DISSERTATION

Electroencephalography-based characterization of human cortical population spikes and ongoing rhythms during functional magnetic resonance imaging

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Frank Freyer
aus Gütersloh

Gutachter: 1. Prof. Dr. Arno Villringer
2. PD Dr. Hubert Dinse
3. Prof. Dr. Viktor Jirsa

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Preliminary Remarks

This synopsis summarizes the three peer-reviewed publications that I contributed to within the scope of my PhD thesis. The structure and extent of the synopsis follows the doctorate regulations of the Charité University Medicine Berlin. In the following the three publications are abbreviated as *Study 1 (*Ritter et al. 2008), *Study 2* (Freyer et al. 2009b) and *Study 3* (Freyer et al. 2009a), respectively. For detailed introduction, methods, results and discussion please see the respective publications which are inserted in their complete form in section 'Publications', starting on page 25.

Abstract

The aim of my PhD thesis was to characterize the spatio-temporal dynamics of two different types of neuronal large-scale oscillatory signals using electroencephalography (EEG) and functional magnetic resonance imaging (fMRI). In this synopsis I present three studies which emerged from this project and to which I contributed within the scope of my PhD thesis.

The first part of my thesis deals with somatosensory evoked high frequency bursts (HFBs). These EEG oscillations at a frequency of 600 Hz constitute a unique possibility to noninvasively record population spikes of thalamocortical and cortical neurons in humans. In *Study 1*, we combined recordings of HFBs and fMRI in order to derive a noninvasive measure of spiking activity together with the slow vascular fMRI signal and the conventional low-frequency EEG, which is dominated by postsynaptic activity. Using an interleaved EEG-fMRI setup, where HFBs were recorded between fMRI acquisition periods, we were able to show that spatially distinct fMRI activations along the thalamocortical pathway could be attributed to spontaneous fluctuations of different HFB components separated only by milliseconds. Conventional EEG-fMRI approaches do not allow the continuous recording of high-frequency EEG signatures such as HFBs, since high-frequency fMRI-related imaging artifacts that contaminate the EEG cannot be removed using available methods. In *Study 2*, we therefore developed an EEG-fMRI setup including an enhanced artifact correction algorithm allowing for the continuous recovery of HFBs during fMRI. We thoroughly evaluated our setup not only for HFBs but also for spontaneous and evoked EEG signals ranging from 1 to 1000 Hz.

Large-scale neuronal activity also occurs in the absence of any external stimuli or task, reflected in the EEG as ongoing oscillations. In the second part of my PhD thesis, I aimed to characterize such EEG oscillations with respect to nonlinearity and multistability. These are the classic hallmarks of complex, self-organizing systems, of which the brain is widely assumed to be a paradigmatic example. However, at the large scale of neocortical dynamics there is little empirical evidence for such features. In *Study 3*, we studied the

temporal fluctuations of power in human resting-state EEG acquired both with and without fMRI and showed that key brain rhythms exhibit qualities such as bistability (bursting between high- and low-amplitude modes) in the alpha rhythm and irregular appearance of high amplitude “extremal” events in beta rhythm power fluctuations. These results challenge existing frameworks for understanding large-scale brain activity and suggest the development of more sophisticated generative models of brain dynamics.

Introduction

The human brain is a complex system comprising billions of heavily interconnected neurons. Despite this vast number, the brain's anatomy as well as the emerging dynamics is highly structured. In fact it is widely assumed that the spatially and temporally coordinated activity of large coherent neuronal populations give rise to higher order phenomena such as cognition and behavior (Engel et al. 2001). This coordinated and cumulative neuronal activity becomes manifest in large scale oscillations and fluctuations, which can be recorded noninvasively in humans with methods such as electroencephalography (EEG) and functional magnetic resonance imaging (fMRI).

High-frequency bursts as a noninvasive measure of population spikes during fMRI

FMRI has become a cornerstone of cognitive neuroscience, since it allows the non-invasive investigation of whole-brain activity with high spatial resolution. However, fMRI has a major limitation as all underlying neuronal events which occur on a time scale of milliseconds, such as excitatory and inhibitory synaptic activity and action potentials, are represented by means of an indirect slow blood oxygenation level dependent (BOLD) signal (Heeger and Ress 2002). In contrast to fMRI, EEG allows direct recording of neuronal activity with high temporal resolution on the order of milliseconds, albeit with rather low spatial resolution. One way to approach the limitations of both methods is to combine them. Simultaneous EEG-fMRI aims at recording spontaneous and event-related brain activity with high temporal and spatial precision. Numerous types of EEG signatures obtained during fMRI have been investigated so far, including epileptiform activity, ongoing rhythms and evoked potentials (for detailed reviews, see Ritter and Villringer 2006, Laufs et al. 2008).

But even with the combined use of conventional EEG and fMRI, not all aspects of neuronal activity are captured. The indirect vascular BOLD fMRI signal is known to be mainly correlated to postsynaptic activity (Logothetis et al. 2001). Also the conventional scalp EEG is dominated by low frequency signals that mainly reflect postsynaptic activity

and the contribution of action potentials to the EEG is minor due to their temporal and frequency characteristics, small generator volumes and tissue low-pass filtering (Nunez and Silberstein 2000). However, it is the spiking (i.e. action potential) activity, which reflects the actual way of communication between neurons, not the postsynaptic potential, which can be subthreshold and hence not necessarily leads to a transfer of information. Spiking activity is thus highly under-represented in EEG and fMRI. But there is an exception to the rule: the median-nerve derived somatosensory evoked potential (SEP) contains at least two high frequency components that represent scalp projections of population spikes of subcortical as well as cortical origin (Baker et al. 2003; Curio 2000, 2005). These high frequency bursts (HFBs) represent a unique proxy option for obtaining a noninvasive measure of spiking activity in humans by means of EEG. A combination of fMRI, conventional EEG and recordings of HFB would thus allow for the simultaneous and noninvasive acquisition of population spikes, postsynaptic activity and the vascular-metabolic activity in human subjects. For the truly continuous monitoring of HFBs during fMRI however, a number of caveats have to be considered. FMRI-related artifacts that are induced in the EEG constitute a serious challenge, particularly with increasing frequency of the EEG signal of interest. For the continuous recovery of HFBs during fMRI acquisition, a modified EEG-fMRI setup is necessary, and an optimized algorithm for the removal of imaging artifact has to be introduced.

Non-Gaussian characteristics of spontaneous cortical activity

Large-scale coordinated neuronal activity does not only occur on response to external stimuli or tasks. Even during so-called rest, i.e. in the absence of any external input, the brain generates such activity continuously. Recently, fMRI has become a major tool for investigating this so-called ‘resting state’ activity, in particular since the discovery of consistent resting-state networks in human fMRI maps (Greicius et al. 2003; Gusnard et al. 2001; Raichle et al. 2001). Also EEG is an ideal tool in these regards, as its high temporal resolution allows the study of activity from long to very short time scales. Resting

brain activity is reflected in the EEG as ongoing oscillations, such as the alpha or beta rhythm. The functional role and characteristics of resting brain activity is still unclear. The brain has dense internal connectivity with long-range projections that scale hierarchically (Hilgetag and Kaiser 2004; Sporns and Zwi 2004). Through its abundant use of energy, the brain resides in a strongly non-equilibrium state, even during so-called rest. Thus the brain exhibits the hallmarks of complex systems, which exist in a wide variety of physical and biological fields and exhibit self organization, multiple excited modes and highly correlated, non-diffusive processes (Zaslavsky 2002). However, in many computational models of neural population dynamics this aspect of complexity is not given enough consideration. The brain is rather modeled as a stochastic system close to equilibrium that generates Gaussian statistics. One example is the Fokker-Plank formulation (Deco et al. 2008), which is premised upon the “diffusion approximation” which assumes that the inputs on individual neurons within a population can be treated as temporally uncorrelated, allowing to replace the discharge rate of individual neurons by a common population activity. That means, although comprised of complex local units, the brain would be of sufficiently high dimension, that its large-scale statistics are nonetheless uncorrelated. Is it valid to describe cortical activity simply as filtered Gaussian noise or does the cortex exhibit non-Gaussian processes that suggest the need for more sophisticated generative models? One way to address this question is to examine the statistics of neuronal activity in humans across a wide range of temporal and spatial scales by applying non-invasive methods such as EEG and fMRI.

Aims

The aim of this PhD project was to utilize EEG and fMRI in humans for the investigation and characterization of two different types of neuronal oscillatory activity.

As first part of the thesis, I aimed at recording a non-invasive measure of spiking activity in humans together with fMRI. To this end, we capitalized on somatosensory-evoked HFBs in the human EEG, which are known to reflect scalp projection of population spikes of thalamocortical as well as corticocortical origin. As a first step to record HFBs during fMRI, we tested the feasibility, sensitivity and utility of our approach in an interleaved EEG-fMRI setup, circumventing the problem of imaging artifacts that contaminate the EEG when recorded during fMRI acquisition periods. The second step was to enable the truly continuous and simultaneous acquisition of HFBs and fMRI, i.e. the recovery of ultrahigh-frequency EEG signatures even during imaging-artifact afflicted fMRI acquisition periods. This required a modified EEG-fMRI setup and an enhancement of existing imaging-artifact correction (IAC) algorithms. By introducing a new IAC approach, the aim was to evaluate both the recovery of ultrahigh-frequency EEG signatures during fMRI acquisition and the general applicability of this approach to the broadband EEG spectrum.

In the second part of the thesis I studied ongoing rhythms abundant in human resting state EEG. The central question here was if the brain exhibits features of a complex, self-organizing system such as nonlinearity and multistability, even on a macroscopic spatial scale as measured by EEG or fMRI. To this end, I examined the likelihood distribution of power fluctuations across different frequencies and tested the null hypothesis that these distributions could be described by a simple one parameter family of exponential distributions, which would argue that the underlying system (i.e. the brain) is close to thermodynamic equilibrium and that cortical activity only reflects uncorrelated stochastic events describable as filtered Gaussian noise. The final aim was to reject this null hypothesis, which would imply the presence of non-Gaussian processes in the cortex. This in turn would suggest the need to revise existing simplified models of brain dynamics.

Methods

For more detailed methods, please refer to publications Ritter et al. (2008), Freyer et al. (2009a), and Freyer et al. (2009b), which are inserted in their complete form in section 'Publication' starting on page 25.

Subjects and experimental design

All subjects were healthy and right-handed and gave written informed consent according to the declaration of Helsinki prior to investigation. The studies were conducted in compliance with the relevant laws and institutional guidelines and approved by the local ethics committee.

Study 1 and 2: Transcutaneous constant-current electro-stimulation was delivered to the right median nerve in a blocked stimulation-versus-rest design. Depending on the study, stimulation frequencies varied between 4, 8 and 15 Hz.

Study 3: Subjects were requested to rest with eyes closed, whilst maintaining alertness. There were no tasks or stimuli.

Simultaneous EEG-fMRI

Simultaneous EEG-fMRI was acquired with MR-compatible EEG caps and amplifiers (BrainAmp, Brainproducts, Inc., Munich, Germany) in two different 1.5T MR-Scanners (Siemens Vision and Sonata, Erlangen, Germany) using a T2*-weighted BOLD sensitive gradient echo planar imaging (EPI) sequence. In *Study 1* and *2*, an interleaved fMRI protocol was employed (periods MR data acquisition alternate with acquisition-free periods). In *Study 2,* the EEG and fMRI devices were synchronized in order to prevent variant sampling of the imaging artifacts to improve IAC, particularly in the ultrahigh-frequency range. Additionally, a modified EPI sequence ('stepping stone') was employed, which was specifically developed for imaging-artifact minimization during EEG-fMRI acquisition (Anami et al. 2003). In *Study 2* and *3* a number of EEG datasets without fMRI acquisition were additionally recorded.

Data analysis

All data analysis was carried out using Matlab (The Mathworks Inc., Natick, MA, USA) and Vision-Analyzer software (Brain Products, Inc., Munich, Germany). FMRI data was analyzed using the Matlab-based SPM toolbox (www.fil.ion.ucl.ac.uk/spm).

Study 1: EEG data of periods without fMRI acquisition were filtered, segmented, baseline-corrected, and averaged in order to extract high- and low-frequency SEP components, i.e. HFBs and the primary cortical component N20. HFBs were further partitioned into an early and a late component, as defined by previous studies (Gobbele et al. 2003). Stimulus-frequency dependent amplitude attenuation of early and late HFB components was tested for statistical significance (paired Student's t-test). Furthermore, we looked for differential fMRI activation sites of high- and low-frequency SEP components, in particular of HFBs as indices of population spikes. To this end regressors reflecting spontaneous amplitude fluctuations of early and late HFB and the N20 component were correlated on a voxel-by-voxel basis with the fMRI BOLD-signal.

Study 2: Gradient-switching induced imaging artifacts in the EEG were corrected with an in-house-developed algorithm representing a modification of the widely used averaged-artifact-subtraction (AAS) method (Allen et al. 2000), which was extended to recover ultrahigh-frequency EEG. The extended algorithm featured a new type of template calculation, including a similarity measure for imaging artifacts and optimized exponential weighting according to similarity. A refined removal of ultrahigh-frequency imaging artifact residuals was ensured by a cascade of broad-band and band-specific principal component analysis (PCA). The success of our new IAC approach was thoroughly evaluated for evoked ultrahigh-frequency signals (i.e. HFBs) and unaveraged broadband EEG spectra up to 1 kHz. The evaluation was based on ratios between imaging-artfiact afflicted ("scan") periods and imaging artifact-free ("non-scan") periods before and after IAC. Using these ratios, different EEG-fMRI scenarios were compared with respect to EEG and fMRI signal-to-noise ratios (SNRs) and experimental design flexibility.

Study 3: EEG-datasets acquired during fMRI were corrected for imaging artifacts, ballistocardiogram effects, eye movements and scalp-muscle artifacts. Dynamic spectrograms were derived by convolving the EEG data with complex Morlet wavelets. Frequency-specific probability distribution functions (PDF's) were then obtained by partitioning the fluctuations of power separately at each frequency and counting the number of observations in each bin. PDF's were then fitted by a simple exponential PDF, resembling the null hypothesis of an underlying Gaussian process. In order to gain a better insight into their functional form, particularly the asymptotic scaling behavior at the tails, the fitted PDF's were evaluated in log-linear and log-log coordinates. To exclude the possibility that observed deviations from the empirical fit to the exponential PDF were due to trivial causes such as finite sample set, measurement bias or methodological processes all analyses were also repeated on surrogate data constructed by Fourier-based phase randomization of the original EEG data.

Results

Study 1: High-frequency (600 Hz) population spikes in human EEG delineate thalamic and cortical fMRI activation sites

In the first study, we investigated whether HFBs as indices of population spikes can be recorded by means of EEG during fMRI. We found that in all subjects HFBs could reliably be recovered. HFB amplitudes, latencies and frequencies were in concordance with previous studies outside the MR-environment (Curio 2005). To test the sensitivity of our approach we measured stimulus frequency dependent amplitude modulations of HFBs. Our EEG-fMRI setup proved sensitive enough to resolve subtle amplitude attenuations at higher stimulation frequencies, again in agreement with earlier findings (Klostermann et al. 1999). Based on this reliable sensitivity to frequency dependent population spike variations, we finally utilized the combination of ultrahigh-frequency EEG and fMRI, and correlated the fMRI BOLD signal on a voxel-by-voxel basis with spontaneous fluctuations of early and late HFB components. We found focal fMRI activation sites along the somatosensory thalamocortical pathway. Fluctuations of the early HFB component were associated with a single activation cluster in the thalamus contralateral to stimulation. For the late HFB component an isolated positive correlation with the BOLD signal in the contralateral primary somatosensory cortex was detected. Both activation sites were in concordance with earlier suggested generator structures of HFB components (Baker et al. 2003; Gobbele et al. 1998; Ikeda et al. 2002).

Study 2: Ultrahigh-frequency EEG continuously acquired during fMRI

The purpose of the second study was to show that the recovery of ultrahigh-frequency EEG signatures during fMRI acquisition is feasible by introducing a new IAC approach and to demonstrate the applicability of this approach to the EEG spectrum below the ultrahigh-frequency range. We evaluated low- and ultrahigh-frequency evoked EEG signals (by means of HFBs and N20, respectively) and for unaveraged ongoing EEG signals (by means of EEG spectra partitioned into several frequency bands from 1-1000

Hz). The evaluation was performed by calculating ratios between different artifact conditions, i.e. scan and non-scan periods before and after IAC. Our modified approach proved to be suitable for the recovery of HFBs even during imaging-artifact afflicted scan periods as reflected in identical averaged waveforms and dipole sources of evoked HFBs in all artifact conditions. The achieved SNR of single-trial HFBs turned out to be sufficient to ensure continuous recording of HFBs during constant fMRI acquisition without a loss of SNR compared to an interleaved EEG-fMRI scenario with HFB analysis of only non-scan periods, as applied in *Study 1*. Also our approach allowed full recovery of the evoked low-frequency component N20 and unaveraged EEG up to 100 Hz.

Study 3: Bistability and Non-Gaussian Fluctuations in Spontaneous Cortical Activity

In contrast to the first two studies, which mainly focused on evoked HFBs, in the third study we examined the statistics of ongoing neuronal activity measured non-invasively in humans by means of EEG. We tested how well empirical frequency-specific PDF's of EEG log power values could be fitted by a simple exponential PDF, reflecting the null hypothesis of an underlying diffusive uncorrelated Gaussian process. We found that at some frequencies, empirical distributions were observed to exhibit a unimodal form with featureless tails above and below the mean and simple exponential PDF's fitted to these distributions captured the observed variability across the entire power domain. However, two striking deviations from the unimodal exponential distribution were found: firstly, in most subjects, PDF's in the alpha frequency band (8-12 Hz) exhibited two distinct modes. The second mode was well fitted by a second exponential PDF, indicating a form of bistability. Secondly, in all subjects and across a broad range of frequencies - typically in the beta range (~13-30 Hz) - the empirical PDF's showed a consistent upward bias of the right side tail (i.e., above the mean) from exponential towards power-law scaling. This bias could be well fitted by a double exponential form, also known as the 'Fisher Tippett distribution'. This preferential performance of the Fisher Tippett fit implies that large amplitude ('extremal') events occurred far more frequently than predicted by the null hypothesis as reflected in the simple exponential PDF. Both observations, bimodality in

the alpha range and non-Gaussian, extremal events in the beta range, were not existent in the phase-randomized surrogate data, confirming their statistical robustness and reliability.

Discussion

Within the framework of my PhD thesis I investigated and characterized two types of neuronal oscillations by using simultaneous EEG-fMRI recordings.

Firstly, I aimed at the noninvasive monitoring of spiking activity during fMRI in humans, a concept, which has not been realized before. In order to achieve this goal, I capitalized on somatosensory evoked HFBs, which can be acquired by EEG and which have been shown to reflect population spikes of sub-cortical and cortical origin. Simultaneous EEG-fMRI has become an attractive tool for the noninvasive investigation of human brain function. Despite the technical challenges complicating the assessment of EEG acquired during fMRI, numerous types of EEG signatures have been successfully investigated together with fMRI. The main obstacle that has to be overcome in simultaneous EEG-fMRI is the removal of imaging artifacts that are introduced into the EEG due to the magnetic properties of the MR-scanner. Although solutions for IAC have improved in the past years, the acquisition of HFBs during fMRI still constitutes a particularly difficult case. This is partly due to the fact that HFBs are among the most subtle physiological signals measurable with EEG with amplitudes in the nanovolt range and durations of a few milliseconds. The main reason why the recording of HFBs during fMRI is highly challenging is that these bursts oscillate at a frequency of about 600 Hz. The removal of imaging artifacts gets increasingly difficult at higher frequencies and none of the available IAC methods allows for the recovery of a signal in this frequency range. Therefore, one of the challenges within the scope of my thesis was to develop an EEG-fMRI setup including an enhanced IAC algorithm that enabled the recovery of HFB from imaging artifact afflicted periods. There are several reasons why it is attractive to combine fMRI with a noninvasive measure of spiking activity. Although fMRI has developed into a cornerstone of modern cognitive neuroscience, a huge gap still exists between direct invasive electrophysiological recordings of neuronal activity and the indirect BOLD fMRI signal. In order to bridge this gap it is crucial to relate the fMRI signal to different aspects of the underlying neural events. Particularly spiking activity is of high interest in this aspect,

since it represents the way neurons convey information among each other. In animal experiments, fMRI has already been combined with invasive recordings of local field potentials and neuronal spikes (Caesar et al. 2003; Logothetis et al. 2001). An analogous approach in healthy humans is difficult to realize due to the need of non-invasiveness. One way to measure neuronal activity noninvasively and directly in human is by means of EEG. The conventional EEG, however, does not directly reflect spiking activity, but rather summed excitatory and inhibitory postsynaptic potentials. HFBs constitute an exception to this rule and a combination of HFBs and fMRI allows identifying hemodynamic responses related to noninvasive correlates of cerebral population spikes. Possible applications for the integration of fMRI and HFBs are cases where it is crucial to differentiate whether a phenomenon is of vascular/metabolic or of neuronal origin. A clinical example is the recovery period after stroke, where it frequently cannot be distinguished whether the reoccurrence of an evoked fMRI signal is due to the recovery of the neurovascular coupling or due to true neuronal plasticity. Integrating a measure of spiking activity could help to resolve this ambiguity. In neurological disorders such as migraine and dystonia, it has been shown that HFBs are affected (Cimatti et al. 2007; Coppola et al. 2005; Restuccia et al. 2005). In such cases HFBs may be correlated to changes in fMRI activation patterns in order to gain a more complete picture of the disease pattern. All this can be done without the need for an invasive intervention.

To summarize the first part of my thesis I demonstrated that high-frequency EEG signals, representing a unique noninvasive window to spiking activity in humans, can be recovered noninvasively during fMRI from simultaneous EEG recordings. In a first interleaved EEG-fMRI setup, I showed that distinct fMRI activation sites in the thalamus and primary somatosensory cortex can be attributed to different HFB components unfolding at a millisecond timescale (*Study 1*). As a second step, I introduced a new IAC approach which allowed the recovery of ultrahigh-frequency EEG signatures such as HFBs even during artifact-afflicted fMRI acquisition periods. The integration of HFBs into fMRI introduces an improvement to conventional EEG-fMRI by increasing its sensitivity to

activity associated with specified neuronal events unfolding on a millisecond timescale that cannot otherwise be recovered (*Study 2*).

The second part of my PhD thesis aimed at characterizing a different type of neuronal oscillation, namely the ongoing rhythms of various frequencies that are abundant in human resting state EEG. The classical approach in neuroscience and psychology is to study the neuronal / behavioral response to a stimulus or task, such as the evoked potential in the EEG, the BOLD response in fMRI or psychophysical features such as reaction times. However, the brain is constantly active, also in the absence of any specific stimulus or task. In recent years there has been growing interest in the investigation of the so-called 'resting state' brain activity (Biswal et al. 1995), and it has been shown, that the brain's state at rest is an influential precursor to sensory processing (Makeig et al. 2002) or motor activity (Fox et al. 2006). It is now appreciated that neuronal data acquired during rest is highly structured and exhibits characteristic spatiotemporal dynamics that can act as a window into the highly structured nature of spontaneous large scale brain activity *per se* (Achard et al. 2006; Greicius et al. 2003). As the second part of my thesis I intended to shed more light on the structure of resting brain dynamics by studying the temporal fluctuations of power in human resting-state EEG. The specific question I tried to answer was whether resting state EEG data reflects the typical features of a complex, self-organizing system, of which the brain is widely suggested to be a paradigmatic example. The approach used here was motivated by the characterization of correlated, non-Gaussian processes in a wide variety of other complex systems (e.g. stock markets, sandpiles, turbulent fluids or ignited trees in forest fires), whereby a simple functional form is sought for the probability distribution of a measure of system activity (Bramwell et al. 1998; Bramwell et al. 2000). The crucial feature that allows to distinguish systems with non-trivial, strongly correlated fluctuations from those dominated by uncorrelated, diffusive ones is the presence of non-vanishing higher order moments (Chapman et al. 2002). Previous applications of this approach revealed universal power law distributions in

human locomotor activity (Nakamura et al. 2007) and non-Gaussian statistics in heart-rate variability during daily activity (Kiyono et al. 2005). Surprisingly, despite the apparent complexity of the brain, there is little empirical evidence showing that the brain exhibits the classical features of a complex system, such as nonlinearity, multistability and 'non-diffusivity' (i.e. large coherent fluctuations), at least at the very large-scale of neocortical dynamics as represented by EEG or fMRI. Hence most computational and methodological frameworks for healthy brain activity have been placed in a purely linear and stochastic framework. Many popular computational models of neural population dynamics are premised upon this perspective and assume that the inputs impinging on individual neurons within a population can be treated as temporally uncorrelated when computing instantaneous postsynaptic firing rates (Deco et al. 2008). The results of the here presented study (*Study 3*) challenge such existing frameworks for understanding large-scale brain systems. We found that there is strong evidence for bistability and non-diffusivity in key brain rhythms. Bistability is manifest as non-classic bursting between high- and low-amplitude modes in the alpha rhythm with a high-power mode expressed irregularly in discrete time windows. This is reflected in a distinctly bimodal distribution of the EEG log power values in the alpha band. Non-diffusivity is expressed through the irregular appearance of high amplitude 'extremal' events in beta-rhythm power fluctuations, reflected in the empirical PDF's as a consistent upward bias above the mean from exponential towards power-law scaling. Interestingly, the occurrence of such types of large amplitude events where suggested by Buzsaki (2006, p.128). Following an extensive survey of neuronal oscillations across a hierarchy of scales and the 1/*f* scaling laws of their power spectrum, he speculated that "rare but extremely large events are inevitable, because at one point 1/*f* dynamics become supersensitive to either external perturbations or its internal processes, responding with very large synchronized events". However, he then concluded that "such large events never occur". The present study suggests that such events in fact occur, but that their identification relies on a proper representation of the null-hypothesis for their non-occurrence. The null-hypothesis used

here was that the empirical PDF of EEG power values at all frequencies could be well described by the simple one parameter family of exponential distributions, which contain no further information than could be inferred from knowledge of the mean. Such distributions arise when the underlying system generates uncorrelated stochastic events and have near-maximum entropy (i.e., are close to thermodynamic equilibrium). This would accord with the view that cortical activity is well described as filtered Gaussian noise. In contrast, we could reject this null hypothesis in the above mentioned cases, implying the presence of non-Gaussian processes in human large-scale cortical activity during rest.

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Selected Publications

The following three peer-reviewed publications are submitted within the scope of this PhD Thesis.

Publication 1

Petra Ritter, Frank Freyer, Gabriel Curio, Arno Villringer (2008). High-frequency (600 Hz) population spikes in human EEG delineate thalamic and cortical fMRI activation sites. Neuroimage 42: 483-490

Impact factor (2008): 5.694

Publication 2

Frank Freyer, Robert Becker, Gabriel Curio, Arno Villringer, Petra Ritter (2009). Ultrahigh-frequency EEG during fMRI: Pushing the limits of imaging-artifact correction. Neuroimage 48: 94-108

Impact factor (2008): 5.694

Publication 3

Frank Freyer, Kevin Aquino, Peter A. Robinson, Petra Ritter, Michael Breakspear (2009). Bistability and Non-Gaussian Fluctuations in Spontaneous Cortical Activity. The Journal of Neuroscience 29: 8512-24

Impact factor (2008): 7.452

Please note: Due to copyright reasons, the complete published versions of Ritter et al. (2008), Freyer et al. (2009a) and Freyer et al. (2009b) are replaced by a link to the online version of the articles on the publishers' websites.

Publication 1

Petra Ritter, Frank Freyer, Gabriel Curio, Arno Villringer (2008). High-frequency (600 Hz) population spikes in human EEG delineate thalamic and cortical fMRI activation sites. Neuroimage 42: 483-490

The original article is available at http://dx.doi.org/10.1016/j.neuroimage.2008.05.026

Publication 2

Frank Freyer, Robert Becker, Gabriel Curio, Arno Villringer, Petra Ritter (2009). Ultrahigh-frequency EEG during fMRI: Pushing the limits of imaging-artifact correction. Neuroimage 48: 94-108

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Publication 3

Frank Freyer, Kevin Aquino, Peter A. Robinson, Petra Ritter, Michael Breakspear (2009). Bistability and Non-Gaussian Fluctuations in Spontaneous Cortical Activity. The Journal of Neuroscience 29: 8512-24

The original article is available at http://www.jneurosci.org/cgi/content/abstract/29/26/8512

Complete List of Publications

Publications in peer-reviewed journals

Freyer F, Aquino K, Robinson PA, Ritter P, Breakspear M (2009). Bistability and non-Gaussian fluctuations in spontaneous cortical activity. J Neurosci 29: 8512-24.

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Curriculum Vitae

Mein Lebenslauf wird aus Datenschutzgründen in der elektronischen Version meiner Arbeit nicht mit veröffentlicht.

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Eidesstattliche Erklärung

Ich, Frank Freyer, erkläre, dass ich die vorgelegte Dissertation mit dem Thema: “Surface electroencephalography analysis of human cortical population spikes and ongoing rhythms during functional magnetic resonance imaging” selbst verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel benutzt, ohne die (unzulässige) Hilfe Dritter verfasst und auch in Teilen keine Kopien anderer Arbeiten dargestellt habe.

Berlin, 29.07.2009

Frank Freyer