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NeuroImage

www.elsevier.com/locate/ynimg
NeuroImage 37 (2007) 149–163

Heart beats brain: The problem of detecting *alpha waves* by *neuronal current imaging* in joint EEG–MRI experiments

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Received 27 November 2006; revised 10 March 2007; accepted 7 April 2007
Available online 27 April 2007

It has been suggested recently that the influence of the *neuro-magnetic* field should make electrical brain activity directly detectable by MRI. To test this hypothesis, we performed combined EEG–MRI experiments which aim to localize the neuronal current sources of alpha waves (8–12 Hz), one of the most prominent EEG phenomena in humans. A detailed analysis of cross-spectral coherence between simultaneously recorded EEG and MRI time series revealed no sign of alpha waves. Instead the EEG–MRI approach was found to be hampered by artefacts due to cardiac pulsation, which extend into the frequency band of alpha waves. Separate brain displacement mapping experiments confirmed that not only the EEG but also the MRI signal is confounded by harmonics of the cardiac frequency even at 10 Hz and beyond. This well-known *ballistocardiogram* artefact cannot be avoided or eliminated entirely by available signal processing techniques. Therefore we must conclude that current EEG–MRI methodology based on correlation analysis lacks not only the sensitivity but also the specificity required for the reliable detection of alpha waves.

Keywords: EEG; fMRI; Neuronal current imaging; Alpha waves; Ballistocardiogram

Introduction

Ionic currents generated by neurons in the human brain are arguably the very essence of brain activity and potentially a key to understanding brain function. Present-day techniques for measuring brain activity non-invasively in humans include the electroencephalogram (EEG) and the magnetoencephalogram (MEG), both of which have a spatio-temporal resolution on the order of cm and ms. Alternatively, *functional magnetic resonance imaging* (fMRI), based on the *blood oxygenation level dependent* (BOLD) effect, offers a resolution on the order of millimeters and seconds.

These techniques differ not only in resolution *per se*, but mostly in the assumptions underlying the localization of brain activity. In EEG and MEG the location of neuronal current sources is estimated by fitting a model usually consisting of one or more electrical dipoles (Michel et al., 2004). The spatio-temporal resolution of BOLD fMRI, on the other hand, depends on the neuro-vascular coupling, i.e. the extent to which neuronal activity is reflected by changes in brain perfusion coincident in space and time (Logothetis and Pfeuffer, 2004).

The growing popularity of functional brain mapping in neuroscience creates a strong incentive to further develop non-invasive imaging techniques with improved resolution because none of the techniques applicable to humans offers a resolution on the length and time scale of neuronal processes (roughly μm and ms, respectively). In this respect the combination of EEG and MRI measurements and the prospects of directly detecting neuronal currents by MRI (rather than blood oxygenation, flow or volume) have received increasing attention in recent years. For example, work from the laboratories of R. Bowtell (Konn et al., 2003) and P. Bandettini (Bodurka and Bandettini, 2002; Petridou et al., 2006) suggests that spontaneous neuronal bulk activity in the human brain like *alpha waves*, and possibly even the much weaker *event-related potentials* (ERP) may indeed be detectable *directly* by MRI. Specifically, their theoretical models and phantom experiments show consistently that the detection limit for localized magnetic field changes lies around

Abbreviations: BCG, ballistocardiogram; CNR, contrast to noise ratio; CZT, chirp z-transform; DENSE, displacement encoding with stimulated echoes; DFT, discrete Fourier transform; DOF, degrees of freedom; ECD, equivalent current dipole; ECG, electrocardiogram; EEG, electroencephalogram; EPI, echo planar imaging; ERP, event-related potential; fMRI, functional MRI; FFTW, fastest Fourier transform in the west; FT, Fourier transform; MEG, magnetoencephalogram; MGA, MRI gradient artefact; MRI, magnetic resonance imaging; MSC, magnitude squared coherence; MTS, mean template subtraction; SNR, signal to noise ratio.

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Available online on ScienceDirect (www.sciencedirect.com).

1053-8119/$ - see front matter © 2007 Elsevier Inc. All rights reserved.
doi:10.1016/j.neuroimage.2007.04.034

0.1–0.2 nT on modern MRI systems at 3 T field strength and that consequently, oscillating current dipoles of about 5–8 nAm strength are detectable at least *in vitro*. Since alpha waves are thought to involve current dipole strengths of up to 100 nAm, they should in principle be detectable, provided that the dipole approximation is valid. Indeed Konn et al. (2004) presented *in vivo* experiments in which they observed MRI phase fluctuations in the alpha band which they tentatively interpreted as originating from alpha waves. By the same token, the detection of evoked potentials by MRI is thought to be less likely since their equivalent dipole strength on the order of 10 nAm is close to the detection limit (Konn et al., 2004; Hamalainen et al., 1993). Accordingly, experimental results in this area are a matter of controversy (Konn et al., 2004; Chu et al., 2004; Hagberg et al., 2006; Bianciardi et al., 2004; Xiong et al., 2003).

The concept of *neuronal current imaging* is based on the fact that any electrical current in the brain, contributing to the EEG, will be accompanied by a magnetic field, contributing to the MEG, which must have a small influence on the MRI signal as well (review: Hagberg et al., 2006). Our experiments aim to detect neuronal currents in the human brain by analysing the cross-spectral coherence of simultaneously recorded EEG and MRI data. This rationale only requires a constant phase relationship between the two signals compared, an assumption which seems well justified by physical considerations: EEG and MEG studies have established that the propagation of weak electromagnetic fields (of neuronal origin) through the human brain and skull is well described by Maxwell's equations in the electrostatic regime and thus essentially independent of the biological sources of such fields (Hamalainen et al., 1993; Plonsey, 1982). Basic electrodynamics also govern the relationship between local magnetic field, local magnetization and the resulting contribution to an MRI signal (Eq. (3)) (Konn et al., 2004). Based on these physical constraints it is all but inevitable that a stationary neuronal current source, its contribution to the EEG signal and the affected local MRI signal are interrelated and form a *linear time-invariant system*. This specifically implies constant amplitude and phase relationships between these three signal components.

Alpha waves (Berger, 1929) would seem to afford a good chance for the detection by MRI because they are one of the strongest and most prevalent EEG phenomena in humans. EEG and MEG studies characterize alpha waves as 8–12 Hz oscillations with amplitudes commonly exceeding ±50 μV on the scalp. They are thought to originate from dipolar current sources of up to 100 nAm strength located in the visual cortex (Salmelin and Hari, 1994; Manshanden et al., 2002). This should make them detectable, given the sensitivity and imaging speeds of modern MRI systems (Konn et al., 2004).

Methods

We conducted simultaneous EEG–MRI experiments in order to use the alpha wave signal detectable by EEG as a reference to probe the MRI voxel time series for possible correlations. Since the signal of interest is localized in the frequency domain, the analysis of cross-spectral coherence should capture its essence, utilizing all timing information available by EEG–MRI. Additionally, it offers a few practical advantages over the theoretically equivalent correlation analysis in the time domain:

- Periodic signals and artefacts such as cardiac pulsation are separated and more easily discernable in the frequency domain than in the time domain where such signals are mixed.
- The measure is independent of the relative phase and (unequal) sampling rates of the signals compared.
- Efficient spectral estimators, computational methods and statistical tests are readily found in literature.

Hardware and software

Experiments were performed on a Philips Achieva scanner at 3 Tesla field strength (Philips Medical Systems, Best, Netherlands) with 80 mT/m and 200 mT/m/ms gradients using the standard quadrature head coil in transmit and receive mode. Electrophysiological signals were recorded from 63 EEG channels and 2 ECG channels using MR-compatible equipment (BrainProducts GmbH, Munich, Germany) which features a sampling rate of 5 kHz, hardware filters at 250 Hz and a phase-locking device for synchronization with the clock of the MRI system (Mandelkow et al., 2006). The sintered Ag–AgCl ring electrodes incorporated 5 kΩ resistors and were mounted in an MR-optimized electrode cap (EASYCAP GmbH, Herrsching-Breitbrunn, Germany) which covered all positions of the 10–20 system, as well as most electrodes of the 10–10 system, plus two electrodes below the outer *canthus* of each eye. For optimal detection of focal occipital activity such as alpha waves, the electrodes *O1* and *O2* were placed at 15%, i.e. 5% more laterally than normal. Also, additional electrodes *PO1* and *PO2*, as well as *Ol1* and *Ol2* were placed to the left and right of the midline halfway between *Oz* and *Iz*. *Fz* served as recording reference and *AFz* as ground (see Brem et al., 2006 for more detail). The software BESA (MEGIS Software GmbH, Gräfelfing, Germany) was used for modeling the electrical sources of alpha waves from EEG data alone. All other signal processing and data analysis was implemented using the software package Matlab (The MathWorks Inc., Natick, MA, USA).

Experimental design

While alpha waves are a common EEG phenomenon readily detectable in over 80% of the population (Zschocke, 1995), their prevalence and amplitude are a variable and individual trait. Based on prior screening by EEG, we selected subjects that exhibit frequent alpha waves of large amplitude to improve our chances of a successful detection experiment. Four volunteers with strong alpha wave activity were scanned with their eyes closed, presumably in a state of wakeful relaxation conducive to the production of alpha waves. The volunteers were instructed to relax but not sleep in the darkened scanner and to open their eyes only when the room lights were turned on. This simple visual stimulus was used for suppressing alpha wave activity as a control condition for 10–20 s during each experiment. Experimental runs lasted for 3–6 min and were repeated several times to increase the sample size and thereby statistical power in the data analysis. Subjects in this study gave informed consent in accordance with regulations by the ethics committee of the canton of Zurich.

MRI methods

Spontaneous EEG activity, such as alpha waves, is not accompanied by any external stimulus to which the MRI acquisition can easily be phase locked. For this reason we are bound to record the full bandwidth of the signal of interest (8–12 Hz). In order to fulfil the Nyquist criterion for sampling a signal of 12 Hz bandwidth and at the same time maximize sensitivity to magnetic field