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Yuji Wada · Yuko Nanbu · Mitsuru Kikuchi
Yoshifumi Koshino · Takuma Hashimoto
Nariyoshi Yamaguchi

Abnormal functional connectivity in Alzheimer's disease: intrahemispheric EEG coherence during rest and photic stimulation

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Abstract Electroencephalography (EEG) coherence provides a measure of functional correlations between two EEG signals. The present study was conducted to examine intrahemispheric EEG coherence at rest and during photic stimulation (PS; 5, 10 and 15 Hz) in ten unmedicated patients with presenile dementia of the Alzheimer type (AD; mean age at onset 56 years). In the resting EEG, the AD patients had significantly lower coherence than gender- and age-matched control subjects in the alpha-1, alpha-2 and beta-1 frequency bands. The EEG analysis during PS also showed that the patients had significantly lower coherence in the frequency corresponding to PS at 10 and 15 Hz. In this study, the changes in coherence from the resting state to the stimulus condition (i.e. PS-related coherence reactivity) were examined. The patients were found to show significantly smaller coherence reactivity to PS at 5 and 15 Hz. These findings suggest that, in addition to the resting state, AD patients have an impairment of intrahemispheric functional connectivity during PS. They also suggest that AD shows a failure of PS-related functional reorganization.

Key words Alzheimer's disease · Coherence analysis · Photic stimulation · EEG · Functional connectivity

Introduction

Coherence is a frequency-specific quantitative measure for the similarity of two different signals. Applied to electroencephalographic (EEG) registrations, coherence can be interpreted as a quantitative measure of the degree of connectivity between distinct brain regions (French and Beaumont 1984). Previous studies have applied coherence to examine functional changes associated with performance of a perceptual or cognitive task, and coherence measure obtained from spectral EEG analysis is thought to be a useful technique in the assessment of cognitive function (Busk and Galbraith 1975; Shaw et al. 1977; Beaumont et al. 1978; Gasser et al. 1987; Wada et al. 1996). Although there have been numerous EEG studies of dementia of the Alzheimer type (DAT), which show background EEG slowing with a reduction in alpha and beta activity (see reviews by Soininen et al. 1990; Fenton 1994), only a small number of studies have investigated EEG coherence in demented patients (Leuchter et al. 1987, 1992, 1994; Besthorn et al. 1994; Dunkin et al. 1994; Sloan et al. 1994; Jelic et al. 1996).

Photic stimulation (PS) has been the most commonly used method of cerebral activation in routine EEG examinations and is known to be a useful method for eliciting paroxysmal EEG activity (Takahashi 1987). Recent studies have reported abnormal EEG responses to PS in patients with schizophrenia (Wada et al. 1994, 1995). In addition, there is renewed interest in the diagnostic value of quantitative EEG analysis during PS in demented patients (Drake et al. 1989; Politoff et al. 1992). Complex visual disturbances have been described in patients with DAT, including constructional and visuoperceptual disorientation, spatial agnosia and facial identification problems (Mendez et al. 1990, 1992; Rizzo et al. 1992). Previous studies have shown neuropathological changes in the primary or associative visual cortex (Armstrong et al. 1990; Beach et al. 1989; Hof and Morrison 1990) as well as retinal and optic nerve degeneration (Hinton et al. 1986). In addition, electrophysiological studies have shown abnormal findings in visual evoked potentials (VEPs; Coben et al. 1983; Katz et al. 1989; Orwin et al. 1986; Philpot et al. 1990) and electroretinograms (Katz et al. 1989; Trick et al. 1989). It is assumed therefore that coherence analysis of EEGs recorded during PS would provide a useful

Y. Wada (✉) · M. Kikuchi · Y. Koshino
Department of Neuropsychiatry,
Kanazawa University School of Medicine, 13-1 Takara-machi,
Kanazawa, 920-8641, Japan
Tel.: +81-76-265-2301, Fax: +81-76-234-4254

Y. Nanbu · T. Hashimoto
Department of Central Clinical Laboratory,
Kanazawa University Hospital, 13-1 Takara-machi,
Kanazawa, 920-8641, Japan

N. Yamaguchi
Matsubara Hospital, Kanazawa, 920-0935, Japan

means to assess demented patients. To our knowledge, however, no studies have specifically investigated EEG coherence during PS in dementia.

In addition to the resting state, therefore, intrahemispheric coherence of EEGs recorded during PS was also analysed in patients with presenile dementia of the Alzheimer type (AD; onset before the age of 65 years). The results provided evidence that AD patients showed coherence abnormalities in both conditions as well as smaller changes of coherence in association with PS.

Subjects and methods

The patient group consisted of ten patients (three men and seven women) who consulted the psychiatric outpatient clinic of, or who were admitted to, Kanazawa University Hospital. The patients fulfilled the NINCDS-ADRDA Work Group criteria for the diagnosis of probable Alzheimer's disease (McKhann et al. 1984) and DSM-III-R criteria for primary degenerative dementia, presenile onset (age ≤ 65 years; American Psychiatric Association 1987). Their mean age (± SD) was 59 ± 2.4 years (range 55–63 years). Their mean age at onset of illness was 56 ± 3.8 years (range 50–60 years). Other medical conditions known to cause dementia were excluded following neurological, serological and neuroimaging (MRI and/or CT scan) studies. None of the patients were receiving central nervous system (CNS)-active medications including antipsychotic drugs or cerebral vasodilators. Each patient was evaluated by the Functional Assessment Stages (FAST; Reisberg et al. 1986) and a Japanese version of the Mini-Mental State Examination (MMSE; Folstein et al. 1975). According to the FAST, five patients had mild (FAST 4) and five had moderate dementia (FAST 5). The mean MMSE score was 15.6 ± 4.0 (range 10–22).

The control group consisted of ten healthy volunteers (three men and seven women) with no personal or family history of psychiatric or neurological abnormality. Their mean age (± SD) was 59 ± 2.6 years (range 56–63 years). Patients were not significantly different from controls in age or gender. All patients and control subjects had visual acuity of 20/40 or better. They had normal colour vision, pupil reaction and visual fields. All patients and control subjects were right-handed. They agreed to participate in the study with full knowledge of the experimental nature of the research; if the patient was unable to give the consent, it was given by a near relative.

EEG recording and analysis

All subjects were studied while seated in a semi-darkened, electrically shielded, soundproof recording room. Disc electrodes were attached to the scalp with paste, according to the International 10–20 System. The EEG was recorded by trained EEG technologists with an 18-channel electroencephalograph (EEG-4418, Nihon Kohden, Tokyo, Japan). In addition, movements of the eye and of the lid were monitored by bipolar electro-oculographic (EOG) derivations. The EOG activity was recorded through electrodes placed at the upper canthus of the right eye and lower canthus of the left eye. Recording was carried out with electrodes referenced to linked ears with a time constant of 0.3 s and a high filter setting of 60 Hz. The EOG activity was recorded with a 1-s time constant. Impedance of electrode/skin conductance was kept below 5000 ohms.

Five to 10 min of the resting EEG were recorded for each subject. Each subject was observed via a video monitoring system. When the subjects appeared to be drowsy, they were told to open their eyes to remain awake and the EEG recording was repeated. Verbal communication was also used if necessary to maintain an awake state. Selection of EEG segments recorded during eyes-closed wakefulness was done by visual inspection of EEG and EOG recordings. Segments containing eye movements, blinks or muscle activity were excluded from the analysis. The process of eliminating contaminated data was performed blind to the diagnosis. The EEG data were digitized with a Signal Processor 7T18A (NEC San-ei, Tokyo, Japan) at a sampling rate of 256 per epoch. An artefact-free epoch of 2-s duration of the EEG in the eyes-closed resting state was subjected to spectral analysis by a fast Fourier transform (FFT), and a total of 25 artefact-free epochs per subject were processed with a spectral resolution of 0.5 Hz. In this study, intrahemispheric EEG coherence was calculated between the five electrode pairs over the left hemisphere (F3–C3, F3–F7, C3–P3, P3–O1, T5–O1), and the corresponding electrode pairs over the right hemisphere (F4–C4, F4–F8, C4–P4, P4–O2, T6–O2). Data were banded into delta (2.0–3.5 Hz), theta-1 (4.0–5.5 Hz), theta-2 (6.0–7.5 Hz), alpha-1 (8.0–9.0 Hz), alpha-2 (9.5–12.5 Hz), beta-1 (13.0–19.5 Hz) and beta-2 (20.0–28.0 Hz).

Photic stimulation

After a routine EEG examination in the resting state, a PS was given to each subject. The PS used was a white flicker with flash intensity of 5023 cd/m^2, which was delivered by a photostimulator and a stroboscopic lamp placed 25 cm from the subject's eyelids. The stimulus frequencies were 5, 10 and 15 Hz. The stimulus train at each frequency was applied for 30 s with a 10-s time interval. All subjects were instructed to remain awake and keep their eyes closed throughout the testing period. When the subject became drowsy, the stimulation was repeated in the waking condition. Ten artefact-free 2-s epochs were selected for each stimulus frequency in each subject. Since the initial part of the recording was occasionally contaminated by artefact, the 2-s EEG segment after the beginning of PS was excluded from the analyses. The EEG data during PS was analysed using the same procedure described previously for the non-stimulus condition. For the three stimulus conditions of the experiment, intrahemispheric EEG coherence was measured on the frequency corresponding to each stimulus frequency: 5, 10 and 15 Hz.

Statistics

Fisher's Z transformation was used to normalize the distribution of coherence values. Differences between control subjects and AD patients were analysed on each frequency band using a repeated measures analysis of variance (ANOVA) with a grouping factor (patients vs controls) and a within-subject factor (electrode pairs). A Greenhouse-Geisser correction was applied to non-conservative *p*-values. Then, two-tailed Student's *t*-test was performed to compare Z-transformed coherence value between groups. Statistical significance was defined as $p < 0.05$.

Results

EEG coherence in the resting state

The repeated measures ANOVA revealed that significant group differences were restricted to the alpha-1 ($F = 9.807$; $df = 1{,}18$; $p = 0.0058$), alpha-2 ($F = 24.835$; $df = 1{,}18$; $p < 0.0001$), and beta-1 frequency bands ($F = 4.974$; $df = 1{,}18$; $p = 0.0387$). As shown in Fig. 1, subsequent analysis by *t*-test revealed that the AD patients had significantly lower coherence than the control subjects in these frequency bands, particularly for the electrode pairs over the precentral regions (i.e. between frontal and central regions and between frontal and antero-temporal regions). No significant group differences were found in the delta

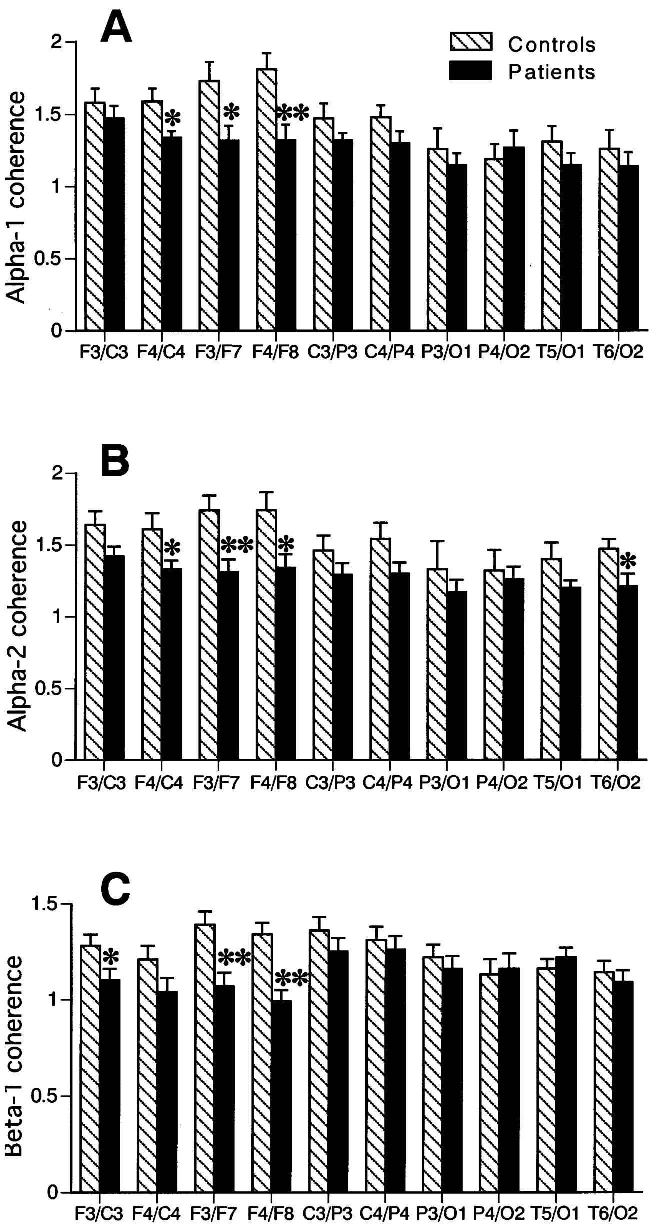


Fig. 1 A–C Intrahemispheric coherence of the resting EEG in control and patient groups. **A** Alpha-1 band coherence (8.0–9.0 Hz); **B** alpha-2 band coherence (9.5–12.5 Hz); **C** beta-1 band coherence (13.0–19.5 Hz). Values are mean ± SEM of coherence values transformed to Fisher's Z scores (n = 10 per group). *$p < 0.05$, **$p < 0.01$ compared with control group (two-tailed t-test)

(F = 1.884; df = 1,18; p = 0.1868), theta-1 (F = 1.988; df = 1,18; p = 0.1756), theta-2 (F = 0.718; df = 1,18; p = 0.4081), or beta-2 frequency band (F = 0.648; df = 1,18; p = 0.4315).

EEG coherence in the stimulus condition

Figure 2 shows coherence values of the EEGs recorded during PS in the control and AD groups. The analysis of the stimulus data showed significant group differences in the frequency corresponding to PS at 10 Hz (repeated measures ANOVA; F = 4.594; df = 1,18; p = 0.046) and 15 Hz (F = 6.142; df = 1,18; p = 0.0233). As shown in Fig. 2 A, subsequent t-test revealed that the AD patients had significantly lower coherence during 10-Hz PS than the control subjects for F4–F8 electrode pair. The AD patients were also found to have significantly lower coherence for T6–O2 during 15-Hz PS (Fig. 2 B). No significant group differences were found in the frequency corresponding to PS at 5 Hz (F =2.079; df = 1,18; p = 0.1665).

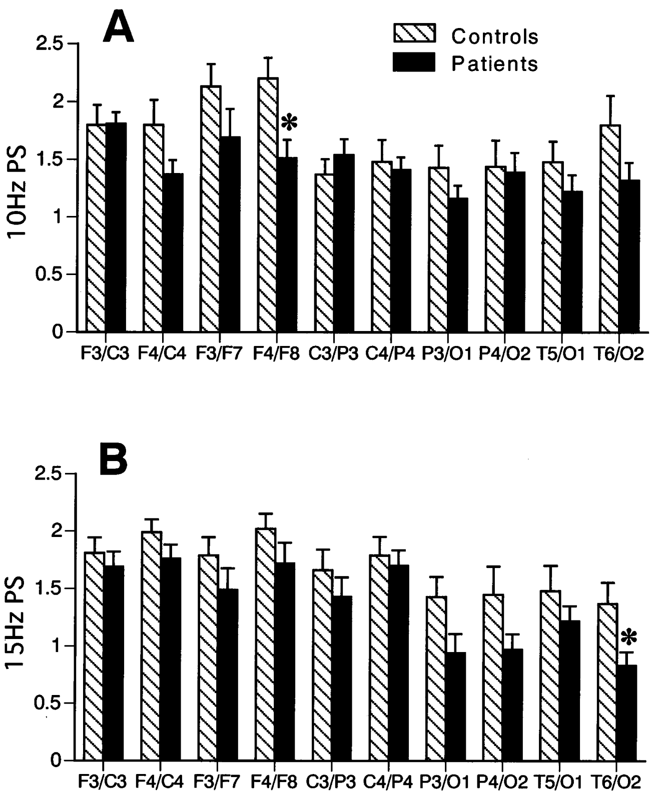
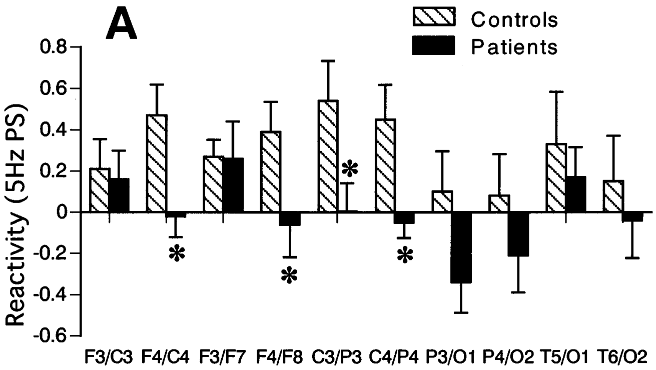


Fig. 2 A, B Intrahemispheric EEG coherence during photic stimulation (PS) in control and patient groups. **A** Coherence during 10-Hz PS; **B** coherence during 15-Hz PS. Values are mean ± SEM of coherence values transformed to Fisher's Z scores (n = 10 per group). *$p < 0.05$ compared with control group (two-tailed t-test)

Reactivity to photic stimulation

In this study, PS-related coherence reactivity was also calculated; coherence reactivity was obtained by subtracting the Z-transformed coherence value measured in the resting state from that measured during PS for each of three stimulus frequencies in each subject. Thus, a positive value of coherence reactivity indicates that intrahemispheric coherence increases in association with PS. The repeated measures ANOVA revealed significant group differences in coherence reactivity to PS at 5 Hz (F = 6.189; df = 1,18; p = 0.0229) and 15 Hz (F = 5.222; df = 1,18; p = 0.0347). As compared with the control subjects, the AD patients generally showed a smaller increase, or



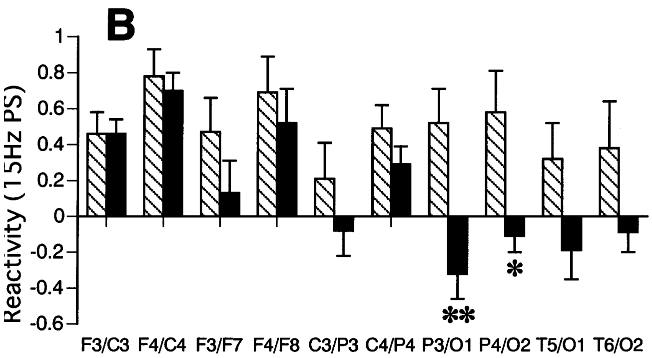


Fig. 3 A, B Changes in intrahemispheric EEG coherence from the resting state to the stimulus condition (i.e. PS-related coherence reactivity) in control and patient groups. **A** Coherence reactivity to 5-Hz PS; **B** coherence reactivity to 15-Hz PS. Values are mean ± SEM (n = 10 per group). *$p < 0.05$, **$p < 0.01$ compared with control group (two-tailed t-test)

even a decrease, in coherence values in association with PS, and subsequent t-test showed that the patients had significantly less coherence reactivity for the electrode pairs as indicated in Fig. 3. No significant group differences were found, however, in the frequency corresponding to 10 Hz PS ($F = 0.69$; $df = 1,18$; $p = 0.4172$).

Discussion

The present study examined intrahemispheric coherence of the resting EEG, and showed that the AD patients generally had lower coherence values than the gender- and age-matched normal controls. Significant group differences were found in the alpha-1, alpha-2, and beta-1 frequency bands, mainly over the precentral regions. Although it is difficult to compare across studies because of differences in frequency bands, electrode pairing and diagnostic criteria, our findings are in general agreement with those of previous studies showing reduced intrahemispheric coherence in DAT (Leuchter et al. 1987; Besthorn et al. 1994; Dunkin et al. 1994; Sloan et al. 1994; Jelic et al. 1996). A lack of significant changes in delta band coherence is also consistent with these previous studies. In accordance with the present results, Besthorn et al. (1994) recently reported that DAT patients have decreased coherence mainly in the alpha and beta bands at fronto-central electrode locations. Similarly, Sloan et al. (1994) demonstrated that DAT patients tended to show lower intrahemispheric EEG coherence than patients with major depression who displayed normal imaging of regional cerebral blood flow (rCBF), with significant group differences confined to the alpha band.

In addition to the resting state, significant group differences were found on EEGs recorded during PS; the AD patients showed significantly lower intrahemispheric EEG coherence than the control subjects in the frequency corresponding to PS at 10 and 15 Hz. Considering that EEG coherence can be interpreted as a quantitative measure of the degree of connectivity between distinct brain regions (French and Beaumont 1984), the present findings suggest that, in addition to the resting state, AD patients have a defective functional interaction within hemispheres in the stimulus condition. Although it has been well described that DAT patients have abnormalities in flash VEPs (i.e. prolonged latency of the later components; Coben et al. 1983; Katz et al. 1989; Orwin et al. 1986; Philpot et al. 1990) as well as in pattern-reversal electroretinograms (Katz et al. 1989; Trick et al. 1989), there have been no studies which have specifically investigated EEG coherence during PS in demented patients. Our findings are consisted with those of Celesia et al. (1993) who reported that DAT patients showed intrahemispheric coherence abnormalities during visual stimulation of square-wave gratings, and suggested functional impairment of cortico-cortical connectivity and processing.

There have been several studies indicating that coherence increases in association with performance-related activation in normal subjects (Busk and Galbraith 1975; Shaw et al. 1977; Beaumont et al. 1978; Gasser et al. 1987). In this study, as reflected by coherence reactivity, the non-demented control subjects showed an enhancement of coherence from rest to the stimulus condition, indicating that PS can also lead to an increased coherence. This was not the case, however, for the AD patients; they showed negative mean values in coherence reactivity for several electrode pairs and had significantly less coherence reactivity to PS at 5 and 15 Hz, suggesting that AD shows a failure of PS-related functional reorganization in anatomically distinct cortical regions. These findings are consistent with those of previous studies using quantitative EEG analysis and neuroimaging techniques. In their linear and nonlinear analysis of occipital EEG activity, Stam et al. (1996) recently showed decreased EEG reactivity to eye opening in DAT patients. Watanabe et al. (1993) also reported that DAT patients showed diminished EEG changes when conducting mental tasks such as reverse recitation of three-digit numbers and mental calculation. In addition, Ingvar et al. (1975) reported that AD patients had a smaller increase, or even decrease, in rCBF than control subjects when performing various forms of psychological tests. Similarly, Mentis et al. (1996) recently reported that DAT patients had smaller striate activations in rCBF in response to patterned flash stimulus.

These findings, together with the present results, suggest that DAT may be characterized by abnormality in the mechanism underlying task- or stimulation-related brain activation, although further studies are needed to examine the sensitivity and specificity of this abnormality.

Although the precise mechanism underlying coherence abnormalities is unclear, it has been suggested that the interneuronal distance for information propagation grows and coherence is then lowered, as DAT shows diffuse and widespread cerebral degenerations (Besthorn et al. 1994). Leuchter et al. (1994) have reported that a decrease in intrahemispheric coherence is associated with the presence of periventricular white matter lesions, which can cause functional disconnection between brain regions. Since neuroimaging studies have shown that periventricular white matter lesions or leuko-araiosis are more frequently observed in DAT patients than in control subjects (Meyer et al. 1992; Kawamura et al. 1992), such changes may be another factor that reduces functional connectivity in our patients. Cortical cholinergic dysfunction (Davies and Maloney 1976) and loss of cholinergic neurons in the nucleus basalis of Meynert (Whitehouse et al. 1981), a main source of the cholinergic projection to the cerebral cortex, have been described in patients with DAT. Numerous clinical and experimental studies have provided evidence indicating a relationship between background EEG slowing and cholinergic deficit in DAT (see review by Soininen et al. 1990; Riekkinen et al. 1991). Although little work has been reported on the neurochemical correlates of coherence abnormality, Sloan et al. (1992) have shown that scopolamine, a centrally acting anticholinergic agent, can reduce intrahemispheric coherence in the alpha and beta bands when administered to normal subjects. This finding suggests that a reduction in cholinergic activity is attributable, at least in part, to diminished intrahemispheric coherence observed in our AD patients.

Methodological aspects, including drug influences and the effects of hypoarousal, need to be considered. However, our patients had not received any CNS-active drug, indicating that reduced EEG coherence did not result from the direct action of drugs or effects following drug withdrawal. In the present study, EEG segments recorded even during light drowsiness were carefully screened out on the basis of eye-movement patterns and EEG activity. In addition, our recent study has shown that intrahemispheric coherence values during light drowsiness significantly increase, rather than decrease, as compared with those in the awake state (Wada et al. 1996). It is unlikely therefore that reduced arousal level was related to the coherence abnormalities observed in our AD patients.

In conclusion, the present study shows that AD patients have a significant decrease in intrahemispheric EEG coherence in the resting state and during PS, suggesting that AD shows an impairment of intrahemispheric functional connectivity in both conditions. In addition, AD patients showed diminished coherence reactivity to PS, also suggesting a failure of PS-related functional reorganization in AD. Further studies are necessary to determine whether other neurological or psychiatric disorders (e.g. late-onset DAT, vascular dementia and depression) produce coherence abnormalities different from those observed in this study. In a recent study using positron emission tomography, Pietri et al (1996) reported that DAT patients with prominent visual symptoms showed larger deficits of glucose metabolism than those without visual disturbances over the parieto-occipital cortical regions. Further studies are also needed, therefore, to clarify the relationship of coherence abnormalities during PS to neuropsychological findings of visual disturbances.

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