Memory-related EEG power and coherence reductions in mild Alzheimer’s disease

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Abstract

Objectives: To examine memory-related EEG power and coherence over temporal and central recording sites in patients with early Alzheimer’s disease (AD) and normal controls. Method: EEG was recorded from central (Fz, Cz and Pz) and temporal (T3 and T4) electrodes while ten very mild AD patients and ten controls performed a Sternberg-type memory scanning task with three levels of working memory load. Spectral power in delta (0–3 Hz), theta (3–5 Hz), lower alpha1 (5–7 Hz), lower alpha2 (7–9 Hz), upper alpha (9–11 Hz) and beta (15–30 Hz) was averaged for temporal and central electrodes. Coherence was averaged between central electrodes, between central and right temporal electrodes and between central and left temporal electrodes. Results: While behavioral performance of very mild AD patients did not differ significantly from that of normal controls, findings suggest that normal controls but not AD patients respond to memory demands by increasing upper alpha power over temporal cortex. When compared with normal controls, AD patients had reduced upper alpha coherence between central and right temporal cortex. Discussion: Results are consistent with previous research on the role of upper alpha in semantic memory and suggest that very mild AD may inhibit selective synchronization of upper alpha in temporal lobes. Reduced coherence between central and temporal cortex is discussed in light of a neurological model of AD that hypothesizes reduced electrocortical efficiency and a breakdown of neural network communication to temporal lobes possibly resulting from temporal lobe atrophy.

Keywords: Spectral power; Coherence; Alzheimer’s disease; Working memory

1. Introduction

Structures within the medial temporal lobe, particularly the hippocampus, have long been implicated in human episodic memory. One of the earliest markers of Alzheimer’s disease (AD) onset is memory loss associated with medial temporal lobe atrophy (Bobinski et al., 1995). The utility of electrophysiological measures as diagnostic markers of AD has been controversial. The major-
ity of studies have investigated event-related potentials (ERPs), showing age- and dementia-related latency and amplitude reductions during a variety of stimulus and task conditions (Goodin et al., 1978; see Polich, 1991, 1997a,b; for reviews). However, while ERP components were often able to discriminate between patient and control groups, they have not proved sufficiently sensitive for the diagnosis of individual patients (Castaneda et al., 1997; Phillips et al., 1997, for reviews see Barrett, 2000; Polich and Herbst, 2000). Quantitative electroencephalography (qEEG) and coherence provide additional sources of information about the topography of synchronous oscillatory activity and potential cortico–cortical interactions during cognitive testing (Gevins and Smith, 2000; Schurmann and Basar, 2001; Weiss and Rappelsberger, 2000).

1.1. Spectral power and AD

In AD, the earliest spectral changes at rest are an increase in theta activity, accompanied by a decrease in beta activity, which are followed by a decrease of alpha activity (Prinz and Vitiello, 1989; Dierks et al., 1991; Giannitrapani et al., 1991; Soininen and Riekkinen, 1992; Jelic et al., 1996), and delta frequency increases later during the course of disease (Soininen and Riekkinen, 1992; Elmstahl et al., 1994). Topographically, Dierks et al. (1993) reported a correlation between higher slow-frequency amplitudes and a shift of alpha and beta activity toward frontal brain regions and the degree of dementia in AD patients at rest. Topographical EEG power changes may thus reflect early signs of cortical atrophy and/or compensatory cortical reorganization early during the course of disease.

The present study was based on the idea that such early disease-related changes may become more apparent during the performance of a memory task than that during rest. In healthy individuals, there are well-known associations between memory retrieval and spectral power including frontal and occipital theta power increases, and occipital alpha power decreases for the comparison of recalled vs. not recalled words in an incidental learning paradigm (Klimesch et al., 1997), and event-related desynchronization (ERD) in both lower and upper alpha bands to recalled words (Klimesch et al., 1996). Normal aging appears to attenuate this ERD pattern (Dujardin et al., 1994).

No studies are available that have examined topographical differences between AD and normal controls in either spectral power or coherence during memory processing. However, age-related topographical ERP differences have been reported during semantic processing, recognition memory and source memory (Czigler, 1996; Friedman et al., 1993; Miyamoto et al., 1998; Van Petten and Senkfor, 1996; Senkfor and Van Petten, 1998; see Friedman, 2000 for a review), suggesting e.g. an inability to selectively activate frontal areas during memory encoding (Friedman et al., 1993). While research on normal aging cannot provide insights into dementia-related processes, they suggest the possibility that subtle alterations in the dynamics of electrophysiological processing may reflect the earliest signs of AD even in the absence of significant memory failure. In the context of a distinction that is sometimes made between processing effectiveness (i.e. behavioral performance) and processing efficiency (i.e. efficiency of underlying mechanisms; see Eysenck, 1992, 1996), the failure of neuropsychological memory assessments to detect earliest stages of AD may be associated with compensatory processes (e.g. effort) that serve to maintain processing effectiveness while concealing an underlying reduction in processing efficiency. Used in conjunction with behavioral indices, qEEG methodologies provide a rich source of information about patterns of cortical activation supplementing the examination of differences in processing efficiency.

1.2. Coherence

Coherence between two EEG signals, which is the squared cross-correlation in the frequency domain between two EEG time series measured simultaneously at different scalp locations (Nunez, 1981), has been interpreted as a measure for the degree of synchronization between brain signals of certain brain regions. Research suggests that patterns of high coherence between EEG signals recorded at different scalp sites have functional significance and be correlated with different kinds
of cognitive information processing, like memory, language, concept retrieval and music processing (e.g. Petsche et al., 1993, 1997; Krause et al., 1998; Basar et al., 1999; Schack et al., 1999a,b; Weiss and Rappelsberger, 1998; Weiss et al., 1999). In relation to memory processes, studies in healthy humans (Beaumont and Rugg, 1979; Krause et al., 1998; Sarnthein et al., 1998; Weiss et al., 1998; Weiss and Rappelsberger, 2000) have generally reported an increase of synchronization between brain regions involved in the respective task. In normal adults, interhemispheric coherence at rest decreases with advancing age (Duffy et al., 1996; Knott and Harr, 1997; Kikuchi et al., 2000). Furthermore, studies comparing normal older adults to patients with AD have reported further reductions in interhemispheric alpha band (8–12 Hz) coherence between occipital sites (Anghinah et al., 2000) and in temporo–parieto–occipital areas (Locatelli et al., 1998). Locatelli et al. (1998) also reported an increase in delta (0–3 Hz) coherence between frontal and posterior regions in AD patients and suggested that the alpha coherence decrease could be related to alterations in cortico–cortical connections, whereas the delta coherence increase could be related to the lack of influence of subcortical cholinergic structures on cortical electrical activity. Given that AD is associated with degeneration of the basal forebrain and medial temporal cortices believed to play a conjoint role in memory processes along with other cortical sites (e.g. in the parietal lobes), a hypothesis would be that, during memory retrieval, the earliest stages of AD would be marked by alterations in the electrocortical activity over these areas and a breakdown of the functional link between relevant cortical areas.

1.3. Rationale for the current study

The above overview suggests, firstly, that spectral power and coherence measures are functionally related to memory processes. Secondly, spectral power and coherence measures can discriminate between normal older adults and AD patients. What is unclear from the current research is whether or not the information processing mechanisms underlying the memory function of very mild AD cases can be characterized by any specific spectral power or coherence signature. The central focus of the study was to investigate task-related differences in spectral power and coherence during retrieval of letters in a memory scanning task with three levels of working memory (WM) load. We used a method adapted from deToledo-Morrell et al. (1991) to investigate behavioral and electro-physiological differences between normal controls and AD patients using a memory scanning paradigm that experimentally manipulated WM load by increasing the target memory set size. P300 amplitude and latency were also examined and have been reported elsewhere (Swanwick et al., 1997; see Beuzeron-Mangina and Mangina, 2000 for a similar study). This study focuses on interactions between AD group (i.e. normal vs. very mild AD) and WM load in an attempt to elucidate EEG power/coherence correlates of memory processing.

Our general conceptual framework, based on an understanding of the memory research, led us to believe that more efficiency memory processing would be characterized by more efficient and less diffuse patterns of synchronization and coherence (i.e. specific to memory-related spectral bands and more localized to functionally interacting memory-related brain regions, see Klimesch, 1999; Grady, 2000, for reviews).

Given the exploratory nature of the study, and the absence of a body of previous research literature or theory in relation to dementia-related changes in qEEG parameters during memory, our a priori hypotheses here are tentative. It should also be noted that there is no simple relationship between the localization of the generating structure and the surface EEG pattern, but findings compatible with data obtained with brain imaging techniques may provide convergent evidence regarding underlying cortical dynamics. Given the involvement of the medial temporal lobe in AD-related memory failures (Bobinski et al., 1995), we hypothesized that AD patients would show less task-specific power changes in the medial temporal cortex during memory scanning when compared with normal older adults. Conversely, patterns of cortical activation in response to memory demands were predicted to be more diffuse across frequency
bands and sites in the AD group. Secondly, given the finding that AD patients show reduced coherence at rest (Anghinah et al., 2000; Locatelli et al., 1998), we hypothesized that similar reductions would be seen during memory scanning. Specifically, we predicted significantly reduced coherence between frontal–central–parietal and temporal cortex in the AD group when compared with normal controls. In other words, a dementia-related functional breakdown (i.e. reduced coherence) between central sites and temporal sites was predicted. Thirdly, we hypothesized that dementia-related reductions in processing efficiency would be revealed in response to WM demands. Finally, we predicted that because of the adaptive nature of cortical activity in response to localized damage (see Robertson and Murre, 1999 for a review), suppressed activity in medial temporal lobes of very mild AD would be observed in parallel with compensatory cortical activity of central cortex in response to WM demands.

2. Methods

2.1. Participants

Ten very mild AD subjects (4 men and 6 women: mean age of 69 years, range 58–77) were recruited from Mercer’s memory clinic. The clinical assessments (Swanwick et al., 1996) included the following: thyroid function, serum B12/folate, computed tomography brain scan, ischemic score (Hachinski et al., 1975), Cambridge cognitive examination (Roth et al., 1986), Mini-mental state examination (MMSE, Folstein et al., 1975) and Clinical Dementia Rating (CDR, Hughes et al., 1982). A matched control group (4 men and 6 women: mean age of 68.6 years, range 60–67 years) were community dwelling adults recruited from local active retirement groups. Psychiatric and neurological disorders (other than AD) were excluded by history and examination. Informed consent was obtained from all subjects.

At the time of testing the AD patients had very mild dementia in that they had a CDR of 0.5, did not meet the criteria for probable AD (Mckhann et al., 1984) and had an MMSE score of ≥20. The mean MMSE for the AD and control groups (carried out on the same day as electrophysiological testing) were 23.7 (range 20–26) and 28.7 (range 27–30), respectively. At follow up (6–12 months), but not at the time of testing, all of these patients met the criteria for probable AD (McKHan et al., 1984). All subjects were right handed and free from psychotropic medication.

2.2. Procedure

All aspects of stimulus presentation, EEG recording and analysis, and collection of behavioral data were carried out with the STIMSCAN computer system (Neurosoft, Inc.). The paradigm was designed to replicate that of deToledo-Morrell et al. (1991) involving a Sternberg-type memory scanning task (Sternberg, 1969). On a computer screen the subjects were shown a letter set, which they were asked to memorise. The letter sets contained one (I), three (B, F, T) or five (E, M, L, A, C) letters. The letter set remained on the screen for 30 s. Then there was an 800-ms pause followed by the consecutive presentation of 100 single letters. Each letter remained on the screen for 700 ms with an interstimulus interval of 3.5 s. The subjects were asked to respond to letter(s) from the set (‘targets’) by pressing one key with the thumb of the dominant hand and to any other letter (‘nontargets’) by pressing another key with the nondominant thumb. Subjects were asked to give equal importance to accuracy and speed. Targets were presented with a probability of 24%. Testing never started with the five-letter set. Otherwise, the sets were presented in random order.

2.3. EEG recordings

Silver chloride electrodes were affixed to the scalp with collodion at the following International 10/20 System (Jasper, 1958) sites: Fz (midline frontal), Cz (midline vertex), Pz (midline parietal), T3 (left medial temporal), T4 (right medial temporal), A1 (left mastoid), A2 (right mastoid) and a midline forehead electrode (to monitor eyeblink artifact). Fz, Cz, Pz, T3 and T4 were referenced to linked mastoids A1 and A2 with an additional mastoid placement at A2 used as ground electrode. Electrode impedance was kept below 5
Bio-electric activity was amplified (Grass model 12; 20 × 1000) with filter settings between 0.1 and 100 Hz, sampled at 200 Hz between 100 ms prior to the stimulus and 900 ms poststimulus. STIMSCAN allowed ocular artifact correction (algorithm based on midline forehead electrode), baseline correction (on the basis of the 100-ms prestimulus sample interval), artifact rejection (any sweep with voltage in excess of ±80 μV after ocular artifact reduction) and digital filtering (low-pass frequency 30 Hz; low-pass slope 48 dB/octave; high-pass frequency 0.5 Hz; high-pass slope 46 dB/octave). Letters were presented for 700 ms. The interstimulus interval was 3.5 s. Of the 100 trials sampled during memory scanning for each level of WM load, the mean number of accepted sweeps was 89 and 85 for normal older adults and AD patients, respectively. Two participants were excluded from the spectral and coherence analysis. One AD patient had an extremely small number of acceptable sweeps (<40 for some electrodes), particularly over the temporal electrodes. A second AD patient was found to have an irretrievably corrupted EEG file on later review.

### 2.4. Data analysis

The analyses presented below are based on Fz, Cz, Pz, T3 and T4 recordings. The power spectrum was computed via Fast Fourier Transform (FFT) using a cosine window (length: 10%). Spectral power was computed on the basis of 1000-ms epochs containing 128 sampling points (calculated on the basis of sampling rate, 128), resulting in a frequency resolution of 1 Hz. Coherence between two waveforms x and y was calculated as $T_{xy}^2(f) = \left(\frac{G_{xy}(f)}{G_{xx}(f)G_{yy}(f)}\right)^2$, where $G_{xy}(f)$ is the mean cross-power spectral density and $G_{xx}(f)$ and $G_{yy}(f)$ are the respective mean autopower spectral densities (Glaser and Ruchkin, 1976). Spectral power and coherence averaging for the frequency bands outlined below was task-related (i.e. averaged across three levels of WM load) rather than event-related (i.e. compared with a pre-task baseline).

In order to control for group differences in total spectral power, the power within each frequency band was expressed as the ratio of absolute power in the frequency band divided by absolute power for 0.5–30 Hz. One advantage of such indices is to be independent of the absolute value of power spectral densities, which may vary from subject to subject. Recent studies of WM and recognition memory processes (see Klimesch, 1999 for a review) also suggest that narrow band analysis is preferable to broad band analysis in studies that examine both memory processes and task difficulty. The main reason for this is that the slower and faster alpha frequencies respond selectively to task difficulty and memory demands, respectively. Klimesch (1999) suggests computing spectral band power using mean frequency (MF) in the alpha range as follows: MF to MF + 2 Hz = upper alpha, MF-2 to MF Hz = lower alpha2, MF-4 to MF-2 Hz = lower alpha1, MF-6 to MF-4 Hz = theta. Analysis of MF in the alpha range (7–13 Hz) across all electrodes and levels of WM load revealed an MF of 8.84 (S.D. = 0.50) and 8.77 (S.D. = 0.49) Hz for AD and normal older adults, respectively. Because groups did not differ statistically on mean alpha frequency, a common alpha MF of 9 Hz was chosen to define the following spectral bands filtered for further analysis: delta (0.5–3 Hz), theta (3–5 Hz), lower alpha1 (5–7 Hz), lower alpha2 (7–9 Hz), upper alpha (9–11 Hz), beta1 (15–20 Hz), beta2 (20–25 Hz) and beta3 (25–30 Hz). The frequency band 12–14 Hz was not analyzed in this study. Having defined the narrow band alpha frequencies, we believed that it was not appropriate to label the frequency band 12–14 as beta. Therefore, we defined beta activity as the frequency range 15–30 Hz. Three beta bands were used to assess the specificity and generalizability of any fast frequency differences across groups, conditions and sites. Narrow band beta analysis also done to see if muscle artifact in beta frequency associated with a manual response or tension in the neck was generally increased over temporal sites in any specific narrow beta band. Positive skew for normal older adults, AD patients and the full sample data was observed in each spectral band for both spectral power and coherence measures. Square root transformation normalized the distributions.
2.5. Statistical analysis

In the spectral analysis, an independent subject $2 \times 3 \times 5$ mixed factor MANOVA design was used. The between group factor, Group, had two levels (AD patients and age-matched controls). Within subject factors, WM load and site had three (one, three or five items to be stored) and five (electrode sites: Fz, Cz, Pz, T3, T4) levels, respectively. As spectral power in each of the narrow band frequencies can be functionally significant (see Klimesch, 1999 for a review), separate ANOVAs were run for the frequency ranges delta, theta, lower alpha1, lower alpha2, upper alpha, beta1, beta2 and beta3. In the coherence analysis, Group and WM factors were entered along with a second within subject factor, direction, with three levels: coherence between central sites (averaged coherence across the following electrode pairs: Fz–Cz, Fz–Pz, Cz–Pz), coherence between central and right temporal and central and left temporal sites (averaged coherence across the following electrode pairs: Fz–T4, Cz–T4, Pz–T4 and Fz–T3, Cz–T3, Pz–T3 for right and left, respectively). Bonferroni tests were used to assess statistical significance of all pairwise comparisons.

3. Results

All of the AD subjects and matched controls were able to complete the task with greater than 90% accuracy. The means and S.D.s for RTs and errors are shown in Table 1. Conducting a 2 (group) $\times$ 3 (WM load) ANOVA on errors revealed no main effects or interaction effects. In contrast, a separate 2 $\times$ 3 ANOVA run on RTs revealed that AD subject’s decision times were significantly slowed when compared with normal controls ($F(1, 18) = 12.69$, $P < 0.001$). RTs became more prolonged as memory load increased ($F(2, 27) = 15.62$, $P < 0.001$). However, there was no significant interaction between diagnosis and memory load ($F(5, 54) = 2.17$, $P = 0.13$).

3.1. Spectral power

The means and S.D.s of relative spectral power in the delta to beta range across three levels of WM load in both AD patients and normal controls can be seen in Table 2. A $2 \times 3 \times 5$ ANOVA was carried out on relative power in each spectral band. Although not a central focus of this analysis, it should be noted that main effects for site were observed in all frequency bands ($P < 0.001$ for all frequency bands). In the delta to upper alpha range, power over the three central sites was significantly greater than power over the two temporal sites ($P < 0.01$ for all six comparisons in each frequency band). In the three beta frequency ranges, this effect was accounted for by the fact that beta power was greater over both temporal sites compared with three central sites ($P < 0.05$ for all six comparisons between two temporal and three central sites). Given the use of a mastoid reference, one possibility is that activity recorded over temporal cortices and mastoids picked up activity from the same underlying source, thus artefactually inflating coherence. Therefore, the lower power at temporal electrodes may have been related to the proximity between site and reference electrodes.

There was a main effect ($F(2, 32) = 5.83$; $P < 0.01$) for WM load in delta, which was accounted for by significant reductions in power as WM load increased from 1 to 3 or 5 items stored during memory scanning ($P < 0.001$ for both comparisons). On the other hand, there was no delta power difference between the WM load of 3 and 5 items ($F(1, 16) = 1.38$; ns). No other significant main effect or interaction effect was observed. However,
<table>
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<tr>
<td></td>
<td>Fz</td>
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<tr>
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<tr>
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**Note:** Means and S.D.s for relative spectral power across eight frequency bands, five electrode sites and three levels of WM load in AD patients and normal controls.

*Mean relative power = absolute power in the frequency band divided by absolute power for 0.5–3 Hz. Values in parentheses are S.D.s.

Delta (0.5–3 Hz), theta (3.5–5 Hz), lower alpha (5.5–7 Hz), lower alpha2 (7.5–9 Hz), upper alpha (9.5–11 Hz), beta1 (15–20 Hz), beta2 (20–25 Hz) and beta3 (25–30 Hz).

WM load during memory scanning consisted to three levels, WM 1=1 letter, WM 2=3 letters, WM 3=5 letters.
there was a non-significant trend whereby delta power was reduced in AD compared to normal control over both central and temporal recording sites ($F(1, 16) = 4.105; P = 0.059$).

Spectral frequencies in the theta to upper alpha range are believed to be of functional significance for understanding WM and semantic memory processes (Gevins et al., 1997; Klimesch, 1999). In the current study, there was a main effect for WM in the theta band ($F(2, 32) = 3.54; P < 0.05$). When one or three sample items were to be held in memory, theta power was significantly greater ($P < 0.05$ for both comparisons) than that when five items were to be held in memory. No significant theta power difference was observed when storage of one or three items in WM was compared.

Fig. 1 illustrates the differences between AD patients and controls for three alpha frequency bands over the five recording sites. Significant group differences emerged when lower alpha1 was examined. Firstly, there was a main effect of group ($F(1, 16) = 6.12; P < 0.05$) with AD patients having more power in lower alpha1 than normal controls. Furthermore, a group×site interaction was observed ($F(4, 64) = 2.96; P < 0.05$). Post hoc analysis revealed significant differences between AD patients and normal controls for central sites ($P < 0.01$ for comparisons at Fz, Cz, and Pz), but no difference between groups at temporal sites ($P > 0.05$ for both comparisons). The main effect for WM was non-significant ($F(2, 32) = 2.02; P > 0.05$) and no other interactions were observed.

A group×site interaction effect ($F(4, 64) = 6.38; P < 0.001$) was also observed for lower alpha2. Post hoc analysis revealed significant differences between AD patients and normal controls for central sites ($P < 0.01$ for comparisons at Fz, Cz, and Pz), but no difference between groups for either temporal electrode ($P > 0.05$ for both comparisons). The main effect for group did not reach significance ($F(1, 16) = 1.99; ns$). The main effect for WM was non-significant ($F(2, 32) = 0.34; ns$) and no other interactions were observed.

In the upper alpha frequency range, there was a highly significant group×site interaction ($F(4, 64) = 13.70; P < 0.0001$), which was accounted for on post hoc analysis by the fact that AD patients showed a non-significant trend toward greater power at central sites, particularly at Pz ($F(1, 16) = 3.96; P = 0.06$), but significantly less power at both left temporal ($F(1, 16) = 8.29; P < 0.01$)
Fig. 2. Beta2 (20–25 Hz) and beta3 (26–30 Hz) power in both AD and normal controls for three levels of WM difficulty.

and right temporal (F(1, 16) = 12.98; P < 0.01) sites when compared with normal controls. Normal controls showed significantly greater power over both temporal sites when compared to three central sites (P < 0.05 for all six comparisons). Thus, unlike the delta, theta and lower alpha frequencies, where power over central recording sites was greater than power over temporal recording sites, normal controls showed greater power over the temporal lobes within the upper alpha range, while AD patients continued to show suppressed temporal relative to central cortex power. The main effect for WM was non-significant (F(2, 32) = 1.65; P > 0.05) and no other interactions were observed.

An examination of spectral means for the three spectral frequencies in the beta range suggested a role for beta in WM demands. A main effect of WM was also seen for beta1 (F(2, 32) = 4.08; P < 0.05), with an increase in power associated with increasing WM load from one item to either three or five items stored (P < 0.05 for both comparisons). No significant difference between three and five items stored in WM was observed. Unlike beta1, both beta2 and beta3 showed WM × Group interaction effects (beta2, F(2, 32) = 4.67, P < 0.01; beta3, F(2, 32) = 5.13, P < 0.01). These interaction effects are illustrated in Fig. 2 showing that while AD patients responded to WM demands by increasing power in both beta2 and beta3, normal controls did not respond to the difficulty level of the task. Post hoc analysis revealed that for both beta2 and beta3 the AD and control groups did not differ significantly for one or three items stored in WM (P > 0.05 for all four comparisons), but AD patients had significantly more power for five items stored (beta2, F(1, 16) = 4.09, P < 0.05; beta3 F(1, 16) = 5.07, P < 0.05).

3.2. Coherence

The means and S.D.s for coherence in the delta to beta range across three levels of WM load in both AD patients and normal controls can be seen in Table 3. As previously noted, coherence was analyzed in the context of a 2 × 3 × 3 ANOVA. Across all frequency ranges examined, only upper alpha produced a significant group difference. Specifically, analyses comparing central–central and central–right temporal coherence revealed a significant group × direction interaction (F(1, 16) = 6.35; P < 0.05) as illustrated in Fig. 3. Although AD and controls did not differ significantly when central–
Table 3
Means and S.D.s of coherence for central–central (CC), central–right (CR) temporal and central–left (CL) temporal for three levels of WM load in AD patients and normal controls

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<tr>
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<td>0.52 (0.09)</td>
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<td>Beta 2</td>
<td>0.66 (0.16)</td>
<td>0.10 (0.13)</td>
<td>0.11 (0.11)</td>
</tr>
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</table>

| Controls |           |           |           |           |           |           |           |           |           |
| Delta | 0.54 (0.10) | 0.09 (0.09) | 0.11 (0.08) | 0.50 (0.14) | 0.06 (0.04) | 0.08 (0.05) | 0.53 (0.07) | 0.09 (0.06) | 0.12 (0.07) |
| Theta | 0.67 (0.12) | 0.10 (0.07) | 0.15 (0.15) | 0.64 (0.19) | 0.09 (0.09) | 0.12 (0.12) | 0.66 (0.14) | 0.05 (0.04) | 0.15 (0.14) |
| Lower A1 | 0.65 (0.12) | 0.10 (0.06) | 0.17 (0.18) | 0.63 (0.19) | 0.09 (0.08) | 0.13 (0.16) | 0.63 (0.13) | 0.06 (0.04) | 0.15 (0.16) |
| Lower A2 | 0.65 (0.12) | 0.08 (0.05) | 0.14 (0.16) | 0.67 (0.17) | 0.09 (0.09) | 0.15 (0.17) | 0.65 (0.13) | 0.08 (0.07) | 0.14 (0.17) |
| Upper A | 0.64 (0.14) | 0.07 (0.05) | 0.10 (0.10) | 0.67 (0.17) | 0.08 (0.09) | 0.12 (0.12) | 0.65 (13) | 0.06 (0.05) | 0.12 (0.12) |
| Beta 1 | 0.60 (0.18) | 0.08 (0.12) | 0.11 (0.12) | 0.60 (0.12) | 0.08 (0.13) | 0.11 (0.16) | 0.61 (0.11) | 0.05 (0.04) | 0.10 (0.09) |
| Beta 2 | 0.63 (0.15) | 0.05 (0.04) | 0.12 (0.15) | 0.61 (0.10) | 0.05 (0.05) | 0.10 (0.10) | 0.66 (0.10) | 0.04 (0.03) | 0.11 (0.08) |

Note 1: Values in parentheses are S.D.s. Note 2: Beta2 is average coherence in the 20–30 Hz range.

central and central–right temporal coherence were examined individually ($P > 0.05$ for both comparisons), the interaction is suggestive of an altered cortical dynamic with suppression of coherence from central–right temporal being compensated for by enhanced central–central coherence in the

![Fig. 3. Coherence averaged across three central electrode pairs (central–central) and three central and right temporal pairs (central–right) for AD patients and normal controls in the upper alpha range.](image-url)
AD group. Comparison of central–right temporal and central–left temporal coherence revealed that although normal controls showed enhanced central–right temporal coherence when compared with central–left temporal coherence \((F(1, 9)=5.38; P<0.05)\), AD patients showed no difference \((F(1, 7)=0.03; P>0.05)\). WM manipulations did not have a significant effect on coherence measures.

Finally, in line with the frontal-lobe model of aging memory (see e.g. West, 1996), we used coherence to investigate whether or not AD was associated with an acceleration of an age-related ‘functional breakdown’ between frontal cortex and other areas of the brain. To do this we compared frontal–temporal coherence with parietal–temporal coherence. Pairwise comparisons were conducted to compare WM and group differences for frontal–temporal \((Fz–T3 \text{ and } Fz–T4)\) and parietal–temporal \((Pz–T3 \text{ and } Pz–T4)\) coherence, respectively. There was no frequency band for which significant group or WM coherence differences were observed when frontal–temporal and parietal–temporal pairs were compared.

4. Discussion

The present study examined spectral power and coherence changes associated with memory scanning demands in a group of early AD patients and a group of healthy controls. Behavioral results were consistent with a model of generalized slowing (Salthouse, 1996) indicating that AD patients when compared to normal controls were slower to identify targets and reject nontargets, but were able to maintain high levels of memory scanning accuracy. On the other hand, electrophysiological activity recorded during memory scanning revealed a complex pattern of group differences that may shed light on the underlying nature of reduced efficiency of information processing observed in very mild AD.

It is important to note that findings from this study are not strictly comparable with the bulk of previous research that has compared AD patients and controls on spectral power or coherence indices. While recent research has suggested a correlation between cortical theta activity at rest and hippocampal volumes in mild dementia (Grunwald et al., 2001), the current study found no differences between AD patients and controls in the theta \((3–5 \text{ Hz})\) range during retrieval. However, the current study did find that theta power responded to WM demands in both AD patients and controls, with a reduction of theta power being observed for higher levels of WM load.

Results from quantitative EEG analysis did reveal a number of differences between AD patients and controls in the alpha range \((5–11 \text{ Hz})\). Firstly, AD patients had greater spectral power in lower alpha1 and lower alpha2 when compared with controls. Significant group differences were observed for central \((Fz, Cz \text{ and } Pz)\) but not temporal \((T3 \text{ and } T4)\) electrodes. In the light of previous research suggesting a role for lower alpha in (WM) task effort and difficulty (Gevins et al., 1997; Klimesch, 1999), the present results could be interpreted as possibly reflecting generally enhanced effort in patients. The current study cannot make any definitive conclusions regarding the localization of spectral power differences. However, group differences in power over central, but not over temporal, recording sites in the lower alpha range suggest that if task effort or task difficulty were accounting for electrocortical differences, future research using source analysis could investigate if this influence is specific to areas of the cortex not normally damaged by the earliest stages of AD.

Specific behavioral and spectral power changes associated with increased WM demands were observed in both groups (i.e. a slowing of RTs, and a relative decrease in delta and in theta power). Also, evidence for a more selective effect of WM demands in AD patients was seen in the beta \((20–30 \text{ Hz})\) frequency range. Specifically, while AD patients responded to WM demands by increasing power in the 20–30 Hz range, normal controls did not. Thus, although the behavioral data suggested that AD patients experienced reductions in processing speed, with no group×WM interaction observed, the WM-related increase in beta power in the AD group suggests differences in the electrocortical correlates of behavioral output. One possibility here is that the increase in synchronous activity in the 20–30 Hz range represents compensatory activation associated with increased atten-
tional effort in the AD group as WM demands increased. This is consistent with previous research suggesting that beta power (Valentino et al., 1993) and coherence (Cudmore et al., 2000) increase in response to increasing task demand.

Analysis of spectral power in upper alpha revealed that when compared to normal controls the AD patients had greater power over central cortex, but significantly less power over temporal cortex. Thus, unlike delta, theta and lower alpha frequencies, where power over central recording sites was greater than power over temporal recording sites, normal controls showed a relative power shift in the upper alpha range with greater power over the temporal lobes. On the other hand, AD patients continued to show suppressed temporal relative to central cortex power in the upper alpha range. These results are consistent with recent research suggesting a relationship between hippocampal atrophy and suppressed spectral power in frequency ranges associated with memory functioning (see e.g. Grunwald et al., 2001).

However, the use of task-related rather than event-related averaging in the current study means that we can only speculate as to why upper alpha power over temporal sites is lower in the AD group. One possibility is that early AD is associated with suppressed upper alpha power at baseline (i.e. before memory retrieval) and less desynchronization of upper alpha during retrieval. For example, Klimesch (1999) argues that better memory performance is associated with both higher baseline alpha and greater alpha desynchronization. Given the involvement of the medial temporal lobe in AD-related memory failures (Bobinski et al., 1995) and upper alpha power in semantic memory processes (Klimesch, 1999), we might speculate that AD is associated with generalized suppression of upper alpha over medial temporal lobes both at rest and during memory performance.

As noted in Section 1, research does suggest that AD is associated with a decrease of alpha activity at rest (Prinz and Vitiello, 1989; Dierks et al., 1991; Giannitrapani et al., 1991; Soininen and Riekkinen, 1992; Jelic et al., 1996). However, it is unclear from this research if upper alpha or lower alpha changes are more or less important for the declines in memory functioning observed.

Given that upper alpha is more sensitive to semantic memory demands, while lower alpha is more sensitive to generalized task demands (see, Klimesch, 1999 for a review), then it might be speculated that generalized reduction in baseline power and reduced ERD of upper alpha, particularly over medial temporal sites, is more highly correlated with the specific memory failures of AD than are band power changes in lower alpha or beta. However, further research using a series of event-related memory paradigms is needed before any conclusions can be made in this regard.

Damage to the medial temporal cortex in the earliest stages of AD may disrupt the activation of semantic networks supported by the medial temporal cortex, making it difficult for AD patients to access semantic representations stored there. Following this same logic, the generalized slowing of memory decisions seen in the AD group may be related to a failure to synchronize upper alpha power in temporal cortex. A failure to access semantic networks supported by the temporal lobe may result in compensatory activation elsewhere in the cortex, which in turn reduces processing efficiency, resulting in a slowing of retrieval. A failure on the part of AD patients to activate semantic representations would also increase the probability of memory failures during more difficult declarative memory processes like recall memory. Recent models of memory (see e.g. Tulving and Markowitsch, 1998) propose that declarative memory, supported by structures within the medial temporal cortex, is defined in terms of features and properties that are common to both episodic and semantic memory.

The pattern of dementia-related spectral power differences observed in the current study (i.e. reduced upper alpha over temporal sites, increased lower alpha power over central sites and increased beta in response to WM demands) is suggestive of cortical suppression with compensatory neural processing. Although this suggestion that the early stage of AD is associated with compensatory activation pattern will require follow-up investigations, the hypothesis is consistent with a growing body of research suggesting that normal aging is associated with a pattern of hemispheric asymmetry reduction (see Backman et al., 1997; Cabeza,
2001; Madden et al., 1999; Reuter-Lorenz et al., 2000; see Cabeza, 2002 for a review). For example, using functional neuroimaging (fMRI), Cabeza (2001) found that, compared to younger adults, older adults showed a more bilateral pattern of prefrontal activation during verbal recall, and interpreted this change as reflecting functional compensation associated with prefrontal atrophy. Cabeza proposed a network model to account for Hemispheric Asymmetry Reductions in Old Age (HAROLD, Cabeza, 2002), which proposes a global compensatory reorganization of task-specific neurocognitive networks in response to neural degeneration. EEG research also supports the idea that compensatory activity may be a characteristic of normal aging. For example, Sailer et al. (2000) reported greater overall activation and, more specifically, a pronounced bilateral activation of sensorimotor regions in elderly subjects for both low alpha (10–11 Hz) and high alpha (12–13 Hz). Sailer et al. concluded that the functional anatomy of the human motor system changes during normal aging. Specifically, it appears that, for a given motor task, the aging brain recruits additional primary sensorimotor and premotor regions of both hemispheres.

One potentially fruitful avenue for future investigation lies in an analysis of the distinction between processing effectiveness and processing efficiency (Eysenck, 1992, 1996). Specifically, if patients in the earliest stages of AD engage in compensatory processing in response to WM demands that served to maintain processing effectiveness (i.e. memory scanning accuracy) while concealing an underlying reduction in processing efficiency (i.e. failure to activate temporal lobes), then this should be apparent by reference to topographical differences in response to increased memory demands.

If it is assumed that cognitive performance is mediated by a neural network of highly interconnected regions, the effects of AD on the anatomical and physiological integrity of the brain can be expected to affect not only the function of specific regions but also the interactions between them. We attempted to assess possible cortico–cortical interactions by means of coherence. In general, coherence values were relatively low, which may have been attributable to the subjects’ advanced age (Duffy et al., 1996; Knott and Harr, 1997; Kikuchi et al., 2000). Regional coherence differences, i.e. higher values for midline electrode pairs than e.g. centro-temporal pairs, may be explained by differences in electrode distance. Interestingly, coherence did not decrease with increasing frequency band. Here we can only speculate that this may have been due to task-specific activations. In the current study, group differences in upper alpha coherence suggestive of functional and possibly compensatory alterations in cortical organization were observed. When compared with normal controls, AD patients had a relative suppression of coherence between central and right temporal electrodes, but enhanced coherence between central electrodes. Furthermore, whereas normal controls showed enhanced central–right temporal coherence when compared with central–left temporal coherence, AD patients showed no difference. It is unclear why upper alpha coherence between central and right temporal cortex should be enhanced in normal controls, but not in AD patients. As noted in the introduction, spectral power and coherence estimates reflect different aspects of physiological processing that are mathematically independent. Thus, even in the absence of upper alpha power differences between right and left temporal cortices in the normal controls and AD patients, the coherence findings may be of functional significance. While this study may be seen as a first attempt at understanding the dynamics of memory-related coherence interactions in early AD, future research is warranted, using more appropriate methods such as high-density EEG, MEG of fMRI.

One possibility is that normal older adults were using the greater visuo-spatial abilities of the right hemisphere either to support maintenance of letter representation stored in WM or to aid in match-to-sample letter comparisons. While research on lexical decision making processes has suggested that left frontal EEG coherence reflects modality independent language processes (Weiss and Rappelsberger, 1998), no research study using coherence analysis has been carried out to suggest a role for the right hemisphere in the processing of letters. Therefore, the possibility that the right
hemisphere functionally interacts with other areas of cortex during efficient letter comparison performance remains a speculation. Nonetheless, the findings of this study suggest that both localized reductions in upper alpha power in the temporal lobes and upper alpha functional interactions between central and right temporal cortex are part of the signature that distinguishes cortical processing of AD and controls during memory scanning. The results provide convergent evidence using two methodologies to support the importance of upper alpha activity during memory processes. Because coherence analysis is assumed to reflect functional interactions between neural networks represented on the cortex, there has been recent interest in the application of coherence analysis in the evaluation of treatments for dementia (see e.g. Cassidy and Brown, 2001). Cassidy and Brown (2001) examined whether alleviation of dopamine deficits in Parkinsonian patients enhanced functional interaction between neural networks during controlled visuo-motor performance. After levodopa, extensive task-specific cortico–cortical coherence was observed. Off levodopa, cortico–cortical coherence was much reduced. Cassidy and Brown (2001) concluded that ascending dopaminergic projections from the ventral mesencephalon may be important in determining the pattern and extent of cortico–cortical coupling during executive tasks.

In conclusion, although a handful of studies have compared AD patients and normal controls on spectral power and frequency, particularly in the alpha range, this is the first study to have examined spectral power and coherence differences between very mild AD and normal controls during memory scanning. The results of the current study are consistent with previous research suggesting a role for upper alpha in memory processes and the role of beta in task demand. The results highlight the importance of understanding topographical patterns of activation during cognitive activity, and suggests that even in cases where neuroimaging scans are insensitive in picking up atrophy in medial temporal lobes or when behavioral performance provides no way to distinguish underlying processing deficits, measurement of spectral power and coherence may offer insight into underlying cortical disruption and/or cortical reorganization.

Future studies should aim to examine more closely the topography of event-related spectral and coherence changes in AD and normal controls in an attempt to understand alterations in the different stages of information processing pre- and post-stimulus (see e.g. Klimesch, 1999). In a similar vein, EEG data can help shed light on a useful distinction that has been made between processing efficiency and processing effectiveness (Eysenck, 1992, 1996). We believe that a fuller understanding of the neuro-cognitive changes observed in very mild AD will require researchers to elaborate on the role of compensatory cortical reorganization and the link between performance effectiveness and cortical activity patterns. We hypothesize that AD will impair processing efficiency before it impairs processing effectiveness. Furthermore, we predict that differential diagnosis using electrophysiological techniques may provide the most sensitive method for observing altered patterns of cortical reorganization associated with reductions in processing efficiency.

A dynamic approach to the problem of clinical identification of mild AD needs to be developed so that the cognitive functions impaired early in the disease process (Kraiuhin et al., 1990) are investigated across the full spectrum of cognitive processes and appropriate difficulty levels. Electrophysiological analysis can enrich the behavioral information gathered during this dynamic assessment by providing a window into the aging brain (see e.g. deToledo-Morrell et al., 1991). Further application of experimental electrophysiological techniques will help to shed light on the dynamics of cortical functioning and adaptation in the earliest stages of AD.

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