Neuroscience Letters 558 (2014) 47–52

Contents lists available at ScienceDirect

Neuroscience Letters

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

Altered source-based EEG coherence of resting-state sensorimotor network in early-stage Alzheimer's disease compared to mild cognitive impairment

Fu-Jung Hsiao[a,c,d,e,*], Wei-Ta Chen[a,b,f], Yuh-Jen Wang[d], Sui-Hing Yan[d], Yung-Yang Lin[a,b,e,f,*]

[a] Institute of Brain Science, National Yang-Ming University, Taipei, Taiwan
[b] Department of Neurology, School of Medicine, National Yang-Ming University, Taipei, Taiwan
[c] Department of Education and Research, Taipei City Hospital, Taipei, Taiwan
[d] Department of Neurology, Taipei City Hospital, Taipei, Taiwan
[e] Laboratory of Neurophysiology, Department of Medical Research and Education, Taipei Veterans General Hospital, Taipei, Taiwan
[f] Department of Neurology, Taipei Veterans General Hospital, Taipei, Taiwan

HIGHLIGHTS

- The resting-state sensorimotor activities were examined in AD and MCI.
- Increased delta coherences within the sensorimotor network were found in AD.
- No significant difference of spectral powers was observed between AD and MCI.
- Enhanced cortical coupling at delta band characterizes the alterations in AD.

ARTICLE INFO

Article history:
Received 1 May 2013
Received in revised form 27 October 2013
Accepted 29 October 2013

Keywords:
Alzheimer's disease (AD)
Mild cognitive impairment (MCI)
Spectral power
Sensorimotor
Coherence
Electroencephalography (EEG)

ABSTRACT

Although the altered coherence between cortical areas in Alzheimer's disease (AD) has been widely studied, it remains unclear whether the source-based coherence measures within sensorimotor network show significant difference between mild cognitive impairment (MCI) and AD. In the present study, resting-state electroencephalographic signals were recorded from 21 MCI and 21 mild AD patients. The spectral power and coherence in the sensorimotor areas were analyzed using the minimum norm estimate (MNE) combined with fast Fourier transform and coherence analysis in delta (1–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (13–25 Hz), and gamma (25–40 Hz) bands. Our results indicated that source-based coherence in AD showed increased delta coherences between the bilateral precentral, left supplementary motor area (SMA) and right precentral, and left SMA and right postcentral areas. However, no significant difference of spectral powers was observed between AD and MCI. To conclude, the phenotype conversion from MCI to AD may be associated with an altered connectivity of the sensorimotor cortical network. This is a promising finding; however, further large-scale studies are needed.

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder that is characterized by cognitive deficits and behavioral disturbances, as well as pathological changes as shown by the senile plaques, neurofibrillary tangles, and neuronal loss in the frontal, temporal and parietal neocortical association areas [4]. Although, in the early stages of AD, motor cortex was found to be relatively spared of pathological change [36], deteriorated fine motor skill performance [24] and subclinical motor slowing of reaction and movement time [20] were found for the disease. Transcranial magnetic stimulation (TMS) studies also demonstrated that early-stage AD exhibited the motor hyperexcitability and subclinical motor cortical reorganization [21]. It is feasible that the early changes of motor cortex in AD reflect a functional, but not structural, alteration of the cortical motor network [33].

The sensorimotor network, which is crucial for the execution of voluntary movements and comprised of postcentral, precentral and supplementary motor areas, is one of the resting state networks

* Corresponding authors at: Institute of Brain Science, National Yang-Ming University, No. 155, Sec. 2, Linong Street, Taipei 112, Taiwan. Tel.: +886 2 28757398; fax: +886 2 28757579.
E-mail addresses: fujunghsiao@gmail.com, fjhsiao2@ym.edu.tw (F.-J. Hsiao), yylin@vghtpe.gov.tw (Y.-Y. Lin).

0304-3940/$ – see front matter © 2013 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.neulet.2013.10.056

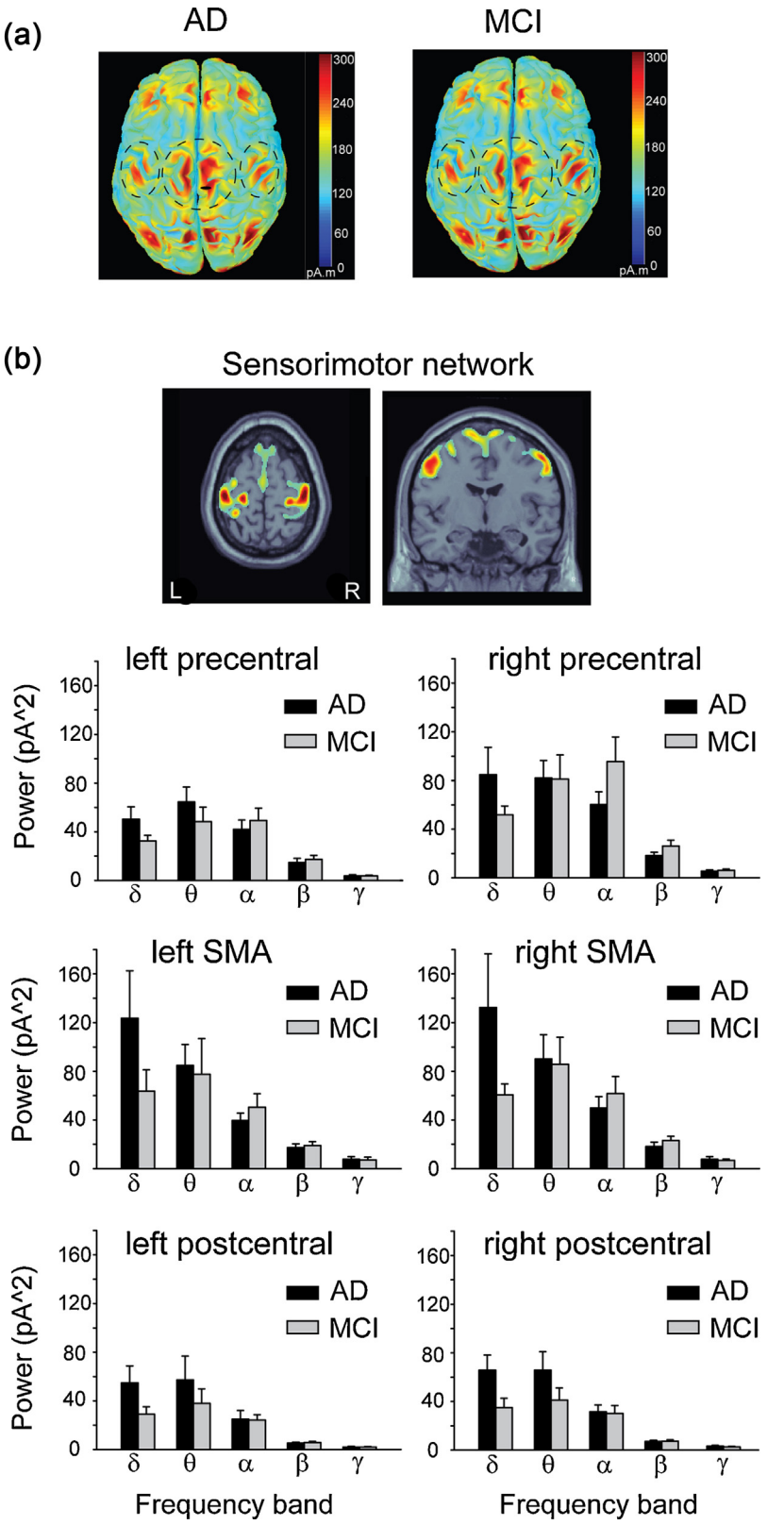

Fig. 1. (a) Distributions of averaged cortical activation during resting-state condition in 21 AD and 21 MCI patients, respectively. Cortical areas encircled by dashed circles indicate the sensorimotor areas. The strength of cortical sources is color coded; large values are represented in red, and small values are in blue. (b) Upper: Map of sensorimotor network on the axial and coronal MR images is shown. Lower: The bar plots show the power values in each frequency band in AD and MCI. δ, delta; θ, theta; α, alpha; β, beta; γ, gamma. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

[28]. The neural activities within the network significantly coactivated without any sensory, cognitive or motor task. In the previous functional magnetic resonance imaging (fMRI) studies, compared with mild cognitive impairment (MCI), mild AD was associated with decreased [14] or rewired [1] sensorimotor network connections. In a recent fMRI study, Vidoni et al. [41] found that early-stage AD more recruited multiple motor association and execution areas to maintain the motor performance. Though these fMRI studies displayed altered activation within sensorimotor network in AD, the changes of resting-state electrophysiological activities, reflecting the motor functions with high temporal resolution and providing a relevant picture of summated neural activities, remain unclear.

Previous studies using EEG source-based spectral power analysis [6–8,10,12] and sensor-based synchronization analysis [5,8,9,11] suggested that EEG could provide an useful measure to investigate the alterations of the local cortical activities and cortico-cortical connections in MCI and AD. Of note, analysis of frontoparietal or frontomedial cortical couplings in MCI or AD yielded contradictory results, which may be enhanced [4,10] and reduced [7,8]. These findings illuminate the need for further investigations exploring the source-based EEG functional connectivity within resting state network. The findings from these investigations could potentially elucidate the functional changes that underlie the pathologic mechanisms of neurodegeneration, especially important as the conversion from MCI to AD.

It is well known that treatment at the early stage of AD may delay the onset and progression of this disease. The present study aimed to measure the source-based rhythmic activities and coherence within the sensorimotor network via the resting-state EEG recording in MCI and mild AD subjects.

2. Methods

2.1. Subjects

This study recruited 21 AD patients and 21 MCI patients, which were diagnosed according to NINCDS-ADRDA [30] and DSM IV criteria, and previous published guidelines [34], respectively. Each subject was first visit to the neurological institute of Taipei City Hospital. An experienced neurologist (YJW) excluded any subject with brain lesions or other abnormalities that can lead to atypical AD symptoms, such as frontotemporal dementia, vascular dementia, extrapyramidal syndromes, reversible dementias, and Lewy body dementia.

The inclusion criteria for AD and MCI were clinical dementia rating (CDR) score of 1 and 0.5, respectively. According to the rule of CDR [32], the level of severity in all AD enrolled in this study was mild. The exclusion criteria were (1) no daily use of medications prior to EEG recording; (2) evidence of other neurological or psychiatric diseases characterized by the cognitive impairment; and (3) uncontrolled or complicated systemic diseases or traumatic brain injuries. This study was approved by the Institutional Review Board of Taipei City Hospital.

2.2. EEG recordings and preprocessing

Resting-state EEG data were recorded using a Nihon-Kohden system (Nihon-Kohden Inc., Tokyo, Japan) with 19 electrodes, which were positioned according to the International 10–20 System and consisted of Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5, T6, Fz, Cz, and Pz. All EEG data were commonly referenced to the average of the two linked mastoid electrodes, sampled at 200 Hz, and filtered offline between 1 and 40 Hz. To ensure that subjects remained awake and alert, eyes-closed and eyes-opened conditions were performed for 20–30 s alternately, and totally each condition was recorded about 3 min. The EEG data of the eyes-closed condition were extracted and fragmented into consecutive epochs of 2 s for further analysis. To eliminate the ocular, muscular, heart and other types of artifacts, three processes were used including: (1) the data were reviewed, and the epochs with aberrant waveforms were manually discarded by an expert EEG technician; (2) automatic detection and rejection of artifacts were completed using the EEGLAB toolbox (available at sccn.ucsd.edu/eeglab); (3) independent component analysis (ICA) was applied to the recordings to effectively remove noise [15]. For each subject, 30 artifact-free epochs were randomly selected for further analysis.

2.3. Data analysis

2.3.1. Minimum norm estimate analysis

Depth-weighted minimum-norm estimation (MNE) was used to obtain the current strength dynamics of cortical sources of the EEG data [22]. This method offers greater spatial accuracy than it without depth weighting [26] and is able to detect simultaneous current sources that are distributed along the entire cortical surface [22]. The details of MNE parameters could be found in our previous work [23]. In the present study, the activation at each vertex (an equilateral triangle in the tessellation of the cortical surface) was estimated every 5 ms. Cortical maps of distributed current activity in each subject were displayed on the same source space: the cortex from Colin27 anatomy. Six regions of interest (ROIs), which included the precental, postcentral, and supplementary motor area (SMA) in the bilateral hemispheres, were selected from the cortical surface of default anatomy (MNI/Colin27) according to the automatic anatomical labeling template [40]. The time-varying current source strengths at these ROIs were extracted from each epoch. MNE analysis was performed with Brainstorm [37], which is a documented program that is available for free download online under the GNU general public license (http://neuroimage.usc.edu/brainstorm).

2.3.2. Spectral power and coherence analysis

To obtain the source-based spectral power of cortical activity, fast Fourier transformed (FFT) spectral analysis was used to transform the time-varying current source strength of each ROI, in each epoch, into power spectrums of 0.5 Hz frequency resolution from 1 to 40 Hz. The spectral power was derived from the averaged spectrum across epochs. The coherence between two ROIs at each frequency was obtained from the ratio of squared cross-spectrum to the product of the two auto-spectra, taking on a value between 0 and 1. In this study, coherence was typically estimated by averaging over 30 epochs. Coherence values were calculated for all 15 possible combinations between the 6 ROIs. To minimize the spurious coherence due to volume conduction, the coherence between paired ROIs with anatomical distance <5 cm was excluded from further analysis. A high coherence can be associated with a highly functional coupling between the linked brain regions. The spectral powers and coherences are defined as the mean values within delta (1–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (13–25 Hz), and gamma (25–40 Hz) bands.

2.4. Statistical analysis

An ANOVA was performed to examine significant differences for the effect of Group (AD and MCI), Region (6 ROIs) and Band (5 frequency bands) on the spectral power of cortical sources. Coherences were tested using ANOVA with the covariate of spectral power for the effect of Group (AD and MCI). The Bonferroni correction was used for multiple comparisons. Statistical analysis

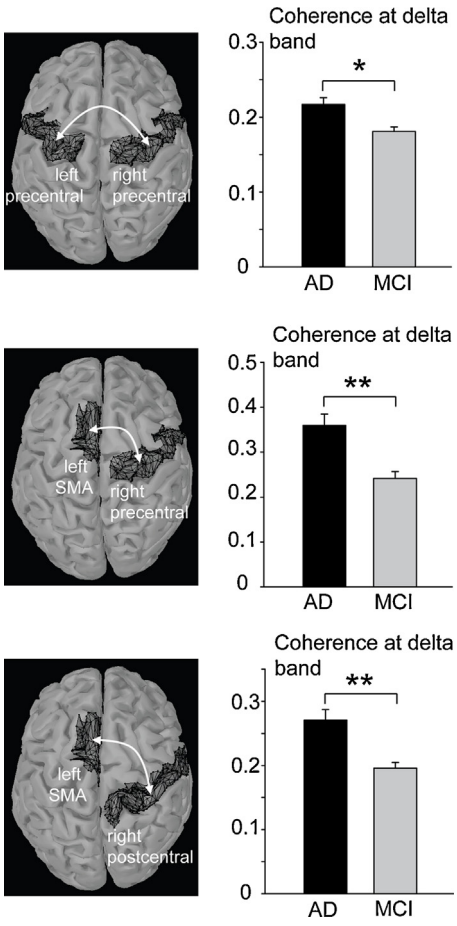

Fig. 2. The difference of coherence at delta band for the ROI pairs between AD and MCI. *, corrected $p < 0.05$; **, corrected $p < 0.01$.

was carried out using SPSS software package (SPSS Inc., Chicago). A corrected p-value < 0.05 was considered statistically significant.

3. Results

There was no significant difference with age between the AD and MCI groups (AD, 82.7 ± 7.5; MCI, 80.4 ± 5.6). MMSE scores were significantly lower in AD than in MCI (AD, 14.9 ± 5.4; MCI, 22.7 ± 2.2; $p < 0.0001$); the scores of both groups were below normal (MMSE cutoff value > 25/30).

Fig. 1(a) depicts grand-averaged activation distributions on cortical surfaces with upper view across the AD and MCI, respectively. The activation maps distributing over the frontal, parietal, temporal, occipital and midline regions are similar between two groups. The current strength of underlying cortical sources is color coded; large activation is denoted with red. Sensorimotor areas are encircled by dashed circles. These activated brain regions are mapped onto the axial and coronal MR images and located over the bilateral precentral, postcentral and SMA areas (upper part of Fig. 1(b)). The bar plots in Fig. 1(b) show the spectral powers of the cortical activation in the bilateral precentral, postcentral and SMA areas in AD and MCI. For the spectral powers, ANOVA tests exhibited no main effect for Group × ROI × Band interaction ($F = 0.604$, $p = 0.912$). It indicates that no significant difference was observed between AD and MCI (all $p > 0.1$), although the averaged power values in AD were larger for delta and theta bands and smaller alpha and beta bands.

Fig. 2 illustrates the plots reporting the significant difference of coherence between AD and MCI. Left part of the plots displays the ROI pairs; right exhibits the mean and standard error of the coherence values in AD and MCI. ANOVA examinations with covariant of spectral power did not showed significant interaction between Group and spectral power (all $p > 0.2$). Regarding the effect for Group, larger coherences at delta band in AD than in MCI were observed between bilateral precentral (AD, 0.217 ± 0.009; MCI, 0.18 ± 0.006; $p < 0.05$), left SMA and right precentral (AD, 0.359 ± 0.025; MCI, 0.242 ± 0.015; $p < 0.01$), and left SMA and right postcentral areas (AD, 0.271 ± 0.016; MCI, 0.196 ± 0.009; $p < 0.01$). There was no correlation between coherences and the spectral power. No significance was found with other frequency bands and ROI pairs, either.

4. Discussion

Using EEG recording combined with MNE analysis to assess the sensorimotor activities during resting state condition, source-based spectral power and coherence were obtained to compare the difference between MCI and mild AD. This study demonstrates that altered coherences within the sensorimotor network could be correlated with the transition from MCI to AD. Such alteration is characteristic of, augmented delta coherences between the bilateral precentral, left SMA and right precentral, and left SMA and right postcentral areas. In early AD, gray matter loss and its rates were asymmetry and greater in the left hemisphere [38,39]. It might explain that, with relatively intact functions, coherences in right SMA exhibited no difference between early-stage AD and MCI.

With or without simple motor task, the alteration of sensorimotor system was reported by fMRI [1,14,41] and EEG [5,11], suggesting that the reorganization of sensorimotor cortical coupling characterized the functional change in early-state AD. In this study, the altered and augmented coherences in mild AD may not only show the adaptation of sensorimotor network, but reflect the increased recruitments of association areas. This fits with previous AD studies reporting (i) in EEG, high frontoparietal or frontomedial cortical coupling [5,11], (ii) in fMRI, the greater cingulum activation and connection [1], and increased bilateral motor coactivation [41], (iii) in TMS, cortical hyperexcitability in motor cortex, and the shift of main motor cortical output toward the frontal and medial regions [16]. Consequently, a compensatory mechanism in AD has been proposed for maintaining the motor performance despite the disease-related impairment [16,41]. Another possibility is that cortical recruitment in AD may be caused by aberrant dendritic arborization with functional enlargement of motor-related circuitries [3] and a loss of transcallosal inhibition [25].

Prominent coherence magnification for AD was noted at delta band. Delta activities have been treated as one of the diagnostic markers of AD [13,29]. Previous studies have interpreted the increased delta coherence for the intra- and inter-hemispheric connections as being due mainly to an impairment of the cholinergic pathways [27]. In addition, AD has been ascribed to a defect of cholinergic innervation [16]. The loss of intracortical inhibition [16,21] and the functional unbinding with association cortex [17] could cause the increases of delta connectivity in the sensorimotor network. It is possible to speculate the relationship between the delta coherence within sensorimotor network and the dysfunction of cholinergic structures in AD.

Various studies report that EEG spectral power increases at delta and theta bands could characterize the manifestation and progression of AD [13,29]. In this study, larger delta and theta activities but not significant were observed in AD in comparison with MCI (Fig. 1). It could be because of relatively spared of pathological change in motor cortex [36] and large inter-individual variability [8], as well as the methodological discrepancies including the medication effect (drug-naïve patients enrolled in the study) and the EEG analysis (source-based analysis in the study). In this early stage

of the disease, the absolute power changes could be partly correlated with the progression. On the other hand, coherence measures probably act an important hallmark.

Several methodological considerations: (1) in the present study, using MNE analysis, the solutions of EEG inverse problem were underdetermined and ill-conditioned. As a result, this model disentangled the cortical sources of these ROIs with low spatial resolution and distinction of cortical sources between two neighboring ROIs (i.e. MI and SI) could not be guaranteed. Nevertheless, the patterns of spectral activities and coherence among ROIs were notably dissimilar to each other. (2) Goldman et al. [20] have reported that slowed motor responses, including the gait velocity, reaction time and movement time, represent the motor dysfunction of mild AD. Unfortunately, the present study which lacked motor measures cannot examine the correlation between behavioral and EEG data; nevertheless, the findings inspire the further investigations with regard to the interplay of resting-state neurophysiological alterations and motor dysfunction in AD. (3) Resting state network with significant and dynamic interaction among distributed brain regions was observed when subjects rest with their eye closed [28]. In contrast, eye opened condition often require attentional demand that could deactivate the resting state network [35]. Therefore, the measure of altered resting state network in mental disorders has been performed during eye closed condition [6–10,12,18]. Moreover, Franciotti and colleagues [19] exhibited that the spectral change in the closed eye condition with respect to opened eye condition distinguished the control group from the AD group. The experimental design could be a good candidate to obtain the spectral difference of sensorimotor cortex between groups in the future work. (4) One caveat of the present study is lack of neuropsychiatric assessment and it may be of concern whether the findings here reflect the extent of neuropsychiatric involvement. However, the prevalence of neuropsychiatric symptoms in MCI and in AD did not differ significantly [2,31]. Moreover, it remains undetermined whether neuropsychiatric factors may affect the electrophysiological trait in patients with MCI or AD.

In order to obtain the cortical activities with less confounding factors, such as medication and aging effect, small sample size was enrolled using strict criteria in this study. Regarding the cortical deterioration for the disease, recruitment of elder controls may contribute to a better understanding of the neuropathological changes. Further studies in a larger population are needed to confirm and extend these findings. In addition, comparisons between groups with varying severity of cognitive impairment, and longitudinal follow-up studies probing into the effect of progression in MCI patients, may advance the understanding of dementing processes.

5. Conclusions

In conclusion, resting-state cortical EEG coherence within the sensorimotor network may characterize the pathological changes in mild AD. It exhibited the cortical recruitment as enhanced cortical coupling at delta band. Our findings also demonstrate the need to further investigations through longitudinal studies.

Acknowledgements

This study was supported in part by research grants from Taipei City Hospital (99TPECH04), Taipei Veterans General Hospital (V101C-023, V102C-103, VGHUST 102-G7-6-2), and from the National Science Council (NSC 98-2321-B-010-007, NSC 99-2321-B-010-004, NSC 99-2628-B-010-011-MY3, NSC 100-2218-E-010-002, NSC 100-2321-B-010-004, NSC 101-2314-B-010-068-MY3, NSC 101-2314-B-075-068-MY2, NSC 102-2221-E-010-003), Taipei, Taiwan.

References

[1] F. Agosta, M.A. Rocca, E. Pagani, M. Absinta, G. Magnani, A. Marcone, M. Falautano, G. Comi, M.L. Gorno-Tempini, M. Filippi, Sensorimotor network rewiring in mild cognitive impairment and Alzheimer's disease, Hum. Brain Mapp. 31 (2010) 515–525.
[2] L.G. Apostolova, J.L. Cummings, Neuropsychiatric manifestations in mild cognitive impairment: a systematic review of the literature, Dement. Geriatr. Cogn. Disord. 25 (2008) 115–126.
[3] T. Arendt, M.K. Bruckner, V. Bigl, L. Marcova, Dendritic reorganisation in the basal forebrain under degenerative conditions and its defects in Alzheimer's disease. III. The basal forebrain compared with other subcortical areas, J. Comp. Neurol. 351 (1995) 223–246.
[4] S.E. Arnold, B.T. Hyman, J. Flory, A.R. Damasio, G.W. Van Hoesen, The topographical and neuroanatomical distribution of neurofibrillary tangles and neuritic plaques in the cerebral cortex of patients with Alzheimer's disease, Cereb. Cortex 1 (1991) 103–116.
[5] C. Babiloni, F. Babiloni, F. Carducci, F. Cincotti, C. Del Percio, G. De Pino, S. Maestrini, A. Priori, P. Tisei, O. Zanetti, P.M. Rossini, Movement-related electroencephalographic reactivity in Alzheimer disease, Neuroimage 12 (2000) 139–146.
[6] C. Babiloni, G. Binetti, E. Cassetta, D. Cerboneschi, G. Dal Forno, C. Del Percio, F. Ferreri, R. Ferri, B. Lanuzza, C. Miniussi, D.V. Moretti, F. Nobili, R.D. Pascual-Marqui, G. Rodriguez, G.L. Romani, S. Salinari, F. Tecchio, P. Vitali, O. Zanetti, F. Zappasodi, P.M. Rossini, Mapping distributed sources of cortical rhythms in mild Alzheimer's disease. A multicentric EEG study, Neuroimage 22 (2004) 57–67.
[7] C. Babiloni, F. Carducci, R. Lizio, F. Vecchio, A. Baglieri, S. Bernardini, E. Cavedo, A. Bozzao, C. Buttinelli, F. Esposito, F. Giubilei, A. Guizzaro, S. Marino, P. Montella, C.C. Quattrocchi, A. Redolfi, A. Soricelli, G. Tedeschi, R. Ferri, G. Rossi-Fedele, F. Ursini, F. Scrascia, F. Vernieri, T.J. Pedersen, H.G. Hardemark, P.M. Rossini, G.B. Frisoni, Resting state cortical electroencephalographic rhythms are related to gray matter volume in subjects with mild cognitive impairment and Alzheimer's disease, Hum. Brain Mapp. (2012).
[8] C. Babiloni, R. Ferri, G. Binetti, A. Cassarino, G. Dal Forno, M. Ercolani, F. Ferreri, G.B. Frisoni, B. Lanuzza, C. Miniussi, F. Nobili, G. Rodriguez, F. Rundo, C.J. Stam, T. Musha, F. Vecchio, P.M. Rossini, Fronto-parietal coupling of brain rhythms in mild cognitive impairment: a multicentric EEG study, Brain Res. Bull. 69 (2006) 63–73.
[9] C. Babiloni, R. Ferri, D.V. Moretti, A. Strambi, G. Binetti, G. Dal Forno, F. Ferreri, B. Lanuzza, C. Bonato, F. Nobili, G. Rodriguez, S. Salinari, S. Passero, R. Rocchi, C.J. Stam, P.M. Rossini, Abnormal fronto-parietal coupling of brain rhythms in mild Alzheimer's disease: a multicentric EEG study, Eur. J. Neurosci. 19 (2004) 2583–2590.
[10] C. Babiloni, R. Lizio, F. Vecchio, G.B. Frisoni, M. Pievani, C. Geroldi, F. Claudia, R. Ferri, B. Lanuzza, P.M. Rossini, Reactivity of cortical alpha rhythms to eye opening in mild cognitive impairment and Alzheimer's disease: an EEG study, J. Alzheimers Dis. 22 (2010) 1047–1064.
[11] C. Babiloni, C. Miniussi, D.V. Moretti, F. Vecchio, S. Salinari, G. Frisoni, P.M. Rossini, Cortical networks generating movement-related EEG rhythms in Alzheimer's disease: an EEG coherence study, Behav. Neurosci. 118 (2004) 698–706.
[12] C. Babiloni, F. Vecchio, R. Lizio, R. Ferri, G. Rodriguez, N. Marzano, G.B. Frisoni, P.M. Rossini, Resting state cortical rhythms in mild cognitive impairment and Alzheimer's disease: electroencephalographic evidence, J. Alzheimers Dis. 26 (Suppl. 3) (2011) 201–214.
[13] K. Bennys, G. Rondouin, C. Vergnes, J. Touchon, Diagnostic value of quantitative EEG in Alzheimer's disease, Neurophysiol. Clin. 31 (2001) 153–160.
[14] M.R. Brier, J.B. Thomas, A.Z. Snyder, T.L. Benzinger, D. Zhang, M.E. Raichle, D.M. Holtzman, J.C. Morris, B.M. Ances, Loss of intranetwork and internetwork resting state functional connections with Alzheimer's disease progression, J. Neurosci. 32 (2012) 8890–8899.
[15] A. Delorme, S. Makeig, EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis, J. Neurosci. Methods 134 (2004) 9–21.
[16] F. Ferreri, F. Pauri, P. Pasqualetti, R. Fini, G. Dal Forno, P.M. Rossini, Motor cortex excitability in Alzheimer's disease: a transcranial magnetic stimulation study, Ann. Neurol. 53 (2003) 102–108.
[17] F. Ferreri, F. Vecchio, D. Ponzo, P. Pasqualetti, P.M. Rossini, Time-varying coupling of EEG oscillations predicts excitability fluctuations in the primary motor cortex as reflected by motor evoked potentials amplitude: an EEG-TMS study, Hum. Brain Mapp. (2013).
[18] R. Franciotti, N.W. Falasca, L. Bonanni, F. Anzellotti, V. Maruotti, S. Comani, A. Thomas, A. Tartaro, J.P. Taylor, M. Onofrj, Default network is not hypoactive in dementia with fluctuating cognition: an Alzheimer disease/dementia with Lewy bodies comparison, Neurobiol. Aging 34 (2013) 1148–1158.
[19] R. Franciotti, D. Iacono, S. Della Penna, V. Pizzella, K. Torquati, M. Onofrj, G.L. Romani, Cortical rhythms reactivity in AD, LBD and normal subjects: a quantitative MEG study, Neurobiol. Aging 27 (2006) 1100–1109.
[20] W.P. Goldman, J.D. Baty, V.D. Buckles, S. Sahrmann, J.C. Morris, Motor dysfunction in mildly demented AD individuals without extrapyramidal signs, Neurology 53 (1999) 956–962.
[21] A. Guerra, F. Assenza, F. Bressi, F. Scrascia, M. Del Duca, F. Ursini, S. Vollaro, L. Trotta, M. Tombini, C. Chisari, F. Ferreri, Transcranial magnetic stimulation studies in Alzheimer's disease, Int. J. Alzheimers Dis. 2011 (2011) 263817.

[22] M.S. Hämäläinen, R.J. Ilmoniemi, Interpreting magnetic fields of the brain: minimum norm estimates, Med. Biol. Eng. Comput. 32 (1994) 35–42.
[23] F.J. Hsiao, C.H. Cheng, W.T. Chen, Y.Y. Lin, Neural correlates of somatosensory paired-pulse suppression: a MEG study using distributed source modeling and dynamic spectral power analysis, Neuroimage 72 (2013) 133–142.
[24] A. Kluger, J.G. Gianutsos, J. Golomb, S.H. Ferris, A.E. George, E. Franssen, B. Reisberg, Patterns of motor impairement in normal aging, mild cognitive decline, and early Alzheimer's disease, J. Gerontol. B. Psychol. Sci. Soc. Sci. 52 (1997) 28–39.
[25] Y. Lakmache, M. Lassonde, S. Gauthier, J.Y. Frigon, F. Lepore, Interhemispheric disconnection syndrome in Alzheimer's disease, Proc. Natl. Acad. Sci. U. S. A. 95 (1998) 9042–9046.
[26] F.H. Lin, T. Witzel, S.P. Ahlfors, S.M. Stufflebeam, J.W. Belliveau, M.S. Hamalainen, Assessing and improving the spatial accuracy in MEG source localization by depth-weighted minimum-norm estimates, Neuroimage 31 (2006) 160–171.
[27] T. Locatelli, M. Cursi, D. Liberati, M. Franceschi, G. Comi, EEG coherence in Alzheimer's disease, Electroencephalogr. Clin. Neurophysiol. 106 (1998) 229–237.
[28] D. Mantini, M.G. Perrucci, C. Del Gratta, G.L. Romani, M. Corbetta, Electrophysiological signatures of resting state networks in the human brain, Proc. Natl. Acad. Sci. U. S. A. 104 (2007) 13170–13175.
[29] K. Maurer, T. Dierks, Functional imaging procedures in dementias: mapping of EEG and evoked potentials, Acta Neurol. Scand. Suppl. 139 (1992) 40–46.
[30] G. McKhann, D. Drachman, M. Folstein, R. Katzman, D. Price, E.M. Stadlan, 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 34 (1984) 939–944.
[31] R. Monastero, F. Mangialasche, C. Camarda, S. Ercolani, R. Camarda, A systematic review of neuropsychiatric symptoms in mild cognitive impairment, J. Alzheimers Dis. 18 (2009) 11–30.
[32] J.C. Morris, The Clinical Dementia Rating (CDR): current version and scoring rules, Neurology 43 (1993) 2412–2414.
[33] G. Pennisi, R. Ferri, G. Lanza, M. Cantone, M. Pennisi, V. Puglisi, G. Malaguarnera, R. Bella, Transcranial magnetic stimulation in Alzheimer's disease: a neurophysiological marker of cortical hyperexcitability, J. Neural Transm. 118 (2011) 587–598.
[34] R.C. Petersen, Mild cognitive impairment as a diagnostic entity, J. Intern. Med. 256 (2004) 183–194.
[35] M.E. Raichle, A.M. MacLeod, A.Z. Snyder, W.J. Powers, D.A. Gusnard, G.L. Shulman, A default mode of brain function, Proc. Natl. Acad. Sci. U. S. A. 98 (2001) 676–682.
[36] D. Suva, I. Favre, R. Kraftsik, M. Esteban, A. Lobrinus, J. Miklossy, Primary motor cortex involvement in Alzheimer disease, J. Neuropathol. Exp. Neurol. 58 (1999) 1125–1134.
[37] F. Tadel, S. Baillet, J.C. Mosher, D. Pantazis, R.M. Leahy, Brainstorm: a user-friendly application for MEG/EEG analysis, Comput. Intell. Neurosci. 2011 (2011) 879716.
[38] P.M. Thompson, K.M. Hayashi, G. de Zubicaray, A.L. Janke, S.E. Rose, J. Semple, D. Herman, M.S. Hong, S.S. Dittmer, D.M. Doddrell, A.W. Toga, Dynamics of gray matter loss in Alzheimer's disease, J. Neurosci. 23 (2003) 994–1005.
[39] P.M. Thompson, M.S. Mega, R.P. Woods, C.I. Zoumalan, C.J. Lindshield, R.E. Blanton, J. Moussai, C.J. Holmes, J.L. Cummings, A.W. Toga, Cortical change in Alzheimer's disease detected with a disease-specific population-based brain atlas, Cereb. Cortex 11 (2001) 1–16.
[40] N. Tzourio-Mazoyer, B. Landeau, D. Papathanassiou, F. Crivello, O. Etard, N. Delcroix, B. Mazoyer, M. Joliot, Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain, Neuroimage 15 (2002) 273–289.
[41] E.D. Vidoni, G.P. Thomas, R.A. Honea, N. Loskutova, J.M. Burns, Evidence of altered corticomotor system connectivity in early-stage Alzheimer's disease, J. Neurol. Phys. Ther. 36 (2012) 8–16.