

On the Physiological Basis of the 15–30 Hz Motor-Cortex Rhythm

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Abstract

In vitro work on the rat brain and theoretical investigations have established that networks of GABAergic coupled interneurons play a fundamental role in creating the rhythmicity and synchrony necessary for neuronal oscillations in the gamma (30–80 Hz) and beta (15–30 Hz) bands. To test if related mechanisms are involved in producing the human ~20 Hz cortical rhythms, we recorded the magnetoencephalogram (MEG) from 8 subjects before and after orally administered benzodiazepine (0.08 mg/kg) which is known to upregulate GABAergic transmission. The power of the 15–25 Hz rhythm increased dramatically with benzodiazepine, whereas the mean frequency decreased slightly (~1 Hz). The most prominent sources of the benzodiazepine-induced rhythm were identified in the primary sensorimotor cortex bilaterally, suggesting that the sensorimotor cortex is the primary effector site of benzodiazepines. Numerical simulations of a physiologically plausible network model, in which excitatory neurons fire at 20 Hz at every second cycle of a 40 Hz rhythm produced by inhibitory interneurons, could account for these experimental findings. Thus the human sensorimotor-cortex beta rhythm and the rat hippocampal beta rhythm could be modelled according to similar biophysical mechanisms.

1 Introduction

The physiological mechanisms responsible for generating spontaneous neuronal oscillatory activity have been studied extensively both in hippocampal slice preparations and theoretically. The GABAergic interneurons seem to be crucially involved in synchronizing the neuronal population and determining the network frequency of spontaneous 30–80 Hz (gamma) oscillations [1,2,3]. Several studies suggest that related mechanisms are responsible for the generation of spontaneous 15–30 Hz (beta) oscillations [4,5,6]. How do these results relate to beta oscillations produced in the human brain? It is well known from clinical EEG recordings that benzodiazepines, which are GABA agonists, increase the beta band power [7]. Thus the GABAergic interneurons could play an important role in the production of spontaneous beta oscillations also in humans.

The aim of this study is first to characterize how beta power and frequency are modulated by benzodiazepines and to identify the brain regions responsible for producing the beta oscillations sensitive to benzodiazepine. These observations will be used to constrain physiologically realistic computational models, which aim at explaining the experimental findings.

2 Methods

Magnetoencephalographic (MEG) signals were recorded from 8 healthy subjects using a 306-channel Vectorview neuromagnetometer (Neuromag Ltd.; 204 planar gradiometers and 102 magnetometers). The subjects, seated in a relaxed position under the MEG helmet, were instructed to keep their eyes closed while ongoing MEG signals were recorded for 3 min. Benzodiazepine (Diapam) was then administered orally to the subjects (~80 µg/kg, i.e. 4–7.5 mg). Following a 1-hour break, the MEG measurement was repeated. Power spectra estimates of the neuromagnetic signals were calculated using Welch method. To identify the sources of the beta activity, the minimum current estimates were calculated in the frequency domain [8]. This allowed us to locate the sources of the 15–30 Hz oscillations and to superimpose them onto the subject's own MRIs.

The network model was constructed of 20 excitatory and 8 inhibitory Hodgkin-Huxley type model neurons with all-to-all connection (see Fig.3A). The synaptic connections were modelled using realistic kinetics for AMPA and GABA receptors. During the numerical integration, noise was added to the excitatory neurons. The total field produced by the excitatory neurons was calculated as the sum of the excitatory currents lowpass filtered at 20 Hz.

3 Results

Figure 1A shows power spectra averaged for sensors located over the left/right sensorimotor areas for a representative subject before (dotted line) and after (solid line) the administration of benzodiazepine. Benzodiazepines caused an increase in the beta power and a broadening of the peak towards lower frequencies. Figure 1B shows the grand average (N=8) of the relative increase in beta band power (15–30 Hz). The beta increase, which was strongest over sensorimotor areas, was highly significant ($p < 0.05$ at 88 sensor locations).

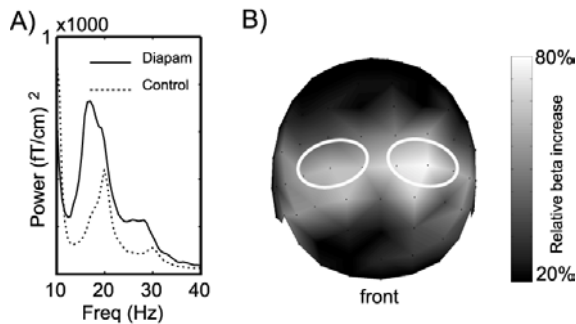


Fig. 1. A) The power spectra for subject S2 averaged across 36 sensors over the right/left sensorimotor cortex. B) The relative increase of the beta power with benzodiazepine represented on the geometry of the helmet; grand average of 8 subjects. The rings indicate sensor locations most sensitive to sensorimotor activity.

To quantify the change in beta frequency with benzodiazepines, we averaged the power spectra from sensors over the sensorimotor areas, and the dominant peak in the beta band was identified for each subject. The frequency was decreased slightly (~1 Hz) but significantly ($p < 0.05$) with benzodiazepines.

Figure 2A shows the minimum current estimate in the frequency domain explaining the 19 Hz activity projected to the brain surface of subject S2. The current estimates for the benzodiazepine case is stronger than for the control case, however, the spatial distributions are similar.

The source is superimposed on the subjects MRI (Fig. 2B) and agrees with the 'hand area' of the central sulcus. The locations of the sources before and after benzodiazepine were virtually indistinguishable.

In order to simulate the increase in beta power, we considered a network of single compartment excitatory and inhibitory neurons (Fig. 3A). The model neurons have been previously described [6]. The 20 excitatory and 8 inhibitory neurons had variations in the amount of applied current so that, in absence of coupling, individual cells fired at a range of

frequencies. To model the effects of benzodiazepine, we increased both the inhibitory-excitatory coupling as well as the inhibitory-inhibitory coupling. At control strengths (low inhibitory coupling), the inhibitory neurons fired at a rate, which was fast enough to prevent most of the excitatory neurons to fire. As the self-inhibition increased, the inhibitory cells slowed down, allowing some of the excitatory cells to escape and fire. The excitatory-excitatory coupling encouraged other excitatory cells to fire and helped synchronize them. If the inhibitory coupling was increased further, the firing of the inhibitory cells decreased even more allowing most of the excitatory cells to fire. However, the presence of a slow outward potassium current in the excitatory cells prevented them from firing at every cycle. Thus, while the inhibitory cells fired roughly at 40 Hz, the excitatory cells fired at half that and the network produces a strong component in the beta range of about 20 Hz (here, the peak occurs at 18 Hz). Figure 3 shows the dramatic increase in the beta power of the total field produced by the excitatory currents for low and high GABAergic inhibition.

4 Discussion

By magnetoencephalographic recordings we observed a strong (about 80%) increase in the power of beta oscillations with benzodiazepines. The increase in beta power was associated with a small decrease in beta frequency. The sources producing the beta oscillations sensitive to benzodiazepine were identified to the hand area of sensorimotor cortex. This is consistent with previous work identifying the sources of the spontaneous and induced beta activity to the primary motor cortex [9]. Computer simulations of a network of physiologically realistic model neurons could account for the increase in beta oscillations with an increase in inhibitory drive. As the recurrent inhibition increased, the firing frequency of the inhibitory neurons decreased allowing the excitatory neurons to fire a beta frequency.

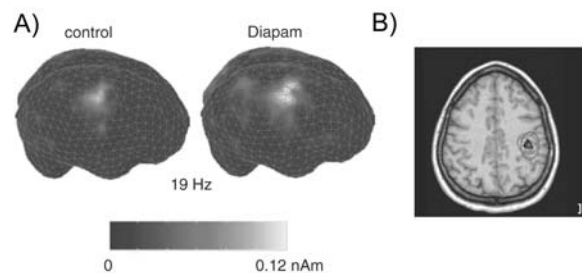


Fig. 2. A) Minimum current estimates of the beta band activity projected to the brain surface. B) Co-registration of the centre of the beta band sources on

the subjects MRI. The centres before and after application of benzodiazepines (light and dark symbols) are virtually identical.

In conclusion, we have proposed a biophysical model for the human sensorimotor-cortex beta rhythm, which can account for the increase in beta power with benzodiazepine. This model was initially proposed to account for findings in the beta rhythm of the rat hippocampus. Thus, the human beta rhythm and the rat hippocampal beta rhythm can be modelled according to similar biophysical mechanisms.

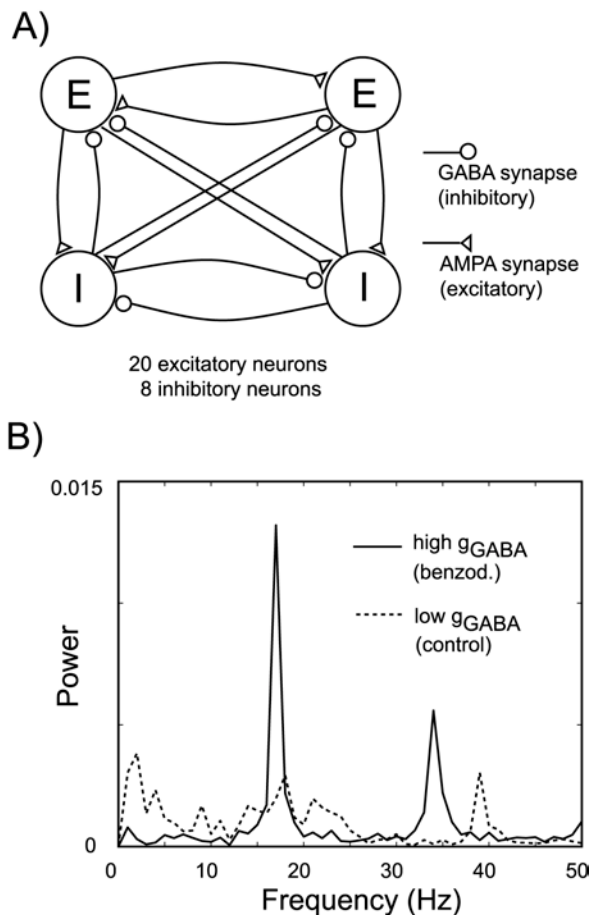


Fig. 3. A) A schematic illustration of the synaptic connectivity in the network model. B) The powerspectra calculated from the summed excitatory synaptic currents.

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6 Literature

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