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Prediction and verification of nonlinear sleep spindle harmonic oscillations

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HIGHLIGHTS

- We model sleep spindles using a corticothalamic neural field model of the brain.
- Nonlinearity in the thalamic relay nuclei produces a spindle harmonic oscillation.
- We have observed the spindle harmonic in pilot EEG data.

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ABSTRACT

This paper examines nonlinear effects in a neural field model of the corticothalamic system to predict the EEG power spectrum of sleep spindles. Nonlinearity in the thalamic relay nuclei gives rise to a spindle harmonic visible in the cortical EEG. By deriving an analytic expression for nonlinear spectrum, the power in the spindle harmonic is predicted to scale quadratically with the power in the spindle oscillation. By isolating sleep spindles from background sleep in experimental EEG data, the spindle harmonic is directly observed.

1. Introduction

Sleep spindles are transient bursts of neural activity that occur in slow wave sleep, particularly in sleep stage 2, and are visible in the EEG at a characteristic frequency of 12–15 Hz (Contreras et al., 1997; Niedermeyer and Lopes da Silva, 1999). The physiological mechanisms underlying sleep spindles are an open question. It is known that spindles originate in the thalamus (Steriade et al., 1985; Steriade, 2003) and that they depend on the connectivity between the thalamic reticular nucleus, the thalamic relay nuclei, and the cortex.

Neural field modeling has proved to be a powerful technique for constructing relatively simple, physiologically based models of the brain that are capable of predicting EEG and correlate well with experimental data (Deco et al., 2008; Pinotsis et al., 2012). We have developed a neural field corticothalamic model of the brain (Robinson et al., 2005; Rowe et al., 2004; Robinson et al., 2001a, 2002) that we have previously used to investigate the alpha rhythm (Robinson et al., 2003; O'Connor and Robinson, 2004), age-related changes to the physiology of the brain (van Albada et al., 2010), and evoked response potentials (Rennie et al., 2002). Based on physiology, the model predicts sleep spindles originating in the intrathalamic loop between the reticular nucleus and relay nuclei. The frequency of the spindle oscillation matches experimental data, and the sleep spindles are transferred to the cortex via thalamocortical projections.

One source of nonlinearity in the brain arises because the firing response of neural populations is not a linear function of the cell potential. Therefore, we expect to see nonlinear effects when strong population voltage oscillations are present. Nonlinear effects in the brain have been investigated in previous studies examining seizures, in which high amplitude oscillations lead to observable nonlinear features in the power spectrum (Robinson et al., 2002; Breakspear et al., 2006). Nonlinearity has also been observed when the alpha oscillation is strong (Stam et al., 1999), and is implicated by experimental observations of bistability of the alpha rhythm (Freyer et al., 2009). The spindle oscillation is a

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similarly strong oscillation, and we may therefore observe nonlinearity in sleep spindles as well. For seizures, analysis of nonlinear effects can be hampered by muscle artifacts in the recordings. Similarly, the alpha rhythm displays a harmonic oscillation due to the delay in the corticothalamic loop (Robinson et al., 2001a; van Albada et al., 2010) which results in a linear harmonic that obscures the observation of nonlinear features at the same frequency. Neither of these limitations apply to the spindle oscillation, and it is therefore a particularly good phenomenon for examining nonlinear effects, because they occur in normal sleep and without any linear harmonic.

In the present study, we extend our analysis of our existing model by retaining nonlinear effects in the mathematical analysis. Nonlinear effects were already present in the theory and in numerical results, but were not examined analytically and effects in the sleep spindle regime were not investigated. Here, we apply a nonlinear framework we have previously outlined (Robinson et al., 2001b) to sleep spindles, and examine the resulting EEG power spectrum. Section 2 outlines the mathematical formulation of the linearized model used in the previous studies. In Section 3 we derive an analytic approximation to the nonlinear power spectrum and outline model predictions that can be tested against experimental data. Finally, in Section 4 we present our theoretical and experimental results.

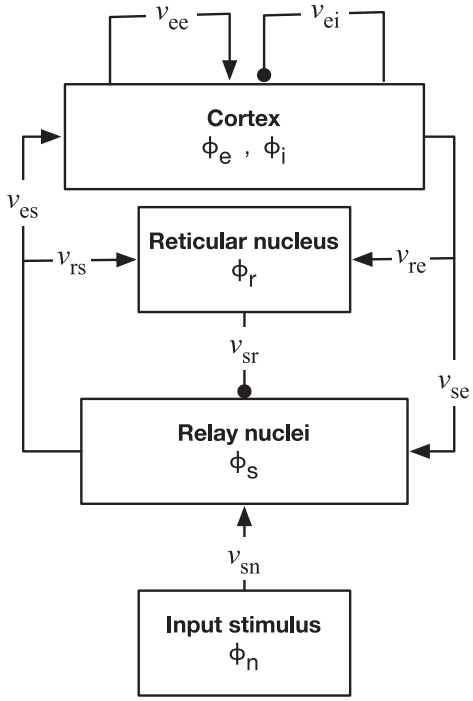

Fig. 1. Schematic diagram outlining the structure of our corticothalamic neural field model of the brain. Neural populations are denoted cortical excitatory *e* and inhibitory *i*, thalamic reticular *r* and relay *s*. The parameter ν_{ab} quantifies the connection to population *a* from population *b*. Inhibitory connections are shown with round arrowheads.

2. Theory

We begin by reviewing the neural field corticothalamic model used in previous studies (van Albada et al., 2010, 2007; Roberts and Robinson, 2012; Robinson et al., 2004, 2002, 1997).

2.1. Neural field model

The model consists of four neural populations, as shown in Fig. 1. Each population has a mean soma voltage V_a, which is related to its mean firing rate Q_a by a nonlinear sigmoid function

$$Q_a = S(V_a) = \frac{Q_{\max}}{1+\exp[-(V_a-\theta)/\sigma']}, \tag{1}$$

where θ is the mean threshold voltage, $\sigma'\pi/\sqrt{3}$ is the standard deviation of the threshold distribution, and $Q_{\max}$ is the maximum possible firing rate.

The population potential V_a is dependent on firing activity ϕ_b in presynaptic populations, the strength of the connection between the presynaptic and postsynaptic populations, and temporal smoothing effects arising from synaptodendritic dynamics and soma capacitance, giving

$$V_a(\mathbf{r},t) = \Sigma_b V_{ab}(\mathbf{r},t), \tag{2}$$

$$D_\alpha(t) V_{ab}(\mathbf{r},t) = \nu_{ab}\phi_b(\mathbf{r},t-\tau_{ab}), \tag{3}$$

$$D_\alpha(t) = \frac{1}{\alpha\beta}\frac{d^2}{dt^2} + \left(\frac{1}{\alpha}+\frac{1}{\beta}\right)\frac{d}{dt} + 1. \tag{4}$$

The quantity ν_{ab} is defined as $\nu_{ab} = s_{ab}N_{ab}$ where N_{ab} is the mean number of synapses per neuron *a* from neurons of type *b*, and s_{ab} is the mean time-integrated strength of soma response per incoming spike (Roberts and Robinson, 2012). The connections ν_{ei} and ν_{sr} are inhibitory, while all other connections in the model are excitatory. The effect of reversal potentials can be included by allowing the ν_{ab} to vary with voltage, $\nu_{ab}(V_a)$. Previous analysis has shown that this is a potential mechanism for generation of a 40 Hz gamma oscillation, but its effects are otherwise minimal (Rennie et al., 2000), hence we do not include these effects here. Moreover, we have checked that the voltages in our results do not approach the reversal potentials of the relevant neurons.

The parameters $1/\beta$ and $1/\alpha$ are the characteristic rise-time and decay-time, respectively, of the cell body response to a synaptic input, and these can be different for each of the connections in the model. However, we take a weighted average over the corticothalamic system to provide a single effective value for α and β that preserves the key aspects of the system dynamics (Robinson et al., 2004). The only nonzero time delays τ_{ab} in the system are for connections between the thalamus and cortex due to their physical separation, so $\tau_{es} = \tau_{is} = \tau_{se} = \tau_{re} = t_0/2$.

The field of firing activity ϕ_a is governed by a damped wave equation with firing in the presynaptic population as a source

$$D_a(\mathbf{r},t)\phi_a(\mathbf{r},t) = Q_a, \tag{5}$$

$$D_a(\mathbf{r},t) = \frac{1}{\gamma_a^2}\frac{\partial^2}{\partial t^2} + \frac{2}{\gamma_a}\frac{\partial}{\partial t} + 1 - r_a^2\nabla^2, \tag{6}$$

Here, r_a is the characteristic propagation distance for the population *a*, v_a is the pulse velocity, and $\gamma_a = v_a/r_a$ represents the field damping rate.

There are a number of simplifications that can be made to these equations: First, we only consider the connections as shown in Fig. 1. There are 16 possible connections between the four neural populations, but only 10 of them are nonzero in our model. Second, we assume that the number of connections between populations is proportional to the number of synapses available (Robinson et al., 1998; Wright and Liley, 1994; Liley and Wright, 1994. This *random connectivity* assumption provides a symmetry in the number of synaptic connections $N_{ib} = N_{eb}$ for all *b*, which implies that the connection strengths are also symmetric, with $\nu_{ee} = \nu_{ie}$, $\nu_{ei} = \nu_{ii}$ and $\nu_{es} = \nu_{is}$ (Robinson et al., 1998, 2004), giving the eight unique connections shown in Fig. 1.