Narrowing of the ventral CA1 excitability margin in schizophrenia, depression and PTSD

Preprint (not peer-reviewed)

Stress, magnetite, hot-spots and ELF synchronization—a mechanistic hypothesis

Patryk Rosa*

Independent researcher, Warsaw, Poland

ORCID: https://orcid.org/0009-0009-6495-6750

*Correspondence: Patryk Rosa, Rosapatryk55@gmail.com

Warsaw, July 2025

Abstract

We introduce the Rosa-Margin Hypothesis (RMH): when the excitability buffer in ventral CA1 (ΔV_{margin}) narrows below ≈ 5 mV, ordinary network transients begin to trigger involuntary replay of emotional engrams.

A meta-analysis of chronic-restraint-stress recordings shows that four convergent processes—KCC2 down-regulation, NKCC1 up-regulation, loss of GIRK/TASK leak currents and reduced Na^+/K^+-ATPase α1—**depolarise vCA1 by 11.3 ± 1.4 mV**. Risk alleles such as *CACNA1C* rs1006737 A and common psychoactive agents further prolong EPSPs or lower rheobase, while four forced recalls add a transient **+3.2 mV to ≈ 5 % of CREB-high neurons**. In a realistic CRS + hot-spot + *CACNA1C* rs1006737 A scenario the safety margin shrinks to 5.7 mV; a gain-of-function *SCN2A* variant leaves only 2.7 mV, so theta and ripple events routinely cross threshold.

Once this critical buffer is breached, the content (valence) of the spontaneously re-activated hot-spot steers the ensuing neuromodulatory cascade: fear-laden engrams drive a dopamine–cortisol loop that reproduces the circuit signature of schizophrenia, sadness-laden engrams recruit a CRF-dominated loop converging on major depression, whereas trauma-laden engrams engage a noradrenaline burst that evolves towards the PTSD phenotype.

We further hypothesise that 7–30 Hz extremely-low-frequency magnetic fields, transduced by brain magnetite, **phase-lock the theta generator and double co-activation probability in urban settings** (relative risk ≈ 2.4). A prospective environment-to-clinical beta loop (β-loop) study will test this ELF–magnetite coupling.

RMH predicts that **long-term remission requires widening ΔV_{margin} to ≥ 7 mV**. We therefore outline **Four-Axis Reset (FAR)**: concurrent hyperpolarisation of V_{rest}, chloride reset, restoration of PV/KCC2 with ROS reduction, and narrowing of the γ/θ integration window.

A pilot randomised trial (n = 30) will examine whether FAR **raises PET-KCC2 binding ≥ 15 %, suppresses γ-band bursts ≥ 35 % and increases HRV rMSSD ≥ 5 ms**. Meeting ≥ 2 of these criteria would constitute the first in-vivo validation of RMH.

Keywords

schizophrenia; depression; post-traumatic stress disorder; ventral hippocampus; KCC2; extremely low-frequency magnetic fields, oxidative stress, *CACNA1C* rs1006737 A, magnetite bioreception;

1 Introduction

1.1 Clinical problem and research gap

Psychotic disorders, major depressive disorder (MDD) and post-traumatic stress disorder (PTSD) continue to increase the global burden of disease despite successive generations of pharmacotherapy (Ferrari et al. 2024). Evidence points to three broad classes of risk factors:

(i) environmental stress, especially chronic restraint stress (CRS);
(ii) genetic risk alleles (n = 9; e.g., *CACNA1C* rs1006737 A, *SCN2A* R1882Q);
(iii) substances or infections that raise IL-6 levels (THC, ethanol, COVID-19).

All three converge on hyperactivity of the ventral hippocampus – basolateral amygdala – medial prefrontal cortex circuit (vHPC ↔ BLA ↔ mPFC). Yet a coherent causal chain that connects cellular-level changes to clinical risk—and yields testable causal interventions—remains elusive.

1.2 vCA1 as the "bottleneck" of the limbic network

Ventral CA1 (vCA1) integrates contextual signals from DG/CA3 with the amygdala's emotional code and with prefrontal control. Hyperactivity of vCA1 increases anxiety in rodents (Jimenez et al. 2018) and elevates the BOLD signal in first-episode psychosis patients (McHugo et al. 2019). It is still unknown by how many millivolts the excitability margin ($V_{thr} - V_{rest}$) contracts, and whether that reduction is sufficient for typical network transients (θ peak, SWR, $[K^+]_o$ burst) to cross the firing threshold.

1.3 Four convergent depolarising pathways

CRS activates four processes that together depolarise vCA1 neurons by 11.3 ± 1.4 mV: ↓ KCC2 → ↑ E_{GABA}, ↑ IL-6 / NKCC1, ↓ GIRK/TASK and a deficit of NKA α1 (Results § 3.1).

1.4 Risk alleles and psychoactive agents—shared regulatory nodes

GWAS risk alleles and common psychoactive substances prolong EPSPs, lower rheobase or weaken perisomatic inhibition (Kroener et al. 2012; Kim and Johnston 2015) however, how these effects sum within a single neuron remains unclear.

1.5 Engram hot-spots—local amplification

Repeated recall strengthens ≈ 5 % of engram cells. In dorsal CA1, a transient depolarisation of ≈ 3.2 mV was observed after four forced fear reminders (Han et al. 2007). In-vivo data for vCA1 are lacking; we conservatively assume +3.2 mV (Methods).

1.6 ELF fields as a population synchroniser

Magnetite chains (r ≈ 30 nm; Q ≈ 12) may phase-tune the θ generator in ELF fields of 7–30 Hz (Kirschvink 1996). Psychosis risk in urban agglomerations—richer in 16–28 Hz noise—is ~2.4-fold higher than in rural areas (Vassos et al. 2012).

1.7 Working hypothesis

We propose that narrowing the vCA1 ΔV_{margin} to < ≈ 5 mV:

(a) allows network transients to trigger engram replay spontaneously;

(b) initiates a "replay → ROS/KCC2 ↓" positive-feedback loop;

(c) leads—depending on valence—to schizophrenia (SZ), MDD or PTSD;

(d) is further aggravated by ELF entrainment.

This integrated scheme is provisionally termed the **Rosa-Margin Hypothesis (RMH)**.

1.8 Objectives

1. Quantify the fall in ΔV_{margin} after CRS.

2. Integrate the impact of risk alleles, psychoactive agents and engram hot-spots in a multicellular model.

3. Translate network-level consequences to the population scale (city vs countryside, geomagnetic storms).

4. Validate whether the four-vector intervention **Four-Axis Reset (FAR)**—hyperpolarisation of V_{rest}, Cl^- reset, restoration of PV/KCC2, γ/θ entrainment—raises ΔV_{margin} to ≥ 7 mV (PET-KCC2, MEG, HRV); the full effect ≥ 9 mV will be assessed once new tracers are available.

1.9 Significance

By combining electrophysiology, modelling and epidemiology, we present the first testable programme of causal therapy aimed at permanently widening the vCA1 excitability margin and closing the pathological replay loop in schizophrenia, MDD and PTSD. RMH captures the mechanism, whereas FAR provides a protocol for its clinical falsification.

2 Materials and methods

A complete description of all data-extraction procedures, modelling workflows and statistical analyses is provided in **Supplementary_Methods.pdf**.

3 Results

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

Four independent cellular processes (Table 3.1) act in parallel to shift both the resting membrane potential (V_{rest}) and the $GABA_A$ reversal potential (E_{GABA}) towards the spike threshold (V_{thr}). The reduction in excitability margin is defined as

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

After 14–21 days of CRS, ΔV_{margin} decreased by 11.3 ± 1.4 mV.

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

Mechanism	ΔV_{margin} (mV)	Key sources	Methods
↓ activity of the K^+/Cl^- cotransporter KCC2 (Ser^{940}) → ΔE_{GABA}	+8.2	(MacKenzie and Maguire 2015) Fig. 3C–E	§S2.1
↑ interleukin-6 (IL-6) → KCC2 ↓ / $Na^+/K^+/Cl^-$ cotransporter NKCC1 ↑	+1.5	(Rivera et al. 2004 Fig. 5; Pieraut 2011 Fig. 4)	§S2.3
↓ leak currents through GIRK and TASK two-pore K^+ channels	+0.6	(Kim and Johnston 2015 Fig. 8A–C; Malik and Johnston 2017 Fig. 3C–E)	§S2.4
↓ activity of the Na^+/K^+-ATPase α1 subunit (NKAα1) in microglia → activation of $P2X_7$ receptors	+1.0	(Huang et al. 2024) Fig 3D	§S2.5

3.2 Independent network-level markers of increased excitability

Four electrophysiological markers reported after CRS were re-analysed; all confirmed a net excitatory shift (Table 3.2).

Table 3.2 Changes in intrinsic and synaptic properties following CRS

Marker	% change	References	Methods
Rheobase	↓ 44% ± 17%	(MacKenzie and Maguire 2015) Fig. 3F	§S2.6.1
EPSP time constant (τ_{EPSP})	↑ 15%	(Ghosal et al. 2020) Fig. 4C	§S2.6.2
IPSC amplitude from PV interneurons to pyramidal cells ($IPSC_{PV→pyr}$)	↓ 16%	(Hu et al. 2010) Fig. 2B (CA1 PV counts) & Fig. 3A (sIPSC)	§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 multi-compartment model showed that electrotonic attenuation (Att = 12 %) and a supra-additive synergy term (Synergy = 17 %) nearly cancel each other (Booth and Rinzel 1995

Fig. 6B ; Doyon et al. 2011 Fig. 4C; Migliore et al. 2018 Fig. 3A; Currin and Raimondo 2022 Suppl. Fig. S3) (Methods §S2.7.1–2). After correction:

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

The 0.3 mV difference relative to the uncorrected value lies within the propagated error (± 1.4 mV; Methods §S2.5.6). We therefore continue to use the conservative figure of 11.3 ± 1.4 mV in all subsequent analyses.

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

We analysed nine genetic or molecular risk factors for major neuro-psychiatric disorders (Methods §S2.8.2).

The most common effect was a prolongation of glutamatergic excitation (τ_{EPSP} ↑; 4 out of 9 alleles).

Table 3.3 summarises two representative variants: one with a strong impact on the threshold (*SCN2A* R1882Q) and one with a moderate impact (*CACNA1C* rs1006737 A).

Table 3.3 Risk alleles that shift the excitability threshold in the vHPC–BLA–mPFC loop

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 %	EPSP ↑	(Tesli et al. 2013; Wild et al. 2015; Mertens et al. 2015 Fig. 3C)
SCN2A R1882Q*	mPFC / BLA	Spike threshold (V_{thr}) −3 mV; rheobase ↓ 15 %	Threshold ↓; burst ↑	(Ben-Shalom et al. 2017 Fig. 1E)

† Region in which the largest effect is expected. * Modelled value; see Supplementary Tables S12/S15.

3.5 Common psychoactive agents that modulate the same loop

Four widely used substances target the identical vHPC – BLA – mPFC circuit (Methods §S2.8.3) affected by the risk alleles above.

Table 3.4 Psychoactive agents that lower the excitability threshold of the vHPC–BLA–mPFC loop

Substance / protocol	Principal target †	Core cellular findings	Exposure window ‡	Net effect	References
Amphetamine 2 mg kg^{-1} i.p.*	BLA	Dopamine (DA) ↑; rheobase ↓ 12 %	acute	Excitability ↑	(Di Chiara and Imperato 1988 Fig. 2B; Rosenkranz and Grace 2002 Fig. 3D)

Δ^9-tetrahydrocannabinol (THC) ≥ 21 days (adolescence)	vHPC / BLA	Parvalbumin interneuron (PV-IN) dysfunction; γ-band power ↓ ≈ 50 %	chronic	Recruitment ↓	(Raver et al. 2013 Fig. 3B)
Alcohol, chronic intermittent ethanol (CIE) 5 weeks*	vHPC / BLA	NMDA/AMPA ↑ 30 %; miniature IPSC (mIPSC) ↓ 15 %	chronic	Gain ↑	(Kroener et al. 2012 Fig. 4C)
Alcohol withdrawal 72 h*	BLA	PV R_{in} ↑ 20 %; $IPSC_{GABA}$ ↓	withdrawal	mPFC control ↓	(Quadir et al. 2024 Fig. 3A–B)[Preprint]

‡ acute ≤ 1 h; chronic ≥ 7 days; withdrawal = 24–96 h. † Region with strongest expected effect. * Modelled value; see Supplementary Tables S16–S18.

3.6 Recurring cellular motifs

Across 9 alleles + 4 substances we identified five dominant motifs (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)

Together, these five motifs account for ≈ 90 % of the reported excitability changes within the vHPC – BLA – mPFC loop.

3.7 The vCA1 “hot-spot”

Repeated recall of a memory engram selectively strengthens ≈ 5 % of vCA1 pyramidal neurons (Liu et al. 2012; Ryan et al. 2015; Pignatelli et al. 2019).

Table 3.6 Hot-spot parameters for CREB-high clusters in vCA1 (n ≈ 5 %)

Parameter	Change †	Key references
V_{margin}	+3.2 mV (BE) (< 1 h after four forced recalls; decays by ≈ 70 % within 6–12 h and to ≤ 1 mV at 24 h) ((Pignatelli et al. 2019) Fig. 3D; (Cai et al. 2016) Fig. 3B)	(Han et al. 2009 Fig. 6B)
Rheobase	−15 % (BE)	(Pignatelli et al. 2019 Fig. 1E)

τ_{EPSP}	+25 % (UB)	(Sibille et al. 2014; Ryan et al. 2015)
$IPSC_{PV→pyr}$	No data	—
R_{in}	No data	—

† UB = upper-bound (maximal reported value); LB = lower-bound (minimal value); BE = best-estimate. See Methods §S2.9.

High expression of immediate-early genes (IEGs; *c-Fos*, *Arc*) keeps this "primed" state active for ≈ 48 h in vivo (Reijmers et al. 2007; Nomoto et al. 2023).

3.8 Cumulative narrowing of the vCA1 excitability margin

We combined three components: (1) CRS, (2) the hot-spot, and (3) a single allele with either a large effect (*SCN2A* R1882Q) or a moderate effect (*CACNA1C* rs1006737 A).

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 Σ ΔV_{margin} persists for ≈ 1 h after the last hot-spot activation and then declines (Ryan et al. 2015; Pignatelli et al. 2019).

Given a reference margin of 20.2 ± 2 mV in mouse vCA1 (Methods §S2.10.2), the combination CRS + hot-spot + *CACNA1C* rs1006737 A shortens the margin to 5.7 ± 2 mV, whereas the *SCN2A* GoF variant drives it down to 2.7 ± 2 mV (Methods §S2.7.3; §S2.12).

3.9 Additional long-term and short-term factors

Tables 3-8 to 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.

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)
Micro-plastics → 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 Fig. 3D)
Astrogliosis + shrinkage of extracellular space (ECS) — K^+ volume fraction f_K ↓ 0.03	+0.56*	≥ 1 week	(Syková and Nicholson 2008)

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

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 Fig. 3E)
Caffeine 400 mg per os	+ 2.0 – 2.8*	3 – 5 h	(Dimpfel, Schober and Spüler, 1993; Nehlig, 2018; Lopes, Pliássova and Cunha, 2019 Fig. 2D)
Caffeine 100 mg per os	+ 0.8 – 1.1*	0.5 – 2 h	(Blanchard and Sawers 1983)
Nicotine 0.25 µM	+0.09–0.13*	15–30 min	(Ji and Dani 2000 Fig. 2B)

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

Table 3.10 ***Fast triggers***

Trigger	ΔV_{soma} (mV)	Time window	Reference
Dendritic plateau potential / replay event	+4 – 5	0.1 – 0.3 s	(Cash and Yuste 1999; Grienberger et al. 2014)
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 (Methods §S2.2).

3.10 Extremely-low-frequency (ELF, 7–30 Hz) fields and biogenic magnetite: phase-tuning the θ-oscillator

ELF magnetic fields of 1 pT – 0.15 µT do not cause appreciable depolarisation (< 0.1 mV). However, injection locking onto chains of $\approx 10^3$ magnetite crystals (radius r ≈ 30 nm; quality factor Q ≈ 12) could precisely adjust the phase of θ-oscillators in vCA1 neurons.

Such chains would amplify B-field modulations with a field-to-voltage sensitivity $\kappa = 8.27\ \mu V\ \mu T^{-1}$ (Kirschvink et al. 1992; Kirschvink 1996; Winklhofer and Kirschvink 2010).

Table 3.11 Somatic ELF amplitude after magnetite amplification

Environment	B_{rms} (root-mean-square flux density)	f_{ELF} (Hz)	$\Phi_{eff} = \lvert H(f)\rvert \cdot \Phi_{nom}$	ΔV_{soma}
Urban (≤ 200 m from train power lines)	0.15 µT	16.7 Hz	100	6.2×10^{-2} mV
Rural (Schumann resonance)	1 pT	7.83 Hz	40	1.7×10^{-7} mV

Even though ΔV_{soma} represents < 1 % of the firing threshold ($V_{thr} \approx 4.7$ mV) it suffices for detectable phase shifts (Methods §S2.11).

Hence the 7.83 Hz Schumann background (1 pT) could phase-set θ oscillations. Convergence of human EEG α/θ phase with the Schumann band has been reported repeatedly (Kirschvink et al. 1992; Kirschvink 1996; Buzsáki and Draguhn 2004; Winklhofer and Kirschvink 2010; Nickolaenko and Hayakawa 2014; Saroka et al. 2016).

Table 3.12 Injection-locking of θ: experimental evidence

Preparation	Phase effect	Reference
Mice, transcranial alternating-current stimulation (tACS) 10 Hz / 1 mA	θ-coherence ↑ ≈ 40 %	(Reato et al. 2010 Fig. 4C)
Humans, tACS 6 Hz / 0.18 mA	Persistent δ/θ synchronisation	(Huang et al. 2021 Fig. 2A)

3.11 ELF × θ × SWR synchrony under CRS + hot-spot + *CACNA1C* rs1006737 A

In the CRS → hot-spot → *CACNA1C* rs1006737 A scenario the effective EPSP time constant lengthens to $\tau_{EPSP,eff} \approx 25$ ms. Simultaneously, R_{in} ↑ 29 % and the perisomatic PV shunt ↓ 16 %, so each network event (θ-oscillation or sharp-wave ripple, SWR) generates a larger somatic depolarisation (Methods §S2.13).

Table 3.13. Somatic depolarisation after rescaling

Transient	ΔV_{soma} (mV)	References
θ-oscillation	1.21	(Lubenov and Siapas 2009; Núñez and Buño 2021)
Sharp wave + ripple	0.52	(Liu et al. 2022; Schieferstein et al. 2024)

We computed the phase-coincidence probability P_{phase}: the chance that within the same 25 ms integration window at least one crest occurs from three independent ELF bands—7.83 Hz (Schumann), 16–18 Hz (railway power) and 20–28 Hz (industrial drives).
In the absence of phase-correlation data between ELF bands, we assumed independence ($|r| < 0.05$) and tested r = 0.02–0.10 (Table S39)

Table 3.14 P_{phase} for urban vs rural settings

Location	P_{phase}	95 % CI
Urban	0.468	0.39 – 0.54
Rural	0.195	0.18 – 0.21
Gradient	2.40	1.9 – 3.0

A gradient of 2.40 mirrors the relative risk (RR) of psychosis in cities (RR ≈ 2.37 ± 0.5;(Vassos et al. 2012); Methods §S2.14).

The expected number of theta-associated-ripple alignments per minute, N_{hit}, was then derived as described in Methods §S2.15 (values not reproduced here).

Table 3.15 Adjusted rate of theta-associated-ripple synchronisations, N_{hit}

State	N_{hit} baseline [min^{-1}]	Urban	Rural
Rest	4.90	2.29	0.96
Slow walking	4.37	2.05	0.85
β-arousal	6.43	3.01	1.25

3.12 Geomagnetic storms (planetary K index $K_p \geq 6$): a global 7.83 Hz phase clock

A geomagnetic storm narrows the Schumann-resonance peak by ≈ 11 % (Sátori et al. 2007; Pazos et al. 2019; Rodríguez-Camacho et al. 2022), raising P_{phase} to **0.553** in metropolitan areas (+19 %) and **0.325** in rural areas (+69 %). Methods §S2.16

The corresponding N_{hit} increases by **≈ 28 %**. Converting this micro-scale change to population-level impact with $\beta = 0.67$ predicts a **19 % rise in hospital admissions** during the 48 h following a storm (RR ≈ 1.19; see Discussion §4.4.1).

3.13 Residual excitability buffer

Stacking CRS → hot-spot → *CACNA1C* rs1006737 A lowers the vCA1 safety margin from **5.7 ± 2 mV** to **2.57 mV** (55 % of rheobase; Methods §2.17).

A single 100 mg caffeine dose (cup of coffee; EFSA, 2015) blocks GIRK channels and depolarises the soma by **+0.9 mV**, collapsing the margin to **1.67 ± 2 mV**.

- A θ + SWR packet (1.73 mV) now breaches the margin ≥ 2 times per minute in an urban setting and ≈ 1 time per minute in rural areas, triggering involuntary engram replays.
- A burst of $[K^+]_o = 6$ mM or a dendritic plateau of 4–5 mV crosses threshold regardless of ELF fields or stimulants.
- The critical risk is confined to the ≈ 5 % CREB-high neurons; the remaining pyramidal cells retain a > 3.2 mV buffer.

3.14 Integrated causal model for the vCA1 emotional loops

Chronic, involuntary replay of emotional engrams generates discrete hot-spots in vCA1 and along the vCA1 → BLA projection. The dominant valence of each hot-spot (fear, sadness, trauma) steers circuit-wide plasticity towards three distinct clinical phenotypes.

Table 3.16 Disease trajectory as a function of prevailing emotion

Dominant valence	Network loop	Clinical phenotype
Fear	vCA1 ↔ BLA ↔ dorsomedial PFC (dmPFC) (fast θ–γ)	Schizophrenia (SZ)
Sadness	vCA1 ↔ subgenual ACC (sgACC) ↔ default-mode network (DMN) (slow δ–θ)	Major depressive disorder (MDD)
Trauma	BLA ↔ ventromedial PFC (vmPFC) ("alarm" β–γ)	Post-traumatic stress disorder (PTSD)

Values in subsequent bullet points are illustrative; error propagation was not performed. Parameters marked † in the Supplement originate from other regions and were rescaled by rules R1–R4 (Methods §2.18).

3.14.1 Fear loop → progression to the SZ phenotype

Architecture. In SZ patients neutral faces over-activate the BLA and DG/CA1 (Hall et al. 2008). vCA1 projects to dmPFC via subiculum; strongly aversive stimuli additionally recruit a thalamus → amygdala route (Phelps and LeDoux 2005). During hallucinations EEG shows enhanced θ–γ phase coupling between hippocampus and frontal cortex (Koutsoukos et al. 2013).

Neuromodulatory trigger. A single fear reminder elevates DA in mPFC to ~160 % (Yoshioka et al. 1996) and salivary cortisol AUC by ~55–60 % (Schwabe and Wolf 2012). A 4 Hz oscillation from vHPC entrains DA/NA bursts in VTA and locus coeruleus (Fujisawa and Buzsáki 2011).

E/I shift, oxidative stress and PV loss. ^{1}H-MRS reveals ↓[Glu] ≈ 10 % and ↓[GABA] ≈ 8 % in PFC (Rowland et al. 2016). Repeated fear recalls generate reactive oxygen species and deplete glutathione specifically in PV interneurons (Grabnar et al. 2011; Cabungcal et al. 2013). Concomitantly, the perineuronal nets that stabilise these cells are eroded (Mauney et al. 2013), which—together with redox pressure—leads to a ≈ 30 % drop in PV-IN density (Czeh et al. 2005).

Oscillatory output. PV loss > 25 % produces a γ-shift: dmPFC loses γ, BLA gains γ power (Steullet et al. 2017). EEG/MEG in SZ is θ-dominant, γ-deficient (Uhlhaas and Singer 2010).

Morphology / epigenetics. Stress shortens layer II/III dmPFC apical dendrites by ~20 % (Radley et al. 2004) and **increases histone H3/H4 acetylation** at the BDNF promoter (Lubin et al. 2008). Layer III dmPFC is ~3–4 % thinner (Hoftman et al. 2017).

Driving sequence.

Fear → DA/cortisol ↑ → Glu/GABA ratio ↑ → ROS ↑ → PNN ↓ → PV ↓ → γ shift → dmPFC control ↓ → more fear

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

3.14.2 S*adness loop → progression to the MDD phenotype*

A selective fall in CSF HVA (**g ≈ - 0.30 SD**) with no change in 5-HIAA (Ogawa et al. 2018) lifts CRF inhibition; **CSF-CRF rises by ≈ 45 – 80 % (mean ≈ +65 %)** (Nemeroff et al. 1984) and prolongs slow (< 4 Hz) vCA1 ↔ sgACC replay (Hamilton et al. 2015; Higgins et al. 2021). The vCA1 hot-spot then shifts E/I (**Glu ↑ ≈ 15 %, GABA ↓ ≈ 8 %**; (Godfrey et al. 2018; Hu et al. 2023)), depolarises pyramids by ≈ +5 mV† (IL-mPFC, rat → vCA1 via R2; (McKlveen et al. 2016)) and triggers **ROS ↑ / GSH ↓** (Cabungcal et al. 2013), **PNN ↓** (Yu et al. 2020) and ~ 30 % PV loss (Czeh et al. 2005).

During rumination, scalp EEG shows **β ↑ / α ↓** in proportion to replay frequency (Moon et al. 2018; Forner-Phillips et al. 2020; Benschop et al. 2021). ROS and stress hormones hyper-methylate the **BDNF promoter** (Cheng et al. 2023); combined with a **12 – 18 % spine loss** in dlPFC (Kang et al. 2012; Kassem et al. 2013) this locks the loop, reproducing the network pattern observed in MDD (Schmaal et al. 2016).

Sadness **cycle**

Monoamines ↓ → CRF ↑ → slow replay ↑ → E/I shift → PV ↓ → β ↑ / α ↓ → plasticity ↑ → next rumination

Full quantitative values and transfer rules (R1–R4) are given in Methods § 2.18.3 and Supplementary Table S50

3.14.3 Trauma loop → progression to the PTSD phenotype

A single trauma reminder triggers an **NA surge of ≈ 3–4 × baseline** in basolateral amygdala terminals (McCall et al. 2015; Ronzoni et al. 2016) and a **DA rise of ≈ 60 %†** (Rosenkranz and Grace 2002; Giustino et al. 2020). **CSF-CRF increases by ≈ 30–40 %†** (29 ± 8 vs 22 ± 6 pg ml^{-1}) and stays elevated for several minutes (Bremner et al. 1997). 7 T-MRS shows **Glu ↑ ≈ 14 %†** in the right hippocampus and **GABA ↓ 20 ± 10 %†** in the anterior insula; chronic stress also shifts $\boldsymbol{E_{GABA}}$ **by +5 ± 2 mV†** in CA1 (Inoue et al. 2013). Fast-spiking **PV interneurons fall by ≈ 30 %†** (Shepard et al. 2016). Immediately before a flashback MEG reveals a **state-dependent γ-burst frontally** with **α-suppression posteriorly** (Dunkley et al. 2015; Shaw et al. 2023), while vmPFC activity is reduced during recall (Shin and Liberzon 2010).

Trauma **cycle**

NA/DA ↑ → CRF ↑ → E/I shift → PV ↓ → γ ↑ / α ↓ → vmPFC hypo → flashback → next NA/DA burst

Full quantitative values and transfer rules (R1–R4) are provided in Methods § 2.18.4 and Supplementary Table S51.

3.14.4 Loop convergence – the "AMPA-high" vCA1 ↔ BLA hot-spot

Repeated activation of *any* loop:

1. Un-silences ≈ 30 % of previously GluN-only synapses in the lateral/basolateral amygdala by activity-dependent AMPA-receptor insertion, boosting EPSP amplitude by ≈ 25 % (Rumpel et al. 2005; Clem and Huganir 2010).

2. Raises spontaneous EPSC amplitude in CA1 engram neurons by ≈ 40 % (Ryan et al. 2015; Kitamura et al. 2017).
3. Expands the DG → CA3 → vCA1 engram by ≈ 35 % (Stefanelli et al. 2016).
4. Astrocytes and microglia stabilise these synaptic and structural changes (Jellinger et al. 2024; Rangel-Gomez et al. 2024).

Functional outcome. The hot-spot can recruit additional negative memories < 6 h after an event (Yiu et al. 2014; Rashid et al. 2016), incorporates newborn DG neurons into fear traces (Anacker and Hen 2017) and lowers the LTP threshold in the vCA1 → BLA pathway (Kim and Cho 2020). A shared electro-synaptic core thus drives SZ, MDD and PTSD symptoms.

4 Discussion

Our conclusions rest on three co-equal pillars: **(i)** a drastic narrowing of the vCA1 excitability margin, **(ii)** phase-synchronisation of extremely-low-frequency (ELF) fields with endogenous θ-oscillations, and **(iii)** valence-specific cascades that transform an engram into a clinical phenotype.

4.1 Shrinking the vCA1 margin

The difference ($V_{thr} - V_{rest}$) falls from ≈ 20.2 mV to **5.7 ± 2 mV** under CRS + hot-spot + *CACNA1C* rs1006737 A, or to **2.7 ± 2 mV** with the *SCN2A* R1882Q gain-of-function variant.

Within such a narrow buffer, micro-stimuli—caffeine, nicotine, interleukin-6, particulate matter ≤ 10 µm (PM_{10})—and brief $[K^+]_o$ bursts or θ + SWR packets readily cross threshold (§ 3.1 – 3.9, 3.13).

4.2 ELF phase synchronisation

Model suggests injection-locking of magnetite chains ($\kappa = 8.27\ \mu V\ \mu T^{-1}$) raises both P_{phase} and N_{hit}; the observed city : countryside gradient (2.4) and the ≈ 20 % surge in hospitalisations when the planetary K index $K_p \geq 6$ (RR ≈ 1.19) fit the model's predictions (§ 3.10 – 3.12). Chronic adolescent exposure to high-THC (> 10 %) cannabis suppresses γ-band power in the vHPC/BLA circuit by **≈ 70 %** (range 50–83 %;(Raver et al. 2013)). In our model, such a loss weakens the PV-γ brake and widens the EPSP "coincidence window" from **5 ms to ~8.5 ms**; the probability of ELF phase-locking therefore rises by **~1.7 ×**. Combined with the urban ELF gradient (× 2.4), this yields a composite risk factor of ≈ **4.1**, matching the EU-GEI multicentre study (**OR = 4.8; 95 % CI 2.5–6.8** for daily use of > 10 % THC cannabis;(Di Forti et al. 2019)). This quantitative convergence reinforces our mechanism: **γ-deficit → broader coincidence window → easier ELF synchronisation → higher psychosis risk**. The ELF contribution will be tested prospectively in the planned β-loop study.

4.3 From engram to full phenotype—three cascades

Breaching the margin activates the dominant emotional engram, which then propagates a neuromodulator → E/I shift → ROS/PV sequence that biases the entire circuit toward one of three disorders (§ 3.14).

Table 4.1 Neuro-cascades linking engram valence to phenotype

Engram (valence)	Fast cascade (schematic)	Network signature	Resulting phenotype
Fear	DA ↑ → cortisol ↑ → IL-6 ↑ → KCC2 ↓ →	γ-burst ↑ (BLA ↑, mPFC ↓)	Schizophrenia – positive symptoms

	Glu ↑ / GABA ↓ → ROS ↑ → PV ↓		
Sadness	5-HT ↓ + DA ↓ → CRF ↑ → BDNF ↓ → spine Glu ↑ → PV ↓	β ↑ / α ↓ (frontal DMN)	Major depression – rumination
Trauma	NE ↑ (+ DA) → cortisol dysregulation → Glu ↑ / GABA ↓ → microglial M1 ↑ → ROS ↑ → PV ↓	frontal γ ↑, occipital α ↓	PTSD – flashback

4.4 Environmental and population-level evidence

Viral infections. Seasonal viruses (e.g. influenza A/PR8) raise IL-6 in the hippocampus; via trans-signalling in CA1 neurons this de-phosphorylates KCC2 and depolarises E_{GABA} by ≈ +3 mV (estimate, Methods § 2.5) (Jurgens et al. 2012; Hu et al. 2022; Kurki et al. 2023).

Caffeine. Self-reported intake ≥ 330 mg day^{-1} (≈ 3–4 strong coffees) triples the risk of stress-induced psychotic-like experiences (PLEs) (Crowe et al. 2011). The 330 mg threshold originates from a prospective study: 333 mg day^{-1} ⇒ 3.2 × more PLEs (Jones and Fernyhough 2009).

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 (Table S25) but narrows the γ–θ phase window: γ coherence in mPFC rises ≈ 25 % (Bueno-Junior et al. 2017). When ΔV_{margin} is already tight (post-CRS or in a CREB-high hot-spot) this reduced jitter facilitates phase-aligned network events (θ/SWR, $[K^+]_o$ bursts, dendritic plateaux) and involuntary engram replays, explaining the smoker surplus in SZ and PTSD. 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), lowers KCC2 function and Ser^{940} phosphorylation (rat stress + nicotine model) (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, Methods § 2.5).

Micro-plastic / PM_{10}. Summing four micro-pathways—IL-6 (+1.6 mV); ATP/$[K^+]$ (+0.16 mV); ROS/Kir (+0.3 mV); ECS shrinkage (+0.56 mV)—yields ≈ +2.5 mV (Table 3.8). Top-quartile exposure raises depressive symptoms by 38 % (Luo and Lin 2025).

Genetics. The *CACNA1C* rs1006737 A allele prolongs EPSPs and lowers rheobase; fMRI shows BOLD ↑ 8–15 % in vHPC/BLA and a stronger cortisol peak (Bigos et al. 2010; Klaus et al. 2018) — corresponding to axes A + C.

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

Magnetite + ELF (urban). Railway-frequency bands 16–28 Hz raise P_{phase} 2.4-fold; the city–countryside psychosis gradient is RR ≈ 2.37 (Vassos et al. 2012) — an exploratory ELF signature for the β-loop.

Axis E – engram rewiring therapies. Cognitive-behavioural therapy for psychosis (CBT-p), eye-movement desensitisation and reprocessing (EMDR) and recall + propranolol all damp active traces: a single EMDR session lowers amygdala BOLD by 25–30 % (Pagani et al. 2012); three propranolol sessions reduce CAPS-5 by ≈ 10 points (−16 %) (Brunet et al. 2018).

Additional clues. Complex, weak magnetic fields containing a 20–30 Hz component (≤ 1 μT) can induce a "sensed presence" in healthy volunteers (Cook and Persinger 1997). In a small uncontrolled pilot (n = 8) shielding that band by ≈ 35 dB reduced symptom scores by ~30 % (Van Moorselaar et al. 2017); replication is required.

4.4.1 Geomagnetic storms—a global crash-test of the phase hypothesis

Storms with $K_p \geq 6$ 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). The model predicts

1. ELF coherence ↑ ⇒ P_{phase} +28 %.

2. N_{hit} +28 %.

3. Activation of the HPA axis and LC–NE system, favouring psychotic/depressive decompensation, suicidal ideation and plaque rupture (myocardial infarction / acute coronary syndrome).

A meta-analysis of eight datasets (psychiatry + cardiology; Table S46) yields RR ≈ 1.19 for hospital admissions within 48 h after a storm. Single studies report +21–29 % MI/ACS/stroke (Gaisenok et al. 2025) and +0.13–0.54 % all-cause mortality in 44 million US residents per +1 *SD* K_p (Zilli Vieira et al. 2019).

Notably, the pooled RR ≈ 1.19 corresponds to the conservative scenario that assumes a 6.5 % narrowing of the 7.83 Hz peak. When the full 11 % average constriction observed during strong storms is applied (Table S45B), the model predicts a relative risk of RR ≈ 1.33 for hospital admissions within the same 48 h window.

4.5 Convergence of single-vector interventions

Although the pharmacological classes and delivery techniques differ, each intervention in Table 4.2 enlarges the vCA1 excitability margin **via exactly one** of the four model vectors:

- **Axis A** – ionic buffer (hyper-polarise 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 4.2 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 80 mg (5-HT_{1A} agonist, Ca^{2+} channel block)	Hamilton Anxiety Rating Scale ↓ ≈ 60 % (GAD, 10 weeks)	↓ Ca^{2+} influx + GIRK activation → V_{rest} more negative (Axis A)	(Kasper et al. 2010)
2	Magnesium L-threonate	Novel-object recognition ↑ 18 % (aged mice, 4 weeks)	↑ slow after-hyperpolarisation + partial NMDA block → higher V_{thr} (Axis A)	(Slutsky et al. 2010)
3	N-acetyl-cysteine 2–3 g day^{-1}	PANSS-Negative ↓ ≈ 2 pt; MADRS ↓ ≈ 1.6 pt (meta-RCT)	↑ GSH → IL-6 ↓; KCC2 phosphorylation ↑; EAAT2 ↑ (Axis C)	(Yolland et al. 2020; Peng et al. 2024)
4	ω-3 EPA ≥ 1 g	MADRS / HDRS ↓ ≈ 2 pt (meta-RCT)	Membrane insertion → R_{in} ↓ + smoothed EPSP (Axis B/C)	(Mocking et al. 2016)

4.6 Why monotherapies—even high-tech ones—fade

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 4.3 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 20 mg day^{-1}, 12 weeks – non-competitive NMDA blocker	A	↓ Ca^{2+} entry via NMDA; Mg^{2+} block at ≈ −50 mV ⇒ V_{rest} more negative, sAHP ↑	PANSS-Total ↓ 7.3 pt; PANSS-Negative ↓ 4.6 pt (add-on to clozapine)	(De Lucena et al. 2009)
2	Bumetanide 0.5 mg b.i.d., 6 weeks – NKCC1 antagonist	B	E_{GABA} shifted to more negative values	Positive SX improve in 2–4 weeks → plateau by ≈ 6 weeks	(Rahmanzadeh et al. 2017)
3	N-acetyl-cysteine 2–3 g day^{-1}, ≥ 12 weeks – GSH donor / GLT-1 modulator	C	↑ KCC2 phosphorylation, ↓ ROS, ↑ EAAT2	PANSS-Negative ↓ ≈ 2 pt; effect wanes ≤ 4 weeks after stop	(Zheng et al. 2018; Yolland et al. 2020)
4	Esketamine 56–84 mg i.n., 2× weeks (4 weeks + extension) – NMDA modulator	C + D	Narrows γ window; transient threshold depolarisation	Response 50–60 %; remission maintained 27–31 % at 4 mo	(Daly et al. 2018)
5	Clozapine ≈ 400 mg day^{-1}, ≥ 6 mo – atypical antipsychotic	D	↓ dopaminergic gain; restores fronto-limbic gating	30–45 % durable remission in TR-schizophrenia	(Siskind et al. 2017)

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

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

FAR is the experimental test-bed derived from the Rosa-Margin Hypothesis. Our model predicts that the vicious circle

narrow margin → spontaneous replay → still narrower margin

can be broken only by closing all four principal “valves” of excitability (axes A–D) simultaneously within the vCA1 ↔ BLA ↔ mPFC loop.

Two auxiliary axes (E, F) remove secondary drivers—engrams already consolidated and the external ELF phase synchroniser.

Table 4.4 Axes A–F of the FAR programme

Axis	Biophysical / network goal	Illustrative interventions *
A — ionic buffer	Hyper-polarise V_{rest}, stabilise the soma	$MgSO_4$ i.v. † · magnesium L-threonate + glycine/taurine · Silexan · memantine
B — Cl^- reset	Shift E_{GABA} back toward ≈ −70 mV	Bumetanide ± torasemide · sarcosine · CLP-257 (in development)
C — PV/KCC2 restoration & anti-ROS	Reinstate perisomatic inhibition, quench ROS	Sulforaphane · N-acetyl-cysteine + liposomal GSH · ω-3 · riluzole/lamotrigine · iTBS 40 Hz · ketamine/esketamine (BDNF window)
D — oscillatory entrainment	Narrow and homogenise the γ/θ window	GENUS 40 Hz · tACS 2 Hz · rTMS / iTBS · at-home tVNS
E — engram rewiring	Extinguish / rewrite hot-spots	CBT-p · EMDR · recall + propranolol · MDMA-assisted therapy

F — ELF screen	Limit 7–30 Hz injection-locking	μ-metal booth · active field-cancellation

* Final choice is personalised. † $MgSO_4$ i.v. only in hospital settings.

4.7.1 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.

4.7.2 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.

4.7.3 Role of the auxiliary axes

- **E** (CBT-p / EMDR / propranolol) extinguishes existing hot-spots, reducing involuntary activations.
- **E+** = ketamine-opened plasticity window timed with iTBS / tVNS (Supplementary Table S52).
- **F** is activated only when the β-loop (ELF signature) is positive (Table S58).

Table 4.5 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

4.8 Dual-track validation — from environment to biomarkers

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

Table 4.6 Proposed falsification models

Track	Boundary question	Positive result	Consequence
β-loop (environment → clinic)	Do real-world fluctuations of ELF 7–30 Hz precede an increase in hospitalisations with ICD-F + ICD-I codes?	β_{ELF} (regression coefficient from GAM / DLNM) ≠ 0 at both macro- and micro-scales; pooled Bayesian estimate excludes 0	Justifies activating Axis F; confirms ELF influence
Pilot RCT "A–D ± E/E⁺/F"	Does simultaneous A–D widen the vCA1	≥ 2 of 3 markers hit target: PET-KCC2 ↑ ≥ 15 %	Confirms efficacy of the four-axis strategy

	margin by > 2 mV in vivo?	MEG γ-burst ↓ ≥ 35 % HRV rMSSD ↑ ≥ 5 ms ($p < 0.05$)	

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

4.8.1 β-loop — three-step causal test (18–24 mo)

Table 4.7 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 ($K_p \geq 6$ or ΔFWHM 7.83 Hz ≥ 2 *SD*) precede a rise in admissions with ICD-10 F-chapter (psychiatric) and I-chapter (cardiovascular) codes?	ΔFWHM from Schumann Resonance Network (SRN); admissions WHO / HCUP; GAM with splines for DOY + DOW, T_{max}, RH	95 % CI $\beta_{macro} \neq 0$
1 – prospective	Do daily narrowings of FWHM (< 20 pT A_{rms}) predict admissions?	1–300 Hz magnetometer ≤ 1 pT RMS; DLNM	β_{micro} ($p < 0.05$) with same sign
2 – Bayesian hierarchy	Does β_{pooled} remain ≠ 0 after removing season / weather / smog?	2-level model (countries / cities); prior N(0, 1); $\hat{R} < 1.1$† (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 practical only — it does not affect falsification. → *Tab. S53*

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

4.8.2 vCA1-margin validation (≈ 24 mo horizon)

Table 4.8 Step-wise falsification — from cultures to RCT II

Phase	Key question → metric	Protocol (abridged)	Pass / fail criterion	Est. time *
0 in vitro	Does buffer A + B reverse a KCC2 deficit? → ΔE_{GABA}	CA1 cultures ± shKCC2; 4 arms – / A / B / A+B; patch + 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 CRS? → ΔV_{margin}	Mice CRS + KD KCC2; veh / A / A+B; ≥ 60 cells	$\Delta V_{margin} > 0$ in ≥ 70 % cells	8–10 weeks
1 pilot	Do A–D ± E ↑KCC2, ↓γ, ↑HRV?	30 patients (10 SZ / 10 MDD / 10 PTSD); PET KCC2 (TOF) ROI vCA1; on-scalp MEG 0–80 Hz; 5-min ECG rMSSD	≥ 2/3: PET ↑ ≥ 15 %; γ ↓ ≥ 35 %; HRV ↑ ≥ 5 ms	7–8 mo
2 RCT II	Is the effect durable vs standard care?	1:1 A–D ± E/E^+ vs S.C.+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.

4.8.3 "2-out-of-3" is enough — but not the finish line

Table 4.9 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 %	≈ +2.2 mV	+30–35 % → +4.3 – +5.0 mV	(Medina et al. 2014; Keramidis et al. 2023)
MEG γ-burst	–35 %	≈ +1.0 mV	–60 % → +2.0 mV	sym. NEURON_gamma_gain.hoc; (Kim and Johnston 2015; Malik and Johnston 2017)
HRV rMSSD	+5 ms	≈ +0.4 mV*	+10 ms → +0.8 mV	(Thayer et al. 2012; Rowland et al. 2016; Shaffer and Ginsberg 2017)

*Sum: currently measurable +3.6 mV (min) → +7.1–7.8 mV (upper bound).

Second-generation tracers (PET-PV, PET-Kir4.1, ^{23}Na / ^{35}Cl CEST-MRI) should add +1.5–2 mV (Methods §2.19.5). Thus today we can measure ~7 mV directly; with new tracers full remission reserve is ≈ 9 mV. HRV is caffeine/nicotine-sensitive, so it remains auxiliary (Table S57).

4.8.4 Excitability buffer — thresholds, escalation, role of hot-spots

With today's markers (PET-KCC2 + MEG γ + HRV) we can directly estimate a buffer of ~7 mV. Until new tracers become routine, 7 mV serves as the operational threshold ("observable remission").

Table 4.10 ***Excitability buffer tiers***

Stable V_{margin}	Clinical meaning	Algorithm
≥ 7 mV (*observable*; ≈ 9 mV full)	Ca^{2+} plateau 5 mV + common triggers cannot cross threshold	Booster D every 6 weeks; Axis E as "hygiene"
5 – 7 mV	Remission; strong stress may cause replay	Booster D every 4 weeks; while PET & MEG ≥ 90 % maximum; taper A/B gradually
3 – 5 mV	Network stable, but coincident transients → incidental replay	Full A–D + weekly E; < 5 mV at 8 weeks → E^+ (μ-metal + ketamine)
< 3 mV	Vulnerability zone — replay ↻ stress → ROS → KCC2↓	Full A–D + E and E^+; Axis F if β-loop (+)

Monitoring: PET-KCC2, MEG γ, rMSSD every 4 weeks. Booster D continues while PET + MEG ≥ 90 % peak.

Rescue E^+ — 90-min μ-metal session at peak BDNF if < 3 mV at 4 weeks or < 5 mV at 8 weeks (details Table S52).

The DSMB may authorise one Rescue E^+ during the pilot if ΔV_{margin} < 3 mV after 4 weeks of A–D + E and no safety contra-indications. β-loop data will be shown to DSMB at interim (month 6) but are not required to trigger E^+ in the pilot.

Rescue F — 7–14 d of 24 h day^{-1} shielding (details Table S58); allowed only if β-loop (+) and no progress after E^+.

If RCT II (A–D ± E) misses the MCID and the β-loop is meanwhile positive, we launch RCT III: identical A–D ± E protocol but under ELF shielding (μ-metal ≥ 35 dB / active compensation, 24 h day^{-1}).

Falsification cascade (SZ / MDD / PTSD)

1. No progression in any marker → project STOP.
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.

4.9 Study limitations

The present framework integrates in vitro, in vivo and computational data into a single quantitative scaffold, yet several key assumptions remain unverified or carry elevated uncertainty (Table 4.11). These caveats do not overturn the main trends but they narrow numerical precision and limit the scope of extrapolation. A full list of secondary caveats is provided in Table S59.

Table 4.11 Model limitations and their implications

Area / module	Key limitation	Impact on interpretation / design
ELF detection (7–30 Hz magnetic field)	No confirmed, organised "magnetite chain"; with $\kappa = 8.27\ \mu V\ \mu T^{-1}$ the induced $\Delta V_{soma} \approx 0.06$ mV — requires patch-clamp in vitro	The ELF module remains a *working* hypothesis; it may be dropped if the environmental β-loop test is negative
$\Delta E_{GABA} \rightarrow \Delta V_{margin}$ scaling	Transfer factor 0.60 derived from simulations; no human *in vivo* measurement	If the true factor < 0.5, PET-KCC2 weighting may be too low and false-negatives could arise at the +2 mV threshold
Biomarker sensitivity	Current set (PET-KCC2, on-scalp MEG γ-burst, HRV rMSSD) covers ≈ 70 % of the margin; HRV is caffeine/nicotine-sensitive	Actual ΔV_{margin} could be higher or lower; second-generation tracers — ^{23}Na / ^{35}Cl MRI and PET-Kir4.1 / PET-PV — are needed
Pilot sample size	$N = 30$ (10 per phenotype) limits power and rare-SAE detection	Results are exploratory; definitive inference awaits RCT II ($N \approx 120$)
β-loop heterogeneity	Geomagnetic $K_p \geq 6$ effect derived from psychiatry + cardiology meta-analysis; $I^2 \approx 45$ %	β-estimate uncertainty ≈ 0.70; subgroup analyses and prospective DLNMs required
Animal-to-human transfer	ΔE_{GABA}, PV loss, R_{in} increase extrapolated indirectly	Clinical values may be over- or underestimated; invasive electrode studies warranted
Placebo / blinding	Full masking of rTMS, tVNS and μ-metal shielding is difficult	Dedicated shams + sensory/acoustic masking are mandatory
Cost & logistics	A–D ± E/E^+/F combines drugs, stimulation and shielding booths; high CAPEX/OPEX	Parallel cost-effectiveness analysis planned with RCT II

Patient adherence	Multiple visits + environmental sensors ⇒ potential treatment fatigue	e-Monitoring (app) and behavioural incentives planned
Population scope	Pilot: adults 18–45 y, male-skewed	Extrapolation to women, 50 +, pregnancy needs separate validation

4.10 Future research directions

The high-priority research axes outlined so far (Table 4-12) are now expanded to cover additional disorders and channelopathies that also satisfy the "narrow-margin" criterion for ventral CA1 (vCA1) excitability. Full experimental aims and proposed methods are listed in Supplements S60–S61. Beyond the canonical SZ, MDD and PTSD phenotypes, the model could potentially account for Nav1.6 channel encephalopathy (SCN8A EIEE), KCNQ2 encephalopathy, β-dominant obsessive–compulsive disorder, and the epilepsy-prone subtype of multiple sclerosis (MS + seizures). All share a chronic IL-6 / TNF-α inflammatory milieu that down-regulates KCC2 and astroglial Kir4.1, further shrinking the vCA1 margin (see Suppl. Tab. S61).

Table 4.12 Priority research gaps

#	Knowledge gap / objective	Scientific rationale
1	Identify the ELF biosensor (7–30 Hz) — pursued only if the environmental β-loop test is positive	Axis F depends on an ELF receptor; unclear whether the sensor is magnetite, cryptochromes, or TRP channels (Ca^{2+}-permeable, field-sensitive)
2	Second-generation biomarker panel ("mV-meter")	Current markers (PET-KCC2, MEG γ-burst, HRV rMSSD) capture ≈ 70 % of the margin; add ^{23}Na / ^{35}Cl MRI (ionic reserve) and PET-Kir4.1 / PET-PV interneurons
3	Cross-species & demographic validation	Data so far: male mice, young adults; need females, ages 18-80, *CACNA1C* rs1006737 A carriers, SCN2A GoF
4	Non-linearities at $\Delta V > 10$ mV	Models assume additivity; CREB-high clusters may respond supra-additively — patch- and dynamic-clamp studies required
5	Landscape of fast network transients	Number & amplitude of theta-associated ripple (TAR) / β-bursts (1–200 Hz) set the minimum remission margin; ≥ 24 h on-scalp MEG needed
6	Extend model to other "narrow-margin" disorders	GAD, bipolar/juvenile depression, ASD, temporal-lobe epilepsy, addictions, AD/MCI, MS + epilepsy, Dravet (SCN1A LoF), Rett (MECP2), Fragile X (FMR1), SCN8A EIEE, KCNQ2 EE, OCD
7	Clinical–economic translation	Randomised controlled trial III ($n \geq 400$) + cost-effectiveness (ICER / QALY) to assess scalability of A–D ± E

4.11 Final conclusions

Across humans and animal models, clinically distinct disorders share a single biophysical bottleneck: a narrowed vCA1 excitability margin. Stress, inflammation, risk alleles, psychoactive agents and CREB-high "hot spots" each subtract millivolts from the difference $V_{thr} - V_{rest}$; once the margin drops below ≈ 5 mV, everyday network transients or mild pharmacological stimuli can trigger involuntary replay of the dominant emotional engram. When the buffer falls below ≈ 2 mV, a θ/SWR peak crosses threshold every few tens of

seconds — the same CA1 hyperactivity observed in first-episode psychosis and treatment-resistant MDD.

Although the oscillatory signature differs for fear (θ–γ), sadness (δ–θ) and trauma (β–γ), all three converge on an "AMPA-high" vCA1 ↔ BLA hot spot. This implies that interventions restoring PV-interneuron function or blocking memory reconsolidation may work trans-diagnostically.

A putative contribution of ELF fields — potentially transduced by magnetite chains — could further increase transient coincidence in urban settings. The β-loop test will adjudicate this hypothesis: a negative result removes axis F, whereas a positive outcome activates the full ELF-screen module.

We close the translational loop: from in-silico prediction (buffer ≥ 7 mV), through non-invasive "mV counters" (PET-KCC2, MEG γ-burst, HRV rMSSD), to the RCT decision gate. The Four-Axis (FAR) Reset protocol assumes that simultaneous action on the ionic buffer (A), Cl^- gradient (B), oxidative/PV axis (C) and oscillatory gating (D) will widen the margin by ≥ 7 mV. The pilot RCT will test whether PET-KCC2 rises ≥ 15 %, γ-bursts fall ≥ 35 % and rMSSD increases ≥ 5 ms; meeting ≥ 2 of 3 criteria ($p < 0.05$) will trigger RCT-II.

If the "narrow-margin" hypothesis is refuted, the search will pivot to alternative mechanisms of hippocampal excitability regulation. If confirmed, it delivers the first multi-vector treatment programme that targets the electro-network origin of affective-psychotic disorders, with possible extensions to Nav1.6 and KCNQ2 encephalopathies, OCD, and MS + epilepsy.

Data and Code Availability

The complete set of NEURON scripts (*.hoc*, *.mod*) used in this study is openly hosted on GitHub:

https://github.com/PatrykRosa-55/vCA1-margin-calibration

The repository is automatically archived in Zenodo and distributed under the Creative Commons Attribution 4.0 licence (CC-BY-4.0).

- **Concept DOI (all versions):** https://doi.org/10.5281/zenodo.15837800
- When citing a specific release (e.g. for replication), please use the corresponding DOI and release tag, for example:
    - **v0.1 →** https://doi.org/10.5281/zenodo.15837801

Planned External Datasets

Validation of the β-loop (phases 1–3) will draw on public hospital-discharge statistics that are *not* part of the present work:

Provider	**Resource**	**Access date**
World Health Organization	Global Health Observatory (GHO)	09 Jul 2025
Agency for Healthcare Research and Quality	Healthcare Cost and Utilization Project (HCUP)	09 Jul 2025

Author Contributions (CRediT taxonomy)

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

Author Note

The designations “Rosa-Margin Hypothesis” (RMH) and “Four-Axis Reset” (FAR) are introduced for citation convenience. Researchers are welcome to adopt alternative terminology should a more accurate descriptor emerge.

Funding

The study received no external funding. All research and publication costs were covered by the authors.

Conflict of Interest

The authors declare no commercial or financial conflicts of interest.

Ethics Statement

This manuscript is entirely theoretical; no new studies involving humans or animals were conducted. All analyses are based exclusively on previously published data and therefore did not require additional ethics approval.

Clinical-Trial Registration

The authors plan to register the future clinical protocol with ClinicalTrials.gov before patient enrolment.

A detailed study protocol, including full CONSORT/SPIRIT checklists, will be released as a separate preprint on medRxiv prior to first-patient-first-visit.

Clinical / Regulatory Disclaimer

All drug doses, routes and stimulation parameters reported in this manuscript are presented solely for mechanistic modelling. They are not intended as medical recommendations and must not be applied outside IRB-approved clinical trials and regulatory-authorised protocols.

Safety Note on ELF Shielding

ELF-field shielding (e.g. μ-metal booths or active cancellation) is an experimental technique that should be used only under professional supervision within controlled studies. Unsupervised or home-made shielding could pose physical and psychological risks.

Supplementary Information

Three auxiliary files accompany the article:

1. **Supplementary_Methods.pdf** – detailed procedures (Methods §S2)
2. **Supplementary_Tables.pdf** – Tables S1–S61 (spreadsheets)
3. **Supplementary_References.pdf** – complete bibliography

All files will be uploaded together with the main document (**Main.pdf**) and made freely available on the bioRxiv site.

Licence

Abbreviations

Abbreviation	Expanded term
5-HIAA	5-Hydroxyindoleacetic acid
A_{ms}	Root-mean-square magnetic-field amplitude
ACC	Anterior cingulate cortex
ACS	Acute coronary syndrome
AD	Alzheimer disease
AD/MCI	Alzheimer disease / Mild cognitive impairment
AE	Adverse event
AMPA	α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AMPAR	AMPA receptor
ASD	Autism spectrum disorder
Att	Electrotonic attenuation
ATP	Adenosine triphosphate
BD	Bipolar disorder
BDNF	Brain-derived neurotrophic factor
BLA	Basolateral amygdala
BOLD	Blood-oxygen-level-dependent (fMRI)
β-LOOP	Environment-to-clinical beta loop
CAPEX	Capital expenditure
CAPS-5	Clinician-Administered PTSD Scale, 5th ed.
CBT-p	Cognitive Behavioural Therapy for Psychosis
CEST	Chemical-exchange-saturation transfer (MRI)
CI	Confidence interval
CIE	Chronic-intermittent ethanol
CLP-257	Experimental KCC2 positive allosteric modulator
CrI	Bayesian credible interval
CRF	Corticotropin-releasing factor
CRS	Chronic restraint stress
CSF	Cerebrospinal fluid

Abbreviation	Expanded term
DA	Dopamine
DG	Dentate gyrus
DLNM	Distributed-lag non-linear model
DMN	Default mode network
dmPFC	Dorsomedial prefrontal cortex
DOY	Day-of-year
DOW	Day-of-week
DSMB	Data and Safety Monitoring Board
dTMS	Deep transcranial magnetic stimulation
DLPFC	Dorsolateral prefrontal cortex
EAAT2	Excitatory amino-acid transporter-2
ECG	Electrocardiogram
ECS	Extracellular space
EEG	Electroencephalogram
EFSA	European Food Safety Authority
E_{GABA}	$GABA_A$ reversal potential
ELF	Extremely-low-frequency (7–30 Hz) field
EMDR	Eye-movement desensitisation & reprocessing
EPA	Eicosapentaenoic acid
EPSC	Excitatory postsynaptic current
EPSP	Excitatory postsynaptic potential
FDR	False-discovery rate
FEP	First-episode psychosis
FWHM	Full width at half maximum
GABA	γ-Aminobutyric acid
GAD	Generalised anxiety disorder
GAM	Generalised additive model
GBD	Global Burden of Disease study
GBM	Gradient-boosting machine

Abbreviation	Expanded term
GENUS	Gamma Entrainment Using Sensory Stimuli
GHO	WHO Global Health Observatory
GIRK	G-protein-activated inward-rectifying K^+ channel
GSH	Glutathione
HAM-A	Hamilton Anxiety Rating Scale
HDRS	Hamilton Depression Rating Scale
HCUP	Healthcare Cost and Utilization Project
HPA	Hypothalamic–pituitary–adrenal axis
HRV	Heart-rate variability
HVA	Homovanillic acid
ICD-10	International Classification of Diseases, 10th rev.
ICER	Incremental cost-effectiveness ratio
IEG	Immediate-early genes
IL-6	Interleukin-6
iTBS	Intermittent theta-burst stimulation
KD	Knock-down
Kir2.1	Inward-rectifying potassium channel 2.1
Kir4.1	Inward-rectifying potassium channel 4.1
KCC2	K^+/Cl^- cotransporter-2
K_p	Planetary K-index (geomagnetism)
LC	Locus coeruleus
LOF	Loss-of-function (mutation)
LPS	Lipopolysaccharide
LSTM	Long short-term memory (NN)
LTP	Long-term potentiation
MADRS	Montgomery–Åsberg Depression Rating Scale
MCID	Minimal clinically-important difference
MECP2	Methyl-CpG-binding protein-2
MEG	Magnetoencephalography

Abbreviation	Expanded term
MDD	Major depressive disorder
MI	Myocardial infarction
MMRM	Mixed-model repeated-measures
MRI	Magnetic-resonance imaging
mIPSC	Miniature inhibitory postsynaptic current
mPFC	Medial prefrontal cortex
MS	Multiple sclerosis
NAC	N-Acetylcysteine
Nav	Voltage-gated Na^+ channel
NE	Norepinephrine
NKCC1	$Na^+/K^+/Cl^-$ cotransporter-1
NOR	Novel-object recognition
OPEX	Operating expenditure
PANSS	Positive and Negative Syndrome Scale
PET	Positron-emission tomography
PFC	Prefrontal cortex
PLE	Psychotic-like experience
PL	Prelimbic cortex
PM_{10}	Particulate matter ≤ 10 μm
PNN	Perineuronal net
PRCC	Partial-rank correlation coefficient
PTSD	Post-traumatic stress disorder
PV	Parvalbumin
PV IN	Parvalbumin-positive interneuron
Q	Quality factor (magnetite chain)
QALY	Quality-adjusted life-year
RCT	Randomised controlled trial
RH	Relative humidity
Rin	Input resistance

Abbreviation	Expanded term
ROC AUC	Receiver-operating-characteristic area-under-curve
ROI	Region of interest
ROS	Reactive oxygen species
RR	Relative risk
rMSSD	Root-mean-square of successive differences
rTMS	Repetitive transcranial magnetic stimulation
sAHP	Slow after-hyperpolarisation
SAE	Serious adverse event
sEPSC	Spontaneous EPSC
sgACC	Subgenual anterior cingulate cortex
shKCC2	Short-hairpin knock-down of KCC2
SNRI	Serotonin-noradrenaline re-uptake inhibitor
SRN	Schumann Resonance Network (geomagnetic station)
SSRI	Selective serotonin re-uptake inhibitor
SUVR	Standardised uptake-value ratio
SWR	Sharp-wave ripple
SZ	Schizophrenia
TASK	TWIK-related acid-sensitive K^+ channel
tACS	Transcranial alternating-current stimulation
TAR	Theta-associated ripple
TLE	Temporal-lobe epilepsy
TOF	Time-of-flight (PET)
TR MDD	Treatment-resistant major depressive disorder
TRS	Treatment-resistant schizophrenia
TRPM2	Transient-receptor-potential melastatin-2 channel
tVNS	Transcutaneous vagus-nerve stimulation
UHR	Ultra-high risk
vCA1	Ventral hippocampal CA1
vHPC	Ventral hippocampus

Abbreviation	Expanded term
vmPFC	Ventromedial prefrontal cortex
V_{rest}	Resting-membrane potential
VTA	Ventral tegmental area
V_{thr}	Spike threshold
WHO	World Health Organization
XGBoost	eXtreme Gradient Boosting algorithm
μ-metal	High-permeability nickel–iron shielding alloy

References

Anacker, C. and Hen, R. 2017. Adult hippocampal neurogenesis and cognitive flexibility — linking memory and mood. *Nature Reviews Neuroscience* 18(6), pp. 335–346. doi: 10.1038/nrn.2017.45.

Benschop, L. et al. 2021. Electrophysiological scarring in remitted depressed patients: Elevated EEG functional connectivity between the posterior cingulate cortex and the subgenual prefrontal cortex as a neural marker for rumination. *Journal of Affective Disorders* 281, pp. 493–501. doi: 10.1016/j.jad.2020.12.081.

Ben-Shalom, R., Keeshen, C.M., Berrios, K.N., An, J.Y., Sanders, S.J. and Bender, K.J. 2017. Opposing Effects on Na V 1.2 Function Underlie Differences Between SCN2A Variants Observed in Individuals With Autism Spectrum Disorder or Infantile Seizures. *Biological Psychiatry* 82(3), pp. 224–232. doi: 10.1016/j.biopsych.2017.01.009.

Bigos, K.L. et al. 2010. Genetic Variation in CACNA1C Affects Brain Circuitries Related to Mental Illness. *Archives of General Psychiatry* 67(9), p. 939. doi: 10.1001/archgenpsychiatry.2010.96.

Blanchard, J. and Sawers, S.J.A. 1983. The absolute bioavailability of caffeine in man. *European Journal of Clinical Pharmacology* 24(1), pp. 93–98. doi: 10.1007/bf00613933.

Booth, V. and Rinzel, J. 1995. A minimal, compartmental model for a dendritic origin of bistability of motoneuron firing patterns. *Journal of Computational Neuroscience* 2(4), pp. 299–312. doi: 10.1007/bf00961442.

Bremner, J.D. et al. 1997. Elevated CSF corticotropin-releasing factor concentrations in posttraumatic stress disorder. *The American Journal of Psychiatry* 154(5), pp. 624–629. doi: 10.1176/ajp.154.5.624.

Brunet, A., Saumier, D., Liu, A., Streiner, D.L., Tremblay, J. and Pitman, R.K. 2018. Reduction of PTSD Symptoms With Pre-Reactivation Propranolol Therapy: A Randomized Controlled Trial. *American Journal of Psychiatry* 175(5), pp. 427–433. doi: 10.1176/appi.ajp.2017.17050481.

Bueno-Junior, L.S., Simon, N.W., Wegener, M.A. and Moghaddam, B. 2017. Repeated Nicotine Strengthens Gamma Oscillations in the Prefrontal Cortex and Improves Visual Attention. *Neuropsychopharmacology* 42(8), pp. 1590–1598. doi: 10.1038/npp.2017.15.

Buzsáki, G. and Draguhn, A. 2004. Neuronal Oscillations in Cortical Networks. *Science* 304(5679), pp. 1926–1929. doi: 10.1126/science.1099745.

Cabungcal, J.-H., Steullet, P., Kraftsik, R., Cuenod, M. and Do, K.Q. 2013. Early-Life Insults Impair Parvalbumin Interneurons via Oxidative Stress: Reversal by N-Acetylcysteine. *Biological Psychiatry* 73(6), pp. 574–582. doi: 10.1016/j.biopsych.2012.09.020.

Cai, D.J. et al. 2016. A shared neural ensemble links distinct contextual memories encoded close in time. *Nature* 534(7605), pp. 115–118. doi: 10.1038/nature17955.

Cash, S. and Yuste, R. 1999. Linear Summation of Excitatory Inputs by CA1 Pyramidal Neurons. *Neuron* 22(2), pp. 383–394. doi: 10.1016/s0896-6273(00)81098-3.

Chan, Y.L. et al. 2016. Impact of maternal cigarette smoke exposure on brain inflammation and oxidative stress in male mice offspring. *Scientific Reports* 6(1). Available at: https://www.nature.com/articles/srep25881 [Accessed: 14 July 2025].

Cheng, S., Wang, W., Zhu, Z., Zhao, M., Li, H., Liu, D. and Pan, F. 2023. Involvement of brain-derived neurotrophic factor methylation in the prefrontal cortex and hippocampus induced by chronic unpredictable mild stress in male mice. *Journal of Neurochemistry* 164(5), pp. 624–642. doi: 10.1111/jnc.15735.

Clem, R.L. and Huganir, R.L. 2010. Calcium-Permeable AMPA Receptor Dynamics Mediate Fear Memory Erasure. *Science* 330(6007), pp. 1108–1112. doi: 10.1126/science.1195298.

Cook, C.M. and Persinger, M.A. 1997. Experimental Induction of the "Sensed Presence" in Normal Subjects and an Exceptional Subject. *Perceptual and Motor Skills* 85(2), pp. 683–693. doi: 10.2466/pms.1997.85.2.683.

Crowe, S.F. et al. 2011. The effect of caffeine and stress on auditory hallucinations in a non-clinical sample. *Personality and Individual Differences* 50(5), pp. 626–630. doi: 10.1016/j.paid.2010.12.007.

Currin, C.B. and Raimondo, J.V. 2022. Computational models reveal how chloride dynamics determine the optimal distribution of inhibitory synapses to minimise dendritic excitability. Rubin, J. ed. *PLOS Computational Biology* 18(9), p. e1010534. doi: 10.1371/journal.pcbi.1010534.

Czeh, B., Simon, M., Van Der Hart, M.G., Schmelting, B., Hesselink, M.B. and Fuchs, E. 2005. Chronic Stress Decreases the Number of Parvalbumin-Immunoreactive Interneurons in the Hippocampus: Prevention by Treatment with a Substance P Receptor (NK1) Antagonist. *Neuropsychopharmacology* 30(1), pp. 67–79. doi: 10.1038/sj.npp.1300581.

Daly, E.J. et al. 2018. Efficacy and Safety of Intranasal Esketamine Adjunctive to Oral Antidepressant Therapy in Treatment-Resistant Depression: A Randomized Clinical Trial. *JAMA Psychiatry* 75(2), p. 139. doi: 10.1001/jamapsychiatry.2017.3739.

De Lucena, D. et al. 2009. Improvement of Negative and Positive Symptoms in Treatment-Refractory Schizophrenia: A Double-Blind, Randomized, Placebo-Controlled Trial With Memantine as Add-On Therapy to Clozapine. *The Journal of Clinical Psychiatry* 70(10), pp. 1416–1423. doi: 10.4088/jcp.08m04935gry.

Di Chiara, G. and Imperato, A. 1988. Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. *Proceedings of the National Academy of Sciences* 85(14), pp. 5274–5278. doi: 10.1073/pnas.85.14.5274.

Di Forti, M. et al. 2019. The contribution of cannabis use to variation in the incidence of psychotic disorder across Europe (EU-GEI): a multicentre case-control study. *The Lancet. Psychiatry* 6(5), pp. 427–436. doi: 10.1016/S2215-0366(19)30048-3.

Dimpfel, W., Schober, F. and Spüler, M. 1993. The influence of caffeine on human EEG under resting condition and during mental loads. *The Clinical Investigator* 71(3). Available at: http://link.springer.com/10.1007/BF00180102 [Accessed: 14 July 2025].

Ding, F., O'Donnell, J., Xu, Q., Kang, N., Goldman, N. and Nedergaard, M. 2016. Changes in the composition of brain interstitial ions control the sleep-wake cycle. *Science* 352(6285), pp. 550–555. doi: 10.1126/science.aad4821.

Donato, F., Rompani, S.B. and Caroni, P. 2013. Parvalbumin-expressing basket-cell network plasticity induced by experience regulates adult learning. *Nature* 504(7479), pp. 272–276. doi: 10.1038/nature12866.

Doyon, N., Prescott, S.A., Castonguay, A., Godin, A.G., Kröger, H. and De Koninck, Y. 2011. Efficacy of Synaptic Inhibition Depends on Multiple, Dynamically Interacting Mechanisms Implicated in Chloride Homeostasis. Morrison, A. ed. *PLoS Computational Biology* 7(9), p. e1002149. doi: 10.1371/journal.pcbi.1002149.

Dunkley, B.T. et al. 2015. Theta, Mental Flexibility, and Post-Traumatic Stress Disorder: Connecting in the Parietal Cortex. Ishii, R. ed. *PLOS ONE* 10(4), p. e0123541. doi: 10.1371/journal.pone.0123541.

Epsztein, J., Brecht, M. and Lee, A.K. 2011. Intracellular Determinants of Hippocampal CA1 Place and Silent Cell Activity in a Novel Environment. *Neuron* 70(1), pp. 109–120. doi: 10.1016/j.neuron.2011.03.006.

Ferrari, A.J. et al. 2024. Global incidence, prevalence, years lived with disability (YLDs), disability-adjusted life-years (DALYs), and healthy life expectancy (HALE) for 371 diseases and injuries in 204 countries and territories and 811 subnational locations, 1990–2021: a systematic analysis for the Global Burden of Disease Study 2021. *The Lancet* 403(10440), pp. 2133–2161. doi: 10.1016/s0140-6736(24)00757-8.

Forner-Phillips, N.A., Mills, C. and Ross, R.S. 2020. Tendency to ruminate and anxiety are associated with altered alpha and beta oscillatory power dynamics during memory for contextual details. *Cognitive, Affective, & Behavioral Neuroscience* 20(4), pp. 698–716. doi: 10.3758/s13415-020-00797-2.

Fujisawa, S. and Buzsáki, G. 2011. A 4 Hz Oscillation Adaptively Synchronizes Prefrontal, VTA, and Hippocampal Activities. *Neuron* 72(1), pp. 153–165. doi: 10.1016/j.neuron.2011.08.018.

Gaisenok, O., Gaisenok, D. and Bogachev, S. 2025. The Influence of Geomagnetic Storms on the Risks of Developing Myocardial Infarction, Acute Coronary Syndrome, and Stroke: Systematic Review and Meta-analysis. *Journal of Medical Physics* 50(1), pp. 8–13. doi: 10.4103/jmp.jmp_122_24.

Ghosal, S. et al. 2020. Ketamine rapidly reverses stress-induced impairments in GABAergic transmission in the prefrontal cortex in male rodents. *Neurobiology of Disease* 134, p. 104669. doi: 10.1016/j.nbd.2019.104669.

Giustino, T.F., Ramanathan, K.R., Totty, M.S., Miles, O.W. and Maren, S. 2020. Locus Coeruleus Norepinephrine Drives Stress-Induced Increases in Basolateral Amygdala Firing and Impairs Extinction Learning. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience* 40(4), pp. 907–916. doi: 10.1523/JNEUROSCI.1092-19.2019.

Godfrey, K.E.M., Gardner, A.C., Kwon, S., Chea, W. and Muthukumaraswamy, S.D. 2018. Differences in excitatory and inhibitory neurotransmitter levels between depressed patients

and healthy controls: A systematic review and meta-analysis. *Journal of Psychiatric Research* 105, pp. 33–44. doi: 10.1016/j.jpsychires.2018.08.015.

Grabnar, I., Vovk, T., Kores Plesnicar, B. and Boskovic, M. 2011. Oxidative Stress in Schizophrenia. *Current Neuropharmacology* 9(2), pp. 301–312. doi: 10.2174/157015911795596595.

Grienberger, C., Chen, X. and Konnerth, A. 2014. NMDA Receptor-Dependent Multidendrite Ca 2+ Spikes Required for Hippocampal Burst Firing In Vivo. *Neuron* 81(6), pp. 1274–1281. doi: 10.1016/j.neuron.2014.01.014.

Hall, J. et al. 2008. Overactivation of Fear Systems to Neutral Faces in Schizophrenia. *Biological Psychiatry* 64(1), pp. 70–73. doi: 10.1016/j.biopsych.2007.12.014.

Hamilton, J.P., Farmer, M., Fogelman, P. and Gotlib, I.H. 2015. Depressive Rumination, the Default-Mode Network, and the Dark Matter of Clinical Neuroscience. *Biological Psychiatry* 78(4), pp. 224–230. doi: 10.1016/j.biopsych.2015.02.020.

Han, J.-H. et al. 2007. Neuronal Competition and Selection During Memory Formation. *Science* 316(5823), pp. 457–460. doi: 10.1126/science.1139438.

Han, J.-H. et al. 2009. Selective Erasure of a Fear Memory. *Science* 323(5920), pp. 1492–1496. doi: 10.1126/science.1164139.

Higgins, C., Liu, Y., Vidaurre, D., Kurth-Nelson, Z., Dolan, R., Behrens, T. and Woolrich, M. 2021. Replay bursts in humans coincide with activation of the default mode and parietal alpha networks. *Neuron* 109(5), pp. 882-893.e7. doi: 10.1016/j.neuron.2020.12.007.

Hoftman, G.D., Datta, D. and Lewis, D.A. 2017. Layer 3 Excitatory and Inhibitory Circuitry in the Prefrontal Cortex: Developmental Trajectories and Alterations in Schizophrenia. *Biological Psychiatry* 81(10), pp. 862–873. doi: 10.1016/j.biopsych.2016.05.022.

Hu, J., Zhang, Y., Huang, C., Feng, X., He, S., Zhang, Y. and Maze, M. 2022. Interleukin-6 trans-signalling in hippocampal CA1 neurones mediates perioperative neurocognitive disorders in mice. *British Journal of Anaesthesia* 129(6), pp. 923–936. doi: 10.1016/j.bja.2022.08.019.

Hu, W., Zhang, M., Czéh, B., Flügge, G. and Zhang, W. 2010. Stress Impairs GABAergic Network Function in the Hippocampus by Activating Nongenomic Glucocorticoid Receptors and Affecting the Integrity of the Parvalbumin-Expressing Neuronal Network. *Neuropsychopharmacology* 35(8), pp. 1693–1707. doi: 10.1038/npp.2010.31.

Hu, Y.-T., Tan, Z.-L., Hirjak, D. and Northoff, G. 2023. Brain-wide changes in excitation-inhibition balance of major depressive disorder: a systematic review of topographic patterns of GABA- and glutamatergic alterations. *Molecular Psychiatry* 28(8), pp. 3257–3266. doi: 10.1038/s41380-023-02193-x.

Huang, S. et al. 2024. Disruption of the Na+/K+-ATPase-purinergic P2X7 receptor complex in microglia promotes stress-induced anxiety. *Immunity* 57(3), pp. 495-512.e11. doi: 10.1016/j.immuni.2024.01.018.

Huang, W.A. et al. 2021. Transcranial alternating current stimulation entrains alpha oscillations by preferential phase synchronization of fast-spiking cortical neurons to stimulation waveform. *Nature Communications* 12(1). Available at: https://www.nature.com/articles/s41467-021-23021-2 [Accessed: 14 July 2025].

Inoue, W. et al. 2013. Noradrenaline is a stress-associated metaplastic signal at GABA synapses. *Nature Neuroscience* 16(5), pp. 605–612. doi: 10.1038/nn.3373.

Jellinger, A.L. et al. 2024. Chronic activation of a negative engram induces behavioral and cellular abnormalities. *eLife* 13. Available at: https://elifesciences.org/articles/96281 [Accessed: 14 July 2025].

Ji, D. and Dani, J.A. 2000. Inhibition and Disinhibition of Pyramidal Neurons by Activation of Nicotinic Receptors on Hippocampal Interneurons. *Journal of Neurophysiology* 83(5), pp. 2682–2690. doi: 10.1152/jn.2000.83.5.2682.

Jimenez, J.C. et al. 2018. Anxiety Cells in a Hippocampal-Hypothalamic Circuit. *Neuron* 97(3), pp. 670-683.e6. doi: 10.1016/j.neuron.2018.01.016.

Jin, H. et al. 2022. Evaluation of Neurotoxicity in BALB/c Mice following Chronic Exposure to Polystyrene Microplastics. *Environmental Health Perspectives* 130(10). Available at: https://ehp.niehs.nih.gov/doi/10.1289/EHP10255 [Accessed: 14 July 2025].

Jones, S.R. and Fernyhough, C. 2009. Caffeine, stress, and proneness to psychosis-like experiences: A preliminary investigation. *Personality and Individual Differences* 46(4), pp. 562–564. doi: 10.1016/j.paid.2008.10.032.

Jurgens, H.A., Amancherla, K. and Johnson, R.W. 2012. Influenza Infection Induces Neuroinflammation, Alters Hippocampal Neuron Morphology, and Impairs Cognition in Adult Mice. *The Journal of Neuroscience* 32(12), pp. 3958–3968. doi: 10.1523/jneurosci.6389-11.2012.

Kang, H.J. et al. 2012. Decreased expression of synapse-related genes and loss of synapses in major depressive disorder. *Nature Medicine* 18(9), pp. 1413–1417. doi: 10.1038/nm.2886.

Kasper, S., Gastpar, M., Müller, W.E., Volz, H.-P., Möller, H.-J., Dienel, A. and Schläfke, S. 2010. Silexan, an orally administered Lavandula oil preparation, is effective in the treatment of ‘subsyndromal’ anxiety disorder: a randomized, double-blind, placebo controlled trial. *International Clinical Psychopharmacology* 25(5), pp. 277–287. doi: 10.1097/yic.0b013e32833b3242.

Kassem, M.S. et al. 2013. Stress-Induced Grey Matter Loss Determined by MRI Is Primarily Due to Loss of Dendrites and Their Synapses. *Molecular Neurobiology* 47(2), pp. 645–661. doi: 10.1007/s12035-012-8365-7.

Kelly, M.M., Jensen, K.P. and Sofuoglu, M. 2015. Co-occurring tobacco use and posttraumatic stress disorder: Smoking cessation treatment implications: Tobacco Use in Posttraumatic Stress Disorder. *The American Journal on Addictions* 24(8), pp. 695–704. doi: 10.1111/ajad.12304.

Keramidis, I. et al. 2023. Restoring neuronal chloride extrusion reverses cognitive decline linked to Alzheimer's disease mutations. *Brain* 146(12), pp. 4903–4915. doi: 10.1093/brain/awad250.

Kim, B. and Im, H. 2021. Chronic nicotine impairs sparse motor learning via striatal fast-spiking parvalbumin interneurons. *Addiction Biology* 26(3). Available at: https://onlinelibrary.wiley.com/doi/10.1111/adb.12956 [Accessed: 14 July 2025].

Kim, C.S. and Johnston, D. 2015. A1 adenosine receptor-mediated GIRK channels contribute to the resting conductance of CA1 neurons in the dorsal hippocampus. *Journal of Neurophysiology* 113(7), pp. 2511–2523. doi: 10.1152/jn.00951.2014.

Kim, W.B. and Cho, J.-H. 2020. Encoding of contextual fear memory in hippocampal–amygdala circuit. *Nature Communications* 11(1). Available at: https://www.nature.com/articles/s41467-020-15121-2 [Accessed: 14 July 2025].

Kirschvink, J.L. 1996. Microwave absorption by magnetite: A possible mechanism for coupling non-thermal levels of radiation to biological systems. *Bioelectromagnetics* 17(3), pp. 187–194. doi: 10.1002/(SICI)1521-186X(1996)17:3.

Kirschvink, J.L., Kobayashi-Kirschvink, A. and Woodford, B.J. 1992. Magnetite biomineralization in the human brain. *Proceedings of the National Academy of Sciences* 89(16), pp. 7683–7687. doi: 10.1073/pnas.89.16.7683.

Kitamura, T. et al. 2017. Engrams and circuits crucial for systems consolidation of a memory. *Science* 356(6333), pp. 73–78. doi: 10.1126/science.aam6808.

Klaus, K., Butler, K., Gutierrez, H., Durrant, S.J. and Pennington, K. 2018. Interactive effects of early life stress and CACNA1C genotype on cortisol awakening response. *Biological Psychology* 136, pp. 22–28. doi: 10.1016/j.biopsycho.2018.05.002.

Koutsoukos, E., Angelopoulos, E., Maillis, A., Papadimitriou, G.N. and Stefanis, C. 2013. Indication of increased phase coupling between theta and gamma EEG rhythms associated with the experience of auditory verbal hallucinations. *Neuroscience Letters* 534, pp. 242–245. doi: 10.1016/j.neulet.2012.12.005.

Kroener, S., Mulholland, P.J., New, N.N., Gass, J.T., Becker, H.C. and Chandler, L.J. 2012. Chronic Alcohol Exposure Alters Behavioral and Synaptic Plasticity of the Rodent Prefrontal Cortex. Manzoni, O. J. ed. *PLoS ONE* 7(5), p. e37541. doi: 10.1371/journal.pone.0037541.

Kurki, S.N., Srinivasan, R., Laine, J., Virtanen, M.A., Ala-Kurikka, T., Voipio, J. and Kaila, K. 2023. Acute neuroinflammation leads to disruption of neuronal chloride regulation and consequent hyperexcitability in the dentate gyrus. *Cell Reports* 42(11), p. 113379. doi: 10.1016/j.celrep.2023.113379.

Lasser, K., Boyd, J.W., Woolhandler, S., Himmelstein, D.U., McCormick, D. and Bor, D.H. 2000. Smoking and Mental Illness: A Population-Based Prevalence Study. *JAMA* 284(20), p. 2606. doi: 10.1001/jama.284.20.2606.

Leonard, S., Mexal, S. and Freedman, R. 2007. Genetics of Smoking and Schizophrenia. *Journal of Dual Diagnosis* 3(3–4), pp. 43–59. doi: 10.1300/j374v03n03_05.

Liu, X. et al. 2022. E-Cannula reveals anatomical diversity in sharp-wave ripples as a driver for the recruitment of distinct hippocampal assemblies. *Cell Reports* 41(1), p. 111453. doi: 10.1016/j.celrep.2022.111453.

Liu, X., Ramirez, S., Pang, P.T., Puryear, C.B., Govindarajan, A., Deisseroth, K. and Tonegawa, S. 2012. Optogenetic stimulation of a hippocampal engram activates fear memory recall. *Nature* 484(7394), pp. 381–385. doi: 10.1038/nature11028.

Lopes, J.P., Pliássova, A. and Cunha, R.A. 2019. The physiological effects of caffeine on synaptic transmission and plasticity in the mouse hippocampus selectively depend on adenosine A1 and A2A receptors. *Biochemical Pharmacology* 166, pp. 313–321. doi: 10.1016/j.bcp.2019.06.008.

Lubenov, E.V. and Siapas, A.G. 2009. Hippocampal theta oscillations are travelling waves. *Nature* 459(7246), pp. 534–539. doi: 10.1038/nature08010.

Lubin, F.D., Roth, T.L. and Sweatt, J.D. 2008. Epigenetic Regulation of*bdnf*Gene Transcription in the Consolidation of Fear Memory. *The Journal of Neuroscience* 28(42), pp. 10576–10586. doi: 10.1523/jneurosci.1786-08.2008.

Luo, J. and Lin, S. 2025. Association between microplastics exposure and depressive symptoms in college students. *Ecotoxicology and Environmental Safety* 295, p. 118142. doi: 10.1016/j.ecoenv.2025.118142.

MacKenzie, G. and Maguire, J. 2015. Chronic stress shifts the GABA reversal potential in the hippocampus and increases seizure susceptibility. *Epilepsy Research* 109, pp. 13–27. doi: 10.1016/j.eplepsyres.2014.10.003.

Malik, R. and Johnston, D. 2017. Dendritic GIRK Channels Gate the Integration Window, Plateau Potentials, and Induction of Synaptic Plasticity in Dorsal But Not Ventral CA1 Neurons. *The Journal of Neuroscience* 37(14), pp. 3940–3955. doi: 10.1523/jneurosci.2784-16.2017.

Mauney, S.A., Athanas, K.M., Pantazopoulos, H., Shaskan, N., Passeri, E., Berretta, S. and Woo, T.-U.W. 2013. Developmental Pattern of Perineuronal Nets in the Human Prefrontal Cortex and Their Deficit in Schizophrenia. *Biological Psychiatry* 74(6), pp. 427–435. doi: 10.1016/j.biopsych.2013.05.007.

McCall, J.G., Al-Hasani, R., Siuda, E.R., Hong, D.Y., Norris, A.J., Ford, C.P. and Bruchas, M.R. 2015. CRH Engagement of the Locus Coeruleus Noradrenergic System Mediates Stress-Induced Anxiety. *Neuron* 87(3), pp. 605–620. doi: 10.1016/j.neuron.2015.07.002.

McHugo, M. et al. 2022. Increased amplitude of hippocampal low frequency fluctuations in early psychosis: A two-year follow-up study. *Schizophrenia Research* 241, pp. 260–266. doi: 10.1016/j.schres.2022.02.003.

McHugo, M., Talati, P., Armstrong, K., Vandekar, S.N., Blackford, J.U., Woodward, N.D. and Heckers, S. 2019. Hyperactivity and Reduced Activation of Anterior Hippocampus in Early Psychosis. *American Journal of Psychiatry* 176(12), pp. 1030–1038. doi: 10.1176/appi.ajp.2019.19020151.

McKlveen, J.M. et al. 2016. Chronic Stress Increases Prefrontal Inhibition: A Mechanism for Stress-Induced Prefrontal Dysfunction. *Biological Psychiatry* 80(10), pp. 754–764. doi: 10.1016/j.biopsych.2016.03.2101.

Medina, I., Friedel, P., Rivera, C., Kahle, K.T., Kourdougli, N., Uvarov, P. and Pellegrino, C. 2014. Current view on the functional regulation of the neuronal K+-Cl− cotransporter KCC2. *Frontiers in Cellular Neuroscience* 8. Available at: http://journal.frontiersin.org/article/10.3389/fncel.2014.00027/abstract [Accessed: 14 July 2025].

Mertens, J. et al. 2015. Differential responses to lithium in hyperexcitable neurons from patients with bipolar disorder. *Nature* 527(7576), pp. 95–99. doi: 10.1038/nature15526.

Migliore, R. et al. 2018. The physiological variability of channel density in hippocampal CA1 pyramidal cells and interneurons explored using a unified data-driven modeling workflow. Lytton, W. W. ed. *PLOS Computational Biology* 14(9), p. e1006423. doi: 10.1371/journal.pcbi.1006423.

Mocking, R.J.T., Harmsen, I., Assies, J., Koeter, M.W.J., Ruhé, H.G. and Schene, A.H. 2016. Meta-analysis and meta-regression of omega-3 polyunsaturated fatty acid supplementation for major depressive disorder. *Translational Psychiatry* 6(3), pp. e756–e756. doi: 10.1038/tp.2016.29.

Moon, S.-Y., Choi, Y.B., Jung, H.K., Lee, Y.I. and Choi, S.-H. 2018. Increased Frontal Gamma and Posterior Delta Powers as Potential Neurophysiological Correlates Differentiating Posttraumatic Stress Disorder from Anxiety Disorders. *Psychiatry Investigation* 15(11), pp. 1087–1093. doi: 10.30773/pi.2018.09.30.

Nehlig, A. 2018. Interindividual Differences in Caffeine Metabolism and Factors Driving Caffeine Consumption. *Pharmacological Reviews* 70(2), pp. 384–411. doi: 10.1124/pr.117.014407.

Nemeroff, C.B. et al. 1984. Elevated Concentrations of CSF Corticotropin-Releasing Factor-Like Immunoreactivity in Depressed Patients. *Science* 226(4680), pp. 1342–1344. doi: 10.1126/science.6334362.

Nickolaenko, A. and Hayakawa, M. 2014. *Schumann Resonance for Tyros: Essentials of Global Electromagnetic Resonance in the Earth–Ionosphere Cavity*. Tokyo: Springer Japan. Available at: https://link.springer.com/10.1007/978-4-431-54358-9 [Accessed: 14 July 2025].

Nomoto, M., Ohkawa, N., Inokuchi, K. and Oishi, N. 2023. Requirement for hippocampal CA3 NMDA receptors in artificial association of memory events stored in CA3 cell ensembles. *Molecular Brain* 16(1). Available at: https://molecularbrain.biomedcentral.com/articles/10.1186/s13041-023-01004-2 [Accessed: 14 July 2025].

Núñez, A. and Buño, W. 2021. The theta rhythm of the hippocampus: from neuronal and circuit mechanisms to behaviour'. *Frontiers in Cellular Neuroscience* 15, p. 649262. doi: 10.3389/fncel.2021.649262.

Ogawa, S., Tsuchimine, S. and Kunugi, H. 2018. Cerebrospinal fluid monoamine metabolite concentrations in depressive disorder: A meta-analysis of historic evidence. *Journal of Psychiatric Research* 105, pp. 137–146. doi: 10.1016/j.jpsychires.2018.08.028.

Ostroumov, A., Thomas, A.M., Kimmey, B.A., Karsch, J.S., Doyon, W.M. and Dani, J.A. 2016. Stress Increases Ethanol Self-Administration via a Shift toward Excitatory GABA Signaling in the Ventral Tegmental Area. *Neuron* 92(2), pp. 493–504. doi: 10.1016/j.neuron.2016.09.029.

Pagani, M. et al. 2012. Neurobiological Correlates of EMDR Monitoring – An EEG Study. Schmidt, U. ed. *PLoS ONE* 7(9), p. e45753. doi: 10.1371/journal.pone.0045753.

Pazos, M., Mendoza, B., Sierra, P., Andrade, E., Rodríguez, D., Mendoza, V. and Garduño, R. 2019. Analysis of the effects of geomagnetic storms in the Schumann Resonance station data in Mexico. *Journal of Atmospheric and Solar-Terrestrial Physics* 193, p. 105091. doi: 10.1016/j.jastp.2019.105091.

Peng, T.-R. et al. 2024. Efficacy of N-acetylcysteine for patients with depression: An updated systematic review and meta-analysis. *General Hospital Psychiatry* 91, pp. 151–159. doi: 10.1016/j.genhosppsych.2024.10.018.

Phelps, E.A. and LeDoux, J.E. 2005. Contributions of the Amygdala to Emotion Processing: From Animal Models to Human Behavior. *Neuron* 48(2), pp. 175–187. doi: 10.1016/j.neuron.2005.09.025.

Pieraut, S. 2011. An autocrine neuronal interleukin 6 loop mediates chloride accumulation and NKCC1 phosphorylation in axotomized sensory neurons'. *Journal of Neuroscience* 31, pp. 13516–13526. doi: 10.1523/JNEUROSCI.3382-11.2011.

Pignatelli, M., Ryan, T.J., Roy, D.S., Lovett, C., Smith, L.M., Muralidhar, S. and Tonegawa, S. 2019. Engram Cell Excitability State Determines the Efficacy of Memory Retrieval. *Neuron* 101(2), pp. 274-284.e5. doi: 10.1016/j.neuron.2018.11.029.

Quadir, S.G., Danyal Zaidi, S., Cone, M.G. and Patel, S. 2024. Alcohol Withdrawal Alters the Inhibitory Landscape of the Prelimbic Cortex in an Interneuron- and Sex-specific Manner. Available at: http://biorxiv.org/lookup/doi/10.1101/2024.11.19.624401 [Accessed: 14 July 2025].

Radley, J.J. et al. 2004. Chronic behavioral stress induces apical dendritic reorganization in pyramidal neurons of the medial prefrontal cortex. *Neuroscience* 125(1), pp. 1–6. doi: 10.1016/j.neuroscience.2004.01.006.

Rahmanzadeh, R. et al. 2017. Effect of bumetanide, a selective NKCC1 inhibitor, on hallucinations of schizophrenic patients; a double-blind randomized clinical trial. *Schizophrenia Research* 184, pp. 145–146. doi: 10.1016/j.schres.2016.12.002.

Rangel-Gomez, M., Alberini, C.M., Deneen, B., Drummond, G.T., Manninen, T., Sur, M. and Vicentic, A. 2024. Neuron–Glial Interactions: Implications for Plasticity, Behavior, and Cognition. *The Journal of Neuroscience* 44(40), p. e1231242024. doi: 10.1523/jneurosci.1231-24.2024.

Rashid, A.J. et al. 2016. Competition between engrams influences fear memory formation and recall. *Science* 353(6297), pp. 383–387. doi: 10.1126/science.aaf0594.

Raver, S.M., Haughwout, S.P. and Keller, A. 2013. Adolescent Cannabinoid Exposure Permanently Suppresses Cortical Oscillations in Adult Mice. *Neuropsychopharmacology* 38(12), pp. 2338–2347. doi: 10.1038/npp.2013.164.

Reato, D., Rahman, A., Bikson, M. and Parra, L.C. 2010. Low intensity electrical stimulation affects network dynamics by modulating population rate and spike timing'. *Journal of Neuroscience* 30(45), pp. 15067–15079.

Reijmers, L.G., Perkins, B.L., Matsuo, N. and Mayford, M. 2007. Localization of a Stable Neural Correlate of Associative Memory. *Science* 317(5842), pp. 1230–1233. doi: 10.1126/science.1143839.

Rivera, C. et al. 2004. Mechanism of Activity-Dependent Downregulation of the Neuron-Specific K-Cl Cotransporter KCC2. *The Journal of Neuroscience* 24(19), pp. 4683–4691. doi: 10.1523/jneurosci.5265-03.2004.

Rodríguez-Camacho, J., Salinas, A., Carrión, M.C., Portí, J., Fornieles-Callejón, J. and Toledo-Redondo, S. 2022. Four Year Study of the Schumann Resonance Regular Variations Using the Sierra Nevada Station Ground-Based Magnetometers. *Journal of Geophysical Research: Atmospheres* 127(6). Available at: https://agupubs.onlinelibrary.wiley.com/doi/10.1029/2021JD036051 [Accessed: 14 July 2025].

Ronzoni, G., Del Arco, A., Mora, F. and Segovia, G. 2016. Enhanced noradrenergic activity in the amygdala contributes to hyperarousal in an animal model of PTSD. *Psychoneuroendocrinology* 70, pp. 1–9. doi: 10.1016/j.psyneuen.2016.04.018.

Rosenkranz, J.A. and Grace, A.A. 2002. Cellular Mechanisms of Infralimbic and Prelimbic Prefrontal Cortical Inhibition and Dopaminergic Modulation of Basolateral Amygdala Neurons*In Vivo*. *The Journal of Neuroscience* 22(1), pp. 324–337. doi: 10.1523/jneurosci.22-01-00324.2002.

Rowland, L.M. et al. 2016. Frontal Glutamate and γ-Aminobutyric Acid Levels and Their Associations With Mismatch Negativity and Digit Sequencing Task Performance in Schizophrenia. *JAMA Psychiatry* 73(2), p. 166. doi: 10.1001/jamapsychiatry.2015.2680.

Rumpel, S., LeDoux, J., Zador, A. and Malinow, R. 2005. Postsynaptic receptor trafficking underlying a form of associative learning. *Science (New York, N.Y.)* 308(5718), pp. 83–88. doi: 10.1126/science.1103944.

Ryan, T.J., Roy, D.S., Pignatelli, M., Arons, A. and Tonegawa, S. 2015. Engram cells retain memory under retrograde amnesia. *Science* 348(6238), pp. 1007–1013. doi: 10.1126/science.aaa5542.

Sara, S.J. and Bouret, S. 2012. Orienting and Reorienting: The Locus Coeruleus Mediates Cognition through Arousal. *Neuron* 76(1), pp. 130–141. doi: 10.1016/j.neuron.2012.09.011.

Saroka, K.S., Vares, D.E. and Persinger, M.A. 2016. Similar spectral power densities within the Schumann resonance and a large population of quantitative electroencephalographic profiles'. *PLOS ONE* 11(1), p. 0146595.

Sátori, G., Neska, M., Williams, E. and Szendrői, J. 2007. Signatures of the day-night asymmetry of the Earth-ionosphere cavity in high time resolution Schumann resonance records. *Radio Science* 42(2), p. 2006RS003483. doi: 10.1029/2006RS003483.

Schieferstein, J.N., Vuong, S. and Cano, G. 2024. Sharp wave ripple duration predicts hippocampal–prefrontal reactivation strength during learning'. *Journal of Physiology* 602(19), pp. 5039–5059. doi: 10.1113/JP285671.

Schmaal, L. et al. 2016. Subcortical brain alterations in major depressive disorder: findings from the ENIGMA Major Depressive Disorder working group. *Molecular Psychiatry* 21(6), pp. 806–812. doi: 10.1038/mp.2015.69.

Schnell, C., Janc, O.A., Kempkes, B., Callis, C.A., Flügge, G., Hülsmann, S. and Müller, M. 2012. Restraint Stress Intensifies Interstitial K+ Accumulation during Severe Hypoxia. *Frontiers in Pharmacology* 3. Available at: http://journal.frontiersin.org/article/10.3389/fphar.2012.00053/abstract [Accessed: 14 July 2025].

Schwabe, L. and Wolf, O.T. 2012. Stress Modulates the Engagement of Multiple Memory Systems in Classification Learning. *The Journal of Neuroscience* 32(32), pp. 11042–11049. doi: 10.1523/jneurosci.1484-12.2012.

Shaffer, F. and Ginsberg, J.P. 2017. An Overview of Heart Rate Variability Metrics and Norms. *Frontiers in Public Health* 5. Available at: http://journal.frontiersin.org/article/10.3389/fpubh.2017.00258/full [Accessed: 14 July 2025].

Shan, S., Zhang, Y., Zhao, H., Zeng, T. and Zhao, X. 2022. Polystyrene nanoplastics penetrate across the blood–brain barrier and induce activation of microglia in the brain of mice'. *Chemosphere* 298, p. 134261. doi: 10.1016/j.chemosphere.2022.134261.

Shaw, S.B. et al. 2023. Increased top-down control of emotions during symptom provocation working memory tasks following a RCT of alpha-down neurofeedback in PTSD. *NeuroImage: Clinical* 37, p. 103313. doi: 10.1016/j.nicl.2023.103313.

Shepard, R., Page, C.E. and Coutellier, L. 2016. Sensitivity of the prefrontal GABAergic system to chronic stress in male and female mice: Relevance for sex differences in stress-related disorders. *Neuroscience* 332, pp. 1–12. doi: 10.1016/j.neuroscience.2016.06.038.

Shin, L.M. and Liberzon, I. 2010. The Neurocircuitry of Fear, Stress, and Anxiety Disorders. *Neuropsychopharmacology* 35(1), pp. 169–191. doi: 10.1038/npp.2009.83.

Sibille, J., Pannasch, U. and Rouach, N. 2014. Astroglial potassium clearance contributes to short-term plasticity of synaptically evoked currents at the tripartite synapse. *The Journal of Physiology* 592(1), pp. 87–102. doi: 10.1113/jphysiol.2013.261735.

Siskind, D., Siskind, V. and Kisely, S. 2017. Clozapine Response Rates among People with Treatment-Resistant Schizophrenia: Data from a Systematic Review and Meta-Analysis. *The Canadian Journal of Psychiatry* 62(11), pp. 772–777. doi: 10.1177/0706743717718167.

Slutsky, I. et al. 2010. Enhancement of Learning and Memory by Elevating Brain Magnesium. *Neuron* 65(2), pp. 165–177. doi: 10.1016/j.neuron.2009.12.026.

Stefanelli, T., Bertollini, C., Lüscher, C., Muller, D. and Mendez, P. 2016. Hippocampal Somatostatin Interneurons Control the Size of Neuronal Memory Ensembles. *Neuron* 89(5), pp. 1074–1085. doi: 10.1016/j.neuron.2016.01.024.

Steullet, P. et al. 2017. Oxidative stress-driven parvalbumin interneuron impairment as a common mechanism in models of schizophrenia. *Molecular Psychiatry* 22(7), pp. 936–943. doi: 10.1038/mp.2017.47.

Syková, E. and Nicholson, C. 2008. Diffusion in Brain Extracellular Space. *Physiological Reviews* 88(4), pp. 1277–1340. doi: 10.1152/physrev.00027.2007.

Tesli, M., Skåtun, K.C. and Ousdal, O.T. 2013. CACNA1C risk variant and amygdala activity in bipolar disorder, schizophrenia and healthy controls'. *PLOS ONE* 8(2), p. 56970. doi: 10.1371/journal.pone.0056970.

Thayer, J.F., Åhs, F., Fredrikson, M., Sollers, J.J. and Wager, T.D. 2012. A meta-analysis of heart rate variability and neuroimaging studies: Implications for heart rate variability as a marker of stress and health. *Neuroscience & Biobehavioral Reviews* 36(2), pp. 747–756. doi: 10.1016/j.neubiorev.2011.11.009.

Tsukahara, S. 2015. Chronic repeated stress alters expression of chloride transporters KCC2 and NKCC1 in the female mouse hippocampus'. *Biochemical and Biophysical Research Communications* 465, pp. 145–151. doi: 10.1016/j.bbrc.2015.07.153.

Uhlhaas, P.J. and Singer, W. 2010. Abnormal neural oscillations and synchrony in schizophrenia. *Nature Reviews Neuroscience* 11(2), pp. 100–113. doi: 10.1038/nrn2774.

Valenti, O., Lodge, D.J. and Grace, A.A. 2011. Aversive Stimuli Alter Ventral Tegmental Area Dopamine Neuron Activity via a Common Action in the Ventral Hippocampus. *The Journal of Neuroscience* 31(11), pp. 4280–4289. doi: 10.1523/jneurosci.5310-10.2011.

Van Moorselaar, I. et al. 2017. Effects of personalised exposure on self-rated electromagnetic hypersensitivity and sensibility – A double-blind randomised controlled trial. *Environment International* 99, pp. 255–262. doi: 10.1016/j.envint.2016.11.031.

Vassos, E., Pedersen, C.B., Murray, R.M., Collier, D.A. and Lewis, C.M. 2012. Meta-Analysis of the Association of Urbanicity With Schizophrenia. *Schizophrenia Bulletin* 38(6), pp. 1118–1123. doi: 10.1093/schbul/sbs096.

Wang, S., Han, Q., Wei, Z., Wang, Y., Xie, J. and Chen, M. 2022. Polystyrene microplastics affect learning and memory in mice by inducing oxidative stress and decreasing the level of acetylcholine. *Food and Chemical Toxicology* 162, p. 112904. doi: 10.1016/j.fct.2022.112904.

Wild, A.R., Bollands, M., Morris, P.G. and Jones, S. 2015. Mechanisms regulating spill over of synaptic glutamate to extrasynaptic NMDA receptors in mouse substantia nigra dopaminergic neurons'. *European Journal of Neuroscience* 42(9), pp. 2633–2643. doi: 10.1111/ejn.13075.

Winklhofer, M. and Kirschvink, J.L. 2010. A quantitative assessment of torque transducer models for magnetoreception'. *Journal of the Royal Society Interface* 7(Suppl 2), pp. 273–289. doi: 10.1098/rsif.2009.0435.focus.

Yiu, A.P. et al. 2014. Neurons Are Recruited to a Memory Trace Based on Relative Neuronal Excitability Immediately before Training. *Neuron* 83(3), pp. 722–735. doi: 10.1016/j.neuron.2014.07.017.

Yolland, C.O. et al. 2020. Meta-analysis of randomised controlled trials with *N*-acetylcysteine in the treatment of schizophrenia. *Australian & New Zealand Journal of Psychiatry* 54(5), pp. 453–466. doi: 10.1177/0004867419893439.

Yoshioka, M., Matsumoto, M., Togashi, H. and Saito, H. 1996. Effect of conditioned fear stress on dopamine release in the rat prefrontal cortex. *Neuroscience Letters* 209(3), pp. 201–203. doi: 10.1016/0304-3940(96)12631-8.

Yu, Z. et al. 2020. Decreased Density of Perineuronal Net in Prelimbic Cortex Is Linked to Depressive-Like Behavior in Young-Aged Rats. *Frontiers in Molecular Neuroscience* 13, p. 4. doi: 10.3389/fnmol.2020.00004.

Zheng, W. et al. 2018. *N*-acetylcysteine for major mental disorders: a systematic review and meta-analysis of randomized controlled trials. *Acta Psychiatrica Scandinavica* 137(5), pp. 391–400. doi: 10.1111/acps.12862.

Zilli Vieira, C.L., Alvares, D., Blomberg, A., Schwartz, J., Coull, B., Huang, S. and Koutrakis, P. 2019. Geomagnetic disturbances driven by solar activity enhance total and cardiovascular mortality risk in 263 U.S. cities. *Environmental Health* 18(1). Available at: https://ehjournal.biomedcentral.com/articles/10.1186/s12940-019-0516-0 [Accessed: 14 July 2025].