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ScienceDirect
Neuroscience Research 62 (2008) 112–117
Neuroscience Research
www.elsevier.com/locate/neures

Decreased EEG synchronization and its correlation with symptom severity in Alzheimer's disease

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Received 25 March 2008; accepted 25 June 2008
Available online 10 July 2008

Abstract

Background: Global field synchronization (GFS) has recently been introduced to measure functional synchronization in frequency-domain EEG data. This study explored GFS values and its clinical significance in patients with Alzheimer's disease (AD).
Method: EEGs were recorded from 22 AD patients and 23 age-matched healthy controls. GFS values were computed in the delta, theta, alpha, beta1, beta2, beta3, gamma, and full frequency bands. The Mini-Mental Status Examination (MMSE) and the Clinical Dementia Rating scale (CDR) were used to assess the symptom severity in AD patients.
Results: GFS values in the beta1, beta2, beta3, and full bands were lower in AD patients than in healthy controls. GFS values in the alpha, beta1, beta2, beta3, and full bands were positively correlated with the MMSE and CDR scores in combined group (AD patients and healthy controls). In AD patients, GFS values were positively correlated with MMSE scores in the beta1, beta 3, and full bands, and with CDR scores in the delta band.
Conclusion: GFS values were significantly lower in AD patients than in healthy controls, and they were positively correlated with MMSE and CDR scores. Our results suggest that GFS values are a useful biological correlate of cognitive decline in AD patients.

Keywords: Alzheimer's disease; Global field synchronization; Synchronization; EEG; MMSE; CDR

1. Introduction

Alzheimer's disease (AD) is the most common cause of dementia and is characterized by the degeneration of brain regions. The clinical symptoms of AD are progressive amnesia followed by a gradual but persistent decline in all cognitive domains, eventually resulting in global dementia (Sunderland et al., 2006). The neuropathology of AD involves widespread neuronal cell loss, neurofibrillary tangles, and senile plaques that starts in the entorhinal cortex and limbic areas during the early stage of the disease, and then spreads to other parts of the cortex (Selkoe, 1994). A few recent studies have suggested that pharmacological treatment for mild cognitive impairment and early AD can slow the progression of the disease (Feldman and Jacova, 2005). Therefore, early diagnosis and symptom quantification is an important issue.

Many studies have found electroencephalogram (EEG) abnormalities in AD patients, the hallmark of which is a slowing of the rhythms and alterations in each frequency band. An increase in theta and delta activity and a decrease in alpha and beta activity are commonly observed (Coben et al., 1983, 1985; Giaquinto and Nolfe, 1986; Brenner et al., 1986; Pijnenburg et al., 2004). Moreover, these abnormalities are correlated with the severity of the disease (Hughes et al., 1989; Kowalski et al., 2001). The EEG has been a useful tool for diagnosing dementias for the last three decades (Jonkman, 1997; Jeong, 2004; Jung et al., 2007). However, there is no simple relation between EEG slowing/impaired activity and cognitive dysfunction (Stam et al., 2003). For example, there is no correlation between the frequency of the dominant alpha rhythm and intelligence (Posthuma et al., 2001).

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0168-0102/$ – see front matter
doi:10.1016/j.neures.2008.06.009

Another approach focuses on the notion that higher brain functions invariably require cooperation of widely distributed specialized brain regions. Synchronous oscillations, which can be studied with EEG and magnetoencephalogram (MEG) data, have been proposed as a mechanism to achieve these neural cooperative networks (von Stein and Sarnthein, 2000). The disconnection of this cooperation in AD is caused by the degeneration of the large cortical pyramidal neurons (Hardy et al., 1986; Haxby et al., 1986). A ''disconnection syndrome'' is hypothesized as a model for AD symptomatology (Delbeuck et al., 2003).

The synchronous activity in different frequency bands may underlie different functions (Stam et al., 2003). Synchronization in the theta band, in particular between frontal- and post-central association cortices, is becoming increasingly associated with working memory processes (Sarnthein et al., 1998; Anokhin et al., 1999; Stam, 2000). The lower alpha band is hypothesized to reflect attention process, whereas the upper alpha band may reflect long-term semantic memory (Klimesch, 1996, 1999). Synchronous oscillations at higher frequencies, particularly in the so-called gamma band, are proposed to reflect the representation of complex information in consciousness (Rodriguez et al., 1999; Tallon-Baudry and Bertrand, 1999; Csibra et al., 2000; Müller et al., 2000; Başar et al., 2001). Thus, synchronous oscillations might reflect the degree of activity integration in multiple brain regions. Functional interactions between brain regions in AD have been mainly studied using coherence estimations (Stam et al., 2003). Coherence is a linear measure of the correlations between two signals as a function of frequency (Nunez et al., 1997, 1999). Most studies have found that coherence in the alpha band is decreased in AD (Leuchter et al., 1987, 1992; Besthorn et al., 1994; Locatelli et al., 1998; Berendse et al., 2000; Jelic et al., 2000). However, coherence might not be the optimal measure for studying synchronization between brain regions (Stam et al., 2005).

A novel method called global field synchronization (GFS) has been introduced to measure functional synchronization in frequency-domain EEG data. GFS can estimate the functional connectivity between brain processes in different EEG frequency bands. In contrast to coherence, where the stability of the phase relation between two preselected electrodes across analysis epochs is assessed and usually taken as an indicator of cooperativity between the underlying regions, GFS makes no assumption about the spatial location of the activity (Koenig et al., 2005). Koenig et al. (2001) performed the first clinical study using GFS in schizophrenic patients, and found that the GFS in the theta band was decreased in the theta band in schizophrenic patients who had never received medication and had experienced the acute onset of their first episode of positive symptomatology, indicating a loosened functional connectivity of processes at these frequencies. There is another method that is conceptually closely related to the GFS measure, called Omega complexity. Yoshimura et al. (2004) reported that the spatial complexity of multichannel EEG assessed by global complexity showed significantly higher values in mild AD patients in comparison with age-matched control subjects and that there was a significant correlation between the generalized frequency value and scores on MMSE, and WAIS-R.

An early application of GFS in AD showed that GFS values were reduced in the alpha, beta, and gamma frequency bands in AD patients, and increased in the delta band (Koenig et al., 2005). That study used GFS to analyze EEG databases from New York (264 subjects) and Stockholm (155 subjects), including healthy controls and patients with varying degrees of cognitive decline or AD. The relation between GFS and the degree of cognitive decline was similar for all subjects, and varied with the frequency band, with the effects being most pronounced in the alpha band. The decrease in GFS with increasing cognitive impairments was almost continuous in the New York group. In the Stockholm data set, the GFS values were lower in patients with a diagnosis of probable AD than in all the other groups (Koenig et al., 2005).

The present study compared GFS values between AD patients and healthy controls, and investigated the correlation between the GFS values in each frequency band and cognitive variables. Furthermore, we evaluated whether GFS values could be a useful indicator of cognitive decline in AD patients.

2. Materials and methods

2.1. Subjects

The AD patient group consisted of 22 subjects (19 females and 3 males) who fulfilled DSM-IV criteria for the dementia of AD. They were recruited from patients visiting the Psychiatry Department of Inje University Ilsan Paik Hospital. Other medical conditions known to cause dementia were excluded by neurological, serological, and imaging tests including computed topography and magnetic resonance imaging. The AD patients were aged 73.8 ± 7.7 (mean $\pm$ S.D.) years, had received 5.2 ± 4.7 years of education, and had been ill for 32.3 ± 20.6 months (Table 1). The symptom severity was assessed using the Mini-Mental Status Examination (MMSE) and the Clinical Dementia Rating scale (CDR), which revealed an overall MMSE score of 17.9 ± 3.8 and an overall CDR score of 1.3 ± 0.5.

The group of healthy controls consisted of 23 volunteers (9 females and 14 males) with no personal history of psychiatric or neurological abnormalities who were recruited from social communities around the hospital. They were aged 72.0 ± 4.8 years, had received 6.2 ± 4.9 years of education, and had an MMSE score of 26.4 ± 1.0 and a CDR score of 0. The education level varies greatly in Korean elderly subjects, and the MMSE score can be influenced significantly by the education level and age even in healthy subjects (Lee et al., 2004). It was well proved that the education level is a critical factor to consider for studying AD patients in Korea (Han et al., 2007). We therefore matched the duration of education as well as the age when comparing between the two

Table 1
Clinical characteristics of patients with Alzheimer's disease (AD) and healthy control subjects

	AD patients ($N = 22$)	Controls ($N = 23$)	P
Age (years)	73.8 ± 7.7	72.0 ± 4.8	0.35
Females: males	19:3	9:14	
Education duration (years)	5.2 ± 4.7	6.2 ± 4.9	0.49
MMSE score	17.9 ± 3.8	26.4 ± 1.0	<0.01
GDS score	3.6 ± 0.91	1.0 ± 0.0	<0.01
CDR score	1.3 ± 0.5	0.0 ± 0.0	<0.01

MMSE: Mini-Mental Status Examination; GDS: Global Deterioration Scale; CDR: Clinical Dementia Rating scale.

groups. All of the participants in this study signed a written informed consent approved by the Institutional Review Board of Inje University Ilsan Paik Hospital prior to their participation.

2.2. EEG recording

With a subject in a resting condition, the EEG was recorded from 18 scalp locations (Fp1, F3, C3, P3, Fp2, F4, C4, P4, F7, T3, T5/P7, O1, F8, T4, T6/P8, O2, T1, and T2) with eyes alternating between closed and open for 10 min according to the international 10–20 system with a linked ear reference. The EEG data were collected using a conventional 32-channel EEG system (Nicolet Biomedical, Madison, WI, USA) in a dim, soundproof room. Horizontal and vertical eye movements were recorded using electrodes 1-cm lateral to the outer canthus of each eye. The EEG data were recorded at a sampling rate of 250 Hz with a sensitivity of 7 μV and band-pass filtered at 1–70 Hz, with 60-Hz noise filtered out using a notch filter. Eye-blinking artifacts and segments contaminated by other artifacts were excluded by visual inspection by one person who was blind to the data origin. Five artifact-free 10-s epochs recorded in a resting condition with eyes closed were used for each subject.

2.3. GFS computation

GFS as proposed by Koenig et al. (2001) estimates the relative phase synchrony over all electrodes at a given frequency. The frequency-transformed EEG signal recorded at an electrode can be represented as a vector in a complex plane, where the direction of the vector represents the phase of the signal at a particular frequency. GFS then measures the phase synchrony of EEG signals from all electrodes by inspecting if the endpoints of the vectors lie on a straight line. The GFS is defined as

$$\mathrm{GFS}(f) = \frac{|E(f)_1 - E(f)_2|}{E(f)_1 + E(f)_2}, \quad (1)$$

where $E(f)_1$ and $E(f)_2$ are two eigenvalues obtained from principal-component analysis at a given frequency f. A GFS value close to 1 means that the distribution of the complex vectors can be explained by a single principal-component, and hence higher GFS values can be interpreted as the presence of increased functional connectivity over all electrodes. In contrast, low GFS values indicate the absence of common phase, and thus can be interpreted as decreased functional connectivity.

We calculated the GFS values in 30 2-s EEG epochs and averaged them separately for the following frequency bands within each subject: delta (1–3 Hz), theta (4–7 Hz), alpha (8–12 Hz), beta1 (13–18 Hz), beta2 (19–21 Hz), beta3 (22–30 Hz), gamma (30–50 Hz), and full (1–70 Hz).

2.4. Statistical analyses

Student's t-test and Spearman's correlation were used to compare GFS values between and within groups, respectively. All of the analyses were performed using standard software (SPSS for Windows), and P values smaller than 0.05 were considered statistically significant.

3. Results

Age and education level did not differ significantly between AD patients and healthy subjects (Table 1). However, the MMSE score differed significantly between healthy controls (26.4 ± 1.0, range: 25–30) and AD patients (17.9 ± 3.8, range: 11–26).

The GFS values in each frequency band are presented in Table 2. The GFS values differed significantly between the two groups in the beta1 ($P = 0.001$), beta2 ($P = 0.035$), beta3 ($P = 0.002$), and full ($P = 0.005$) bands. However, no significant differences were found in the alpha, theta, delta, and gamma bands.

Table 2
GFS values in AD patients and healthy controls in each frequency band

Band	AD patients ($N = 22$)	Controls ($N = 23$)	P
Delta (1–3 Hz)	0.547 ± 0.040	0.561 ± 0.036	0.190
Theta (4–7 Hz)	0.540 ± 0.023	0.555 ± 0.032	0.075
Alpha (8–12 Hz)	0.560 ± 0.055	0.575 ± 0.037	0.295
Beta1 (13–18 Hz)	0.499 ± 0.026	0.523 ± 0.020	0.001
Beta2 (19–21 Hz)	0.496 ± 0.027	0.514 ± 0.029	0.035
Beta3 (22–30 Hz)	0.482 ± 0.021	0.505 ± 0.026	0.002
Gamma (30–50 Hz)	0.475 ± 0.041	0.486 ± 0.027	0.280
Full (1–70 Hz)	0.498 ± 0.019	0.514 ± 0.018	0.005

Table 3
Spearman's correlation between each frequency band and cognitive scales in all subjects (AD patients and healthy controls, $N = 45$)

	MMSE (r)	P	CDR (r)	P
Delta (1–3 Hz)	0.09	0.562	−0.07	0.641
Theta (4–7 Hz)	0.07	0.652	−0.16	0.287
Alpha (8–12 Hz)	0.35	0.018	−0.32	0.032
Beta1 (13–18 Hz)	0.49	0.001	−0.49	0.001
Beta2 (19–21 Hz)	0.46	0.001	−0.39	0.009
Beta3 (22–30 Hz)	0.52	0.0002	−0.47	0.001
Gamma (30–50 Hz)	0.25	0.092	−0.22	0.155
Full (1–70 Hz)	0.46	0.001	−0.42	0.004

To assess the association between GFS values and the severity of the disease, we estimated Spearman's correlation between GFS values and scores on the severity scales (MMSE and CDR). The correlation between severity scale scores and GFS values was assessed in each frequency band for the entire cohort as well as for only the AD group.

The MMSE scores of all participants (both AD patients and healthy controls, $N = 45$) were positively correlated with GFS values in the alpha ($r = 0.35$, $P = 0.018$), beta1 ($r = 0.49$, $P = 0.001$), beta2 ($r = 0.46$, $P = 0.001$), beta3 ($r = 0.52$, $P = 0.0002$), and full ($r = 0.46$, $P = 0.001$) bands. In contrast, the CDR scores of all participants were negatively correlated with GFS values in the alpha ($r = -0.32$, $P = 0.032$), beta1 ($r = -0.49$, $P = 0.001$), beta2 ($r = -0.39$, $P = 0.009$), beta3 ($r = -0.47$, $P = 0.001$), and full ($r = -0.42$, $P = 0.004$) bands (Table 3).

For AD patients only ($N = 22$), the GFS values were positively correlated with MMSE scores in the beta1 ($r = 0.47$, $P = 0.029$), beta3 ($r = 0.51$, $P = 0.016$), and full ($r = 0.45$, $P = 0.034$) bands, and with CDR scores in the delta band ($r = 0.43$, $P = 0.045$; Table 4).

Table 4
Spearman's correlation between each frequency band and cognitive scales in AD patients ($N = 22$)

	MMSE (r)	P	CDR (r)	P
Delta (1–3 Hz)	−0.19	0.397	0.43	0.045
Theta (4–7 Hz)	−0.23	0.309	0.35	0.106
Alpha (8–12 Hz)	0.36	0.101	−0.12	0.585
Beta1 (13–18 Hz)	0.47	0.029	−0.36	0.098
Beta2 (19–21 Hz)	0.31	0.156	−0.20	0.372
Beta3 (22–30 Hz)	0.51	0.016	−0.28	0.199
Gamma (30–50 Hz)	0.21	0.344	0.05	0.812
Full (1–70 Hz)	0.45	0.034	−0.10	0.658

The MMSE scores of all female participants (both AD patients and healthy controls, $N = 28$) were positively correlated with GFS values in the beta1 ($r = 0.48$, $P = 0.011$), beta2 ($r = 0.49$, $P = 0.008$), beta3 ($r = 0.48$, $P = 0.009$), and full ($r = 0.50$, $P = 0.007$) bands. However, the MMSE scores of all male participants (both AD patients and healthy controls, $N = 17$) were not correlated with any other GFS values. Instead, the CDR scores of all male participants were negatively correlated with GFS values in only alpha ($r = -0.58$, $P = 0.016$). This difference in gender might not be generalized because of uneven gender distribution across AD group and healthy control group.

4. Discussion

The present study investigated whether GFS values differed significantly between AD patients and age-matched, healthy subjects, and whether any such differences were correlated with the severity of AD. We found that AD patients showed significantly decreased in GFS values in the beta1, beta2, beta3, and full bands. Moreover, GFS values in the alpha, beta1, beta2, beta3, and full bands were positively correlated with the MMSE and CDR scores.

Our results are similar to those of Koenig et al. (2005), who found that beta band synchronization was lower in AD patients than in patients with mild cognitive impairment. Stam et al. (2003) found (using a different method—synchronization likelihood) a significant reduction in EEG synchronization of the beta band in AD patients, which was correlated with the severity of cognitive dysfunction as indicated by the MMSE score. However, they found no significant changes in the alpha, theta, delta, and gamma bands. These findings suggest that decreased beta band synchronization reflects the specific pathology in AD. Koenig et al. (2005) found that the effects were most pronounced in the alpha band, whereas we found these mainly in the beta band. Moreover, we found no significant differences in the alpha band between AD and healthy subjects.

The beta band may have a special significance in AD, especially in the early stages of the disease (Stam et al., 2003). The importance of high-frequency synchronization for cognitive process has recently been emphasized by several studies (Rodriguez et al., 1999; Tallon-Baudry and Bertrand, 1999; Csibra et al., 2000; Müller et al., 2000; Başar et al., 2001).

In our study, the correlation between the GFS value and MMSE scores was highest in the beta3 band ($r = 0.52$, $P = 0.0002$), which contains the highest frequencies among beta bands. The beta band has classically been related to excitatory activity and cognitive processes that deteriorate during AD (Koenig et al., 2005). Furthermore, beta spectral power has also been shown to decrease in AD and the decrease of beta spectral power was most prominent in central and parietal regions for AD subjects (Holschneider and Leuchter, 1995).

Whilst GFS values in the alpha band were positively correlated with the MMSE and CDR scores, there was no significant difference in the alpha band between the two groups in the present study. Several studies that used coherence as a measure of interdependencies between EEG or MEG data found a significant loss of alpha band coherence in AD (Haxby et al., 1986; Hof and Bouras, 1991; Holschneider and Leuchter, 1995; Jelic et al., 1996, 1998). As mentioned above, the GFS value decreased monotonically as cognitive impairments in the AD patients increased (Koenig et al., 2005). There are several possible reasons why we found no differences in the alpha band. First, our sample was relatively small, which could have reduced the statistical power. Second, the illness duration (32.3 ± 20.6 months) was relatively short, which means that our AD subjects were in the early stages of the disease. Third, most of our AD subjects were only mildly affected (CDR score of 1), with only seven AD patients exhibiting moderate AD (CDR score of 2). Fourth, although it is a slightly different method, the synchronization likelihood is more sensitive to differences in high-frequency synchronization, whereas coherence is more sensitive to alpha band differences (Stam et al., 2003).

The theta band synchronization did not differ between the two groups. Furthermore, in this band there was a non-significant trend towards lower GFS values in AD patients. However, in the delta band there was a positive correlation between GFS values and CDR scores within AD, even though GFS values did not differ significantly between AD patients and healthy controls. This means that the delta band GFS increased almost continuously with increasing cognitive impairments. These findings are consistent with those of Koenig et al. (2005). Furthermore, Jelic et al. (1998) reported that the response to long-term acetylcholinesterase-inhibitor therapy in AD patients included reductions in delta and theta activity. However, there are still conflicting findings concerning coherence in the delta and theta bands, with some studies finding a decreased coherence (Leuchter et al., 1992; Dunkin et al., 1994) and others finding an increased coherence (Locatelli et al., 1998).

GFS values in the gamma band did not differ significantly between AD patients and healthy controls, and were not positively correlated with the MMSE or CDR score. However, one study found decreased GFS values in the gamma band in AD patients (Koenig et al., 2005). They found that the inter-individual variance in GFS values was much larger in the gamma band than in the other frequency bands, with there being no obvious differences in gamma band GFS among the compared groups. Therefore, its relevance for EEG synchronization in AD remains unclear.

The study was subject to several limitations. The first is that the EEG data were obtained only in the resting condition. Obtaining a more precise understanding of functional brain activity and its association with synchronization requires EEG data obtained during resting and task-performing states to be compared. The degree of change in EEG data between resting and task-performing state seem to be different in AD patients compared with normal controls. We expect to find less prominent changes in the AD patients than those seen in normal controls since the available cognitive capacity is presumably decreased in AD. Hidasi et al. (2007) reported that EEG data following the completion of a cognitive task clearly

differentiated patients with AD from normal controls. The electrophysiological changes found in AD may correspond to the decrease of functional connectivity of cortical areas and to the malfunctioning of the networks engaged in the cognitive task investigated. Second, the abilities of MMSE and CDR scores to evaluate the severity of AD are rather limited. The use of a variety of dementia rating and cognitive function scales would provide more informative functional correlations with synchronization. Third, we did not control for the possible confounding effects of psychotropic drugs. Although most of our AD patients had been treated with cholinesterase inhibitors on EEG recording, most of EEG data were collected as soon as medication started. There were several findings of EEG-based monitoring of the drug therapy in AD patients (Leuchter et al., 1991; Balkan et al., 2003; Alhainen et al., 1991; Alhainen and Riekkinen, 1993). These monitoring accuracies can be significant. Knott et al. (2000, 2001) reported qEEG could distinguish between AD patients with cholinesterase inhibitor and those not treated. However, Reeves et al. (2002) found no significant EEG changes for AD patients treated with donepezil. Therefore, this relationship remains controversial. Future studies of AD patients with and without pharmacological treatment are required to elucidate the extent to which this impacts on EEG synchronization in AD brains. Notwithstanding these limitations, one of the strengths of our study is using GFS to replicate the findings of Koenig et al. (2005), such as the decreased synchronization of beta bands and correlation with cognitive impairment.

Our results indicate that GFS can be used to evaluate AD. We intend applying GFS to AD patients both at rest and when they are performing cognitive tasks in order to assess whether EEG synchronization could be used for the early detection of AD patients with certain risk factors. We expect that novel methods for EEG analysis will help improve the accuracy of early detection of AD (Musha et al., 2002; Stam et al., 2003; Koenig et al., 2005). In future, the electrophysiological measure such as GFS as well as neuroimaging and genetics will become routine screening methods for early detection of MCI patients.

Acknowledgement

This work was supported by a grant from the Korea Science and Engineering Foundation (KOSEF) funded by the Korean government (MOST) (No. M10644000005-06N4400-00510).

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