Altered generation of spontaneous oscillations in Alzheimer’s disease

Daria Osipova, a,b,c,* Jyrki Ahveninen, b,d Ole Jensen, e Ari Ylikoski, f and Eero Pekkonen a,b,g

aCognitive Brain Research Unit, Department of Psychology, University of Helsinki, Finland
bBioMag Laboratory, Engineering Centre, Helsinki University Central Hospital, Finland
cHelsinki Brain Research Center, Helsinki, Finland
dMassachusetts General Hospital/Massachusetts Institute of Technology/Harvard Medical School Athinoula A. Martinos Center for Biomedical Imaging, Charlestown, MA 02129, USA
eF. C. Donders Center for Cognitive Neuroimaging, Nijmegen, The Netherlands
fHospital of Koskela, Helsinki, Finland
gDepartment of Neurology, Helsinki University Central Hospital, Finland

Received 15 November 2004; revised 22 March 2005; accepted 9 May 2005
Available online 15 June 2005

Slowing of spontaneous alpha oscillations and an anterior shift of a source of alpha activity (8–13 Hz) have been consistently reported in the EEG studies of Alzheimer’s disease (AD). It is unknown whether these changes are associated with a gradual shift in location and frequency of existing sources or rather with the involvement of a new set of oscillators. We addressed this question by applying source modeling (minimum current estimates, MCE) to spontaneous alpha activity recorded with a 306-channel MEG system from eleven non-medicated AD patients with mild to moderate cognitive impairment and twelve age-matched controls during the eyes-closed session. AD patients had predominant lower alpha band sources in the temporal regions, whereas in the controls, robust alpha sources were found near the parieto-occipital sulcus. Activation within the parieto-occipital region was significantly weaker, and activation in the right temporal area was significantly enhanced in the AD patients. These results suggest an increased temporal-lobe contribution coinciding with parieto-occipital deficits. We propose that MCE, which provides simultaneous mapping of several oscillatory sources, might be useful for detecting neurophysiological abnormalities associated with AD in combination with other neuropsychological and neurological measures.

© 2005 Elsevier Inc. All rights reserved.

Keywords: Alzheimer’s disease; EEG; MEG; Alpha activity; Oscillatory sources

Introduction

Alzheimer’s disease (AD) is the most common form of dementia that affects approximately 11% of world population older than 65 years of age (Hof and Morrison, 1999). The prevalence of AD increases rapidly in age groups of 65 years and older, thus becoming a major healthcare and economic problem due to the proportional increase of elderly people. AD diagnosis is based on a history of progressive cognitive deterioration, on results of neuropsychological testing, and on structural brain images obtained with magnetic resonance imaging (MRI) or computer tomography (CT). Although the accuracy of clinical diagnosis using NINCDS criteria is about 80–90% (Rosser, 2001), it may often be problematic to identify AD, especially at early stage of the disease. Therefore, brain dynamics measured with magnetoencephalography (MEG) could add accuracy to the AD diagnosis early in the course of dementia.

Slowing of oscillatory activity is a prominent functional abnormality that has been reported in EEG and MEG studies of AD (Berendsse et al., 2000; Coben et al., 1983; Huang et al., 2000; Penttilä et al., 1985; Schreiter-Gasser et al., 1993). In other words, delta (2–4 Hz) and theta (4–7 Hz) power appear to be enhanced, whereas alpha (7–12 Hz) and beta (12–30 Hz) power tend to be decreased in AD. Fewer studies have attempted to investigate the spontaneous rhythm generation by using distributed source analysis that allows modeling of multiple generators. For example, in their EEG study, Babiloni et al. (2004) reported changes in the configuration of alpha sources, found to be more...
profoundly attenuated in the posterior rather than anterior brain regions. However, the EEG source modeling approach utilized in this study did not reveal specific source locations since the analysis rather concentrated on the activation in entire brain regions.

MEG is a reference-free non-invasive imaging technique with millisecond temporal resolution that has proved to be a useful tool in measuring spontaneous brain rhythms, both in healthy subjects (Ciulla et al., 1999; Salmelin and Hari, 1994) and in AD patients (Berendse et al., 2000; Fernandez et al., 2002; Stam et al., 2002). MEG has a higher sensor density than conventional electroencephalography (EEG) and is less affected by the differences in the conductivity of the brain, skull and scalp, thus exceeding EEG in its spatial resolution (Hämäläinen et al., 1993). These properties of MEG also facilitate source modeling as compared to EEG, although source localization is generally complicated due to the non-uniqueness of the inverse problem. A popular way to characterize the sources of EEG/MEG activity is an equivalent current dipole (ECD) model. It is thought to approximate synchronized post-synaptic currents in the dendrites of cortical pyramidal neurons, considered to be the main source of EEG and MEG signals (Hämäläinen et al., 1993). However, the ECD approach requires a priori assumptions, such as the number of dipoles, which is difficult to make. The low resolution brain electromagnetic tomography (LORETA) technique, although allowing of representation of distributed sources, produces quite diffuse estimates (Babiloni et al., 2004). An alternative way is to model multiple MEG sources by calculating minimum current estimates (MCE) (Uutela et al., 1999), based on minimum L1-norm estimates, which could provide an improved spatial representation of oscillatory pattern (Jensen and Vanni, 2002).

In this study, we used MEG and MCE to investigate the distribution of oscillatory sources in the alpha band in AD patients and age-matched controls.

Methods

Subjects

Eleven patients (mean age 72 ± 7.5, 6 females) with a recent diagnosis of probable AD following 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) and twelve controls (mean age 71 ± 5.8, 5 females) participated in the study. AD patients were recruited from the Outpatient Clinics of the Department of Neurology. The study was approved by the Ethics Committee of the Helsinki University Central Hospital, Finland, and a written informed consent was obtained from the subjects or his/her close relatives. Control subjects had no history of neurological, psychiatric, or other severe diseases. Patients had no history of stroke, head trauma, or any other neurological diseases except gradual decline of cognitive functions and memory. All patients underwent head CT or MRI scans to exclude brain lesions such as infarcts, brain tumors, and normal pressure hydrocephalus. The patients took various antihypertensive drugs, statins, and antiplatelet agents, but none of them had diabetes or thyroid disease. Neither AD patients nor controls had any medication affecting central nervous system. The cognitive assessment included Mini-Mental State Examination (MMSE) and the following five subtests of Consortium to Establish a Registry for Alzheimer’s Disease (CERAD): Word List Memory; Constructional Praxis; Word List Recall; Word List Recognition; Constructional Praxis Recall. Only controls with MMSE score exceeding 25/30 were included in the study (Folstein et al., 1975). The results of neuropsychological tests are presented in Table 1.

Data acquisition

The data were recorded with a 306-channel Neuromag Vectorview system (pass-band 0.1–190 Hz, sampling rate 600 Hz) (Elekta-Neuromag, Helsinki, Finland). The subject was seated comfortably in a magnetically shielded room (Euroshield, Eura, Finland) with his/her head inside the helmet for 2 min with eyes closed. Vigilance of the subjects was observed by on-line video monitoring during the recordings. Respective locations of marker coils to cardinal points of the head (nasion, left and right pre-auricular points) were determined with an Isotrax 3D-digitizer (Polhemus, Colchester, VT). The magnetic fields produced by the coils were used in determining the position of the subject’s head in relation to the MEG sensor array. A set of additional physiological landmarks was digitized for the individual characterization of a spherical conductor model used in MCE.

Power calculations

Off-line artifact rejection was performed, and all epochs containing deflections exceeding 3000 fT/cm were rejected. On the average, 60 epochs (minimum 35) 3.4 s each underwent Fast Fourier Transform (2048 points, Hanning window with 50% overlap). The mean power spectra were obtained for five brain regions by averaging activity from 22 frontal, 32 central, 32 occipital, and 38 left and 38 right temporal planar gradiometers. Furthermore, relative MEG activity was calculated for 4 frequency bands: delta (2–4 Hz), theta (4–7), alpha (7–12), and beta (12–30) by dividing the mean band power by the total power at 2–30 Hz.

Since MCE source modeling is the most reliable in case a significant peak is present in a power spectrum (Jensen and Vanni, 2002) and alpha rhythm is known to be the strongest over the posterior regions (Ciulla et al., 1999; Salmelin and Hari, 1994), peak frequencies were determined from the mean spectra of the posterior (bilateral temporal and occipital) channels (Fig. 1).

In case of bimodal peaks, the peak of greater magnitude was chosen. MCEs were then calculated from Fourier-transformed consecutive data segments with respect to the individual peak frequency (6–12.5 Hz). The current estimates for all data segments were averaged (Jensen and Vanni, 2002), resulting in a distributed current estimation for a specific frequency. The lattice constant was 10 mm, and points closer than 30 mm to the sphere origin were excluded from the current estimates. A spherical conductor model

Table 1

<table>
<thead>
<tr>
<th>Test</th>
<th>Score Mean ± SD</th>
<th>Maximum score</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE</td>
<td>20.8 ±4</td>
<td>30</td>
</tr>
<tr>
<td>Wordlist learning</td>
<td>4 ±1.7</td>
<td>10</td>
</tr>
<tr>
<td>Copy of figures</td>
<td>8.1 ±1.9</td>
<td>11</td>
</tr>
<tr>
<td>Wordlist recalling</td>
<td>37.3 ±3.6</td>
<td>100%</td>
</tr>
<tr>
<td>Wordlist recognizing</td>
<td>63.5 ±27.6</td>
<td>100%</td>
</tr>
<tr>
<td>Recall of drawings</td>
<td>47.7 ±39.3</td>
<td>100%</td>
</tr>
</tbody>
</table>
was applied with the origin individually determined for every subject. Three regions of interest (ROIs) of identical size were placed individually for each subject in the parieto-occipital and right and left temporal areas (Fig. 2). The ROIs were selected after visual inspection based on the loci of the strongest activation in single subjects (single subject data strongly resembling the GA distribution presented in Fig. 4). ROIs were positioned with respect to the individually digitized head coordinate system, in which the $x$ axis points from the left to the right preauricular point, $y$ axis is perpendicular to the $x$ axis and passes through the nasion, and $z$ axis is orthogonal to $x$ and $y$. The center of the parieto-occipital ROI (mean coordinates across subjects: $x = 0 \pm 0.3$ mm; $y = -31 \pm 6.7$; $z = 82.8 \pm 9.2$) was placed at the midline of the head, and the temporal ROIs (left: $x = -42.8 \pm 3.7$; $y = 0.4 \pm 4.2$; $z = 61.5 \pm 8.3$; right: $x = 44.7 \pm 3.1$; $y = -0.3 \pm 4.7$; $z = 62.7 \pm 7.0$) were located above the line connecting preauricular points. The uniform-sized ROIs were selected to standardize the magnitude of activation within an ROI between the subjects. Activities in ROIs were calculated using a Gaussian kernel with a radius of 15 mm (60% activation defined the radius). The absolute value of the total current at the frequency of interest was used to normalize the activation within the ROI, thus reducing the variance between the subjects.

**Statistical analysis**

A three-way repeated measures ANOVA (group by frequency by region) with contrasts was carried out to compare power values between the groups. The activations within the ROIs, as well as the peak frequencies, were compared using $t$-tests. The distribution of...
the results of neuropsychological testing and the activation in ROIs were tested for normality and compared using two-tailed Pearson correlation coefficient.

Results

Relative band power

A three-way ANOVA (group by frequency by region) revealed a significant group effect \((F(1,21) = 11.2, P < 0.01)\) and a significant group by frequency band interaction \((F(3,63) = 5.0, P < 0.01)\), indicating increased slower and reduced faster activity in AD patients. Contrasts revealed an increase in delta power in the frontal \((F(1,21) = 7.3, P < 0.05)\) and occipital \((F(1,21) = 5.7, P < 0.05)\) regions; overall increase in theta power (frontal: \(F(1,21) = 6.3, P < 0.05\); central: \(F(1,21) = 6.2, P < 0.05\); left temporal: \(F(1,21) = 8.7, P < 0.01\); right temporal: \(F(1,21) = 7.3, P < 0.05\); occipital: \(F(1,21) = 6.9, P < 0.05\); and decrease in beta power in the frontal region \((F(1,21) = 7.1, P < 0.05)\) in AD group (Fig. 3).

ROI activity

Activation in the parieto-occipital ROI was significantly weaker in AD patients \((P < 0.01)\), whereas activation in the right temporal ROI was enhanced \((P < 0.05)\) (Fig. 4). In addition, there was a statistically insignificant trend toward the increase in the left temporal ROI in the AD. The neuropsychological test scores, presented in Table 1, were correlated against the ROI activations. The results indicated that only one out of eighteen correlations was found to be significant. The scores of the constructional praxis (figure copying) subtest inversely correlated with the activation in the right ROI in AD patients \((r = -0.73, P < 0.05)\).

Peak frequency

The peak frequency for the AD group was 8.5 Hz \((\pm 1.36)\) and 9.5 Hz \((\pm 1.25)\) for the controls. The peak frequency showed a trend for decrease in the AD group, but the result was not significant \((P < 0.07)\). However, in the AD group, peak frequency inversely correlated with the activation in the right ROI \((r = -0.8, P < 0.01)\). The grand average MCEs at 1-Hz steps are shown in Fig. 5.

Discussion

We studied the distribution of oscillatory sources in the alpha band in AD by applying MCE (Uutela et al., 1999), which allows simultaneous mapping of several oscillatory sources in the brain (Jensen and Vanni, 2002). In the control subjects, sources of spontaneous alpha band activity were concentrated, as expected (Ciulla et al., 1999; Hari and Salmelin, 1997; Williamson and Kaufman, 1989), in or near the parieto-occipital sulcus. AD patients, on the other hand, had reduced parieto-occipital activation, accompanied by enhanced sources in the temporal regions. Our findings thus suggest that changes in electromagnetic activity in AD are mostly not due to slowing of existing sources but are rather caused by an increase in activation of temporal generators.

Fig. 3. Mean relative power and standard errors in delta, theta, alpha, and beta bands in both groups in the frontal (A), left temporal (B), central (C), right temporal (D), and occipital (E) regions. *P < 0.05; **P < 0.01.
oscillating in the frequency of 6–12.5 Hz. Functionally, these generators might represent either upper theta or lower alpha band activity.

One possible interpretation is that the temporal sources represent tau rhythm, and the observed activity might reflect increased relative contribution of the 6–10 Hz sources in the temporal cortex, which have been suggested to coincide or replace occipital alpha when the subject is drowsy (Hari, 1993). However, given that the duration of the measurement did not exceed 2 min and the data were subsequently checked for the presence of sleep spindles and no increase was found at 12–15 Hz (Zygierewicz et al., 1999), we have no reason to believe that AD patients were drowsier than controls. The second possible interpretation is related to the theta rhythm. The peak frequencies for which source localization was performed varied from 6 to 10.2 Hz in the AD group, but due to blurred definitions of frequency bands in neurodegenerative diseases, it is problematic to strictly differentiate alpha and theta bands in AD. Furthermore, as Niedermeyer (1997) has pointed out, the mid-temporal alpha band rhythm may partially overlap with the upper theta. Thus, we could interpret the temporal activation in AD as an increase in upper theta power, also supported by the results of power analysis. Even though not statistically significant, the peak frequencies showed a strong trend for being lower in AD as compared to the controls. Moreover, the peak frequency in AD patients inversely correlated with the activation in the right ROI, indicating the possible involvement of the upper theta band (up to 8.5 Hz) in patients with specifically pronounced temporal activation. These results are in line with the data of Fernandez et al. (2002), who reported increased dipole density of slow activity (up to 8 Hz) in the temporo-parietal regions of AD patients, and PET studies, which demonstrated correlation between the increased slow rhythms and reduced oxygen metabolism in temporo-parietal regions in AD (Buchan et al., 1997).

The enhanced temporal-lobe contribution associated with parieto-occipital deactivation suggests that the “anterior shift” in sources identified with ECD modeling in AD shown in EEG studies of Dierks et al. (1993) and Huang et al. (2000) can be interpreted as a relative change in posterior/temporal generators. This pattern of generator changes is partly in agreement with the interpretations of Babiloni et al. (2004) who found that suppression of alpha sources in AD is specifically pronounced in the posterior brain regions as compared with their central counterparts. Their study, on the other hand, revealed no enhancement of sources in the temporal regions in AD patients. Fernandez et al. (2002), however, reported the increased temporo-parietal sources of slow activity, and this finding is consistent with our results. The reasons for the discrepancy between our results, as well as the results of Fernandez et al. (2002), and the data of Babiloni et al. (2004) are unclear at present. One reason could be that the EEG/LORETA approach used by Babiloni et al. (2004) produced quite diffuse sources for the spontaneous rhythms, although other source modeling methods, such as ECD, MCE, and Dynamic imaging of coherent sources (DICS), seem to point to fairly focal generators of oscillatory sources (Liljestrom et al., 2005). Our MCE models of MEG activity, with relatively narrow point-spread function, indicated a clear pattern of focal loci of activity at the individual level, robust in most controls but mainly abnormal in AD patients.

Notably, differences in the temporal ROI activation between the two groups were statistically significant only in the right hemisphere and inversely correlated with the results of a constructional
praxis subtest. It is noteworthy that this change in the right hemisphere MEG source pattern correlated with performance in a neuropsychological test which is generally believed to measure predominantly right hemispheric functions (Lezak, 1995). Although this result requires further empirical corroboration, it suggests that our MCE estimates measure clinically relevant functional changes in the brains of AD patients.

Animal studies have shown that alpha rhythm is likely to be generated by networks of both thalamic and cortical oscillators (Lopes da Silva et al., 1973, 1980) modulated by brainstem cholinergic neurons (Steriade et al., 1990). Given that deficits in the brain cholinergic transmission are suggested to be the major neurochemical phenomenon underlying cognitive and functional changes associated with AD (Arendt et al., 1984; Davies and Maloney, 1976; Reinikainen et al., 1988; Rylett et al., 1983), it is possible that the present abnormalities in MEG oscillatory sources and power spectra could reflect pathological changes in the cholinergic system. Interestingly, the increased delta and theta power and the trend toward the peak frequency reduction of alpha resemble the pattern of spontaneous MEG changes observed at the sensor level in aged healthy subjects after administration of scopolamine, a centrally acting antagonist of muscarinic acetylcholine receptors (Osipova et al., 2003).

In conclusion, mapping of oscillatory sources with MCE revealed the decreased power of alpha sources within the parieto-occipital region often accompanied by the enhanced activation in the temporal lobes. Source analysis could thus be a sensitive marker of neuronal dysfunction in AD.

Acknowledgments

We thank Dr. Kimmo Uutela for technical discussions and Dr. Timo Erkinjuntti for recruiting patients.
References


Dierks, T., Ihl, R., Frolich, L., Maurer, K., 1993. Dementia of the Alzheimer type: effects on the spontaneous EEG described by dipole sources. Psychiatr Res. 50, 151–162.


Folstein, M.F., Folstein, S.E., McHugh, P.R., 1975. ‘‘Mini-mental state’’. A practical method for grading the cognitive state of patients for the clinician. J. Psychiatry Res. 12, 189–198.


