Clinical Neurophysiology 127 (2016) 1269–1278

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Functional connectivity assessed by resting state EEG correlates with cognitive decline of Alzheimer's disease – An eLORETA study

Masahiro Hata [a], Hiroaki Kazui [a], Toshihisa Tanaka [a], Ryouhei Ishii [a,*], Leonides Canuet [b], Roberto D. Pascual-Marqui [c,d], Yasunori Aoki [a], Shunichiro Ikeda [a,e], Hideki Kanemoto [a], Kenji Yoshiyama [a], Masao Iwase [a], Masatoshi Takeda [a]

[a] Department of Psychiatry, Osaka University Graduate School of Medicine, Osaka, Japan
[b] UCM-UPM Centre for Biomedical Technology, Department of Cognitive and Computational Neuroscience, Complutense University of Madrid, Madrid, Spain
[c] The KEY Institute for Brain-Mind Research, University Hospital of Psychiatry, Zurich, Switzerland
[d] Department of Psychiatry, Kansai Medical University, Osaka, Japan
[e] Osaka Psychiatric Medical Center, Osaka, Japan

ARTICLE INFO

Article history:
Accepted 7 October 2015
Available online 19 October 2015

Keywords:
EEG
LORETA
Dementia
Alzheimer's disease
Functional connectivity
Lagged phase synchronization
MMSE (Mini-Mental State Examination)
CDR (Clinical Dementia Rating)

HIGHLIGHTS

- Patients with Alzheimer's disease (AD) showed decreased lagged phase synchronization in delta band between most cortical regions.
- Several functional connections in delta band were shown to be associated with cognitive decline and global function in AD.
- Our findings offer new insight into neurophysiological features of AD based on physiological lagged connectivity.

ABSTRACT

Objective: To explore neurophysiological biomarkers of Alzheimer's disease (AD), we investigated electroencephalography (EEG) of AD patients, and assessed lagged phase synchronization, a measure of brain functional connectivity.
Methods: Twenty-eight probable AD patients and 30 healthy controls (HC) were enrolled. Forty seconds of artifact-free EEG data were selected and compared between patients with AD and HC. Current source density (CSD) and lagged phase synchronization were analyzed by using eLORETA.
Results: Patients with AD showed significantly decreased lagged phase synchronization between most cortical regions in delta band relative to controls. There also was a decrease in lagged phase synchronization between the right dorsolateral prefrontal cortex (DLPFC) and the right posterior-inferior parietal lobule (pIPL) in theta band. In addition, some connections in delta band were found to be associated with cognitive function, measured by MMSE. This involved specifically interhemispheric temporal connections as well as left inferior parietal connectivity with the left hippocampus, lateral frontal regions, and the anterior cingulate cortex (aCC). Right temporal connections in delta band were related to global function, as estimated by CDR. No differences were found in CSD analysis between patients and HC.
Conclusions: Functional connectivity disruptions between certain brain regions, as measured with lagged phase synchronization, may potentially represent a neurophysiological biomarker of AD.
Significance: Our study indicated that AD and healthy elderly could have the different patterns of lagged phase synchronization.

1. Introduction

Alzheimer's disease (AD), the most common type of dementia, is characterized by progressive degeneration of brain networks associated with memory and cognition (Sanchez-Mut et al.,

* Corresponding author at: Department of Psychiatry, Osaka University Graduate School of Medicine, 2-2 D3, Yamadaoka, Suita City 565-0871, Japan. Tel.: +81 6 6879 3051; fax: +81 6 6879 3059.
E-mail address: ishii@psy.med.osaka-u.ac.jp (R. Ishii).

http://dx.doi.org/10.1016/j.clinph.2015.10.030
1388-2457/

2013). Although at present there is no definitive cure for AD, therapeutic interventions in the early stage of AD might delay the onset or progression of the disease (Hsiao et al., 2013). Possible biomarkers of early AD include beta-amyloid and tau protein levels in cerebrospinal fluid, genetic mutations of the apolipoprotein E, and brain amyloid deposition revealed by positron emission tomography (PET) imaging. These markers may potentially increase diagnostic accuracy (Hatz et al., 2013). In addition, neurophysiological evidence of cortical dysfunction in AD has been provided by recent magnetoencephalography (MEG) studies (Ishii et al., 2010; Kurimoto et al., 2008; Kurimoto et al., 2012). However, unlike EEG, MEG systems are not widely distributed in clinical centers, and recordings are expensive. Thus, MEG is available to a small number of AD patients only. The low-cost and wide distribution of electroencephalography (EEG) devices are important factors for the detection of brain functional abnormalities of the early stage of AD.

In the context of EEG, AD is thought to represent a disconnection syndrome (Delbeuck et al., 2003). EEG has recently been used to evaluate the functional connectivity of brain regions in AD. In these studies, the clinical stage of AD was closely correlated with the functional connectivity assessed by EEG analysis (Chen et al., 2013). Analyses of coherence, a measure of linear functional connectivity, were useful in evaluating the risk of conversion from mild cognitive impairment (MCI) to AD (Rossini et al., 2006). This suggests that brain network analysis (i.e., functional connectivity) of AD patients may aid in diagnosing early stage of AD.

Brain activity based on simple, anatomically segregated responses is not adequate to describe the complexity of AD symptomatology. Recent studies have instead focused on functional connectivity among brain regions, utilizing functional magnetic resonance imaging (fMRI) (Pievani et al., 2011), MEG (Stam et al., 2006), or EEG (Sankari et al., 2011). Functional connectivity represents the temporal synchrony or correlation among signals of two or more segregated regions, generating indices of functional integration among neural activities. Recent neuroimaging and neurophysiological findings suggest that disintegrated functional connectivity denotes the core of the pathophysiological mechanism underlying AD pathology (Canuet et al., 2011). These findings are supported by the study of white matter structural abnormalities in AD, using MRI tractography to evaluate anatomical connectivity (Lo et al., 2010). This evidence points to the importance of regarding AD as a structural and functional network disorder.

Recently, great interest has been paid to the intrinsic functional networks in the brain resting state of patients with dementia (Pievani et al., 2011). The brain resting state is considered to be an energetically costly condition, with rich neural activity and interneuronal connections in particular circuits (e.g., the default mode network; DMN) that are interrupted and attenuated during sensorimotor or cognitive tasks (Greicius et al., 2003). This intrinsic function in the resting state allows the brain to be ready for changes or stimuli of internal and external surroundings (Canuet et al., 2012). Thus, exploring functional connectivity in the resting state rather than during performance of a specific task might elucidate an intrinsic functional disintegration of brain regions in AD patients.

To evaluate resting-state synchronization in the functional networks, various methods of connectivity assessment have been applied to EEG data. Most AD studies of functional connectivity have used coherence, a linear connectivity measure that is based on the amplitude or power of the EEG signals, showing decreased connections in various brain networks (Jelles et al., 2008; Sankari et al., 2011). To date, only few studies have examined EEG nonlinear connectivity (Canuet et al., 2012). Nonlinear measures have the potential of providing higher sensitivity because of the property of the dependence structures they can capture (Hlinka et al., 2011). However, EEG analysis may be hindered by the problem of volume conduction, providing pseudo-correlations recorded from neighboring electrodes (Stam et al., 2007). Thus, for evaluating functional connectivity, EEG source analysis provides instantaneous (zero-lag) activity from the information of different scalp electrodes.

Exact Low Resolution Electromagnetic Tomography (eLORETA) (Pascual-Marqui et al., 2011) is a three-dimensional, discrete, linear, and weighted minimal norm inverse solution method. It is uniquely endowed with the property of exact localization to a test point source at any location, albeit with low spatial resolution. Due to the principles of linearity and superposition, the method produces a low resolution estimate of any distribution of electric neuronal activity. In a detailed and exhaustive comparison to other competing linear inverse solution, it was shown that eLORETA has improved localization properties in the presence of noise, and in multiple source situations (Pascual-Marqui et al., 2011).

A recently developed method of nonlinear functional connectivity called "lagged phase synchronization" (Pascual-Marqui et al., 2011), implemented in the eLORETA statistical package, is resistant to non-physiological artifacts, particularly low spatial resolution and volume conduction. In comparison to the imaginary coherence (Nolte et al., 2004), it is shown in (Pascual-Marqui et al., 2011) that in the presence of a common source (corresponding to either volume conduction or low spatial resolution), the imaginary coherence decreases to zero as the source strength increases, while the lagged coherence does not. This provides proof for the fact that the imaginary coherence, as well as for the imaginary phase coherence related to phase synchronization (Stam et al., 2007) are biased and strongly affected by volume conduction and low spatial resolution.

This lagged connectivity method is considered to be accurately corrected because it depicts the connectivity of two signals after the artifactual instantaneous (zero-lag) components have been excluded. The connectivity patterns of the classic phase synchronization which contains the instantaneous (zero-lag) artifact are not often associated with the true physiological interactions (Pascual-Marqui et al., 2011). The lagged connectivity measure is relatively robust to the strength of the instantaneous components. Thus it can detect physiological "non-zero" lagged connectivity even when large instantaneous artifacts exists, while the conventional coherence indices fail to identify a lagged connection in the presence of the large instantaneous component (Pascual-Marqui et al., 2011). Due to a proper modeling of the two components of a functional connection (i.e., instantaneous and lagged), the eLORETA algorithm is considered to identify true physiological connectivity. Furthermore, it can be utilized to filtered data, therefore providing a frequency decomposition of the functional brain connectivity (Pascual-Marqui et al., 2011).

In the present study, we aimed to identify the abnormal EEG patterns or functional connectivity of AD patients with eLORETA. We also evaluated the correlations between the functional connectivity and cognitive function, and aimed to identify the brain regions related to cognitive decline of patients with AD, thus providing new possible neurophysiological evidence that might prove helpful in early detection of AD.

2. Methods

2.1. Subjects

The study included 53 probable AD patients who visited the psychiatry outpatient clinic of Osaka University Hospital and underwent neuropsychological examination and EEG between June 2005 and September 2012. We also recruited 61 elderly

subjects as healthy controls (HC). They were psychiatrically and neurologically normal subjects who entered our clinical trial for medical check-up screening.

All patients met the criteria of the DSM-IV (APA, 1994) and the National Institute of Neurological and Communicative Disorders and Stroke/the Alzheimer's disease and Related Disorders Association (NINCDS–ADRDA) (McKhann et al., 1984) for probable AD. They underwent general screening that included a neuropsychiatric examination, laboratory measurements (e.g., blood cell count, blood chemistry measurements, thyroid hormones, vit B12, folic acid), neuroimaging examination with Computed Tomography (CT) or MRI, and EEG. We assessed the severity of dementia using Mini-Mental State Examination (MMSE) (Folstein and Folstein, 1975) and Clinical Dementia Rating (CDR) for all patients. CDR is a general dementia staging scale, assessing the presence (or absence) and severity of dementia. The global CDR scores are 0, meaning cognitive normality, 0.5, 1, 2, and 3, meaning very mild cognitive impairment, and mild, moderate, severe dementia, respectively (Vos et al., 2013). Based on these examinations, we were able to exclude cerebral structural lesions and progressive or reversible dementia types of different etiology. Subjects with a history of brain injury or drug/alcohol abuse were excluded from the study. Like the patients, healthy controls also underwent screening that included neuropsychiatric investigation, neurophysiological tests, and neuroimaging examination (i.e., brain MRI). Out of 53 probable AD patients that were initially enrolled, 25 patients were excluded for insufficient EEG data (e.g., lots of artifacts, drowsiness, and so on) that did not allow us to obtain 40-s resting-state data. Out of 61 healthy controls, 31 were excluded. Thus, our study analyzed EEG of 28 probable AD patients and 30 HC.

We excluded about half of EEG recordings in both healthy controls and patients.

In healthy controls we recorded the EEG in only about 5 min included both eyes open and closed state. So the time of resting state, in eye closed and arousal state, was very limited. In the limited time of EEG recording we excluded EEG artifact strictly, in the result, half of EEG recordings were excluded.

On the other hand, in AD patients we recorded the EEG during eye open and eye closed state in about 10 min in order to detect EEG abnormality, such as epileptic discharges and so on, to rule out treatable disturbance. In the EEG recordings many of AD patients could not sustain their resting state or artifact-free state because of disability of following instructions and body motions. Instead of the longer EEG recordings we had to exclude half of their recordings.

Prior to enrollment, we explained to all participants the utilization of their clinical data for our research and obtained written informed consent. In the case of patients who were considered to have insufficient cognitive ability to understand the informed consent document, informed consent was obtained from a caregiver or legal representative of the patient. This study was approved by the ethical committee of Osaka University.

2.2. EEG recordings and data acquisition

The subject's EEG were recorded with a digital 19-channel scalp EEG device, using the International 10–20 system (i.e., Fp1, Fp2, F7, F3, Fz, F4, F8, T7, C3, Cz, C4, T8, P7, P3, Pz, P4, P8, O1, O2). The EEG data were acquired with a linked ears reference, sampled at 500 Hz, and filtered offline between 0.53 Hz and 30 Hz. Electrode impedance was kept below 5 kΩ. EEG recording included eyes open and closed states with vigilance control. For all subjects, we selected 40 s of artifact-free EEG data and fragmented them into 2-s segments off-line. EEG artifacts were manually excluded by visual inspection of skilled and certified electroencephalographers. Segments including blink artifact, muscle artifact, electrocardiograph (ECG) artifact, and signs of drowsiness were rejected, and only reliable, awake EEG data were selected, so that we could adequately estimate brain function during the resting-state. EEG data were analyzed with the LORETA-KEY software package.

At least 2-s data of continuous artifact-free EEG recordings as one epoch are required for LORETA analyses. Thus, we excluded EEG data with continual artifact which did not include merely 2 s of artifact-free interval. In order to avoid behavioral and EEG drowsiness, the skilled experimenter monitored the participants and eventual appearance of EEG drowsiness, if any, verbally gave them instructions and warnings. Such EEG drowsiness was additionally rejected in data processing. Furthermore, EEG data with low-amplitude (less than 10 μV) basic rhythms were excluded, avoiding the relative overestimation of non-physiological signals. Ocular and muscular artifacts were also rejected. These activities usually exhibited more than 100 μV amplitude. However, we also excluded ocular and muscular artifacts less than 100 μV if some suspicious activities could be considered these kinds of artifacts from its wave form and distribution. The epochs, including sporadic slow waves, were excluded for exploring the steady resting-state.

2.3. EEG source localization

We analyzed the cortical distribution of current source density, using eLORETA. The head model of eLORETA and the electrode coordinates are based on the Montreal Neurological Institute average MRI brain map (MNI152) (Mazziotta et al., 2001). The solution space was limited to the cortical gray matter, including 6239 voxels of 5 cubic mm spatial resolution. The eLORETA tomography has been validated in several previous studies using fMRI (Mulert et al., 2004; Vitacco et al., 2002), structural MRI (Worrell et al., 2000), PET (Dierks et al., 2000) and intracranial EEG (Zumsteg et al., 2006).

Selected artifact-free EEG fragments were analyzed to calculate the eLORETA cortical current source density from 0.53 Hz to 30 Hz. The current source density of the eLORETA cortical functioning image was calculated for six frequency bands: delta (2–4 Hz), theta (4–8 Hz), alpha1 (8–10 Hz), alpha2 (10–13 Hz), beta1 (13–20 Hz), beta2 (20–30 Hz).

2.4. Functional connectivity analysis

To analyze the functional connectivity we adopted a voxel-wise approach to determine cortical regions of interest (ROI). To create the ROIs, eLORETA defined the MNI coordinates of the cortical voxels underlying the electrode sites. Although detailed information on eLORETA connectivity algorithm has been published recently elsewhere (Canuet et al., 2011; Pascual-Marqui et al., 2011), we briefly summarize about this method. We defined 24 cortical ROIs which are shown in Table 1. Based upon previous research of functional connectivity (Vincent et al., 2008), 21 ROIs were selected. Three additional ROIs (Aud, auditory fields; Vis, Visual fields) as they have recently attracted attention in studies on brain functional networks (Pascual et al., 2013; Li et al., 2013).

To analyze functional connectivity between all pairs of ROIs, we used lagged phase synchronization. Lagged phase synchronization is a method for evaluating the similarity between signals in the frequency domain, based on normalized Fourier transforms. Thus, lagged phase synchronization is associated with nonlinear functional connectivity. This lagged connectivity measure is considered to be accurately corrected as it represents the connectivity of two signals after excluding the instantaneous zero-lag component (i.e., a lot of artifact elements). Such a correction is necessary because scalp EEG signals or estimated intracranial signals (EEG tomography) often include non-physiological components or physical

Table 1
24 cerebral regions of interest (ROIs) decided by eLORETA.

Anatomical regions	Brodmann area	ROI centroid MNI coordinates		
		x	*y*	*z*
Left middle temporal area (lMT)	37	−50	−70	−5
Right middle temporal area (rMT)	37	45	−70	−5
Left frontal eye fields (lFEF)	6	−25	−10	50
Right frontal eye fields (rFEF)	6	25	−10	50
Left superior parietal lobule (lSPL)	7	−25	−50	55
Right superior parietal lobule (rSPL)	7	25	−50	55
Left anterior prefrontal cortex (laPFC)	10	−35	55	5
Right anterior prefrontal cortex (raPFC)	10	35	55	5
Left dorsolateral prefrontal cortex (ldlPFC)	9	−50	15	40
Right dorsolateral prefrontal cortex (rdlPFC)	9	50	15	40
Anterior cingulate cortex (aCC)	32	5	30	25
Left anterior inferior parietal lobule (laIPL)	40	−50	−50	45
Right anterior inferior parietal lobule (raIPL)	40	50	−50	45
Left anterior insula (laINS)	47	−30	20	−5
Right anterior insula (raINS)	47	30	20	−5
Left hippocampal formation (lHF)	28	−20	−20	−20
Right hippocampal formation (rHF)	28	20	−20	−20
Ventromedial prefrontal cortex (vmPFC)	10	−5	50	−5
Posterior cingulate cortex (pCC)	23	0	−55	15
Left posterior inferior parietal lobule (lpIPL)	39	−50	−70	30
Right posterior inferior parietal lobule (rpIPL)	39	50	−70	30
Visual fields (Vis)	18	0	−90	−5
Left auditory fields (lAud)	41	−55	−25	10
Right auditory fields (rAud)	41	55	−25	10

artifacts, such as volume conduction that usually affect other connectivity indices. Thus, the lagged phase synchronization is considered to include only physiological connectivity information.

2.5. Statistical analyses

For statistical analysis of current source density, eLORETA applies a statistical nonparametric mapping method (SnPM) (Holmes et al., 1996). We assessed the difference of cortical source localization between groups in each frequency band with voxel-by-voxel independent *F*-ratio-tests, based upon eLORETA log-transformed current source density power. In the resulting three-dimensional statistical mapping, cortical voxels with significant differences were identified by means of a nonparametric permutation/randomization procedure (i.e., based on the Fisher's permutation method, with the threshold set at the 5% probability level), comparing the mean source power in each voxel and the distribution in the permutated values. By evaluating the empirical probability distribution of the "maximal-statistics" in the null hypothesis, permutation and randomization tests have demonstrated to be effective in controlling the Type I error in neuroimaging studies (Nichols and Holmes, 2002). eLORETA used 5000 data randomizations to determine the critical probability threshold values for the actually observed log *F*-ratio values with correction for multiple comparisons across all voxels and all frequencies, without the need to rely on Gaussianity. The use of SnPM for LORETA images has been confirmed in several studies (Pascual-Marqui et al., 1999; Anderer et al., 1998).

For the sake of completeness, a brief description of the multivariate non-parametric randomization method follows. Technical details are not included here because they can found in the specialized literature, see e.g., Nichols and Holmes (2002), and the cited literature therein. Consider an example where the data from two different groups is represented as X_{ji} and Y_{ki} respectively, consisting of $i = 1 \ldots R$ variables, measured on $j = 1 \ldots N_X$ subjects for one group and on $k = 1 \ldots N_Y$ subjects for other group. The variables may correspond to cortical spectral power at each voxel and each frequency, or to any measure of physiological connectivity strength between each pair of regions of interest and each frequency.

In this example, the aim is the discovery of the variables that are significantly different between the two groups. For this purpose, the simple variable-by-variable *t*-statistic or log-*F* ration can be used as a statistical measure of "distance" between the two groups. From the set of "*R*" *t*-statistics (one for each variable), the absolute maximum is chosen. Then its empirical probability distribution is estimated by repeatedly randomizing the "group membership" (all "$N_X + N_Y$" are mixed, and randomly reassigned to the two groups, regardless of their actual membership), and recalculation the maximum-*t*'s under the null hypothesis. This empirical probability gives the threshold with correction for multiple ("*R*" tests) testing, as explained in (Nichols and Holmes, 2002). The correction is exact (in the sense of Fisher's exact test) for a large number of randomizations, regardless of the original probability distribution of the variables.

To estimate the statistical difference in lagged phase synchronization between the pairs of 24 ROIs in each frequency band across groups, eLORETA applied independent sample *t*-test, thus generating *t*-statistic values of brain connectivity. For the functional connectivity analysis, we performed 1656 tests by using eLORETA to examine all connections between the 24 ROIs (276 connections) in six frequency bands ($276 \times 6 = 1656$). Furthermore, for correcting multiple comparisons, we applied the eLORETA non-parametric randomization method based on "maximal statistic" (Holmes et al., 1996; Nichols and Holmes, 2002).

To evaluate the association between functional connectivity and the cognitive and global function, we assessed the correlation between lagged phase synchronization values of all pairs of ROIs in each frequency bands and MMSE and CDR scores, using eLORETA software. The critical probability threshold for *r*-values was set at $p = 0.05$ and determined by nonparametric randomization (Nichols and Holmes, 2002). To analyze the demographic (i.e., age and sex) and clinical (i.e., MMSE scores) data we carried out chi square and *t*-test analyses, using SPSS software (SPSS Inc. Chicago, IL).

3. Results

3.1. Demographic and clinical characteristics

Table 2 shows the demographic and clinical data of our subjects. There was a female predominance among patients with AD ($p = 0.01$) in this study, no significant difference in age was found

Table 2
Demographic and clinical characteristics.

	AD (n = 28)	Controls (n = 30)	p-value
Age (mean ± SD)	74.2 ± 8.9	70.6 ± 5.6	0.07
Gender (F/M)	22/6	14/16	0.01
MMSE (mean ± SD)	18.7 ± 4.5	29.2 ± 1.0	<0.001
CDR	0.5 (n = 6)	0 (n = 30)	
	1 (n = 11)		
	2 (n = 11)		
Oral administration	None (n = 9)	None (n = 30)	
	Donepezil 5 mg (n = 14)		
	Donepezil 10 mg (n = 3)		
	Donepezil 5 mg + Memantine 20 mg(n = 1)		
	Donepezil 10 mg + Memantine 20 mg (n = 1)		

MMSE, Mini-Mental State Examination; CDR, Clinical Dementia Rating.

between groups. According to the neuropsychological evaluation, patients with AD exhibited significantly lower MMSE scores than the healthy controls ($p < 0.001$). With regard to CDR scale, all healthy controls scored 0, while the patients scored 1 or 2. Some patients with AD were taking anti-dementia drugs, mainly the anticholinesterase agent donepezil. Healthy controls were not taking any medication at the time of the EEG recordings (Table 2).

3.2. Source localization

Fig. 1 illustrates the averaged eLORETA solutions in patients and controls for each frequency band. The highest current source density values were found in the delta band (AD: 0.863 HC: 0.871), followed by theta band in AD (with a value of 0.642) and by alpha1 band in HC (with a value of 0.861). There was a similar distribution of maximal delta activity across groups over the frontal cortex bilaterally, whereas alpha1 cortical sources with high current density over the parieto-occipital cerebral regions were found only in controls. However, statistical analysis revealed no significant differences between groups.

3.3. Functional connectivity in AD patients compared with HC

Functional connectivity of patients with AD, compared with healthy controls, showed significantly decreased delta lagged phase synchronization over most cortical regions ($t_{max} = -5.85$, $p < 0.05$) (Fig. 2, the upper row). In addition, there was also significantly reduced lagged phase synchronization in the theta band between the right dorsolateral prefrontal cortex (DLPFC) and right posterior inferior parietal lobule (pIPL) ($t_{max} = -4.31$, $p < 0.05$) (Fig. 2, lower row).

3.4. Correlation of functional connectivity with MMSE and CDR scores

The eLORETA correlation analysis revealed that four functional connections in the delta band had a positive correlation with cognitive scores (MMSE): the higher the functional connectivity in the delta band of these connections the better the cognitive function (higher MMSE scores). These four cortical connections included (1) the left and right middle temporal area (MT) (Fig. 3) ($r = 0.51$, $p < 0.001$), (2) the right frontal eye field (FEF) and left posterior inferior parietal lobule (pIPL) (Fig. 4(a)) ($r = 0.51$, $p < 0.001$), (3) the anterior cingulate cortex (aCC) and left pIPL (Fig. 4(b)) ($r = 0.49$, $p < 0.001$), and (4) the left anterior inferior parietal lobule (aIPL) and left hippocampal formation (HF) (Fig. 4(c)) ($r = 0.51$, $p < 0.001$). Furthermore, a delta functional connection between right MT and right Aud had a negative correlation with CDR scores. (Fig. 4(d)) ($r = -0.44$, $p = 0.001$): this means that the higher the functional connectivity of delta band the better the global function (lower CDR scores).

4. Discussion

In the present study, we applied a method of physiological nonlinear connectivity called lagged phase synchronization, to evaluate differences in resting-state functional connectivity in patients

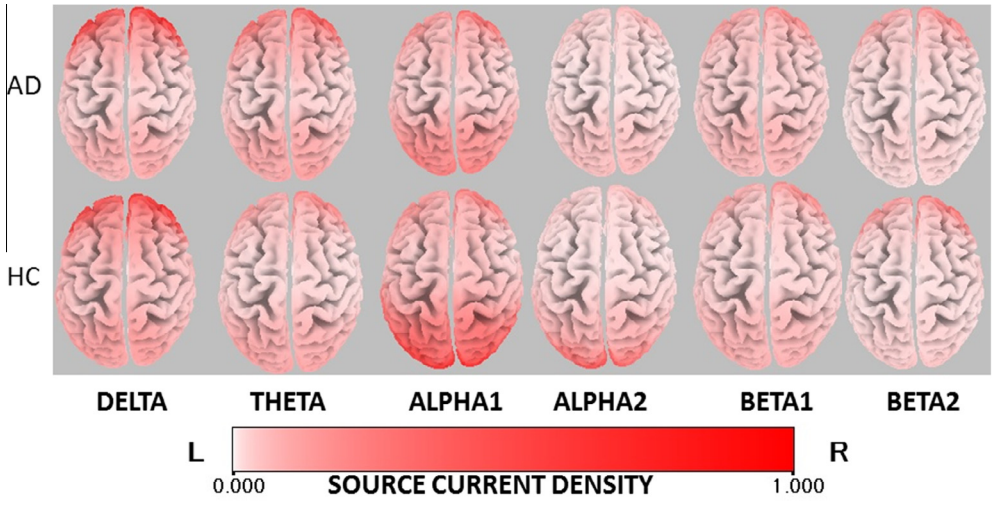

Fig. 1. Averaged eLORETA source current density in each frequency band in AD patients and healthy controls. AD, Alzheimer's disease; HC, healthy controls.

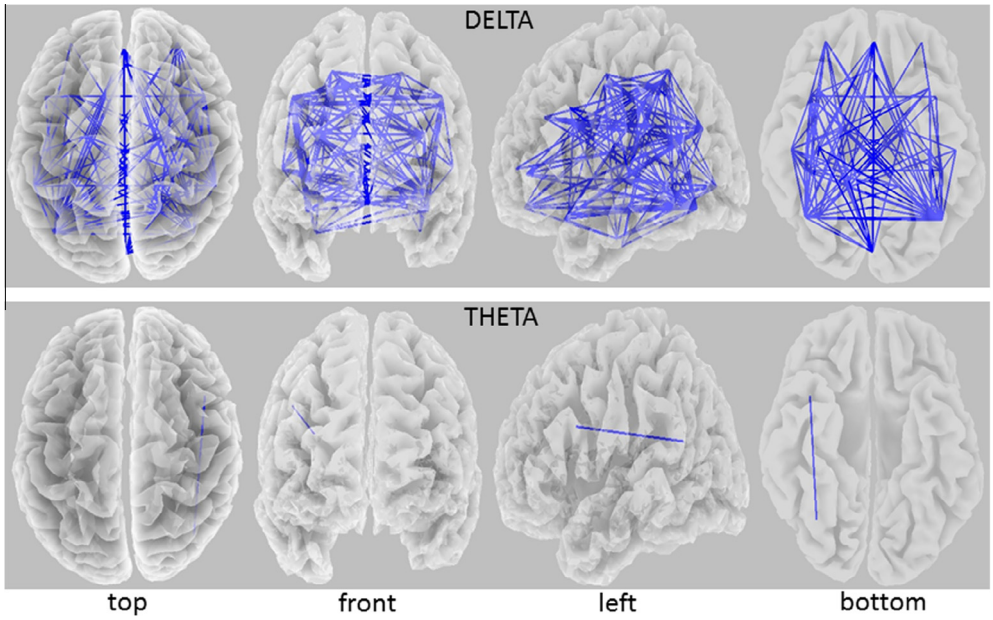

Fig. 2. eLORETA wire diagram indicating cortical regions with significantly decreased delta and theta lagged phase synchronization (threshold; $t = 4.28$, $p < 0.05$) in patients with Alzheimer's disease compared with healthy controls. Delta lagged phase synchronization decreases over the global cortical regions, and theta one is reduced between right dorsolateral prefrontal cortex (rdlPFC) and right posterior inferior parietal lobule (rpIPL).

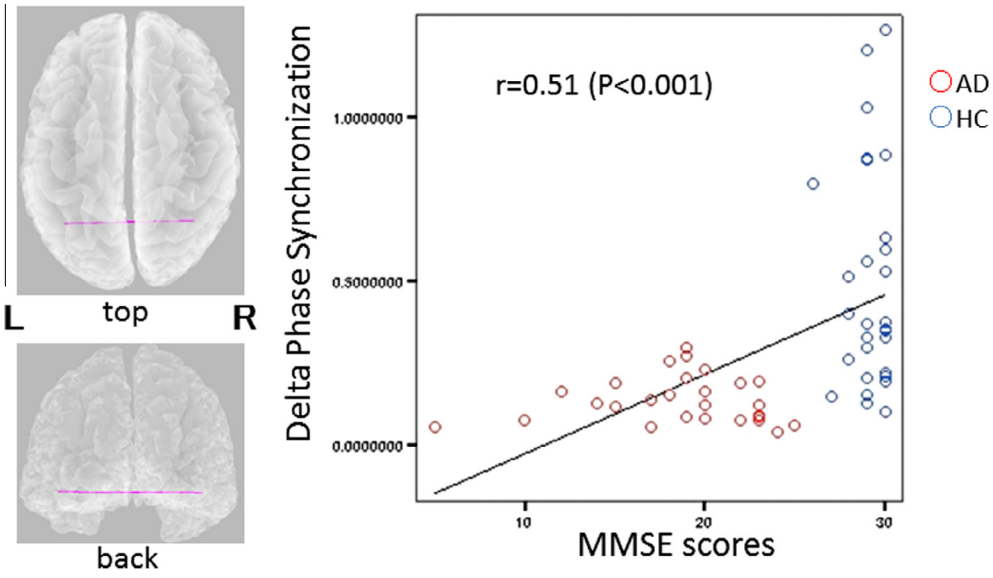

Fig. 3. eLORETA wire diagram of left middle temporal area (MT) and right MT with significant positive correlation between Mini-Mental State Examination (MMSE) scores and delta lagged phase synchronization of patients with Alzheimer's disease and healthy controls. The purple wire indicates the location, left MT and right MT, with significant positive correlation between MMSE scores and delta lagged phase synchronization (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

with AD compared to elderly healthy controls. In addition, abnormalities in cortical current density were also explored. Our patients showed decreased delta lagged phase synchronization over a wide range of cortical regions, and reduced theta connectivity between the right DLPFC and right pIPL. Interestingly, four of the delta band connections positively correlated with MMSE scores, and one of them exhibited negative correlation with CDR scores.

Patients with AD showed no significant difference in current source density in any of the frequency bands compared with healthy controls. Canuet et al. (2012) noted a decrease in parieto-occipital current source density bilaterally in patients with AD in alpha1 activity. In our study, patients with AD exhibited more reduced current source density in bilateral parieto-occipital cortex in alpha 1 activity compared with HC. However, there was no significant difference. The inconsistent results are probably due to difference in the severity of cognitive decline (i.e., their study included more severe AD patients, as indicated by the MMSE scores). There might be a potential relationship between decline in cognitive function and decreased parieto-occipital current source density in alpha1 activity.

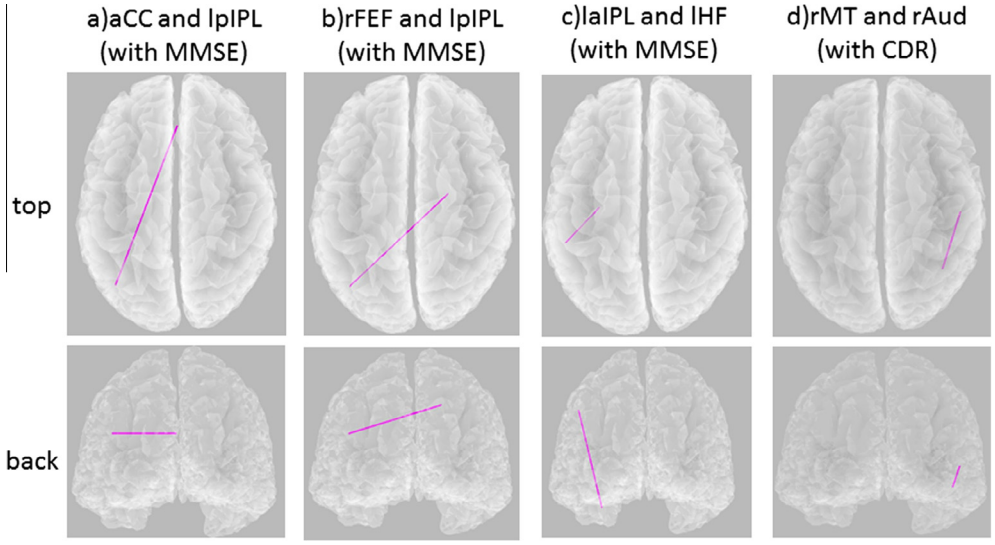

Fig. 4. eLORETA purple wire diagram indicating cortical regions with significant correlations between delta lagged phase synchronization and cognitive, global function measured by MMSE, CDR, respectively. (a) Significantly positive correlation between delta lagged synchronization of aCC (Anterior cingulate cortex) and lpIPL (Left posterior inferior parietal lobule), and MMSE scores ($r = 0.49$, $p < 0.001$). (b) The same as rFEF (Right frontal eye field) and lpIPL (Left posterior inferior parietal lobule) ($r = 0.51$, $p < 0.001$). (c) The same as laIPL (Left anterior inferior parietal lobule) and lHF (Left hippocampal formation) ($r = 0.51$, $p < 0.001$). (d) Significantly negative correlation between delta lagged synchronization of rMT (Right middle temporal area) and rAud (Right auditory fields), and CDR ($r = -0.44$, $p = 0.001$). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

4.1. Abnormal patterns of delta and theta functional connectivity

Our analysis of functional connectivity revealed the presence of a decrease in lagged phase synchronization, affecting delta and theta frequency band, respectively. We found reduced delta connectivity over most cortical regions. This is consistent with previous neurophysiological studies using EEG, which noted that delta coherence of most electrode pairs was significantly decreased in patients with AD (Sankari et al., 2011). Taken together, these findings and our results show that reduced functional connectivity in delta band in AD are confirmed using both linear (i.e. coherence) and nonlinear (i.e., lagged phase synchronization) connectivity methods. Decreased functional connectivity over most of cortical regions in AD could be a neurophysiological feature of this disease. Sankari et al. (2011) suggested that the overall decrease in coherence in AD patients was often caused by reduced cholinergic connectivity among brain regions, related to the presence of plaques and tangles in AD brains. Our finding of decreased delta connectivity over a wide range of cortical regions in AD could be attributed to the disruption of the diffuse cholinergic neural connectivity in impaired brains of patients with AD.

In addition, we found reduced theta band connectivity between the right DLPFC and right pIPL. EEG oscillations in the theta band are considered to reflect cognitive and memory performance (Klimesch, 1999). A previous study found reduced functional connectivity between the right DLPFC and right IPL in patients with mild cognitive impairment. This connection was significantly correlated with cognitive performance, such as the immediate recall and short delayed recall (Liang et al., 2011). The DLPFC is also known to be related with decision of action scheme (Genovesio et al., 2005) and spatial information processing (Hoshi, 2006). The IPL has been reported to have an important role in manipulation of objects (Yoon et al., 2012). There are strong anatomical connections between the parietal cortex and the DLPFC, which are activated by motor imagery rather than by the actual execution of movements (Vry et al., 2012). Thus, the front-parietal networks may play an important role in simulation of feeling associated with movement execution (Mizuguchi et al., 2013). The disintegration of cooperative execution of certain brain regions, such as the DLPFC and IPL, could cause respective functional disabilities in AD patients. This might provide new insight into pathological and neurophysiological processes underlying cognitive dysfunction.

4.2. Correlation between functional connectivity and MMSE and CDR

In our study, some significant functional connections in delta band, as indicated by lagged phase synchronization, had a positive correlation with cognitive scores, and one of them, a negative correlation with CDR scores (Figs. 3 and 4). Lagged phase synchronization between the right and left MT was included among those delta connections showing positive correlation with MMSE scores. According to an event-related potential (ERP) study (Yamasaki et al., 2012), AD patients have visuospatial disability due to parietal dorsal stream dysfunction, as indicated by prolonged N170 (V5/middle temporal area origin) latencies. The disruption of connectivity between bilateral MT seen in our study may reflect visuospatial dysfunction in AD patients.

As shown in Fig. 4(a), lagged phase synchronization between the aCC and left pIPL in delta band also showed positive correlation with cognitive function. The IPL is associated with intrinsic brain activity as a core region of the DMN (Golland et al., 2007), and it is implicated in self-awareness and internally oriented process (Fox and Raichle, 2007). The aCC is considered to play an important role in attentional and executive functions (Bush et al., 2000). Due to rich anatomical connections, the aCC has input from diverse sources of emotional and cognitive networks, and influences activity of other brain regions, therefore it is associated with a broad range of responses (e.g., motor, endocrine, and cognitive) (Bush et al., 2000). The aCC is also involved in working memory. In the Baddeley and Hitch's model (Baddeley, 2003), working memory comprises a control system (the "central executive"), acting as a supervisory system, and two short-term reserve systems (namely, the visual sketchpad, which contains visuospatial information, and the phonological loop which includes verbal information). The aCC and the IPL are thought to be involved in verbal working memory, and to be functionally connected (Collette and Van der Linden, 2002; Parisi et al., 2014). Thus, the abnormality in lagged phase synchronization between the aCC and the IPL might reflect the

disintegration of collaborative brain activity in these regions, and may be associated with attentional and executive dysfunction caused by brain pathology in AD.

Lagged phase synchronization between FEF and left pIPL in delta band positively correlated with cognitive scores (see Fig. 4 (b)). Using fMRI, evoked responses in the FEF and IPL during voluntary goal-oriented processes have been observed. Activation of these regions is considered to be associated with the network involved in endogenous orientation of attention (Pessoa et al., 2009). Therefore, this disruption in functional connectivity might be related to dysfunction of the attentional network in patients with AD. Our study demonstrates a potential relationship between cognitive function in AD patients and the neurophysiological activity of the aCC, FEF, and IPL, which are reported in association with the attentional network and working memory.

A striking finding of our study is the positive correlation observed between left aIPL and left HF functional connectivity and the MMSE scores Fig. 4(c). The hippocampus is known to play an important role in the generation of a wide range of memory processes, including episodic memory processing (Eichenbaum, 2001), which is progressively impaired in typical AD patients. In fMRI studies, impaired functional connectivity from the hippocampus to other regions of the brain was explored in AD patients, demonstrating markedly varied local and global hippocampal network activity in AD brain (Supekar et al., 2008). Another study using fMRI (Greicius et al., 2004) suggests that the hippocampus may be part of the DMN, and that hippocampal network activity is poor in AD. This suggests that assessment of the hippocampal network is an important issue in the search of clinical marker of AD. On the other hand, the connectivity of DMN regions including IPL may be relevant to predict the progression from MCI to AD (Petrella et al., 2011). Taken together, the impaired connectivity between the IPL and hippocampus, associated with cognitive function in our study, might be an early detectable neurophysiological feature of AD in longitudinal observations.

In this study, we also found that CDR scores correlated negatively with lagged phase synchronization between right MT and right Aud in delta band. Patients with AD have been associated with functional deficits of audiovisual integration (Wu et al., 2012). Our results suggest that the impairment in the integration of multiple sensory modalities is associated with a decline of global function in AD.

Reduced cortical connectivity in patients with AD is considered to be caused by the disintegration of axonal connections between various regions of the brain caused by neurofibrillary tangles and amyloid plaques, disturbing the normal electrical communication between different regions of the brain (Sankari et al., 2012). In our study, patients with AD exhibited decreased lagged phase synchronization over most cortical regions in delta band and several of these connections correlated with cognitive or global function in AD. Recently, MEG studies suggest that delta activity may improve diagnosis in AD (Besga et al., 2010; Fernández et al., 2013), and may aid in the evaluation of the risk of conversion from MCI to AD (Fernández et al., 2006). In the context of AD, delta activity has drawn great attention toward brain dysfunction. Our results suggest that although delta activity is generally considered to have little physiological function, functional connectivity in delta band has some physiological meaning in patients with AD.

In comparison with the previous study, different results were seen between this study and Canuet et al. (2012) study, both exploring for neurophysiological features of patients with AD satisfying the same criteria, by using LORETA. The same setting of ROIs between these studies in supplementary analysis did not yield consistent results (Supplementary Fig. S1). Discrepancy of study samples (i.e., different cognitive function), ethnicity (Zahodne et al., 2015), and sample size could affect the results.

Our study demonstrates aberrant lagged phase synchronization in delta and theta activity in AD patients, and correlation between some of these functional connections with cognitive decline or global function, measured by MMSE and CDR, respectively. The disruption of functional connectivity is considered to be associated with functional deficits, and most likely indicate a loss of structures involved in the neural networks. The characterization of connectivity loss could prove useful in the differential diagnosis of neurodegenerative diseases (Stam, 2010; Georgopoulos et al., 2007). The patterns of aberrant lagged phase synchronization identified in our study could be helpful for the diagnosis of AD. Application of a new theoretical scheme to the research of neural network alterations may provide insights into the underlying pathophysiological mechanisms of this disease.

On the other hand, Tijms et al. have reviewed graph theoretical studies in AD patients recently (Tijms et al., 2013) and pointed out that diverging results had been yielded in the graph theoretical studies in AD patients, affected by several confounders, such as the lack of a standard method to design graphs. Like the graph theoretical studies, functional connectivity studies in AD patients have not always yielded the consistent results at the present. Future research, investigating for standard measurements evaluating the functional connectivity in AD patients, could be demanded.

5. Limitations

Our results should be cautiously interpreted because of the relatively small sample size. In this study we excluded half of the study samples of both the patients and normal controls. Prolonged recording time might enable us to investigate more study samples. However, limitation in cost, manpower and machine time did not allow us to prolong the recording time. Our department as one of national centers of dementia is accepting severe demented patients who cannot adequately follow instructions, and such deflection of clinical samples could partly contribute to the high exclusion rate of EEG data. In addition, we strictly excluded EEG data with moderate artifact which were sufficiently available for clinical practice, to avoid non-physiological signals. Thus, we made it sure to obtain high quality artifact-free EEG data enough to investigate the genuine resting state, even if the study samples were reduced. In the future research, we think that prolonged recording time or the use of correction methods including ICA-based analyses should be required. In order to examine the neurophysiological features of AD, we diagnosed the patients strictly. Further studies with larger samples may confirm our results. Another potential limitation is the existence of a possible confounding effect of the medication for AD. However, there was no statistically significant difference in CSD and functional connectivity between donepezil users ($n = 19$) and donepezil non-users ($n = 9$) among AD patients, suggesting that pharmacological agents may have not affected our results.

Although several studies had validated the LORETA source localization with 19 electrodes, our results could be construed with deliberation because of utilizing the relative small number of electrodes. However, clinical EEG measurements are usually performed with 19 scalp electrodes and investigation for EEG in AD patients with 19 electrodes can have clinical significance.

The analyses with LORETA may have methodological limitation when exploring the brain function. For instance, LORETA results are model-dependent and may not accurately represent the neuronal origins of the brain activity despite its utility and reproducibility. This should be taken into consideration for the interpretation of our results.

Other potential limitation is the lack of investigation for other neurodegenerative diseases, such as dementia with Lewy bodies,

frontotemporal dementia, Parkinson's disease and so on, in this study. For demonstrating that our results were specific for AD patients, further studies about other neurodegenerative diseases were required.

In this study we investigated the property of AD group, not individual subjects. The application of our results to individual diagnosis could have lots of limitations. Henceforth, the accumulation of AD studies exploring the neurophysiological property of the impaired brains could be required for improvement in individual diagnosis.

This study adopted the exploratory approach for exploring the brain function of patients with AD. Our study showed aberrant functional connectivity in AD as well as several functional connectivity abnormalities associated with cognitive decline in these patients, assessed with eLORETA. This should be verified in the future studies in AD.

6. Conclusion

Overall, our findings show that there were no significant differences in CSD analysis between patients with AD and healthy controls. However, the patients showed significantly decreased lagged phase synchronization in delta and theta bands relative to controls. Decreased lagged phase synchronization in theta band was observed between the right DLPFC and the right pIPL, whereas delta band connectivity affected a wide range of cortical regions. Some of these delta functional connections correlated with cognitive decline. This involved specifically interhemispheric temporal connections as well as left inferior parietal connectivity with the left hippocampus, lateral frontal regions, and the aCC. Right temporal connections in delta band correlated with global function, as well. These findings suggest that disruption of global neural networks is related to AD pathophysiology. Furthermore, our results indicate that abnormalities in lagged phase synchronization, as a non-linear connectivity measure, may potentially represent a neurophysiological biomarker of AD, and aid in the early detection of the disease.

Acknowledgements

This research is partially supported by the Center of Innovation Program from Japan Science and Technology Agency, Japan.

Conflict of interest statement: None of the authors have potential conflicts of interest to be disclosed.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.clinph.2015.10.030.

References

American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington, DC: American Psychiatric Association; 1994 (DSM-IV).

Anderer P, Pascual-Marqui RD, Semlitsch HV, Saletu B. Electrical sources of P300 event-related brain potentials revealed by low resolution electromagnetic tomography: effects of normal aging. Neuropsychobiology 1998;37:20–7.

Baddeley A. Working memory: looking back and looking forward. Nat Rev Neurosci 2003;4:829–39.

Besga A, Ortiz L, Fernández A, Maestu F, Arrazola J, Gil-Gregorio P, Fuentes M, Ortiz T. Structural and functional patterns in healthy aging, mild cognitive impairment, and Alzheimer disease. Alzheimer Dis Assoc Disord 2010;24:1–10.

Bush G, Luu P, Posner MI. Cognitive and emotional influences in anterior cingulate cortex. Trends Cogn Sci 2000;4:215–22.

Canuet L, Ishii R, Pascual-Marqui RD, Iwase M, Kurimoto R, Aoki Y, Ikeda S, Takahashi H, Nakahachi T, Takeda M. Resting-state EEG source localization and functional connectivity in schizophrenia-like psychosis of epilepsy. PLoS One 2011;6:e27863.

Canuet L, Tellado I, Couceiro V, Fraile C, Fernandez-Novoa L, Ishii R, Takeda M, Cacabelos R. Resting-state network disruption and APOE genotype in Alzheimer's disease: a lagged functional connectivity study. PLoS One 2012;7:e46289.

Chen CC, Hsu CY, Chiu HW, Hu CJ, Lee TC. Frequency power and coherence of electroencephalography are correlated with the severity of Alzheimer's disease: a multicenter analysis in Taiwan. J Formos Med Assoc 2013. http://dx.doi.org/10.1016/j.jfma.2013.07.008. pii: S0929-6646(13)00232-5 [Epub ahead of print].

Collette F, Van der Linden M. Brain imaging of the central executive component of working memory. Neurosci Biobehav Rev 2002;26:105–25.

Delbeuck X, Van der Linden M, Collette F. Alzheimer's disease as a disconnection syndrome? Neuropsychol Rev 2003;13:79–92.

Dierks T, Jelic V, Pascual-Marqui RD, Wahlund L, Julin P, Linden DE, Maurer K, Winblad B, Nordberg A. Spatial pattern of cerebral glucose metabolism (PET) correlates with localization of intracerebral EEG-generators in Alzheimer's disease Clin Neurophysiol 2000;111:1817–24.

Eichenbaum H. The hippocampus and declarative memory: cognitive mechanisms and neural codes. Behav Brain Res 2001;127:199–207.

Fernández A, Turrero A, Zuluaga P, Gil P, Maestú F, Campo P, Ortiz T. Magnetoencephalographic parietal delta dipole density in mild cognitive impairment: preliminary results of a method to estimate the risk of developing Alzheimer disease. Arch Neurol 2006;63(3):427–30.

Fernández A, Turrero A, Zuluaga P, Gil-Gregorio P, del Pozo F, Maestu F, Moratti S. MEG delta mapping along the healthy aging-Alzheimer's disease continuum: diagnostic implications. J Alzheimers Dis 2013;35:495–507.

Folstein M, Folstein SE, McHugh PR. "Mini-mental state" a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–98.

Fox MD, Raichle ME. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat Rev Neurosci 2007;8:700–11.

Genovesio A, Brasted PJ, Mitz AR, Wise SP. Prefrontal cortex activity related to abstract response strategies. Neuron 2005;47:307–20.

Georgopoulos AP, Karageorgiou E, Leuthold AC, Lewis SM, Lynch JK, Alonso AA, Aslam Z, Carpenter AF, Georgopoulos A, Hemmy LS, Koutlas IG, Langheim FJ, McCarten JR, McPherson SE, Pardo JV, Pardo PJ, Parry GJ, Rottunda SJ, Segal BM, Sponheim SR, Stanwyck JJ, Stephane M, Westermeyer JJ. Synchronous neural interactions assessed by magnetoencephalography: a functional biomarker for brain disorders. J Neural Eng 2007;4:349–55.

Golland Y, Bentin S, Gelbard H, Benjamini Y, Heller R, Nir Y, Hasson U, Malach R. Extrinsic and intrinsic systems in the posterior cortex of the human brain revealed during natural sensory stimulation. Cereb Cortex 2007;17:766–77.

Greicius MD, Krasnow B, Reiss AL, Menon V. Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. Proc Natl Acad Sci USA 2003;100:253–8.

Greicius MD, Srivastava G, Reiss AL, Menon V. Default-mode network activity distinguishes Alzheimer's disease from healthy aging: evidence from functional MRI. Proc Natl Acad Sci USA 2004;101:4637–42.

Hatz F, Benz N, Hardmeier M, Zimmermann R, Rueegg S, Schindler C, Miserez AR, Gschwandtner U, Monsch AU, Fuhr P. Quantitative EEG and apolipoprotein E-genotype improve classification of patients with suspected Alzheimer's disease. Clin Neurophysiol 2013;124:2146–52.

Hlinka J, Palus M, Vejmelka M, Mantini D, Corbetta M. Functional connectivity in resting-state fMRI: is linear correlation sufficient? Neuroimage 2011;54:2218–25.

Holmes AP, Blair RC, Watson JD, Ford I. Nonparametric analysis of statistic images from functional mapping experiments J Cereb Blood Flow Metab 1996;16:7–22.

Hoshi E. Functional specialization within the dorsolateral prefrontal cortex: a review of anatomical and physiological studies of non-human primates. Neurosci Res 2006;54:73–84.

Hsiao FJ, Wang YJ, Yan SH, Chen WT, Lin YY. Altered oscillation and synchronization of default-mode network activity in mild Alzheimer's disease compared to mild cognitive impairment: an electrophysiological study. PLoS One 2013;8:e68792.

Ishii R, Canuet L, Kurimoto R, Ikezawa K, Aoki Y, Azechi M, Takahashi H, Nakahachi T, Iwase M, Kazui H, Takeda M. Frontal shift of posterior alpha activity is correlated with cognitive impairment in early Alzheimer's disease: a magnetoencephalography-beamformer study. Psychogeriatrics 2010;10:138–43.

Jelles B, Scheltens P, van der Flier WM, Jonkman EJ, da Silva FH, Stam CJ. Global dynamical analysis of the EEG in Alzheimer's disease: frequency-specific changes of functional interactions. Clin Neurophysiol 2008;119:837–41.

Klimesch W. EEG alpha and theta oscillations reflect cognitive and memory performance: a review and analysis. Brain Res Rev 1999;29:169–95.

Kurimoto R, Ishii R, Canuet L, Ikezawa K, Azechi M, Iwase M, Yoshida T, Kazui H, Yoshimine T, Takeda M. Event-related synchronization of alpha activity in early Alzheimer's disease and mild cognitive impairment: an MEG study combining beamformer and group comparison. Neurosci Lett 2008;443:86–9.

Kurimoto R, Ishii R, Canuet L, Ikezawa K, Iwase M, Azechi M, Aoki Y, Ikeda S, Yoshida T, Takahashi H, Nakahachi T, Kazui H, Takeda M. Induced oscillatory responses during the Sternberg's visual memory task in patients with Alzheimer's disease and mild cognitive impairment. Neuroimage 2012;59:4132–40.

Li R, Wang S, Zhu L, Guo J, Zeng L, Gong Q, He L, Chen H. Aberrant functional connectivity of resting state networks in transient ischemic attack. PLoS One 2013;8:e71009.

Liang P, Wang Z, Yang Y, Jia X, Li K. Functional disconnection and compensation in mild cognitive impairment: evidence from DLPFC connectivity using resting-state fMRI. PLoS One 2011;6:e22153.
Lo CY, Wang PN, Chou KH, Wang J, He Y, Lin CP. Diffusion tensor tractography reveals abnormal topological organization in structural cortical networks in Alzheimer's disease. J Neurosci 2010;30:16876–85.
Mazziotta J, Toga A, Evans A, Fox P, Lancaster J, Zilles K, Woods R, Paus T, Simpson G, Pike B, Holmes C, Collins L, Thompson P, MacDonald D, Iacoboni M, Schormann T, Amunts K, Palomero-Gallagher N, Geyer S, Parsons L, Narr K, Kabani N, Le Goualher G, Boomsma D, Cannon T, Kawashima R, Mazoyer B. A probabilistic atlas and reference system for the human brain: International Consortium for Brain Mapping (ICBM). Philos Trans R Soc Lond B Biol Sci 2001;356:1293–322.
McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. Neurology 1984;34:939–44.
Mizuguchi N, Nakata H, Hayashi T, Sakamoto M, Muraoka T, Uchida Y, Kanosue K. Brain activity during motor imagery of an action with an object: a functional magnetic resonance imaging study. Neurosci Res 2013;76:150–5.
Mulert C, Jäger L, Schmitt R, Bussfeld P, Pogarell O, Möller HJ, Juckel G, Hegerl U. Integration of fMRI and simultaneous EEG: towards a comprehensive understanding of localization and time-course of brain activity in target detection. Neuroimage 2004;22:83–94.
Nichols TE, Holmes AP. Nonparametric permutation tests for functional neuroimaging: a primer with examples. Hum Brain Mapp 2002;5:1–25.
Nolte G, Bai O, Wheaton L, Mari Z, Vorbach S, Hallett M. Identifying true brain interaction from EEG data using the imaginary part of coherency. Clin Neurophysiol 2004;115:2292–307.
Parisi L, Rocca MA, Valsasina P, Panicari L, Mattioli F, Filippi M. Cognitive rehabilitation correlates with the functional connectivity of the anterior cingulate cortex in patients with multiple sclerosis. Brain Imaging Behav 2014;8:387–93.
Pascual B, Masdeu JC, Hollenbeck M, Makris N, Insausti R, Ding SL, Dickerson BC. Large-scale brain networks of the human left temporal pole: a functional connectivity MRI study. Cereb Cortex 2013. http://dx.doi.org/10.1093/cercor/bht260.
Pascual-Marqui RD, Lehmann D, Koenig T, Kochi K, Merlo MC, Hell D, Koukkou M. Low resolution brain electromagnetic tomography (LORETA) functional imaging in acute, neuroleptic-naive, first-episode, productive schizophrenia. Psychiatry Res 1999;90:169–79.
Pascual-Marqui RD, Lehmann D, Koukkou M, Kochi K, Anderer P, Saletu B, Tanaka H, Hirata K, John ER, Prichep L, Biscay-Lirio R, Kinoshita T. Assessing interactions in the brain with exact low-resolution electromagnetic tomography. Philos Trans A Math Phys Eng Sci 2011;369:3768–84.
Pessoa L, Rossi A, Japee S, Desimone R, Ungerleider LG. Attentional control during the transient updating of cue information. Brain Res 2009;9:149–58.
Petrella JR, Sheldon FC, Prince SE, Calhoun VD, Doraiswamy PM. Default mode network connectivity in stable vs progressive mild cognitive impairment. Neurology 2011;76:511–7.
Pievani M, de Haan W, Wu T, Seeley WW, Frisoni GB. Functional network disruption in the degenerative dementias. Lancet Neurol 2011;10:829–43.
Rossini PM, Del Percio C, Pasqualetti P, Cassetta E, Binetti G, Dal Forno G, Ferreri F, Frisoni G, Chiovenda P, Miniussi C, Parisi L, Tombini M, Vecchio F, Babiloni C. Conversion from mild cognitive impairment to Alzheimer's disease is predicted by sources and coherence of brain electroencephalography rhythms. Neuroscience 2006;143:793–803.
Sanchez-Mut JV, Aso E, Panayotis N, Lott I, Dierssen M, Rabano A, Urdinguio RG, Fernandez AF, Astudillo A, Martin-Subero JI, Balint B, Fraga MF, Gomez A, Gurnot M, Roux JC, Avila J, Hensch TK, Ferrer I, Esteller M. DNA methylation map of mouse and human brain identifies target genes in Alzheimer's disease. Brain 2013;136:3018–27.
Sankari Z, Adeli H, Adeli A. Intrahemispheric, interhemispheric, and distal EEG coherence in Alzheimer's disease. Clin Neurophysiol 2011;122:897–906.
Sankari Z, Adeli H, Adeli A. Wavelet coherence model for diagnosis of Alzheimer disease. Clin EEG Neurosci 2012;43:268–78.
Stam CJ. Use of magnetoencephalography (MEG) to study functional brain networks in neurodegenerative disorders. J Neurol Sci 2010;289:128–34.
Stam CJ, Jones BF, Manshanden I, van Cappellen van Walsum AM, Montez T, Verbunt JP, de Munck JC, van Dijk BW, Berendse HW, Scheltens P. Magnetoencephalographic evaluation of resting-state functional connectivity in Alzheimer's disease. Neuroimage 2006;32:1335–44.
Stam CJ, Nolte G, Daffertshofer A. Phase lag index: assessment of functional connectivity from multichannel EEG and MEG with diminished bias from common sources. Hum Brain Mapp 2007;28:1178–93.
Supekar K, Menon V, Rubin D, Musen M, Greicius MD. Network analysis of intrinsic functional brain connectivity in Alzheimer's disease. PLoS Comput Biol 2008;4:e1000100.
Tijms BM, Wink AM, de Haan W, van der Flier WM, Stam CJ, Scheltens P, Barkhof F. Alzheimer's disease: connecting findings from graph theoretical studies of brain networks. Neurobiol Aging 2013;34:2023–36.
Vincent JL, Kahn I, Snyder AZ, Raichle ME, Buckner RL. Evidence for a frontoparietal control system revealed by intrinsic functional connectivity. J Neurophysiol 2008;100:3328–42.
Vitacco D, Brandeis D, Pascual-Marqui R, Martin E. Correspondence of event-related potential tomography and functional magnetic resonance imaging during language processing. Hum Brain Mapp 2002;17:4–12.
Vos SJ, Xiong C, Visser PJ, Jasielec MS, Hassenstab J, Grant EA, Cairns NJ, Morris JC, Holtzman DM, Fagan AM. Preclinical Alzheimer's disease and its outcome: a longitudinal cohort study. Lancet Neurol 2013;12:957–65.
Vry MS, Saur D, Rijntjes M, Umarova R, Kellmeyer P, Schnell S, Glauche V, Hamzei F, Weiller C. Ventral and dorsal fiber systems for imagined and executed movement. Exp Brain Res 2012;219:203–16.
Worrell GA, Lagerlund TD, Sharbrough FW, Brinkmann BH, Busacker NE. Localization of the epileptic focus by low-resolution electromagnetic tomography in patients with a lesion demonstrated by MRI. Brain Topogr 2000;12:273–82.
Wu J, Yang J, Yu Y, Li Q, Nakamura N, Shen Y, Ohta Y, Yu S, Abe K. Delayed audiovisual integration of patients with mild cognitive impairment and Alzheimer's disease compared with normal aged controls. J Alzheimers Dis 2012;32:317–28.
Yamasaki T, Goto Y, Ohyagi Y, Monji A, Munetsuna S, Minohara M, Minohara K, Kira J, Kanba S, Tobimatsu S. Selective impairment of optic flow perception in amnestic mild cognitive impairment: evidence from event-related potentials. J Alzheimers Dis 2012;28:695–708.
Yoon EY, Humphreys GW, Kumar S, Rotshtein P. The neural selection and integration of actions and objects: an fMRI study. J Cogn Neurosci 2012;24:2268–79.
Zahodne LB, Manly JJ, Narkhede A, Griffith EY, DeCarli C, Schupf NS, Mayeux R, Brickman AM. Structural MRI predictors of late-life cognition differ across African Americans, Hispanics, and Whites. Curr Alzheimer Res 2015. http://dx.doi.org/10.2174/1567205012666150530203214.
Zumsteg D, Friedman A, Wieser HG, Wennberg RA. Propagation of interictal discharges in temporal lobe epilepsy: correlation of spatiotemporal mapping with intracranial foramen ovale electrode recordings. Clin Neurophysiol 2006;117:2615–26.