Toward a brain functional connectivity mapping modality by simultaneous imaging of coherent brainwaves

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Matching the proton-magnetic-resonance frequency to the frequency of a periodic neural oscillation (e.g., alpha or gamma band waves) by magnetic resonance imaging techniques, enables direct visualization of brain functional connectivity. Functional connectivity has been studied by analyzing the correlation between coherent neural oscillations in different areas of the brain. In electro- or magneto-encephalography, coherent source reconstruction in a source-space is very tricky due to power leaking from the correlation among the sources. For this reason, most studies have been limited to sensor-space analyses, which give doubtful results because of volume current mixing. The direct visualization of coherent brain oscillations can circumvent this problem. The feasibility of this idea was demonstrated by conducting phantom experiments with a SQUID-based, micro-Tesla NMR/MRI system. We introduce an experimental trick, an effective step-up of the measurement B-field in a pulse sequence, to decouple the magnetic resonance signal from the strong magneto-encephalographic signal at the same frequency.

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Introduction

Currently, one of the main issues in the field of brain research is to clarify the functional connectivity in the brain. Since Roentgen invented the first medical X-ray system in 1895, computerized tomography (CT) and magnetic resonance imaging (MRI) techniques have been developed to obtain non-invasive anatomical information about a brain. Afterward, electro- and magneto-encephalography (EEG, MEG) (Hamalainen et al., 1993) and functional MRI (fMRI) enabled researchers to map the primary functions. Then, diffusion tensor imaging (DTI) began to reveal details of anatomical connectivity in the white matter. This got people interested not only in the basic primary functions of the brain, but also in how the different areas of the brain are functionally-connected and how they work cooperatively. This is termed brain functional connectivity (BFC). However, any modality that can directly detect the functional connectivity has not yet been developed. Although EEG, MEG and fMRI have been used for the purpose, the fMRI measurement is based on blood oxygen-consumption at nearby vessels connected to the active neurons. For this reason, there are significant temporal and spatial discrepancies between the real neuronal activation and the measured signals (Ahlfors and Simpson, 2004). The EEG and MEG rely on indirect source estimation by solving an inverse problem.

The first suggestion to directly measure neuronal currents by the nuclear magnetic resonance (NMR) technique was by Bodurka (Bodurka et al., 1999). Direct neuronal current imaging (DNI), is able to measure additional dephasing by the magnetic fields generated by an active neuronal current. However, in high field MRI (>1.5 T), such measurement was reported to be infeasible because the susceptibility change from hemoglobin (2%) dominates the NMR dephasing effect from neural activity (2%–0.002%) (Parkes et al., 2007). Another obvious hindrance is the huge difference in the strengths of the Larmor field (~T) and the small change of the magnetic field strength of the neuronal currents (~hundreds of pT; Burghoff et al., 2010).

Recently, micro-Tesla NMR and MRI (Clarke et al., 2007; Dabek et al., 2012; Ledbetter et al., 2008; Liao et al., 2010; McDermott et al., 2002, 2004; Myers et al., 2005; Vesani et al., 2013; Xu et al., 2006; Zotev et al., 2008) have been thought to be potential candidates for implementing DNI (Cassar et al., 2009; Kraus et al., 2008). By replacing the inductive detection coil in the NMR with a superconducting quantum interference device (SQUID) sensor, we were able to eliminate the sensitivity reduction which is inversely proportional to the detection frequency; the superconducting screening current transferred to the SQUID sensor does not depend on its oscillation frequency. This feature enabled detection of the NMR signal under an extremely weak static magnetic field; the huge difference of nine orders in the magnetic field strengths could drop to three orders under the micro-Tesla Larmor field.

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field and the susceptibility change is negligible as well. A more interesting feature of the micro-Tesla NMR is to utilize a periodically-oscillating, neuronal magnetic field as a tipping pulse like the Bp field in the conventional NMR. Based on this feature, several detection ideas were suggested for matching the proton resonance to the neuronal-pulse-trains (Cassará et al., 2009; Kraus et al., 2008), high frequency component suggested for matching the proton resonance to the neuronal-pulse-trains (Höfner et al., 2011; Scheer et al., 2011).

Going back to the problematic current issues dealing with the study of BFC, both EEG and MEG are believed to be appropriate tools to study connectivity because of their high detection bandwidth (covering all bands of brainwaves) and multichannel detection capability. Thus, a lot of studies aimed at revealing BFC have reported calculating the coherence, correlation, and phase synchronization of the brainwaves of a specific frequency band, between different detection channels. However, there was an interesting report that even two unsynchronized sources could show a strong correlation between different sensor-channel recordings because of volume current mixing (Tass et al., 1998). The report is quite striking because it could make doubtful all the functional connectivity studies conducted so far, that were based on correlation between sensor channels. In order to be clear, we need to analyze the connectivity with source-space waveforms. We could have obtained the signals using a direct measurement tool such as a deep-brain-stimulation (DBS) probe. However, this is an invasive means which is not applicable to normal subjects. We might also have reconstructed the source signal waveform from the multichannel measurement records of an EEG or MEG with spatial filtering, like a minimum variance beam-former (Sekihara and Nagarajan, 2008; Van Veen and Buckley, 1988; Van Veen et al., 1997) or a multiple signal classification (MUSIC) algorithm (Hayes, 1996; Schmidt, 1986). Such algorithms reconstruct the source power and waveform based on a covariation feature among different channels, so to speak, covariant spatial patterns of multichannel recordings; they are appropriate for source analysis of a periodically oscillating signal. However, where closely-placed, correlated sources exist, a ghost source appears to exist between the correlated sources (Sekihara and Nagarajan, 2008; Van Veen et al., 1997). Even if a method of correlated source suppression with linear constraints (Kim, 2011) is effective for estimating the positions of the real sources, we still would have to know the exact position of the correlated sources to suppress them. An imaginary coherence image (Nolte et al., 2004; Sekihara et al., 2011) is useful for rejecting spurious interference from coherent sources, but it does not work properly for phase-matched, correlated sources.

As an alternative, we propose a functional connectivity imaging idea that involves direct mapping of coherently oscillating currents in a brain, so that we could visualize its functional connectivity (spontaneous or induced coherent brainwaves connecting regions in a brain that are active simultaneously). Our approach can be included as a specific application of a wide concept of DNI in a methodological point of view. Here, in order to specify the application of our proposal, we will call our technique brainwave magnetic resonance (BMR) since it measures the NMR signal of protons around active coherent brainwave sources; the goal of BMR is to match the proton NMR resonance, not the high frequency activity from neural spike-train generation, but to the alpha- to gamma-band (10–100 Hz) brainwaves (Fig. 1). Therefore the static field of BMR should be on the order of a couple of micro-Tesla; much weaker than the usual target fields for previously suggested DNI applications.

Beside the difference in frequency ranges, BMR measurement requires that we decouple the magnetic resonance signal from the MEG signal of the same frequency since we cannot switch spontaneous brainwave activity off and on. This decoupling was accomplished by the simple but effective trick with the pulse sequence, of stepping up the magnetic field (Bm). Although such a change in the static magnetic field, or gradient field strength, in a conventional NMR/MRI pulse sequence has already been reported (Haacke et al., 1999), it provides many specific benefits for measurements of micro-Tesla BMR, in particular. These are described below.

In this article, we will introduce the basic principles and describe in detail the experimental setup for BMR. We also present the preliminary experimental BMR imaging results for a small-animal-brain phantom by using our SQUID-based NMR system to estimate the potential of the BMR idea.

Brain wave magnetic resonance

The BMR proposal is to perform direct localization of coherent brainwaves using SQUID-based micro-Tesla NMR (McDermott et al., 2002). The main idea of BMR is to resonate proton spins around the coherent brainwave excitation of a specific frequency band. The cyclic excitation of collective neuronal potential generates periodic electric currents producing magnetic fields around the currents. The frequency of the alternating magnetic field corresponds to a specific band frequency, depending on the relevant cortical network: theta (4–7 Hz), alpha (8–12 Hz), beta (13–30 Hz), and gamma (30–200 Hz) (Uhlhaas and Singer, 2010). The strengths of the static magnetic fields corresponding to those Larmor frequencies are about 0.1–5 μT. The NMR signal of such a weak magnetic field is not easy to detect due to the insufficient sample polarization, even after utilizing the SQUID measurement mentioned in the Introduction. Therefore, we need to apply a pre-polarization field, Bp, before applying the static Bm (McDermott et al., 2002). In principle, there is no limit to signal detection, even for a deep source, if we could apply a strong enough Bp. However, there are technical barriers that prevent arbitrary increases in the Bp (e.g., SQUID protection, eddy-current ringing along the wall of a magnetically shielded room (MSR), and the switch-off time versus sample relaxation time).

There were several reports of technically similar ideas for use with DNI (Burghoff et al., 2010; Cassará et al., 2009; Höfner et al., 2011; Kraus et al., 2008; Scheer et al., 2011), but mostly they were aimed at the detection of neuronal activity itself, rather than collective behavior like brainwaves. Thus, they were trying to estimate the potential for measuring the spike train of neurons, some high frequency components of evoked responses (Höfner et al., 2011; Scheer et al., 2011) or DC components (Burghoff et al., 2010). Here, we concentrate on the
measurement of brainwave (e.g., alpha or gamma band) oscillations. Such oscillations are known to contain the cortico-cortico or cortico-thalamic network information, and also to contribute to long range functional connectivity for perception, attention, corollary discharge, memory, consciousness, and synaptic plasticity (Uhlhaas and Singer, 2010). The excitation is strong enough to be measured by EEG or MEG, which means that the strength of the collective oscillatory magnetic field in the source region would be strong enough to make a detectable tipping of the magnetization. Such event-induced activity is usually measured without averaging. Another benefit is that the coherency of such an oscillatory field lasts several hundred milli-seconds, which provides a measurable tipping of spins on the nearby protons.

**Material and methods**

Currently, micro-Tesla NMR research is mostly being conducted by groups with experience in sensitive SQUID bio-magnetic measurement since the technique requires specific know-how. However, micro-Tesla NMR is also challenged by the switching on and off of the magnetic fields. Most groups who conducted such bio-magnetic measurements were still using MSRs designed for MEG or magneto-cardiography (MCG). Recently, people noticed that such an MSR is not suitable for a micro-Tesla NMR application because of the generation of eddy current loops along the closed metallic wall. An eddy current along the MSR wall generates a nT-level magnetic field inside the MSR persisting for a second or more. This is much stronger than the expected strength of an NMR signal. Meanwhile, waiting for enough decay of the eddy current would result in decay of the sample magnetization beforehand. Another problem with an MSR is the magnetization of its walls. To prevent these problems, several researchers suggested the introduction of a compensation coil. Recently, a compensation coil placed inside the MSR in such a way that its magnetic field could neutralize the magnetic field on the MSR wall has been suggested, where the compensation coil could be designed numerically (Hwang et al., 2011, 2012), or analytically (Nieminen et al., 2011). The compensation coil, if properly designed and implemented, could significantly reduce eddy currents around the MSR by neutralizing the magnetic field on the MSR wall generated by the strong Bp coil. For our research, in addition to the cancelation coil, we built a specially designed MSR to further reduce the eddy current problem. The inner-most shell of the aluminum panels of our MSR is separated into small panels to prevent the generation of an electrically-closed circuit (Kim et al., 2013). Of course, the outermost aluminum shell forms a closed surface to serve as the conventional RF shield. Between the aluminum shells, Mu-metal layers are placed to shield from low-frequency magnetic noises. The Mu-metal shells are designed to be effectively demagnetized wall-by-wall using an orthogonal, magnetic-flux-circuit scheme (Kim et al., 2013) (Fig. 2a).

We adopted a DC-SQUID (CE2Blue; Supracon AG, Germany), with a second-order gradiometric pickup coil made of a 125 μm Nb wire with 65 mm diameter and 50 mm baseline, as the NMR signal detector for the micro-Tesla NMR/MRI system. The second-order gradiometer is wrapped with island-aluminized Mylar film to reduce RF interference, and the DC-SQUID is additionally shielded with a superconducting Nb cast can of 99.9% purity to protect the detector from the strong magnetic field generated by the Bp coil. The total environmental noise floor of the system was about 2.2 fT/√Hz at 100 Hz.

In a conventional NMR system, the magnetization and relaxation characteristics of a sample are decided only by its main external magnetic field. However, in the micro-Tesla NMR, the main field can be separated into two sorts of fields, the Bp and the Bmm. The micro-Tesla NMR system is operated in the lower strength field of the Bmm (micro-Tesla range). The Bp is supplied by a coil separate from the Bmm coil, and should be turned off after providing the sample with the magnetization needed to produce an NMR signal. Fig. 2a shows the coil configuration of our micro-Tesla MRI system. A 240-turn, copper-wire-wound, solenoid Bp coil (outer diameter 38 mm, length 62 mm) was used to generate ~52 mT. The homogeneity of the Bmm coil was improved by making it a double Helmholtz coil (Franzen, 1962). The current source was connected to the Bmm coil through two different switchable power resistors for the K-step (following paragraph) and solid state relays (SSR). The switchable resistors determined two different magnetic field strengths, one corresponding to the Larmor frequency of the simulated brainwave (SWB) and the other for the NMR measurement. A Maxwell-type coil was used for the Gx gradient. Gx and Gy gradient coils were constructed with four-paired, rectangular coils. Bipolar power supplies are used as the current sources for the gradient coils. The currents of all the coils were controlled by SSRs or mechanical relays. These relays were remotely switched by a timing board and connected by optical fibers to prevent interference from outside electronic noises, and the formation of a ground loop. Bidirectional, transient-voltage-suppressing diodes and non-inductive resistors were connected in parallel with all coils for shunting the dark current noise during switch-off. A two-channel, arbitrary-function generator was used as an AC current source for each dipole in the phantom. High-pass filters were used to remove the DC-offset. Since the phases of the applied AC currents at each dipole
must be constant during experiments, we precisely controlled the duration to make an integer multiple of the frequency of the SBW.

Fig. 2b shows a two-dipole phantom for the micro-Tesla BMR experiment. We made two current dipoles with 0.5 mm copper wires of 9 mm length. The center of one dipole was placed 22 mm away from that of the other. The phantom was made of a glass bottle of 27 mm outer diameter and 73 mm length. In order to generate an ionic volume-current effect, the bottle was filled with 0.8% saline.

Fig. 3 shows the pulse sequences used in this study. Initially the Bp was applied to form a net sample-magnetization toward the direction of B0 in the case of the BMR experiment. After Bp was turned off, Bm and the AC current corresponding to the SBW were applied for the duration of the tSBW. During this process, AC local currents flowed through the current dipoles in the phantom and generated AC magnetic fields. Then the spins around the current dipoles resonated with the AC magnetic fields of Larmor frequency, corresponding to the Bm, and began to be tilted with an angular velocity proportional to the strength of the AC magnetic field. After the tSBW, the Bm was stepped up to a measurement frequency range and produced free precession decay (FPD) or echo signals. In the case of the MRI experiment (Fig. 3b), gradient fields were turned on simultaneously with the step-up of Bm, after the time tSBW. During this process, the spins precessed about the direction of the B0 with different frequencies and phases generated by additional gradient fields. After the time tRSB, the polarity of the Gr was reversed. Then the SQUID measured the echo signal. In the case of the usual MRI experiment (Fig. 7a), however, the time duration of tSBW was removed. By this we mean that after the Bp, with direction perpendicular to that of the B0, is turned off, the Bm and gradient fields are turned on simultaneously.

The step-up of Bm is an essential technique for BMR and we call it K-step (Kim, 2012). There are two major advantages to using K-step. One advantage is that the brain signal is continuous in the BMR scheme. It is impossible to control the spontaneous brain signal. Therefore, it is necessary to separate the NMR/MRI signal from the brain MEG signal of the same frequency. The main purpose of the K-step is to decouple the FPD or spin echo signal from the MEG signal by changing the frequency of the detection signal. For example, once a magnetization component projected into the plane orthogonal to the B0 direction was formed by the BMR tipping process with a 1 μT Bm, we could alter the detection frequency arbitrarily by changing the Bm, so we could choose to step up the Bm to 100 μT, to give a signal of about 4.2 kHz. The other advantage is related to a concomitant gradient field. Maxwell equations indicate that gradient fields are always related with another gradient field component, the concomitant gradient field (Myers et al., 2005; Norris and Hutchinson, 1990). If the strength of Bm is comparable with that of the gradient fields when the spins are mainly aligned to the direction of the weak Bm, then the relatively high concomitant field influences the spin motion. Due to this effect, the spin begins rotating along the axis of the vector sum of the Bm and the concomitant field connected with the frequency encoding gradient (Gx), and makes an echo signal. For example, when we were trying to detect a 43 Hz gamma wave, the Bm was about 1 μT. For the Gx of 0.13 μT/cm and the dimensions of the bottle, the maximum strength of the concomitant field was about 0.47 μT. The comparable concomitant field strength messed up the expected spin dynamics. Therefore, the measurement frequency had to be stepped up to a much higher frequency to ignore the concomitant field effect. In our experiment, we used K-step to increase the measurement frequency to about 1.45 kHz, corresponding to a Bm of 34 μT. The maximum strength of the concomitant field was only 1.4% of the Bm. A similar trial for the purpose of reducing the effects of the concomitant field by changing Bm during phase encoding has been introduced (Myers et al., 2005). Moreover, there are some other advantages from using the K-step. The low frequency of the BMR signal and the relatively wide bandwidth of the proton resonance peak, make it difficult to use a conventional image sequence for the micro-Tesla MRI. Several steps in the gradient field strength, due to such a weak external Bm, will touch zero frequency. This problem can be solved by stepping up the Bm up to several tenths or hundreds of μT. Also we might arbitrarily choose a low-noise band as a detection band. Usually, we can detect 1/f noise in a low frequency range because of flicker-current noise from the coil system in the micro-Tesla NMR system. Besides, current sources for gradient fields could be severely contaminated by the power line noise and its harmonics. We could be free from those particular noise peaks.

During the BMR experiment, the frequency of the applied AC current at the dipole was 43.33 Hz (gamma brainwave) which corresponds to a Bm strength of 1.02 μT. Afterward, the measurement field strength was stepped up to 34 μT. The Gx and Gz were used as frequency and phase encoding gradients, respectively. The strength of Gx used in this study was fixed at 0.13 μT/cm. The increment of the phase encoding gradient (ΔGz) and the number of phase encoding steps were also fixed at 0.013 μT/cm and 41, respectively. Other experimental parameters will be given with the specific results.

Before each of the BMR experiments reported in this paper was performed, the resonance frequency at which the magnetic field resonated with the frequency of the SBW, was checked using an FPD experiment since the resonance frequency of Bm can vary slightly depending on the state of the power resistor and the Bm coil although we use a stable DC power supply as the current source of Bm. In a practical human measurement, the frequency can be determined by a simultaneous EEG or MEG measurement.

When the current was applied to only one of the current dipoles, the ends of the leads of the other dipole had to be terminated with a 50 Ω resistor, because the ionic–volume current induced a displacement AC current to the other dipole.

The region for which an image was obtainable was estimated by simulation (Fig. 4). The region for the simulation, and the voxel sizes, were 40 × 40 mm2 and 1 × 1 mm2, respectively. The simulated signal was the calculated magnetic flux by the second-order gradiometric pickup coil. The total magnetic flux produced by the proton magnetic moments was calculated by considering the volume of the magnetic moment at each voxel, the dimension of the pickup coil and the distance. As a result, an area of 59 × 19 × 25 mm3 can be imaged with
only to the left-side current dipole; at a frequency (fSBW) of 43.33 Hz.

The SBW, obtained by the FPD experiment. AC currents were applied
treatment = 150 s, fSBW = 43.33 Hz, ISBW = 6.2 mA (open circle) and 3.1 mA (closed
As tSBW was increased, the signal intensity (denoted by the closed circle
in Fig. 5) increased up to about 760 ms and then decreased. This result is
associated with a tilting angle,

\[ \gamma \mathbf{B} \mathbf{r} \]

mean standard deviation (SD) in the repetitive measurements. The SDs are smaller than
the symbol sizes in most cases. The inset shows the magni
definition of the AC magnetic field, the axial symmetry and the magnetic moments polarized by the applied Bp.

Fig. 4. Simulation of the region for which an image is obtainable for our micro-Tesla MRI
system: (a) the simulation configuration, (b) the calculated dipole magnetic-field distribu-
tion (i.e., the magnetic field at the SQUID for each voxel) and (c) the region of the sample
for which an image is obtainable by using our micro-Tesla MRI system, in consideration of
the dipole magnetic field distribution, the axial symmetry and the magnetic moments polarized by the applied Bp.

our system. Moreover, the minimum image size was 9 mm² based on
consideration of our system noise.

Results

Fig. 5 shows the BMR signal intensity versus the duration (tSBW) of
the SBW, obtained by the FPD experiment. AC currents were applied
only to the left-side current dipole; at a frequency (fSBW) of 43.33 Hz.
As tSBW was increased, the signal intensity (denoted by the closed circle
in Fig. 5) increased up to about 760 ms and then decreased. This result is
associated with a tilting angle, \( \gamma \mathbf{B} \mathbf{r} \) in the conventional NMR/MRI, and a
relaxation time, as calculated by:

\[
S(t_{SBW}) = \sin(\gamma B_{eff} t_{SBW})e^{-t_{SBW}/T_{relaxation}}
\]

where \( B_{eff} \) is the spatially-merged effective magnetic field. The solid
lines in Fig. 5 represent the fitting curves.

The current was doubled, while the duration of the maximum signal
was reduced by almost half, as shown in the open circle in Fig. 5. This
phenomenon can be confirmed in the inset of Fig. 5. The slopes of the
data obtained at ISBW = 3.1 and 6.2 mA are in the ratio of 1:2.23. Al-
though the ratio of the slopes is not exactly twice due to the volume
distribution of the AC magnetic field strength, the results in Fig. 5 show that
the spins around the current dipole resonated well with the AC magnetic
field, and that the spins tilted with an angular velocity proportional to
the strength of that field.

Fig. 6 shows the selectivity of the BMR frequency. The current (ISBW =
3.1 mA) was applied only to one current dipole. The full width at half
maximum (FWHM) was about 1.8 Hz. The 2 Hz-away sideband excitation
came from the sinc functional distribution in the frequency domain of the
760 ms-duration, rectangular SBW pulse. In practice, the selectivity of the
excitation frequency is expected to depend on the duration of the target
brainwave.

Fig. 7a shows the MR image of saline solution in the bottle. Since the
echo signal is not measurable in the BMR experimental configuration
without the AC current being applied to the dipoles (Fig. 7c), the
image was acquired when the Bp and Bm were perpendicular to each other.
The bottle, in the inset of Fig. 7a, was clearly imaged. The two
holes inside the square image represent support structures for the cur-
cent dipoles.

To demonstrate the direct imaging of multiple, coherently oscillating
dipole currents using the BMR phantom experiment, we applied AC cur-
rents at each dipole with no phase difference to create perfectly-
correlated sources. In Fig. 7b, two regions corresponding to the volume
of the spins resonating with the AC magnetic field in the saline solution,
are visualized distinctively. When AC currents were not applied, there
was only a noisy background pattern (Fig. 7c). In addition, the MR im-
geases of the BMR phantom, with the SBW applied individually to the

Fig. 5. The BMR signal intensity as a function of the duration of the SBW. The error bars
mean standard deviation (SD) in the repetitive measurements. The SDs are smaller than
the symbol sizes in most cases. The inset shows the magnified view of the beginning
part of the graph. The solid lines represent the fitting curves. The following experimental
parameters were used in this experiment (see Fig. 3a): tBP = 5 s, tMeasurement = 2 s,
tRepetition = 150 s, ISBW = 43.33 Hz, ISBW = 6.2 mA (open circle) and 3.1 mA (closed
circle), respectively. The current was applied only to the left-side current dipole
(see Fig. 2b).

Fig. 6. The BMR frequency selectivity. The magnitudes of the FPD signals were plotted as a
function of the frequency of the excitation SBW. The error bars mean the SD in the repet-
tive measurements. The SDs are smaller than the symbol sizes in most cases. The dashed
line represents the frequency domain sinc function fitting for the 760 ms SBW pulse. The
following experimental parameters were used in this experiment (see Fig. 3a): tBP = 5 s,
tMeasurement = 2 s, tRepetition = 150 s and ISBW = 3.1 mA. The duration of the SBW was
slightly varied from 0.76 s to maintain constant phase and to contain integer multiples of
the oscillation period. The current was applied only to the left-side current dipole
(see Fig. 2b).
left- and right-sides of the current dipole are plotted in Figs. 7d and e, respectively. The results in Fig. 7 indicate that closely-placed, correlated sources can be localized well using the BMR scheme with the micro-Tesla MRI system.

Discussion

One advantageous feature in BMR measurements is a strong resonance with a spontaneousbrainwave from the collective activity of lots of neurons. For example, the strength of an alpha wave is tens to hundreds of times stronger than that of an evoked field. When we want to know the strength of the magnetic field next to the current source, we can make a rough estimate by reducing the distance between the sensor and the source according to the Biot-Savart law (Bodurka and Bandettini, 2002). Considering the reduction of the usual MEG detection distance of 40 mm to 2 mm, the field strength will be increased by a factor of 400. The MEG strength of a measured alpha wave, 10–100 pT, could exert a field of 4–40 nT on the protons 2 mm from the source; e.g., say that the magnetic field 2-mm away from the source was 10 nT, corresponding to a 0.4 Hz Larmor frequency, then the maximum tipping would happen at the 1/4 period, over about 600 ms. The spins on the 2-mm-radius shell around the source will give a maximum signal and the spins inside the shell, of course, can contribute to the signal, too. However, the tipping direction is antisymmetric about the center of the source, and the SQUID-detected signal from the opposite inner tipping pairs would be canceled more severely than that of outer pairs (Kim, 2012). Therefore, the spot radius of the BMR image would be approximately 2 mm. In the previous experiment, \( I_{SBW} = 3.1 \text{ mA} \) through a free-space current dipole (Sarvas, 1987) generated 10 nT at a position 16 mm away from the dipole. By adding volume currents making a close loop through the saline, which is spatially constrained by the glass wall, the magnetic field near the dipole is expected to strengthen and the BMR image spot shrink to a radius of around 10 mm. The BMR detectability is determined by the size of the spin-tilted spot. A weak brainwave has a small spin-tilted volume, and we need stronger pre-polarization to detect the BMR signal from such a small volume.

On the other hand, we used a phantom–with-saline with a longer relaxation time compared to the shorter relaxation time (\(<100 \text{ ms}\)) of gray and white matter (Koenig and Brown, 1984). With the realistic tissue, we could expect \(-25\%\) of the total magnetization for the tilted projection component in the direction of detection during the short relaxation time. This is still a significant portion for detecting the BMR signal under a reasonable strength of \(B_p\), and the coherence of the alpha wave easily persists for longer than the relaxation time. Meanwhile another optimistic aspect is the fact that we estimated the local magnetic field strength based on clinical MEG measurements. MEG is not sensitive to the radial component of neuronal currents but only sensitive to the current components tangential to the head surface (Hämäläinen et al., 1993). Presumably, the strength of the local neuronal current was underestimated because MEG omitted the radial component. This factor will give a stronger signal during practical measurement as the radial component of the neuronal currents can generate the tipping magnetic field, too. Therefore, the BMR technique could be more useful for mapping brain function since it can observe both the tangential and radial components of the neuronal current, while MEG is blind to the radial and EEG is blind to the tangential.

Our experimental trick, K-step, has more advantages than simply decoupling the strong MEG signal from the nuclear biomagnetic resonance signal; we can get a higher signal-to-noise ratio (SNR) by shifting the detection band arbitrarily. Besides, the \(T_1\) and \(T_2\) relaxation times tend to elongate in a field of greater strength (Koenig and Brown, 1984; Solomon, 1955). The longer relaxation time gives a narrower line-width as well as we have more time to detect the signals during the pulse sequence. This implies that measuring the NMR signal in a higher strength field enables a narrower detection bandwidth, and a higher SNR.

Conclusions

We showed that the BMR technique enables visualization of the coherent sources of brainwaves, and be utilized as a tool to visualize BFC using a multi-dipole source phantom.

The application of BMR might also be extended. Matching the nuclear magnetic resonance frequency to the frequency of a periodic electrophysiological activity enables direct visualization of the corresponding bio-function; not only for the brain, but also for heart applications localizing periodic-reentry-excitation of the myocardium (Kim, 2012). We could categorize the techniques into a new measurement research area, perhaps, bio-magnetic resonance. Technically, one of the trickiest problems in biomagnetic resonance was finding a way to separate the
NMR signal from the direct bio-magnetic signal. If this is not done, both sets of signals with the same frequency would be mixed at the sensor. Here, we introduced an experimental trick. K-step, a non-adiabatic change of the external field to decouple the NMR signal from the direct measurement of the bio-magnetic fields. The K-step made it possible to obtain functional images under conditions of very low external magnetic-field strengths, where the concomitant gradient field distortion was dominant. The development and demonstration of K-step for use with micro-Tesla MRI, could initiate a new field of research, bio-magnetic resonance (including BMR).

As a future work, the next step after our technical demonstration could be to find a specific physiological target such as a preferable or practical frequency range based on experiments with the living human brain or realistic neural network models. We expect the suggested BMR technique could play an important role as a new brain research tool that will enable the illumination of BFC in the future.

Conflict of Interest

A US patent application has been filled for the decoupling K-step imaging methods presented in this manuscript.

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References


