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Understanding the Effects of Anesthetic Agents on the EEG through Neural Field Theory.

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Abstract— **Anesthetic and analgesic agents act through a diverse range of pharmacological mechanisms. Existing empirical data clearly shows that such "microscopic" pharmacological diversity is reflected in their "macroscopic" effects on the human electroencephalogram (EEG). Based on a detailed mesoscopic neural field model we theoretically posit that anesthetic induced EEG activity is due to selective parametric changes in synaptic efficacy and dynamics. Specifically, on the basis of physiologically constrained modeling, it is speculated that the selective modification of inhibitory or excitatory synaptic activity may differentially effect the EEG spectrum. Such results emphasize the importance of neural field theories of brain electrical activity for elucidating the principles whereby pharmacological agents effect the EEG. Such insights will contribute to improved methods for monitoring depth of anesthesia using the EEG.**

I. INTRODUCTION

In the ≈150 years since its discovery general anesthesia has become one of the safest and most routine of clinical procedures. However despite such clinical certitude our knowledge of the neurophysiological mechanisms underlying anesthetic action, and its corollary effects on brain networks controlling consciousness and behavior, remains limited. While genuine advances have been achieved in understanding the cellular and molecular actions of most anesthetic agents, what is most lacking in the neuroscience of anesthesia is a connection between the microscopic actions of anesthetic drugs and their macroscopic effects on large-scale neural activity.

The electroencephalogram (EEG) provides arguably the most sensitive and practical method for monitoring the neurophysiological consequences of anesthetic action in clinical and research environments. Because the EEG predominantly represents the summed activity of many thousands of cortical neurons its dynamics, and subsequent modulation by anesthetic agents, is particularly amenable to theoretical characterizations that involve the modeling of populations of neurons, approaches generally referred to as mean, or neural, field theories. Because these theories are formulated at a physical scale intermediate to that of the single neuron and the whole brain it is hoped that such mesoscopic approaches, when biophysically constrained, will assist in functionally linking the effects of anesthetic agents on a range of microscopic ligand-gated channels with their macroscopic electroencephalographic and behavioral effects [1].

While at the cellular and molecular level general anesthetics (GA) are generally characterized as simple depressants of neural activity, their actions in networks of interacting neurons can be quite different [2]. For example increasing inhibition at the level of the single neuron, can, when viewed at the level of the neuronal network, produce an increase in activity through disinhibition. Attempts to account for such large scale effects are complicated not only by the panoply of identified targets of anesthetic action [3] but also because of considerable variability in the measurable phenomena associated with their clinical effect. For example anesthetic action can be associated with either increases or decreases in EEG activity, which may be more or less pronounced during emergence when compared with induction [4].

Because neural field theories are capable of incorporating the bulk effects of many of the identified sites of anesthetic action they will provide a unifying framework for understanding the myriad effects of anesthetics on the collective activity of neuronal populations as revealed by the EEG [1].

A. Anesthetic Targets

The majority of GAs are thought to produce their suppressive effects by enhancing inhibitory neurotransmission at gamma amino-butyric acid A receptors ($GABA_A$). However, depending on the agent, synaptic $GABA_A$ receptors are neither the major or the only molecular targets of GA action. Additional neuronal molecular targets of anesthetics that have been identified include extrasynaptic $GABA_A$ receptors, two-pore K^+ channels (2PK), and ionotropic *N*-methyl-D-aspartate (NMDA) glycine and nicotinic acetylcholine (nACh) receptors [2]. This diversity of post-synaptic targets helps to explain the common and divergent effects of GA and analgesic agents on the human EEG.

B. Neural Field Models

The typical mesoscopic approach to EEG modeling consists of physiologically motivated, spatially coarse grained equations describing the dynamics of excitatory and inhibitory populations of cortical neurons. The resolution of the spatial coarse graining is generally chosen to match the scale of some aspect of cortical modularity, for example the cortical macrocolumn. The small set of equations describing a neural mass is more amenable to numerical investigation and theoretical analysis than the corresponding formulations

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for networks of many individual model neurons, but nevertheless retains a great deal of anatomical and physiological plausibility. Typically, though not always, the dynamics of the mean soma membrane potential of excitatory neurons is the state variable taken to best represent the sources of the recorded EEG (given the orientation of neocortical pyramidal neurons and their apical process).

1) Liley Model: The neural field model of Liley et al. [5], [6], [7] provides one of the most physiologically comprehensive descriptions of electrocortical activity. It can produce the main features of the spontaneous human EEG within the context of biologically plausible parametrizations. The Liley et al. model identifies inhibitory synaptic activity as a particularly sensitive modulator of EEG dynamics and hypothesizes that the important 8-13 Hz alpha rhythm emerges through reverberant oscillations between populations of inhibitory neurons. This theory is therefore well placed to account for the electrocortical effects of altered inhibitory activity that attends the action of the majority of GAs.

As is appropriate for a description of EEG data the model is spatially coarse-grained over roughly the extent of a cortical macrocolumn. The multiple interactions between individual neuronal elements are replaced by effective interaction between the "mean fields" of populations of neurons. In contrast to earlier works (e.g. the Wilson and Cowan equations [8]), no averaging in time takes place. The essential components of the theory are schematically represented in Fig. 1, which depicts the interactions taking place within and between two different macrocolumns. The two functionally distinct types of cortical neuronal populations, excitatory (E) and inhibitory (I), subsume a much wider variety of dynamically and morphologically differentiated cortical neuronal subtypes. Within a cortical macrocolumn excitatory neurons (pyramidal and spiny stellate neurons) and inhibitory neurons (interneurons) interact with each other by all possible axo-dendritic synaptic connections.

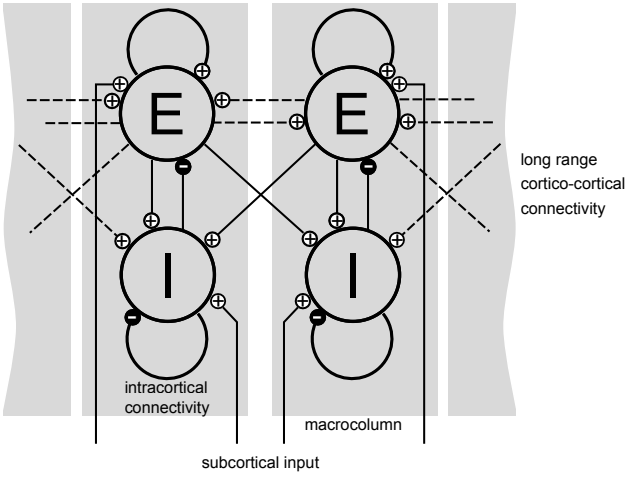

Fig. 1. Schematic overview of the essential intracortical and cortico-cortical interactions between excitatory and inhibitory neuronal populations in the model of Liley et al.[5], [6], [7]

Cortical activity is here locally described by the mean soma membrane potentials of the spatially distributed excitatory neuronal population, h_e, and its inhibitory counterpart, h_i. The connection with physiological measurement is through h_e, which is assumed to be linearly related to surface recorded EEG/ECoG (electrocorticogram) [9], [10]. Excitatory and inhibitory neuronal populations are modeled as single passive RC compartments into which all synaptically induced postsynaptic currents flow. Thus the response of the mean soma membrane potential h_k with $k = e,i$ to induced postsynaptic activity Ilk is given by

$$\tau_k \frac{\partial h_k}{\partial t} = h_k^r - h_k(\vec{x},t) + \sum_{l=e,i} \frac{h_{lk}^{eq} - h_k(\vec{x},t)}{|h_{lk}^{eq} - h_k^r|} I_{lk}(\vec{x},t) \ , \qquad (1)$$

where $\vec{x} \in \mathbb{R}^2$ is the position on the cortical sheet. The induced excitatory and inhibitory postsynaptic activity, Ilk, is described respectively by a critically damped oscillator, describing PSP (postsynaptic potential) shape, driven by the mean rate of incoming axonal pulses from excitatory and inhibitory neuronal populations

$$\left(\frac{1}{\gamma_{lk}}\frac{\partial}{\partial t} + 1\right)^2 I_{lk}(\vec{x},t) = \frac{\Gamma_{lk} e}{\gamma_{lk}} \cdot A_{lk}(\vec{x},t) \ , \qquad (2)$$

$$A_{ek}(\vec{x},t) = N_{ek}^{\beta} S_e[h_e(\vec{x},t)] + \phi_{ek}(\vec{x},t) + p_{ek}(\vec{x},t) \ , \qquad (3)$$

$$A_{ik}(\vec{x},t) = N_{ik}^{\beta} S_i[h_i(\vec{x},t)] \ . \qquad (4)$$

where A_{lk} comprises the different sources of incoming axonal pulses. $N_{lk}^{\beta} S_l$, the mean number of connections from local neuronal population l times their mean firing rate, models local inputs to target population k. p_{ek} represents extracortical (thalamic) excitatory sources. ϕ_{ek} corresponds to pulses arriving across larger distances via the excitatory cortico-cortical fibre system and in the simplest case that they have a single conduction velocity propagate approximately by the following two-dimensional telegraph equation

$$\left[\left(\frac{1}{v_{ek}\Lambda_{ek}}\frac{\partial}{\partial t} + 1\right)^2 - \frac{3}{2\Lambda_{ek}^2}\nabla^2\right] \phi_{ek}(\vec{x},t) = N_{ek}^{\alpha} S_e[h_e(\vec{x},t)] \ . \qquad (5)$$

All model parameters are described in Table I.

2) Anesthetic Action and Model Parameters: Currently the most prominent molecular and cellular loci for the action of anesthetic agents are those that involve the inhibition of neural activity [3]. Therefore modeling the macroscopic dynamical consequences of altered inhibition in the central nervous system would appear to be a critical step towards understanding anesthetic action. Therefore those macroscopic approaches that are able to systematically investigate the effects of altered inhibition would seem to offer the most promise in this regard. Based on the parametrization of sufficiently detailed electrophysiological characterizations of the effects that halogenated volatile agents have on inhibition, we show how the electrocortical model of Liley et al. [5], [6], [7] can go some way to explaining how anesthetic agents may modulate electroencephalographic activity.

TABLE I

LIST OF SPATIALLY AVERAGED PARAMETERS FOR DIFFERENT TYPES $k = e, i$ OF NEURONAL TARGET POPULATIONS IN THE ELECTROCORTICAL MODEL OF LILEY ET AL. [5], [6], [7]. TABLE ADAPTED FROM [11].

	Definition	Units
h_k^r	resting membrane potential	mV
τ_k	passive membrane decay time	ms
h_{ek}^{eq}	excitatory reversal potential	mV
h_{ik}^{eq}	inhibitory reversal potential	mV
Γ_{ek}	EPSP peak amplitude	mV
Γ_{ik}	IPSP peak amplitude	mV
$1/\gamma_{ek}$	EPSP rise time to peak	ms
$1/\gamma_{ik}\,(1/\gamma_{ik}^0)$	IPSP rise time to peak (at c = 0)	ms
N_{ek}^{α}	no. of excitatory cortico-cortical synapses	–
N_{ek}^{β}	no. of excitatory intracortical synapses	–
N_{ik}^{β}	no. of inhibitory intracortical synapses	–
v_{ek}	axonal conduction velocity	$\frac{\mathrm{mm}}{\mathrm{ms}}$
$1/\Lambda_{ek}$	decay scale of cortico-cortical connectivity	mm
$S_k^{\max}$	maximum firing rate	ms^{-1}
μ_k	firing threshold	mV
σ_k	standard deviation of firing threshold	mV
p_{ek}	extracortical synaptic input rate	ms^{-1}
c	aqueous isoflurane concentration	mM

II. METHODS

Empirical data describing the concentration dependent modification of inhibitory and excitatory neurotransmission by the volatile anesthetic agent isoflurane was used to parameterize the actions of anesthetics in the neural field model of Liley et al. Specifically the patch clamp data of Banks and Pearce [12] and McIver et al. [13] were used to to define how the amplitude of excitatory and inhibitory PSPs and the shape of inhibitory PSPs varies as a function of the aqueous concentration of isoflurane. While other identified sites of anesthetic action (see Tab. II) could potentially be modeled corresponding empirical data as a function of anesthetic concentration is not readily available.

TABLE II

RELATIONSHIP BETWEEN MAJOR EXPERIMENTALLY IDENTIFIED SITES OF CORTICAL ANESTHETIC ACTION AND PARAMETERS OF THE ELECTROCORTICAL MODEL OF LILEY ET AL. [5], [6], [7]

Site of action	Main anesthetic effect	Parameters
2PK channels & extrasynaptic $\mathrm{GABA_A}$	increase in tonic inhibition	$p_{ik},\ h_k^r$
nACh receptors	reduction in tonic excitation	$p_{ek},\ h_k^r$
synaptic $\mathrm{GABA_A}$	increase of IPSPs	$\gamma_{ik},\ \Gamma_{ik}$
AMPA/kainate receptors & NMDA receptors*	reduction of EPSPs	γ_{ek}, Γ_{ek}
myelinated axons	slowdown of conduction†	v_{ek}
Na channels	alteration of neuronal firing	$S_k^{max},\ \mu_k,\ \sigma_k$

* Parameters will depend on membrane potential in this case.
† Effect demonstrated in periphery, speculative in cortex [14].

Empirical Hill equation fits were used directly to parameterize isoflurane dependent variations in PSP peak amplitudes Γ_{lk}. In contrast the utilization of the empirical data regarding isoflurane induced variations in the decay times of IPSPs required modification of the mathematical form for the induced inhibitory postsynaptic activity

$$\left(\frac{1}{\gamma_{ik}}\frac{\partial}{\partial t}+1\right)\left(\frac{1}{\tilde{\gamma}_{ik}}\frac{\partial}{\partial t}+1\right) I_{lik}(\vec{x},t) = \frac{\Gamma_{ik}\exp(\gamma_{ik}/\gamma_{ik}^0)}{\gamma_{ik}}\cdot A_{ik}(\vec{x},t)\ , \tag{6}$$

$$\tilde{\gamma}_{ik} = \exp[\varepsilon(c)]\gamma,\ \gamma_{ik} = \frac{\varepsilon(c)}{\exp[\varepsilon(c)]-1}\gamma_{ik}^0 \tag{7}$$

where the explicit dependence of $\gamma_{ik}, \tilde{\gamma}_{ik}$ and Γ_{ik} on aqueous isoflurane concentration has been dropped, and $\varepsilon(c) \geq 0$ describes the experimental concentration dependent increase in IPSP decay time where it is assumed, on the basis of empirical observation, that the time to peak of the IPSP $1/\gamma_{ik}^0$ remains unchanged.

Given the large parameter space of the Liley model and also the emphasis on restricting model parameters to biophysically plausible ranges a selection criteria was enforced on parameter sets. The chief aim of this process was to generate power spectra that resemble resting eyes-closed human EEG. Therefore the shape of the power spectrum should display an overall "$1/f$"-type decay plus a relatively sharp resonance at alpha frequencies ($f = 8$-13 Hz). For a detailed list of the other criteria see [11]. Ultimately, 73,454 parameter sets were selected as satisfactory and used for the parametric simulation of anesthesia. Clinically the standard metric of anesthetic potency is the minimum alveolar concentration (MAC), corresponding to the end-tidal inspired anesthetic gas concentration required to abolish response to noxious stimuli in 50% of subjects. For isoflurane 1 MAC = 1.17% = 0.243 mM aqueous, with MAC values ranging from 0.9 to 3 during anesthetic maintenance depending on the co-administration of adjuvant agents.

III. RESULTS

We calculated the power spectral density (PSD) for all 73,454 sets at 0, 1, and 2 MAC isoflurane using an eigendecomposition approach as described in Bojak and Liley [11]. However, it is difficult to display the full variability of these results: the PSDs differ not only in the shape, but also considerably in total power (area under the PSD curve) and location of the alpha resonance (8 to 13 Hz). Hence we perform two transformations: First, we normalise the total power at 0 MAC to one. Second, we scale frequencies so that at 0 MAC the peak of the alpha resonance always occurs at $f = 11.03$ Hz, the mean alpha peak frequency over all 73,454 sets. Next we compute PSD quantiles from 4.5% to 95.5% in steps of 1% for all frequencies and plot these steps as bands in frequency each with a grayscale color, where the 49.5% to 50.5% (median) band is colored black and the other bands linearly lighter according to the difference from median.

The above procedure was repeated for 1 MAC and 2 MAC isoflurane, but we use the same 0 MAC total power norm and alpha frequency scaling on a set-by-set basis. Finally, we add constants to all PSD values for 0 MAC and 1 MAC, in order to separate the bands along the ordinate. The resulting Fig. 2 shows the considerable variation of alpha peak and "1/f" amplitude, respectively, possible at 0 MAC

for different parameters. Nevertheless, these variations all look quite natural for human EEG. The PSDs for 1 MAC and 2 MAC show that the former alpha peak moves to lower frequencies while at the same time becoming broader. The "1/f" part at lower frequencies is less affected. Significantly, the PSDs do not "wash out" for the induction with isoflurane, as one would expect if there was a large variation in the dynamic responses of different parameter sets to the GA-induced parameter changes. Instead there occurs a largely stereotypical response, which keeps the quantile bands at non-zero concentration roughly as spread out around the median as for 0 MAC. Overall we obtain very stable predictions compatible with known changes of the EEG during isoflurane anesthesia. Whereby alpha power is progressively suppressed and spectral power shifts leftward to lower frequencies, reflective of the transition from low amplitude desynchronized EEG to large amplitude slow wave activity in the time domain.

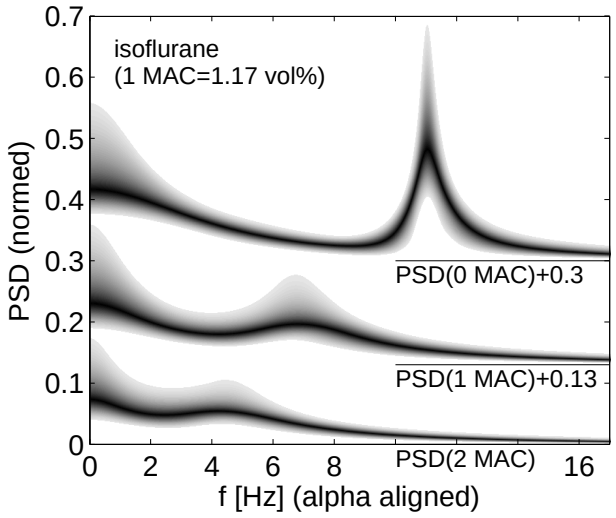

Fig. 2. Distribution of predicted power spectral densities (PSDs) for 73,454 "realistic alpha" parameter sets, and its change under induction with isoflurane. In order to separate the different stages of anesthesia visually, PSDs for 0 MAC and 1 MAC have been shifted up along the ordinate with fixed offsets (0.3 and 0.13, respectively), as indicated by horizontal lines from 9 to 17 Hz showing the corresponding zero baseline.

IV. CONCLUSION

Advances in our understanding of the cellular and molecular mechanisms of general anesthesia have not been matched by similar advances in our knowledge of how these low-level effects influence the neural systems involved in conscious awareness, memory and pain perception. As a robust and practical measures of global brain states the human EEG is a useful approach for observing the consistent and divergent effects anesthetic agents have on neural dynamics. Consequently, linking the experimental data from microscopic and macroscopic levels with biologically plausible models which capture both of these physical scales can assist in better interpreting the process of anesthesia. Using a detailed biophysically plausible model (neural field) which relies on mean-field treatment of neocortical neuronal activity, we have shown that the effects of anesthetic agents can be in-part understood through their action on synaptic neurotransmission, in particular its systematic modification of its time course. As shown in Table II, a range of other anesthetic targets can similarly be modelled as shown above and in doing so potentially further capture the diverse dynamical features of anesthetic action. Of particular interest is the simulation of the EEG effects produced by dissociative agents such as nitrous oxide, ketamine and xenon, which, unlike most GAs, appear to suppress neural activity by antagonizing the glutamatergic NMDA recepetor. Moving forward one clear avenue for improvement will be the shift toward explicitly modeling the anatomical/geometrical attributes of cerebral cortex [15] and the modification of EEG topography produced by anesthesia (e.g. alpha anteriorization) [16].

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