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Global synchronization index as a biological correlate of cognitive decline in Alzheimer's disease

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ABSTRACT

Objective: The recently developed global synchronization index (GSI) quantifies synchronization between neuronal signals at multiple sites. This study explored the clinical significance of the GSI in Alzheimer's disease (AD) patients.
Methods: Electroencephalograms were recorded from 25 AD patients and 22 age-matched healthy normal controls (NC). GSI values were computed both across the entire frequency band and separately in the delta, theta, alpha, beta1, beta2, beta3, and gamma bands. The Mini-Mental Status Examination (MMSE) and Clinical Dementia Rating scale (CDR) were used to assess the symptom severity.
Results: GSI values in the beta1, beta2, beta3, and gamma bands were significantly lower in AD patients than in NC. GSI values in the beta and gamma bands were positively correlated with the MMSE scores in all participants (AD and NC). In AD patients, GSI values were negatively correlated with MMSE scores in the delta bands, but positively correlated in the beta1 and gamma band. Also, GSI values were positively correlated with CDR scores in the delta bands, but negatively correlated in the gamma band.
Conclusions: GSI values of mainly high-frequency bands were significantly lower in AD patients than in NC, they were significantly correlated with scores on symptom severity scales.
Significance: Our results suggest that GSI values are a useful biological correlate of cognitive decline in AD patients.

1. Introduction

Dementia is one of the most common disorders among the elderly population. The clinical symptoms of Alzheimer's disease (AD) are progressive amnesia followed by a gradual but persistent decline in all cognitive domains, eventually resulting in global dementia (Sunderland et al., 2006). During the course of the disease, the degenerative process spreads in a characteristic manner starting in the entorhinal cortex and processing through the hippocampus and the limbic areas toward the neocortical association areas (Braak and Braak, 1991).

AD is also characterized by widespread loss of anatomical and functional connections between brain regions caused by the degeneration of the large cortical pyramidal neurons (Hardy et al., 1986). A "disconnection syndrome" is hypothesized as a model for AD symptomatology (Delbeuck et al., 2003). Since coherent firing of a sufficiently large number of neurons produces a detectable voltage field on the scalp, it is plausible that electroencephalogram (EEG) data can be used to study changes in synchronization of neural circuits in AD that possibly occur at an early stage of the disease (Koenig et al., 2005). A few recent studies have suggested that pharmacological treatment of mild cognitive impairment (MCI) or early AD can slow the progression of the disease (Feldman and Jacova, 2005), indicating the importance of early diagnosis and symptom quantification.

Many studies have found EEG abnormalities in AD patients, the hallmark of which is a slowing of the rhythms and alterations in each frequency band. Increases in activities in the theta and delta frequency bands and decreases in those in the alpha and beta bands are commonly observed (Coben et al., 1985; Brenner et al., 1986; Giaquinto and Nolfe, 1986; Pijnenburg et al., 2004; Jung et al., 2007). 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 over the past 3 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).

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

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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 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. A conceptually similar method called Omega complexity was published with a first summary of results and the method earlier (Wackermann, 1999). Omega complexity produces a single value for the complexity of multichannel brain electric field data. Yoshimura et al. (2004) found that the values of Omega complexity were significantly higher in patients with mild AD than in age-matched healthy normal controls (NC). From previous studies showing decreased synchronization and increased Omega complexity in AD patients, we assume that the interneuronal synchronization and loosening (complexity) are inversely related.

The early application of GFS in AD showed that GFS values were reduced in the alpha, beta, and gamma bands, 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 NC 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. There was an almost continuous decrease of GFS with increasing cognitive impairments 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). Park et al. (2008) also found that GFS values in the entire frequency band and in the low beta (13–18 Hz), middle beta (19–21 Hz), and high beta (22–30 Hz) bands were lower in AD patients than in NC, and that GFS values in the entire frequency band and in the alpha, low beta, middle beta, and high beta bands were positively correlated with the scores in the Mini-Mental Status Examination (MMSE) and negatively correlated with Clinical Dementia Rating scale (CDR) scores in the combined group (AD patients and NC). In AD patients, GFS values were positively correlated with MMSE scores in the entire frequency band and in the low beta and high beta bands, and with CDR scores in the delta band.

A new synchronization index for analyzing multiple time series was recently proposed by Li et al. (2007). The new method, which we refer to here as the global synchronization index (GSI), can quantify the global synchronization from multiple oscillators and the neuronal population as measured by multiple electrodes. The new measure is derived from the largest eigenvalue of a correlation matrix produced by an equal-time correlation method. Equal-time correlation matrix is a method to measure synchronization when the delay between two signals is very small. All elements of the equal-time correlation matrix varies from −1 to 1, meaning prefect anti-correlation to perfect correlation between two time series. Lie et al. verified their method by applying it to an in vitro model of epileptic seizures and demonstrated that their method can successfully estimate global synchronization between multiple time series. Unlike the conventional methods to measure synchronization between two time series such as cross-correlation, mutual information, coherence, and phase synchronization, the new method can estimate global synchronization of multiple time series. Moreover, Li et al. (2007) insisted that the new method has the advantage over the other global synchronization measures in that their method gives information about the strength of the synchronized cluster and has no need to determine a threshold. But it is hard to evaluate the superiority between two synchronization methods, because these two methods have their own strength to calculate the EEG synchrony.

Our earlier report showed that GFS is a useful method to evaluate the symptom severity of AD patients (Park et al., 2008). As a second attempt, the present study compared GSI values between AD patients and NC, and investigated the correlation between the GSI values in each frequency band and the symptom severity of AD. Furthermore, we evaluated whether GSI values are a useful indicator of cognitive decline in AD patients. The use of multiple synchronization indexes to evaluate the EEG of AD patients has produced slightly different findings, with there still being no definitive consensus about EEG synchronization in AD patients. The GSI is a newly developed synchronization index that could be useful for exploring AD pathology. In this study we compared GSI values of AD patients and NC, and explored the clinical significance of this index in patients with AD.

2. Materials and methods

2.1. Subjects

The AD-patient group consisted of 25 subjects (20 females and 5 males) who fulfilled the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (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 ± 7.2 (mean ± SD) years, had received 5.1 ± 4.6 years of education, and had been ill for 32.2 ± 20.6 months (Table 1). The symptom severity as quantified by the overall MMSE and CDR scores was 17.9 ± 3.8 and 1.3 ± 0.5, respectively (the MMSE score ranges from 0 to 30, with a higher score indicating higher cognitive function, and the CDR score ranges from 0 to 5, with a higher score indicating lower cognitive and behavioral function). All AD patients were taking anti-dementic medications [donepezil (range 5–10 mg) $N = 21$; galantamine (range 8–24 mg) $N = 4$].

The NC group consisted of 22 volunteers (9 females and 13 males) with no personal history of psychiatric or neurological abnormalities. They were recruited from social communities around the hospital through poster and local newspaper. There was no EEG screening of recruited normal control subjects to restrict the variety of EEG types among the subjects. Their EEG data had no particular finding under visual inspection even though there was no EEG screening of recruited normal control subjects. They were aged 72.8 ± 4.5 years, had received 5.8 ± 4.7 years of education, and had an MMSE score of 26.1 ± 1.4 and a CDR score of 0. The education level varies greatly in Korean elderly subjects, and the MMSE score can be significantly influenced by the education level and age even in healthy subjects (Lee et al., 2004). It has been shown that the education level is a critical factor to consider when studying AD patients in Korea (Han et al., 2008). We therefore matched the duration of education as well as the age when comparing between the two groups. Because the sex distribution differed between the two groups, and sex is an important variable that can influence the education duration and acquired intelligence in Korean elderly (Lee et al., 2004; Han et al., 2008). So we used Mann–Whitney *U*-test for comparing clinical characteristic between both genders in each AD and NC groups. But we did not find any significant differences between both genders (Table 1). So we could assume that the gender was no longer significant controlling variable in this cohort. All of the participants in this study signed written informed-consent forms approved by the Institutional Review Board of Inje University Ilsan Paik Hospital prior to their participation.

Table 1
Clinical characteristics of patients with Alzheimer's disease (AD) and normal controls (NC).

	AD ($N=25$)	NC ($N=22$)	P
Age (years)	73.8 ± 7.2	72.8 ± 4.5	0.57
Females:males	20:5	9:13	<0.01
Education duration (years)	5.1 ± 4.6	5.8 ± 4.7	0.66
MMSE score	18.2 ± 3.7	26.1 ± 1.4	<0.01
CDR score	1.2 ± 0.5	0.0 ± 0.0	<0.01
Duration of illness (months)	32.2 ± 20.6		

	Female[a] ($N=20$)	Male[a] ($N=5$)	Female[b] ($N=9$)	Male[b] ($N=13$)
Age (years)	73.4 ± 7.7	75.4 ± 5.1	73.0 ± 4.5	72.6 ± 4.6
Education duration (years)	4.7 ± 4.7	8.0 ± 3.4	5.5 ± 4.3	6.0 ± 5.1
MMSE score	18.0 ± 3.4	19.0 ± 5.0	25.3 ± 1.2	26.5 ± 1.3
CDR score	1.2 ± 0.4	1.2 ± 0.7		
Duration of illness (months)	29.7 ± 20.8	48.0 ± 12.0		

MMSE: Mini-Mental Status Examination, CDR: Clinical Dementia Rating scale.
a and b: Mann–Whitney *U*-test did not show any significant difference between both genders.

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 eye was either closed or open and was maintained alternately for 1 min, each repeated 5 times. 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 removed 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. Three artifact-free 30-s epochs recorded in a resting condition with eyes closed were used for each subject.

2.3. Global synchronization index

The newly developed GSI quantifies the global synchronization of multiple time series recorded simultaneously from multiple sites. To calculate the GSI value, a matrix containing information of synchronization between all possible pairs of time series has to be evaluated. In this study, we used an equal-time correlation method to calculate a correlation matrix **C** whose values ranged from −1 to 1. The calculated equal-time correlation matrix **C**, is then decomposed by eigenvalue decomposition and the resultant eigenvalues are used to evaluate the GSI values. The normalized GSI was computed using the following equation:

$$\mathrm{GSI}_k = \begin{cases} (\lambda_k - \bar{\nu}_k)/(M - \bar{\nu}_k) & \text{if } \lambda_k > \bar{\nu}_k + K \times SD_k \\ 0 & \text{otherwise} \end{cases}$$

where $k = 1, \ldots, M$, M represents the number of time series, and λ and ν represent the eigenvalues obtained from matrix **C** and a surrogate correlation matrix **R**, respectively. The over-bar of ν_k and SD_k denote the mean and standard deviation values of the surrogate correlation matrix, and K is a constant that determines the threshold and 2 was used for an overall significance of 0.05. The surrogate data were generated using the amplitude-adjusted Fourier transform (Schreiber and Schmitz, 1996). The number of eigenvalues is equal to the number of channels (18 scalp locations in this study) and they are listed in order from λ_1 (smallest) to λ_{18} (largest). Here we focus on the largest GSI_{18}, and refer to it as the GSI value.

We calculated the GSI values in 45 epochs of 2-s EEGs for the following frequency bands in 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; and gamma, 31–50 Hz. The datasets of GSI values were revealed to obey normal distribution.

2.4. Statistical analyses

The Bonferroni-corrected independent *t*-test for multiple comparisons was used to compare GSI values between AD and NC. For controlling different sex distribution between two groups, we used Mann–Whitney *U*-test for comparing clinical characteristic between both genders in each AD and NC groups. And we used Spearman's correlation to explore the correlation between AD symptom severity and GSI values. 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 and NC (Table 1). However, the MMSE score was significantly lower in AD patients (18.2 ± 3.7, range: 11–26) than in NC (26.1 ± 1.4, range: 25–30).

The GSI values in each frequency band are presented in Fig. 1. They differed significantly between the AD and NC groups in the

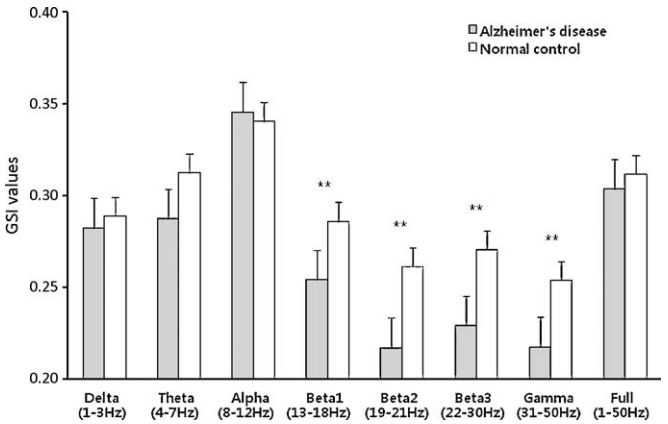

Fig. 1. Comparison of global synchronization index (GSI) values in patients with Alzheimer's disease ($N = 25$) and normal controls ($N = 22$) for each frequency band. Error bars are standard errors. Asterisks (**) indicate significant differences in GSI values between the two groups by the Bonferroni-corrected independent *t*-test for multiple comparisons (corrected $P < 0.01$).

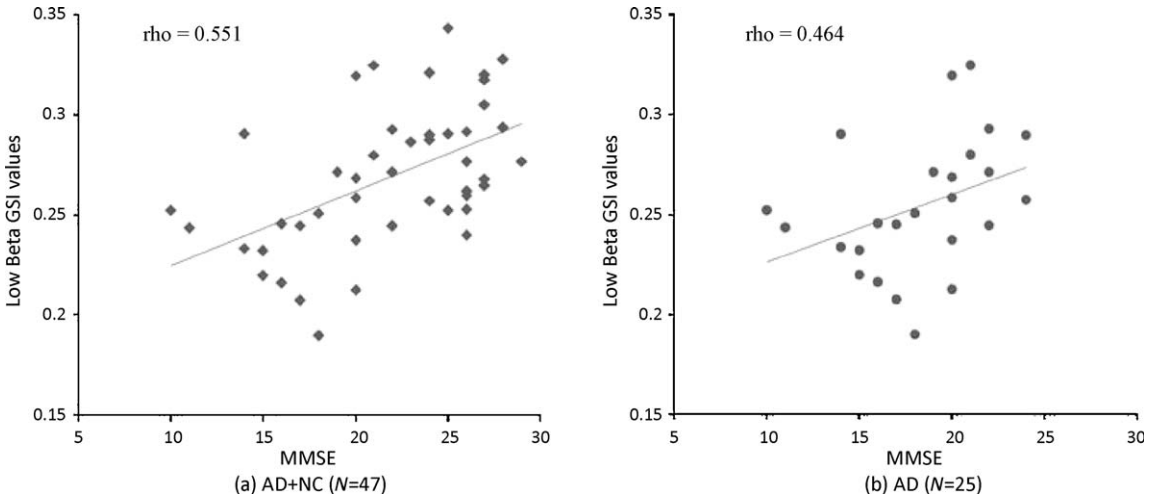

Fig. 2. Scattered distribution of Mini-Mental Status Examination (MMSE) scores and global synchronization index (GSI) values of low beta (13–18 Hz) frequency band in (a) all subjects ($N = 47$, Spearman's $\rho = 0.551$, $P = 0.000$) and (b) AD patient group ($N = 25$, Spearman's $\rho = 0.464$, $P = 0.020$).

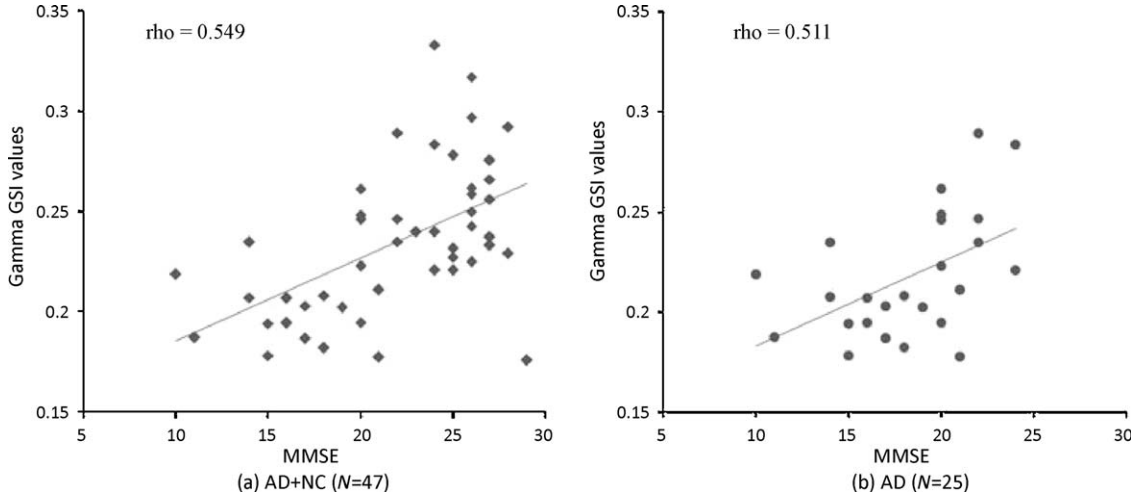

Fig. 3. Scattered distribution of Mini-Mental Status Examination (MMSE) scores and global synchronization index (GSI) values of gamma (31–50 Hz) frequency band in (a) all subjects ($N = 47$, Spearman's $\rho = 0.549$, $P = 0.000$) and (b) AD patient group ($N = 25$, Spearman's $\rho = 0.511$, $P = 0.009$).

beta1 (0.25 ± 0.03 vs. 0.28 ± 0.02, respectively; corrected $P = 0.008$), beta2 (0.21 ± 0.28 vs. 0.26 ± 0.03, corrected $P = 0.000$), beta3 (0.22 ± 0.02 vs. 0.27 ± 0.02, corrected $P = 0.000$), and gamma (0.21 ± 0.03 vs. 0.25 ± 0.03, corrected $P = 0.000$) bands (Fig. 1).

We assessed the association between GSI values and the severity of the disease by estimating the Spearman's correlation (ρ) between GSI values and symptom severity (scores on the MMSE and CDR scales) for the entire cohort as well as for only the AD group. The MMSE scores of all participants (AD and NC, $N = 47$) were positively correlated with GSI values in the beta1 ($\rho = 0.551$, $P = 0.000$, Fig. 2), beta2 ($\rho = 0.539$, $P = 0.000$), beta3 ($\rho = 0.648$, $P = 0.000$), and gamma ($\rho = 0.549$, $P = 0.000$, Fig. 3) bands (Table 2). The CDR scores of all participants were negatively correlated with GSI values in the beta1 ($\rho = -0.497$, $P = 0.000$), beta2 ($\rho = -0.625$, $P = 0.000$), beta3 ($\rho = -0.700$, $P = 0.000$), and gamma ($\rho = -0.609$, $P = 0.000$) bands (Table 2).

For AD patients only ($N = 25$), the GSI values were negatively correlated with MMSE scores in the delta ($\rho = -0.421$, $P = 0.036$) band but positively correlated in the beta1 ($\rho = 0.464$, $P = 0.020$, Fig. 2) and gamma ($\rho = 0.511$, $P = 0.009$, Fig. 3) band (Table 3). The GSI values were positively correlated with CDR scores in the delta

Table 2
Spearman's correlation between the global synchronization index (GSI) and scores on symptom severity scales (MMSE and CDR) in all subjects (AD patients and NC, $N = 47$).

	GSI-MMSE (ρ)	P	GSI-CDR (ρ)	P
Delta (1–3 Hz)	−0.127	0.397	0.099	0.509
Theta (4–7 Hz)	0.197	0.184	−0.294	0.045
Alpha (8–12 Hz)	0.185	0.214	−0.144	0.333
Beta1 (13–18 Hz)	0.551	0.000	−0.497	0.000
Beta2 (19–21 Hz)	0.539	0.000	−0.625	0.000
Beta3 (22–30 Hz)	0.648	0.000	−0.700	0.000
Gamma (31–50 Hz)	0.549	0.000	−0.609	0.000
Full (1–50 Hz)	0.149	0.319	−0.162	0.276

Table 3
Spearman's correlation between the GSI and symptom severity scores in AD patients ($N = 25$).

	GSI-MMSE (ρ)	P	GSI-CDR (ρ)	P
Delta (1–3 Hz)	−0.421	0.036	0.591	0.002
Theta (4–7 Hz)	−0.380	0.061	0.338	0.098
Alpha (8–12 Hz)	0.314	0.127	−0.201	0.335
Beta1 (13–18 Hz)	0.464	0.020	−0.211	0.312
Beta2 (19–21 Hz)	0.344	0.093	−0.361	0.077
Beta3 (22–30 Hz)	0.343	0.093	−0.338	0.098
Gamma (31–50 Hz)	0.511	0.009	−0.565	0.003
Full (1–50 Hz)	0.085	0.687	−0.023	0.913

band ($\rho = 0.591$, $P = 0.002$) but negatively correlated in the gamma ($\rho = -0.565$, $P = 0.003$) bands (Table 3).

4. Discussion

Several methods have been successfully used to analyze the synchronization between multiple neural signals, including cluster analysis (Stuart et al., 2005), graph theoretic analysis (Stam et al., 2007), multichannel phase synchronization (Rudrauf et al., 2006), and mixture-of-Gaussians analysis (Matsumoto et al., 2005). However, each of these methods has limitations and gives only partial information about synchronization. The GSI proposed by Li et al. (2007) is a novel method that can quantify global synchronization of multiple time series recorded simultaneously from multiple sites by bringing together all the relevant information.

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

The first major finding of our study is the decreased GSI value in the beta bands. This is similar to those of our previous study (Park et al., 2008) obtained using the GFS method, showing that GFS values in AD patients were significantly decreased in the beta bands (beta1, beta2, and beta3 bands). Our results are also similar to those of Koenig et al. (2005), who found that alpha- and beta-band synchronization were lower in AD patients than in NC. 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. They also suggested that the beta band has a special significance in AD, especially in the early stages of the disease (Stam et al., 2003). 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 been shown to be decreased in AD patients, most prominently in central and parietal regions (Holschneider and Leuchter, 1995). In our study, there were significant correlations between the GSI value and symptom severity (scores on the MMSE and CDR scales) in the beta1, beta2, beta3, and gamma bands (Fig. 2, Tables 2 and 3). These findings suggest that decreased beta band synchronization reflects the specific pathology in AD.

Furthermore, in our study, GSI values in the gamma band differed significantly between AD patients and NC, and were also well correlated with the MMSE and CDR scores (Fig. 3, Tables 2 and 3). 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); the importance of gamma oscillations had previously been underestimated (compared to slower oscillations) due to their small amplitudes. However, it has been suggested that gamma-band EEG oscillations are associated with binding of multiple features of an object, and cognitive processes such as attention and memory, language, and motor functions (Singer and Gray, 1995; Lee et al., 2003). Furthermore, significant changes in gamma-band EEG activity were found in neuropsychiatric disorders including schizophrenia, attention-deficit hyperactivity disorder, and AD (Herrmann and Demiralp, 2005). Therefore, alteration of gamma-band neural oscillations during the course of brain disorders, particularly AD and MCI, is a critical issue in clinical neuroscience.

Koenig et al. (2005) found that the GFS value in the gamma band was decreased in AD. They also 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. Our data did not show any larger inter-individual variance in gamma-band GSI values compared to other frequency bands. We observed the reduced gamma-band synchronization and its correlation with symptom severity in AD patients. Furthermore, in the AD group, we observed more significant correlations in the gamma band rather than in the beta bands. Carefully, from our result at least, we can suggest the importance of gamma-band abnormality in AD pathology. Further researches are needed in this area.

Koenig et al. (2005) also found that AD patients showed increased synchronization in the delta band, whereas we found that GSI values in the delta and theta bands were not lower in AD patients than in NC. However, in the AD group, we observed a significant correlation between GSI values in the delta and theta bands and symptom severity (scores on the MMSE and CDR scales). We also need to consider a previous report of reductions in activities in the delta and theta bands induced by long-term acetylcholinesterase-inhibitor therapy in AD patients (Jelic et al., 1998). However, there have been conflicting findings concerning coherence in the delta and theta bands, with some studies finding a decreased coherence (Leuchter et al., 1992; Dunkin et al., 1993) and others finding an increased coherence (Locatelli et al., 1998). There is a general consensus that EEG power changes in AD begin in the theta band (increased) and then in the beta band (decreased), followed by the alpha band (decreased) (Huang et al., 2000), with increased delta activity appearing later in the course of AD (Huang et al., 2000). The change in spectral power is not directly applicable to the change in synchronization. However, the previous results suggest that the stage of AD progression and medication effects could be important controlling factors in EEG synchronization studies. From previous studies showing decreased synchronization (Koenig et al., 2005; Park et al., 2008) and increased Omega complexity (Yoshimura et al., 2004) in AD patients, we can assume that the interneuronal synchronization and loosening (complexity) are inversely related. For the anti-dementic drug effects, Wackermann et al. (1993) and Kondakor et al. (1999) reported a decrease in Omega complexity value after oral intake of a single dose of a nootropic drug, piracetam. It was interpreted as indicating that anti-dementic drug, piracetam, increased cooperativities and harmonization in brain function. If these nootropic effects are true, we can also assume that the powerful anti-dementic drugs (donepezil or galantamine) might increase EEG synchronization (increased harmonization) rather than decrease synchronization. Furthermore, we evaluated the GSI value of 6 AD patients (3 male and 3 female, mean age = 72.3 ± 6.5 years, duration of illness = 30.2 ± 15.5 months), before and after taking donepezil (mean dosage = 12.5 ± 5.5 mg). Time duration between the measurements was 6.2 ± 4.5 months. However we did not find any significant change on these values (delta, 0.216 ± 0.057 vs. 0.213 ± 0.042, $P = 0.600$; theta, 0.293 ± 0.059 vs. 0.309 ± 0.068, $P = 0.345$; alpha, 0.410 ± 0.086 vs. 0.369 ± 0.087, $P = 0.116$; beta1, 0.268 ± 0.021 vs. 0.232 ± 0.055, $P = 0.917$; beta2, 0.232 ± 0.034 vs. 0.227 ± 0.046, $P = 0.600$; beta3, 0.227 ± 0.041 vs. 0.230 ± 0.041, $P = 0.917$; gamma, 0.224 ± 0.057 vs. 0.230 ± 0.041, $P = 0.173$; full, 0.322 ± 0.051 vs. 0.314 ± 0.078, $P = 0.753$).

In conclusions, our results indicating decreased GSI value (decreased harmonization) in AD patients can be thought to reflect original neuropathological processing of AD rather than anti-dementic drug effect. In future study, the GSI changes of anti-dementic drugs with different mechanism of actions and their dosages effects would be an interesting research subjects. Also the time point of significant change of EEG dynamic should be

explored carefully because the cognitive symptoms of AD patients dose not response to anti-dementic drug so quickly.

It is hard to say that the GSI is a more sensitive method than GFS from results of this study. However it can be suggested that the GSI is another useful synchronization measurements for evaluating pathophysiology of AD patients. Further study would be needed to compare the usefulness among GSI, GFS, and other synchronization measurement with large sample size.

Our study was subject to several limitations. First, as mentioned above, we did not control for the possible confounding effects of anti-dementic drugs. Future studies of AD patients with and without pharmacological treatment are required to elucidate the extent to which such treatment impacts on EEG synchronization in AD brains. Second, our sample was relatively small, making additional studies with larger samples necessary to generalize our conclusions. Notwithstanding these limitations, one of the strengths of our study is that it is the first to apply the GSI method to AD.

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

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References

Braak, H., Braak, E., 1991. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol. 82, 239–259.

Brenner, R.P., Ulrich, R.F., Spiker, D.G., Sclabassi, R.J., Reynolds 3rd, C.F., Marin, R.S., Boller, F., 1986. Computerized EEG spectral analysis in elderly normal, demented and depressed subjects. Electroencephalogr. Clin. Neurophysiol. 64, 483–492.

Csibra, G., Davis, G., Spratling, M.W., Johnson, M.H., 2000. Gamma oscillations and object processing in the infant brain. Science 290, 1582–1585.

Coben, L.A., Danziger, W.L., Storandt, M., 1985. A longitudinal EEG study of mild senile dementia of Alzheimer type: changes at 1 year and at 2.5 years. Electroencephalogr. Clin. Neurophysiol. 61, 101–112.

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

Dunkin, J.J., Leuchter, A.F., Newton, T.F., Cook, I.A., 1993. Reduced EEG coherence in dementia: state or trait marker? Biol. Psychiatry 35, 870–879.

Feldman, H.H., Jacova, C., 2005. Mild cognitive impairment. Am. J. Geriatr. Psychiatry 13, 645–655.

Giaquinto, S., Nolfe, G., 1986. The EEG in the normal elderly: a contribution to the interpretation of aging and dementia. Electroencephalogr. Clin. Neurophysiol. 63, 540–546.

Han, C., Jo, S.A., Jo, I., Kim, E., Park, M.H., Kang, Y., 2008. An adaptation of the Korean mini-mental state examination (K-MMSE) in elderly Koreans: demographic influence and population-based norms (the AGE study). Arch. Gerontol. Geriatr. 47, 302–310.

Hardy, J.A., Mann, D.M., Wester, P., Winblad, B., 1986. An integrative hypothesis concerning the pathogenesis and progression of Alzheimer's disease. Neurobiol. Aging 7, 489–502.

Herrmann, C.S., Demiralp, T., 2005. Human EEG gamma oscillations in neuropsychiatric disorders. Clin. Neurophysiol. 116, 2719–2733.

Holschneider, D.P., Leuchter, A.F., 1995. Beta activity in aging and dementia. Brain Topogr. 8, 169–180.

Huang, C., Wahlund, L., Dierks, T., Julin, P., Winblad, B., Jelic, V., 2000. Discrimination of Alzheimer's disease and mild cognitive impairment by equivalent EEG sources: a cross-sectional and longitudinal study. Clin. Neurophysiol. 111, 1961–1967.

Hughes, J.R., Shanmugham, S., Wetzel, L.C., Bellur, S., Hughes, C.A., 1989. The relationship between EEG changes and cognitive functions in dementia: a study in a VA population. Clin. Electroencephalogr. 20, 77–85.

Jelic, V., Dierks, T., Amberla, K., Almkvist, O., Winblad, B., Nordberg, A., 1998. Longitudinal changes in quantitative EEG during long-term tacrine treatment of patients with Alzheimer's disease. Neurosci. Lett. 254, 85–88.

Jeong, J., 2004. EEG dynamics in patients with Alzheimer's disease. Clin. Neurophysiol. 115, 1490–1505.

Jonkman, E.J., 1997. The role of the electroencephalogram in the diagnosis of dementia of the Alzheimer type: an attempt at technology assessment. Neurophysiol. Clin. 27, 211–219.

Jung, H.T., Lee, S.H., Kim, J.N., Lee, K.J., Chung, Y.C., 2007. Quantitative electroencephalography and low resolution electromagnetic tomography imaging of Alzheimer's disease. Psychiatry Invest. 4, 31–37.

Koenig, T., Lehmann, D., Saito, N., Kuginuki, T., Kinoshita, T., Koukkou, M., 2001. Decreased functional connectivity of EEG theta-frequency activity in first-episode, neuroleptic-naïve patients with schizophrenia: preliminary results. Schizophr. Res. 50, 55–60.

Koenig, T., Prichep, L., Dierks, T., Hubl, D., Wahlund, L.O., John, E.R., Jelic, V., 2005. Decreased EEG synchronization in Alzheimer's disease and mild cognitive impairment. Neurobiol. Aging 26, 165–171.

Kondakor, I., Michel, C.M., Wackermann, J., Koenig, T., Tanaka, H., Peuvot, J., Lehmann, D., 1999. Single-dose piracetam effects on global complexity measures of human spontaneous multichannel EEG. Int. J. Psychophysiol. 34, 81–87.

Kowalski, J.W., Gawel, M., Pfeffer, A., Barcikowska, M., 2001. The diagnostic value of EEG in Alzheimer disease: correlation with the severity of mental impairment. J. Clin. Neurophysiol. 18, 570–575.

Lee, D.Y., Lee, K.U., Lee, J.H., Kim, K.W., Jhoo, J.H., Kim, S.Y., Yoon, J.C., Woo, S.I., Ha, J., Woo, J.I., 2004. A normative study of the CERAD neuropsychological assessment battery in the Korean elderly. J. Int. Neuropsychol. Soc. 10, 72–81.

Lee, K.H., Williams, L.M., Breakspear, M., Gordon, E., 2003. Synchronous gamma activity: a review and contribution to an integrative neuroscience model of schizophrenia. Brain Res. Brain Res. Rev. 41, 57–78.

Leuchter, A.F., Newton, T.F., Cook, I.A., Walter, D.O., Rosenberg-Thompson, S., Lachenbruch, P.A., 1992. Changes in brain functional connectivity in Alzheimer-type and multi-infarct dementia. Brain 115, 1543–1561.

Li, X., Cui, D., Jiruska, P., Fox, J.E., Yao, X., Jefferys, J.G., 2007. Synchronization measurement of multiple neuronal populations. J. Neurophysiol. 98, 3328–3341.

Locatelli, T., Cursi, M., Liberati, D., Franceschi, M., Comi, G., 1998. EEG coherence in Alzheimer's disease. Electroencephalogr. Clin. Neurophysiol. 106, 229–237.

Matsumoto, N., Okada, M., Sugase-Miyamoto, Y., Yamane, S., Kawano, K., 2005. Population dynamics of face-responsive neurons in the inferior temporal cortex. Cereb. Cortex 15, 1103–1112.

Müller, M.M., Gruber, T., Keil, A., 2000. Modulation of induced gamma band activity in the human EEG by attention and visual information processing. Int. J. Psychophysiol. 38, 283–299.

Musha, T., Asada, T., Yamashita, F., Kinoshita, T., Chen, Z., Matsuda, H., Uno, M., Shankle, W.R., 2002. A new EEG method for estimating cortical neuronal impairment that is sensitive to early stage Alzheimer's disease. Clin. Neurophysiol. 113, 1052–1058.

Park, Y.M., Che, H.J., Im, C.H., Jung, H.T., Bae, S.M., Lee, S.H., 2008. Decreased EEG synchronization and its correlation with symptom severity in Alzheimer's disease. Neurosci. Res. 62, 112–117.

Pijnenburg, Y.A., van der Made, Y., van Cappellen van Walsum, A.M., Knol, D.L., Scheltens, P., Stam, C.J., 2004. EEG synchronization likelihood in mild cognitive impairment and Alzheimer's disease during a working memory task. Clin. Neurophysiol. 115, 1332–1339.

Rodriguez, E., George, N., Lachaux, J.P., Martinerie, J., Renault, B., Varela, F.J., 1999. Perception's shadow: long-distance synchronization of human brain activity. Nature 397, 430–433.

Rudrauf, D., Douiri, A., Kovach, C., Lachaux, J.P., Cosmelli, D., Chavez, M., Adam, C., Renault, B., Martinerie, J., Le Van Quyen, M., 2006. Frequency flows and the time-frequency dynamics of multivariate phase synchronization in brain signals. Neuroimage 31, 209–227.

Schreiber, T., Schmitz, A., 1996. Improved surrogate data for nonlinearity tests. Phys. Rev. Lett. 77, 635–638.

Singer, W., Gray, C.M., 1995. Visual feature integration and the temporal correlation hypothesis. Annu. Rev. Neurosci. 18, 555–586.

Stam, C.J., van der Made, Y., Pijnenburg, Y.A., Scheltens, P., 2003. EEG synchronization in mild cognitive impairment and Alzheimer's disease. Acta Neurol. Scand. 108, 90–96.

Stam, C.J., Jones, B.F., Nolte, G., Breakspear, M., Scheltens, P., 2007. Small-world networks and functional connectivity in Alzheimer's disease. Cereb. Cortex 17, 92–99.

Stuart, L., Walter, M., Borisyuk, R., 2005. The correlation grid: analysis of synchronous spiking in multi-dimensional spike train data and identification of feasible connection architectures. Biosystems 79, 223–233.

Sunderland, T., Hampel, H., Takeda, M., Putnam, K.T., Cohen, R.M., 2006. Biomarkers in the diagnosis of Alzheimer's disease: are we ready? J. Geriatr. Psychiatry Neurol. 19, 172–179.

Tallon-Baudry, C., Bertrand, O., 1999. Oscillatory gamma activity in humans and its role in object representation. Trends Cogn. Sci. 3, 151–162.

Wackermann, J., Lehmann, D., Dvorak, I., Michel, C.M., 1993. Global dimensional complexity of multi-channel EEG indicates change of human brain functional

state after a single dose of a nootropic drug. Electroencephalogr. Clin. Neurophysiol. 86, 193–198.
Wackermann, J., 1999. Towards a quantitative characterization of functional states of the brain: from the non-linear methodology to the global linear description. Int. J. Psychophysiol. 34, 65–80.
Yoshimura, M., Isotani, T., Yagyu, T., Irisawa, S., Yoshida, T., Sugiyama, M., Minami, T., Sugimoto, T., Nobuhara, K., Okugawa, G., Kinoshita, T., 2004. Global approach to multichannel electroencephalogram analysis for diagnosis and clinical evaluation in mild Alzheimer's disease. Neuropsychobiology 49, 163–166.