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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  $\alpha_5$ GABA<sub>A</sub>  
64 receptors in the hippocampus. Overexpression of GluN2B NMDA receptors, which are located mostly in  
65 extrasynaptic regions, downregulates the expression of  $\alpha_5$ GABA<sub>A</sub> 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 GABA<sub>A</sub>, 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  $\rho$  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  $\tau_\rho$  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  $\tau_{ca}$  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  $\mu$  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,  $\tau_r$  is the recovery  
 130 timescale,  $\tau_f$  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  $\tau_U$  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
$\theta_d$	depression threshold	0.1
$\theta_p$	potentiation threshold	0.4
$\gamma_d$	depression amplitude	1
$\gamma_p$	potentiation amplitude	5
$\beta_d$	depression slope	80
$\beta_p$	potentiation slope	80
$\mu$	slope of NMDA-dependent postsynaptic depolarization	1
$V_{th}$	threshold of NMDA-dependent postsynaptic depolarization	5 V
$h_{ca}$	calcium current scaling factor	10
$\tau_d$	presynaptic short-term depression time constant	0.200 sec
$\tau_f$	presynaptic short-term facilitation time constant	0.05 sec
$\tau_{ca}$	the calcium influx decay time constant	0.05 sec
$\tau_\rho$	synaptic efficacy time constant	50 sec
$\tau_U$	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  $W/\tau_w t \exp(-t/\tau_w)$ , where  $W$  represents the average PSP amplitude and  $\tau_w$  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 <sub>$i$</sub>  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<sub>*i*</sub>. The net polarization of P  
 165 subpopulation of NMM<sub>*i*</sub>,  $V_p^{(i)}$ , reads,

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

166 for NMM<sub>1</sub>, and,

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

167 for NMM<sub>2</sub>, which is subject to the excitatory AMRAergic and NMDAergic signals from NMM<sub>1</sub> 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 NMM<sub>1</sub> and NMM<sub>2</sub> and the dynamics of NMM<sub>1</sub> in the interictal and**  
 173 **ictal regimes.** (A) Model diagram of unidirectionally coupled NMM<sub>1</sub> and NMM<sub>2</sub>. 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<sub>*i*</sub>, respectively. The PSP generated by a subpopulation  $k$  are denoted by  $y_k^{(i)}$ .  
 178 NMM<sub>2</sub> is subject to an excitatory input from NMM<sub>1</sub>, denoted by  $Input_{NMM_1 \rightarrow NMM_2}$ . (B-E) Dynamics of of  
 179 (10)-(11) for NMM<sub>1</sub> 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<sub>i</sub> 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 NMM<sub>1</sub> 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 <sub>1</sub>	NMM <sub>2</sub>
$A^{(i)}$	EPSP amplitude [mV]	5	5
$G^{(i)}$	IPSP <sub>PV</sub> amplitude [mV]	20	2
$\tau_a$	EPSP time constant [s]	0.01	0.01
$\tau_b$	IPSP <sub>SOM</sub> time constant [s]	0.03	0.03
$\tau_g$	IPSP <sub>PV</sub> 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 <sub>SOM</sub> amplitude [mV]	(11a)	
$n^{(i)}(t)$	Auxiliary variable	(11b)	
	Parameters of (11)	NMM <sub>1</sub>	NMM <sub>2</sub>
$p_1$	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
$\delta$	timescale parameter	50	50
$\varepsilon$	timescale parameter	0.05	0.05
	Variables of (12)-(15)	Equation number	
$y_{AMPA}(t)$	AMPAergic-EPSP emitted by the input from NMM <sub>1</sub> onto NMM <sub>2</sub>	(12)	
$y_{NMDA}(t)$	NMDAergic-EPSP emitted by the input from NMM <sub>1</sub> onto NMM <sub>2</sub>	(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 <sub>1</sub>	NMM <sub>2</sub>
$A_{AMPA}^{(2)}$	AMPAergic-EPSP amplitude [mV]	-	10
$A_{NMDA}^{(2)}$	NMDAergic-EPSP amplitude [mV]	-	2
$A_{NMDA,ext}^{(2)}$	Extrasynaptic NMDAergic-EPSP amplitude [mV]	-	1
$\tau_{AMPA}$	AMPAergic-EPSP time constant [s]	-	0.005
$\tau_{NMDA}$	NMDAergic-EPSP time constant [s]	-	0.02
$\tau_{NMDA,ext}$	Extrasynaptic NMDAergic-EPSP time constant [s]	-	0.04
$C_{NMDA}$	NMDAergic coupling coefficient	-	$C_{AMPA,min}$
$\tau_K$	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  $m_1$ ,  $p_1$ ,  $\delta$  and  $\epsilon$  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<sub>i</sub>. 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 NMM<sub>1</sub> and NMM<sub>2</sub>. 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 NMM<sub>2</sub> and its response to the epileptic  
 243 activity when coupled to NMM<sub>1</sub> (Fig 2) are given in S1 Figure and S2 Figure.

244

## 245 Modeling plasticity with coupled neural mass models

246 We consider two populations NMM<sub>1</sub> and NMM<sub>2</sub> modelled by the NMM formulation given in (10)-(11).

247 NMM<sub>2</sub> receives excitatory inputs from NMM<sub>1</sub> through AMPAergic and NMDAergic signaling. Let  $F_P^{(1)}$  be

248 the firing rate of the P subpopulation of the NMM<sub>1</sub>,  $r^{(1)}(t)$  and  $u^{(1)}(t)$  are the variables describing the

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

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

250 where  $\tau_{AMPA}$  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

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

252 where  $\tau_{NMDA}$  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 NMM<sub>1</sub>, 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 NMM<sub>2</sub> 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 NMM<sub>2</sub> 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 NMM<sub>1</sub> 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  $\rho$ .

## 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  $\rho$ , 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  $\rho$  (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  $\rho$  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  $(\theta_p, \theta_d)$ . 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  $\rho^*$  as a function of  $(U_s, F_p^{(1)})$  as the LTD and LTP thresholds,  
365  $\theta_d$  and  $\theta_p$ , 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  $\theta_p$  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  $\theta_d$ . Lowering the potentiation threshold  $\theta_p$  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  $\theta_d$  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 NMM<sub>1</sub> and  
376 NMM<sub>2</sub>, 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<sub>i</sub> (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  $\rho$  changes in response to single spikes of NMM<sub>1</sub> and NMM<sub>2</sub> elicited by a pulse  
380 stimulation when  $\rho$  is initiated at  $\rho(0) = 0.5$ . The synaptic variable  $\rho$  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 NMM<sub>2</sub> spikes  $\Delta t = 0.02$  sec before NMM<sub>1</sub>, the calcium concentration stays  
384 between  $(\theta_d, \theta_p)$  and  $\rho$  decreases (Fig 5B). When NMM<sub>2</sub> and NMM<sub>1</sub> spike simultaneously, the calcium  
385 concentration exceeds  $\theta_p$  and  $\rho$  increases (Fig 5C). Finally, when NMM<sub>2</sub> spikes  $\Delta t = 0.02$  sec after  
386 NMM<sub>1</sub>,  $\rho$  decreases since the calcium concentration stays between  $(\theta_d, \theta_p)$  (Fig 5D).

387

388 **Fig 5. Change in synaptic efficacy under epileptic spikes.** (A) Rate of change in the synaptic efficacy  
389 variable  $\rho$  under single epileptic spike in NMM<sub>1</sub> and NMM<sub>2</sub> 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  $\Delta t$  (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  $\rho$  are shown in the middle and bottom panels, respectively. The orange dotted and  
395 green dotted lines in the middle panels mark  $\theta_d$  and  $\theta_p$ , 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 NMM<sub>1</sub> is in interictal spiking mode as in Fig 2B, and the less excitable NMM<sub>2</sub> responds to  
401 NMM<sub>1</sub> by generating spikes. If the potentiation threshold is high, then initially depressed synapses  
402 between NMM<sub>1</sub> and NMM<sub>2</sub> remain depressed. For a lower potentiation threshold, the depolarization in  
403 NMM<sub>2</sub> is high enough to increase the calcium concentration above  $\theta_p$ , hence causing a positive change in  
404 the synaptic variable  $\rho$  ( $\Delta\rho > 0$ ). If this regime is maintained long enough and  $(\theta_d, \theta_p)$  are in a suitable  
405 range for LTP,  $\rho$  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 NMM<sub>1</sub> and NMM<sub>2</sub> spikes  
407 decreases. In the same configuration but with potentiated synapses, increasing the difference between  
408  $\theta_d$  and  $\theta_p$  causes pre- and postsynaptic LTD since the calcium concentration remains in  $(\theta_d, \theta_p)$  (Fig 6C).  
409 Consequently, the time lag between the NMM<sub>1</sub> and NMM<sub>2</sub> spikes increases. If both depression and  
410 potentiation thresholds are high, despite the interaction between NMM<sub>1</sub> and NMM<sub>2</sub>, 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  $\theta_p$ , and cause LTP, while the  
420 interictal activity with the same values of  $(\theta_d, \theta_p)$  does not change synaptic efficacy (Fig. 6A vs 7A).  
421 Alternatively, if calcium concentration is already above  $\theta_p$ , 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 NMM<sub>1</sub> undergoes seizures, and NMM<sub>2</sub> responds  
440 by epileptic spikes since NMM<sub>2</sub> has a low excitability. Activation of the extrasynaptic NMDAR drives the  
441 variable  $K(t)$  to 0 as it causes "structural" changes within NMM<sub>2</sub>. In particular, the amount of the  
442 GABAergic loss in NMM<sub>2</sub>, which is represented by the parameter  $k_B^{(2)}$ , can decrease the excitability  
443 threshold of NMM<sub>2</sub> and cause seizures in NMM<sub>2</sub>. The relation between the GABAergic loss and seizure in  
444 NMM<sub>2</sub> 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  $0 \leq k_B^{(2)} < 7.4$ , NMM<sub>2</sub> responds  
447 to the seizures of NMM<sub>1</sub> by interictal spikes only. For  $7.4 \leq k_B^{(2)} < 9.5$ , the fluctuations in  $K(t)$  due to the  
448 activity of NMM<sub>1</sub> 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 NMM<sub>2</sub>. 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 NMM<sub>2</sub> to the interictal regime. For  $9.5 \leq k_B^{(2)}$ ,  
451 NMM<sub>2</sub> 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 NMM<sub>2</sub>.** (A) Phase portrait of  $(B^{(2)}, n^{(2)})$ -subsystem showing  
455 the effect of the parameter  $k_B^{(2)}$  on the excitability of NMM<sub>2</sub>. NMM<sub>2</sub> 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 NMM<sub>1</sub> that exhibits two seizures in  $t = [160, 197]$  and in  $t = [408, 447]$ . (E)  
459 Dynamics of NMM<sub>2</sub> for  $(k_B^{(2)}, k_G^{(2)}) = (0, 0)$ . (F) Dynamics of NMM<sub>2</sub> for  $(k_B^{(2)}, k_G^{(2)}) = (9, 20)$ , where  
460 NMM<sub>2</sub> 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. NMM<sub>2</sub> 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 NMM<sub>1</sub> for  $k_B^{(2)} = 9$  (Fig 8C). Figure 8E and F show the response of NMM<sub>2</sub> 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 NMM<sub>1</sub>,  
 469 respectively. NMM<sub>2</sub> exhibits a seizure in  $t = [180, 220]$  after spiking as a response to the first seizure in  
 470 NMM<sub>1</sub> in  $t = [160, 197]$ , and a second one in  $t = [412, 451]$  as a response to the second seizure in  
 471 NMM<sub>1</sub> in  $t = [408, 447]$ . The time delay between the first seizure in NMM<sub>1</sub> and NMM<sub>2</sub>'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 NMM<sub>1</sub> and NMM<sub>2</sub>'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 NMM<sub>2</sub> 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 NMM<sub>2</sub>, in particular, in  
 483 its GABAergic structure. How significant these changes are can be observed from the difference between  
 484 the activities of NMM<sub>1</sub> and NMM<sub>2</sub>. For this we compute the spike frequencies of NMMs before the first  
 485 seizure in NMM<sub>1</sub> in  $t = [0, 160]$ , which corresponds to the beginning of the pathological plasticity  
 486 process, and between the first and second seizures in NMM<sub>1</sub> in  $t = [200, 400]$ , which corresponds to the

487 late phase of the pathological plasticity process. The spike frequency of NMM<sub>2</sub> is computed for the  
488 intervals  $t = [0, 160]$  and  $t = [210, 400]$ , so after its response to the NMM<sub>1</sub>'s seizures (Fig 9A). The spike  
489 frequencies of NMM<sub>1</sub> in these time windows remain intact. The spike frequencies in NMM<sub>2</sub> are  
490 indistinguishable from the ones of NMM<sub>1</sub> 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 NMM<sub>2</sub> decreases and the amplitude of  
492 fluctuations in  $K(t)$  increases. These two actors trigger additional spikes (Fig 8E) and seizures in NMM<sub>2</sub>  
493 (Fig 8B for  $k_B^{(2)} = 10$ ). Then the question is what happens to NMM<sub>2</sub> if NMM<sub>1</sub> 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 NMM<sub>1</sub> to NMM<sub>2</sub> abolishes interictal spikes in NMM<sub>2</sub> 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 NMM<sub>2</sub>, despite a completely silent NMM<sub>1</sub>.

498

499 **Fig 9. Resection of the primary focus.** (A) Spike frequencies of NMM<sub>1</sub> and NMM<sub>2</sub> for different values of  
500  $k_B^{(2)}$  before NMM<sub>1</sub>'s first seizure between  $t = [0, 160]$  and between NMM<sub>1</sub>'s first and second seizures in  
501  $t = [210, 400]$  in Figure 8. The simulations are continued starting from  $t = 500$  sec of the solutions in  
502 Figure 8. After the cessation of any form of activity in NMM<sub>1</sub> at  $t = 500$ sec (B), NMM<sub>2</sub> 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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## 638 References

- 639 1. Turrigiano GG, Nelson SB. Homeostatic plasticity in the developing nervous system. *Nat Rev*  
640 *Neurosci.* 2004 Feb;5(2):97–107.
- 641 2. Zhang W, Linden DJ. The other side of the engram: experience-driven changes in neuronal intrinsic  
642 excitability. *Nat Rev Neurosci.* 2003 Nov;4(11):885–900.
- 643 3. Abraham WC, Bear MF. Metaplasticity: the plasticity of synaptic plasticity. *Trends Neurosci.* 1996 Apr  
644 1;19(4):126–30.
- 645 4. Scimemi A. Structure, function, and plasticity of GABA transporters. *Front Cell Neurosci* [Internet].  
646 2014 [cited 2023 Dec 12];8. Available from:  
647 <https://www.frontiersin.org/articles/10.3389/fncel.2014.00161>
- 648 5. Hennequin G, Agnes EJ, Vogels TP. Inhibitory Plasticity: Balance, Control, and Codependence. *Annu*  
649 *Rev Neurosci.* 2017;40(1):557–79.
- 650 6. Chiu CQ, Barberis A, Higley MJ. Preserving the balance: diverse forms of long-term GABAergic  
651 synaptic plasticity. *Nat Rev Neurosci.* 2019 May;20(5):272–81.
- 652 7. Khalilov I, Holmes GL, Ben-Ari Y. In vitro formation of a secondary epileptogenic mirror focus by  
653 interhippocampal propagation of seizures. *Nat Neurosci.* 2003 Oct;6(10):1079–85.
- 654 8. Ben-Ari Y. Epilepsies and neuronal plasticity: for better or for worse? *Dialogues Clin Neurosci.* 2008  
655 Mar 31;10(1):17–27.
- 656 9. Ben-Ari Y, Holmes GL. Effects of seizures on developmental processes in the immature brain. *Lancet*  
657 *Neurol.* 2006 Dec 1;5(12):1055–63.
- 658 10. Citri A, Malenka RC. Synaptic Plasticity: Multiple Forms, Functions, and Mechanisms.  
659 *Neuropsychopharmacology.* 2008 Jan;33(1):18–41.
- 660 11. Zucker RS, Regehr WG. Short-Term Synaptic Plasticity. *Annu Rev Physiol.* 2002;64(1):355–405.
- 661 12. Malenka RC, Bear MF. LTP and LTD: An Embarrassment of Riches. *Neuron.* 2004 Sep 30;44(1):5–21.
- 662 13. Nevian T, Sakmann B. Spine Ca<sup>2+</sup> Signaling in Spike-Timing-Dependent Plasticity. *J Neurosci.* 2006 Oct  
663 25;26(43):11001–13.
- 664 14. Graupner M, Brunel N. Mechanisms of induction and maintenance of spike-timing dependent  
665 plasticity in biophysical synapse models. *Front Comput Neurosci* [Internet]. 2010 [cited 2022 May  
666 18];4. Available from: <https://www.frontiersin.org/article/10.3389/fncom.2010.00136>

- 667 15. Schulz PE. Long-term potentiation involves increases in the probability of neurotransmitter release.  
668 Proc Natl Acad Sci. 1997 May 27;94(11):5888–93.
- 669 16. Yang Y, Calakos N. Presynaptic long-term plasticity. Front Synaptic Neurosci [Internet]. 2013 [cited  
670 2023 Jan 24];5. Available from: <https://www.frontiersin.org/articles/10.3389/fnsyn.2013.00008>
- 671 17. Abegg MH, Savic N, Ehrenguber MU, McKinney RA, Gähwiler BH. Epileptiform activity in rat  
672 hippocampus strengthens excitatory synapses. J Physiol. 2004;554(2):439–48.
- 673 18. Goddard GV, Douglas RM. Does the Engram of Kindling Model the Engram of Normal Long Term  
674 Memory? Can J Neurol Sci J Can Sci Neurol. 1975 Nov;2(4):385–94.
- 675 19. Wu K, Castellano D, Tian Q, Lu W. Distinct regulation of tonic GABAergic inhibition by NMDA receptor  
676 subtypes. Cell Rep. 2021 Nov 9;37(6):109960.
- 677 20. Hardingham GE, Bading H. Synaptic versus extrasynaptic NMDA receptor signalling: implications for  
678 neurodegenerative disorders. Nat Rev Neurosci. 2010 Oct;11(10):682–96.
- 679 21. Lee HHC, Deeb TZ, Walker JA, Davies PA, Moss SJ. NMDA receptor activity downregulates KCC2  
680 resulting in depolarizing GABAA receptor-mediated currents. Nat Neurosci. 2011 Jun;14(6):736–43.
- 681 22. Kahle KT, Deeb TZ, Puskarjov M, Silayeva L, Liang B, Kaila K, et al. Modulation of neuronal activity by  
682 phosphorylation of the K–Cl cotransporter KCC2. Trends Neurosci. 2013 Dec 1;36(12):726–37.
- 683 23. Kahle KT, Khanna AR, Duan J, Staley KJ, Delpire E, Poduri A. The KCC2 Cotransporter and Human  
684 Epilepsy: Getting Excited About Inhibition. The Neuroscientist. 2016 Dec 1;22(6):555–62.
- 685 24. Wu C, Sun D. GABA receptors in brain development, function, and injury. Metab Brain Dis. 2015  
686 Apr;30(2):367–79.
- 687 25. Chen Q, He S, Hu XL, Yu J, Zhou Y, Zheng J, et al. Differential Roles of NR2A- and NR2B-Containing  
688 NMDA Receptors in Activity-Dependent Brain-Derived Neurotrophic Factor Gene Regulation and  
689 Limbic Epileptogenesis. J Neurosci. 2007 Jan 17;27(3):542–52.
- 690 26. Goldensohn ES. The Relevance of Secondary Epileptogenesis to the Treatment of Epilepsy: Kindling  
691 and the Mirror Focus. Epilepsia. 1984;25(s2):S156–68.
- 692 27. Shen Y, Gong Y, Ruan Y, Chen Z, Xu C. Secondary Epileptogenesis: Common to See, but Possible to  
693 Treat? Front Neurol [Internet]. 2021 [cited 2024 Jan 25];12. Available from:  
694 <https://www.frontiersin.org/articles/10.3389/fneur.2021.747372>
- 695 28. Kuang Y, Xu C, Zhang Y, Wang Y, Wu X, Wang Y, et al. Low-frequency stimulation of the primary focus  
696 retards positive transfer of secondary focus. Sci Rep. 2017 Mar 23;7(1):345.
- 697 29. Shouval HZ, Bear MF, Cooper LN. A unified model of NMDA receptor-dependent bidirectional  
698 synaptic plasticity. Proc Natl Acad Sci. 2002 Aug 6;99(16):10831–6.
- 699 30. Chindemi G, Abdellah M, Amsalem O, Benavides-Piccione R, Delattre V, Doron M, et al. A calcium-  
700 based plasticity model for predicting long-term potentiation and depression in the neocortex. Nat  
701 Commun. 2022 Jun 1;13(1):3038.

- 702 31. Kumar A, Mehta M. Frequency-Dependent Changes in NMDAR-Dependent Synaptic Plasticity. *Front*  
703 *Comput Neurosci* [Internet]. 2011 [cited 2022 May 18];5. Available from:  
704 <https://www.frontiersin.org/article/10.3389/fncom.2011.00038>
- 705 32. Graupner M, Brunel N. Calcium-based plasticity model explains sensitivity of synaptic changes to  
706 spike pattern, rate, and dendritic location. *Proc Natl Acad Sci*. 2012 Mar 6;109(10):3991–6.
- 707 33. Cai Y, Gavornik JP, Cooper LN, Yeung LC, Shouval HZ. Effect of Stochastic Synaptic and Dendritic  
708 Dynamics on Synaptic Plasticity in Visual Cortex and Hippocampus. *J Neurophysiol*. 2007  
709 Jan;97(1):375–86.
- 710 34. Inglebert Y, Aljadeff J, Brunel N, Debanne D. Synaptic plasticity rules with physiological calcium levels.  
711 *Proc Natl Acad Sci*. 2020 Dec 29;117(52):33639–48.
- 712 35. Shouval HZ, Castellani GC, Blais BS, Yeung LC, Cooper LN. Converging evidence for a simplified  
713 biophysical model of synaptic plasticity. *Biol Cybern*. 2002 Dec 1;87(5):383–91.
- 714 36. Senn W, Markram H, Tsodyks M. An Algorithm for Modifying Neurotransmitter Release Probability  
715 Based on Pre- and Postsynaptic Spike Timing. *Neural Comput*. 2001 Jan 1;13(1):35–67.
- 716 37. Costa RP, Froemke RC, Sjöström PJ, van Rossum MC. Unified pre- and postsynaptic long-term  
717 plasticity enables reliable and flexible learning. Nelson SB, editor. *eLife*. 2015 Aug 26;4:e09457.
- 718 38. Fung PK, Robinson PA. Neural field theory of calcium dependent plasticity with applications to  
719 transcranial magnetic stimulation. *J Theor Biol*. 2013 May 7;324:72–83.
- 720 39. Modolo J, Thomas A, Legros A. Neural mass modeling of power-line magnetic fields effects on brain  
721 activity. *Front Comput Neurosci* [Internet]. 2013 [cited 2023 Feb 24];7. Available from:  
722 <https://www.frontiersin.org/articles/10.3389/fncom.2013.00034>
- 723 40. Wendling F, Bartolomei F, Bellanger JJ, Chauvel P. Epileptic fast activity can be explained by a model  
724 of impaired GABAergic dendritic inhibition. *Eur J Neurosci*. 2002;15(9):1499–508.
- 725 41. Tsodyks M, Pawelzik K, Markram H. Neural Networks with Dynamic Synapses. *Neural Comput*. 1998  
726 May;10(4):821–35.
- 727 42. Markram H, Wang Y, Tsodyks M. Differential signaling via the same axon of neocortical pyramidal  
728 neurons. *Proc Natl Acad Sci*. 1998 Apr 28;95(9):5323–8.
- 729 43. Wang Y, Markram H, Goodman PH, Berger TK, Ma J, Goldman-Rakic PS. Heterogeneity in the  
730 pyramidal network of the medial prefrontal cortex. *Nat Neurosci*. 2006 Apr;9(4):534–42.
- 731 44. Sjöström PJ, Turrigiano GG, Nelson SB. Rate, Timing, and Cooperativity Jointly Determine Cortical  
732 Synaptic Plasticity. *Neuron*. 2001 Dec;32(6):1149–64.
- 733 45. Lagarde S, Buzori S, Trebuchon A, Carron R, Scavarda D, Milh M, et al. The repertoire of seizure onset  
734 patterns in human focal epilepsies: Determinants and prognostic values. *Epilepsia*. 2019  
735 Jan;60(1):85–95.
- 736 46. Köksal Ersöz E, Modolo J, Bartolomei F, Wendling F. Neural mass modeling of slow-fast dynamics of  
737 seizure initiation and abortion. *PLOS Comput Biol*. 2020 Nov 9;16(11):e1008430.

- 738 47. Zito K, Scheuss V. NMDA Receptor Function and Physiological Modulation. In: Squire LR, editor.  
739 Encyclopedia of Neuroscience [Internet]. Oxford: Academic Press; 2009 [cited 2023 Feb 3]. p. 1157–  
740 64. Available from: <https://www.sciencedirect.com/science/article/pii/B9780080450469012250>
- 741 48. Müller L, Tokay T, Porath K, Köhling R, Kirschstein T. Enhanced NMDA receptor-dependent LTP in the  
742 epileptic CA1 area via upregulation of NR2B. *Neurobiol Dis.* 2013 Jun 1;54:183–93.
- 743 49. Wilder BJ. The mirror focus and secondary epileptogenesis. In: International Review of Neurobiology  
744 [Internet]. Academic Press; 2001 [cited 2024 Jul 2]. p. 435–46. (Brain Plasticity and Epilepsy; vol. 45).  
745 Available from: <https://www.sciencedirect.com/science/article/pii/S0074774201450227>
- 746 50. Doedel EJ, Champneys A, Fairgrieve TF, Yu AB, Kuznetsov, A.P., Oldeman BE, et al. Auto-07p:  
747 Continuation and bifurcation software for ordinary differential equations [Internet]. 2007. Available  
748 from: <http://cmvl.cs.concordia.ca/auto/>
- 749 51. Szente MB, Boda B. Cellular mechanisms of neocortical secondary epileptogenesis. *Brain Res.* 1994  
750 Jun 20;648(2):203–14.
- 751 52. Gilmore R, Morris H, Van Ness PC, Gilmore-Pollak W, Estes M. Mirror focus: function of seizure  
752 frequency and influence on outcome after surgery. *Epilepsia.* 1994;35(2):258–63.
- 753 53. Arnth-Jensen N, Jabaudon D, Scanziani M. Cooperation between independent hippocampal synapses  
754 is controlled by glutamate uptake. *Nat Neurosci.* 2002 Apr;5(4):325–31.
- 755 54. Wendling F, Benquet P, Bartolomei F, Jirsa V. Computational models of epileptiform activity. *J*  
756 *Neurosci Methods.* 2016 Feb;260:233–51.
- 757 55. Moran RJ, Stephan KE, Dolan RJ, Friston KJ. Consistent spectral predictors for dynamic causal models  
758 of steady-state responses. *NeuroImage.* 2011 Apr 15;55(4):1694–708.
- 759 56. Sheheitli H, Jirsa V. Incorporating slow NMDA-type receptors with nonlinear voltage-dependent  
760 magnesium block in a next generation neural mass model: derivation and dynamics [Internet].  
761 bioRxiv; 2023 [cited 2023 Nov 23]. p. 2023.07.03.547465. Available from:  
762 <https://www.biorxiv.org/content/10.1101/2023.07.03.547465v1>
- 763 57. Kurbatova P, Wendling F, Kaminska A, Rosati A, Nabbout R, Guerrini R, et al. Dynamic changes of  
764 depolarizing GABA in a computational model of epileptogenic brain: Insight for Dravet syndrome. *Exp*  
765 *Neurol.* 2016 Sep;283:57–72.
- 766 58. Lopez-Sola E, Sanchez-Todo R, Lleal È, Köksal-Ersöz E, Yochum M, Makhalova J, et al. A personalizable  
767 autonomous neural mass model of epileptic seizures. *J Neural Eng.* 2022 Sep;19(5):055002.
- 768 59. Magloire V, Cornford J, Lieb A, Kullmann DM, Pavlov I. KCC2 overexpression prevents the paradoxical  
769 seizure-promoting action of somatic inhibition. *Nat Commun.* 2019 Mar 15;10(1):1225.
- 770 60. Marlin JJ, Carter AG. GABA-A Receptor Inhibition of Local Calcium Signaling in Spines and Dendrites. *J*  
771 *Neurosci.* 2014 Nov 26;34(48):15898–911.
- 772 61. Urban-Ciecko J, Barth AL. Somatostatin-expressing neurons in cortical networks. *Nat Rev Neurosci.*  
773 2016 Jul;17(7):401–9.

- 774 62. Goldberg JH, Lacefield CO, Yuste R. Global dendritic calcium spikes in mouse layer 5 low threshold  
775 spiking interneurons: implications for control of pyramidal cell bursting. *J Physiol*. 2004  
776 Jul;558(2):465–78.
- 777 63. Mihaly A, Szente M, Dubravcsik Z, Boda B, Kiraly E, Nagy T, et al. Parvalbumin- and calbindin-  
778 containing neurons express c-fos protein in primary and secondary (mirror) epileptic foci of the rat  
779 neocortex. *Brain Res*. 1997 Jun 27;761(1):135–45.
- 780 64. Dhaher R, Gruenbaum SE, Sandhu MRS, Ottestad-Hansen S, Tu N, Wang Y, et al. Network-Related  
781 Changes in Neurotransmitters and Seizure Propagation During Rodent Epileptogenesis. *Neurology*  
782 [Internet]. 2021 May 4 [cited 2024 Jul 16];96(18). Available from:  
783 <https://www.neurology.org/doi/10.1212/WNL.0000000000011846>
- 784 65. Desroches M, Faugeras O, Krupa M. Slow-Fast Transitions to Seizure States in the Wendling-Chauvel  
785 Neural Mass Model. *Opera Medica Physiol*. 2015 Dec 1;2(3–4):228–34.
- 786 66. Gnatkovsky V, Librizzi L, Trombin F, Curtis M de. Fast activity at seizure onset is mediated by  
787 inhibitory circuits in the entorhinal cortex in vitro. *Ann Neurol*. 2008;64(6):674–86.
- 788 67. Ben-Ari Y, Crepel V, Represa A. Seizures Beget Seizures in Temporal Lobe Epilepsies: The Boomerang  
789 Effects of Newly Formed Aberrant Kainatergic Synapses. *Epilepsy Curr*. 2008 May 1;8(3):68–72.
- 790 68. Ben-Ari Y, Dudek FE. Primary and Secondary Mechanisms of Epileptogenesis in the Temporal Lobe:  
791 There is a before and an After. *Epilepsy Curr*. 2010 Sep 1;10(5):118–25.
- 792 69. Bartolomei F, Lagarde S, Wendling F, McGonigal A, Jirsa V, Guye M, et al. Defining epileptogenic  
793 networks: Contribution of SEEG and signal analysis. *Epilepsia*. 2017;58(7):1131–47.
- 794 70. Lehnertz K, Bröhl T, Wrede R von. Epileptic-network-based prediction and control of seizures in  
795 humans. *Neurobiol Dis*. 2023 Jun 1;181:106098.
- 796 71. Bartolomei F, Cosandier-Rimele D, McGonigal A, Aubert S, Régis J, Gavaret M, et al. From mesial  
797 temporal lobe to temporoparietal seizures: A quantified study of temporal lobe seizure networks.  
798 *Epilepsia*. 2010;51(10):2147–58.
- 799 72. Bartolomei F, Chauvel P, Wendling F. Epileptogenicity of brain structures in human temporal lobe  
800 epilepsy: a quantified study from intracerebral EEG. *Brain*. 2008 Jul 1;131(7):1818–30.
- 801 73. Bjellvi J, Olsson I, Malmgren K, Wilbe Ramsay K. Epilepsy duration and seizure outcome in epilepsy  
802 surgery. *Neurology*. 2019 Jul 9;93(2):e159–66.
- 803 74. Mauritz M, Hirsch LJ, Camfield P, Chin R, Nardone R, Lattanzi S, et al. Acute symptomatic seizures: an  
804 educational, evidence-based review. *Epileptic Disord*. 2022;24(1):26–49.
- 805 75. Alashjaie R, Kerr EN, AlShoumer A, Hawkins C, Yau I, Weiss S, et al. Surgical outcomes in children with  
806 drug-resistant epilepsy and hippocampal sclerosis. *Epilepsy Res*. 2024 Jul 1;203:107367.
- 807 76. Ying Z, Wang I, Blümcke I, Bulacio J, Alexopoulos A, Jehi L, et al. A comprehensive clinico-pathological  
808 and genetic evaluation of bottom-of-sulcus focal cortical dysplasia in patients with difficult-to-  
809 localize focal epilepsy. *Epileptic Disord*. 2019;21(1):65–77.
- 810 77. Macdonald-Laurs E, Warren AEL, Lee WS, Yang JYM, MacGregor D, Lockhart PJ, et al. Intrinsic and  
811 secondary epileptogenicity in focal cortical dysplasia type II. *Epilepsia*. 2023;64(2):348–63.

- 812 78. Halász P, Bódizs R, Ujma PP, Fabó D, Szűcs A. Strong relationship between NREM sleep, epilepsy and  
813 plastic functions — A conceptual review on the neurophysiology background. *Epilepsy Res.* 2019 Feb  
814 1;150:95–105.
- 815 79. Gelinas JN, Khodagholy D, Thesen T, Devinsky O, Buzsáki G. Interictal epileptiform discharges induce  
816 hippocampal-cortical coupling in temporal lobe epilepsy. *Nat Med.* 2016 Jun;22(6):641–8.
- 817 80. Dahal P, Ghani N, Flinker A, Dugan P, Friedman D, Doyle W, et al. Interictal epileptiform discharges  
818 shape large-scale intercortical communication. *Brain.* 2019 Nov 1;142(11):3502–13.
- 819 81. Yu H, Kim W, Park DK, Phi JH, Lim BC, Chae JH, et al. Interaction of interictal epileptiform activity with  
820 sleep spindles is associated with cognitive deficits and adverse surgical outcome in pediatric focal  
821 epilepsy. *Epilepsia* [Internet]. 2023 [cited 2023 Nov 24];n/a(n/a). Available from:  
822 <https://onlinelibrary.wiley.com/doi/abs/10.1111/epi.17810>
- 823 82. Khalife MR, Scott RC, Hernan AE. Mechanisms for Cognitive Impairment in Epilepsy: Moving Beyond  
824 Seizures. *Front Neurol* [Internet]. 2022 [cited 2022 Aug 22];13. Available from:  
825 <https://www.frontiersin.org/articles/10.3389/fneur.2022.878991>
- 826 83. Dallmer-Zerbe I, Jiruska P, Hlinka J. Personalized dynamic network models of the human brain as a  
827 future tool for planning and optimizing epilepsy therapy. *Epilepsia.* 2023;64(9):2221–38.
- 828 84. Jiruska P, Freestone D, Gnatkovsky V, Wang Y. An update on the seizures beget seizures theory.  
829 *Epilepsia.* 2023;00(n/a):1–12.
- 830 85. Berg AT, Shinnar S. Do Seizures Beget Seizures? An Assessment of the Clinical Evidence in Humans. *J*  
831 *Clin Neurophysiol.* 1997 Mar;14(2):102.
- 832 86. Kullmann DM, Lamsa KP. Long-term synaptic plasticity in hippocampal interneurons. *Nat Rev*  
833 *Neurosci.* 2007 Sep;8(9):687–99.
- 834 87. Honoré E, Khlaifia A, Bosson A, Lacaille JC. Hippocampal Somatostatin Interneurons, Long-Term  
835 Synaptic Plasticity and Memory. *Front Neural Circuits* [Internet]. 2021 [cited 2023 Jul 28];15.  
836 Available from: <https://www.frontiersin.org/articles/10.3389/fncir.2021.687558>
- 837 88. Karnani MM, Agetsuma M, Yuste R. A blanket of inhibition: functional inferences from dense  
838 inhibitory connectivity. *Curr Opin Neurobiol.* 2014 Jun 1;26:96–102.
- 839 89. Wenzel M, Hamm JP, Peterka DS, Yuste R. Acute focal seizures start as local synchronizations of  
840 neuronal ensembles. *J Neurosci.* 2019 Aug 19;39:176–18.
- 841 90. Magloire V, Mercier MS, Kullmann DM, Pavlov I. GABAergic Interneurons in Seizures: Investigating  
842 Causality With Optogenetics. *The Neuroscientist.* 2019 Aug 1;25(4):344–58.
- 843 91. Zarnadze S, Bäuerle P, Santos-Torres J, Böhm C, Schmitz D, Geiger JR, et al. Cell-specific synaptic  
844 plasticity induced by network oscillations. *Bartos M, editor. eLife.* 2016 May 24;5:e14912.
- 845 92. Hadler MD, Tzilivaki A, Schmitz D, Alle H, Geiger JRP. Gamma-Oscillation Plasticity Is Mediated by  
846 Parvalbumin Interneurons [Internet]. *bioRxiv*; 2023 [cited 2023 Aug 25]. p. 2023.06.21.545901.  
847 Available from: <https://www.biorxiv.org/content/10.1101/2023.06.21.545901v1>
- 848 93. Litwin-Kumar A, Doiron B. Formation and maintenance of neuronal assemblies through synaptic  
849 plasticity. *Nat Commun.* 2014 Nov 14;5(1):5319.



- 850 94. Issa NP, Nunn KC, Wu S, Haider HA, Tao JX. Putative roles for homeostatic plasticity in  
851 epileptogenesis. *Epilepsia*. 2023;64(3):539–52.
- 852 95. Abraham WC, Jones OD, Glanzman DL. Is plasticity of synapses the mechanism of long-term memory  
853 storage? *Npj Sci Learn*. 2019 Jul 2;4(1):1–10.
- 854 96. Caputi A, Melzer S, Michael M, Monyer H. The long and short of GABAergic neurons. *Curr Opin  
855 Neurobiol*. 2013 Apr 1;23(2):179–86.
- 856 97. Cho KKA, Shi J, Phensy AJ, Turner ML, Sohal VS. Long-range inhibition synchronizes and updates  
857 prefrontal task activity. *Nature*. 2023 May;617(7961):548–54.
- 858 98. Bikbaev A, Manahan-Vaughan D. Relationship of hippocampal theta and gamma oscillations to  
859 potentiation of synaptic transmission. *Front Neurosci [Internet]*. 2008 [cited 2023 Mar 2];2. Available  
860 from: <https://www.frontiersin.org/articles/10.3389/neuro.01.010.2008>

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 NMM<sub>1</sub> and NMM<sub>2</sub> during the ictal phase under a unidirectional interaction from**  
887 **NMM<sub>1</sub> to NMM<sub>2</sub> for the parameter set given in Table 2 of the main text.** (A) Bifurcation diagram of  
888 NMM<sub>1</sub> 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 NMM<sub>2</sub> 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.