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1

# Anesthetic action on extra-synaptic receptors: effects in neural population models of EEG activity.

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General anesthesia: from theory to experiments

## 2 ABSTRACT

3 The role of extra-synaptic receptors in the regulation of excitation and inhibition in the brain  
4 has attracted increasing attention. Because activity in the extra-synaptic receptors plays a role in  
5 regulating the level of excitation and inhibition in the brain, they may be important in determining  
6 the level of consciousness. This paper reviews briefly the literature on extra-synaptic GABA  
7 and NMDA receptors and their affinity to anesthetic drugs. We propose a neural population  
8 model that illustrates how the effect of the anesthetic drug propofol on GABAergic extra-  
9 synaptic receptors results in changes in neural population activity and the electroencephalogram  
10 (EEG). Our results show that increased tonic inhibition in inhibitory cortical neurons cause a  
11 dramatic increase in the power of both  $\delta$  and  $\alpha$  bands. Conversely, the effects of increased tonic  
12 inhibition in cortical excitatory neurons and thalamic relay neurons have the opposite effect and  
13 decrease the power in these bands. The increased  $\delta$ -activity is in accord with observed data  
14 for deepening propofol anesthesia; but is absolutely dependent on the inclusion of extrasynaptic  
15 (tonic) GABA action in the model.

16 **Keywords:** GABA receptor, neural mass, propofol, power spectrum, general anesthesia

## 1 INTRODUCTION

17 General anesthesia is used daily to enable surgery, but its underlying mechanisms of action are still  
18 largely a mystery. In recent decades there have been successful efforts to reveal the drug action on  
19 single receptors (1, 2, 3), however their effect on neural populations, networks of neural populations,  
20 and brain areas, still remains unsolved. To explain the underlying neural mechanism during the loss  
21 of consciousness, two prominent hypotheses are the loss of integration information, developed by  
22 Tononi (4, 5, 6), and a sharp phase transition of the brain activity involving a drop of neural activity,  
23 put forward by Steyn-Ross et al. (7, 8). These hypotheses are not mutually exclusive. For instance,  
24 a recent experimental study on the effects of propofol on neural activity measured at various spatial  
25 scales (9) has revealed both decreased functional connectivity between brain areas and a dramatic  
26 drop of neuron firing rates after loss of consciousness. A large amount of experimental literature  
27 has revealed characteristic spectral signal changes in electroencephalographic data (EEG) and Local

28 Field Potentials (LFPs) during general anesthesia (10, 11, 9, 12, 13). Moreover, several previous  
29 theoretical studies have proposed neural models to explain certain EEG signal features observed during  
30 anesthesia (14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25). Although these studies may incorporate realistic  
31 neurobiological details of the brains' network topology and neuronal function, they have simplified  
32 dramatically the anesthetic action by considering only synaptic excitatory and inhibitory receptors. There  
33 is a growing amount of experimental research that has revealed the importance of extra-synaptic receptors  
34 (ESR) for neural interactions in general (3, 26), and for anesthesia especially, see (27, 2) and references  
35 therein.

36 To elucidate the role of ESR in the context of anesthesia, one approach might be to do a theoretical study  
37 of a realistic neural population model which reproduces the characteristic signal features observed in EEG.  
38 To perform such a theoretical study, it is necessary to incorporate physiological properties of extrasynaptic  
39 receptors into neural population models.

40

41 Gamma-aminobutyric acid (GABA) receptors are a large and important class of ionotropic receptors.  
42 These receptors are located in the neuron's membrane and respond to the neurotransmitter GABA by  
43 opening  $\text{Cl}^-$  channels and inducing an inward hyperpolarising membrane current. This response may  
44 either be: phasic at synaptic receptors or, tonic at ESR which lie distant from synaptic terminals (28, 29,  
45 30, 31, 32, 33). The phasic response evolves on a time scale of 10–200 ms whereas tonic response evolves  
46 on a much longer time scale (34, 35).

47 The precise biochemical origin of tonic inhibition is still heavily debated (36, 37). A rather simple and  
48 intuitive model explains the tonic current as a spillover of excess neurotransmitter from synapses. This is  
49 due to incomplete GABA uptake by nearby synaptic  $\text{GABA}_A$ -receptors. The remaining neurotransmitter  
50 is thus able to diffuse to more distant  $\text{GABA}_A$ -receptors via extracellular space (36, 31, 38, 39). This  
51 spillover may explain the longer time scale of tonic responses found experimentally. In addition, this  
52 explanation implies that even small concentrations of neurotransmitters are sufficient to generate tonic  
53 activity because of the high sensitivity of ESRs.

54 The effect of extra-synaptic receptors on the dendritic activity has not attracted much attention. This may  
55 because there are only a relatively small number of such receptors as compared to synaptic receptors (40,  
56 36). Moreover, only recently have experimental studies been able to classify and localize different sub-  
57 types of  $\text{GABA}_A$  receptors (31, 36).  $\text{GABA}_A$  receptors are pentameric ligand-gated ion channels and it  
58 has been found that  $\delta$ -sub units of  $\text{GABA}_A$  receptors occur exclusively at ESRs (32, 36, 41, 42, 43). This  
59 indicates a specific role of these receptors for the neural information processing in general with specific  
60 implications in diseases (3) and consciousness (40).

61 Tonic inhibition induced by extra-synaptic  $\text{GABA}_A$ -receptors represents a persistent increase in the  
62 cell membrane's conductance. On the single neuron level, this diminishes the membrane time constant  
63 and, consequently, reduces the size and duration of excitatory post-synaptic potentials propagating on  
64 the dendrite. Hence tonic inhibition reduces the excitability of the membrane and increases the effective  
65 firing threshold (36). At the neural population level, extra-synaptic receptors affect the excitability of  
66 interneuron-pyramidal cell networks and thus modify network oscillations (30). Kopanitsa (40) argues  
67 that the sustained spatially widespread tonic inhibition is energetically more effective for the system to  
68 diminish neural population activity than short-lasting local phasic inhibition, since lower neurotransmitter  
69 concentrations are sufficient. The critical factor in this mechanism is the the relatively high sensitivity of  
70 ESRs to modulations by anesthetic agents (36, 44, 28, 45). The brain areas that have been shown to be  
71 affected by anesthetic-induced tonic inhibition are the hippocampus (46), brain stem (47), cerebellum (45)  
72 and the thalamus (32). Since these areas are supposed to play a role in general anesthesia (2), extra-  
73 synaptic receptors may mediate clinical anesthetic effects, such as hypnosis and amnesia (48). Thus it is  
74 reasonable to argue that  $\text{GABA}_A$  ESRs set the background inhibition of neural populations and the brain  
75 network and mediate slow consciousness phenomena, such as loss of consciousness, sleep or arousal (40).

76

77 Converse to GABAergic receptors, N-methyl-D-aspartate (NMDA) receptors respond to the  
78 neurotransmitter glutamate by excitatory inward  $\text{Na}^+$  and  $\text{Ca}^{2+}$  currents and  $\text{K}^+$  outward currents. The

79 response of NMDA receptors to glutamate depends on their spatial location with respect to synaptic  
80 terminals and the presence of co-agonists. A recent experimental study has revealed that the population  
81 of NMDA receptors, which are close to synaptic terminals, are primarily activated by the co-agonist d-  
82 serine in the presence of glutamate; while extra-synaptic NMDA receptors (more distant from the synaptic  
83 terminals) respond primarily to glutamate and the co-agonist glycine (49, 50). D-serine and glycine are  
84 endogenous amino acids found naturally in the brain (d-serine is a derivative of glycine). Similar to  
85 GABAergic ESRs, it has been shown that there exists a significant ambient glutamate concentration which  
86 induces a tonic excitatory current (51, 52). This current is evoked primarily at extra-synaptic NMDA  
87 receptors (53) and may be regulated by other cells, such as neighbouring astrocytes (52, 54) which control  
88 glutamate uptake and also synthesize d-serine (55).

89 Commonly-used GABAergic anesthetic drugs directly modify the corresponding receptors. However  
90 various anesthetics are also known to affect the endogenous co-agonists of NMDA receptors (56, 49, 57).  
91 Hence, the possible anesthetic effect on NMDA receptors is more complex and indirect than for  
92 GABAergic ESRs. There is a large class of NMDA receptor antagonists, that inhibit the excitatory action  
93 of NMDA receptors. These anesthetics induce so-called dissociative anesthesia (58) leading to amnesia  
94 and analgesia without depressing respiration, but also characterised by distorted perceptions of sight and  
95 sound and feelings of dissociation from the environment. An example of a dissociative anesthetic drug  
96 is the inhalational anesthetic xenon which - amongst other actions - binds primarily to the extra-synaptic  
97 glycine site of NMDA receptors (59) and attenuates long term potentiation present in the hippocampus by  
98 reducing extrasynaptic receptor currents (60).

99

100 To understand how the anesthetic effect of extra-synaptic receptor activity on the microscopic single  
101 neuron scale could lead to changes in EEG and behavior that can be observed at macroscopic scales, it  
102 is necessary to establish a bridge between the two scales. This bridge may be formulated as a dynamical  
103 theoretical model. Neural population models represent a good candidate for a dynamic description of  
104 neural activity at an intermediate mesoscopic scale (61, 62, 63). These models describe properties of  
105 ensembles of neurons, such as the mean firing rate and the mean dendritic current (64), whilst their output  
106 variables can be strongly linked to macroscopic experimental quantities such as Local Field Potentials  
107 (LFPs) and EEG (63, 65). An increasing number of theoretical studies have used neural population  
108 models to describe signal features in LFPs and EEG observed during anesthesia (21, 17). Most of these  
109 studies take into account anesthetic action on excitatory and/or inhibitory synapses (14, 66, 7, 67, 68)  
110 while few consider extra-synaptic receptors (69). This link between the synaptic receptor properties in  
111 an ensemble of neurons and the average population dynamics is straight-forward, since classical neural  
112 population models already involve the average synaptic response function. The situation is different for  
113 extra-synaptic receptors, since their action is not incorporated into the classical models. A very recent  
114 work has filled this gap (24). This theoretical work demonstrated a method to include mathematically  
115 extra-synaptic GABA<sub>A</sub> receptor action in neural population models; which enables researchers to study  
116 how changing anesthetic extra-synaptic receptor action modifies spectral features in the EEG, which might  
117 then be observed experimentally.

118

119 The current work uses a cortico-thalamic neural population model involving anesthetic synaptic  
120 inhibition with a well-established connection topology; and then extends this model by including the  
121 effects of extra-synaptic GABAergic receptor action in the presence of the anesthetic drug propofol.  
122 With the help of this model, we demonstrate the role of extra-synaptic GABAergic inhibition, and the  
123 importance of tonic inhibition in the cortical inhibitory neuronal population, in explaining experimental  
124 EEG power spectra.

## 2 MATERIAL & METHODS

### EEG DATA

125 We re-analysed previously-obtained experimental data from subjects that had been given a short propofol  
 126 anesthetic. The details of the methods can be found in (70). In brief, after obtaining regional ethical  
 127 committee approval and written informed consent, five healthy subjects (mean age 27.7 yrs, four males)  
 128 were studied. They were on no psychoactive drugs and had been starved for at least 6 hours prior to  
 129 the study. They were monitored and managed as per clinical anesthesia, according to the Australia and  
 130 New Zealand College of Anaesthetists best practice guidelines. The induction consisted of an intravenous  
 131 infusion of propofol at 1500 mg/hr until the subject no longer responded to verbal command. Typically  
 132 this occurred about 5 minutes into the infusion. The estimated effect-site concentrations of propofol were  
 133 calculated using standard population-based pharmacokinetic models.

134 The EEG was acquired using the Electrical Geodesics 128 channel Ag/AgCl electrode system (Eugene,  
 135 CO, USA) referenced to Cz. Electrode impedances were below 30 KOhm (100 MOhm input impedance  
 136 amplifier). The sampling frequency was 250 Hz, with a 0.1 – 100 Hz analogue band pass filter, and A-D  
 137 conversion was at 12 bits precision. The EEG data were re-referenced to a grand mean, and band-pass  
 138 filtered using 3-rd order Butterworth filters 0.2 – 45 Hz to eliminate line-noise. An additional Whittaker  
 139 filter was applied to reduce movement and blink artifacts. The power in each frequency was obtained  
 140 applying a short-time Fourier transform with a moving window of 60 sec and 54 sec overlap. The power  
 141 spectra have been computed 1 min before infusion start ( $t = 1$  min) and 4 min after infusion ( $t = 5$   
 142 min). For visualization reasons, these power spectra at different time instances have been smoothed by a  
 143 running average over frequencies with a 1 Hz window and a 0.017 Hz frequency step.

### THALAMO-CORTICAL MODEL

144 The body of the model (71, 72) is based on a population-level description of a single thalamo-cortical  
 145 module comprising four populations of neurons, namely excitatory (E) and inhibitory (I) cortical  
 146 population, a population built of thalamo-cortical relay neurons (S) and of thalamic reticular neurons  
 147 (R). The details of the model and the nominal parameter values are taken from a previous work (72, 73).  
 148 This model is based on the original idea of Lopes da Silva et al., stating that the  $\alpha$ -rhythm represents  
 149 the noisy thalamic input signal band-pass filtered by feedback-connected cortical and thalamic neural  
 150 populations (74). Here we just briefly describe the key concepts of the model. The average soma  
 151 membrane potential denoted by  $V_a$ , for  $a = E, I, S, R$  is modeled by

$$V_a(t) = \sum_{b=E,I,R,S} h_b(t) \otimes \nu_{ab} \phi_b(t - \tau_{ab}), \quad (1)$$

152 where  $\otimes$  represents the temporal convolution,  $h_b(t) = H_b \bar{h}_b(t)$  where  $\bar{h}_b(t)$  denotes the mean synaptic  
 153 response function defined by

$$\bar{h}_b(t) = \frac{\alpha \beta_b}{\alpha - \beta_b} \left( e^{-\beta_b t} - e^{-\alpha t} \right), \quad (2)$$

154 and  $\alpha$  and  $\beta_b$  (with units Hz) are the synaptic rise and decay rates of the synaptic response, respectively.  
 155 The synaptic decay rates and synaptic response functions depend on the source neurons of type  $b$  only  
 156 and are independent of the target neurons. The constant prefactor  $H_b$  defines the response function  
 157 amplitude subject to the anesthetic concentration. Here, we assume identical excitatory synaptic receptors  
 158 with constant rise and decay rate. Inhibitory synaptic receptors are also assumed to exhibit identical  
 159 constant rise and decay rates while their decay rates depend on the anesthetic concentration. This strong  
 160 approximation is taken from a previous study (68) to be able to compare our results, while preliminary

161 studies with more realistic parameters show similar results (not shown).

162 The constants  $\nu_{ab}$  are the strengths of the connections from population of type  $b$  to population of type  $a$   
 163 (in mVs), and  $\phi_b$  is the average firing rate of the population  $b$  (in Hz). The connections between cortex  
 164 and thalamus are associated with a same nonzero time delay,  $\tau_{ab} = \tau$ , while the delay term is assumed to  
 165 be zero within the cortex and within the thalamus (75).

166 By virtue of long-range axonal projections of excitatory cortical neurons and by assuming the spatially-  
 167 homogeneous dynamics on the cortex, the average firing rate  $\phi_E$  obeys the damped oscillator equation

$$D\phi_E = S(V_E), \quad (3)$$

168 where the operator  $D$  is defined as

$$D = \left( \frac{1}{\gamma} \frac{\partial}{\partial t} + 1 \right)^2 \quad (4)$$

169 and  $\gamma$  is the cortical damping rate. It is assumed that the spatial spread of activity is very fast in other  
 170 populations and the activity variable can be approximated by a sigmoidal function as  $\phi_b = S(V_b)$ , for  
 171  $b = I, S, R$ . Conversely to the original model (72, 73, 75) we use a more realistic transfer function  
 172 derived from properties of type I-neurons given by (24)

$$S(V_a) = \text{Sig}(V_a, 0) - \text{Sig}(V_a, \rho), \quad (5)$$

173 with

$$\text{Sig}(V_a, \rho) = \frac{S_a^{max}}{2} \left( 1 + \text{erf} \left( \frac{V_a - \theta_a - \rho\sigma^2}{\sqrt{2}\sigma} \right) \right) e^{-\rho(V_a - \theta_a) + \rho^2\sigma^2/2}, \quad (6)$$

174 with  $\sigma = 10$  mV and  $\rho = 0.08$  mV<sup>-1</sup>, where  $\sigma$  is related to the standard deviation of firing thresholds, the  
 175 parameter  $\rho < \infty$  reflects the properties of type I-neurons,  $S_a^{max}$  is the maximum population firing rate,  
 176 and  $\theta_a$  is the mean firing threshold of neurons in population  $a$ . In contrast to the standard transfer function  
 177 given in (72), the transfer function in Eq. (6) is not anti-symmetric to its inflection point anymore (27) and  
 178 exhibits a larger nonlinear gain (slope) for large potentials  $V_a > \theta_a$  compared to small potentials  $V_a < \theta_a$ .  
 179 This asymmetry results from the firing properties of type-I neurons, see (24, 27) for more details. For  
 180  $\rho \rightarrow \infty$ , the sigmoid function becomes the conventional symmetric transfer function.

181 The external input to the system is considered as a non-specific input to thalamo-cortical relay neurons  
 182 as

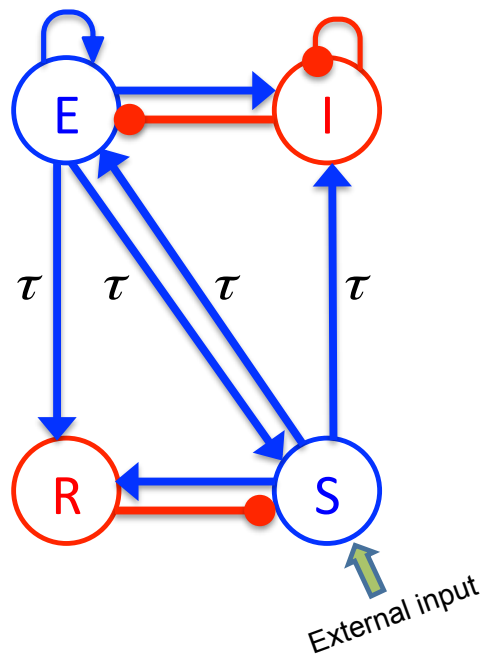
$$\phi_N = \langle \phi_N \rangle + \sqrt{2\kappa}\xi(t), \quad (7)$$

183 where  $\langle \phi_N \rangle$  indicates its mean value and  $\xi(t)$  is a zero average Gaussian white noise and  $\kappa$  is the noise  
 184 intensity.

185 The power spectrum characterises small fluctuations about the resting state of the system defined by  
 186  $dV_a(t)/dt = 0$ . Following (63, 72), it is assumed that the activity of excitatory cortical neurons generates  
 187 the EEG, and due to the specific choice of external input to thalamo-cortical relay neurons, the power  
 188 spectrum of the EEG is related to the Greens function of linear deviations about the resting state by (25)

$$P_E(\omega) = 2\kappa\sqrt{2\pi} \left| \tilde{G}_{1,3}(\omega) \right|^2, \quad (8)$$

189 in which  $P_E(\omega)$  depends just on one matrix component of the matrix Greens function  $\tilde{G}(\omega)$ , see the  
 190 Appendix for its definition. We point out that the subsequent power spectrum analysis is based on  
 191 Eq. (8) and changing a system parameter, such as the factor  $p$ , changes the resting state, the corresponding  
 192 nonlinear gains and consequently the power spectrum. In addition, the power spectrum analysis is valid  
 193 only if the resting state is stable and hence the fluctuations do not diverge. We have taken care of this  
 194 additional condition and all given parameters guarantee the existence and stability of the resting state.



**Figure 1.** The schematic of a thalamo-cortical module. The blue arrows indicate excitatory connections while the red connections with filled circle ends denote inhibitory connections. The symbols  $E$ ,  $I$ ,  $S$ , and  $R$  denote the excitatory and inhibitory cortical neurons, thalamo-cortical relay, and thalamic reticular neurons respectively. In addition thalamocortical and corticothalamic connections exhibit the same nonzero time delay  $\tau$ .

### EFFECT OF PROPOFOL ON NEURAL POPULATIONS

195 In order to mimic anesthetic action, we consider the general anesthetic propofol which affects synaptic  
 196 and extra-synaptic GABAergic receptors. We assume that the decay rate of inhibitory synapses is identical  
 197 in all neural populations under study, and decreases with increasing propofol concentration in accordance  
 198 with experimental findings (76, 67). Mathematically, such a dependence on the anesthetic concentration  
 199 can be taken into account by a concentration factor  $p \geq 1$  and  $\beta_b = \beta_0/p$  while increasing  $p$  reflects an  
 200 increase of the on-site concentration of propofol (21, 17, 68).

201 Since propofol has been shown to retain the amplitude of inhibitory synaptic response functions (76),  
 202 one can define  $H_b = \Gamma(\alpha, \beta_0)/\Gamma(\alpha, \beta_b)$  for  $b = I, R$ , where

$$\Gamma(\alpha, \beta) = \frac{\alpha\beta}{\alpha - \beta} \left[ (\alpha/\beta)^{\frac{-\beta}{\alpha-\beta}} - (\alpha/\beta)^{\frac{-\alpha}{\alpha-\beta}} \right],$$

203 i.e.,  $\Gamma(\alpha, \beta_b) = \bar{h}_b(t_0)$  is the peak amplitude of  $\bar{h}_b(t)$  at time  $t_0 = \ln(\alpha/\beta_b)/(\alpha - \beta_b)$ . Thereby the  
 204 maximum height of  $h_b(t)$  is  $h_{max} = \Gamma(\alpha, \beta_0)$  which is independent of the action of propofol (68).  
 205 Moreover, since it is assumed that propofol does not act on excitatory synaptic transmission,  $H_b = 1$   
 206 and  $h_b(t) = \bar{h}_b(t)$  for  $b = E, S$ .

207 The GABAergic ESR tonic inhibition can be represented in the model as a constant shift of the firing  
 208 threshold in neural population models (24). For simplicity, we assume a linear relationship between the  
 209 anesthetic concentration parameter  $p$  and the extra-synaptic threshold shift

$$\theta_a = \theta_0 + (p - 1)k_a \quad (9)$$

210 with the unique firing threshold  $\theta_0 = 15$  mV identical for all populations in the absence of propofol  
 211 and the extra-synaptic anesthetic sensitivity  $k_a > 0$ . Here,  $(p - 1)k_a$  is the tonic inhibition induced by

212 extra-synaptic action which depends linearly on the propofol concentration. Future experimental studies  
 213 may motivate a more realistic relationship of threshold shift and the anesthetic concentration parameter.  
 214 Summarizing, synaptic and extra-synaptic inhibition, and hence anesthetic action, is present in the cortical  
 215 populations  $E$  and  $I$  and in the thalamic population of relay neurons  $S$ .

### POWER SPECTRUM

216 The present study examines the effect of tonic inhibition in various populations  $E$ ,  $I$ ,  $S$  on the power  
 217 spectrum of neural activity in cortical excitatory neurons, i.e., population  $E$ . We will focus on the power  
 218 in the  $\delta$ - and  $\alpha$ - frequency ranges in the interval [0.5Hz–4Hz] and [8Hz–12Hz], respectively.  
 219

220 The subsequent analysis reveals power peaks in these frequency ranges, whose magnitude changes with  
 221 the level of tonic inhibition. These power peaks exhibit a maximum of power, expressed mathematically as  
 222 a local maximum of the function  $P_E(f)$  where  $P_E$  is taken from Eq. (8). The local maximum at frequency  
 223  $f_0$  is defined as  $dP_E/df = 0$ ,  $d^2P_E/df^2 < 0$  computed at  $f_0$ . If there is a local maximum of power in the  
 224  $\delta$ - frequency range, then  $\delta$ -activity is present, whereas a missing local maximum in the  $\delta$ -frequency  
 225 range indicates missing  $\delta$ -activity. Since the magnitude and frequency of power peaks change with the  
 226 propofol concentration and extra-synaptic threshold, the concentration factor  $p$  and the extra-synaptic  
 227 anesthetic sensitivity  $k_a$  are the parameters of the power spectrum, i.e.  $P_E = P_E(p, k_a, f)$ .  
 228

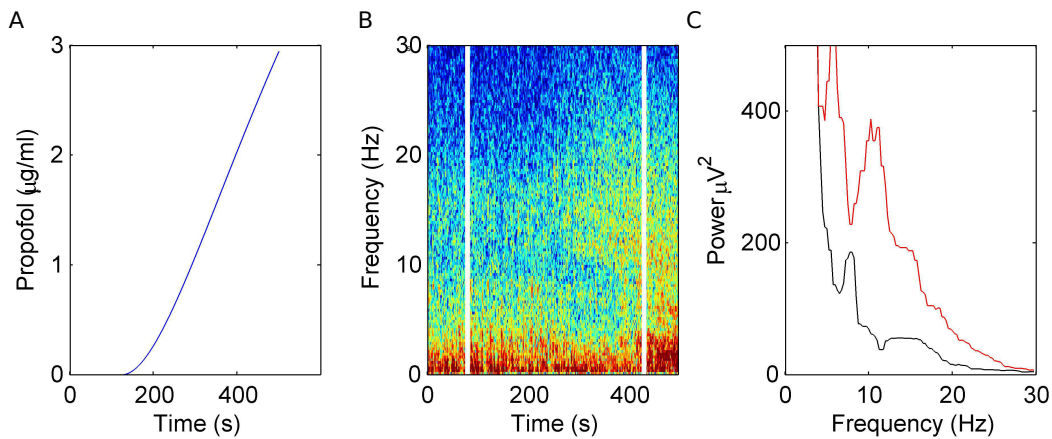
229 To illustrate the usefulness of this parametrization, let us assume a factor  $k_{a0}$  for which no  $\delta$ -power  
 230 peak exists in the power spectrum  $P_E(p, k_{a0}, f)$ , and  $k_{a1}$ ,  $k_{a1} > k_{a0}$  is the extra-synaptic anesthetic  
 231 sensitivity leading to a spectral  $\delta$ -power peak in  $P_E(p, k_{a1}, f)$  with  $dP_E(p, k_{a1}, f_{max})/df_{max} = 0$  where  
 232  $f_{max}$  is a frequency in the  $\delta$ -frequency range. Mathematically, then the continuity of all model functions  
 233 and variables guarantee that there is a threshold for the emergence of  $\delta$ -activity at a certain extra-  
 234 synaptic anesthetic sensitivity  $k_{a,thr}$  with  $k_{a0} \leq k_{a,thr} \leq k_{a1}$ . Consequently, if a threshold extra-synaptic  
 235 anesthetic sensitivity for  $\delta$ -activity exists, then the variation of model variables about this critical point  
 236 guarantees the emergence of  $\delta$ -activity. This mathematical reasoning allows us to investigate conditions  
 237 under which  $\delta$ -activity may emerge.

## 3 RESULTS

238 Figure 2 illustrates how the EEG power spectrum depends on the concentration of propofol for a single  
 239 subject. After starting the infusion at  $t = 0$  min, the estimated propofol effect-site concentration  
 240 increases gradually with time (Fig. 2(A)); resulting in increased power in the  $\delta$ - and  $\alpha$ -frequency ranges  
 241 (Fig. 2(B)). Over the period of the spectrogram the subject has become progressively more sedated; until  
 242 a  $t = 5$  min the subject no longer responds to verbal command but would still be responsive to nociceptive  
 243 stimuli. Figure 2(C) shows the power spectra in the awake and sedation conditions. We observe a power  
 244 enhancement primarily in the  $\delta$ - and  $\alpha$ -frequency ranges.  
 245

246 To understand how propofol might enhance  $\delta$ - and  $\alpha$ -power, we study the power spectrum of our  
 247 theoretical model for different anesthetic concentration levels and examine the impact of adding tonic  
 248 inhibition via extra-synaptic GABA<sub>A</sub> receptors. Figure 3(A) shows the interaction between propofol and  
 249 tonic inhibition in the cortical inhibitory neuronal population. If we set the tonic inhibition to zero ( $k_I =$   
 250 0mV), we observe a decrease in spectral power as propofol concentrations increase (i.e. the power moves  
 251 from the black line to the blue line in the figure). If we set the tonic inhibition to  $(p - 1) \cdot 15$  mV we  
 252 see the opposite effect - there is an increase of  $\delta$ - and  $\alpha$ -power (black line to red line), with increasing  
 253 propofol concentration.





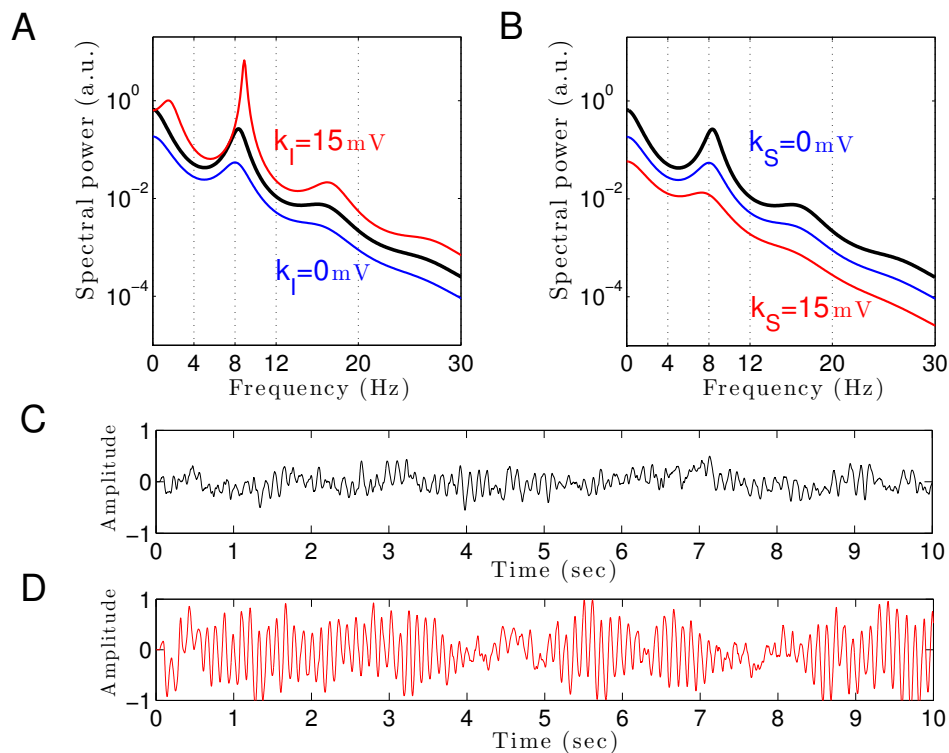
**Figure 2.** Electroencephalographic data observed under anesthesia sedation in a single subject while increasing the propofol concentration. (A) Blood plasma concentration of propofol with respect to administration time. (B) Spectrogram of frontal EEG power. The vertical lines denote time windows well before the administration (left line) and at about 5min after the start of propofol infusion (right side); (C) Power spectra computed before the infusion of propofol (black) and 5 min after the start of infusion (red).

254 Previous studies have indicated that extra-synaptic inhibition in thalamic relay neurons may control the  
 255 level of inhibition in the brain (3). However Fig. 3(B) reveals that adding a non-zero tonic inhibition in  
 256 the thalamic relay neurons causes a decrease in the spectral power, similar to the previous case of absent  
 257 tonic inhibition in the inhibitory cortical neurons.

258 It is well-known that GABAergic anesthetics change the EEG from high frequency-low amplitude  
 259 signals to low frequency-high amplitude signals (77, 78). Figure 3(C,D) show simulated time series in  
 260 the absence and presence of tonic inhibition in cortical inhibitory cells reproducing this experimental  
 261 finding.  
 262

263 Our results elucidates that tonic inhibition in cortical interneurons and thalamic relay neurons affect  
 264 the cortical power spectrum differently. This finding is similar to results of a previous computational  
 265 neural population study of a cortico-thalamic feedback single-neuron model (69). Figure 4 shows how  
 266 the resting membrane potential (Fig. 4(A)) and the nonlinear gain (Fig. 4(B)) in the cortical excitatory  
 267 population change with differing extra-synaptic anesthetic sensitivity in cortical inhibitory neurons ( $k_I$ )  
 268 and in the thalamic relay neurons ( $k_S$ ). We observe that both the resting potential and the nonlinear gain  
 269 of cortical excitatory neurons increase when the cortical inhibitory extra-synaptic anesthetic sensitivity  
 270  $k_I$  increases, whereas resting potential and nonlinear gain of cortical excitatory neurons decrease when  
 271 the extra-synaptic anesthetic sensitivity in thalamic relay neuron  $k_S$  increases. Since the nonlinear gain  
 272 is proportional to the systems responsiveness to external stimuli, the power enhancement in population  $I$   
 273 may be explained by the augmented responsiveness of the cortical excitatory neurons. This responsiveness  
 274 depends on the sub-circuit in which the neurons are involved. Since relay neurons are part of the thalamo-  
 275 cortical feedback loop, while cortical inhibitory neurons contribute to the cortical loop, the cell types  
 276 respond differently to the thalamic input. Essentially assuming tonic inhibition in the population of  
 277 cortical excitatory neurons  $E$ , the study reveals a similar propofol concentration dependence of the power  
 278 spectrum, the resting state potential and the nonlinear gain as for the thalamic tonic inhibition  $S$ . This  
 279 shows the unique tonic inhibition effect in the cortical inhibitory neurons.  
 280

281 Figure 3(A) shows the power spectrum for single values of the extra-synaptic sensitivity  $k_I$ , for single  
 282 values of the concentration factor  $p$  and fixed strength of self cortical inhibition  $\nu_{ii}$ , while Fig. 4 gives more  
 283 details on the role of extra-synaptic sensitivity for fixed values of the concentration factor  $p$  and fixed  
 284 cortical self-inhibition. To understand better the interplay between tonic inhibition, synaptic inhibition

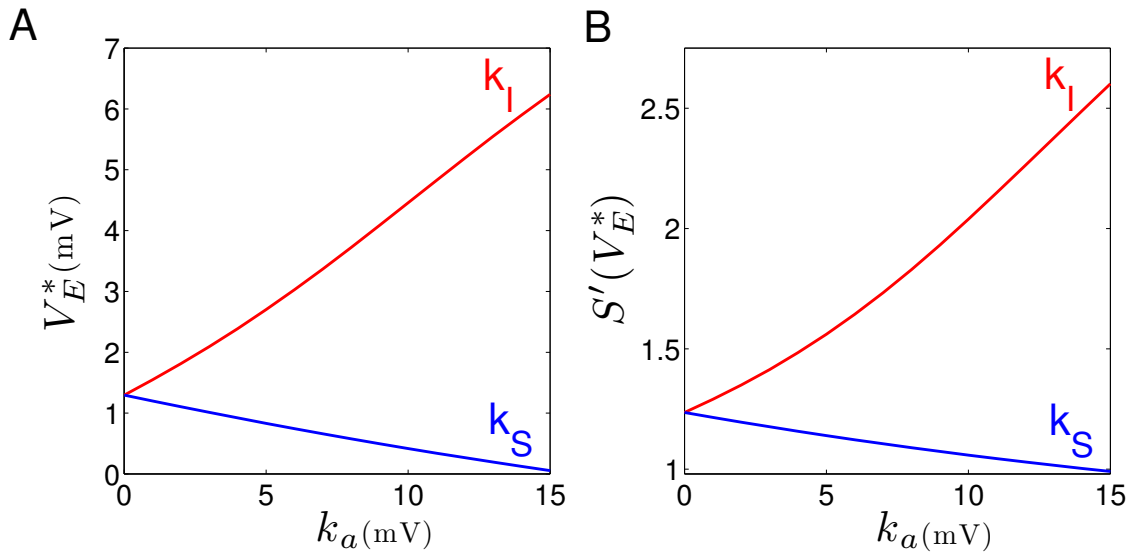


**Figure 3.** The theoretical EEG power spectrum in the baseline and in the sedation condition with and without tonic inhibition in the cortical inhibitory neurons  $I$  in (A) and the thalamic relay neurons  $S$  in (B) and corresponding simulated EEG time-series. In (A) the administration of propofol without tonic inhibition (blue line) attenuates the power spectrum compared to the baseline condition (black line) while the tonic inhibition (red line) increases the global power and generates oscillatory activity in the  $\delta$ -frequency range. In (B) increasing the anesthetic concentration yields a global power decrease in the sedation condition without tonic inhibition (blue line) and a further power decrease in the presence of tonic inhibition (red line). In (A) and (B), the black lines indicate the EEG-spectral power in the baseline condition ( $p = 1$ ), and the blue and red lines show the power spectrum in anesthesia condition ( $p = 1.125$ ) in the absence ( $k_a = 0$ ) and in the presence ( $k_a = 15$  mV) of tonic inhibition, respectively. (C) The simulated EEG time-series ( $\phi_E(t)$  defined in Eq. (3)) in the absence of extra-synaptic effects, i.e.  $k_E = k_I = k_S = 0$  mV. (D) The EEG time-series in the presence of extra-synaptic action in cortical inhibitory neurons with  $k_I = 15$  mV,  $k_E = k_S = 0$  mV. The tonic inhibition changes the EEGs from low-amplitude, high-frequency pattern to high-amplitude, low-frequency pattern. In addition, the strength of self cortical inhibition is  $\nu_{ii} = -1.8$  mVs.

285 and the strength of cortical self-inhibition, Figure 5 shows the parameter pairs of synaptic inhibition  $p$   
 286 and the threshold of extra-synaptic sensitivity  $k_{I,thr}$  at different self-inhibition levels, for which a peak  
 287 in the  $\delta$ -frequency range emerges. Recall that the  $k_{I,thr}$  is the critical (smallest) value of extra-synaptic  
 288 sensitivity in cortical inhibitory neurons  $k_I$ , that lead to  $dP_E/df = 0$ ,  $d^2P_E/df^2 < 0$  computed at  $f_{max} \in$   
 289  $\delta$ -range, cf. the subsection on the power spectrum in section 2. Parameter values beyond the respective  
 290 curves lead to  $\delta$ -activity power peaks. We observe that  $\delta$ -activity always emerges for sufficiently strong  
 291 tonic inhibition (large extra-synaptic sensitivity  $k_I$ ) and sufficiently strong self-inhibition  $\nu_{ii}$ , while the  
 292 weaker the self inhibition is the larger is the necessary extra-synaptic sensitivity or the synaptic inhibition  
 293 to generate  $\delta$ -activity. Even for vanishing self cortical inhibition ( $\nu_{ii} = 0$ ), mathematical analysis (not  
 294 shown) reveals that there is still a  $\delta$ -peak in the power spectrum for large enough synaptic or tonic  
 295 inhibition (for  $p$  or  $k_I$  large enough).

296 Moreover, Fig. 5 reveals a minimum tonic inhibition level (minimum value of  $k_I$ ) beneath which no  
 297  $\delta$ -power peak emerges, irrespective of the level of synaptic inhibition ( $p$ ). This result indicates a major  
 298 role of tonic inhibition in the generation of  $\delta$ -activity, since it may support  $\delta$ -activity even if the synaptic  
 299 inhibition level is not sufficient to support it.

300

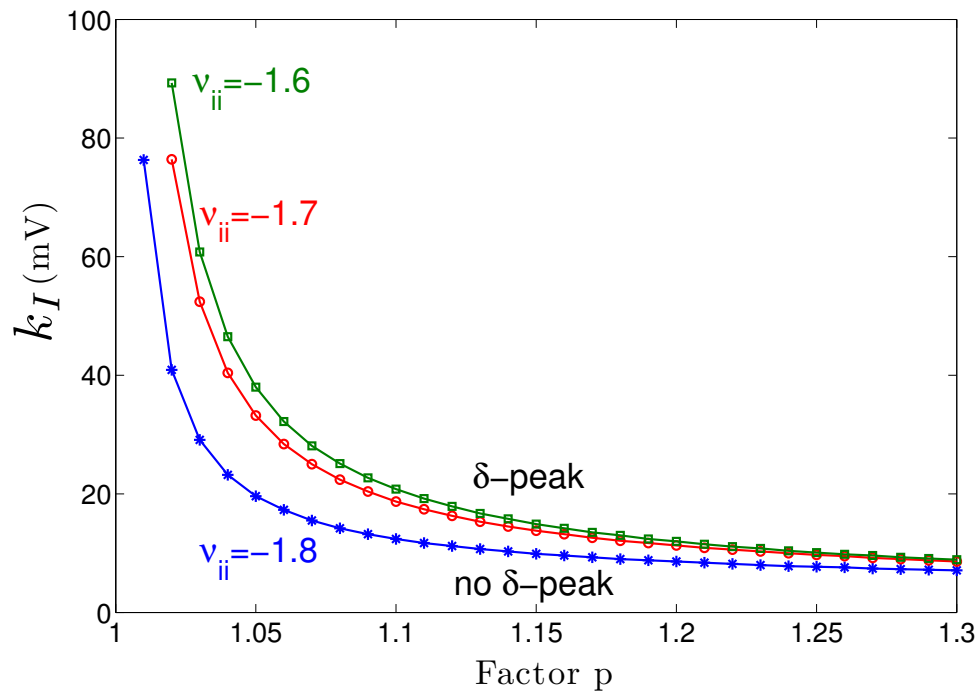


**Figure 4.** Increasing the tonic inhibition (factor  $k_a$  for  $a = I$  and  $S$ ) affects the resting state of excitatory cortical neurons  $V_E^*$  (A) and the corresponding nonlinear cortical gain function (B). Here the anesthetic concentration factor is identical in the populations  $a = E, I$  and  $S$  to ( $p = 1.125$ ). In addition, the strength of self cortical inhibition is  $\nu_{ii} = -1.8$  mVs.

## 4 DISCUSSION

301 In the sedation phase, for modest concentrations of propofol, the EEG power spectrum exhibits an  
 302 increase in the  $\delta$ - and  $\alpha$ -frequency ranges (Fig. 2) as found experimentally in the induction phase  
 303 of propofol anesthesia (79). One possible explanation for these phenomena is by postulating stronger  
 304 GABAergic potentiation within cortical inhibitory neurons than within cortical pyramidal neurons (68).  
 305 We hypothesize, that cortical GABAergic self inhibition plays a decisive role. Figure 3 reveals that  
 306 the power surge in these frequency ranges might also result from extra-synaptic tonic inhibition active  
 307 in cortical inhibitory neurons. Tonic inhibition increases the firing threshold and hence diminishes the  
 308 output of inhibitory neurons to excitatory cortical neurons, which then allows increased excitation in  
 309 the excitatory population and a power surge in the EEG. Conversely tonic inhibition in the thalamic  
 310 relay cells does not induce power surge in EEG since augmented inhibition in the thalamic relay cells  
 311 yields diminished excitation in cortical excitatory neurons, leading to a decrease in EEG power. This  
 312 interpretation is corroborated by Fig. 4 which demonstrates augmented and diminished nonlinear gain  
 313 in cortical excitatory neurons assuming tonic inhibition in inhibitory and thalamic relay population,  
 314 respectively. This reflects enhanced and weakened response to the noisy thalamic external input, see  
 315 previous theoretical studies (68, 25) for a similar line of argument.

316 Figure 3 clearly reveals the emergence of  $\delta$ -activity caused by extra-synaptic tonic inhibition which is  
 317 affirmed by the existence of a minimum level of extra-synaptic inhibition shown in Fig. 5. Conversely,  
 318  $\alpha$ -activity appears to be much less sensitive to tonic inhibition since it is present for all tonic inhibition  
 319 levels. One interpretation may be the generation of  $\alpha$ -activity by the cortico-thalamic feedback as  
 320 hypothesized theoretically (80) while  $\delta$ -activity results from the cortical interaction of excitatory  
 321 and inhibitory neurons. The exact origins of propofol-induced  $\alpha$ - and  $\delta$ -activity are not known for  
 322 certain. We find that the  $\alpha$  oscillations arise from thalamocortical resonances. These oscillations are



**Figure 5.** Parameter space for  $\delta$ -power peak. The lines give the smallest (threshold) value of the extra-synaptic sensitivity  $k_{I,thr}$  that induces  $\delta$ -oscillations in the sedation condition with respect to the concentration factor  $p$  for different values of self-inhibitory connections  $\nu_{ii}$ . The weaker the self cortical inhibition (the smaller  $|\nu_{ii}|$ ), the higher the necessary level of propofol concentration (larger  $p$ ) and the tonic inhibition (larger  $(p - 1) \cdot k_I$ ) to induce  $\delta$ -activity.

323 commonly synchronous across widespread cortical regions and are not easily generated in isolated cortical  
 324 tissue (81, 82). This affirms the original model of Lopes da Silva et al. (74). However, our model results  
 325 are equivalent to results of other models describing  $\alpha$ -activity by purely cortical interactions. We are  
 326 not aware of a methodology ruling out one or the other model and this is not the aim of the present  
 327 work. Our work just reveals the additional possibility that the thalamus serves as a possible (indirect)  
 328 source of  $\alpha$ -activity. Similarly, the origin of  $\delta$ -activity is not clear, but slow activity does increase  
 329 at higher concentrations of propofol - which may be associated with decreasing  $\alpha$ -waves as observed  
 330 during desflurane general anesthesia (83). This is in keeping with  $\delta$ -waves becoming more pronounced  
 331 as the cortico-thalamic systems becomes increasingly hyperpolarized. However there is a lot of variability  
 332 between patients as regards the relative power of  $\alpha$ - and  $\delta$ -activity during general anesthesia; which  
 333 would suggest that the true explanation is more complex, and requires recognition of other factors such as  
 334 the one presented in this paper - the influence of the propofol on extra-synaptic inhibition.

335 Although anesthetic action on synaptic and extra-synaptic GABAergic receptors is different, both  
 336 actions diminish neural activity and hence increase inhibition. Figure 5 elucidates that strong enough  
 337 extra-synaptic or synaptic inhibition induce  $\delta$ -activity. Hence, one may argue that the level of inhibition  
 338 plays an important role while its origin, i.e. synaptic or extra-synaptic, plays a secondary role. This  
 339 interpretation corroborates the idea of the balance of excitation and inhibition as the major mechanism  
 340 in general anesthesia. This interpretation is in good accordance to previous experimental findings on the  
 341 important role of the balance of excitation and inhibition in brain network under anesthesia (84, 85).  
 342 Such global concepts as excitation-inhibition balance are attractive to describe complex processes in  
 343 general anesthesia. For instance, anesthetics alter arousal in several pathways, such as the cholinergic  
 344 pathway (86) and the orexinergic pathway which has been identified to activate a complex functional  
 345 network controlling, inter alia, the emergence from unconsciousness (87).

346

347 Our theoretical study considers the anesthetic propofol and its corresponding action at synaptic and  
 348 extra-synaptic GABAergic receptors only, whereas it is known that propofol induces inhibition at various  
 349 other receptors as well (2, 88) including minor effects on NMDA-receptors and voltage-gated potassium  
 350 channels (2). Propofol also potentiates glycine receptors which are found all over the central nervous  
 351 system and have a major role in regulating inhibition, e.g., in the brain stem (89).

352 Similar to extra-synaptic inhibition resulting from ambient GABA concentrations, the presence of  
 353 ambient concentrations of glycine close to NMDA-receptors entails tonic depolarization. This tonic  
 354 excitation diminishes the firing threshold of neurons and hence may counteract inhibition. The present  
 355 work considers tonic inhibition only and neglects tonic excitation effect. Although it would be important  
 356 to study tonic excitation effects, this additional study would exceed the major aim of the manuscript,  
 357 namely demonstrating the fundamental effect of tonic anesthetic action.

358 In addition, by virtue of the focus on extra-synaptic action, the model proposed neglects known  
 359 anesthetic effects on different receptors and ion channels, although they have been shown experimentally,  
 360 e.g. (2, 90) and references therein, and theoretically (91) to affect EEG activity. Specifically, the latter  
 361 work of Bojak et al. (91) considers anesthetic effects on hyperpolarization-activated cyclic nucleotide-  
 362 gated potassium channel 1 (HCN1) subunits which, effectively, increase the mean firing threshold in  
 363 neural populations and strongly resembles the tonic inhibition induced by extra-synaptic GABA-receptors.

364 The model network topology includes a single module of a closed thalamo-cortical feedback loop (92)  
 365 comprising two thalamic nuclei and cortical excitatory and inhibitory neurons. This model represents a  
 366 first approximation of brain networks since it neglects brain stem activity including the reticular activating  
 367 system (RAS) (93) which has significant modulating effects on attention, arousal and consciousness.  
 368 Future work will include structures of the brain stem, propofol action on glycine receptors, and will take  
 369 into account the RAS - since its neural structures involved exhibit strong extra-synaptic inhibition (94, 95,  
 370 96). The model also neglects the cholinergic pathway originating from the basal forebrain (97) which is  
 371 known to co-regulate the level of consciousness (86).

372 Essentially, our theoretical model assumes population coding implying rate-coding response activity  
 373 of neuron populations subjected to external thalamic noise. The model does not consider specific single  
 374 neuron dynamics found experimentally under anesthetic conditions. For instance, it has been hypothesized  
 375 that, at certain levels of anesthetic concentration, thalamic neurons switch their activity from tonic firing  
 376 to bursting and induce loss of consciousness (98).  
 377

378 In spite of these limitations, our model reproduces qualitatively the action of propofol on EEG and  
 379 reveals the possible impact of extra-synaptic GABAergic receptors on the EEG power. To our knowledge,  
 380 the present work is the first to link extra-synaptic GABAergic action and experimental EEG. Future work  
 381 will refine the model involving additional receptor action, e.g., tonic excitation caused by ambient glycine  
 382 concentrations, and sub-cortical brain structures.

## APPENDIX A. POWER SPECTRUM

383 The resting state (stationary state) of Eqs. (1) defined by  $dV_a(t)/dt = 0$  obeys

$$\begin{aligned} V_E^* &= \nu_{ee}S(V_E^*) + H_b\nu_{ei}S(V_I^*) + \nu_{es}S(V_S^*), \\ V_I^* &= \nu_{ie}S(V_E^*) + H_b\nu_{ii}S(V_I^*) + \nu_{is}S(V_S^*), \\ V_S^* &= \nu_{se}S(V_E^*) + H_b\nu_{sr}S(V_R^*) + \langle\phi_N\rangle, \\ V_R^* &= \nu_{re}S(V_E^*) + \nu_{rs}S(V_S^*), \end{aligned} \quad (10)$$

384 where  $V_a^*$  denotes the resting state value of  $V_a$  for  $a = E, I, S, R$ . Moreover Eq. (3) gives  $\phi_E^* = S(V_E^*)$ .  
 385 Then we linearize Eqs. (1) about the obtained resting state and write them in a general matrix form of a

386 linear DDE as

$$\hat{\mathbf{L}} \left( \frac{\partial}{\partial t} \right) \mathbf{X}(t) = \mathbf{A}\mathbf{X}(t) + \mathbf{B}\mathbf{X}(t - \tau) + \boldsymbol{\xi}(t), \tag{11}$$

where

$$\mathbf{X}(t) = \begin{pmatrix} \phi_E(t) - \phi_E^* \\ V_I(t) - V_I^* \\ V_S(t) - V_S^* \\ V_R(t) - V_R^* \end{pmatrix}, \quad \hat{\mathbf{L}} = \begin{pmatrix} \tilde{L} \frac{\tilde{D}}{K_{11}} & 0 & 0 & 0 \\ 0 & \tilde{L} & 0 & 0 \\ 0 & 0 & \tilde{L} & 0 \\ 0 & 0 & 0 & \tilde{L} \end{pmatrix},$$

$$\mathbf{A} = \begin{pmatrix} K_1 & K_2 & 0 & 0 \\ K_4 & K_5 & 0 & 0 \\ 0 & 0 & 0 & K_8 \\ 0 & 0 & K_{10} & 0 \end{pmatrix}, \quad \mathbf{B} = \begin{pmatrix} 0 & 0 & K_3 & 0 \\ 0 & 0 & K_6 & 0 \\ K_7 & 0 & 0 & 0 \\ K_9 & 0 & 0 & 0 \end{pmatrix}, \quad \boldsymbol{\xi}(t) = \begin{pmatrix} 0 \\ 0 \\ \sqrt{2\kappa}\xi(t) \\ 0 \end{pmatrix}, \tag{12}$$

387 with  $\tilde{L} = (1 + i\omega/\alpha)(1 + i\omega/\beta_0)$ ,  $\tilde{D} = (1 + i\omega/\gamma)^2$ , and

$$K_1 = \nu_{ee}, K_2 = H_b \nu_{ei} \frac{\partial S_I[V]}{\partial V} \Big|_{V=V_I^*}, K_3 = \nu_{es} \frac{\partial S_S[V]}{\partial V} \Big|_{V=V_S^*},$$

$$K_4 = \nu_{ie}, K_5 = H_b \nu_{ii} \frac{\partial S_I[V]}{\partial V} \Big|_{V=V_I^*}, K_6 = \nu_{is} \frac{\partial S_S[V]}{\partial V} \Big|_{V=V_S^*},$$

$$K_7 = \nu_{se}, K_8 = H_b \nu_{sr} \frac{\partial S_R[V]}{\partial V} \Big|_{V=V_R^*}, K_9 = \nu_{re},$$

$$K_{10} = \nu_{rs} \frac{\partial S_S[V]}{\partial V} \Big|_{V=V_S^*}, K_{11} = \frac{\partial S[V]}{\partial V} \Big|_{V=V_E^*}.$$

388 The power spectral density matrix  $\mathbf{P}(\omega)$  of  $\mathbf{X}(t)$  is the Fourier transform of the auto-correlation function  
 389 matrix  $\langle \mathbf{X}(t)^t \mathbf{X}(t - T) \rangle$  (Wiener-Khinchine Theorem) leading to

$$\mathbf{P}(\omega) = 2\kappa\sqrt{2\pi}\tilde{\mathbf{G}}(\omega)\tilde{\mathbf{G}}^t(-\omega),$$

390 where  $\tilde{\mathbf{G}}(\omega)$  is the Fourier transform of the matrix Greens function and the high index t denotes the  
 391 transposed matrix (25).

392 At the end, the model assumes that excitatory activity generates the EEG and by virtue of the specific  
 393 choice of external input to relay neurons, the power spectrum of the EEG depends just on one matrix  
 394 component of the Greens function by

$$P_E(\omega) = 2\kappa\sqrt{2\pi}\tilde{G}_{1,3}(\omega)\tilde{G}_{1,3}(-\omega) = 2\kappa\sqrt{2\pi} \left| \tilde{G}_{1,3}(\omega) \right|^2, \tag{13}$$

395 cf. Eq. (8), where

$$\tilde{\mathbf{G}}(\omega) = \frac{1}{\sqrt{2\pi}}[\hat{\mathbf{L}} - \mathbf{A} - \mathbf{B}e^{-i\omega\tau}]^{-1} = \frac{1}{\sqrt{2\pi}} \begin{bmatrix} \tilde{L} \frac{\tilde{D}}{K_{11}} - K_1 & -K_2 & -K_3 e^{-i\omega\tau} & 0 \\ -K_4 & \tilde{L} - K_5 & -K_6 & 0 \\ -K_7 e^{-i\omega\tau} & 0 & \tilde{L} & -K_8 \\ -K_9 e^{-i\omega\tau} & 0 & -K_{10} & \tilde{L} \end{bmatrix}^{-1}. \tag{14}$$

## APPENDIX B. PARAMETER VALUES

The subsequent table gives the nominal values of model parameters.

Parameter	Symbol	Nominal value
Maximum firing-rate of all populations	$S^{max}$	250 Hz
Mean firing threshold of all populations	$\theta$	15 mV
Firing rate variance of all populations	$\sigma$	10 mV
Type-I population effect constant of all populations	$\rho$	0.08 mV <sup>-1</sup>
Synaptic rise rate	$\alpha$	200 s <sup>-1</sup>
Synaptic decay rate	$\beta_0$	50 s <sup>-1</sup>
Synaptic strength from E to E neurons	$\nu_{ee}$	1.2 mVs
Synaptic strength from E to I neurons	$\nu_{ie}$	1.2 mVs
Synaptic strength from E to S neurons	$\nu_{se}$	1.2 mVs
Synaptic strength from E to R neurons	$\nu_{re}$	0.4 mVs
Synaptic strength from I to I neurons	$\nu_{ii}$	-1.8 mVs
Synaptic strength from I to E neurons	$\nu_{ei}$	-1.8 mVs
Synaptic strength from S to E neurons	$\nu_{es}$	1.2 mVs
Synaptic strength from S to I neurons	$\nu_{is}$	1.2 mVs
Synaptic strength from S to R neurons	$\nu_{rs}$	0.2 mVs
Synaptic strength from R to S neurons	$\nu_{sr}$	-0.8 mVs
Mean value of external input	$\langle \phi_N \rangle$	1 mV
Intensity of external noise	$\kappa$	0.1 mV
Cortical damping rate	$\gamma$	150 s <sup>-1</sup>
Transmission delay between cortex and thalamus	$\tau$	40 ms

396

## DISCLOSURE/CONFLICT-OF-INTEREST STATEMENT

397 The authors declare that the research was conducted in the absence of any commercial or financial  
398 relationships that could be construed as a potential conflict of interest.

## AUTHOR CONTRIBUTIONS

399 MH has chosen the model and performed the model analysis, AH has conceived the study and JS has  
400 acquired and analyzed the experimental data. The authors have written the manuscript to equal parts and  
401 have approved the final version.

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