant excitability changes: τ_{EPSP} ↑, inhibition ↓/R_{in} ↑, V_{thr}/rheobase ↓, dopaminergic gain ↑, and impaired γ-synchrony/connectivity (Table 3.5).

Table 3.5 Repeated cellular motifs

Cellular motif	No. of manipulations (n = 13)	Examples
Prolonged glutamatergic excitation (τ_{EPSP} ↑)	5/13	EAAT2 ↓, *GRM3* (risk), *CACNA1C* rs1006737 A, *GRIN1* mRNA ↓, Alcohol CIE
Reduced inhibition / higher R_{in} (GABA ↓, R_{in} ↑)	5/13	*GABRA1* ↓, *NRG1* HapICE, THC (chronic), Alcohol CIE, Alcohol withdrawal
Lowered spike threshold / decreased rheobase (ΔV_{thr} ↓, rheobase ↓)	4/13	*CACNA1C* rs1006737 A, *SCN2A* R1882Q, Amphetamine (acute), Alcohol withdrawal
Enhanced dopaminergic gain (DA ↑ / catabolism ↓)	3/13	*COMT* Val158Met, Amphetamine (acute), (indirectly) Alcohol CIE
Loss of excitatory connectivity / γ-synchrony deficit	2/13	*C4A* copy ↑, THC (chronic)

3.7 The vCA1 "hot spot"

Using LA and dCA1 engram recordings transferred to vCA1 (Supplementary Methods S2.9), we model a +3.2 mV reduction of the excitability margin together with rheobase ↓ ≈ 15 % and τ_{EPSP} ↑ up to ≈ 25 % (Table 3.6).

Table 3.6 Hot spot parameters transferred to vCA1

Parameter	Change	Key references
V_{margin} (loss)	+3.2 mV < 1 h after four recalls; decays over hours	(Han et al. 2009; Cai et al. 2016; Pignatelli et al. 2019)
Rheobase	−15 %	(Pignatelli et al. 2019) dCA1→vCA1 1:1 justified in Supplementary Methods S2.9.4

τ_{EPSP}	+25% (= 23% ± 4% for k_τ = 0.7 ± 0.1)	(Ryan et al. 2015) mapped via (Sibille et al., 2014)
$IPSC_{PV→pyr}$	No data	—
R_{in}	No data	—

3.8 Cumulative narrowing of the vCA1 excitability margin

Combining CRS + hot spot + a single allele yields a cumulative $\Sigma\Delta V_{margin}$ of ≈ 14.5 mV (*CACNA1C* rs1006737 A) or ≈ 17.5 mV (*SCN2A* R1882Q), with concurrent shifts in rheobase, τ_{EPSP}, R_{in} and PV-shunt (Table 3.7). Using a conservative reference margin of 20.2 ± 2.0 mV for adult ventral CA1 pyramidal neurons — derived from matched resting membrane potential and spike threshold measurements in a single whole-cell dataset (Cembrowski et al. 2016) and consistent with meta-analytic aggregates for ventral CA1 pyramidal cells in NeuroElectro (Tripathy et al. 2014; Supplementary Methods S2.10.2) — the residual static buffer is 5.7 ± 2.0 mV (*CACNA1C*) or 2.7 ± 2.0 mV (*SCN2A*) (Supplementary Methods S2.7.3; S2.12).

Table 3.7 Cumulative scenarios: CRS + hot spot + allele

Combined variant	Σ ΔV_{margin} (mV)	rheobase (%)	τ_{EPSP} (%)	$IPSC_{PV→pyr}$ (%)	R_{in} (%)
SCN2A gain-of-function (GoF) (R1882Q)	≈ +17.5	−60	+44	−16	+29
CACNA1C rs1006737 A	≈ +14.5	−55	+65	−16	+29

The maximal $\Sigma\Delta V_{margin}$ state persists for ≈ 1 h after the last hot-spot activation and then decays over subsequent hours (Ryan et al., 2015; Pignatelli et al., 2019).

3.9 Additional long-term and short-term factors

Tables 3.8–3.10 group environmental and physiological stimuli that shift the somatic membrane potential (ΔV_{soma}). Unless stated otherwise, changes are expressed relative to a baseline V_{rest} = −71 mV. Tier-4 terms contribute only as ΔV_{soma} additions to V_{margin}; they do not enter multiplicative percentage factors.

Table 3.8 Slow biases (days → weeks)

Activated pathway	ΔV_{soma} (mV)	Time window	Reference
IL-6 ↑ → NKCC1 ↑ / KCC2 ↓ → E_{GABA} depolarisation	+1.6*	≥ 4 weeks after ≥ 50 µg kg^{-1} d^{-1}	(Jin et al., 2022)
Microplastics→ ATP ↑ + slow clearance of $[K^+]_o$	+0.16*	≥ 7 days	(Shan et al., 2022)
Reactive oxygen species (ROS) / lipid peroxidation → Kir2.1 ↓ + TRPM2 ↑	+0.34*	24 – 72 h	(Wang et al. 2022)
Astrogliosis + shrinkage of extracellular space (ECS) — ECS shrinkage (extracellular volume fraction α ↓)	+0.56*	≥ 1 week	(Syková and Nicholson, 2008)

* Modelled or extrapolated value (see Supplementary Tables S19–S22).

All ΔV_{soma} values for the microplastic/PM_{10} scenario are extrapolated from generic inflammatory / oxidative paradigms (Syková and Nicholson, 2008; Jin et al., 2022; Shan et al.,

2022; Wang et al., 2022), not from direct microplastic measurements at those exact effect sizes. They are used only as an order-of-magnitude illustration.

Table 3.9 ***Minute- to hour-scale stimuli***

Stimulus	ΔV_{soma} (mV)	Time window	Reference
"Low-PV" state after trauma / REM sleep phase	+0.6*	12 – 24 h	(Donato et al. 2013)
Caffeine (acute intake)	+ 2.1 – 2.9*	3 – 5 h	(Dimpfel, Schober and Spüler, 1993; Nehlig, 2018; Lopes, Pliássova and Cunha, 2019)
Caffeine (low acute intake)	+ 0.8 – 1.2*	0.5 – 2 h	(Blanchard and Sawers, 1983)
Nicotine (acute)	+0.09–0.13*	15–30 min	(Ji and Dani 2000)

* Modelled or extrapolated value (Supplementary Tables S23–S25).

Table 3.10 ***Fast triggers***

Trigger	ΔV_{soma} (mV)	Time window	Reference
Dendritic plateau potential / replay event	+5.9 ± 1.5	0.1 – 0.3 s	(Schiller et al., 2000; Major et al., 2008)
Extracellular K^+ burst, $[K^+]_o$ = 5–6 mM	+2.8 – 3.3*	1.0 – 3.0 s	(Schnell et al., 2012; Ding et al., 2016)
Crosstalk from a neighbouring engram	+0.5 – 1.5	0.3 – 3 s	(Epsztein et al., 2011; Liu et al., 2012)
Phasic release of noradrenaline (NA) during startle	+0.3 – 0.6	0.2 – 0.5 s	(Valenti et al., 2011; Sara and Bouret, 2012)

* Modelled value (Supplementary Methods S2.2).

3.10 Residual excitability buffer

Stacking CRS → hot spot → *CACNA1C* rs1006737 A leaves a static vCA1 buffer of 5.7 mV. After rescaling by the composite rheobase drop (ε_{rheo} = 0.56 × 0.85 × 0.94 ≈ 0.45 of control; Supplementary Methods S2.17), the effective buffer is ≈ 2.57 mV (±10 %: 2.31–2.82 mV).

An extracellular $[K^+]_o$ burst to 6 mM (Schnell et al. 2012; Ding et al. 2016; Supplementary Methods S2.2) or a dendritic plateau potential of +5.9 ± 1.5 mV at the soma (Schiller et al., 2000; Major et al., 2008) is sufficient within model parameters to cross threshold irrespective of ELF fields or stimulants. Within the model, the highest risk concentrates in ~5% of CREB-high neurons; the remaining pyramidal cells retain > 3.2 mV buffer.

Effective buffer = static buffer × ε_{rheo}.

These establish that under realistic stacks the effective buffer can fall to ≈ 2.6 mV (≤ 3 mV), such that common micro-events ($[K^+]_o$ bursts, dendritic plateaus) are sufficient to cross threshold; biological implications are developed in the Discussion.

4 Discussion

Three modules underpin our conclusions: two evidence-anchored (margin collapse and its expression through uncontrolled high-frequency activations; valence-specific cascades) and one explicitly testable biophysical hypothesis (ELF phase synchronisation).

4.1 Margin collapse enables reactive replay

Our quantitative synthesis shows that after CRS (ΔV_{margin} loss of 11.3 ± 1.5 mV), adding a local "hot spot" gain (+3.2 mV) and a single risk variant (e.g., *CACNA1C* rs1006737 A or *SCN2A* R1882Q) narrows the static vCA1 margin to 5.7 ± 2.0 mV (*CACNA1C*) or 2.7 ± 2.0 mV (*SCN2A*) (3.1–3.9). After rescaling by the composite rheobase drop ($\varepsilon_{rheo} \approx 0.45$), the effective buffer for *CACNA1C* is ~2.6 mV. Within such a narrow window, common micro-transients—brief $[K^+]_o$ elevations and dendritic plateaus—readily reach threshold (Table 3.10). The model predicts that risk concentrates in ~5% CREB-high ("hotspot") neurons, while the remaining population retains a few-millivolt buffer, making involuntary replay of dominant emotional engrams likely. Additional environmental and physiological loads (e.g., high-sugar diet, caffeine, microplastics / reactive oxygen species (ROS), viral IL-6) further erode the margin via diverse pathways; although not required to trigger replay once the buffer is <~5 mV, a smaller margin increases the fraction of network transients capable of crossing threshold and thus may accelerate clinical progression.

Phenomenologically, such near-threshold conditions resemble a class of "uncontrolled" high-frequency events that have been repeatedly described but remain mechanistically opaque. In epileptogenic hippocampus, pathological high-frequency oscillations and fast ripples arise from brief bursts of hypersynchronous pyramidal firing in locally hyperexcitable tissue and are widely regarded as a signature of focal network instability (Bragin et al., 1999; Fink et al., 2015; Ewell et al., 2019). We do not equate epileptiform fast ripples with psychosis-related γ activity; rather, we treat both as instances of near-threshold, locally unstable network states in which brief hypersynchronous events reveal an underlying collapse of ΔV_{margin}.

In schizophrenia and related psychotic states, patients and animal models show increased spontaneous gamma-band activity and disorganised gamma bursts that correlate with hallucinations and fragmented cognition, consistent with dysregulated replay-like activity in limbic–cortical circuits (Uhlhaas and Singer, 2010; Mulert et al., 2011; Hirano and Uhlhaas, 2021). In parallel, dendritic Ca^{2+} plateau potentials in CA1 are sufficient to trigger de novo place-field formation and to increase subsequent sharp-wave–ripple–associated spiking, i.e. a single local dendritic event can recruit a full replay sequence (Bittner et al., 2015, 2017;

Sheffield and Dombeck, 2015; Priestley et al., 2022). Within the EMM, we therefore interpret these "spontaneous" high-frequency activations as local micro-ignition events arising in a network whose ΔV_{margin} has been compressed to a few millivolts: once the residual buffer falls into the ~2–5 mV range, even modest inputs such as dendritic plateaus, theta–gamma bursts, $[K^+]_o$ micro-events or crosstalk from neighbouring engrams (Table 3.10) are sufficient to push vulnerable vCA1 neurons across threshold and launch replay of emotional engrams.

4.2 Valence-tuned neuromodulatory cascades from engram to phenotype

When replay breaches threshold in a vCA1 "hot spot", neuromodulatory loops are initiated, with their valence (fear, sadness, or trauma) directing the long-term trajectory of excitation/inhibition balance, oxidative stress, and perisomatic inhibition — and ultimately the clinical phenotype.

4.2.1 Fear replay → schizophrenia trajectory (θ–γ).

Fear-driven replay amplifies vCA1→BLA output and engages dopaminergic bursts together with cortisol release. This combination shifts Glu/GABA balance toward excitation (Rosenkranz and Grace, 2002; Valenti et al., 2011) and imposes oxidative load that depletes glutathione reserves, leaving perineuronal nets unprotected and progressively eroded. PV interneurons become especially vulnerable, resulting in γ desynchronisation and weakened dorsomedial prefrontal cortex (dmPFC) top-down control (Uhlhaas and Singer, 2010; Cabungcal et al., 2013; Mauney et al., 2013; Fawcett et al., 2022) — a positive feedback cycle of fear replay consistent with the early course of schizophrenia.

Importantly, once ΔV_{margin} has been compressed into this near-threshold regime and replay begins to occur, each replay episode is itself a depolarising and metabolically costly event. At the slow end, repeated engram activation tends to sustain pro-inflammatory IL-6 signalling, maintain the KCC2↓/NKCC1↑ chloride shift and place a chronic energetic load on Na^+/K^+-ATPase, thereby stabilising a depolarised operating point (Table 3.1). At the fast end, each replay burst imposes additional Na^+ (spiking) and Ca^{2+} (NMDA/CaV, dendritic plateau events) influx into already sensitised dendritic compartments, adding to the hot-spot plasticity load (Table 3.6) and further tightening the effective ΔV_{margin}. In the EMM, replay therefore not only expresses a low-margin state but actively "burns" away the remaining buffer, trapping vulnerable vCA1 ensembles in a chronically near-threshold regime and making subsequent micro-ignitions increasingly probable.

Fear replay → (Na^+/Ca^{2+} influx → ΔV_{margin} tightening) + (DA + cortisol → IL-6 ↑ → KCC2↓/NKCC1↑ → further ΔV_{margin} tightening → E/I shift → ROS → glutathione (GSH)↓ → perineuronal nets (PNNs)/PV erosion → γ desync → dmPFC control↓) → Next fear replay

This causal sketch illustrates how valence-specific neuromodulatory cascades can progressively reshape the excitability landscape; analogous mechanisms apply for sadness- and trauma-biased replays.

4.2.2 Sadness replay → depression trajectory (δ–θ).

Sadness-biased replay reduces dopaminergic tone and disinhibits the corticotropin-releasing factor (CRF) axis, prolonging δ–θ replay within the vCA1↔subgenual anterior cingulate cortex (sgACC)→default mode network (DMN) loop. The outcome is a progressive tilt toward rumination, with β/α imbalance and strengthened sgACC–DMN coupling, consistent with major depression (Nemeroff et al., 1984; Hamilton et al., 2015; Godfrey et al., 2018; Ogawa et al., 2018; Forner-Phillips et al., 2020; Benschop et al., 2021).

Sadness replay → (Na^+/Ca^{2+} influx → ΔV_{margin} tightening) + (CRF overdrive → cortisol ↑ → IL-6 ↑ → KCC2↓/NKCC1↑ → further ΔV_{margin} tightening → monoaminergic suppression (5-HT/DA ↓) → E/I imbalance → DMN dominance) → Next sadness replay

This captures both the fast dendritic load (Na^+/Ca^{2+}-dependent) and the slower endocrine-inflammatory loop (cortisol → IL-6 → chloride shift) that stabilises the system in a chronically low-margin, high-rumination regime.

4.2.3 Trauma replay → PTSD trajectory (β–γ "alarm").

Trauma-linked replay in vCA1–BLA circuits evokes dominant noradrenergic bursts from locus coeruleus together with HPA/CRF dysregulation, biasing the loop toward a β–γ "alarm" mode (Bremner et al., 1997; Sara and Bouret, 2012; Rosso et al., 2014, 2017; Dunkley et al., 2015; McCall et al., 2017; Shaw et al., 2023). Microglial activation, redox stress and PV/KCC2 erosion destabilise β–γ synchrony, in a pattern consistent with the flashbacks and startle-like replays characteristic of PTSD.

Trauma replay → (Na^+/Ca^{2+} influx → ΔV_{margin} tightening) + (LC–NA surges → HPA dysregulation → cortisol reactivity ↑ → IL-6 ↑ → KCC2↓/PV↓ → β–γ instability → microglial activation → ROS load → perisomatic inhibition ↓) → Next trauma replay

Within the EMM framework, this captures a recurrent β–γ "alarm" loop where noradrenergic bursts and cytokine-driven chloride dysregulation jointly narrow ΔV_{margin} and promote intrusive replays.

Despite distinct neuromodulators, all three cascades converge on an "AMPA-high vCA1↔BLA axis" with PV/KCC2 deficit, establishing a common electro-synaptic bottleneck across SZ, MDD and PTSD. Full arguments and sourcing: SD1–SD4; Supplementary Methods S2.18; Supplementary Tables S49-S51.

Beyond valence-specific cascades, the EMM predicts a second, slower mechanism that shapes long-term clinical trajectories: engram co-allocation under low-margin conditions. High-excitability vCA1 ensembles are known to capture temporally adjacent memories and to recruit new neurons into an existing negative engram (Yiu et al., 2014; Ryan et al., 2015; Rashid et al., 2016; Kitamura et al., 2017). Such clustered ensembles become increasingly cohesive through AMPAR enrichment and glia/ECM stabilisation (Clem and Huganir, 2010; Fawcett et al., 2022).

Within a chronically narrowed ΔV_{margin}, this promotes progressive enlargement and valence-blending of the dominant emotional cluster. As a result, depression-biased ensembles can acquire fear-tagged content, trauma-biased ensembles can incorporate sadness-linked memories, and mixed or transitional phenotypes can emerge when clusters of different valence become co-allocated.

This framework naturally accounts for patient-to-patient variability and for the clinically observed transitions between MDD-like, PTSD-like and SZ-like symptom profiles over time.

4.3 ELF phase synchronisation: an optional, falsifiable module

Taken together, the urban–rural gradient, THC-related γ attenuation, and short-lived geomagnetic-storm-associated fluctuations provide a convergent observational backdrop that motivates (but does not establish) a mechanistically coherent hypothesis: that—only when ΔV_{margin} is critically narrowed—weak 7–30 Hz ELF fields could modestly influence replay probability by phase-synchronising intrinsic θ/SWR transients or other replay-relevant network events rather than through direct depolarisation. In practical terms, such phase bias would increase the coincidence of endogenous transient events within the replay-permissive window, promoting more frequent constructive temporal summation (larger effective depolarisation relative to the residual buffer) and thereby raising the likelihood of unwanted engram activation in already destabilised networks. This possibility is treated as an optional, fully falsifiable extension of the model and is adjudicated solely through the preregistered β-loop time-series programme; a null result removes Axis F without affecting core Axes A–D. The underlying biophysical calculations, phase-locking model, and micro→macro scaling are detailed in

Supplementary Methods S2.11–S2.16 and Supplementary Tables S26–S47, with conceptual elaboration and exemplar scenarios in Supplementary Discussion SD5.

4.4 Environmental and population-level evidence

Diverse real-world exposures map onto the EMM through the four primary axes of excitability control — A (ionic buffer), B (Cl^- reset), C (PV/KCC2 and redox), and D (oscillatory gating) — and predict directional shifts in ΔV_{margin}. Examples include: high-potency adolescent/chronic THC (C,D: PV-interneuron dysfunction and γ-band weakening → ΔV_{margin} narrowing), viral IL-6 surges (B,C: E_{GABA} depolarisation via KCC2 down-regulation → narrowing), habitual high caffeine (A: adenosine A_1 receptor antagonism → GIRK↓ → V_{rest} depolarisation → narrowing), chronic smoking (C: ROS/IL-6 ↑ with PV/KCC2 impairment and Na^+/K^+-ATPase stress → narrowing), and magnesium repletion or ketogenic diets (A,C: sAHP/KATP ↑ and redox quenching → widening). Quantitative effect sizes and $\Delta V_{soma}/\Delta E_{GABA}$ estimates are provided in Supplementary Discussion SD6, where exposure definitions and cohorts are tabulated. No dosing or timing guidance is implied.

4.5 Convergence of single-vector interventions

Across drugs and devices, most monotherapies widen the margin along a single axis (e.g., hyperpolarise V_{rest}, make E_{GABA} more negative, restore perisomatic inhibition, or narrow the γ/θ integration window). In the model, benefits attenuate as network compensation (PV-interneuron stress/loss, ROS rise, KCC2 dephosphorylation) re-narrows the remaining axes. Mapping of exemplar exposures and mechanistic classes appears in Supplementary Discussion SD6–SD7.

4.6 Why monotherapies fade

Single-axis approaches leave residual θ/SWR coincidences and $[K^+]_o$ micro-bursts sufficient to breach the remaining buffer; homeostatic counter-adaptations restore the prior operating point. Mechanistic rationale and RCT/meta-analytic exemplars are provided in Supplementary Discussion SD7.

4.7 Four-Axis Reset (FAR): a multi-vector strategy

FAR operationalises the EMM prediction that ΔV_{margin} collapse becomes self-reinforcing once spontaneous replay emerges. It concurrently engages the four primary axes of excitability control—A: ionic buffering / somatic stabilisation; B: Cl^- gradient reset; C: PV/KCC2 preservation and oxidative protection; D: γ/θ timing stabilisation—while two auxiliary axes target consolidated engrams (E: extinction/rewiring) and, only if independently confirmed, external ELF phase entrainment (F).

The programme is research-only (no dosing guidance) and aims to raise ΔV_{margin} above the replay threshold, tracked by pre-specified non-invasive markers. Full architecture, expected mV contributions, blinding/sham design and safety envelopes are detailed in Supplementary Discussion SD8.

4.8 Dual-track validation — from environment to biomarkers

β-loop (environment → clinic). At the population level we treat ELF as an environmental exposure: in a three-stage time-series framework (Supplementary Table S53) we test whether geomagnetic storms (Kp ≥ 6, ΔFWHM at 7.83 Hz) and day-to-day 7–30 Hz ELF fluctuations show any reproducible association with daily psychiatric (ICD-10 F codes) and cardiovascular (ICD-10 I codes) admissions after adjusting for season, weather, pollution and COVID. A null result keeps axis F inactive; a positive result only justifies considering F as an optional experimental module and does not by itself imply any specific microscopic mechanism (Supplementary Discussion SD9.1; Supplementary Table S53).

Biomarker track (vCA1 margin). Tests whether A–D (±E) achieve the pre-specified primary endpoint: on-scalp MEG γ-burst ↓ ≥ 35 % ($p < 0.05$), with supportive secondary: HRV rMSSD ≥ +5 ms (non-gating). Interpretation uses conservative, mechanistically derived ΔV_{margin} conversions (MEG γ-burst→gain→mV; HRV→ΔV_{rest}→mV), fully specified in Supplementary Discussion SD9.2.

4.9 Study limitations

The EMM is a mechanistic scaffold that integrates in vitro, in vivo and computational data; several components remain uncertain (see Supplementary Table S59 for secondary/domain-specific limitations).

First, key parameters of ΔV_{margin} (e.g. vCA1 rheobase, R_{in}, τ_{EPSP}) are extrapolated across species and preparations, and the stacked effects of chronic stress, genetic variants and neuromodulatory states are inferred from separate datasets rather than measured simultaneously.

Second, the ELF branch is explicitly speculative. Even if the β-loop detects an association between short-term 7–30 Hz variability and clinical endpoints, this would remain an epidemiological signal. The microscopic mechanism proposed here—phase-dependent facilitation of replay—requires not only chronically narrowed ΔV_{margin} but also the broader instability pattern that characterises stress-primed vCA1 (increased input resistance, partial E_{GABA} depolarisation, prolonged EPSPs, weakened PV/γ "brake"). Such conditions may allow

sub-millivolt ΔV_{soma} biases to measurably affect spike timing, but they cannot be inferred from population data and would require dedicated biophysical and source-resolved MEG/EEG experiments. In a healthy network with a wide excitability margin and intact PV/γ control, ELF drivers at the amplitudes considered here would not be expected to trigger replay or spikes.

Third, the nature of the putative biophysical transducer is unknown. Ordered magnetite chains in hippocampal pyramidal neurons have not been demonstrated. Magnetite-based assemblies are used here only as a convenient working model; in principle, disordered aggregates or alternative field-sensitive candidates (e.g. cryptochromes, TRP channels), or as-yet unidentified mechanisms could also convey phase information from weak ELF fields to neuronal membranes, likely with equal or lower effective gain than the ordered chain model used here. All such mechanisms remain hypothetical and would require dedicated patch-clamp and MEG/EEG validation. The ELF module is therefore strictly falsifiable and will be removed entirely if the β-loop is negative.

4.10 Future research directions

Direct micro-to-meso validation of ΔV_{margin}.

Longitudinal in-vivo recordings combining laminar LFP in stress-sensitised animals with perforated-patch measurements of $V_{rest,}$ V_{thr} and E_{GABA} will test whether the CRS → hot-spot → allele stack narrows ΔV_{margin} to the predicted 4–6 mV range. In humans, source-resolved MEG and emerging ionic imaging could provide convergent meso-scale constraints.

Long-term impact of elevated replay load.

It remains unknown whether chronic high replay-hit count (N_{hit}) drives homeostatic recovery or progressive vulnerability (dendritic attrition, PV/PNN erosion, persistent ΔV_{margin} lowering). Longitudinal vCA1–BLA–mPFC recordings, combined with morphometry, will determine whether replay rate should be treated as a dynamic state variable rather than a static risk factor.

Transdiagnostic extension of ΔV_{margin}.

If the ΔV_{margin} framework is empirically supported, a key next step will be to determine whether other neuropsychiatric and neurodevelopmental conditions also arise when the same excitability threshold is breached — but in different network loci. Distinct chronic triggers may drive margin collapse first in PFC–LC circuits (ADHD), CA3/dCA1 loops (temporal lobe epilepsy), CSTC networks (OCD and Tourette), entorhinal–dorsal hippocampal pathways (early Alzheimer's disease), or in channelopathy-driven hyperexcitable fields (SCN8A/KCNQ2 encephalopathies). Moreover, if ΔV_{margin} collapse can occur in distinct nodes, each ignition site

may engage its own neuromodulatory and oscillatory cascade, potentially explaining disorder-specific trajectories across conditions. Systematically estimating region-specific ΔV_{margin} across these candidate ignition sites will be essential for testing whether margin narrowing represents a general transdiagnostic stability constraint rather than a mechanism specific to SZ, MDD and PTSD (see Supplementary Discussion SD10).

Identify a plausible ELF biosensor (only if β-loop is positive).

If population-level ELF–clinic associations are confirmed, the next step is to search for a biophysical transducer. Magnetite-based assemblies are used here only as a convenient working model; alternative field-sensitive candidates (cryptochromes, TRP channels, disordered aggregates) remain viable. Future in-vitro work should test whether any such structures can transduce weak 7–30 Hz fields into reproducible changes in membrane potential, spike timing or θ/γ phase relationships in low-ΔV_{margin} networks.

Multi-axis in-vitro test of cumulative ΔV_{margin} narrowing and rescue.

vCA1 pyramidal cultures or organoids would be driven into low-margin states (e.g. shKCC2 and/or chronic stress-mimetic exposure), then assigned to six arms: (1) control; (2) stress-only (Cl^--axis hit); (3) stress + repeated engram-like activation (Cl^- + Ca^{2+}); (4) stress + activation + Axis A (ionic buffer); (5) stress + activation + Axis B (Cl^- reset); (6) stress + activation + combined A+B. Readouts would include ΔE_{GABA} (perforated patch), intracellular $[Cl^-]_i$ and Ca^{2+} transients (e.g. ClopHensorN), and derived ΔV_{margin} (V_{rest}, V_{thr}). Testing whether combined A+B yields supra-additive widening of ΔV_{margin} compared with single-axis rescue would provide a stringent test of whether multi-axis interventions truly outperform single-axis approaches at the level of cellular excitability margins.

These priorities are expanded in Supplementary Tables S60–S61.

4.11 Final conclusions

In summary, this work introduces two conceptually distinct hypotheses.

First, the Excitability-Margin Collapse Hypothesis — the core of the EMM framework — proposes that a quantitative narrowing of ΔV_{margin} in specific hippocampal-limbic subnetworks constitutes a unifying trigger for diverse psychiatric phenotypes. The exact symptomatology depends on where within the circuit the margin collapses, providing a mechanistically grounded explanation for the shared and disorder-specific features of schizophrenia, depression and PTSD. This hypothesis is directly supported by convergent biophysical, electrophysiological and pharmacological evidence (Axes A–D).

Importantly, once the margin collapses, the subsequent clinical trajectory depends on the valence of the recruited engram: fear-biased replay engages DA/CRF-driven oxidative cascades (promoting schizophrenia-like γ desynchronisation), sadness-biased replay reinforces δ–θ rumination loops (major depression), and trauma-biased replay triggers β–γ "alarm" dynamics via LC–BLA bursts (PTSD). Despite these distinctions, all three converge on an AMPA-high vCA1↔BLA axis with PV/KCC2 erosion.

Second, we outline a strictly optional and fully falsifiable extension: the Conditional ELF Phase-Bias Hypothesis. Here, extremely weak environmental ELF fields (7–30 Hz), although far below depolarisation thresholds, could — only when ΔV_{margin} is already critically narrowed — subtly bias the timing of θ/SWR and other replay-relevant transients via phase synchronisation rather than current injection. Such phase nudging could modestly increase involuntary replay rates and thereby transiently modulate symptom likelihood in already destabilised networks.

This mechanistic interpretation is speculative and not tested in this manuscript; the preregistered β-loop evaluates solely whether any ELF-linked clinical fluctuations exist at the population level. A null result removes Axis F entirely without affecting the core ΔV_{margin} model.

Taken together, the EMM provides a unified biophysical substrate (ΔV_{margin} collapse) for multiple psychiatric conditions, while Axis F remains an experimental module whose validity depends entirely on future β-loop results.

If confirmed, this work proposes a quantitative, multi-vector path to durable remission by targeting the electro-network origin of affective-psychotic disorders — with a clear set of instruments, thresholds and outcomes that can be independently reproduced.

Beyond SZ, MDD and PTSD, the ΔV_{margin} principle may extend to other neuropsychiatric and neurodevelopmental conditions, where distinct chronic triggers and region-specific "ignition sites" (e.g., PFC–LC circuits in ADHD, CA3/dCA1 in TLE, CSTC loops in OCD, or entorhinal–dorsal hippocampal networks in early Alzheimer's disease) may be the first to cross the critical threshold. This suggests that ΔV_{margin} narrowing may represent a transdiagnostic stability constraint rather than a disorder-specific mechanism — a hypothesis that remains to be rigorously tested.

Data Availability

All relevant data, calibration tables and author-generated code are openly available. Code: GitHub PatrykRosa-55/vCA1-margin-calibration archived on Zenodo concept DOI 10.5281/zenodo.16617759 (versioned DOIs cited in the manuscript).

Data: numerical inputs/outputs needed to reproduce figures and tables are within the paper and Supplementary Information, and mirrored on Zenodo under the same concept DOI.

Author Contributions (CRediT taxonomy)

Patryk Rosa: Conceptualization; Methodology; Software; Formal analysis; Data curation; Visualization; Writing – original draft; Writing – review & editing; Funding acquisition.

Author Note

The designations “Excitability-Margin Model” (EMM) and “Four-Axis Reset” (FAR) are working labels used solely for brevity. They may be replaced with more neutral descriptors in secondary publications without loss of generality.

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Conflict of Interest

The author declares no competing interests.

Clinical-Trial Registration

Not applicable (no new human or animal studies).

Clinical and regulatory disclaimer

All references to pharmacological agents and stimulation protocols are included solely as mechanistic parameters within the computational framework. No dosing regimens are proposed, and nothing herein should be construed as medical advice. Experimental doses cited are reported verbatim from the original studies and are not intended as clinical recommendations.

Supplementary Information

Four auxiliary files accompany the article:

1. **Supplementary_Methods.pdf** – detailed procedures

2. **Supplementary_Tables.pdf** – Tables S1–S62 (spreadsheets)
3. **Supplementary_References.pdf** – complete bibliography
4. **Supplementary_Discussion.pdf** – complete discussion

Ethics Statement

This study reports secondary analyses and computational modelling only; no new human or animal experiments were conducted.

Abbreviations

Full glossary appears in Supplementary Table S62.

Licence

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