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Thalamo-cortical mechanisms underlying changes in amplitude and frequency of human alpha oscillations

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ABSTRACT

Although a large number of studies have been devoted to establishing correlations between changes in amplitude and frequency of EEG alpha oscillations and cognitive processes, it is currently unclear through which physiological mechanisms such changes are brought about. In this study we use a biophysical model of EEG generation to gain a fundamental understanding of the functional changes within the thalamo-cortical system that might underly such alpha responses. The main result of this study is that, although the physiology of the thalamo-cortical system is characterized by a large number of parameters, alpha responses effectively depend on only three variables. Physiologically, these variables determine the resonance properties of feedforward, cortico-thalamo-cortical, and intra-cortical circuits. By examining the effect of modulations of these resonances on the amplitude and frequency of EEG alpha oscillations, it is established that the model can reproduce the variety of experimentally observed alpha responses, as well as the experimental finding that changes in alpha amplitude are typically an order of magnitude larger than changes in alpha frequency. The modeling results are also in line with the fact that alpha responses often correlate linearly with indices characterizing cognitive processes. By investigating the effect of synaptic and intrinsic neuronal parameters, we find that alpha responses reflect changes in cortical activation, which is consistent with the hypothesis that alpha activity serves to selectively inhibit cortical regions during cognitive processing demands. As an example of how these analyses can be applied to specific experimental protocols, we reproduce benzodiazepine-induced alpha responses and clarify the putative underlying thalamo-cortical mechanisms. The findings reported in this study provide a fundamental physiological framework within which alpha responses observed in specific experimental protocols can be understood.

Introduction

The most dominant characteristic of electro-encephalographic (EEG) recordings in awake human subjects is alpha oscillation, which refers to periodic fluctuations within the frequency band of 8–13 Hz. Since the first human EEG recordings performed by Hans Berger more than eighty years ago (Berger, 1929), an enormous number of studies have been devoted to establishing correlations between cognitive processes and characteristics of alpha oscillations, in particular changes in their amplitude and frequency, which we will further refer to as *alpha responses*. The diversity of such studies is large and includes manipulation with pharmacological substances such as propofol and thiopental (Feshchenko et al., 2004), nicotine (Domino et al., 2009; Roth, 1991), ethanol (Lukas et al., 1990), MDMA (Dafters et al., 1999), and THC (Volavka et al., 1973), psychiatric, psychological, and neurological syndromes such as schizophrenia (Merrin and Floyd, 1996), attention deficit hyperactivity disorder (ADHD) (Koehler et al., 2009), depression (Gotlib, 1998), mania (Flor-Henry and Koles, 1984), autism (Cantor et al., 1986), and Alzheimer's disease (Kuskowski et al., 1993; Moretti, 2004), as well as emotional and arousal states (Banquet, 1973; Knyazev et al., 2004; Kostyunina and Kulikov, 1996). In such and similar studies, correlations are established between cognitive variables and alpha responses as measured with EEG. In addition to these resting-state paradigms, different lines of research have studied human alpha oscillations during specific cognitive tasks and the presentation of controlled stimuli (ERS/ERD). These task-related paradigms allow for a more specific mapping between cognitive processes and alpha oscillations, thereby allowing hypothesis to be formulated regarding their role in cognition and perception (Jensen et al., 2002; Klimesch et al., 1998; Pfurtscheller et al., 1996). Although such empirical studies as the ones mentioned above establish correlations (and in some cases causal links; Hummel et al., 2002) between cognitive processes and alpha oscillations, by themselves they are incapable of pinpointing the physiological mechanisms through which the observed changes in alpha amplitude and frequency are brought about.

Currently, there is no consensus regarding the physiological mechanisms underlying the generation of human alpha oscillations. While

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some theories stress the importance of intrinsic membrane properties of particular neurons and propose that alpha oscillations are generated by intrinsic rhythmic properties of these neurons, other theories stress the importance of synaptic connections and claim that alpha oscillations emerge from network properties of thalamic (Lopes da Silva et al., 1974) or cortical tissue (Liley and Cadusch, 2002; Nunez, 1989; Nunez, 1974; van Rotterdam and Lopes Da Silva, 1982), or from reverberation within thalamo-cortical feedbacks loops (Rennie et al., 2002; Robinson et al., 2001, 2002). Neuroimaging studies show the existence of correlations between metabolic rates and alpha amplitudes both in cortical as well as in diverse subcortical structures (Sadato et al., 1998), in particular the thalamus (Goldman et al., 2002; Gonçalves et al., 2006; Larson et al., 1998; Schreckenberger et al., 2004). These results show that the functional states of thalamic nuclei are related to alpha amplitudes and suggest that they play a role in either the generation or modulation of alpha oscillations. A recently developed biophysical model of the EEG that makes explicit the thalamo-cortico-thalamic reverberation hypothesis of alpha generation is described in Rennie et al. (2002) and Robinson et al. (2001, 2002). Besides displaying spontaneous alpha oscillations, the model provides an integrated explanation of such diverse EEG phenomena as spontaneous oscillations within different frequency bands, both during wakefulness as well as during sleep (Robinson et al., 2001), event-related potentials (Rennie et al., 2002), and the generation of some of the generalized epilepsies (Breakspear et al., 2006). In this study we employ this model to obtain insight into the thalamo-cortical mechanisms presumably underlying alpha responses observed in EEG experiments.

Although all of the above mentioned empirical studies observe changes in the amplitude and frequency of ongoing alpha oscillations, the physiological causes that are responsible for the observed changes depend on the specific experimental paradigm. Several drugs and pharmacological agents modulate EEG rhythms, including the alpha rhythm. Examples include ethanol and anesthetic agents as propofol, that have strong affinity for the $GABA_A$ receptors in the cortex and thalamus, resulting in dose-dependent effects of both the amplitude and frequency of the alpha rhythm (Feshchenko et al., 2004; Kuizenga et al., 2001). There are many cholinergic pathways in the human brain and the endogenous neurotransmitter acetylcholine has various effects on the alpha rhythm too (Steriade et al., 1990). As the muscarinic or nicotinic acetylcholine receptors are expressed differently in various populations of interneurons, both in cortex and thalamus, a rich phenomenology of modulations of the alpha rhythm seems possible. Indeed, nicotine is reported to increase the dominant alpha frequency (Domino et al., 2009; Roth, 1991). Centrally acting anticholinesterase inhibitors, e.g. donepezil or rivastigmine, approved to treat patients with Alzheimer disease, have been shown to increase centroparietal alpha power during REM sleep (Moraes et al., 2006). Also, during normal aging different effects on muscarinic and nicotinic receptor subtypes were observed in postmortem brain tissue from different regions of the human brain (Nordberg et al., 1992), which may be responsible for the small, but significant decline in the dominant alpha frequency during aging (Lodder and van Putten, 2011). Furthermore, although in general, the physiological processes involved in cognitive processing and psychiatric and mood disorders are not known in detail, they most likely involve several neuromodulatory systems and receptor types with complex interactions.

Complete understanding of the detailed physiological changes underlying alpha responses therefore, requires—in addition to a computational model of the generation of EEG alpha oscillations—detailed physiological mechanisms that are specific to the experimental paradigm that is used to invoke the observed responses. In this study we pursue a more generic approach by determining which features of the thalamo-cortical system determine experimentally observed alpha responses. The assumption underlying this approach is that the physiological changes induced by experimental paradigms, change alpha frequency and amplitude by modulating the functional state of the thalamo-cortical system. Alpha responses are then a direct reflection of this altered functionality. Thus, although the specific physiological changes underlying the alpha responses are left implicit, this approach makes explicit the thalamo-cortical correlates underlying alpha responses that might be common to different experimental protocols.

In the Introduction and Materials and methods sections we provide a description of the thalamo-cortical model of the EEG and the associated theoretical EEG power spectrum, respectively. In the Introduction we show that alpha responses are induced by the non-linear membrane properties of the different neuron types within the thalamo-cortical system and that they are determined by modulations of the resonance properties of the feedforward, thalamo-cortico-thalamic circuits. In the Materials and methods section we investigate the differential effects of modulations in the resonance properties of these circuits. In the Results section we inventarize the effects of changes in synaptic and intrinsic neuronal parameters and analyze through which resonance-modulations the induced alpha responses are brought about. We also apply the methodology to alpha responses induced by administration of benzodiazepines and investigate the underlying thalamo-cortical mechanisms. In the Discussion section we discuss the main findings of this study, its limitations, and possible directions for further research.

Materials and methods

In this section we introduce the ingredients that we will use in the Results section to investigate the physiological mechanisms underlying alpha responses, which is the main focus of this study. Specifically, in the Thalamo-cortical model of EEG generation section we introduce the thalamo-cortical model of EEG generation (Rennie et al., 2002; Robinson et al., 2001). This includes the specification of the different types of neuronal populations comprising the thalamo-cortical circuitry together with their activation properties, the synaptic responses and the corresponding synaptic impacts, as well as the dynamics governing the spreading of neuronal activation over the cortical sheet. In the Theoretical EEG power spectrum section we introduce the theoretical EEG power spectrum, which is derived from linearizing the model equations about a stable equilibrium state. The power spectrum will be expressed in terms of neuronal excitabilities and synaptic frequency responses, which will be defined in the same subsection. In addition, we describe how responses in frequency and amplitude are quantified in this study.

Thalamo-cortical model of EEG generation

In Robinson et al. (2001) and Rennie et al. (2002) a computational model of the generation of EEG rhythms is developed. In contrast to network models, which describe the electrochemical properties of neuronal tissue by simulating large numbers of synaptically coupled neurons, the model developed in Robinson et al. (2001) and Rennie et al. (2002) describes the *average behavior* of such networks. Thus, rather than tracking the behavior of the membrane potentials of a large number of individual neurons, the model captures the average potential dynamics of populations of neurons. This approach therefore, is *macroscopic* hence naturally connects with the EEG, which is a macroscopic signal, reflecting the total synaptic current into large numbers of cortical pyramidal neurons.

The model comprises four types of neuronal populations, namely, cortical pyramidal neurons, cortical inhibitory neurons, thalamic reticular neurons, and thalamo-cortical relay neurons, whose *average membrane potentials* are denoted by V_k, for $k \in \{e,i,r,s\}$, respectively. The synaptic organization of these neuronal populations is illustrated in Fig. 1. Synaptic transmission from neurons of type l to neurons of type k is modeled by a function $h_{kl}(t)$ called the *synaptic response*, which is defined by

$$h_{kl}(t) = \frac{\rho_{kl}}{c_{kl}}\left[\exp(-\alpha_{kl}t) - \exp(-\beta_{kl}t)\right], \tag{1}$$