Supplementary Methods - General Parameters

Parameter	Value	Application
Reference temperature	37 °C	Nernst / GHK equations
Patch-clamp temperature	34 – 35 °C (measurements of V_{rest} and V_{thr})	Difference < 2 mV relative to 37 °C – negligible
$[Cl^-]_o$ (control)	130 mM	Standard ACSF
$[K^+]_o$ (control)	3 mM	Standard ACSF
Nernst constants (log10; 37 °C)	K^+ = +61.54 mV Cl^- = −61.54 mV	*RT/F × 2.303*

A Nernst constant of 61.54 mV (R = 8.314 J mol^{-1} K^{-1}, T = 310 K, F = 96 485 C mol^{-1}) was assumed for 37 °C.

Reducing the temperature to 35 °C lowers this constant to 61.12 mV, shifting all calculated equilibrium potentials by ≈ 0.68 % (≈ 0.57 mV) when Cl^-_i = 5.8 mM.

The numerical value 61.54 mV is positive; the "–" sign appears because Cl^- carries a negative charge in the equation itself.

2.1 Reduction in KCC2 activity (Ser-940 dephosphorylation) — model of the E_{GABA} shift

Rapid dephosphorylation of the Ser-940 residue in the potassium-chloride cotransporter 2 (KCC2) destabilises its membrane expression **during chronic restraint stress (CRS)**—a finding first shown after a 14-day CRS paradigm (MacKenzie and Maguire 2015). Only the procedure used to model the shift in the $GABA_A$-receptor reversal potential (E_{GABA}) is detailed below.

2.1.1 Input parameters

Table 2.1 Parameters used in the E_{GABA} shift model

Parameter	Value (mean ± SD)	Source
$[Cl^-]_o$ (standard artificial cerebrospinal fluid, ACSF)	130 mM (124–132 mM)	(Rivera et al. 2002; Kim and Cho 2017)
$[Cl^-]_i$ (control)	5.8 ± 0.6 mM (n = 9 cells, 6 mice)	(MacKenzie and Maguire 2015)
E_{GABA} (control)*	−83.1 ± 1.2 mV	(MacKenzie and Maguire 2015)
Nernst constant (37 °C, log_{10})	61.54 mV	RT / F × 2.303
Relative *Kcc2* expression (vCA1/dCA1)	1.03 ± 0.04	(Cembrowski et al. 2016)
Contribution of G_{Cl} to V_{rest} stabilisation	0.15 ± 0.03	(Doyon et al. 2011; Migliore et al. 2018)

* Mean of measurements in dorsal CA1 (dCA1) rescaled to 37 °C; see §2.1.4.

The value of 130 mM refers to the main chloride fraction contributed by NaCl; the total extracellular concentration (≈ 136 mM) is 5–7 mM higher owing to KCl and $CaCl_2$, which still falls within the accepted range of 130 ± 5 mM.

The baseline E_{GABA} (−83 mV) is taken from the gramicidin-perforated recordings in Fig 3C of (MacKenzie and Maguire 2015); more depolarised (whole-cell; Fig. 4A) values reported in the same study are artefacts of pipette chloride dialysis.

2.1.2 Equations

At 37 °C:

$$\frac{RT}{F} = 26.70\ \text{mV} \implies \frac{RT}{F} \times 2.303 = 61.54\ \text{mV}.$$

Equilibrium potential for chloride:

$$E_{Cl} = -61.54\ \text{mV} \times \log_{10}\left(\frac{[Cl^-]_o}{[Cl^-]_i}\right).$$

2.1.3 Calculation procedure

1. **Define the reference state** Set baseline values $[Cl^-]_i$, $[Cl^-]_o$ and the calculated $E_{GABA,ctrl}$.
2. **Introduce the perturbation** Assign a new intracellular chloride concentration, $[Cl^-]_{i,test}$, corresponding to the desired reduction in KCC2 activity.
3. **Compute the shift**

$$\Delta E_{GABA} = E_{Cl,CRS} - E_{Cl,ctrl}$$

4. **Inverse equation (estimate $[Cl^-]_i$)**

$$[Cl^-]_{i,CRS} = [Cl^-]_{i,ctrl}\, 10^{\Delta E_{GABA}/61.54}$$

5. **Error propagation** Uncertainties were combined by root-sum-of-squares (see §2.5.5).

A complete worked example for ΔE_{GABA} = +8.25 mV (i.e. 5.8 → 7.9 mM Cl^-) is provided in Supplementary Table 1.

The $[Cl^-]_i$ value (5.8 mM) was calculated from the E_{GABA} (–83 mV) reported by (MacKenzie and Maguire 2015), using the Nernst equation for the chloride equilibrium (reversal) potential.

2.1.4 Sensitivity analysis

- Analysed range: $[Cl^-]_i$ = 5–8 mM and KCC2 loss = 0–50 %.

- The full results matrix and iterative algorithm are presented in Supplementary Table 1.

2.1.5 Methodological notes

E_{GABA} for ventral CA1 (vCA1) was extrapolated from dCA1 measurements (no *Kcc2* expression gradient (Cembrowski et al. 2016)).

A possible up-regulation of the $Na^+/K^+/2Cl^-$ cotransporter 1 (NKCC1) after CRS was not modelled; simulations (Currin and Raimondo 2022) indicate that a 25 % increase would enhance the depolarisation by ≈ 1 mV.

All input data derive from 8–12-week-old males; when females were included in source studies, the male values were treated as upper bounds.

The Kcc2 expression ratio (1.03) was calculated from FPKM values in Table S4 of Cembrowski et al. (2016), whereas the chloride leak fraction ($G_{Cl} = 0.15$) was obtained by recalculating the $g_{Cl}/\Sigma g_{leak}$ ratio from Figure 3 of (Doyon et al. 2011).

The upper bound of 130 mM reflects standard ACSF formulations (124–132 mM Cl^-) commonly used for hippocampal slices.

Values are reported at 37 °C; at the recording temperature of 34 °C they differ by less than 1 mV ($E_{GABA} \approx -82.3$ mV; $\Delta E_{GABA} \approx +8.2$ mV), which does not affect the conclusions.

In Table 3.1, a conservative value of +8.2 mV is reported for ΔE_{GABA}, rounded down from the calculated +8.25 mV.

2.2 Reduction in Kir4.1 conductance and extracellular-space shrinkage — model of $[K^+]_o$ elevation

Loss of astrocytic Kir4.1 channels (inwardly-rectifying K^+ channels), together with a reduction in the extracellular space (ECS), compromises K^+ buffering. Under chronic restraint stress (CRS) this leads to transient or tonic increases in extracellular K^+ concentration $\mathbf{[K^+]_o}$, thereby shifting the K^+ equilibrium potential ($\boldsymbol{E}_K$) and depolarising the resting membrane potential (V_{rest}).

Only the numerical procedure is described below; quantitative outcomes are provided in the *Results* section.

2.2.1 Input parameters

Table 2.2 Parameters used in the $[K^+]_o$ elevation model

Parameter	Value (mean ± SD)	Source
$[K^+]_o$ at rest (CA1)	3.00 ± 0.10 mM	(Krnjević et al. 1982; Schnell et al. 2012)
$\Delta[K^+]_o$ in wakefulness	+0.40 ± 0.05 mM	(Schnell et al. 2012) hippocampus, 21 d CRS; (Ding et al. 2016) comparative cortex only.
Peak $\Delta[K^+]_o$ during CRS + hypoxia	+3.00 ± 0.20 mM	(Schnell et al. 2012)
Nernst constant for K^+ (37 °C, $\log_{10}$)	61.54 mV	RT / F × 2.303
Fractional K^+ conductance in V_{rest} (f_K)	0.15 ± 0.03 (0.12–0.18)	Model edNEG (Sætra et al. 2021); Table 1: 'fractional K^+ leak conductance'

The resting extracellular potassium concentration, $[K^+]_o$ = 3.0 mM, was chosen based on in-vivo CA1 measurements (Krnjević et al. 1982) and the baseline value used by (Schnell et al. 2012) in slice ACSF.

$\Delta[K^+]_o$ = 0.40 mM corresponds to the upper bound of the tonic rise reported by (Schnell et al. 2012) in hippocampal slices after 21 d CRS.

2.2.2 Equations

1. **Shift in the K^+ equilibrium potential**

$$\Delta E_K = 61.54\ \text{mV} \times \log_{10}\left(\frac{3 + \Delta[K^+]_o}{3}\right).$$

2. **Impact on the resting potential**

$$\Delta V_{\text{rest}} = f_K\, \Delta E_K,$$

where f_K is the fraction of total membrane conductance carried by K^+ channels.

2.2.3 Calculation procedure

1. **Define baseline conditions** Set $[K^+]_o$ = 3.00 mM and the nominal f_K from Table 2.2.
2. **Specify change scenarios** Introduce $\Delta[K^+]_o$ representing:

(a) a moderate, tonic rise during wakefulness (e.g. +0.35–0.40 mM),

(b) short-lived "K^+ bursts" linked to network activity (e.g. +3.0 mM).

3. **Compute ΔE_K**. Insert the chosen $\Delta[K^+]_o$ into the ΔE_K equation (see "Shift in the K^+ equilibrium potential").
4. **Determine ΔV_{rest}.** Multiply the resulting ΔE_K by f_K using the ΔV_{rest} equation ("Impact on the resting potential").

5. **Error propagation** The standard error, $\sigma_{\Delta V}$, was obtained by root-sum-of-squares (see §2.5.5).

An illustrative example ($\Delta[K^+]_o = +0.35$ mM → ΔE_K, ΔV_{rest}) is provided in Supplementary Table S2.

$\Delta[K^+]_o = +3$ mM is defined as the difference between the baseline 3 mM and the tonic level of 6 mM immediately before the onset of HSD depolarisation in control slices (Schnell et al. 2012).

2.2.4 Sensitivity analysis

- Analysed range: $\Delta[K^+]_o = 0.2–3.5$ mM and $f_K = 0.15–0.25$.
- The full ΔV_{rest} matrix is presented in Supplementary Table 2.

2.2.5 Methodological notes

- A moderate increase in $\mathbf{[K^+]_o}$ during wakefulness (+0.40 mM) produces $\Delta V_{rest} \approx 0.5$ mV—below the resolution of a typical RMP recording—and is therefore treated as negligible in the overall depolarisation budget.
- Transient "K^+ bursts" ($\Delta[K^+]_o \approx +3$ mM) are examined separately from P2X7-receptor activation (§2.5) to avoid double-counting depolarisation.
- (Schnell et al. 2012) showed that peak $\mathbf{[K^+]_o}$ values of 6 mM also occur under CRS alone (without hypoxia), justifying the upper boundary of the analysis.
- Fractional K^+ conductance was set to $f_k = 0.15 \pm 0.03$, calculated from the passive-leak budget in Table 1 of (Sætra et al. 2021) ($g_k(leak)/\Sigma g_{leak} \approx 0.15$). This value represents the lower bound reported for CA1 pyramidal neurons; to account for models that employ stronger IK(leak), the sensitivity analysis spans $f_k = 0.15–0.25$ (Halnes et al. 2016).
- (Ding et al. 2016) reported a full range of +0.3–0.9 mM; the conservative lower bound of 0.4 mM was used to avoid inflating the depolarisation budget.

2.3 Interleukin-6 elevation — reduced KCC2 activity and NKCC1 induction

Interleukin 6 (IL-6), which rises in the hippocampus after chronic stress (Li et al. 2008), activates the IL-6R / gp130 → JAK-STAT3 signalling cascade. The result is a ↓ in KCC2 and an ↑ in NKCC1, which raises intracellular Cl^-, depolarises E_{GABA} and narrows the $V_{rest} \rightarrow V_{thr}$

distance. Only the modelling procedure is outlined here; numerical outcomes are reported in the Results.

2.3.1 Input parameters

Table 2.3 Parameters used in the IL-6 → KCC2 / NKCC1 model

Parameter	Value (mean ± SD)	Source
NKCC1 expression increase after IL-6 (neurons *in vitro*)	+35 %	(Pieraut et al. 2011) densitometry of Fig. 4; Model DRG → hippocampus extrapolation
KCC2 activity reduction after IL-6 trans-signalling	40 ± 5 %	(Rivera et al. 2004) Fig. 3B; BDNF in-vitro surrogate; qualitative confirmation in CA1: (Hu et al. 2022) (CA1 in vivo); (Jin et al. 2022) benchmark (Kalkman 2019) IL-6/STAT3 qualitative
ΔE_{GABA} at 40 % KCC2 loss	+10.1 ± 1.3 mV	(Rivera et al. 2004) extrapolated from Fig. 5 at 40 % KCC2 loss (BDNF); assumed to scale identically for IL-6
Nernst constant for Cl^- (37 °C, $\log_{10}$)	61.54 mV	RT / F × 2.303
Contribution of G_{Cl} to V_{rest} stabilisation (g_{Cl})	0.15 ± 0.03	(Doyon et al. 2011; Migliore et al. 2018)

2.3.2 Equations

1. E_{GABA} shift — ΔE_{GABA} values for different levels of KCC2 loss were taken directly from (Rivera et al. 2004) (patch-clamp measurements).
2. **Impact on the resting potential**

$$\Delta V_{rest} = g_{Cl}\,\Delta E_{GABA},$$

where $g_{Cl} = 0.15 \pm 0.03$.

2.3.3 Calculation procedure

1. **Reference scenario** Assume a 40 % loss of KCC2 (typical for robust IL-6/STAT3 activation).
2. E_{GABA} shift Use $\Delta E_{GABA} \approx +10.1$ mV.
3. **Compute ΔV_{rest}**

$$\Delta V_{rest} \approx 0.15\,\Delta E_{GABA} \approx +1.5\,\text{mV}$$

4. **Error propagation** Standard uncertainty was combined by the root-sum-of-squares rule (see §S2.5.5).

The complete ΔV_{rest} matrix for 20–50 % KCC2 loss is provided in Supplementary Table 3.

2.3.4 Sensitivity analysis

- **KCC2 loss 20–50 %** → $\Delta E_{GABA} = +5.1 – +12.2$ mV, $\Delta V_{rest} = +0.8 – +1.8$ mV ($g_{Cl} = 0.15$).
- **NKCC1 contribution** — The model does not include the IL-6-induced rise in NKCC1. Simulations (Currin and Raimondo 2022) indicate that a +25 % increase in NKCC1 activity would add ≈ +1 mV of depolarisation.

2.3.5 Methodological notes

- No direct E_{GABA} measurements are available for vCA1 after CRS; the same IL-6 sensitivity as in spinal models was assumed.
- The IL-6 pathway is treated separately from rapid Ser-940 dephosphorylation (§S2.1); the two mechanisms are additive but act on distinct KCC2 phosphorylation motifs.
- Should future data reveal a larger E_{GABA} shift in vCA1 (e.g. +12 mV), ΔV_{rest} will be adjusted linearly using the equation above.
- All input data are from 8–12-week-old males; when females were included, male values were taken as the upper bound.
- The +10 mV E_{GABA} shift at 40 % KCC2 loss was interpolated from Figure 5 of (Rivera et al. 2004), assuming a linear relationship between the 40–50 % protein reduction (Fig. 2D) and the observed depolarisation.
- (Kalkman 2019) provides a qualitative review of IL-6/STAT3-dependent regulation and is not used quantitatively.
- **IL-6 vs. Ser-940 dephosphorylation.** The reduction in active KCC2 was conservatively calculated as the simple sum of individual Δg values. Rapid Ser-940 dephosphorylation after CRS (Lee et al. 2011) and IL-6/BDNF-TrkB signalling, which partially converges on the same motif (Kitayama 2020), overlap only partially; their combined effect is unlikely to exceed the value adopted here.
- Because no gramicidin-perforated recordings quantify IL-6-induced KCC2 down-regulation in CA1 neurones, the BDNF data of (Rivera et al. 2004) were used as an upper-bound surrogate.
- The 35 % NKCC1 increase derives from DRG neuron cultures (Pieraut et al. 2011) and may overestimate the effect in CA1; the sensitivity analysis brackets this uncertainty.

2.4 Reduced GIRK and TASK conductance — model of V_{rest} depolarisation

G-protein-activated inwardly rectifying K^+ channels (GIRK; Kir3.x) and TASK-family two-pore K^+ channels (K2P 3.1/9.1) form the principal leak current in CA1 pyramidal neurones. Chronic restraint stress (CRS) lowers GIRK density in ventral CA1 (vCA1) and does **not** up-regulate the hyperpolarisation-activated current I_h, producing a net depolarisation of the resting membrane potential (V_{rest}). Only the modelling procedure is described below; numerical outcomes appear in the Results section.

2.4.1 Input parameters

Table 2.4 Parameters used in the GIRK/TASK conductance-loss model

Parameter	Value (mean ± SD)	Source / Note
ΔV_m after Ba^{2+} block in dorsal CA1 (dCA1)	+0.90 ± 0.86 mV	(Kim and Johnston 2015) Fig 7 & Fig 8; Difference 5.70 ± 0.70 mV – 4.80 ± 0.50 mV
GIRK conductance ratio vCA1 / dCA1	0.35 ± 0.07	(Malik and Johnston 2017) Fig 3–5; Mean of ratios 0.30 – 0.40 (I_{Ba}, I_{TPN})
Input-resistance ratio $R_{in,v}$ / $R_{in,d}$	1.50 ± 0.20	(Marcelin et al. 2012) Fig 2; P16-P24 rats; adult values are higher (≈ 2.0) → conservative
TASK channels as fraction of GIRK current	0.25 (assumed)	(Torborg et al. 2006) Fig 2C–D P14 interneurons; Extrapolated; no direct data for adult pyramids
Leak currents' contribution to V_{rest} stabilisation	0.65 ± 0.05	(Booth and Rinzel 1995) model; Heuristic 60 – 70 % used in CA1 models

2.4.2 Equations

1. **Scaling the depolarisation from dCA1 to vCA1**

$$\Delta V_{\text{scaled}} = \Delta V_{\text{d}} \left(\frac{R_{\text{in,v}}}{R_{\text{in,d}}} \right) \left(\frac{g_{\text{GIRK,v}}}{g_{\text{GIRK,d}}} \right).$$

2. **Including the TASK component**

$$\Delta V_{\text{GIRK/TASK}} = \Delta V_{\text{scaled}} \, (1 + f_{\text{TASK}}),$$

With $f_{\text{TASK}} \approx 0.25$.

3. **Propagation of total error**

$$\sigma_{\Delta V} = \Delta V_{\text{scaled}} \sqrt{\left(\frac{\sigma_R}{R} \right)^2 + \left(\frac{\sigma_g}{g} \right)^2 + \left(\frac{\sigma_f}{1 + f_{\text{TASK}}} \right)^2}$$

2.4.3 Calculation procedure

1. **Baseline value** $\Delta V_d = 0.90$ mV.

2. **Scale to vCA1** Insert $R_{in,v} / R_{in,d} = 1.50$ and $g_{GIRK,v} / g_{GIRK,d} = 0.35$ into the first equation.
3. **Add the TASK component** Multiply by $(1 + f_{TASK})$ as in the second equation.
4. **Compute $\sigma_{\Delta V}$** Use the standard deviations from the table in the error-propagation formula. This gives $\sigma\Delta V = 0.14$ mV, reported as ≈ 0.15 mV after rounding.
5. **Documentation** A detailed spreadsheet is provided in Supplementary Table S4.

2.4.4 Sensitivity analysis

- Examined range: $g_{GIRK,v} / g_{GIRK,d} = 0.30 – 0.40$ and $R_{in,v} / R_{in,d} = 1.30–1.70$.
- Resulting ΔV_{rest} lies between +0.44 and +0.77 mV (with no I_h compensation).
- The full value matrix is given in Supplementary Table 4.

2.4.5 Methodological notes

- **No direct patch-clamp data in vCA1.** Parameters were scaled using the published R_{in} and g_{GIRK} ratios for this region.
- **Absence of I_h compensation.** In dCA1, CRS increases I_h, partially offsetting depolarisation (Kim et al. 2018); such compensation is absent in vCA1, making the present estimates conservative.
- **TASK channels.** A TASK contribution of 25 % of the GIRK current was assumed, extrapolating the value measured in P14 hippocampus (Torborg et al. 2006) and assuming TASK-1/3 expression stabilises between P7 and P14 and remains constant in adulthood (Talley et al. 2001; Aller et al. 2005). If future data revise this percentage, ΔV_{rest} can be adjusted linearly via the second equation. No direct measurements for adult CA1 pyramidal neurons are currently available.
- The value **0.90 ± 0.86 mV** is the difference between the depolarisation caused by 50 µM Ba^{2+} (Table 8) and the depolarisation already present after blocking tonic A_1AR activity with 100 nM DPCPX (Table 7) in (Kim and Johnston 2015), thereby isolating the contribution of GIRK conductance loss. The tonic A_1AR-dependent depolarization (~ +4.8 mV) is accounted for only in this section (GIRK/TASK) and is not incorporated into the KCC2 modules.

- The 0.15 figure represents the lower bound reported by (Sætra et al. 2021); higher IK(leak) ratios would proportionally increase ΔV_{rest}, as explored in the sensitivity analysis.
- The dominant uncertainty (± 0.86 mV) derives directly from the standard deviation of ΔV_d—the Ba^{2+}-sensitive depolarisation reported by (Kim and Johnston 2015) (Fig. 8); uncertainty contributed by the scaling factors is < 0.1 mV and is therefore omitted from the overall error budget
- The fraction of 0.35 is the upper limit (in vCA1, on average, ≈ 0.22); taking a higher value overestimates ΔV after full GIRK blockade by a maximum of ~0.12 mV.

2.5 Microglial Na^+/K^+-ATPase α1 loss → P2X7-receptor activation

Degradation of the α1 subunit of the Na^+/K^+-ATPase (NKA α1) in microglia diminishes extracellular-K^+ uptake and increases ATP release, which secondarily activates ionotropic purinergic receptors P2X7R on neighbouring neurones. The resulting P2X7R current is depolarising and adds to the V_{rest} shift produced by the K^+ rise itself. Only the modelling steps are given below; numerical outcomes are presented in the Results.

2.5.1 Input parameters

Table 2.5 Parameters used in the NKA α1 → P2X7R model

Parameter	Value (mean ± SD)	Source
$[K^+]_o$ at rest (CA1)	3.00 ± 0.10 mM	(Schnell et al. 2012)
$\Delta[K^+]_o$ after 3 weeks CRS	+0.35 ± 0.05 mM	(Schnell et al. 2012; Ding et al. 2016)
Nernst constant for K^+ (37 °C, $\log_{10}$)	61.54 mV	RT / F × 2.303
Fractional K^+ conductance in V_{rest} (f_K)	0.15 ± 0.03	(Sætra et al. 2021)
Depolarisation of vCA1 after CRS / NKA α1 KO	+1.47 ± 0.18 mV	(Huang et al. 2024) Fig 3D; $\sigma\Delta V_{(P2X7R)} \approx 0.19$ mV

2.5.2 Equations

1. **Shift in the K^+ equilibrium potential**

$$\Delta E_{\mathrm{K}} = 61.54\,\mathrm{mV} \times \log_{10}\left(\frac{3.00 + \Delta[K^+]_o}{3.00}\right).$$

2. **Potassium contribution to V_{rest}**

$$\Delta V_{\mathrm{rest}}(K) = f_K\,\Delta E_{\mathrm{K}}.$$

3. **Pure P2X7R effect**

$$\Delta V_{\mathrm{rest}}(\mathrm{P2X7R}) = \Delta V_m(\mathrm{KO\ NKA\ \alpha1}) - \Delta V_{\mathrm{rest}}(K).$$

2.5.3 Calculation procedure

1. **Compute ΔE_K**

With $\Delta[K^+]_o = +0.35$ mM:

$$\Delta E_K = 61.54 \text{ mV} \times \log_{10}\left(\frac{3.35}{3.00}\right) \approx +2.95 \text{ mV}.$$

2. **Potassium contribution to V_{rest}**

Using $f_K = 0.15$:

$$\Delta V_{rest}(K) = 0.15 \times 2.95 \text{ mV} \approx +0.44 \text{ mV}.$$

3. **Isolate the P2X7R current**

$$\Delta V_{rest}(\text{P2X7R}) = 1.47 \text{ mV} - 0.44 \text{ mV} \approx +1.03 \text{ mV}.$$

4. **Error propagation**

Uncertainty was combined with the root-sum-of-squares rule (see § 2.5.5).

2.5.4 Sensitivity analysis

- Examined range: $\Delta[K^+]_o = 0.25$–0.45 mM, $f_K = 0.15$–0.25.
- Resulting ΔV_{rest}(P2X7R) = +0.54 – +1.15 mV (1.47 mV – ΔV_{rest}(K) from Supplementary Table 5).
- The value +1 mV adopted in subsequent calculations is a conservative minimum (the negative error bars exclude over-estimation).

2.5.5 Methodological notes

- No direct $[K^+]_o$ measurements are available for vCA1 after CRS; the highest published $\Delta[K^+]_o$ (+0.35 mM) was used, making ΔV_{rest}(K) maximal and avoiding under-estimation of the pure P2X7R component.
- Loss of astrocytic Kir4.1 (see § 2.2) would lower f_K, which would in turn raise the estimate of the pure P2X7R current above +1 mV; the +1 mV value therefore remains cautious.
- The +1 mV depolarisation is used in the Results section as the minimal contribution of the P2X7R mechanism to the overall change in V_{margin}.

2.5.6 Uncertainty propagation (summary)

Table 2.6 Summary of contributions and standard deviations

Mechanism	Mean [mV]	SD [mV]	SD/Mean
KCC2 → ΔE_{GABA}	8.20	1.30	0.16
IL-6 → KCC2↓ / NKCC1↑	1.50	0.30	0.20
GIRK/TASK↓	0.60	0.15	0.25
NKA α1↓ → P2X7R	1.00	0.22	0.22

Assuming statistical independence of the four error terms, the total variance is obtained by summing the individual variances:

$$\boldsymbol{\sigma_{tot}^2 = 1.3^2 + 0.30^2 + 0.15^2 + 0.22^2 = 1.851\ mV^2,\ \sigma_{tot} \approx 1.36\ mV.}$$

Signal-to-noise ratio:

$$\mathrm{SNR} = \frac{\sum \Delta V}{\sigma_{\mathrm{tot}}} = \frac{11.3\ \mathrm{mV}}{1.36\ \mathrm{mV}} \approx 8.3$$

2.6 Excitability markers – estimation procedures

Four semi-quantitative indices of neuronal excitability are defined below and used in the Results section solely for descriptive purposes. None of them is added (in mV) to the ΔV_{rest} budget; they serve only as independent confirmation of the depolarisation trend in vCA1 after CRS.

2.6.1 Rheobase

Rheobase—the minimal current needed to elicit a single action potential—is inversely proportional to the input resistance R_{in} (assuming a comparable spike threshold V_{thr}):

$$\text{Rheobase} \propto \frac{1}{R_{\mathrm{in}}}.$$

Experimental data for dorsal CA1 (dCA1)

Control $i_{AP} = 58.7 \pm 7.7$ pA

14 d CRS $i_{AP} = 32.9 \pm 9.0$ pA

(gramicidin perforated-patch recordings; Fig. 3C/3D in (MacKenzie and Maguire 2015))

→ Rheobase reduction: **−44 % ± 17 % SD**

dCA1 ↔ vCA1 differences under control conditions

(Marcelin et al. 2012) Fig. 2B reported:

$R_{in,vCA1} = 89 \pm 4$ MΩ,

$R_{in,dCA1} = 43 \pm 2$ MΩ

yielding

$$\frac{R_{\text{in,v}}}{R_{\text{in,d}}} \approx 2.1$$

Because vCA1 neurones have roughly double the input resistance, they already exhibit a lower rheobase at baseline; therefore the true drop in i_{AP} after CRS in ventral CA1 should be **≥ 44 %**.

Conservative assumption

- For subsequent calculations we **retain a −44 % change** as the **minimum** rheobase reduction in vCA1.
- Any error therefore **under-estimates** depolarisation, keeping the overall estimate conservative.

Table 2.7 Rheobase change after 14 d CRS

Baseline (dCA1)	Δ (14 d CRS, dCA1)	Scaled to vCA1 (R_{in} ≈ 2.1 ×)	Adopted change (vCA1)
58.7 ± 7.7 pA	−44 ± 17 % SD	effect ≥ −44 %	−44 %

2.6.2 EPSP decay time constant τ_{EPSP}

To date, no single-cell measurements of τ_{EPSP} have been published for CA1 pyramidal neurons after stress (acute or chronic).

(Ghosal et al. 2020) (Fig. 4c) reported that 14-day CRS lengthens the decay of the field EPSP (fEPSP) in ventral CA1 by +18 % (mouse slices, 29 °C).

Because an fEPSP integrates multisynaptic contributions (including NMDA currents) and is strongly temperature-dependent (≈ 2 % per 1 °C;(Hestrin 1993; Hardingham et al. 2010)), we correct this value to 34 °C using $Q_{10} \approx 1.7$:

$$\Delta_{34^{\circ}\text{C}} \approx 1.18 \times 1.7^{-0.5} - 1 \approx +14\%$$

We round to +15 % and adopt this as an upper bound (UB), which is incorporated into the *CRS block* in all subsequent cumulative calculations.

2.6.3 PV → pyramidal inhibition strength

Chronic stress reduces the number of parvalbumin-positive interneurons (PV IN) in the CA1 pyramidal layer, weakening fast inhibition onto pyramidal cells.

Morphological data. (Hu et al. 2010) reported a **36 ± 4 %** reduction in PV immunoreactivity (PV-IR) in CA1 of mice after 21 d CRS.

Scaling PV number to inhibitory conductance. (Hengen et al. 2013) found that inhibitory strength increases sub-power-law with contact number, exponent ≈ 0.4; hence

$$g_{\text{inh}} \propto N_{\text{PV}}^{0.4}.$$

A 36 % loss of PV INs yields

$$\Delta g_{\text{inh}} = (1 - 0.36)^{0.4} - 1 \approx -0.16$$

Table 2.8 Change in PV → pyr inhibition after CRS

Component	Value	Source
PV-IR loss in CA1	−36 % ± 4 %	(Hu et al. 2010)
Adopted exponent	0.4	(Hengen et al. 2013)
Resulting Δg_{inh}	−16 %	present calculation

(Exponent 0.3 gives −12 %; linear 1.0 gives −36 %. All variants leave the qualitative conclusion—depolarisation of the excitability margin—unchanged; see § 2.5.6.)

2.6.4 Input resistance R_{in}

Table 2.9 Change R_{in}

Parameter	Value	Source
ΔR_{in} in dCA1 after 14 d CRS	**+29 % ± 9 %** (131 ± 15 → 169 ± 20 MΩ)	(MacKenzie and Maguire 2015) Tab. S1

Extrapolation to vCA1. No experimental data are available; we assume the **same percentage increase** (conservative), though the absolute change (in MΩ) may be larger because baseline R_{in} is higher.

2.6.6 Final notes

- All four indices are qualitative; none is converted to mV.
- The adopted scalings are conservative (lower-bound estimates) to avoid over-stating excitability.
- Input data derive from 8–12-week-old males; where females were included, male values were treated as upper bounds.

2.7 Multicompartment modelling — depolarisation attenuation and supra-additive synergy

Using multicompartment models (single neuron or neuron + glia), we estimated two phenomena that can distort the summed change in V_{rest}:

1. **Depolarisation attenuation (Att %)** — dissipation of a local depolarisation into remote dendritic compartments.

2. **Supra-additive synergy (Synergy %)** — a positive interaction between simultaneous ionic/synaptic perturbations, larger than the sum of the individual effects.

Neither index contributes new values in mV; they serve only to adjust the ΔV_{rest} budget reported in the Results section.

2.7.1 Depolarisation attenuation (Att %)

We define attenuation as

$$\text{Att\%} = \left(1 - \frac{\Delta V_{\text{soma}}}{\Delta V_{\text{inj}}}\right) \times 100\%$$

Table 2.10 Published Att % values

Model	Configuration	Att %	Source
(Booth and Rinzel 1995)	2-compartment CA1 neuron	11	Fig 6B
(Doyon et al. 2011)	Multicomp., dynamic Cl^-	14	Fig 4C
(Migliore et al. 2018)	Single neuron + network	12	Fig 3A
(Currin and Raimondo 2022)	Neuron + astrocyte	13	Suppl. Fig S3

Mean ± SD = 12.5 % ± 1.3 %.

For subsequent calculations we conservatively adopt **−12 %** (lower limit of the 95 % CI ≈ 9–15 %).

2.7.2 Supra-additive synergy (Synergy %)

Percentage synergy is defined as

$$\text{Synergy\%} = \frac{\Delta V_{\text{combo}} - \sum \Delta V_{\text{single}}}{\sum \Delta V_{\text{single}}} \times 100\%.$$

Table 2.11 Examples of supra-additive synergy

Study	Single manipulations	Synergy %
(Doyon et al. 2011)	↓KCC2 −60 % + ↑$GABA_A$ freq +200 %	15
(Currin and Raimondo 2022)	Cl^- dynamics ON + distal inhibition	19

Mean ± SD = 17.0 % ± 2.83%.

We adopt a conservative **+17 %** in the analysis.

2.7.3 Application to the ΔV_{rest} budget

Corrections were applied sequentially:

$$\Delta V_{\text{corr}} = (1 - 0.12)\,(1 + 0.17) \sum \Delta V_{\text{rest}}^{\text{linear}} \;\approx\; 1.03 \sum \Delta V_{\text{rest}}^{\text{linear}}.$$

The resulting **+3 %** falls within the total error ($\sigma \approx 1.4$ mV, see § 2.5.6); therefore, in the minimal scenario we retain the linear sum (no extra +3 %). Full matrices and statistics are in Tables S6–S8.

2.7.4 Notes

Att % and **Synergy %** are used only as weighting factors; they do **not** introduce additional mV entries into the main summary.

All values come from models incorporating adult-mouse CA1 pyramidal neurons or the corresponding *in silico* configurations.

2.8 Risk alleles and psychoactive substances in the vHPC ↔ BLA ↔ mPFC loop

This section lists every numerical value that is later compared in *Results* (Tables 3.3 & 3.4) to gauge the relative impact of various factors on the excitability of the ventral-hippocampus–basolateral-amygdala–medial-prefrontal-cortex (vHPC–BLA–mPFC) network. Asterisks (∗) mark quantities derived by simple modelling or extrapolation; full derivations and input parameters are given in Supplementary Tables 9–18.

2.8.1 Data-inclusion criteria

- **Measurement** — value read directly in an experiment (patch-clamp, qPCR, micro-dialysis, fMRI, …).
- **Model (∗)** — value obtained with elementary analytic formulas (Goldman–Hodgkin–Katz, Lapicque, Booth–Rinzel). No new numerical simulations were run.
- All model-based numbers are treated as **lower estimates** (mV or %) to avoid over-stating the cumulative impact of any single allele or drug.
- When transferring effects between regions (e.g. 1 : 1 mPFC → vHPC), the *least* excitatory scenario was always chosen.

2.8.2 Risk alleles — primary data and model outcome

Table 2.12 Risk factors (genetic + molecular) that lower the excitability threshold

Allele / variant	Key experimental findings	Transfer / scaling	Modelled effect (target region)
EAAT2 ↓	CA1: DL-TBOA ↑τ_{EPSP} 41 % (Diamond 2001) Fig. 3C; cerebellum: PDC ↑τ_{EPSP} 43 % (Overstreet et al. 1999) Fig. 7; ↓EAAT2 protein in vHPC (Shan et al. 2013)	Similar EAAT2 density dCA1 ≈ vCA1 (Yeung et al. 2021) expression dysregulation, cerebellar data used as lower-bound transfer to CA1	+40 % τ_{EPSP}

GRIN1 mRNA 18 % ↓ interpolated centre of probe range	DLPFC qPCR (Weickert et al. 2013); *NR1* KO: g_{NMDA} −86 % (South et al. 2003)	mRNA → g_{NMDA} linear; DLPFC → mPFC (Povysheva and Johnson 2012); weaker IN activation → less feedback inhibition	−18 % $g_{NMDA;}$
GRM3 (risk)*	ΔEAAT2 −30 %; ΔmGlu3 −12.5 % ⇒ $\Delta[Glu]_{extra}$ +35 %	$\Delta\tau = 0.7 \times \Delta[Glu]_{extra}$ (Wild et al. 2015)	+25 % τ_{EPSP}
GABRA1 mRNA ↓ 40 %*	α1 KO: τ_{mIPSC} ↑ 55 % (Bosman et al. 2005)	Correct × 0.45 for 40 % mRNA; charge IPSC A·τ ⇒ Δg_{inh} −7 %;−40 % mRNA (Glausier and Lewis 2011) expression dysregulation	+25 % τ_{IPSC}; −7 % g_{inh}; +1.4 % R_{in}
COMT Val158Met*	CSF HVA −15 % (Ogawa et al. 2018) ; activity COMT ↓ ≈ 45 % mRNA, protein, V_{max} (Chen et al. 2004)	Gain factor = 0.9 × ΔDA (Vijayraghavan et al. 2007)	+14 % gain
CACNA1C rs1006737 A*	$\Delta I_{Ca,L}$ +30 % (Mertens et al. 2015)	$\Delta\tau = 0.5 \times \Delta[Ca]_{post}$; rheobase −6 % Expression in BLA/vHPC confirmed (Tesli et al. 2013)	+15 % τ_{EPSP}; −6 % rheobase
NRG1 HapICE*	PV IN −30 % (Fazzari et al. 2010); IPSC −25 % (Yin et al. 2013)	Booth-Rinzel exponent 0.3 ⇒ $\Delta g_{inh} \approx -10$ %	−10 % g_{inh}
C4A copy-number ↑ (over-expression)*	mPFC L2/3: synapse pruning (PSD95 + inside Iba1 microglia) ↑ ≈ 35 %; apical spine density ↓ 25 %; mEPSC freq ↓ 20 %, amp ↓ 15 % (Yilmaz et al. 2021), Fig 4–6;	1 : 1 transfer mPFC → vHPC (lower bound); $\Delta g_{exc} \approx -20$ % computed as mean of spine & mEPSC loss (Supp. Tab 14).	−20 % g_{exc} (vHPC / mPFC); γ synchrony ↓ (qual.)
SCN2A R1882Q	mPFC patch: $I_{Na,pers}$+40 %; V_{thr} −3 mV (Ben-Shalom et al. 2017)	Same L5-IT projection neurons in mPFC ⇒ 1 : 1 transfer	−15 % rheobase

∗ Modelled or extrapolated value. Full equations & parameters — Tables S9–S15.

Table 2.13 Risk alleles lowering the excitability threshold in the vHPC–BLA–mPFC loop

Allele / gene	Target node†	Cellular data	Direction	Source
EAAT2 ↓	vHPC	τ_{EPSP} ↑ ~40 %	EPSP ↑	(Overstreet et al. 1999; Diamond 2001; Shan et al. 2013; Yeung et al. 2021)
GRIN1 mRNA ↓	mPFC	I_{NMDA} ↓ 18 %	E/I shift → τ_{EPSP} ↑	(South et al. 2003; Povysheva and Johnson 2012; Weickert et al. 2013)
GRM3 (risk)*	mPFC	$\Delta[Glu]_{extra}$ ↑ → τ_{EPSP} ↑ 25 %	EPSP ↑ / noise ↑	(Abdul et al. 2009; Ghose et al. 2009; Wild et al. 2015)
GABRA1 mRNA ↓ 40 %*	mPFC	τ_{IPSC} ↑ 25 %; R_{in} ↑ 1.4 %	GABA ↓ / R_{in} ↑	(Bosman et al. 2005; Glausier and Lewis 2011)
COMT Val158Met (rs4680)*	mPFC / BLA	DA catabolism ↓; gain ↑ 14 %	DA gain ↑	(Chen et al. 2004; Vijayraghavan et al. 2007; Ogawa et al. 2018)

CACNA1C rs1006737 A*	vHPC / BLA	$I_{Ca,L}$ ↑ 30 %; τ_{EPSP} ↑ 15 %; rheobase ↓ 6 %	EPSP ↑	(Tesli et al. 2013 Fig. 1D; Mertens et al. 2015 Fig. 3A; Wild et al. 2015)
NRG1 HapICE (haplotype)*	mPFC	PV GABA ↓ 10 %	GABA ↓ / γ ↓	(Law et al. 2006; Fazzari et al. 2010; Yin et al. 2013)
C4A copy-number ↑ (qual.)*	mPFC / vHPC	Synapse pruning ↑ 35 %; spine ↓ 25 %; mEPSC freq ↓ 20 %; amp ↓ 15 %	Connectivity ↓; γ synchrony ↓	(Yilmaz et al. 2021)
SCN2A R1882Q (rs199473021)	mPFC / BLA	ΔV_{thr} −3 mV; rheobase ↓ 15 %	Threshold ↓ / bursting ↑	(Ben-Shalom et al. 2017)

† Target node = structure where the strongest effect is expected; does not exclude actions in other loop elements.

∗ Modelled or extrapolated value.

2.8.3 Psychoactive substances — primary data and model outcome

Table 2.14 Substances: protocol, data, and modelled effect

Substance / protocol	Primary source	Data type	Value in Table 3.4
Amphetamine 2 mg kg^{-1} i.p.∗	(Di Chiara and Imperato 1988; Rosenkranz and Grace 2002)	measurement + model	DA ↑; rheobase −12 %
THC ≥ 21 dni (adolesc.)	(Raver et al. 2013)	qualitative	PV-IN dysfunction; γ-power ↓ 50 %
Alcohol CIE 5 weeks ∗	(Kroener et al. 2012)	measurement + extrap.	+30 % NMDA/AMPA; −15 % $mIPSC_{GABA}$ ‡
Alcohol withdrawal 72 h ∗	(Quadir et al. 2024) preprint	measurement + scaling	+20 % R_{in} PV; $IPSC_{GABA}$ ↓

∗ Modelled or extrapolated value. Full equations & parameters — Tables S16–S18.

‡ Trend; $p = 0.08$ ((Kroener et al. 2012) Fig. 4C)

Table 2.15 Drugs lowering the excitability threshold of the vHPC–BLA–mPFC loop

Substance / protocol	Target node†	Key data	Window‡	Direction	Source
Amphetamine 2 mg kg^{-1} i.p.∗	BLA	DA ↑; rheobase ↓ 12 %	acute	Excitation ↑	(Di Chiara and Imperato 1988; Rosenkranz and Grace 2002) Fig. 4C
THC ≥ 21 dni (adol.)	vHPC / BLA	PV-IN dysfunction; γ-power ↓ 50 %	chronic	Recruitment ↓	(Raver et al. 2013)
Alcohol CIE 5 weeks ∗	vHPC / BLA	NMDA/AMPA ↑ 30 %; mIPSC ↓ 15 %	chronic	gain ↑	(Kroener et al. 2012) Fig. 4B-C

Alcohol withdrawal 72 h ∗	BLA	R_{in} PV ↑ 20 %; $IPSC_{GABA}$ ↓	withdrawal	mPFC control ↓	(Quadir et al. 2024) Fig. 2B-D preprint

‡ acute ≤ 1 h; chronic ≥ 7 d; withdrawal = 24–96 h post-exposure.

† Target node = structure where the strongest effect is expected; does not exclude actions in other loop elements.

∗ Modelled or extrapolated value.

2.8.4 Auxiliary equations

Table 2.16 Equations used in § 2.8

Equation	Source
$\Delta[Glu]_{extra} = -(\Delta EAAT2 + 0.4 \times \Delta mGlu3)$	(Migliore et al. 2018)
$\Delta\tau_{EPSP} = 0.7 \times \Delta[Glu]_{extra}$	(Sibille et al. 2014; Wild et al. 2015)
$\Delta\tau_{EPSP} = 0.5 \times \Delta[Ca]_{post}$	(Wild et al. 2015)
V_{rest} model = $\Sigma(g \cdot E) / \Sigma g$	(Goldman 1943; Hodgkin and Katz 1949)
$\Delta g_{inh} = 1 - (N_{PV} / N_{PV,ctrl})^{0.3}$	(Booth and Rinzel 1995)
$R_{in} = 1 / G_{leak}$	def. patch clamp
$\Delta V_{SCN2A} = V_{thr,R1882Q} - V_{thr,WT}$	(Ben-Shalom et al. 2017)

2.8.5 Notes on conservatism and model limitations

- All asterisked values (∗) are **lower-bound estimates**—mV or % values have been rounded **downward**.
- When transferring effects between brain regions (e.g. 1 : 1 mPFC → vHPC), the **least** excitatory scenario was selected.
- Where micro-dialysis data for the BLA were lacking (e.g. amphetamine), only an upper constraint sufficient to establish the **direction** of the effect was used.
- For postsynaptic changes (e.g. loss of the $GABA_A$ α1 subunit) we applied a linear reduction of g_{inh} derived from IPSC charge; the Booth–Rinzel rule applies **only** to changes in PV interneuron number.
- **THC:** the actual median drop is 83 % ((Raver et al. 2013), Fig. 3B); a 50 % decrease was adopted to avoid over-estimating the THC impact.
- Some gradients were originally measured in embryonic rat neurones; applying them unchanged to adults is a conservative assumption (in vivo data unavailable).
- A **linear** mRNA → g_{NMDA} transfer was assumed; the sigmoidal model in (South et al. 2003) would produce a larger decrease, so the present value is conservative.

- The $0.7 \times \Delta[\text{Glu}]$ slope was derived in dentate-granule cells; applying it to CA1 pyramids is again a conservative extrapolation.

2.9 vCA1 hot spot — modulation of excitability indices

The scenarios below apply **only** to the ~5 % of ventral-CA1 pyramidal neurons that form CREB-high clusters, for which a depolarisation margin of $\Delta V_{\text{margin}} \approx 3.2$ mV has been demonstrated (Han et al. 2009).

2.9.1 Sources and transfer rules for vCA1

Table 2.17 Input parameters for the vCA1 hot-spot model

Factor	Primary source (fig./table)	Data type	Value used in Table 3.6	Transfer rule to vCA1†
CREB–CBP ↑ → V_{margin}	(Han et al. 2009) Fig 6b & Suppl. Table 1	patch-clamp (LA)	+3.2 mV	lateral amygdala (LA) → vCA1 1 : 1 (BE); no multiplier for the +7 % higher R_{in} in vCA1 (Marcelin et al. 2012)
Rheobase ↓	(Pignatelli et al. 2019) Fig 1E & 3D	patch-clamp (dCA1)	−15 %	Longitudinal CA1 difference in rheobase < 5 % (Dougherty et al. 2012) ⇒ 1 : 1 (best-estimate, BE)
τ_{EPSP} ↑	(Ryan et al. 2015) Fig 8B-C; (Wild et al. 2015) Fig 3B	patch-clamp (dCA1 ΔEPSC) + model (Sibille et al. 2014) 0.7	+25 %	dCA1 → vCA1 1 : 1; τ obliczono: $\Delta\tau = 0.7 \cdot (\Delta\text{EPSC}/I_{\text{EPSC,ctrl}})$ (Sibille et al. 2014) 0.6–0.8 ⇒ Δτ = 21–32 % – correlation ΔI → Δτ; see §2.9.4) (UB)
$\text{IPSC}_{\text{PV}\rightarrow\text{pyr}}$	No data	No data	No data	No data
R_{in}	No data	No data	No data	No data
AMPAR switch (BLA)	(Rumpel et al. 2005) Fig 2	patch clamp + immuno, BLA	40%* GluN-only → AMPAR^{+}	Qualitative BLA phenomenon; listed for context, **not** added to ΔR_{in} / τ sum (LB)

† UB = upper bound (value may be **over-stated**, conservative for depolarisation risk); LB = lower bound (minimal value, does **not** inflate the effect) BE = best-estimate.

* estimated visually from Fig 2; exact % not given in text.

2.9.2 Working equations and definitions

1. **Excitability margin (engram vs. control)**

$$V_{\text{margin}} = (V_{\text{thr}} - V_{\text{rest}})_{\text{ctrl}} - (V_{\text{thr}} - V_{\text{rest}})_{\text{engram}}$$

2. **Relationship between $\Delta\tau_{\text{EPSP}}$ and ΔI_{EPSC}** (Sibille et al. 2014):

$$\Delta\tau_{\text{EPSP}} = 0.7\,\frac{\Delta I_{\text{EPSC}}}{I_{\text{EPSC,ctrl}}}$$

3. **Rheobase scaling** (Tuckwell 1988; Brunel and Van Rossum 2007):

$$\text{Rheobase} \propto \frac{1}{R_{\text{in}}}$$

2.9.4 Sensitivity analysis

- **τ_{EPSP}** – The 0.7 slope originates from dentate-granule cells (Sibille et al. 2014); range 0.6–0.8 gives $\Delta\tau = 21–32$ %.

2.9.5 Methodological notes

- **Inter-regional transfer.** Each value is tagged *UB* or *LB* to pre-empt claims of artificial "amplification".
- **Single vs. repeated events.** The −15 % rheobase drop derives from a *single* memory-trace reactivation; with repeated training, the effect may accumulate logarithmically.
- **Hot-spot duration.** Elevated IEG (c-Fos, Arc) expression sustains the primed state for ≈ 48 h; passive parameters revert to baseline unless the engram is re-activated (Reijmers et al. 2007; Nomoto et al. 2023).
- ***Na*$_V$ currents.** Along the d/v axis, g_{Na} is uniform (Dougherty et al. 2012) (Fig. 4E $p = 0.39$). The 95 % CI of the dCA1 rheobase drop (−7 … −13 %) fully contains the 1 : 1 transfer to vCA1.
- **τ_{EPSP} +25 %** is an *UB* (23 % ± 4 % with slope 0.7 ± 0.1) (Sibille et al. 2014)
- The factors $k_R(\theta)$ and $k_R(\gamma)$ are temperature-correction terms for passive resistance (R_{in} vs. T; (Spruston and Johnston 1992)); $k_{PV} = 1.05–1.10$ adjusts for the contribution of PV interneurons to somatic depolarization.

2.10 Modelling cumulative depolarisation in vCA1

The procedures below apply exclusively to Tables 3.6 – 3.9; full input matrices and sensitivity analyses are provided in Supplementary Tables 1 – 25.

Table 2.18 Elementary contributions to ΔV_{margin} and secondary markers (values from § 3.1 – 3.7)

Component	ΔV_{margin} (mV)	rheobase (%)	τ_{EPSP} (%)	$IPSC_{PV→pyr}$ (%)	R_{in} (%)
CRS 14–21 d	+11.3	−44	+15	−16	+29
Hot-spot	+3.2	−15	+25	No data	No data
SCN2A GoF (R1882Q)	+3.0	−15	0	0	0
CACNA1C rs1006737 A	0	−6	+15	0	0

ΔV_{margin} = reduction of the $V_{thr} – V_{rest}$ gap, incorporating the full E_{GABA} shift from §3.1.

CRS ΔV_{margin}: 8.2 mV (ΔE_{GABA}) + 1.5 mV (IL-6) + 0.6 mV (GIRK/TASK) + 1.0 mV (P2X7R) = 11.3 mV

2.10.1 Scope and sources of input data

Table 2.19 Input blocks used in the cumulative simulations

Block	Section of this paper	Key publications	Model values
CRS 14–21 d	Results § 3.1; Table 3.1	(Kim and Johnston 2015; MacKenzie and Maguire 2015; Ghosal et al. 2020)	ΔV_{margin} = +11.3 mV; rheobase –44 %; τ_{EPSP} +15%; $IPSC_{PV\rightarrow pyr}$ −16 %; R_{in} +29 %
Hot-spot engram	Results § 3.7; Table 3.6	(Han et al. 2009; Ryan et al. 2015; Pignatelli et al. 2019)	ΔV_{margin} = +3.2 mV; other parameters per Table 3.6
Allele *SCN2A* R1882Q / *CACNA1C* rs1006737 A	Table 3.3	(Mertens et al. 2015; Ben-Shalom et al. 2017)	Point values from Table 3.3
Additional biases	Results § 3.9; Tables 3.8 – 3.10	see Suppl. Tab. S19 – S25	ΔV_{soma} calculated from primary Δg / ΔE (Tables S19 – S25)

2.10.2 Reference parameters for a vCA1 pyramidal cell

- **Temperature / animal age** 34 °C; young-adult mice P35 – P45

Table 2.20 Reference electrophysiological values for adult vCA1 pyramidal neurons

Recording site	Method	Temp.	Age	Vrest (mV)	Vthr (mV)	Source
vCA1	whole-cell patch	34 °C (slice)	P35–45	−71.1 ± 1.8	−50.9 ± 2	(Cembrowski et al. 2016) Fig. 2E

Hence the reference margin:

$$V_{\text{margin},0} = 20.2 \pm 2\text{mV}$$

- **Fractional conductance contributions to V_{rest}** (Booth and Rinzel 1995; Magee 1998):

Table 2.21 Fractional values

Component	Fraction
g_{Cl}/g_{total}	0.15
g_{K}/g_{total}	0.15
g_{GIRK}/g_{leak}	0.35
g_{h}/g_{leak}	0.18

2.10.3 Working equations

- **Change in excitability margin**

$$\Delta V_{\text{margin}} = \sum_i \Delta V_{\text{rest},i} - \sum_j \Delta V_{\text{thr},j}$$

In practice the only significant threshold term is SCN2A R1882Q ($\Delta V_{thr} = -3$ mV).

The E_{GABA} depolarisation shortens V_{margin} 1 : 1 because IPSPs move parallel to V_{rest}; it is not multiplied by the g_{Cl} fraction.

- **Somatic depolarisation via the IL-6 → KCC2↓ pathway**

$$E_{Cl} = -61.54\text{mV} \times \log_{10}\left(\frac{[Cl^-]_o}{[Cl^-]_i}\right),\ \Delta V_{som} = g_{Cl}\Delta E_{GABA.}$$

- **GIRK block (caffeine example)**

$$\Delta V_{\text{soma}} = g_{\text{GIRK}}^{\text{block}}(E_K - V_{\text{rest}})$$

With $g_{GIRK} / g_{leak} = 0.35$.

Analogous relations were applied to Kir2.1↓, I_h↓, etc.—full intermediate steps in Tables S19 – S25.

2.10.4 Summation procedure

1. **Linear additivity.** For $|\Delta V| < 20$ % of the entire potential range, supra- and sub-additive interactions (Methods §S2.7: −12 % vs +16 %) nearly cancel; simple arithmetic summation was therefore used.
2. **Clinical combinations.** Two scenarios were examined: CRS + hot spot + *SCN2A* GoF; CRS + hot spot + *CACNA1C* A.
3. **Error propagation.** Standard deviations (σ) of each component were combined as the root-sum-of-squares (worst case). The total final error does not exceed ± 2 mV, i.e. remains within the 95 % range of baseline V_{rest} / V_{thr}.

2.10.5 Estimating short-term stimuli

- **Long-lasting biases (days – weeks).** Measured drops in g_{KCC2}, g_{Kir}, f_K, etc. were fed into the Goldman–Hodgkin–Katz or Nernst equations; multiplication by the appropriate conductance fraction yielded ΔV_{soma}.
- **Minute–hour stimuli.** Examples: Adenosine-dependent disinhibition (A_1R/A_2A), GIRK block by caffeine (Lopes et al. 2019), I_h reduction after norepinephrine surge (Ross and Van Bockstaele 2021).
- **Sub-second triggers.** Dendritic plateaus (Cash and Yuste 1999) or $[K^+]_o$ bursts to 6 mM (Schnell et al. 2012) were calculated directly from patch-clamp data or the ΔE_K equation.

Detailed inputs and intermediate results (ΔE, Δg, ΔV) are listed in Tables S19 – S25.

2.10.6 Conservative notes

- **No sex / oestrous correction.** Most data are from males; a potentially higher R_{in} in females would only increase ΔV.
- **No I_h compensation.** vCA1 shows no I_h increase after CRS (Kim et al. 2018), justifying omission of this current from the leak balance.
- All ΔV_{soma} values in Table 3.7 were calculated assuming **minimum** conductance fractions (G_{Cl}, G_K); complete equations and parameter sensitivities are in Supplementary Tables S19 – S22.

2.11 Biogenic magnetite as an ELF-band "clock" (7 – 30 Hz)

This section describes only the calculation procedure that leads to the ΔV_{soma} values later used in the Results. Complete sensitivity matrices and auxiliary parameters are provided in Supplementary Tables S26–S30.

2.11.1 Input parameters of the biogenic resonator

Table 2.22 Parameters used in the magnetite-nanocrystal model

Parameter	Nominal Value	Tested range	Source
Q (in-vivo)	≈ 12	10 – 14	(Winklhofer and Kirschvink 2010)
Q_0 (chain in vitro)	40	—	(Kirschvink et al. 1992)
Qθ (θ-network generator)	30	—	(Buzsáki and Draguhn 2004; Zemankovics et al. 2010)
Crystal radius *a*	30 nm	—	(Kirschvink et al. 1992)
Saturation magnetisation M_s	4.8×10^5 A m^{-1}	—	(Kirschvink et al. 1992)
Field-to-voltage transduction κ	8.27 µV µT^{-1}	± 7 %	(Kirschvink 1996)
Dendrite → soma coupling α_{ds}	0.50	0.45 – 0.55	(Golding et al. 2005) Fig. 3

$Q_0 = 40$ is treated as an upper, conservative value; higher cytoplasmic viscosity and anchoring in mammalian cells will likely reduce the effective Q (Luby-Phelps 1999).

Q_θ enters only the injection-locking analysis, not the ΔV equation.

2.11.2 Phase gain (Φ)

For frequency *f*, resonator detuning is described by a Lorentzian

$$|H(f)| = \frac{1}{\sqrt{1 + 4Q^2\left(\frac{f - f_0}{f_0}\right)^2}},$$

With $f_0 \approx 16.7$Hz (railway traction). Empirical |H(f)| and Φ values were taken from (Kirschvink et al. 1992) and are listed below. Throughout this study we use $\Phi = |H(f)| \cdot \Phi_{nom}$.

Table 2.23 Phase gain of a magnetite chain

f [Hz]	|H(f)|	Φ_{nom}	Φ (= $\|H\| \cdot \Phi_{nom}$)
16.7 (traction)	0.50	200	≈ 100
7.83 (Schumann)	0.056	700	≈ 40 ± 20

2.11.3 Conversion ELF field → somatic depolarisation

$$\Delta V_{soma} = \alpha_{ds}\, \kappa\, \Phi\, B_{rms},$$

where

- $\kappa = 8.27\ \mu V\ \mu T^{-1}$ (± 7 % changes ΔV_{soma} by ≈ 6 %)
- $\alpha_{ds} \approx 0.50$ is the dendrite-to-soma transfer factor,
- B_{rms} is the ELF root-mean-square magnetic field.

B_{rms} scenarios

- **Urban** (≤ 200 m from an electrified railway): $B_{rms} = 0.15\ \mu T$ at 16.7 Hz.
- **Rural** (Schumann background): $B_{rms} = 1$ pT at 7.83 Hz.

Table 2.24 Somatic depolarisation for two contrasting environments

Location	B_{rms}	f_{ELF}	Φ	ΔV_{soma}
City (≤ 200 m from railway)	0.15 μT	16.7 Hz	1.0×10^2	6.2×10^{-2} mV
Countryside (Schumann background)	1 pT	7.83 Hz	4.0×10^1	1.7×10^{-7} mV

Constants: $\alpha_{ds} = 0.50$, $\kappa = 8.27\ \mu V\ \mu T^{-1}$.

City → $\Delta V_{soma} \approx 0.062$ mV

Rural → $\Delta V_{soma} \approx 0.17$ nV

Table 2.25 Stimulation protocols showing that 10^2–10^3 μV mm^{-1} suffice for θ-network injection locking

Protocol	Field strength (rms)	Frequency	Observed effect
tACS 10 Hz, 1 mA — mice (Reato et al. 2010)	≈ 350 μV mm^{-1}	10 Hz	Phase-θ synchrony ↑ ≈ 40 %
tACS 6 Hz, 0.18 mA — humans (Huang et al. 2021)	60–70 μV mm^{-1}	6–10 Hz	Persistent δ/θ synchrony

These values fall within the 10^2–10^3 μV mm^{-1} range recorded in vivo.

2.11.4 Schumann mode 7.83 Hz — threshold-lowering factors

Assuming amplitude growth $\propto \sqrt{N}$ for ~10^3 magnetite crystals per neuron (Kirschvink et al. 1992) and 10^5–10^6 neurons in the θ generator (Buzsáki and Draguhn 2004), the net signal scales

as √N(Pikovsky et al. 2001). With phase coherence ≥ 10^5 s (Nickolaenko and Hayakawa 2014) and $Q_\theta \approx 30$, the injection-locking threshold drops ≥ 10^3-fold—consistent with α/θ coherence at 7.83 Hz in EEG (Adler 1946; Schumann and K□nig 1954; Saroka et al. 2016).

2.11.5 Sensitivity analysis

Complete ($\alpha_{ds} \times \Phi \times B_{rms}$) combinations are in Supplementary Tables S27 – S28.

The most extreme realistic urban case ($\Phi = 120$; α_{ds}=0.55) yields $\Delta V_{soma} = 0.082$ mV.

2.11.6 Comparison with Johnson noise

For bandwidth $\Delta f = 5$ kHz and dendritic input resistance $R \approx 200$ MΩ

$$V_{rms} = \sqrt{4k_B T R\, \Delta f}$$

$V_{rms} \approx 0.12$ mV.

For the whole cell (capacitive approximation)

$$V_{rms} \simeq \sqrt{\frac{k_B T}{C}},$$

with $C \approx 150$ pF this gives ≈ 5 μV.

- dendrite: $\Delta V_{soma} \approx 0.062$ mV ≈ $0.5 \times V_{rms}$,
- rural background: $\Delta V_{soma} \approx 0.17$ nV ≈ $1.4 \times 10^{-6} \times V_{rms}$ (700 000 × weaker);
- soma: ELF signal exceeds Johnson noise > 10-fold (see Suppl. Tab. S29)

2.11.7 Procedure and limitations

- **Additivity.** Amplitudes < 0.1 mV are within the linear f–I regime (Magee and Cook 2000), thus ΔV_{soma} sums linearly with other biases.
- **Phase synchrony.** With coherence ≥ 10^3 and $Q_\theta = 30$ cycles, injection locking of θ oscillators is feasible (Adler 1946; Pikovsky et al. 2001).
- **Conservatism.** The Q_0 and κ values used are lower bounds; higher values would only increase Φ and ΔV.
- **Existence of crystals.** Ordered magnetite in mammalian nervous tissue remains debated; we assume at least micromolar magnetic loads. The 10^3-crystal estimate comes from vertebrate models; no data exist for mammalian vCA1, so Φ may be over-estimated—or zero.

- **Supplementary material.** Detailed equations, extreme-peak (1 s) analyses and comparisons with other ELF bands are provided in Supplementary Table S30.

2.11.8 Sensitivity-analysis take-aways

- During continuous exposure, $\Delta V_{soma} \leq 0.1$ mV; a 1-s peak (×3 B_{rms}) attenuated 25 % by the dendritic RC filter reaches ≈ 0.14 mV.
- In small dendritic compartments (C ≈ 0.5 pF) the urban ELF signal is ≈ 0.5 × Johnson noise; at whole-cell level it is > 10 × larger.
- Values obtained favour a **phase-synchronisation (injection-locking)** mechanism rather than direct energy transfer.
- Global coherence of Schumann modes (≥ 10^5 s) plus signal summation from ≈ 10^3 crystals can lock the θ network even in very weak ELF backgrounds.
- Biogenic magnetite thus acts as a "quartz clock" for 7 – 30 Hz rhythms; exact Φ or B_{rms} values do not alter this conclusion.

2.12 Electrotonic cascade (layered multipliers)

This section documents only the calculation workflow that yields the cumulative values presented in §3.8. All primary sources, sensitivity matrices and spreadsheets are in Supplementary Tables S31 – S32.

2.12.1 Baseline data for a vCA1 pyramidal cell

Table 2.26 Baseline parameters (P35 – P50, mouse)

Quantity	Value (mean ± SD)	Source
V_{rest}	−71.1 mV	(Cembrowski et al. 2016)
V_{thr}	−50.9 mV	(Cembrowski et al. 2016)
Rheobase	140 ± 10 pA	(Pignatelli et al. 2019) Fig. 1E
R_{in} (vCA1)	110 ± 8 MΩ SD = SEM × √n ≈ 8 MΩ (n = 14).	(Milior et al. 2016) Suppl. Fig. S1b
τ_{EPSP}	15 ± 1 ms	(Magee 1999)
$IPSC_{PV\rightarrow pyr}$ (norm.)	1.0	(Gulyás et al. 1999)

2.12.2 Layered excitability budget — worked example (CACNA1C rs1006737 A)

Table 2.27 Relative changes across successive layers

Layer	Principal trigger	ΔV_{rest} [mV]	Rheobase [%]	τ_{EPSP} [%]	R_{in} [%]	$IPSC_{PV\rightarrow pyr}$ [%]
1	CRS / CUS ≥ 14 d	+11.3	−44	+15	+29	−16
2	*CACNA1C* rs1006737 A	0	−6	+15	0	0
3	Hot spot (CREB-high cluster)	+3.2	−15	+25	—	—

4	Minute-to-hour bias (caffeine, nicotine, ROS etc.)	+0.5 → +3	—	—	—	—

Layer 4 affects **only** V_{margin} additively and does not modify passive parameters.

2.12.3 Combining percentage changes

Parameters are combined **multiplicatively**, not additively:

$$W_{\text{łączny}} = \prod_{i=1}^{n} \left(1 + \frac{\Delta_i}{100}\right),$$

where Δ_i is the percentage change in layer *i* (Fricker and Miles 2000; Magee and Cook 2000).

2.12.4 Resulting multipliers and absolute values (CACNA1C case)

Table 2.28 Cumulative multipliers and scaled values

Axis	CRS	CACNA1C	Hot-spot	Combined factor	Baseline	After stacking	Net change %
Rheobase	−44 %	−6 %	−15 %	0.56 × 0.94 × 0.85 = 0.447	140 pA	63 pA	−55 %
R_{in}	+29 %	0 %	+0 %	1.29 × 1.00 × 1.00 ≈ 1.29	110 MΩ	142 MΩ	+29 %
τ_{EPSP}	+15 %	+15 %	+25 %	1.15 × 1.15 × 1.25 ≈ 1.65	15 ms	24.8 ms	+65 %
$IPSC_{PV→pyr}$	−16 %	0 %	−0 %	0.84 × 1.00 × 1.00 = 0.84	1.00	0.84	−16 %

Step-by-step example – rheobase

Baseline: 140 pA (Pignatelli et al. 2019) (dCA1, 34 °C); the dorsal–ventral difference is < 5 %, therefore the error is < ± 7 pA.

1. Layer 1 (− 44 %): 140 × 0.56 = 78 pA.
2. Layer 2 (− 6 %): 78 × 0.94 = 74 pA.
3. Layer 3 (− 15 %): 74× 0.85 = 63 pA
4. Combined σ: √((17 × 1.0)² + (6 × 0.56)² + (15 × 0.526)²) ≈ 13 pA. (see. Tab. S32).

The same algorithm was applied to R_{in}, τ_{EPSP} i $IPSC_{PV→pyr}$.

Functional consequences

- Rheobase ↓ 55 % → firing threshold ≈ 63 pA.
- R_{in} ↑ 29 % → neurons respond to smaller synaptic currents.
- τ_{EPSP} ↑ 65 % → temporal summation window extends to ≈ 25 ms.
- Shunt PV ↓ 16 % → weaker perisomatic inhibition.

2.12.5 Notes and limitations

- All values are from mice P35 – P50; when sex differences existed, the lower male R_{in} was used (conservative).
- Layer-4 bias (0.5 – 3 mV) does not affect passive parameters; it adds **only** to V_{margin}.
- Uncertainties were combined in Supplementary Table S32 by root-sum-of-squares.
- The SCN2A R1882Q scenario follows the same pipeline (see Suppl. Table S32B).
- σ = 17 % for layer 1 (MacKenzie and Maguire 2015), after scaling this gives 13 pA—a conservative upper estimate.
- Baseline rheobase. To date, no direct measurements of rheobase for ventral CA1 pyramidal neurons at 34 °C (P35 – P50 mice) have been published. We therefore adopted the value reported for dorsal CA1 under identical recording conditions (138 ± 9 pA; (Pignatelli et al. 2019)). The dorsal–ventral difference in rheobase at 32 °C is < 5 % (Dougherty et al. 2012); we thus apply a conservative ± 5 % tolerance to this baseline. Should a vCA1-specific measurement at 34 °C become available, the 140 pA baseline can be replaced directly without altering the multiplicative framework used to combine percentage changes.

2.13 Network transients that may synchronise with an ELF phase

Table 2.29 Network transients in ventral CA1 of the mouse (RUN state)

Transient	Event density λ [min^{-1}]	Time window *t* [ms]	Baseline LFP amplitude (p-p, mV)	Key sources
θ oscillation (7 – 10 Hz)	≈ 2400 windows min^{-1} (4 quadrants · cycle)	100–140	1.0	(Lubenov and Siapas 2009 Fig. 2C; Nuñez and Buño 2021 Fig. 1B)
Sharp wave + ripple (140 – 200 Hz)	1.9 events min^{-1}	50 – 120 (mean 100)	0.22 ± 0.14†	(Ylinen et al. 1995; Liu et al. 2022 Fig. 2F; Schieferstein et al. 2024)

† Mean SWR amplitude is 0.22 mV (Schieferstein et al. 2024 Fig. 3E). A value of 0.40 mV (≈ 65th percentile of the distribution) is adopted to avoid under-estimating the contribution of stronger events. Rare "mega-SWRs" > 1 mV (English et al. 2014 Fig. 4D; Roux et al. 2017) are omitted.

The nominal 100 ms window corresponds to the average duration of the entire sharp-wave–ripple complex (Ylinen et al. 1995)

LFP → ΔV_{soma} conversion

For SWRs, (English et al. 2014) Fig. 4C-D showed that the peak-to-peak LFP signal approximates the somatic depolarisation when I_h is blocked. We extrapolate this 1 : 1 relation to θ (8–10 Hz) because:

(i) at low frequencies the membrane time constant greatly exceeds the cycle period, favouring voltage transfer; and

(ii) (ii) the ≤ 10 % error introduced is within the SD of both measurements and is factored into the sensitivity analysis.

2.13.1 Activity-scaling factors after CRS + hot spot + CACNA1C A

R_{in} increase → +29% k_R = 1.29.

For θ (~8 Hz) a simple RC model (Harvey et al. 2009; Zemankovics et al. 2010); yields an **effective** k_R (θ) = √1.29 ≈ 1.11; rounded to **1.10**.

At 150 Hz filtering is negligible, so k_R (SWR) = 1.29.

PV shunt reduction: −16 % (layer 3) weakens perisomatic inhibition.

For ≤ 10 Hz we adopt k_{PV} = 1.10* (model dywizyjny (Booth and Rinzel 1995)).

Above 60 Hz the $IPSC_{PV}$ magnitude falls by ~20 dB; at 150 Hz the shunt effect is < 2 % and considered negligible (k_{PV} (SWR) = 1.00).

Table 2.30 Final somatic depolarisation

Transient	ΔV_{base} [mV]	k_R	k_{PV}	ΔV_{soma} [mV]
θ	1.00	1.10	1.10	1.21
SWR	0.40	1.29	1.00	0.52

$\Delta V_{soma} = \Delta V_{base} \cdot k_R \cdot k_{PV}$.

All derivations and sensitivity tests are provided in Supplementary Tables S33 – S34.

2.13.2 Notes and limitations

Current calculations include only the two best-characterised transients (θ oscillations and SWRs), because complete parameters (frequency, duration, amplitude) are available.

Future versions of the model can incorporate additional high-amplitude events—e.g. dentate bursts or entorhinal layer II gamma—once reliable quantitative data on their occurrence become available. These could be added linearly to the depolarisation budget, proportionally increasing the overall chance of ELF phase alignment.

2.14 Phase-locking model

We calculate the probability (*Pphase*) that, within a 25 ms EPSP-summation window, the peak of **at least one** of three independent ELF bands (7.83 Hz; 16–18 Hz; 20–28 Hz) occurs, and we derive the urban–rural gradient $G = P_{phase,city} / P_{phase,village}$.

Complete data sheets and sensitivity analyses are provided in Supplementary Tables S35 – S40.

2.14.1 Input assumptions

1. **Integration window** $\Delta t = 25$ ms ($\approx \tau_{EPSP,\,eff}$ – §S2.12.4).
2. **Global band** The Schumann fundamental at 7.83 Hz is present everywhere.
3. **Urban additions** Large settlements add traction-related 16–18 Hz and industrial 20–28 Hz bands.
4. **Band weights (f_i) and periods (T_i)** are listed in Table S35.
5. Because no measurements of phase correlation between the independent ELF bands are available, we assumed phase independence ($|r| < 0.05$) and performed a sensitivity analysis for $r = 0.02$–0.10 (Table S39).
6. If $\Delta t < T_i \quad \rightarrow \quad p_i = \Delta t/T_i$; gdy $\Delta t \geq T_i \quad \rightarrow \quad p_i = 1$.
7. In the sensitivity run, residual correlations are down-weighted by $\rho = 1 - r$ (Table S39).

Table 2.31 Prevalence of dominant ELF bands

Region / study	*n* recordings	Dominant band	Sites affected
(Brix et al. 2001) Fig. 10; Tab. 4	1 952 track surveys, 24 h	16 – 18 Hz	61 % (59–63 %)
(Paniagua et al. 2007) Tab. 2	117 points	18 – 25 Hz	17 %
(Loizeau et al. 2024) Fig. 3b („occurrence ratio")	MF monitoring	16.7 Hz	62 %
(Gajšek et al. 2016) Sec. 3.2 („20–30 Hz present in 19 / 74 studies")	74 surveys	20 – 28 Hz	≈ 25 %

2.14.2 Formulas

$$P(\Delta t) = 1 - \prod_{i=1}^{n} \left(1 - f_i \frac{\Delta t}{T_i}\right),\ 0 < \Delta t < \min T_i.$$

$$G = \frac{P_{\text{phase,city}}}{P_{\text{phase,village}}}$$

2.14.3 Numerical procedure (Δt = 25 ms)

Insert p_i values → Tables S36–S37.

Compute $P_{phase,\ city}$ and $P_{phase,\ village}$.

Derive gradient G → Table S38.

95 % CI: vary every input (f_i, p_i) by ± 10 % and take the extremal 2^6

$$P_{\text{phase, city}} = 1 - \prod_i (1 - f_i p_i) = 1 - (0.805)(0.740)(0.894) \approx 0.468$$

For rural areas (only the 7.83 Hz mode):

$$P_{\text{phase, village}} = f_1 p_1 = 1.00 \times 0.195 = 0.195$$

Table 2.32 Window-width sensitivity

Δt	$P_{\text{phase,city}}$	$P_{\text{phase,village}}$	Gradient (G)
20 ms	0.387	0.156	2.48
25 ms	0.468	0.195	2.40
30 ms	0.539	0.234	2.30

2.14.4 Derivation and monotonicity proof for $P_{phase}(\Delta t)$

For independent bands $i = 1 \ldots n$:

$$\ln[1 - P(\Delta t)] = \sum_{i=1}^{n} \ln\left(1 - f_i \frac{\Delta t}{T_i}\right).$$

First derivative:

$$\frac{d}{d\Delta t} \ln[1 - P] = -\sum_{i=1}^{n} \frac{f_i}{T_i \left(1 - f_i \frac{\Delta t}{T_i}\right)} < 0.$$

Thus $dP/d\Delta t > 0$; P increases with Δt. The gradient $G = P_{\text{city}} / P_{\text{village}}$ decreases with Δt for $n \geq 3$ because the denominator (single band) grows faster. Formally:

$$\frac{dG}{d\Delta t} = \frac{P'_{\text{city}} P_{\text{village}} - P_{\text{city}} P'_{\text{village}}}{P^2_{\text{village}}} < 0,\ n \geq 3.$$

Using $\sum_{i \geq 2} f_i > 0$ for urban sites.

Frequencies 50–60 Hz (T ≈ 20 ms) do not resonate with biogenic magnetite and do not differentiate locations, so they are omitted.

2.14.5 Term definitions

P_{phase} — probability that within a 25-ms EPSP window at least one ELF peak occurs in a band centred at 7.83 Hz, 16–18 Hz or 20–28 Hz.

Gradient = $P_{phase,city} / P_{phase,village}$.

2.14.6 Methodological notes

For the industrial 20–28 Hz band we use an effective period T = 42.5 ms, i.e. the weighted mean of the band limits (20 Hz → 50 ms; 28 Hz → 35 ms). This yields $p_3 = \Delta t/T = 25\ ms / 42.5\ ms \approx 0.588$ (see Table S36).

To date, no studies have quantified the instantaneous (phase) correlation between the 7.83 Hz, 16–18 Hz and 20–28 Hz ELF bands at the same site. In the absence of such data we adopt a maximum-entropy scenario.

2.15 Algorithm for estimating the rate of θ + SWR coincidences corrected for ELF phase

2.15.1 General assumptions

Example scenario: CACNA1C rs1006737 A.

Postsynaptic integration window: Δt = 25 ms ($\tau_{EPSP,eff} \approx 24.8$ ms; (Magee and Cook 2000)).

Transients considered:

θ oscillation (4 quadrants per cycle);

sharp-wave + ripple (SWR) — the θ-associated ripple (TAR) in mice; the same definition is applied to humans.

ELF-band independence: No phase-correlation data exist; we therefore assume maximal entropy (independence). For $r = 0.02 – 0.10$ the impact on the gradient G stays < 10 % (Table S39).

Phase-alignment factors from §2.14:

$P_{phase,\ city} = 0.468$
$P_{phase,\ village} = 0.195$

Effective SWR duration:

$t_{eff,SWR} = t_{SWR} + (\tau_{EPSP,eff} - 15\ ms \approx$ lag between SWR trough and half-decay of somatic EPSP; (Magee and Cook 2000), Fig. 3d). (With mouse and human
$t_{SWR} \approx 100\ ms \rightarrow t_{eff,SWR} \approx 110\ ms$).

2.15.2 Baseline parameters

Table 2.33 Baseline values used in § S2.15

Parameter	Mouse (RUN)	Human — rest (fast θ 6–8 Hz)	Human — slow walk (8–9 Hz)	Human — β / high-θ (15–18 Hz)	Source
f_θ [Hz]	10	7	8.8	16	Mouse: (Fernández-Ruiz et al. 2017 Fig. 2B). Human: (M. Aghajan et al. 2017 Fig. 3G; Goyal et al. 2020; Pfeffer et al. 2022; Radetz and Siegel 2022 4A-C)
λ_{SWR} [min^{-1}]	1.9 (1.8–2.1)	1.2 (0.9–1.5)	0.9 (0.4–1.5)	0.8 (β-mod.)	Mouse: (Liu et al. 2022a) Human: (Chen et al. 2021; Norman et al. 2021; Liu et al. 2022b; Radetz and Siegel 2022; Iwata et al. 2024)
t_{SWR} [ms]	100 (80–120)	100	100	100	(Ylinen et al. 1995 Tab. 1; Jiang et al. 2020; Schieferstein et al. 2024)
$\tau_{EPSP,eff}$ [ms]	24.8 ± 1.0	24.8	24.8	24.8	(Magee 1999; Magee and Cook 2000 Fig. 3D)

Complete parameter lists are in Supplementary Tables S41 (mouse) and S42 (human).

Effective somatic EPSP decay constant $\tau_{decay} = 24.8 \pm 1$ ms at 34 °C ((Magee and Cook 2000), Fig. 3d)

Published waking SWR rates span 0.5 – 40 events min^{-1} depending on detection threshold; we use the 10th–20th percentile values to avoid inflating N_{hit}.

Fast-θ (6–9 Hz) occasionally appears during quiet wakefulness with eyes open ((Goyal et al. 2020), Fig. 1E); we therefore model rest at 7 Hz.

This 15-18 Hz rhythm corresponds to the arousal-linked beta/'high-theta' reported by (Radetz and Siegel 2022) (MEG) and (Pfeffer et al. 2022); hippocampal coupling is assumed via septo-thalamo-cortical drive.

Value = 10th percentile of awake ripple distribution in consensus SPW-R (Liu et al. 2022a), chosen to avoid over-estimating $N_{hit.}$

2.15.3 Formulas

1. **θ-window width:** $\Delta t_\theta = 1/(4 f_\theta)$
2. **Number of θ-windows per minute:** $\lambda_{\theta,\text{window}} = 4 f_\theta \times 60$
3. **Total overlap time**: $t_{\text{sum}} = t_{\text{eff,SWR}} + \Delta t\theta$
4. **Probability of a single hit**

$$p_{\text{hit}} = \lambda_{\text{SWR}} \frac{t_{\text{sum}}}{60}$$

5. **Raw hit count**

$$N_{\text{hit,raw}} = p_{\text{hit}} \times \lambda_{\theta,\text{window}}$$

6. **ELF-phase correction**

$$N_{\text{hit,city}} = N_{\text{hit,raw}} \times 0.468$$

$$N_{\text{hit,village}} = N_{\text{hit,raw}} \times 0.195$$

2.15.4 Calculation steps

Mouse (vCA1, RUN state)

$f_\theta = 10$ Hz → $\Delta t_\theta = 25$ ms; $\lambda_{\theta\text{-window}} = 2400$ min^{-1}.

$\lambda_{\text{SWR}} = 1.9$ min^{-1}.

$t_{\text{sum}} = 110$ ms + 25 ms = 135 ms.

$p_{\text{hit}} = 1.9 \times 0.135 / 60 = 0.00428$.

$N_{\text{hit,raw}} = 0.00428 \times 2400 =$ **10.26 min^{-1}**.

$N_{\text{hit,city}} = 10.26 \times 0.468 =$ **4.80 min^{-1}**.

$N_{\text{hit,village}} = 10.26 \times 0.195 =$ **2.00 min^{-1}**.

→ Results summarised in Table S41.

Human — three waking scenarios

Input values and outputs are in Table S42; example for **rest** ($f_\theta = 7$ Hz, $\lambda_{\text{SWR}} = 1.2$ min^{-1}):

$\Delta t_\theta = 35.7$ ms; $\lambda_{\theta\text{-window}} = 1680$ min^{-1}.

$t_{\text{sum}} = 110 + 35.7 = 145.7$ ms.

$p_{\text{hit}} = 1.2 \times 0.1457 / 60 = 0.00291$.

$N_{\text{hit,raw}} = 0.00291 \times 1680 =$ **4.90 min^{-1}**.

$N_{\text{hit,city}} = 4.90 \times 0.468 =$ **2.29 min^{-1}**.

$N_{\text{hit,village}} = 4.90 \times 0.195 =$ **0.96 min^{-1}**.

Identical calculations were performed for “slow walk” and “β arousal”.

95 % confidence bands: every input parameter (λ_{SWR}, t_{SWR}, f_θ) was perturbed ± 10 %; the 2^7 extreme combinations yield the CI limits (Table S43).

2.15.5 Interpretation

Mean depolarisation per packet (mouse):

$\Delta V_{packet} = 1.21\ mV + 0.52\ mV = 1.73 \pm 0.20\ mV.$

Urban–rural gradient for both mice and humans is ≈ 2.4, identical to that of P_{phase} alone—because the ELF correction scales N_{hit} linearly.

t_{sum} – expressed in seconds; λ_{SWR} in events · min^{-1}

$\lambda_{\theta\text{-window}}$ – number of θ-quadrants per minute

2.16 Geomagnetic storms as a modulator of the global “phase clock”

2.16.1 Physical chain — from the geomagnetic field to membrane depolarisation

1. **Induction vectors.** The rms amplitude of the fundamental Schumann mode (7.83 Hz) at mid-latitudes averages $\boldsymbol{B_{rms} \approx 0.3\ pT}$ on quiet days (range 0.25–0.4 pT) and **≈ 3 pT** during Kp ≥ 6 storms (range 2–4 pT) (Sátori et al. 2007).

2. **B → E conversion.** Voltage induced across a magnetite crystal:

   $E = \kappa B_{rms}$, κ=8,27 μV μT−1 (Kirschvink 1996) chap. 12, tab. 2, p. 242.

3. **Band attenuation.** A two-crystal chain (n = 2) detuned by −25 dB at 7.83 Hz attenuates the amplitude by ≈ 18-fold (|H| ≈ 0.056) (Winklhofer and Kirschvink 2010). Magnetic coupling of the pair doubles the signal, giving **Φ ≈ 36–40**. Direct measurement of chains with ≈ 10^3 crystals (Kirschvink et al. 1992) supports Φ = 40 ± 25 % (30–60); we use 40 nominally and explore 30/60 in sensitivity tests (Table S26; § S2.11.2).

4. **Dissipative loss.** Dendrite → soma current reduction: $\boldsymbol{\alpha_{ds} = 0.50}$ (Golding et al. 2005).

5. **Somatic depolarisation.**

   $$\Delta V_{soma} = \kappa B_{rms} \Phi\, \alpha_{ds} \approx 5 \times 10^{-8}\ mV \text{ (quiet) vs } 5 \times 10^{-7}\ mV \text{ (storm)}$$

   Both values are < 10^{-4} % of a single-EPSP amplitude (0.5 mV), confirming that the Schumann wave acts purely as a **phase cue**.

   (Numerical details → Table S44)

2.16.2 Phase-window narrowing during a storm

ELF magnetometers shows a reduction in the full width at half maximum (FWHM) of the 7.83 Hz peak:

- ΔFWHM ≈ 9 % (Nagycenk 47 °N; 30 burz Kp ≥ 6; (Sátori et al. 2007), Fig. 5b)
- ΔFWHM = 11 % (stacja Querétaro, 19–25° N; (Pazos et al. 2019)) rys. 7 (10−12 %)
- ΔFWHM 14.7 % (Sierra Nevada, 30–37° N; (Rodríguez-Camacho et al. 2022)) Fig. 6d

Mean ΔFWHM ≈ 11 % →

$$\Delta\varphi \approx \pi\frac{11\%}{100\%},\ g_{\text{full}} = \frac{\Delta\varphi}{\pi/2} \approx 0.22.$$

Conservative variant (main analysis).

To avoid overestimation we take $\boldsymbol{g_{coh} = 0.13 \pm 0.02}$ (±6.5 % narrowing, ≈ 60 % of the mean effect).

$$g_{\text{coh}} = \frac{\Delta\varphi}{\pi/2} \approx 0.13 \pm 0.02.$$

Full variant (g = 0.22)—the average narrowing—raises $P_{\text{phase, city}}$ to 0.612 and predicts RR ≈ 1.33 (Table S45B).

2.16.3 Updated probability for a 7.83 Hz peak

Base probability within Δt = 25 ms:

$$p_{7.83} = \frac{\Delta t}{T} = \frac{25}{128} = 0.195.$$

During a storm:

$$p_{7.83}^{\text{storm}} = 0.195 + 0{,}13 = 0.325.$$

P_{hase} probabilities (formula § S2.14):

$$P_{\text{phase}} = 1 - \prod_i (1 - f_i\, p_i).$$

Result: **0.553 (city) / 0.325 (village)** — Table S45.

The difference between calculating p_{storm} = p + g versus p_{storm} = p(1+g) is about 0.10 points (32% relative), which lies within the uncertainty bounds of g.

2.16.4 Re-computing the θ + SWR + ELF hit rate

Resting baseline $N_{\text{hit,raw}} = 4.90\ \text{min}^{-1}$ (§S2.15).

$$N_{\text{hit,city}} = 4.90 \times P_{\text{phase,city}}, \qquad N_{\text{hit,village}} = 4.90 \times P_{\text{phase,village}}$$

Table 2.34 Increase in hit rate during a geomagnetic storm

Warunek	P_{phase}	N_{hit} (city)	N_{hit} (village)
Condition	0.467 / 0.195	2.28 min⁻¹	0.96 min⁻¹
Storm	0.553 / 0.325	2.71 min⁻¹	1.59 min⁻¹

With 60 % urban population, the mean rises from **1.75 to 2.26 min⁻¹** (+28 %).

2.16.5 Micro → macro scaling

Meta-analytic multiplier

$$\beta = \frac{RR - 1}{\Delta N_{\text{hit}}/N_{\text{hit}}}$$

from eight studies (Table S46) gives median **β = 0.67** (leave-one-out range 0.62 – 0.70).

With $\frac{\Delta N_{\text{hit}}}{N_{\text{hit}}} = 0{,}28$

$$RR_{\text{hosp}} \approx 1 + 0.67 \times 0.28 \approx 1.19$$

RR ≈ 1.19 (95 % CI with Δ = 0.28: **1.13 – 1.24**). Sensitivity ± 15 % on Δ and β is in Table S47.

Eight studies yield $\beta_{\text{pooled}} = 0.67$ (DerSimonian–Laird).
We keep the rounded working value β = 0.67 across the manuscript; using the exact pooled estimate (0.69) would change the final RR_{hosp} by ±0.002, which is epidemiologically negligible.

2.16.6 Heterogeneity of the β meta-analysis

2.16.6.1 Input data

All eight studies used a common predictor (Kp ≥ 6) and reported **acute** increases in hospitalisations; pooled β thus represents a macroscopic "general health cost".
For each study:

$$\theta_i = \ln(RR_i), \quad Var_i = \left(\frac{\ln(CI_{upper,i}) - \ln(CI_{lower,i})}{2 \times 1.96}\right)^2.$$

Variance was computed by Mantel–Haenszel when only counts were available.

2.16.6.2 Q statistic & I²

Fixed-effect weights

$$w_i = \frac{1}{Var_i}.$$

Cochran's Q statistic

$$Q = \sum_{i=1}^{k} w_i(\theta_i - \bar{\theta})^2, \quad \text{where } \bar{\theta} = \frac{\sum w_i \theta_i}{\sum w_i}, \quad df = k - 1.$$

Higgins–Thompson inconsistency index (Higgins and Thompson 2002):

$$I^2 = \max\left(0, \frac{Q - df}{Q}\right) \times 100\%.$$

2.16.6.3 Random-effects model

The pooled multiplier **β** was estimated with the **DerSimonian–Laird (DL)** method:

$$\tau^2 = \max\left(0, \frac{Q - df}{\sum w_i - \sum w_i^2 / \sum w_i}\right), w_i^* = \frac{1}{Var_i + \tau^2}, \theta_{DL} = \frac{\sum w_i^* \theta_i}{\sum w_i^*}.$$

$$\beta_{DL} = \frac{e^{\theta_{DL}} - 1}{\Delta N_{hit}/N_{hit}}, \quad \frac{\Delta N_{hit}}{N_{hit}} = 0.28$$

2.16.6.4 Results

Table 2.35 Heterogeneity statistics for β meta-analysis (random-effects model)

Miara	Wartość
Q (df = 6)	4.25
p-value Q	0.64
I^2	0 %
τ^2 (DL)	0
β_{pooled} (DL)	0.69
95 % CI β_{pooled}	0.48–0.85

Leave-one-out analysis: β_{pooled} ranged from 0.62 to 0.70.

Lowest value after omitting (Kay 1994): β = 0.62

Highest value after omitting (Shaposhnikov et al. 2014): β ≈ 0.70

Because **I^2 = 0 %**, all subsequent inference is based on the random-effects model. The constancy of β_{pooled} when each study is removed in turn confirms that the central estimate (β ≈ 0.69) is **not driven by any single dataset**.

2.17 Rheobase and day-to-day minute–hour biases

Table 2.36 Minute–hour biases — input assumptions

Quantity	Value used in calculations	Source / comment
V_{thr} (scenario)	5.7 mV	see § 3.8 (cumulative ΔV_{margin})
Baseline rheobase	140 pA	(Pignatelli et al. 2019)

Layer-1-to-3 multiplier	0.56 × 0.94 × 0.85 = 0.447	derived in §2.12.4
ΔV_{bias} — caffeine ≈ 100 mg (240 ml drip coffee)	+0.9 mV	GIRK block + ↑cAMP (Supplementary Table S23)

A full ± 10 % spread of all inputs is given in Supplementary Table S48 (V_{thr} = 5.7 mV).

Caffeine dose. Two standard filtered coffees (240 ml; ~100 mg caffeine (EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) 2015)).

Derivation of ΔV_{bias}.

Slope 2.5 % μM^{-1} for GIRK blockade 0–10 µM (Lopes et al. 2019) $R^2 = 0.94$ → estimated CSF caffeine after one 240 ml filtered coffee ≈ **5 µM** → GIRK conductance ↓ ≈ **12 %** → ΔV_{raw} ≈ **0.83 mV** → ΔV_{soma} ≈ **+0.9 mV** after applying $k_R \cdot k_{PV} = 1.21$.

Final step ("−55 % rheobase"). The current threshold is converted to an equivalent reduction of the effective excitability margin in mV using the Lapicque formulation (not merely $V_{thr} - V_{rest}$).

The 95 % confidence interval of the margin partially overlaps the packet amplitude, yet the mean excess remains positive.

2.18 Assumptions and modelling procedures for the fear (SZ), sadness (MDD) and trauma (PTSD) loops

All numerical values reported in the main text and in Supplementary Tables S49–S51 are mean changes relative to control groups taken directly from the literature. They serve only to illustrate the direction of network adaptation; we do not perform error propagation or a full sensitivity analysis on these data.

2.18.1 Common data-transfer scheme (R rules)

Table 2.37 Data-transfer scheme

Code	Transfer rule	Neurophysiological rationale	Example in Results
R1	Identical cell population	Parameter measured in the same element (PV IN, AMPAR, etc.)	PV IN −30 % (Czeh et al. 2005)
R2	Shared θ/δ oscillation	Structures operate in-phase at 4–10 Hz	Glu/GABA shift (Mitsushima et al. 2013)
R3	Monosynaptic projection (× 0.7)	Amplitude attenuation across a single synapse	Not used in the present model
R4	Global hormone / neuromodulator	CRF, cortisol, DA/NA reach all nodes systemically	Cortisol ↑ (Schwabe and Wolf 2012)

Parameters measured outside vCA1 are marked with a † and transferred according to R1–R4 **without any additional scaling** (k = 1.0).

2.18.2 Fear loop → schizophrenia phenotype

Start. Reactivation of the vCA1 engram (10 – 15× day^{-1} for ≥ 14 days) synchronises vCA1 and BLA in the θ band (7 – 10 Hz) and drives bursts of dopamine (+≈ 60 %†) and cortisol (+≈ 55 – 60 %†) (Yoshioka et al. 1996; Schwabe and Wolf 2012).

Transfer. Items 1 – 9 in Supplementary Table S49 (fear loop) are mapped to the vCA1/BLA node via rules R1–R4.

- Global neuromodulators (DA, cortisol) retain their full magnitude (R4).
- Local parameters (e.g. PV IN −30 %) are passed 1 : 1 (R1).

Modelling. ΔE/I, elevated ROS (reduced GSH) (Grabnar et al. 2011; Cabungcal et al. 2013), decreased PNNs (Mauney et al. 2013), and the γ-shift are treated qualitatively; we do not calculate ΔV_{margin}.

DA/cortisol ↑ → Glu/GABA ratio ↑ → ROS ↑ → PNN ↓→ PV ↓ → γ-shift → Loss of dmPFC control

Morphology. Chronic stress shortens apical dendrites in the dmPFC by ≈ 20 % (Radley et al. 2004), and increases histone H3/H4 acetylation at the BDNF promoter (Lubin et al. 2008) stabilises this plasticity. Both effects remain within their native regions and are used for clinical validation.

Dominant θ activity, a hyper-reactive BLA, and thinning of dmPFC layer III observed in patients all emerge from the model without additional assumptions.

2.18.3 Sadness loop → progression toward a depressive (MDD) phenotype

Start. A CSF meta-analysis (Ogawa et al. 2018) revealed a **selective fall in the dopamine metabolite HVA (g ≈ 0.30 SD)** without a significant change in 5-HIAA, releasing the tonic brake on the CRF axis. Consequently, CSF CRF rises by **≈ 45 – 80 % (mean ≈ +65 %)†** (Nemeroff et al. 1984) and lengthens slow (< 4 Hz) replays between vCA1 and sgACC (Hamilton et al. 2015; Higgins et al. 2021).

vCA1 hot spot. Roughly **5 % of pyramidal neurons** ("sadness engram") show a local E/I tilt: **Glu ↑ ≈ 15 %†, GABA ↓ ≈ 8 %†** (sgACC, 7 T-MRS; (Godfrey et al. 2018; Hu et al. 2023). A **+5 mV† depolarisation**, measured in rat IL-mPFC (McKlveen et al. 2016), is transferred to vCA1/sgACC via the shared δ/θ oscillation (rule R2). PV interneuron density drops by **≈ 30 %†** (Czeh et al. 2005; Yu et al. 2020). The remaining vCA1 neurons stay hyperpolarised, matching ASL/BOLD studies (Schmaal et al. 2016).

Oscillations. During rumination episodes EEG shows **fronto-central β-power↑ (13–30 Hz)** and **occipital α-power↓ (8–12 Hz)**; the β/α ratio correlates with replay frequency (Moon et al. 2018; Forner-Phillips et al. 2020; Benschop et al. 2021).

Structural consolidation. Oxidative stress (ROS ↑ / GSH ↓†) degrades **PNN ↓†** (Cabungcal et al. 2013; Yu et al. 2020). ROS plus cortisol hyper-methylate the BDNF promoter ↑† in mPFC (Cheng et al. 2023). Dendrites and spines in the dlPFC subsequently thin by **12 – 18 % (mean ≈ 15 %)†** (Kang et al. 2012; Kassem et al. 2013), deepening the executive-control deficit.

Network architecture. MDD patients exhibit global PFC hyper-polarisation, focal hyper-perfusion of vCA1 and increased δ/θ coherence vCA1 ↔ sgACC (Hamilton et al. 2015; Schmaal et al. 2016). The model assumes that ~5 % of vCA1 pyramids remain depolarised, forming a persistent hot spot.

Driving sequence (Supplementary Table S50, rows 1–11)

HVA ↓ → CRF ↑ → slow
replays ↑ → Glu ↑ / GABA ↓ → ROS ↑ / GSH ↓ → PNN ↓ → PV ↓ → β ↑ / α ↓ → BDNF methylation ↑ → spine density −15 % → loss of PFC control → next rumination cycle.

Iterating this cascade progressively shifts control from executive cortex to slow DMN loops, shaping the clinical MDD phenotype.

2.18.4 Trauma loop → progression toward a PTSD phenotype

Start. A single trauma reminder triggers an alarm burst of noradrenaline—about **3–4 × baseline** in the BLA—originating from locus-coeruleus fibres (McCall et al. 2015; Ronzoni et al. 2016) together with dopamine ↑ ≈ **60 %†** (Rosenkranz and Grace 2002; Giustino et al. 2020). CSF CRF rises by ≈ **30–40 %†** (29 ± 8 vs 22 ± 6 pg ml^{-1}) and stays elevated for several minutes (Bremner et al. 1997).

vCA1/BLA hot spot. Ultra-high-field (7 T) MRS shows **Glu ↑ ≈ 14 %†** in the right hippocampus (Rosso et al. 2017) and **GABA ↓ 20 ± 10 %†** in the anterior insula (Rosso et al. 2014). Because the insula phase-locks with the hippocampus in the δ/θ band ~4 Hz (Huang et al. 2014), this variable is transferred to vCA1 via rule R2. A reported shift $\boldsymbol{E_{GABA}}$ **+7 mV** in dCA1 (Inoue et al. 2013) is scaled to **+5 ± 2 mV†**. PV interneuron counts fall by ≈ **30 %†** in both BLA and mPFC (Shepard et al. 2016).

Oscillations. Just before a flashback, MEG records a frontal γ-burst (30–50 Hz) and occipital α-suppression (Dunkley et al. 2015; Shaw et al. 2023); vCA1↔BLA θ/δ coherence increases. The γ ↑ / α ↓ effect is state-dependent (flashback vs resting). vmPFC is hypoactive during recollection (Shin and Liberzon 2010).

Consolidation. Oxidative stress (ROS ↑ / GSH ↓) and **PNN** ↓ in BLA/PFC (Cabungcal et al. 2013; Murthy et al. 2019) further weaken PV networks. Hypermethylation of the BDNF promoter in mPFC (Roth et al. 2009) and a lowered LTP threshold in the BLA → vCA1 pathway (Kim and Cho 2020) stabilise engram susceptibility.

Network architecture. An abrupt reminder co-activates BLA and vCA1 (Rosso et al. 2014) vCA1 signals reach the amygdala via the subiculum → entorhinal → amygdalo-hippocampal route; extremely aversive cues additionally recruit the thalamic pathway (Phelps and LeDoux 2005).

Driving sequence (Supplementary Table S51, rows 1–11):

NA/DA ↑ → CSF CRF ↑ → Glu ↑ / GABA ↓ (+ ΔE_{GABA}) → ROS ↑ / GSH ↓ → PNN ↓ → PV ↓ → γ ↑ / α ↓ → vmPFC hypoactivity → flashback → next NA/DA burst.

Repeated cycles keep the excitability safety margin low and drive the intrusive recollections characteristic of PTSD.

2.18.5 Transfer to vCA1 — practical rules

1. **Oscillatory synchrony (R2).** Phase-locking at 4–10 Hz permits direct transfer of the local ΔE/I between paired structures.
2. **Cellular identity (R1).** PV interneurons and AMPAR synapses display comparable phenotypes across limbic areas (e.g. AMPAR +25 % in BLA (Rumpel et al. 2005; Clem and Huganir 2010))
3. **Neuromodulators (R4).** CRF, cortisol, DA/NA act system-wide; a 1 : 1 transfer is the safest assumption.
4. **No hard numerical scaling.** The model emphasises the *sequence* of events (E/I shift → ROS ↑ → PV loss) rather than an exact ΔV for any single neuron.

2.18.6 Model limits and scope

- **No formal sensitivity analysis.** Varying any input parameter by ±25 % does not alter the order of steps or the conclusion that chronic engram re-activation drives the SZ, MDD or PTSD trajectory, respectively.

- **Effects outside vCA1.** Morphological parameters remain in their native region (e.g. thinning of dmPFC layer III) and serve only for clinical validation.
- **"Qual." parameters.** Qualitative indicators (e.g. γ ↑ / α ↓) are used solely to establish event order and are **not** quantified within the model.

2.19 Conversion of markers into ΔV and the go / no-go threshold

2.19.1 Minimum go / no-go threshold (pilot → RCT II)

Phase I/II success criterion: at least 2 of the 3 key markers shift in a pro-buffering direction ($p < 0.05$).

This corresponds to a **cumulative gain of ≈ +3.2 mV**.

A total gain of **+3.6 mV** would occur if all three markers improve.

Meeting this criterion falsifies the null hypothesis and authorises entry into **RCT II**, but does **not guarantee durable remission**.

2.19.2 HRV sensitivity analysis

- **rMSSD** is recalculated after excluding participants who consume **> 200 mg caffeine/day** or **> 5 cigarettes/day**.
- Assuming an effect of **+5 ms (SD = 5 ms)** for the low-stimulation arm, the statistical power at $\alpha = 0.05$ is ≈ **0.82** (package *pwr* v1.3, R 4.4).
  Details → Supplementary Table S57.

2.19.3 Abstinence criteria at enrolment

- ≥ **12 h** caffeine-free, ≥ **2 h** nicotine-free.
- "Heavy users" are analysed separately (stratification).

2.19.4 Development of the marker panel (second-generation tracers)

- **PET-PV** and **PET-Kir4.1** – phosphorylation state of PV / K^+ homeostasis.
- **MRI-CEST / ^{23}Na-MRI** – ionic reserve (Cl^- / Na^+).
- **Validation** of the SUVR → ΔE_{GABA} equation in a mouse-humanised model.
- **PET-KCC2** – tracer in first-in-human phase (test–retest CV ≈ 6 %; ClinicalTrials.gov NCT05987421).

A selective PET KCC2 tracer has completed IND-enabling toxicology and entered first-in-human evaluation at **Karolinska Institutet (2025 Q2)**. A parallel programme at the

University of Chicago is slated for 2026 Q1, with GMP synthesis expected within 12 – 18 months.

Plan: obtain anonymised calibration data or include a small calibration sub-cohort ($n \approx 10$) at the same centre after a formal MTA/DUA.

If access is **not** confirmed within ≤ 6 months, the primary pilot analysis will rely solely on the **MEG γ-burst + HRV** markers, and PET-KCC2 will remain exploratory.

2.19.5 Rescue pathway

1. No improvement in markers → stop-rule.
2. Partial signal → engage the E-axis; if the β-loop is positive, add the F-axis.
3. Failure after rescue → the "narrow-margin" hypothesis is rejected.

2.19.6 Clinical threshold summary

- Current markers can directly measure ≈ 7 mV of safety margin.
- With second-generation tracers the expected full remission margin is ≈ 9 mV.
- Full success: ≥ 9 mV *and* clinical MCID achieved.
- Minimal success: ≥ 3.2 mV (≥ 2 markers) — sufficient to proceed to RCT II.
- Adverse events are coded under MedDRA 25.1; the DSMB applies the Haybittle-Peto rule ($p < 0.001$) for early stopping.

γ-burst = local burst detected by a beam-former in the vCA1 ROI, not total γ-band power.