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Expansion of epileptogenic networks via neuroplasticity in neural mass models

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1 Abstract

2 Neuroplasticity refers to functional and structural changes in brain regions in response to healthy and
3 pathological activity. Activity dependent plasticity induced by epileptic activity can involve healthy brain
4 regions into the epileptogenic network by perturbing their excitation/inhibition balance. In this article,
5 we present a new neural mass model, which accounts for neuroplasticity, for investigating the possible
6 mechanisms underlying the epileptogenic network expansion. We formulate physiological calcium-
7 mediated synaptic plasticity and pathological extrasynaptic N-methyl-D-aspartate (NMDA) dependent
8 plasticity in a multiple-timescale framework. The model highlights that synaptic plasticity at excitatory
9 connections and structural changes in the inhibitory system can transform a healthy region into a
10 secondary epileptic focus under recurrent seizures and interictal activity occurring in the primary focus.
11 Our results suggest that the latent period of this transformation can provide a window of opportunity to
12 prevent the expansion of epileptogenic networks, formation of an epileptic focus, or other comorbidities
13 associated with epileptic activity.

14 *Key words: epilepsy, synaptic plasticity, secondary focus, neural mass model, multiple timescale systems*

15 Author Summary

16 Repetitive epileptic activity leads to a large variety of plastic changes in brain. Understanding the
17 mechanism and its time course can indicate windows of opportunity for preventing the devastating
18 impact of focal epileptic activity on brain networks. Animal models of focal epilepsy have underlined the
19 role of NMDA receptors and deregulations in the GABAergic system in the expansion of epileptic activity.
20 Here we develop a plastic neural mass model integrating physiological and pathologic plasticity. Our
21 results show that neuroplasticity mediated by epileptic activity increases synaptic efficacy between
22 epileptic and healthy regions, and causes irreversible changes in the GABAergic system in the healthy
23 region. The model gives mechanistic insights into the physio-pathological impact of focal epileptic activity
24 on large-scale networks and suggests that seizures may beget seizures.

25 Introduction

26 The most general definition of neuroplasticity is the ability of neural networks to reorganize over time,
27 which can take place under physiological and pathological conditions. Activity dependent plasticity is the
28 ability of synapses to strengthen or weaken, in response to increases or decreases in their activity. Under
29 physiological conditions, it is accompanied by many regulatory mechanisms through which the
30 excitation/inhibition balance is preserved (for examples [1–6]). However, epileptiform discharges drive
31 not only physiologic synaptic plasticity but also pathological plasticity, which disturbs the
32 excitation/inhibition balance, and can cause expansion of epileptogenic networks during epileptogenesis
33 [7–9]. The aim of this article is to investigate the expansion of epileptogenic networks with a
34 neurophysiologically plausible mathematical model of physio-pathological plasticity under recurrent
35 epileptic activity.

36 Synaptic plasticity occurs on multiple timescales at both presynaptic and postsynaptic sites [10]. Short-
37 term plasticity (STP, in milliseconds) refers to transient changes in the probability of neurotransmitter
38 release at the presynaptic site [11]. Long-term synaptic plasticity (in hours or days), although generally
39 considered as postsynaptic alterations, is related to both (i) the insertion/removal of alpha-amino-3-
40 hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (AMPA) at the postsynaptic site and (ii)
41 the change in the probability of neurotransmitter release at the presynaptic site [12].

42 Postsynaptic long-term potentiation (LTP) and long-term depression (LTD) depend on the calcium
43 concentration at the postsynaptic site [13]. In excitatory (glutamatergic) synapses, an increase in
44 postsynaptic calcium concentration through activation of synaptic N-methyl-D-aspartate (NMDA)
45 receptors (NMDARs), metabotropic glutamate receptors, voltage-gated calcium channels, etc. is
46 necessary and sufficient for synaptic plasticity (see [12,14] and references therein). Calcium-dependent
47 activation of secondary messengers, such as nitric oxide, endocannabinoids, etc., triggers presynaptic
48 long-term plasticity [15,16]. The late phase of long-term plasticity, referred to as maintenance or
49 consolidation, occurs via new protein synthesis and gene transcription [12]. We refer to these processes

50 of postsynaptic long-term plasticity, presynaptic long-term plasticity and consolidation as *physiological*
51 *plasticity*.

52 Epileptic discharges that cause glutamatergic spillover have a twofold impact. First, epileptiform activity
53 strengthens excitatory synapses by increasing the number of AMPARs [17,18], as in the physiological LTP.
54 Second, a high amount of glutamate released during epileptiform activity can activate extrasynaptic
55 NMDARs that cause pathological changes in GABAergic signaling, through inactivation of functional
56 potassium chloride co-transporters 2 (KCC2) and internalization of GABAergic receptors [19,20]. KCC2
57 controls the outflow of the chloride ions from the intracellular space to the extracellular space and
58 maintains the GABAergic reversal potential. Calcium ions flowing through extrasynaptic NMDARs bind on
59 calpain that inactivates KCC2 [20–22]. Reducing the number of functional KCC2 results in the increase of
60 the intracellular chloride concentration and changes GABAergic responses from inhibitory to excitatory.
61 KCC2 dysfunction is related to epileptic activity in the naive site [7], and it is one of the factors
62 contributing to epileptic activity in the mature brain [23].

63 The extrasynaptic NMDAR activity also affects tonic inhibition that is mainly mediated by the α_5 GABA_A
64 receptors in the hippocampus. Overexpression of GluN2B NMDA receptors, which are located mostly in
65 extrasynaptic regions, downregulates the expression of α_5 GABA_A receptors expression, promotes their
66 internalization, and therefore, reduces tonic GABAergic [24] (but see [25] for limbic epileptogenesis). We
67 refer to these two mechanisms, i.e. reduced KCC2 and internalization of extrasynaptic GABAR, as
68 *pathological plasticity*.

69 After several seizures physiological plasticity (LTP, LTS) seems to be occluded. However, pathological
70 plasticity can increase the susceptibility of a brain region to epileptic discharges, expand epileptic
71 network, and generate a secondary (mirror) focus. Secondary focus refers to epileptogenesis in a naive
72 area induced by repetitively uncontrolled epileptic seizures from a primary seizure focus [26,27].

73 Independent epileptic activity in the contralateral area in humans suggests that mirror focus develops via
74 a kindling process mediated by the primary focus. In animal models of epilepsy, for instance, under

75 kindling [28] or kainite application [7] to one of the hippocampi (primary focus), secondary focus appears
76 in the contralateral hippocampus due to recurrent epileptic activity in the primary focus. Khalilov's
77 elegant work in the immature brain [7] showed that activation of NMDARs and long-term alterations in
78 GABAergic synapses are responsible for chronic epileptogenesis in the secondary focus. Despite the key
79 role of plasticity in expansion of epileptogenic networks, there is a lack of computational modeling
80 studies of neuroplasticity under epileptic activity.

81 Previous modeling studies of calcium-mediated postsynaptic LTP/LTD have mainly focused on cellular
82 activity [29–34] (see [35] for a mean-field approximation), as well as presynaptic long-term plasticity
83 [30,33,36,37]. Recently, Chindemi et al. [30] developed a detailed cellular model of the neocortex that
84 integrates the calcium-mediated presynaptic and postsynaptic plasticity mechanisms. However, the
85 literature related to modeling calcium-mediated plasticity with neuro-physiologically plausible neural
86 mass model (NMMs) remains limited, and up to date up to date no computational model implements the
87 activity dependent pathological plasticity. We identified two studies on this phenomenon in the context
88 of magnetic stimulation [38,39]. The originality of this study is to differentiate the impact of physiological
89 plasticity and the pathological plasticity induced by epileptic discharges on epileptogenicity of NMMs.
90 Our computational model concentrates on the physio-pathological plasticity under epileptic activity in a
91 network of two unidirectionally coupled NMMs [40], each representing an epileptic and a non-epileptic
92 brain region, where the epileptic one perturbs the non-epileptic one. First, we study how synaptic
93 connections evolve under epileptic activity. We then investigate the pathological plasticity triggered by
94 the physiological plasticity. The results suggest that the interaction between physiological and
95 pathological plasticity can explain the expansion of epileptogenic networks and the formation of
96 secondary epileptic foci.

97 Methods

98 Mesoscopic model of physiological short- and long-term plasticity

99 The seminal study by Shouval et al. [29] has proposed a calcium control hypothesis for postsynaptic
100 plasticity, in which intra-cellular calcium concentration controls the rate of change of synaptic efficacy.
101 The proposed model in [29] was then developed to account for the synaptic consolidation in [32] by
102 introducing a variable ρ that describes the state of the synaptic efficacy. We combine both formulations
103 as:

$$\frac{d\rho}{dt} = \frac{1}{\tau_\rho} (-\rho(1-\rho)(\rho_* - \rho) + (1-\rho)\Omega_p([Ca]) - \rho\Omega_d([Ca])), \quad (1)$$

104 where τ_ρ is the time constant of the synaptic variations, $\rho_* = 0.5$ is the boundary between the depressed
105 ($\rho = 0$) and potentiated ($\rho = 1$) states. The functions $\Omega_{p,d}([Ca])$ describe how the synaptic efficacy is
106 controlled by the calcium concentration:

$$\Omega_{p,d}([Ca]) = \frac{\gamma_{p,d}}{1 + \exp(-\beta_{p,d}([Ca] - \theta_{p,d}))}, \quad (2)$$

107 where $\gamma_p > \gamma_d$ are potentiation and depression rates, $\beta_{p,d}$ are the slopes at potentiation and depression
108 boundaries $\theta_p > \theta_d$ (Fig 1A). The depression rate is smaller than the potentiation rate for provoking a
109 transition from depressed to potentiated state for a high probability [29,30,32]. We followed [29] for the
110 value of slopes. We studied the impact of the boundaries on the long-term plasticity in the manuscript.

111

112 **Fig 1. Synaptic efficacy and activation functions.** (A) Calcium dependent synaptic efficacy function,

113 $\Omega([Ca]) = -\Omega_d([Ca]) + \Omega_p([Ca])$ (2), and (B) activation function, $H(V_{post})$ (5) for the parameter set

114 given in Table 1.

115

116 The calcium concentration is controlled by the NMDAR-mediated current $I_{NMDA}^{[Ca]}$:

$$\frac{d[Ca]}{dt} = I_{NMDA}^{[Ca]} - \frac{[Ca]}{\tau_{ca}}, \quad (3)$$

117 where τ_{ca} is the decay time constant of calcium influx. The NMDAR-mediated calcium current $I_{NMDA}^{[Ca]}$
 118 depend on both the presynaptic activity via the kinetics of glutamate binding and the postsynaptic
 119 membrane potential [29] expressed as,

$$I_{NMDA}^{[Ca]} = G(F_{pre})h_{ca}H(V_{post}), \quad (4)$$

120 where $G(F_{pre})$ formulates the kinetics of the glutamate binding depending on the firing rate of the
 121 presynaptic population, F_{pre} . The function $H(V_{post})$ (Fig. 1B) formulates the relation between the NMDA
 122 currents and the postsynaptic (population level) depolarization:

$$H(V_{post}) = \frac{1}{1 + \exp(-\mu(V_{post} - V_{th}))}, \quad (5)$$

123 where μ is the slope at $V_{th} = V_{post}$. The function $H(V_{post})$ can be interpreted as the magnesium
 124 blockage at the population level. Parameter h_{ca} is a scaling factor, which distinguishes the NMDAR-
 125 mediated postsynaptic depolarization from calcium entry.

126 Plasticity of excitatory synapses is modeled at both presynaptic and postsynaptic levels. Presynaptic
 127 plasticity corresponds to variations in glutamate release probability, running on short- and long-
 128 timescales. The presynaptic STP rule follows [41]:

$$\frac{dr}{dt} = \frac{1-r}{\tau_r} - u r F_{pre} \quad (6a)$$

$$\frac{du}{dt} = \frac{U_s - u}{\tau_f} + U_s(1-u)F_{pre} \quad (6b)$$

129 where r is the amount of available neurotransmitters, u is the utilization factor, τ_r is the recovery
 130 timescale, τ_f is the facilitation timescale and U_s is the neurotransmitter release probability. Since the
 131 interaction between glutamatergic synapses is depression dominated [42,43], we consider $\tau_r > \tau_f$.

132 The presynaptic long-term plasticity is the long-term variation in the neurotransmitter release probability
 133 U_s controlled by the calcium-dependent retrograde signaling [30],

$$\frac{dU_s}{dt} = \frac{1}{\tau_U} (U_s^d - U_s + \rho(U_s^p - U_s^d)). \quad (7)$$

134 Parameters U_s^d and U_s^p represent the depressed and potentiated states of the release probability U_s , and

135 τ_U is the time constant of the presynaptic long-term plasticity.

136 Postsynaptic long-term plasticity corresponds to an insertion/removal of glutamatergic AMPAR,

$$\frac{d\tilde{C}_{AMPA}}{dt} = \frac{1}{\tau_{C_{AMPA}}} (C_{AMPA}^d - \tilde{C}_{AMPA} + \rho(C_{AMPA}^p - C_{AMPA}^d)). \quad (8)$$

137 Parameters C_{AMPA}^d and C_{AMPA}^p represent the depressed and potentiated states of the AMPAergic

138 coupling strength $\tilde{C}_{AMPA}(t)$, and $\tau_{C_{AMPA}}$ is the time-constant of the postsynaptic long-term plasticity. For

139 simplicity, we assume that presynaptic and postsynaptic long-term changes have the same time

140 constants $\tau_U = \tau_{C_{AMPA}}$. Since the expression of synaptic plasticity is slower than its induction [44], we

141 consider $\tau_p < \tau_U = \tau_{C_{AMPA}}$ as in [30].

142 Whole model of pre- and postsynaptic plasticity reads as follows:

$$\frac{dr}{dt} = \frac{1-r}{\tau_r} - u r F_{pre}, \quad (9a)$$

$$\frac{du}{dt} = \frac{U_s - u}{\tau_f} + U_s(1-u)F_{pre}, \quad (9b)$$

$$\frac{d[Ca]}{dt} = I_{NMDA}^{[Ca]} - \frac{[Ca]}{\tau_{ca}}, \quad (9c)$$

$$\frac{d\rho}{dt} = \frac{1}{\tau_\rho} (-\rho(1-\rho)(\rho_* - \rho) + (1-\rho)\Omega_p([Ca]) - \rho\Omega_d([Ca])), \quad (9d)$$

$$\frac{dU_s}{dt} = \frac{1}{\tau_U} (U_s^d - U_s + \rho(U_s^p - U_s^d)), \quad (9e)$$

$$\frac{d\tilde{C}_{AMPA}}{dt} = \frac{1}{\tau_{C_{AMPA}}} (C_{AMPA}^d - \tilde{C}_{AMPA} + \rho(C_{AMPA}^p - C_{AMPA}^d)). \quad (9f)$$

143 The parameter values of (9) are given in Table 1. Except the values of time constants as mentioned

144 above, the parameter values are chosen in accordance with the dynamics of the interacting NMMs

145 detailed in the following sections.

Table 1: Variables and parameter values of (9) unless otherwise stated

	Variables	Equation number
$r(t)$	amount of available neurotransmitters	(9a)
$u(t)$	utilization factor of neurotransmitters	(9b)
$[Ca](t)$	calcium concentration	(9c)
$\rho(t)$	state of the synaptic efficacy	(9d)
$\tilde{C}_{AMPA}(t)$	AMPAergic coupling strength	(9e)
$U_s(t)$	neurotransmitter release probability	(9f)
	Parameters	Value
θ_d	depression threshold	0.1
θ_p	potentiation threshold	0.4
γ_d	depression amplitude	1
γ_p	potentiation amplitude	5
β_d	depression slope	80
β_p	potentiation slope	80
μ	slope of NMDA-dependent postsynaptic depolarization	1
V_{th}	threshold of NMDA-dependent postsynaptic depolarization	5 V
h_{ca}	calcium current scaling factor	10
τ_d	presynaptic short-term depression time constant	0.200 sec
τ_f	presynaptic short-term facilitation time constant	0.05 sec
τ_{ca}	the calcium influx decay time constant	0.05 sec
τ_ρ	synaptic efficacy time constant	50 sec
τ_U	presynaptic long-term plasticity time constant	100 sec
$\tau_{C_{AMPA}}$	postsynaptic long-term plasticity time constant	100 sec

U_S^d	Value of depressed release probability	0.4
U_S^p	Value of potentiated release probability	0.8
C_{AMPA}^d	Value of depressed AMPAergic coupling strength	50
C_{AMPA}^p	Value of potentiated AMPAergic coupling strength	100

147

148 The revisited neural mass model

149 We revisited a minimal NMM of the CA1 region of the hippocampus [40] for obtaining an autonomous
150 model that can undergoes seizures for a fixed parameter set. The original model includes four interacting
151 neuronal subpopulations: two interconnected subpopulations of glutamatergic pyramidal neurons (P, P'),
152 and two subpopulations of GABAergic inhibitory interneurons (somatostatin positive (SOM), and
153 parvalbumin positive (PV), also called dendrite-projecting slow and soma-projecting fast interneurons,
154 respectively). The activity of each subpopulation is described by a "wave to pulse" function, $S(v) =$
155 $5/(1 + \exp(0.56(6 - v)))$, transforming the net membrane polarization in response to synaptic inputs
156 into a firing rate. The synaptic interactions between the subpopulations is described by a "pulse to wave"
157 that converts the input average firing rate into a postsynaptic potential (PSP), which can be either
158 excitatory – EPSP - or inhibitory - IPSP) at the input of each subpopulation, that is $h(t) =$
159 $W/\tau_w \exp(-t/\tau_w)$, where W represents the average PSP amplitude and τ_w is the time constant. This
160 linear filter, also known as the alpha-function, introduces a second order ordinary differential equation

161 $\frac{d^2y}{dt^2} = \frac{W}{\tau_w} S(v) - \frac{2}{\tau_w} \frac{dy}{dt} - \frac{1}{\tau_w^2} y$ where $y(t)$ is the PSP in response to the input $S(v)$. The equations of an

162 unconnected population i NMM _{i} reads:

$$\frac{d^2y_P^{(i)}}{dt^2} = \frac{A^{(i)}}{\tau_a} S(V_P^{(i)}) - \frac{2}{\tau_a} \frac{dy_P^{(i)}}{dt} - \frac{1}{\tau_a^2} y_P^{(i)}, \quad (10a)$$

$$\frac{d^2y_{P'}^{(i)}}{dt^2} = \frac{A^{(i)}}{\tau_a} (p^{(i)}(t) + C_{P',P}^{(i)} S(C_{P,P'}^{(i)} y_P^{(i)})) - \frac{2}{\tau_a} \frac{dy_{P'}^{(i)}}{dt} - \frac{1}{\tau_a^2} y_{P'}^{(i)}, \quad (10b)$$

$$\frac{d^2 y_{SOM}^{(i)}}{dt^2} = \frac{B^{(i)}}{\tau_b} S(C_{P,SOM}^{(i)} y_P^{(i)}) - \frac{2}{\tau_b} \frac{dy_{SOM}^{(i)}}{dt} - \frac{1}{\tau_b^2} y_{SOM}^{(i)}, \quad (10c)$$

$$\frac{d^2 y_{PV}^{(i)}}{dt^2} = \frac{G^{(i)}}{\tau_g} S(C_{P,PV}^{(i)} y_P^{(i)} - C_{SOM,PV}^{(i)} y_{SOM}^{(i)}) - \frac{2}{\tau_g} \frac{dy_{PV}^{(i)}}{dt} - \frac{1}{\tau_g^2} y_{PV}^{(i)}, \quad (10d)$$

163 with variables $y_k^{(i)}$ representing the PSP generated by a subpopulation k . Parameters $C_{k,p}^{(i)}$ scales the
 164 impact from subpopulation k to subpopulation p within the population NMM_{*i*}. The net polarization of P
 165 subpopulation of NMM_{*i*}, $V_p^{(i)}$, reads,

$$V_p^{(1)} = \Sigma(C_{k,P}^{(1)} y_k^{(1)})$$

166 for NMM₁, and,

$$V_p^{(2)} = \Sigma(C_{k,P}^{(2)} y_k^{(2)}) + \Sigma Input_{NMM_1 \rightarrow NMM_2}$$

167 for NMM₂, which is subject to the excitatory AMRAergic and NMDAergic signals from NMM₁ on its P
 168 subpopulation, $\Sigma Input_{NMM_1 \rightarrow NMM_2}$. We consider $V_p^{(i)}$ as the model output, which is a simplified proxy for
 169 the local field potential recorded by an extracellular electrode positioned in the neuronal population. The
 170 model diagram is given in Figure 2A.

171

172 **Fig 2. Unidirectionally interacting NMM₁ and NMM₂ and the dynamics of NMM₁ in the interictal and**
 173 **ictal regimes.** (A) Model diagram of unidirectionally coupled NMM₁ and NMM₂. Each NMM includes four
 174 interacting subpopulations of pyramidal neurons (P and P') and inhibitory interneurons (PV and SOM)
 175 with excitatory (red connections) and inhibitory (blue connections) interactions between parametrized by
 176 the coupling coefficients $C_{k,p}^{(i)}$ for $i \in \{1,2\}$ with k and p representing the pre- and postsynaptic
 177 subpopulations of NMM_{*i*}, respectively. The PSP generated by a subpopulation k are denoted by $y_k^{(i)}$.
 178 NMM₂ is subject to an excitatory input from NMM₁, denoted by $Input_{NMM_1 \rightarrow NMM_2}$. (B-E) Dynamics of of
 179 (10)-(11) for NMM₁ in the interictal regime for $b_{thr}^{(1)} = 34$. (B) Bifurcation diagram of (10) where the
 180 amplitude of $y_p^{(1)}$ is presented as a function of $B^{(1)}$. The blue curve shows the branch of equilibrium

181 points (bold for stable and dashed for unstable equilibrium points). The red curves show the amplitude of
 182 $y_p^{(1)}$ in the oscillatory regime. The Hopf bifurcations along the branch of equilibrium points are denoted
 183 by red dots and saddle-node bifurcation by blue dots. The range of $B^{(1)}$ values that corresponds to the
 184 fast onset, ictal and interictal periods are marked by purple, yellow and cyan patches, respectively. The
 185 time solution (black curve) is superimposed on the bifurcation diagram. (C) Time trace for $V_p^{(1)}$ showing
 186 interictal spikes. (D) Phase plane of (11) with the $B^{(1)}$ -nullcline (blue curve, bold for stable and dashed for
 187 branches) and the $n^{(1)}$ -nullcline (orange curve). The range of $B^{(1)}$ values that corresponds to the fast
 188 onset, ictal and interictal periods in (10) are marked by green, yellow and cyan patches, respectively. The
 189 time solution (black curve) is superimposed on the bifurcation diagram. (E) Time trace for $B^{(1)}$. (F-I)
 190 Dynamics of (10)-(11) for NMM_i in the ictal regime for $b_{thr}^{(1)} = 32$. Same color codes and markers in (B-E)
 191 is used. Arrows in panel (G) indicates the direction of the trajectory (black curve) on the $(B^{(1)}, n^{(1)})$ -plane
 192 with double arrows indicating the fast transitions. The fast onset, ictal and interictal periods are marked
 193 on the time traces of $V_p^{(1)}$ and $B^{(1)}$ on panels H and I, respectively.

194

195 Intracranial recordings from epileptic patients with focal epilepsy show four distinct phases of activity:
 196 interictal phase with sporadic spikes, preictal phase with periodic preictal spikes, tonic low-voltage fast
 197 onset marked by a gamma-band activity, and clonic discharges [45]. Recordings show sequential
 198 transitions between these phases, that is, interictal, preictal, then, ictal phase (so-called *seizure*, which
 199 starts with a tonic low-voltage fast onset phase followed by clonic discharges). For an appropriate choice
 200 of model parameters, the transitions between these phases in (10) can be obtained by varying the IPSP
 201 amplitude of the SOM interneurons, $B^{(i)}$, (e.g. [40,46]). Figure 2B shows the bifurcation diagram of (10)
 202 for NMM₁ as a function of $B^{(1)}$ with the parameter set in Table 2. The branch of equilibrium points
 203 undergoes four Hopf bifurcations at $B^{(1)} \approx \{0.47, 2.66, 9.98, 32.14\}$ and saddle-node bifurcations at
 204 $B^{(1)} \approx \{2.60, 2.92, 32.01, 50.38\}$. The gamma-band oscillations lie in $B^{(1)} \approx (2.66, 0.47)$ and the tonic
 205 lower frequency oscillations in $B^{(1)} \approx (9.98, 32.14)$. Under a stochastic input, such as $p^{(i)}(t) =$

206 $\mathcal{N}(p_m^{(i)}, p_s)$ in (10b), the gamma-band oscillations can be observed for $0 < B^{(1)} < 4$, the tonic phase for
207 $4 < B^{(1)} < 32$. The low-frequency periodic preictal spikes and aperiodic interictal spikes can be located
208 at the boundary between tonic oscillations and stable equilibrium points for $32 < B^{(1)} < 50$.

209 **Table 2: Variables and parameters values for (10)-(15) unless otherwise stated**

Variables of (10)		Equation number	
$y_P^{(i)}(t)$	EPSP emitted by the subpopulation P	(10a)	
$y_{P'}^{(i)}(t)$	EPSP emitted by the subpopulation P'	(10b)	
$y_{SOM}^{(i)}(t)$	IPSP emitted by the subpopulation SOM	(10c)	
$y_{PV}^{(i)}(t)$	IPSP emitted by the subpopulation PV	(10d)	
Parameters of (10)		NMM ₁	NMM ₂
$A^{(i)}$	EPSP amplitude [mV]	5	5
$G^{(i)}$	IPSP _{PV} amplitude [mV]	20	2
τ_a	EPSP time constant [s]	0.01	0.01
τ_b	IPSP _{SOM} time constant [s]	0.03	0.03
τ_g	IPSP _{PV} time constant [s]	0.003	0.003
$C_{P,P'}^{(i)}$	$P \rightarrow P'$ coupling coefficient	135	135
$C_{P',P}^{(i)}$	$P' \rightarrow P$ coupling coefficient	108	108
$C_{SOM,P}^{(i)}$	$SOM \rightarrow P$ coupling coefficient	35	35
$C_{PV,P}^{(i)}$	$PV \rightarrow P$ coupling coefficient	200	200
$C_{P,SOM}^{(i)}$	$P \rightarrow SOM$ coupling coefficient	25	25
$C_{P,PV}^{(i)}$	$P \rightarrow PV$ coupling coefficient	200	200
$C_{SOM,PV}^{(i)}$	$SOM \rightarrow PV$ coupling coefficient	120	120
$p_m^{(i)}$	mean of the Gaussian input $p^{(i)}(t)$	90	70

$p_s^{(i)}$	standard deviation of the Gaussian input $p^{(i)}(t)$	2	2
	Variables of (11)	Equation number	
$B^{(i)}(t)$	IPSP _{SOM} amplitude [mV]	(11a)	
$n^{(i)}(t)$	Auxiliary variable	(11b)	
	Parameters of (11)	NMM ₁	NMM ₂
p_1	local maximum of the $B^{(i)}$ -nullcline	25	25
p_2	inflection point of the middle branch of the $B^{(i)}$ -nullcline	30	30
p_3	local minimum of the $B^{(i)}$ -nullcline	33	33
m_1	slope of the of the left branch of $B^{(i)}$ -nullcline	0.0015	0.0015
m_3	slope of the of the right branch of the $B^{(i)}$ -nullcline	0.003	0.003
n_k	minimum of the n -nullcline	-0.2	-0.2
n_p	maximum of the n -nullcline sigmoid	1.4	1.4
n_r	slope of the n -nullcline at the inflection point	2	2
$b_{thr}^{(i)}$	inflection point of the n -nullcline	34	44
δ	timescale parameter	50	50
ε	timescale parameter	0.05	0.05
	Variables of (12)-(15)	Equation number	
$y_{AMPA}(t)$	AMPAergic-EPSP emitted by the input from NMM ₁ onto NMM ₂	(12)	
$y_{NMDA}(t)$	NMDAergic-EPSP emitted by the input from NMM ₁ onto NMM ₂	(13)	
$y_{NMDA,ext}(t)$	NMDAergic-EPSP emitted by the activation of extrasynaptic NMDAR	(14)	
$K(t)$	Auxiliary variable representing the changes in GABAergic activity	(15)	

	Parameter values of (12)-(15)	NMM ₁	NMM ₂
$A_{AMPA}^{(2)}$	AMPAergic-EPSP amplitude [mV]	-	10
$A_{NMDA}^{(2)}$	NMDAergic-EPSP amplitude [mV]	-	2
$A_{NMDA,ext}^{(2)}$	Extrasynaptic NMDAergic-EPSP amplitude [mV]	-	1
τ_{AMPA}	AMPAergic-EPSP time constant [s]	-	0.005
τ_{NMDA}	NMDAergic-EPSP time constant [s]	-	0.02
$\tau_{NMDA,ext}$	Extrasynaptic NMDAergic-EPSP time constant [s]	-	0.04
C_{NMDA}	NMDAergic coupling coefficient	-	$C_{AMPA,min}$
τ_K	Extrasynaptic NMDA integration time constant	-	10

210

211 One can ensure an autonomous transition between the phases of epileptic activity by modeling $B^{(i)}$ as a
212 variable that varies in the range where these phases are observed. Here, we introduce a slow-subsystem
213 where the IPSP amplitude of the SOM interneurons $B^{(i)}$ is a variable:

$$\frac{dB^{(i)}}{dt} = \delta \left(n^{(i)} \right) \quad (11a)$$

$$\begin{aligned} & - \left(- \frac{m_1(B^{(i)} - p_1)^2}{1 + \exp(-p_1 + B^{(i)})} + \frac{1}{1 + \exp(-p_2 + B^{(i)})} \right. \\ & \left. + \frac{m_3(B^{(i)} - p_3)^2}{1 + \exp(-p_3 + B^{(i)})} \right), \end{aligned}$$

$$\frac{dn^{(i)}}{dt} = \varepsilon \left(-n^{(i)} + n_k + \frac{n_p}{1 + \exp(-n_r (b_{thr}^{(i)} - B^{(i)})} \right). \quad (11b)$$

214 Parameters of the $B^{(i)}$ - and $n^{(i)}$ -nullclines can be adjusted with respect to the critical (bifurcation) points
215 of (10), desired type and range of behavior. Among these parameters, p_1 and p_3 correspond to the jump
216 points in the $B^{(i)}$ -space from ictal to interictal and from interictal to ictal, respectively. Parameters m_1
217 and m_3 control the stiffness of the left and right branches of the $B^{(i)}$ -nullcline. Parameter m_1 is crucial for

218 covering the different phases of the ictal regime starting with gamma-band oscillations and continuing by
219 tonic spiking. Parameter m_3 contributes to the duration of the silent phase following the jump from ictal
220 to interictal phase. Parameters m_1 , p_1 , δ and ϵ together determine the duration of the ictal phase. The
221 parameter $b_{thr}^{(i)}$ is the main parameter controlling the excitability, hence, the susceptibility of seizing of
222 NMM_i. Parameter values of (11) are given in Table 2.

223 Note that the system (11) is a slow-fast system itself, where $B^{(i)}$ is the fast and $n^{(i)}$ is the slow variable.
224 The $B^{(i)}$ -nullcline of (11) has an N-shape with stable outer and unstable middle branches (Fig 2D). System
225 (10) governs the interictal and preictal phases for the $B^{(i)}$ values on the right branch $B^{(i)}$ -nullcline (Fig 2
226 B-E). The $B^{(i)}$ values on the left and middle branches $B^{(i)}$ -nullcline correspond to the ictal phase (fast-
227 onset and tonic discharges) of (10). Depending on the position of the equilibrium point of (11), defined as
228 the intersection between the N-shaped $B^{(i)}$ -nullcline and sigmoidal $n^{(i)}$ -nullcline, the system (11) follows
229 either a steady state (Fig 2D) or an oscillatory solution (Fig 2G). If the stable equilibrium point is close to
230 the right fold point of the $B^{(i)}$ -nullcline, then (11) is in an excitable state, i.e any perturbation on $B^{(i)}$ can
231 trigger a jump to the left branch of the fast nullcline, which corresponds to the ictal regime starting with a
232 fast-onset activity. As the trajectory of (11) moves along the left branch of the $B^{(i)}$ -nullcline, the system
233 (10) undergoes the fast-onset, then tonic spiking before jumping back to the right branch, that is the
234 interictal regime (Fig 2F-I).

235 Table 2 shows three main differences between the parameters of uncoupled NMM₁ and NMM₂. The first
236 one is the mean values of the external inputs ($p_m^{(i)}$), which determines the range of the IPSP amplitude of
237 the SOM interneurons ($B^{(i)}(t)$) for which sporadic and tonic spiking are observed in the model. The
238 second difference is the IPSP amplitude of the PV interneurons ($G^{(i)}$), for which higher values give
239 gamma-band activity in the model. The third difference is the excitability ($b_{thr}^{(i)}$), which controls both
240 $B^{(i)}(t)$ and the susceptibility of an NMM to jump from the interictal phase to seizure. The lower $b_{thr}^{(i)}$, the
241 more susceptible the NMM is to exhibiting a seizure. For simplicity, we considered the same values for

242 the rest of the parameters. The bifurcation diagram of uncoupled NMM₂ and its response to the epileptic
 243 activity when coupled to NMM₁ (Fig 2) are given in S1 Figure and S2 Figure.

244

245 Modeling plasticity with coupled neural mass models

246 We consider two populations NMM₁ and NMM₂ modelled by the NMM formulation given in (10)-(11).

247 NMM₂ receives excitatory inputs from NMM₁ through AMPAergic and NMDAergic signaling. Let $F_P^{(1)}$ be

248 the firing rate of the P subpopulation of the NMM₁, $r^{(1)}(t)$ and $u^{(1)}(t)$ are the variables describing the

249 presynaptic neurotransmitter release (6). Then the AMPAergic EPSP is given by

$$\frac{d^2 y_{AMPA}}{d^2 t} = \frac{r^{(1)} u^{(1)} A_{AMPA}^{(2)}}{\tau_{AMPA}} F_P^{(1)} - \frac{2}{\tau_{AMPA}} \frac{dy_{AMPA}}{dt} - \frac{1}{\tau_{AMPA}^2} y_{AMPA}, \quad (12)$$

250 where τ_{AMPA} is the synaptic time constant and $A_{AMPA}^{(2)}$ is the amplitude that is modulated by STP variables

251 $r^{(1)}(t)$ and $u^{(1)}(t)$. The NMDAergic-EPSP is given by

$$\frac{d^2 y_{NMDA}}{d^2 t} = \frac{r^{(1)} u^{(1)} A_{NMDA}^{(2)}}{\tau_{NMDA}} F_P^{(1)} - \frac{2}{\tau_{NMDA}} \frac{dy_{NMDA}}{dt} - \frac{1}{\tau_{NMDA}^2} y_{NMDA}, \quad (13)$$

252 where τ_{NMDA} is the synaptic time constant and $A_{NMDA}^{(2)}$ is the amplitude. The NMDAergic EPSP is slower

253 than the AMPAergic EPSP [47], thus $\tau_{AMPA} < \tau_{NMDA}$. The net depolarization of the postsynaptic

254 subpopulation due to the activation of NMDAR depends on the postsynaptic potential, $V_P^{(2)}$ as well as the

255 presynaptic entry $C_{NMDA} y_{NMDA}$, i.e. $C_{NMDA} y_{NMDA} H(V_P^{(2)})$, with C_{NMDA} is the coupling strength.

256 The pathological plasticity is activated when both the probability of vesicle opening U_s and the AMPAR

257 insertion \tilde{C}_{AMPA} are potentiated (9). Under this condition, an afferent epileptic spike from NMM₁, which

258 releases high levels of glutamate, activates the extrasynaptic NMDAR. The EPSP mediated by

259 extrasynaptic NMDR, $y_{NMDA,ext}$, has slower kinetics than the EPSP mediated by synaptic NMDAR [48] (i.e.

260 $\tau_{NMDA} < \tau_{NMDA,ext}$) and $y_{NMDA,ext}$ is given by

$$\frac{d^2 y_{NMDA,ext}}{d^2 t} = \frac{r^{(1)} u^{(1)} A_{NMDA,ext}^{(2)}}{\tau_{NMDA,ext}} F_P^{(1)} - \frac{2}{\tau_{NMDA,ext}} \frac{d y_{NMDA,ext}}{d t} - \frac{1}{\tau_{NMDA,ext}^2} y_{NMDA,ext}, \quad (14)$$

261 with the postsynaptic depolarization $C_{NMDA} y_{NMDA,ext} H(V_P^{(2)})$. The net postsynaptic polarization of the P
 262 subpopulation of the NMM₂ then reads,

$$263 \quad V_P^{(2)} = \Sigma \left(C_{k,P}^{(2)} y_k^{(2)} \right) + \tilde{C}_{AMPA} y_{AMPA} + C_{NMDA} (y_{NMDA} H(V_P^{(2)}) + y_{NMDA,ext} H(V_P^{(2)}))$$

264 with the plastic $\tilde{C}_{AMPA}(t)$ given in (9) and constant C_{NMDA} .

265 The changes in GABAergic activity caused by the activation of extrasynaptic NMDAR is modeled via an
 266 auxiliary variable $K(t)$,

$$\frac{dK}{dt} = \frac{1}{\tau_K} \left(-K(0.5 - K)(1 - K) - C_{NMDA} y_{NMDA,ext} H(V_P^{(2)}) \right). \quad (15)$$

267 When extrasynaptic NMDAR is inactive (i.e. $y_{NMDA,ext} = 0$), the equation (15) has three equilibrium
 268 points at $K^* = \{0, 0.5, 1\}$. The equilibria at $K^* = \{0, 1\}$ are stable, but the equilibrium at $K^* = 0.5$ is
 269 unstable. The extrasynaptic NMDAR activation (i.e. $y_{NMDA,ext} \neq 0$) can lead to a saddle-node bifurcation
 270 of the equilibria $K^* = 0.5$ and $K^* = 1$ leaving (15) with a single equilibrium point at $K^* \approx 0$, which
 271 becomes the global attractor of (15). Inactivation of the extrasynaptic NMDAR reintroduces the three
 272 equilibria but the transition from $K \approx 0$ to $K \approx 1$ state would not be possible in the model unless
 273 $y_{NMDA,ext}$ is negative. The latter is not biologically plausible or computationally possible because NMDA-
 274 mediated currents are excitatory. Therefore, the transition from $K \approx 0$ to $K \approx 1$ is irreversible. This
 275 phenomenological formulation is based on experimental studies in animal models of epilepsy, which
 276 suggest that when the secondary focus ‘‘matures’’, abolition of the primary focus or disruption of cortical
 277 connections does not abolish the secondary epileptic zone [27,49].

278 The variable $K(t)$ modulates the excitability of NMM₂ as,

$$279 \quad b_{thr}^{(2)}(t) = b_{thr}^{(2)} - k_B^{(2)}(1 - K(t)),$$

280 where the parameter $k_B^{(2)}$ scales the impact of $K(t)$ on the excitability. Since the gamma-band activity
 281 observed at the seizure onset can be obtained by increasing the IPSP amplitude of PV interneurons
 282 [40,46], $K(t)$ modulates $G^{(2)}$ as

$$283 \quad G^{(2)}(t) = G^{(2)} + k_G^{(2)}(1 - K(t)),$$

284 where the parameter $k_G^{(2)}$ scales the impact of $K(t)$ on the IPSP amplitude. We assumed that, in the
 285 absence of extrasynaptic NMDAR activity, $K(t) = 1$, for which IPSP amplitude is too small for yielding a
 286 gamma-band activity in (10) and the equilibrium point of (11) is far from the critical point of the seizure
 287 transition (i.e. the $n^{(2)}$ -nullcline intersects the $B^{(2)}$ -nullcline on its right branch). As $K(t) \rightarrow 0$ with the
 288 activation of the extrasynaptic NMDAR, $G^{(2)}(t)$ increases to a suitable level for obtaining gamma-band
 289 activity, whereas $b_{thr}^{(2)}(t)$ decreases and drives the equilibrium point of (10) towards the critical point of
 290 seizure transition in (10)-(11). In other words, how far (11) is from a Hopf bifurcation, hence how far (10)
 291 is from seizing, is controlled by the extrasynaptic NMDAR activity.

292 The parameter values of equations (12)-(15) are given in Table 2. We followed the order of magnitude
 293 between different receptor types [47,48]. The amplitude of PSPs and coupling strengths are chosen to
 294 achieve self-consistency. Stochastic differential equations were iterated using Euler-Maruyama method
 295 with a step size $dt = 10e-5$ second. Simulation files are available at
 296 <https://github.com/elifkoksal/plasticNMM>. Bifurcation analysis was done with AUTO-07p [50].

297

298 Reduced system of physiological plasticity

299 The system of equations describing the physiological plasticity is a multiple timescale system with
 300 $(\tau_d, \tau_f) < \tau_{ca} < \tau_\rho < \tau_U = \tau_{C_{AMPA}}$ (Table 1). We benefit from the multiple timescale structure of (9) to
 301 reduce the complexity of the full model to a lower dimensional system of equations for analyzing the
 302 synaptic plasticity in the long term. We use the elements from the singular perturbation theory to
 303 decompose the system into fast and slow subsystems and focus on the dynamic in the slow regime. We

304 assume that the slow regime is governed by the variables concerning LTP/LTP and consolidation, e.g.
 305 $(\rho, U_s, \tilde{C}_{AMPA})$. In the slow regime, the fast variables describing STP, $r^{(1)}$ and $u^{(1)}$, are slaved to the slow
 306 variables, as:

$$r^{(1)s} = \frac{1}{1 + \tau_d u^{(1)s} F_p^{(1)}}, \quad u^{(1)s} = \frac{U_s(1 + \tau_f F_p^{(1)})}{1 + \tau_f U_s F_p^{(1)}}$$

307 where superscript $(.)^s$ indicates the slow regime. The NMDA-mediated calcium dynamics in the slow
 308 regime is given by

$$309 \quad [Ca]^s = \tau_{ca} G(F_p^{(1)}) h_{ca} H(V_p^{(2)}) = \tau_{ca} C_{NMDA} y_{NMDA}(t) h_{ca} H(V_p^{(2)}).$$

310 If the NMDAergic-EPSP $y_{NMDA}(t)$ is approximated by $y_{NMDA} \approx \tau_{NMDA} A_{NMDA}^{(2)} r^{(1)s} u^{(1)s} F_p^{(1)}$ and the
 311 AMPAergic-EPSP $y_{AMPA}(t)$ by, $y_{AMPA} \approx \tau_{AMPA} A_{AMPA}^{(2)} r^{(1)s} u^{(1)s} F_p^{(1)}$, the postsynaptic potential $V_p^{(2)}$
 312 reads

$$313 \quad V_p^{(2)} = \Sigma(C_{k,p}^{(2)} y_k^{(2)}) + \tilde{C}_{AMPA} \tau_{AMPA} A_{AMPA}^{(2)} r^{(1)s} u^{(1)s} F_p^{(1)} + C_{NMDA} \tau_{NMDA} A_{NMDA}^{(2)} r^{(1)s} u^{(1)s} F_p^{(1)}.$$

314 For the NMDA-mediated calcium entry and postsynaptic depolarization to occur, the postsynaptic
 315 membrane should be sufficiently depolarized, i.e. $V_p^{(2)} > V_{th}$. This depolarization depends on the
 316 AMPAergic input. Assuming that the postsynaptic system is balanced for $F_p^{(1)}$ and intra-population
 317 interactions are independent of the external input, i.e. $\Sigma(C_{k,p}^{(2)} y_k^{(2)}) = 0$, the postsynaptic polarization in
 318 response to the AMPAergic input from NMM₁ can be reduced to

$$319 \quad V_p^{(2)} \approx \tilde{C}_{AMPA} \tau_{AMPA} A_{AMPA}^{(2)} r^{(1)s} u^{(1)s} F_p^{(1)},$$

320 and the calcium concentration to

$$321 \quad [Ca]^s = C_{NMDA} \tau_{NMDA} A_{NMDA}^{(2)} r^{(1)s} u^{(1)s} F_p^{(1)} h_{ca}, \text{ if } V_p^{(2)} > V_{th}, \text{ otherwise } [Ca]^s \approx 0.$$

322 As the fast variables ($r^{(1)}, u^{(1)}, [Ca]$) are expressed as a function of the slow variables, $(\rho, U_s, \tilde{C}_{AMPA})$,
 323 the reduced (slow) system reads:

$$\frac{d\rho}{d\bar{t}} = (-\rho(1-\rho)(\rho_* - \rho) + (1-\rho)\Omega_p([Ca]) - \rho\Omega_d([Ca])), \quad (16a)$$

$$\frac{dU_s}{d\bar{t}} = \frac{\tau_\rho}{\tau_U} (U_s^d - U_s + \rho(U_s^p - U_s^d)). \quad (16b)$$

$$\frac{d\tilde{C}_{AMPA}}{d\bar{t}} = \frac{\tau_\rho}{\tau_{C_{AMPA}}} (C_{AMPA}^d - \tilde{C}_{AMPA} + \rho(C_{AMPA}^p - C_{AMPA}^d)), \quad (16c)$$

324 where $\bar{t} = \frac{t}{\tau_\rho}$. If $\frac{\tau_\rho}{\tau_U} = \frac{\tau_\rho}{\tau_{C_{AMPA}}} \ll 1$, then we can take them to zero limit and treat (U_s, \tilde{C}_{AMPA}) as

325 parameters to investigate the variation of ρ .

326 Results

327 Physiological plasticity

328 The model of physiological plasticity includes presynaptic STP, calcium-driven pre- and postsynaptic
 329 LTP/LTD and consolidation ((9), Fig 3A). These mechanisms run in different timescales, with STP being the
 330 fastest, and consolidation being the slowest. In Section Reduced system of physiological plasticity, we
 331 applied singular perturbation theory to obtain a reduced system of physiological plasticity. Here we
 332 assume that the timescales of calcium-driven long-term plasticity and consolidation are different enough
 333 ($\tau_\rho \ll \tau_U = \tau_{C_{AMPA}}$), to investigate the variation of ρ , which, in turn, controls the long-term variations in
 334 the neurotransmitter release probability, U_s , and the AMPARergic coupling strength, \tilde{C}_{AMPA} , by treating
 335 these two slow variables as parameters. For a simple investigation of ρ (16a) for $\frac{\tau_\rho}{\tau_U} = \frac{\tau_\rho}{\tau_{C_{AMPA}}} = 0$, we
 336 assume that $\tilde{C}_{AMPA} \approx C_{AMPA}^d + \kappa U_s$, ($\kappa > 0$), which is a reasonable assumption since both \tilde{C}_{AMPA} and
 337 U_s depend on ρ in the same manner. Figure 4(A) and (B) show $V_p^{(2)}$ and $[Ca]^s$ as a function of $F_p^{(1)}$ and
 338 U_s with the parameter set given in Table 1. The postsynaptic subpopulation depolarizes monotonically
 339 for increasing $F_p^{(1)}$ and U_s (Fig 4A). The change in the calcium concentration follows a sigmoidal shape
 340 (Fig 4B). It remains close to zero for low values of U_s and $F_p^{(1)}$. It increases sharply for medium values of
 341 U_s and $F_p^{(1)}$, then slowly for higher values of U_s and $F_p^{(1)}$ as it approaches a plateau.

342

343 **Fig 3. Physiological plasticity at presynaptic and postsynaptic sites.** (A) Presynaptic glutamatergic
344 release and subsequent postsynaptic depolarization results in calcium influx via NMDARs. Calcium
345 signaling activates independent biochemical pathways, leading to postsynaptic and presynaptic long-term
346 changes due to the insertion of new AMPARs and an increase in vesicle release probability. Under
347 physiological conditions, excitation is balanced by sufficient chloride trafficking through GABAR and KCC2.
348 (B) Pathological plasticity at postsynaptic site. When the released glutamate is too high to be used by
349 synaptic AMPAR and NMDAR, it diffuses to the extrasynaptic site and activates the extrasynaptic NMDAR.
350 Activation of NMDAR causes internalization of extrasynaptic GABAR. Calcium influx via the extrasynaptic
351 NMDAR activates calpain that perturbs the KCC2 functioning.

352 **Fig 4. Postsynaptic depolarization, calcium concentrating and long-term plasticity in the slow regime.**

353 (A) Postsynaptic polarization $V_p^{(2)}$ and (B) calcium concentration $[Ca]^s$ as a function of $(F_p^{(1)}, U_s)$ for the
354 parameter set given in Table 1 and $\gamma_p = 2$. (C) Equilibrium points of (16a) as function of $(F_p^{(1)}, U_s)$ for
355 different values of (θ_p, θ_d) . In the blue regions (16a) has three equilibrium points at $\rho_{1,2,3}^* \in [0, 1]$, a
356 single equilibrium point at $\rho^* = 0$ in the salmon regions, and a single equilibrium point at $0.5 < \rho^* \leq 1$ in
357 the red regions.

358

359 We then compute the equilibrium points of (16) for $\frac{dU_s}{d\bar{t}} = \frac{d\tilde{c}_{AMPA}}{d\bar{t}} = 0$. In the absence of any pre- or
360 postsynaptic activity, (16a) has three equilibrium points at $\rho^* = \{0, 0.5, 1\}$ with $\rho^* = \{0, 1\}$ being stable
361 and $\rho^* = 0.5$ unstable. If the variations in U_s and $F_p^{(1)}$ are not sufficient to change the number of
362 equilibrium points of (16a), the depressed synapses will remain depressed, and the potentiated ones will
363 remain potentiated. Otherwise, (16a) has a single stable equilibrium point, such that, the synapses will
364 either depress or potentiate. Figure 4C shows ρ^* as a function of $(U_s, F_p^{(1)})$ as the LTD and LTP thresholds,
365 θ_d and θ_p , vary on the calcium concentration surface (Fig 4B). The dark blue regions indicate that (16a)
366 has three equilibrium points at $\rho^* = \{0, 0.5, 1\}$, therefore, the synapses do not change. When the

367 potentiation threshold θ_p is too high ($\theta_p = 1.5$, upper panels), the depressed state (salmon regions) is
368 the only attractor for moderate to high input firing rates $F_p^{(1)}$ and release probability U_s depending on
369 θ_d . Lowering the potentiation threshold θ_p introduces a range of $(U_s, F_p^{(1)})$ for which the potentiated
370 state is an attractor (red regions in Fig 4C for $\theta_p = \{0.4, 0.7\}$). Consequently, both depressed and
371 potentiated synapses are preserved for a low presynaptic activity. Lowering the potentiation threshold
372 expands the range of LTP and, increasing θ_d shrinks the LTD range.

373

374 Physiological plasticity under epileptic activity

375 In our model, long-term plasticity depends on the time lag between the interictal spikes of NMM₁ and
376 NMM₂, as well. Here, the term “spike” refers to shape of the model output assumed as the sum of the
377 input signals to the subpopulation P of NMM_i (see Section The revisited neural mass model). In this
378 section we assume that only the physiological synaptic plasticity mechanism (Fig 3A) is active. Figure 5
379 exemplifies how ρ changes in response to single spikes of NMM₁ and NMM₂ elicited by a pulse
380 stimulation when ρ is initiated at $\rho(0) = 0.5$. The synaptic variable ρ potentiates regardless of the pulse
381 delay for $(\theta_d, \theta_p) = (0.6, 0.7)$, depresses $(\theta_d, \theta_p) = (0.1, 0.7)$ (Fig 5A). We obtain a depression-
382 potentiation-depression curve of $\Delta\rho$ for $(\theta_d, \theta_p) = (0.3, 0.7)$, for which the system response is shown in
383 Figure 5B-D. When NMM₂ spikes $\Delta t = 0.02 \text{ sec}$ before NMM₁, the calcium concentration stays
384 between (θ_d, θ_p) and ρ decreases (Fig 5B). When NMM₂ and NMM₁ spike simultaneously, the calcium
385 concentration exceeds θ_p and ρ increases (Fig 5C). Finally, when NMM₂ spikes $\Delta t = 0.02 \text{ sec}$ after
386 NMM₁, ρ decreases since the calcium concentration stays between (θ_d, θ_p) (Fig 5D).

387

388 **Fig 5. Change in synaptic efficacy under epileptic spikes.** (A) Rate of change in the synaptic efficacy
389 variable ρ under single epileptic spike in NMM₁ and NMM₂ when the system (9)-(11) is initialized from
390 $\rho(0) = 0.5$ with $(U_s, \tilde{C}_{AMPA}) = (U_s^d, C_{AMPA}^d)$. Epileptic spikes are triggered by a pulse stimulation

391 applied with a time delay of Δt (sec) for $(\theta_d, \theta_p) = (0.6, 0.7)$ (green line), $(\theta_d, \theta_p) = (0.3, 0.7)$ (orange
392 line) and $(\theta_d, \theta_p) = (0.1, 0.7)$ (blue line). (B-D) Pre- and post-spiking is triggered by a single pulse with
393 $\Delta t = -0.02$ sec in (B), $\Delta t = 0$ in (C) and $\Delta t = 0.02$ in (D) for $(\theta_d, \theta_p) = (0.3, 0.7)$. The corresponding
394 behaviour of $[Ca]$ and ρ are shown in the middle and bottom panels, respectively. The orange dotted and
395 green dotted lines in the middle panels mark θ_d and θ_p , respectively.

396

397 Depending on the potentiation and depression thresholds, and intrinsic dynamics of the interacting
398 populations, aperiodic but continuous interictal epileptic discharges can cause long-term changes in the
399 presynaptic release probability and coupling strength between the interacting populations (Fig 6). Here,
400 we assume that NMM₁ is in interictal spiking mode as in Fig 2B, and the less excitable NMM₂ responds to
401 NMM₁ by generating spikes. If the potentiation threshold is high, then initially depressed synapses
402 between NMM₁ and NMM₂ remain depressed. For a lower potentiation threshold, the depolarization in
403 NMM₂ is high enough to increase the calcium concentration above θ_p , hence causing a positive change in
404 the synaptic variable ρ ($\Delta\rho > 0$). If this regime is maintained long enough and (θ_d, θ_p) are in a suitable
405 range for LTP, ρ can cross the threshold separating depressed to potentiated states, and a pre- and
406 postsynaptic LTP occurs (Fig 6B). Because of the LTP, the time lag between the NMM₁ and NMM₂ spikes
407 decreases. In the same configuration but with potentiated synapses, increasing the difference between
408 θ_d and θ_p causes pre- and postsynaptic LTD since the calcium concentration remains in (θ_d, θ_p) (Fig 6C).
409 Consequently, the time lag between the NMM₁ and NMM₂ spikes increases. If both depression and
410 potentiation thresholds are high, despite the interaction between NMM₁ and NMM₂, synaptic variables
411 do not change.

412

413 **Fig 6. Physiological plasticity under interictal epileptic discharges.** (A) Potentiation of initially depressed
414 synapses for $(\theta_d, \theta_p) = (0.3, 0.4)$. (B) Depression of initially potentiated synapses for $(\theta_d, \theta_p) =$
415 $(0.1, 1.5)$.

416

417 Experimental studies suggest that a high rate of synchronized activity, during an epileptic seizure for
418 instance, increases the glutamate release. Indeed, the model also suggests that an increased firing rate
419 during a seizure in NMM_1 can drive the calcium concentration above θ_p , and cause LTP, while the
420 interictal activity with the same values of (θ_d, θ_p) does not change synaptic efficacy (Fig. 6A vs 7A).
421 Alternatively, if calcium concentration is already above θ_p , then the increased firing rate can accelerate
422 LTP in NMM_2 (Fig. 6B vs 7B). In Figure 7 the repeated seizures in NMM_1 are triggered by a stochastic input
423 to the $B^{(1)}$ variable.

424

425 **Fig 7. Impact of seizure to physiological plasticity.** Potentiation of depressed synapses for $(\theta_d, \theta_p) =$
426 $(0.3, 0.7)$ (A) and for $(\theta_d, \theta_p) = (0.3, 0.4)$ (B).

427

428 Expansion of the epileptogenic network

429 Physiological plasticity alone increases coupling strength by increasing the probability of
430 neurotransmitter release at the presynaptic site and inserting AMPAR at the postsynaptic site. Unless the
431 extrasynaptic NMDAR are activated at the postsynaptic site, the postsynaptic population can preserve its
432 excitation/inhibition balance, hence, does not undergo seizures. However, the extrasynaptic NMDAR
433 activation triggers different processes that disturb the excitation/inhibition balance by reducing the
434 effect of the GABAergic activity [7,51,52] (Fig 3B).

435 We assumed that the extrasynaptic NMDAR (14) subtype is activated after the synapses are potentiated,
436 i.e. for $U_s > 0.7$. The extrasynaptic NMDAR activity changes the amplitude of the PV interneurons and
437 the excitability of NMM_2 via the auxiliary variable $K(t)$ (15). We investigate the impact of these changes
438 in the whole model given by (9)-(15). We simulate the whole system (9)-(15) starting from the last point

439 of the solution in Fig 7B for $(\theta_d, \theta_p) = (0.3, 0.4)$. When NMM₁ undergoes seizures, and NMM₂ responds
 440 by epileptic spikes since NMM₂ has a low excitability. Activation of the extrasynaptic NMDAR drives the
 441 variable $K(t)$ to 0 as it causes "structural" changes within NMM₂. In particular, the amount of the
 442 GABAergic loss in NMM₂, which is represented by the parameter $k_B^{(2)}$, can decrease the excitability
 443 threshold of NMM₂ and cause seizures in NMM₂. The relation between the GABAergic loss and seizure in
 444 NMM₂ is represented in the phase space of $(B^{(2)}, n^{(2)})$ in Fig 8A, and the time traces are shown in Fig 8B.
 445 For $0 \leq k_B^{(2)} < 9.5$, the equilibrium point of the $(B^{(2)}, n^{(2)})$ -subsystem remains on the right of the critical
 446 point of the seizure transitions (i.e. right fold of the $B^{(2)}$ -nullcline). For $0 \leq k_B^{(2)} < 7.4$, NMM₂ responds
 447 to the seizures of NMM₁ by interictal spikes only. For $7.4 \leq k_B^{(2)} < 9.5$, the fluctuations in $K(t)$ due to the
 448 activity of NMM₁ cause $B^{(2)}$ to cross the critical point and to jump to the left branch of the $B^{(2)}$ -nullcline,
 449 which correspond to an ictal regime in NMM₂. After following the left branch of the $B^{(2)}$ -nullcline, $B^{(2)}$
 450 jumps back to the right branch of the $B^{(2)}$ -nullcline, hence NMM₂ to the interictal regime. For $9.5 \leq k_B^{(2)}$,
 451 NMM₂ generates spontaneous and periodic seizures as the equilibrium point of the $(B^{(2)}, n^{(2)})$ -
 452 subsystem passes to the left of the critical point of the seizure transition.

453

454 **Fig 8. Effect of the pathological plasticity on NMM₂.** (A) Phase portrait of $(B^{(2)}, n^{(2)})$ -subsystem showing
 455 the effect of the parameter $k_B^{(2)}$ on the excitability of NMM₂. NMM₂ crosses the critical point as $k_B^{(2)}$
 456 increases. (B) Time traces of $B^{(2)}$ shown in (A). (C) Normalized PSD of $V_p^{(2)}$ during seizures shows the
 457 effect of $k_G^{(2)}$ for $k_B^{(2)} = 9$. Gamma-band activity appears for $k_G^{(2)} > 8$. (D-E) Example time trace of (9)-
 458 (15). (D) Dynamics of NMM₁ that exhibits two seizures in $t = [160, 197]$ and in $t = [408, 447]$. (E)
 459 Dynamics of NMM₂ for $(k_B^{(2)}, k_G^{(2)}) = (0, 0)$. (F) Dynamics of NMM₂ for $(k_B^{(2)}, k_G^{(2)}) = (9, 20)$, where
 460 NMM₂ exhibits two seizures in $t = [180, 220]$ and in $t = [412, 451]$. (G) Time differences between the
 461 seizures exhibited by NMM.

462

463 One of the markers of the seizure onset zone in the case of focal epilepsy is the gamma-band activity
 464 observed at the seizure onset [45]. Parameter $k_G^{(2)}$ scales the impact of the variable $K(t)$, hence of the
 465 activation of extrasynaptic NMDAR, on the fast GABAergic interneurons. NMM₂ generates a gamma-band
 466 activity at the seizure onset for $k_G^{(2)} > 8$ as demonstrated in the power spectral density (PSD) of $V_p^{(2)}$
 467 during a seizure triggered by NMM₁ for $k_B^{(2)} = 9$ (Fig 8C). Figure 8E and F show the response of NMM₂ for
 468 $(k_B^{(2)}, k_G^{(2)}) = (0, 0)$ and $(k_B^{(2)}, k_G^{(2)}) = (9, 20)$ for the epileptic spikes and seizure of NMM₁,
 469 respectively. NMM₂ exhibits a seizure in $t = [180, 220]$ after spiking as a response to the first seizure in
 470 NMM₁ in $t = [160, 197]$, and a second one in $t = [412, 451]$ as a response to the second seizure in
 471 NMM₁ in $t = [408, 447]$. The time delay between the first seizure in NMM₁ and NMM₂'s response to it
 472 ($\Delta t_{seizure} = t_{seizure1}^{(1)} - t_{seizure1}^{(2)}$) varies between -25 sec and -20 sec, whereas the delay between the
 473 second seizure in NMM₁ and NMM₂'s response ($\Delta t_{seizure2} = t_{seizure2}^{(1)} - t_{seizure2}^{(2)}$) varies between -16
 474 sec and -1 sec (Fig. 8G). This variation in the response times is due to the difference between the
 475 pathological plasticity stages: the first seizure occurs in the early stage (before the transition from $K \approx 0$
 476 to $K \approx 1$ in (15)), whereas the second one is in the late stage (after the transition from $K \approx 0$ to $K \approx 1$ in
 477 (15)), highlighting the progressive nature of the condition and its impact on neural dynamics. We also
 478 notice that $\Delta t_{seizure}$ decreases with increasing $k_B^{(2)}$ (Fig. 8G), hence as NMM₂ loses its GABAergic
 479 integrity.

480

481 Activity in the secondary focus after silencing the epileptic zone

482 The activation of extrasynaptic NMDAR induces irreversible structural changes in NMM₂, in particular, in
 483 its GABAergic structure. How significant these changes are can be observed from the difference between
 484 the activities of NMM₁ and NMM₂. For this we compute the spike frequencies of NMMs before the first
 485 seizure in NMM₁ in $t = [0, 160]$, which corresponds to the beginning of the pathological plasticity
 486 process, and between the first and second seizures in NMM₁ in $t = [200, 400]$, which corresponds to the

487 late phase of the pathological plasticity process. The spike frequency of NMM₂ is computed for the
488 intervals $t = [0, 160]$ and $t = [210, 400]$, so after its response to the NMM₁'s seizures (Fig 9A). The spike
489 frequencies of NMM₁ in these time windows remain intact. The spike frequencies in NMM₂ are
490 indistinguishable from the ones of NMM₁ for $0 \leq k_B^{(2)} \leq 7$, but they are much higher for $k_B^{(2)} = \{8,9,10\}$.
491 This is because as $k_B^{(2)}$ increases, the excitability threshold of NMM₂ decreases and the amplitude of
492 fluctuations in $K(t)$ increases. These two actors trigger additional spikes (Fig 8E) and seizures in NMM₂
493 (Fig 8B for $k_B^{(2)} = 10$). Then the question is what happens to NMM₂ if NMM₁ is silenced. To answer this
494 question, we reinitiate the system (9)-(15) from the last points of the solutions in Figure 8 for $A^{(1)} = 0$
495 (Fig 9B-D). Removing the input from NMM₁ to NMM₂ abolishes interictal spikes in NMM₂ both for $k_B^{(2)} =$
496 9 and $k_B^{(2)} = 10$ and seizures for $k_B^{(2)} = 9$. If the GABAergic loss is important, as it is for $k_B^{(2)} = 10$,
497 stochastic inputs to $B^{(2)}(t)$ can trigger spontaneous seizures NMM₂, despite a completely silent NMM₁.

498

499 **Fig 9. Resection of the primary focus.** (A) Spike frequencies of NMM₁ and NMM₂ for different values of
500 $k_B^{(2)}$ before NMM₁'s first seizure between $t = [0, 160]$ and between NMM₁'s first and second seizures in
501 $t = [210, 400]$ in Figure 8. The simulations are continued starting from $t = 500 \text{ sec}$ of the solutions in
502 Figure 8. After the cessation of any form of activity in NMM₁ at $t = 500 \text{ sec}$ (B), NMM₂ stops exhibiting
503 seizures for $k_B^{(2)} = 9$ (C) but continues spontaneous seizures for $k_B^{(2)} = 10$ (D).

504 Discussion

505 In this study, we presented a neurophysiologically plausible NMM of physiological and pathological
506 plasticity under epileptic activity. Physiological plasticity takes into account short- and long-term
507 variations in the glutamatergic interactions at both presynaptic and postsynaptic sites. Pathological
508 plasticity considers GABAergic modulations at the postsynaptic site. Under epileptic activity, increased
509 connectivity strength resulting from the physiological plasticity triggers the pathological plasticity, which

510 can cause a secondary focus. These mechanisms have been implemented in an autonomous (self-driven)
511 NMM, which generates the typical focal seizure pattern from interictal to seizure termination.

512 In neurobiological studies, spillover has been observed during synchronous activation of a large number
513 of glutamatergic fibers [53]. NMMs, by definition, represent synchronous activity of a neural population
514 and therefore synchronicity is implicitly coded in the model [54]. Physiological synaptic plasticity in the
515 model integrates three main mechanisms. The first one is the presynaptic STP. The second one is the
516 calcium-mediated long-term synaptic plasticity that changes the probability of glutamate release at the
517 presynaptic site and insertion of AMPAR at the postsynaptic site. The third mechanism is the
518 consolidation of the long-term plasticity. Although the description of consolidation remained
519 phenomenological as in [30,32], its integration into the model allowed for a sustained change in synaptic
520 connectivity.

521 We assumed that presynaptic and postsynaptic long-term plasticity are proportional. While this
522 simplified assumption is true for retrograde nitric oxide signaling, retrograde endocannabinoid release
523 works in the opposite direction. Costa et al. [37] suggested a phenomenological model integrating the
524 effects of opposing proteins on long-term presynaptic plasticity. Such effects can be integrated in our
525 model, for instance, by introducing a second variable to track the calcium variations, which modifies the
526 neurotransmitter release probability.

527 Our approach of modeling NMDA currents is quasi-physiological, similar to [38], but without explicitly
528 modeling the magnesium gate. Yet, it does include the essential ingredients mediating the NMDAR
529 activity, which are the presynaptic release and postsynaptic potentiation. Conductance-based modeling
530 of synaptic receptors in the neural mass formulation has been proposed in [55], and more recently, in
531 [56]. While the conductance-based neural mass formulation may provide a more physiological way of
532 modeling neural dynamics, we argue that our approach is consistent with the neural mass formulation
533 we considered and captures the key ingredients necessary for the problem studied. Interictal epileptic
534 discharges in the presynaptic population and the postsynaptic response to them can induce LTP or LTD

535 depending on the plasticity thresholds. The synchronization between pre- and postsynaptic interictal
536 epileptic discharges increases (decreases) with LTP (LTD). Ictal activity in the presynaptic population
537 speeds up the LTP process, and if frequent, it can cause a transition from LTD-trend to LTP-trend. LTP
538 then triggers pathological mechanisms as the postsynaptic region receives higher glutamatergic input
539 from the presynaptic region. The model suggests that preventing LTP by targeting both the presynaptic
540 region (decreasing the epileptic activity) and postsynaptic region (blocking NMDA receptors, increasing
541 the potentiation threshold, or applying GABAergic agonists, etc.) can be crucial to avoid pathological
542 consequences.

543 The pathological plasticity under epileptic activity includes disruption of the GABAergic pathway caused
544 by the activation of the extrasynaptic NMDAR. The model captures possible changes without detailing
545 the process, such as how calcium entry through the extrasynaptic NMDAR acts on calpain, how a
546 decreasing number of KCC2 changes the GABA reversal potential, or how GABAR expression is
547 downregulated, etc. Rather, the impact of the extrasynaptic NMDAR activation is reflected by the
548 auxiliary variable $K(t)$ that acts on the perisomatic and dendritic GABAergic interneurons of the NMM.
549 The former mimics the effect of KCC2 downregulation at the level of interactions between PV
550 interneurons and from PV interneurons to PYR cells that induces a gamma-band activity, which is
551 considered a signature of an epileptogenic zone in focal seizures [57–59]. The latter mimics the effect of
552 GABAR downregulation that reduces the excitability threshold of the population targeted by the epileptic
553 population. Indeed, the dendritic SOM interneurons control the calcium dynamics, for instance by
554 directly inhibiting calcium influx [60–62]. Low dendritic SOM projection may lead to accumulation of
555 intracellular calcium and aggravate KCC2 dysfunctions. The impact of the extrasynaptic NMDAR activation
556 on the GABAergic system is scaled in the model. This scaling factor can be interpreted as an intrinsic
557 property of the region subject to epileptic activity that can maintain the GABAergic integrity. In our
558 simulations, we observe a delay between the seizures when a seizure in the postsynaptic region is
559 triggered by a presynaptic seizure. Such propagation delays have been reported in animal models of focal
560 epilepsy [63], and interestingly, it can decrease during epileptogenesis [64].

561 In this study we extended a widely used model of the hippocampus [40] for ensuring autonomous
562 epileptic activity from interictal to ictal and seizure termination. Essentially, this was achieved by
563 introducing a slow subsystem that modulates the IPSP amplitude of the slow GABAergic interneurons. In
564 other words, we introduced a slow-fast process for obtaining an autonomous interictal-to-ictal transition.
565 Except for very few studies [58,65], the parameter variations leading to an interictal-to-ictal transition
566 has been performed manually, in particular by varying the IPSP amplitude of the slow GABAergic
567 interneurons. In [57,58] a dynamic chloride accumulation in pyramidal neurons caused by GABAergic
568 activity modulates the IPSP amplitude. However, the authors of [58] do not propose a mechanism for
569 seizure termination. In [65] this modulation was obtained through feedback from the activity of the
570 pyramidal cells. Our approach is similar to the phenomenological approach of [65], except the feedback
571 from the pyramidal neurons and the dimension of the slow subsystem. In the transition to seizures, not
572 only pyramidal neurons but also interneurons can play a critical role [66]. Our model can be improved
573 further to reflect the involvement of specific cellular and network mechanisms by considering
574 appropriate feedback mechanisms. Furthermore, the fast-system representing neuronal subpopulations
575 and the slow-subsystem controlling the excitability and the IPSP amplitude have the essential ingredients
576 for studying different bifurcation types, which can be inherent to specific seizure types (absence seizures,
577 focal seizures) with different seizure onset patterns [45]. Furthermore, the slow-fast system can be used
578 to study the effect of electrical stimulation that is a general procedure in clinics to understand the
579 excitability of the brain region to identify epileptogenic networks.

580 Our study of secondary epileptogenesis confirms the so-called *seizures can beget seizures* phenomena:
581 epileptic activity in one brain region can recruit healthy regions and cause the formation of a complex
582 epileptic network [67]. The model suggests that epileptic seizures boosts physio-pathological plasticity, as
583 suggested in the literature [8,68]. Once a healthy zone is driven to the critical point, then it generates
584 epileptic discharges and/or seizures. The phenomenon of secondary epileptogenesis was first
585 demonstrated in animal models [49], including: (1) the electrical stimulation kindling-like model in frogs,
586 rabbits, rats, guinea pigs, and cats; (2) the kainic acid model in rats and mice; and (3) several others [27].

587 In humans, this phenomenon is not rare in clinical practice [27], and it can be related to the organization
588 of epileptic networks. The network concept in epilepsy is a key factor in identifying the anatomic
589 distribution of the epileptogenic process and in the clinical expression of dynamic course of seizures
590 [69,70]. For example, development of the epileptic networks in temporal lobe epilepsy is correlated with
591 time (epilepsy duration) and has been argued to be due to secondary epileptogenesis processes [71,72].
592 Therefore, the timing of interference with epileptic activity may be critical [73]. Indeed, in clinical
593 practice, acute symptomatic seizures are treated with anti-seizure medication [74]. Furthermore, the
594 secondary epileptogenesis is not only limited to the “creation” of a secondary focus or the expansion of
595 an epileptic network but also to the expansion of the dysfunctional tissues. For instance, the epileptic
596 zone can be larger than MRI-visible lesion, which can require larger resections than the lesion [75,76], and
597 related the abnormalities in surrounding cortex [77]. In addition to the role of epileptic activity in
598 epileptogenesis, epileptic activity can interfere with physiological oscillatory activity in distributed neural
599 networks and cause cognitive comorbidity [78–82]. Generalizing our model to personalized dynamic
600 brain network modeling for planning the treatment of epilepsy is a future research direction [83].

601 On the other hand, epilepsy is a complex and patient-specific disease, and it is challenging to propose a
602 “one-fits-all” theory. The “seizures beget seizures” phenomenon has been questioned recently [84,85].
603 The correlation between epilepsy duration and number of high epileptogenic structures was not reported
604 for every case. This suggests that mechanisms of epileptic network's extension (and most likely of
605 secondary epileptogenesis) rely on many factors, such as the intrinsic properties of underlying lesion and
606 the anatomical substrate of the location of the primary epileptogenic zone. Our model has many
607 limitations to address this challenge. First, it only considers glutamatergic plasticity mediated by epileptic
608 activity between unidirectionally coupled neuronal populations. A growing body of literature suggests
609 that inhibitory GABAergic synapses exhibit long-term plasticity, which can have a protective role against
610 the expansion of epileptogenic networks [86,87]. Local GABAergic mechanisms, such as blanket inhibition
611 [88,89] and local circuitry [90], can serve to balance excitation and prevent epilepsy. The model does not
612 address mGluR mediated plasticity [91,92], homeostatic effects [93,94] or other mechanisms, such as

613 epigenetic changes [95]. Another limiting factor can be the structural and pathological differences
614 between the primarily and secondary regions. Indeed, the impact of the pathological changes are scaled
615 in the model, which can be considered to study the propagation of the epileptic activity in a network of
616 connected nodes with different levels of GABAergic integrity. Yet here, we restricted ourselves to a
617 minimal network of glutamatergic feedforward connectivity, where the projection is unidirectional on
618 excitatory neuronal subpopulation. The glutamatergic interactions between brain regions are often
619 bidirectional targeting inhibitory interneurons. As for the inhibitory neuron, recent studies suggest long-
620 range inhibitory projections [96,97]. These inhibitory/excitatory bidirectional interactions would
621 eventually impact the network dynamics under epileptic activity. In addition, the considered NMM is the
622 simplest formulation for the CA1 region of the hippocampus. A laminar NMM can be considered for the
623 distant synaptic rules related to dendritic location, which can be useful for studying the plasticity induced
624 in neocortical regions by non-invasive brain stimulation. Modeling experimental recording could be an
625 asset. Finally, the model simulates epileptiform discharges, whereas the physiological plasticity is also
626 mediated by theta rhythm and theta-gamma oscillations in the hippocampus [98]. These points will be
627 addressed in future works.

628 Conclusion

629 We have proposed a framework based on neural mass modeling for studying physio-pathological
630 plasticity under epileptic activity. We have shown how increased connectivity between an epileptic and
631 non-epileptic brain regions leads to GABAergic dysfunctions in the latter, and it forms an epileptogenic
632 network. Our study can benefit the development of *plastic* large-scale brain models for studying the
633 expansion of epileptogenic networks, formation of secondary foci, and the design of invasive or non-
634 invasive brain stimulation protocols to control the epileptogenic networks.

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861

862 Supporting information captions

863 **S1 Fig. Dynamics of NMM_1 and NMM_2 during the interictal phase under a unidirectional interaction**

864 **from NMM_1 to NMM_2 for the parameter set given in Table 2 of the main text.** (A) Bifurcation diagram of

865 NMM_1 where the amplitude of $y_p^{(1)}$ is presented as a function of $B^{(1)}$. The blue curve shows the branch of

866 equilibrium points (bold for stable and dashed for unstable equilibrium points). The red curves show the

867 amplitude of $y_p^{(1)}$ in the oscillatory regime. The Hopf bifurcations along the branch of equilibrium points

868 are denoted by red dots and saddle-node bifurcation by blue dots. The dynamical regimes that

869 correspond to the fast onset, ictal and interictal periods are marked by purple, yellow and cyan patches,

870 respectively. The time solution (black curve) is superimposed on the bifurcation diagram. (B) Time trace

871 for $V_p^{(1)}$ showing interictal spikes. (C) Phase plane of the $(B^{(1)}, n^{(1)})$ -subsystem with the $B^{(1)}$ -nullcline

872 (blue curve, bold for stable and dashed for branches) and the $n^{(1)}$ -nullcline (orange curve). The $B^{(1)}$

873 values that correspond to the dynamical regimes in (A) are marked by the same color code. The time

874 solution (black curve) is superimposed on the phase plane. (E) Bifurcation diagram of the uncoupled

875 NMM_2 where the amplitude of $y_p^{(2)}$ is presented as a function of $B^{(2)}$. The blue curve shows the branch of

876 equilibrium points (bold for stable and dashed for unstable equilibrium points). The red curves show the

877 amplitude of $y_p^{(2)}$ in the oscillatory regime. The Hopf bifurcations along the branch of equilibrium points

878 are denoted by red dots and saddle-node bifurcation by blue dots. The dynamical regimes that
879 correspond to the oscillatory states is marked in yellow, the steady states in orange for low values of $B^{(2)}$
880 and in cyan for high values of $B^{(2)}$. The time solution (black curve) is superimposed on the bifurcation
881 diagram. (F) Time trace for $V_p^{(2)}$ showing interictal spikes. (G) Phase plane of the $(B^{(2)}, n^{(2)})$ -subsystem
882 with the $B^{(2)}$ -nullcline (blue curve, bold for stable and dashed for branches) and the $n^{(1)}$ -nullcline
883 (orange curve). The $B^{(2)}$ values that correspond to the dynamical regimes in (E) are marked by the same
884 color code. The time solution (black curve) is superimposed on the phase plane.

885

886 **S2 Fig. Dynamics of NMM₁ and NMM₂ during the ictal phase under a unidirectional interaction from**
887 **NMM₁ to NMM₂ for the parameter set given in Table 2 of the main text.** (A) Bifurcation diagram of
888 NMM₁ where the amplitude of $y_p^{(1)}$ is presented as a function of $B^{(1)}$. The blue curve shows the branch of
889 equilibrium points (bold for stable and dashed for unstable equilibrium points). The red curves show the
890 amplitude of $y_p^{(1)}$ in the oscillatory regime. The Hopf bifurcations along the branch of equilibrium points
891 are denoted by red dots and saddle-node bifurcation by blue dots. The dynamical regimes that
892 correspond to the fast onset, ictal and interictal periods are marked by purple, yellow and cyan patches,
893 respectively. The time solution (black curve) is superimposed on the bifurcation diagram. (B) Time trace
894 for $V_p^{(1)}$ showing interictal spikes. (C) Phase plane of the $(B^{(1)}, n^{(1)})$ -subsystem with the $B^{(1)}$ -nullcline
895 (blue curve, bold for stable and dashed for branches) and the $n^{(1)}$ -nullcline (orange curve). The $B^{(1)}$
896 values that correspond to the dynamical regimes in (A) are marked by the same color code. The time
897 solution (black curve) is superimposed on the bifurcation diagram. (E) Bifurcation diagram of the
898 uncoupled NMM₂ where the amplitude of $y_p^{(2)}$ is presented as a function of $B^{(2)}$. The blue curve shows
899 the branch of equilibrium points (bold for stable and dashed for unstable equilibrium points). The red
900 curves show the amplitude of $y_p^{(2)}$ in the oscillatory regime. The Hopf bifurcations along the branch of
901 equilibrium points are denoted by red dots and saddle-node bifurcation by blue dots. The dynamical
902 regimes that correspond to the oscillatory states is marked in yellow, the steady states in orange for low

903 values of $B^{(2)}$ and in cyan for high values of $B^{(2)}$. The time solution (black curve) is superimposed on the
904 phase plane. (F) Time trace for $V_p^{(2)}$ showing interictal spikes. (G) Phase plane of the $(B^{(2)}, n^{(2)})$ -
905 subsystem with the $B^{(2)}$ -nullcline (blue curve, bold for stable and dashed for branches) and the $n^{(1)}$ -
906 nullcline (orange curve). The $B^{(2)}$ values that correspond to the dynamical regimes in (A) are marked by
907 the same color code. The time solution (black curve) is superimposed on the phase plane.