Induced oscillatory responses during the Sternberg’s visual memory task in patients with Alzheimer’s disease and mild cognitive impairment

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A B S T R A C T

In this study we used magnetoencephalography during a modified version of the Sternberg’s memory recognition task performed by patients with early Alzheimer’s disease (AD), mild cognitive impairment (MCI), and by age-matched healthy controls to identify differences in induced oscillatory responses. For analyses, we focused on the retention period of the working memory task. Multiple-source beamformer and Brain Voyager were used for localization of source-power changes across the cortex and for statistic group analyses, respectively. We found significant differences in oscillatory response during the task, specifically in beta and gamma frequency bands: patients with AD showed reduced beta event-related desynchronization (ERD) in the right central area compared to controls, and reduced gamma ERD in the left prefrontal and medial parietal cortex compared to patients with MCI. Our findings suggest that reduced oscillatory responses over certain brain regions in high frequency bands (i.e., beta, gamma), and especially in the beta band that was significantly different between AD patients and healthy subjects, may represent brain electromagnetic changes underlying visual-object working memory dysfunction in early AD, and a neurophysiological indicator of cognitive decline.

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Introduction

Alzheimer’s disease (AD) is the most common type of dementia and one of the main health problems in the elderly worldwide. Its overall prevalence is more than 1% of the general population and reaches 20% for those aged 80 or over (Ramaroson et al., 2003). AD is characterized by neuronal degeneration in several brain regions with widespread neuronal cell loss and the presence of neurofibrillary tangles and senile plaques. In the early stages of the disease, the most commonly recognized symptom is memory loss, in particular difficulty in remembering recently learned facts, as well as problems with thinking and concentration. In addition, the concept of a prodromal stage of AD, termed mild cognitive impairment (MCI), has been proposed (Petersen, 2004). Recent studies have demonstrated that pharmacological treatment for early AD and MCI can slow the progression of the disease (Feldman and Jacova, 2005). Therefore, an early diagnosis and treatment appear to be a very important factor for improving prognosis in patients with AD.

Magnetoencephalography (MEG) is a technique specifically designed to measure neural activity noninvasively featuring high time and spatial resolution. Unlike other neurophysiological techniques (e.g., electroencephalography – EEG), MEG can directly detect the electromagnetic activity of the brain without interferences of skin, skull and cerebral fluid, which act as a low pass filter (Hämäläinen, 1992). Thus, MEG is more suitable to explore brain oscillations, especially fast activity in beta and gamma bands, compared to EEG. However, MEG has not extensively been used for diagnosis of AD. Most MEG studies on AD and MCI have employed single dipole as their core method of analysis (Fernández et al., 2002, 2006; Maestú et al., 2001, 2006). This method has proven useful for studying focal brain activity, particularly epileptic discharges. However, findings from several neuroimaging and neurophysiological studies suggest that a wide area of the brain is activated in higher information processing such as memorization (Cohen et al., 1997; Jokisch and Jensen, 2007), and that induced oscillatory activity may be the key to understanding functional communication in the brain, especially with regard to memory and integrated functions (Başar et al., 2001; Ishii et al., 2009; Pfurtscheller and Lopes da Silva, 1999). Thus, applying MEG-dipole modeling, which identifies center of gravity rather than the volume of activation might not be sufficient to visualize abnormal activity in an extended network of sources underlying cognitive dysfunction in AD.

In the last decades, different approaches have been used to analyze MEG activity during cognitive task performance. For instance,
minimum norm estimation (MNE) procedure has extensively been used to estimate the cortical origin of the brain electromagnetic response. MNE models have already been applied for source reconstruction of MEG data in patients with dementia or in healthy elderly with subjective memory complaints (Maestü et al., 2008, 2011). Beamformers approach is a spatial filtering method which has also become increasingly valuable for source reconstruction of MEG activity (Ishii et al., 1999; Robinson and Rose, 1992). Although beamformers analyses are unable to distinguish two sources if their time-courses are 100% correlated, unlike MNE, they can easily handle both superficial and deep sources, and a variety of statistical analyses can be easily implemented (Huang et al., 2004). These approaches have been most successful in identifying induced changes in cortical oscillatory power that do not result in a strong average signal (Hillebrand et al., 2005). Beamformers, in particular, have given us an insight into the dynamics of oscillatory changes across the cortex not explored previously with traditional analysis that rely on averaged evoked responses (Ishii et al., 2009). By using MEG beamformer, the topographic mapping of source-power changes across the brain is obtained and locations with significant neuronal activation can be detected (Chen et al., 2006). In particular, multiple source beamformer (MSBF), a modified version of the linearly constrained minimum variance vector beamformer in the time frequency domain, has proven to be of great value in the identification of oscillatory activity source-power changes induced by sensory and cognitive tasks in dementia (Kurimoto et al., 2008) and other neuropsychiatric disorders such as psychosis (Canuet et al., 2010) and autism (Honaga et al., 2010).

The assessment of EEG/MEG induced oscillatory response in different frequency bands in terms of power decrease or event-related desynchronization (ERD) and power increase or event-related synchronization (ERS) is a valuable way to reveal different aspects of information processing in the normal and pathological brain (Pfurtscheller and Lopes da Silva, 1999). Earlier ERD/ERS studies during a memory task focused mainly on changes in theta (4–8 Hz), alpha (8–15 Hz) and beta (15–30 Hz) frequency bands. Induced oscillatory responses in theta and alpha activity, for example, have been reported associated with working memory (Bastiaansen et al., 2002; Jensen and Tesche, 2002) and attention (Kahana et al., 2001), while event-related beta oscillatory response, in particular beta ERD, extensively investigated in relation to motor function, has been proposed to underlie working memory processes, as well (Karrasch et al., 2004; Pesonen et al., 2007). In addition, EEG and MEG research on cognitive function has recently shifted to high frequency oscillations (i.e., gamma frequency band). This fast cortical oscillatory activity is thought to be associated with various cognitive processes, and therefore its alteration appears to be an important mechanism underlying psychiatric and neurological disorders (Grabska-Barwińska and Zygierewicz, 2006; Jokisch and Jensen, 2007; Uhlhaas and Singer, 2006).

Based on the fact that memory impairment is a cardinal clinical feature of AD and MCI, and that task-induced oscillatory brain activity in different frequency bands provide important clues to underlying cognitive processes (Bąsar et al., 2001; Pfurtscheller and Lopes da Silva, 1999), several studies have investigated abnormal event-related responses during memory tasks in demented patients. An MEG study by Babiloni et al. (2005) reported that patients with dementia showed increased alpha ERD during the retention period of a memory task. Meanwhile, Karrasch et al. (2006) study using EEG found that patients with MCI showed increased ERD in the frequency range of 10–20 Hz during the encoding period compared to controls, whereas patients with AD showed decreased ERD in the 7–17 Hz frequencies during the retrieval period compared to controls. This activity was observed particularly in anterior and left temporal electrodes (Karrasch et al., 2006). In addition, another EEG study reported decreased 15–25 Hz ERS in parietal electrodes during a 2-back task in patients with progressive MCI and AD relative to controls (Missionnier et al., 2007). However, there are only few functional imaging studies evaluating ERD/ERS during a memory task in patients with AD and MCI in the frequency range from theta to gamma.

In the present study, we used MEG beamformer during a visual working memory task in patients with early AD and compared the results with those of patients with MCI and normal controls using Brain Voyager to identify abnormal spatial patterns of oscillatory activity in the wide frequency range.

**Methods**

**Subjects**

Thirteen patients with early AD, thirteen with amnestic MCI, and fourteen normal elderly controls were enrolled in this study. All patients were recruited from the outpatient clinic of Psychiatry at Osaka University Hospital. The study was carried out in accordance with the Declaration of Helsinki, and approved by the Hospital Ethics Committee. Written informed consent was obtained from all participants. The diagnosis of probable AD was established according to the National Institute of Neurological and Communicative Disorders and Stroke/the Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) criteria (McKhann et al., 1984), while amnestic MCI was diagnosed according to the criteria defined by Petersen (Petersen, 2004). The elderly controls were healthy volunteers who had no cognitive disturbance and no history of neurological or psychiatric disorders. Patients and controls were not taking any medication that might affect the central nervous system at the time of the study, and underwent brain MRI screening to exclude any organic lesion. To evaluate the degree of cognitive function, the Mini-Mental State Examination (MMSE) (Folstein et al., 1975) was performed on all patients and controls. In addition, the Alzheimer’s Disease Assessment Scale-cognitive subscale (ADAS-Cog) (Homma et al., 1992) and the Clinical Dementia Rating (CDR) (Morris, 1993) were performed on all patients. Their demographic and neuropsychological profiles are shown in Table 1.

**MEG data acquisition**

Neuro Magnetic data were recorded at 250 Hz with a bandwidth of 0–80 Hz using a CTF 64-channel MEG system (CTF Systems, Inc., Canada) composed of a whole-head array of 64 radial 1st order gradiometer/SQUID channels housed in a magnetically shielded room. The participants were seated comfortably with the head positioned in the helmet-shaped Dewar. The localization of the subject’s head relative to the sensor array was measured with three coils affixed to the nasion and preauricular points.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographic, clinical and behavioral data.</th>
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<tbody>
<tr>
<td></td>
<td>AD</td>
</tr>
<tr>
<td>Number</td>
<td>13</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>4.9 ± 5.8 5.8 ± 6.8 6.8 ± 8.1</td>
</tr>
<tr>
<td>Age</td>
<td>75.6 ± 5.0 73.9 ± 5.0 71.2 ± 6.8</td>
</tr>
<tr>
<td>MMSE</td>
<td>22.1 ± 2.6 26.8 ± 2.6 28.6 ± 1.5</td>
</tr>
<tr>
<td>ADAS-Cog</td>
<td>14.3 ± 3.3 8.6 ± 3.3 − 0.001</td>
</tr>
<tr>
<td>CDR</td>
<td>0.8 ± 0.2 0.4 ± 0.2 − 0.001</td>
</tr>
<tr>
<td>Accuracy rate of Sternberg’s task (%)</td>
<td>80.5 ± 13.8 88.4 ± 7.7 90.6 ± 7.7</td>
</tr>
</tbody>
</table>

Data are means ± SD unless otherwise noted.

AD, Alzheimer’s disease; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; ADAS-Cog, Alzheimer’s Disease Assessment Scale-cognitive subscale; CDR, Clinical Dementia Rating.

Comparison between AD and controls.

Comparison between AD and MCI.
Working memory task

A modified version of the Sternberg’s probe task was performed during the MEG recording (Sternberg, 1966) (Fig. 1). During the task, sets of five digits, or memory sets, were randomly displayed for 2 s and the subjects were asked to memorize them (memory encoding). After a 5-second memory retention period following the memory set, a series of three single-digit probes (1-s duration with a 2-s interval) was displayed and the subjects were instructed to push a button held in their right hand if the digit was included in the previous set, otherwise they had to push a button in their left hand (memory recognition). The length of a single trial was 27 s and repeated 20 times, resulting in a total duration of the task of approximately 9 min per subject. Before the experiment, all subjects were given complete task instructions; practice trials were performed to ensure familiarity with the procedure. The subject’s recall percentage was determined and deemed task performance.

MEG time-frequency analyses

Artifact rejection was performed off-line. MEG channels and trials with signal variations larger than 3pT were considered as including artifacts and were excluded from further analysis. For source imaging of MEG data, we used the MSBF implemented in Brain Electrical Source Analysis (BESA) software (www.besa.de) that represents a modified version of the linearly constrained minimum variance vector beamformer in the time-frequency domain (Gross et al., 2001). As an adaptive beamformer, the MSBF applies a spatial filter specific...
for each brain voxel that is fully sensitive to activity from the target voxel, while being as insensitive as possible to activity from other brain regions, thus suppressing interference from unwanted signals. The BESA beamformer applied complex demodulation to transform time-domain MEG data into time-frequency data. This provided information on the envelope amplitude and the phase of a specified frequency band as a function of time (Hoechstetter et al., 2004). The complex demodulation consisted of a multiplication of the time-domain signal by a complex periodic potential function with a frequency equal to the frequency analyzed and an additional low-pass filter. In the resulting complex signal, its magnitude corresponded to half the envelope amplitude and its phase to the compound phase of the filtered frequency band. To obtain power values, the time-series MEG data were squared and averaged across all 20 trials. Time frequency representations of changes in power normalized to baseline for each MEG sensor were obtained from each subject. Task-induced oscillatory responses were measured in theta (4–8 Hz), alpha (8–15 Hz), beta (15–30 Hz) and gamma (30–80 Hz) bands. For each trial, a 2-s interval before the memory set (time window: 1–3 s after the trigger) was deemed control state, whereas an interval of equal duration starting 1-s after the memory set in the memory retention period (time window: 6–8 s after the trigger) was deemed active state (Fig. 1). To image induced oscillatory activity, BESA computed the complex cross spectral density matrices (the time-frequency equivalent of the data covariance matrix) for the active and control intervals from single-trial data for each frequency band of interest. Color-coded maps were obtained displaying q-values as a measure of the magnitude change in the active interval relative to the control interval in percentage.

Statistical group analyses

For statistical group analyses, the 3D images of induced oscillatory activity built with BESA software were exported to the Brain Voyager QX software package (Brain Innovation, Maastricht, The Netherlands), and superimposed onto a Talairach-transformed Montreal Neurological Institute (MNI) T1-weighted brain MRI template in Brain Voyager QX (Goebel et al., 2006). The anatomical T1 coordinates in the statistic maps were transformed into Talairach coordinates to identify brain regions with significant between-group differences in source-power changes. Brain activation patterns, as indicated by ERD/ERS values in a given frequency band, were compared between two groups using t-test statistics (two-tailed, unpaired) in BrainVoyager QX. To minimize the risk of false positive findings, all activation foci were set to a minimum cluster size of 20 voxels, and statistical results with p < 0.001 (uncorrected) were considered significant. Details of these neuroimaging procedures can be found in our recent publications (Canuet et al., 2010, Honaga et al., 2010; Kurimoto et al., 2008). The Chi-square test was performed for independence of group and gender. Demographic and clinical variables were analyzed using the Mann Whitney U test or the Kruskal–Wallis test.
test, with the significance level set at $p<0.05$. These statistical analyses were carried out using SPSS software (SPSS, Inc., Chicago, USA).

**Results**

**Demographic, clinical and behavioral results**

The demographic data are shown in Table 1. No significant differences were indicated in either age (d.f. = 38, $p=0.25$) or sex (d.f. = 2, $T=0.43$, $p=0.81$) across the three groups. The neuropsychological assessment revealed significant differences in MMSE scores between AD and MCI patients (Kruskal–Wallis test, $p<0.01$), as well as between AD patients and controls (Kruskal–Wallis test, $p<0.01$). For the ADAS-Cog and CDR scores a significant difference was found between AD patients and normal controls, with the patients showing a lower performance (Kruskal–Wallis test, $p<0.05$).

**Within-group power change analysis**

The averaged percentages of power changes in different frequency bands for each group, superimposed on a standard brain image are shown in Figs. 2–5. Pronounced theta ERD exceeding 10% was observed in the left frontocentral and inferior temporal region in both AD patients and normal controls. Maximal activity (peak ERD) was found in the frontal cortex with values of 11.2% in the patients and 10.4% in the controls. In MCI patients, pronounced theta ERD was observed in a wide area including the frontocentral cortex bilaterally and the left posterior temporal cortex, with a peak ERD value of 12.8% in the frontal area, as well as in the contralateral frontal cortex (peak ERD 11.3%) (Fig. 2).

Alpha power showed marked reduction over a wide cortical area involving the left frontocentral cortex in all three groups, and the adjacent superior temporal region in MCI patients and controls. Maximal ERD was observed in the left frontal cortex in all groups with values of 15.3%, 15.5% and 12.5% in controls, and patients with MCI and AD, respectively. In MCI patients there was also alpha ERD greater than 10% in the right frontal cortex (peak ERD 13.6%) (Fig. 3).

In the beta frequency band, pronounced ERD was observed only in MCI patients and controls. This activity was widely distributed over the frontocentral cortex bilaterally, dominant over the left hemisphere. Maximal beta ERD was found in the left frontal cortex in both groups, with peak values of 16.4% in controls and 15.6% in MCI patients. The maximum value of beta ERD in AD patients was 9% and is was also found over the left frontal region (Fig. 4).

Gamma frequency band showed no power change greater than 10%. At a threshold of 5% power changes, gamma ERD was observed...
in all groups. This activity appeared mainly in the frontocentral cortex bilaterally in normal controls, with a peak value of 8.1% in the right frontal region, and in MCI patients, in the left frontocentral and medial parietal cortex, with a peak value of 8.5% over the prefrontal area. Patients with AD showed gamma reduction greater than 5% in a small area over the right prefrontal cortex, with a peak value of 6.2% (Fig. 5). Pronounced ERS was not observed in any of the frequency bands.

Between-group power change analysis

The between-group comparisons of source-power changes in brain oscillatory activity during the retention period of the Sternberg’s working memory task indicated significant difference in beta and gamma frequency bands only. Patients with AD had reduced magnitude of beta ERD in the right central area relative to controls, with t_{maxima} in the precentral cortex (Fig. 6). Patients with AD also

Fig. 5. Averaged source-power changes in the gamma band (30–80 Hz) across all groups at a threshold of 6%. The color bars represent the percentages of decreased power or event-related desynchronization (blue/green, ERD) and increased power or event-related synchronization (red/yellow, ERS). L, left; R, right; A, anterior; P, posterior; TRA, transverse; SAG, sagittal; COR, coronal; MCI, mild cognitive impairment; AD, Alzheimer’s disease.

Fig. 6. Statistical maps showing cortical regions with significant differences in beta (15–30 Hz) power changes during working memory retention between patients with Alzheimer’s disease versus healthy controls projected onto a Talairach-transformed T1-weighted anatomical MRI (threshold: t = 3.73, P < 0.001). A significant decrease in beta ERD was shown in the right central area in patients with Alzheimer’s disease relative to healthy controls. L, left; R, right; A, anterior; P, posterior; TRA, transverse; SAG, sagittal; COR, coronal.
showed reduced magnitude of gamma ERD relative to MCI patients, specifically in the left dorsolateral prefrontal cortex (DLPFC) over the superior frontal gyrus, and in the left medial parietal cortex (i.e., precuneus), with Tmaxima in the DLPFC source. The findings in peak beta and gamma ERD values at Tmaxima are summarized in Table 2.

Discussion

In the present study, we compared induced oscillatory activity during the retention period of a modified version of the Sternberg’s memory recognition task in patients with early AD and MCI, and in normal controls in an attempt to detect early brain electromagnetic changes underlying memory impairment in AD. We found pronounced power changes (i.e., decrease in power or ERD) exceeding 10% in theta, alpha and beta frequency bands in patients and controls, with a similar topographic pattern. This activity was distributed mainly over the left frontocentral area, and the left temporal cortex to a lesser extent, with AD patients showing smaller cortical areas of activation than the other groups. We also noted ERD source over the contralateral frontal cortex in these three frequency bands in patients with MCI, and it was also seen in normal controls but only for the beta band. Gamma activity exhibited a small magnitude of power changes across the cortex in all three groups. However, the statistical group comparison using Brain Voyager indicated significant differences in the left dorsolateral prefrontal cortex (DLPFC) over the superior frontal gyrus, and in the left medial parietal cortex (i.e., precuneus), with Tmaxima in the DLPFC source (Fig. 7). The findings in peak beta and gamma ERD values at Tmaxima are summarized in Table 2.

Table 2

<table>
<thead>
<tr>
<th>ERD</th>
<th>Location</th>
<th>Talairach (x, y, z)</th>
<th>BA</th>
<th>ERD at Tmaxima (%)</th>
<th>T-value</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>AD</td>
<td>MCI</td>
</tr>
<tr>
<td>Beta ERD</td>
<td>Right MFG</td>
<td>46, 5, 52</td>
<td>6</td>
<td>−1.45 ± 4.39</td>
<td>−4.36 ± 3.61</td>
</tr>
<tr>
<td></td>
<td>Gamma ERD</td>
<td>−24, 9, 58</td>
<td>6</td>
<td>−1.62 ± 2.97</td>
<td>−7.11 ± 3.99</td>
</tr>
<tr>
<td></td>
<td>Gamma ERD</td>
<td>−11 to −65, 44</td>
<td>7</td>
<td>−0.66 ± 2.73</td>
<td>−6.18 ± 4.00</td>
</tr>
</tbody>
</table>

ERD values are means ± SD.
ERD, event-related desynchronization; BA, Brodmann’s area; AD, Alzheimer’s disease; MCI, mild cognitive impairment; MFG, middle frontal gyrus; SFG, superior frontal gyrus; PreC, precuneus.

a Comparison between AD and controls.
b Comparison between AD and MCI.
reports of decreased gamma oscillations in AD, in particular over the prefrontal region which is linked to working memory processing, and with findings from previous studies indicating that gamma activity is particularly affected by aging, probably due to age-dependent loss of dopamine D2 receptors in cortical circuits (Li et al., 2001). In addition to the left prefrontal cortex, the ipsilateral precuneus also showed gamma abnormalities in patients with AD that differentiated them from those with MCI. This supports evidence from functional imaging studies indicating that hyperfusion or hypometabolism in the precuneus might be an early functional marker of AD (Herholz et al., 2002; Kogure et al., 2002). Furthermore, from a different angle, it could be said that patients with MCI tended to show higher gamma ERD compared to AD and controls (Table 2). This tendency might reflect a compensatory mechanism that allows patients with MCI to achieve similar behavioral results to those of controls during a memory task, as suggested by findings from previous MEG studies (Bajo et al., 2010; Maestú et al., 2008).

Several MEG studies reported significant differences in oscillatory activity between MCI and controls during a memory task (Maestú et al., 2006, 2008, 2011). In our study, however, the comparison between these two groups showed no statistical significance. The fact that we could not divide MCI patients into subgroups may partly explain the difference in the findings. Interestingly, results from recent studies looking at MCI progression to AD have demonstrated that some patients with MCI do not progress to AD (Petersen, 2004), and in an MEG study MCI patients were divided into converters who progressed to AD, and non-converters who did not progress to AD (Maestú et al., 2006). Follow up studies and subgroup analyses will help clarify the significant differences in source-power changes between MCI and controls.

A number of studies suggest a role for other frequency bands, in particular theta and alpha bands, in working memory processing (Pesonen et al., 2006, 2007; Stam, 2000), and reported that abnormalities in these bands are commonly involved in working memory deficits in several neuropsychiatric diseases such as schizophrenia and dementia (Babiloni et al., 2005; Ince et al., 2009; Monteaz et al., 2009). While we applied a visual-object working memory task using digits, most previous studies, however, used different working memory tasks (e.g., auditory memory search, visual–spatial or verbal memory tasks). This raises the question as to whether the discrepancy in the findings concerning the frequency bands across studies might be due to difference in working-memory paradigm and disease-related factors. Overall, our findings suggest that reduced oscillatory responses in high frequency bands (i.e., beta, gamma), and especially in the beta band that was significantly different between AD patients and age-matched healthy subjects, may reflect neural activity underlying visual-object working memory dysfunction in early AD.

Our findings should be interpreted in the context of potential limitations, including a small sample size and the brain atrophy of the patients that was not considered. Nevertheless, all patients groups and healthy controls were carefully matched by age and sex, and those with structural brain lesions were not included. In addition, since all AD patients in this study were in the early stage of the disease, and consequently did not show severe brain volume reduction, our results are unlikely to be affected by the brain atrophy factor. Further larger studies with a longitudinal design may help clarify the specific role of beta and gamma power changes in terms of ERD/ERS as a neurophysiological indicator of cognitive decline in AD. It should also be noted that we did not carry out separate analysis for the MEG data of correct and incorrect answers but averaged the data together. This was done because only 24 probes were presented in our version of Sternberg’s memory task, and even patients with AD performed quite well on the task, having an average accuracy rate of 80%. Larger sample size would provide enough statistical power to investigate the differences of MEG activities between correct and incorrect answers.

Finally, we should consider the relatively small number of channels of the MEG system used, as more than 100 channels is standard for MEG systems nowadays. However, striking findings of recent studies using MEG equipped with 64–channels indicating an accurate localization of auditory evoked fields (Johnson et al., 2010) as well as of oscillatory activity associated with language dominance (Hirata et al., 2010) and brain tumors (Oshino et al., 2007) speak in favor of the neuroimaging quality of this MEG system.

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**Conflicts of interest**

None.

**References**


