Apolipoprotein E ε4 allele decreases functional connectivity in Alzheimer's disease as measured by EEG coherence

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Abstract

***Objectives*—The ε4 allele of apolipoprotein E (APOE) represents a major biological risk factor for late onset Alzheimer's disease. However, it is still not known whether the APOE genotype affects the progression of the disease, assessed by different functional methods.**

***Methods*—The study sample included 41 patients with probable Alzheimer's disease. Subjects had similar severity of disease, age of onset, and duration of illness, and were subcategorised according to their APOE genotypes: 17 with no ε4 allele, 14 with one ε4 allele, and 10 with two ε4 alleles. The control group consisted of 18 healthy subjects comparable with the patients in age and education. Analysed quantitive EEG (qEEG) variables were the ratio of alpha and theta absolute power and EEG coherence in alpha frequency band, representing major cortical association pathways.**

***Results*—There was pronounced EEG slowing in all three patient subgroups compared with the controls for the alpha/theta ratio, but there was no significant difference across the patient subgroups. Patients homozygous for the APOE ε4 allele had reduced right and left temporoparietal, right temporofrontal, and left occipitoparietal coherence. Patients without and with one ε4 allele showed an overlap between the control group and group with two ε4 alleles in coherence measures.**

***Conclusions*—APOE ε4 does not influence EEG slowing, an index which reflects severity of the disease in patients with Alzheimer's disease, but seems to be associated with selective decreases in functional connectivity as assessed by EEG coherence. This finding might be of clinical importance when considering different pathogenetic mechanisms.**

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The ε4 allele of apolipoprotein E (APOE) is associated with an increased risk for late onset familial as well as sporadic Alzheimer's disease.[1–3] Some studies reported that APOE ε4 allele predisposes to cognitive decline in a general population of elderly men.[4] It is also reported to be associated with episodic memory changes in non-demented older adults.[5] Furthermore, PET studies have shown that cognitively normal subjects who are homozygous for the APOE ε4 allele have a pattern of reduced glucose metabolism similar to that of patients with probable Alzheimer's disease.[6] Patients with Alzheimer's disease with two ε4 alleles had lower scores on immediate and delayed memory tests, even though the global disease severity was equal.[7] Taken together, this could indicate that the ε4 allele interferes with the course of the disease and affects the structures involved in memory processing. Further evidence of a possible functional pathogenetic role for APOE is its presence in the neuropathological lesions that are the hallmarks of Alzheimer's disease. APOE has been shown immunohistochemically in senile plaques, neurofibrillary tangles, and cerebrovascular amyloid.[1 8] The APOE ε4 isoform is associated with greater β-amyloid protein accumulation in the Alzheimer's disease brain than other genotypes.[9]

However, it is still not known whether or not genetic heterogeneity of APOE can influence the findings of some functional laboratory tests, such as quantitative EEG (qEEG) in patients with Alzheimer's disease. It has recently been reported that there was a tendency to more pronounced EEG slowing in patients with Alzheimer's disease carrying the ε4 allele.[10] Slowing of the EEG is a characteristic electrophysiological feature of Alzheimer's disease.[11 12] Early changes are observed in theta and alpha frequency bands.[13 14] Clinical progression of the disease is reflected by worsening of qEEG variables.[15 16] Furthermore, heterogeneity of cognitive profiles in patients with Alzheimer's disease is reflected by different electrophysiological features.[17]

EEG coherence reflects functional connectivity between different brain regions, which is likely to be related to structural connectivity.[18] It has been shown that coherence is affected by degenerative and vascular diseases of the brain in elderly people.[19 20] Changes in qEEG power in different spectral bands are related to severity of dementia and have been seen in many areas of the brain, even though some studies pointed out that EEG slowing was particularly

Table 1 Descriptive statistics for study population

Variable	*Controls*	*AD group 0 (no ε4 allele)*	*AD group 1 (one ε4 allele)*	*AD group 2 (two ε4 alleles)*
Total number	18	17	14	10
Sex ratio (M/F)	9 / 9	10 / 7	6 / 8	5 / 5
Age (y)	63.4 (11.0)	61.8 (8.6)	61.2 (7.4)	65.7 (5.7)
Age of onset (y)	—	58.9 (7.6)	59.1 (6.9)	62.6 (5.4)
Duration of illness (y)	—	2.9 (2.1)	2.1 (0.9)	3.2 (2.1)
Education (y)	10.5 (3.6)	10.4 (3.5)	9.7 (3.9)	12.2 (4.5)
MMSE	28.9 (1.1)*	23.2 (3.7)	21.6 (4.0)	22.7 (2.6)
FSIQ	104.9 (10.0)*	80.1 (16.2)	77.2 (14.0)	88.1 (13.5)

Values in parentheses are means (SD).
*Control group was significantly different (P<0.0001) in MMSE and FSIQ scores from the rest of study population. AD=Alzheimer's disease.

pronounced in temporal and parietal areas.[11 21] Findings related to changes in EEG coherence show a more specific regional distribution, representing major associative pathways between anatomically defined and separate regions.[14 19]

The aim of this study was to explore the relation between qEEG power and coherence measures in patients with Alzheimer's disease subcategorised according to their APOE genotype. Possible differences in electrophysiological variables between these subgroups of patients with Alzheimer's disease with the same severity of disease and duration of illness may suggest differences in pathogenetic mechanisms and be of clinical importance.

Methods

STUDY POPULATION

The study population included a total of 59 subjects recruited from a prospective series of patients and subjects consequtively referred to the inpatient and outpatient geriatric department. Table 1 presents demographic data.

Forty one patients with mild to moderate Alzheimer's disease were diagnosed according to the National Institute of Neurological Disorders (NINCDS-ADRDA) criteria.[22] All of them were living in the communitiy independently and in all cases an interview with a family member or other reliable informant was perfomed. Patients were subcategorised according to their APOE genotype in three groups: no APOE ε4 allele (0), one APOE ε4 allele (1), and two APOE ε4 alleles (2). Patients and controls were comparable in terms of educational level and age. Patient subgroups had a similar severity of cognitive decline as measured by mini mental state examination (MMSE) and by Wechsler's full scale intelligence quotient (FSIQ).[23 24] The six tests from the Wechsler adult intelligence scale-revised (WAIS-R) were used to estimate the FSIQ. There was no significant difference in the age of disease onset and duration of illness between the patients' subgroups.

The control group consisted of 18 healthy subjects of comparable ages and educational levels to that of the patients. They were significantly different from all three patient subgroups in MMSE and FSIQ scores.

All subjects were right handed and passed through general medical, neurological, psychiatric, and neuropsychological investigation, as well as neuroimaging diagnostic procedures such as MRI and SPECT, to rule out treatable causes of dementia. Other exclusion criteria were depression and psychotropic medication because of possible influence on EEG indices and neuropsychological performance.

QUANTITATIVE EEG (QEEG) RECORDINGS

All spontaneous EEGs were recorded in the morning, in a resting awake condition with the eyes closed. The EEG data were acquired on a computer based system (Bio-Logic Brain Atlas) from standard 10/20 electrode locations.

Samples were selected by visual inspection to get a minimum of 15 two second epochs, a total of 30 seconds, free of eye blink, drowsiness, muscle movements, or any other kinds of artefacts. These samples were then digitised at 128 samples per second and filtered at 0.5-30 Hz for each electrode location. Frequency analysis was performed using FFT algorithm with Hanning window.[25]

Eight bipolar derivations were chosen representing left and right frontal (F3-C3, F4-C4), left and right temporal (T3-T5, T4-T6), left and right parietal (C3-P3, C4-P4), and left and right temporo-occipital (T5-O1, T6-O2) regions. To reduce the number of qEEG variables involved in multiple comparisions we have chosen the alpha/theta ratio (absolute alpha power divided by absolute theta power, logarithmically transformed to normalise the distribution). The ratio is a sensitive indicator of EEG slowing resulting from changes in both spectral bands.[26] Theta and alpha power have been shown to be significantly changed early in the course of the disease.[14]

EEG coherence was analysed in the alpha frequency band (8-13 Hz). A set of electrode pairings was used representing average left (Fp1-Fp3 paired with Fp1-F7, F3-C3) and right (Fp2-F4 paired with Fp2-F8, F4-C4) frontal, left (Fp1-F3, F3-C3 paired with P3-O1) and right (Fp2-F4, F4-C4 paired with P4-O2) fronto-occipital, left (T3-T5 paired with Fp1-F7, Fp1-F3, F3-C3) and right (T4-T6 paired with Fp2-F8, Fp2-F4, F4-C4) temporofrontal, left (T3-T5 paired with C3-P3, P3-O1; T5-O1 paired with C3-P3) and right (T4-T6 paired with C4-P4, P4-O2; T6-O2 paired with C4-P4) temporoparietal, and left (P3-O1 paired with P3-C3, T3-T5) and right (P4-O2 paired with P4-C4, T4-T6) occipitoparietal coherence, as was designed and described in detail by Leuchter and Newton.[20 27] These authors originally described electrode pairings making up the occipitoparietal coherence set as visual. To remain consistent with the description of other

Table 2 Values of alpha/theta ratio in the diagnostic subgroups

Scalp electrode locations	*Controls*	*AD group 0 (no ε4 allele)*	*AD group 1 (one ε4 allele)*	*AD group 2 (two ε4 alleles)*	*F value (3,55)*	*P value*
Right frontal	0.96 (0.64 to 1.28)	0.17 (−0.12 to 0.45)	0.06 (−0.41 to 0.53)	0.12 (−0.38 to 0.62)	6.62	0.001
Left frontal	0.79 (0.49 to 1.09)	0.04 (−0.22 to 0.30)	−0.12 (−0.50 to 0.28)	0.11 (−0.34 to 0.56)	7.50	0.0005
Right parietal	1.61 (1.32 to 1.90)	0.61 (0.19 to 1.03)	0.43 (−0.08 to 0.95)	0.30 (−0.31 to 0.92)	9.12	0.0001
Left parietal	1.51 (1.18 to 1.84)	0.43 (0.07 to 0.80)	0.26 (−0.18 to 0.70)	0.09 (−0.45 to 0.63)	12.61	0.0001
Right temporal	1.66 (1.43 to 1.90)	0.71 (0.27 to 1.16)	0.55 (0.03 to 1.08)	0.38 (−0.16 to 0.92)	8.94	0.0001
Left temporal	1.54 (1.22 to 1.85)	0.40 (0.01 to 0.80)	0.16 (−0.24 to 0.56)	0.12 (−0.47 to 0.72)	13.59	0.0001
Right temporo-occipital	1.45 (1.13 to 1.78)	0.66 (0.29 to 1.02)	0.44 (−0.05 to 0.94)	0.40 (−0.18 to 0.99)	6.74	0.001
Left temporo-occipital	1.64 (1.35 to 1.92)	0.67 (0.32 to 1.01)	0.24 (−0.29 to 0.77)	0.27 (−0.27 to 0.81)	12.94	0.0001

Values are means (95 % CIs). AD=Alzheimer's disease.

coherence electrode sets based on the specific anatomical regions, we use in the text term occipitoparietal coherence.

Values for EEG coherence obtained in this way were transformed using the arcsin $\sqrt{\times}$ transformation.[28]

DETERMINATION OF APOE GENOTYPE

DNA was extracted from peripheral white blood cells of patients with Alzheimer's disease and control subjects using standard methods. APOE genotype was determined using a microsequencing method on microtitre plates (AffiGen APOE Sangtec Medical, Bromma, Sweden).

STATISTICAL ANALYSIS

The significance of differences between the groups was evaluated by one way analysis of variance (ANOVA), after the normality of the distribution of the EEG data had been tested by Schapiro-Wilk *W* test. Comparison between age and qEEG variables was made using Pearson's correlation coefficient. Scheffé's post hoc analysis was used to determine which groups differed from others. Because of multiple comparisions, we declared a critical P value<0.01 to reduce the chance of a type 1 (false positive) error, which is less extreme than the Bonferroni correction.

Results

ALPHA/THETA RATIO

The alpha/theta ratio was significantly lower in the total sample of patients with Alzheimer's disease (n=41) when they were compared with the controls in all bipolar electrode pairings representing eight regions of the scalp (P<0.0001). No correlation was found between the age of the patients and subjects and the qEEG variables. When the patients were subcategorised according to their genotype, all three groups were significantly different from the controls in both temporal and parietal regions as well as in the left temporo-occipital region (table 2, fig 1). In the right temporo-occipital region there was an overlap between diagnostic subgroups and controls, so the difference between each of the Alzheimer's disease subgroups and the controls was not significant at the previously proposed level of significance. In the right and left frontal region, the ε4 homozygous group did not differ significantly from the control group.

In addition, a trend in means was examined across the patient subgroups with respect to the alpha/theta ratio in regions presented in figure 1. No linear trends in means were found for the alpha/theta ratio in the right parietal ($F(1,38)<1$, NS), left parietal ($F(1,38)=1.32$, NS), right temporal ($F(1,38)=1.95$, NS), and left temporal region ($F(1,38)<1$, NS).

ALPHA BAND COHERENCE

When the total Alzheimer's disease sample was compared with the controls with respect to alpha band coherence, significant differences between the two groups were found in right temporofrontal (P<0.005), right temporopari-

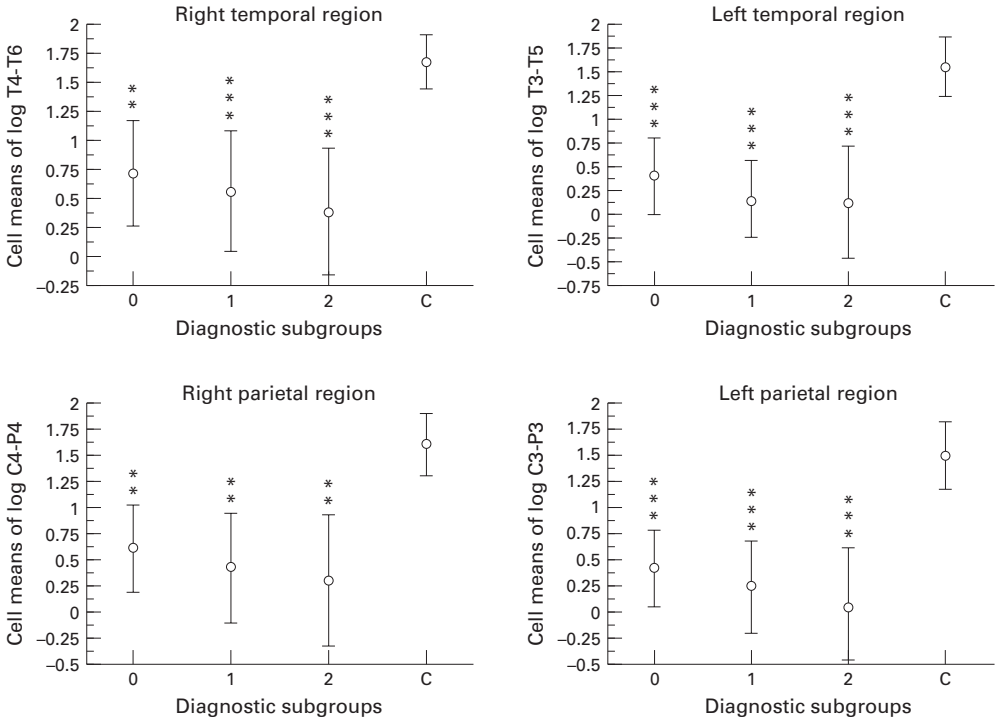

*Figure 1 Differences in alpha/theta ratio among the studied groups. 0= Alzheimer's disease group without ε4 allele; 1= group with one ε4 allele, 2=group with two ε4 alleles, C= controls. Circles indicate means, bars 95% confidence intervals. * P<0.01; ** P<0.005; ***P<0.001.*

etal (P<0.01), right occipitoparietal (P<0.05), left temporofrontal (P<0.05), and left temporoparietal (P<0.01) coherence. Coherence measures did not correlate with the age of the study population.

After subcategorisation of the patients into three groups according to their genotype, only the ε4 homozygous group was significantly different from the controls in the right temporofrontal, right temporoparietal, left temporoparietal, and left occipitoparietal coherence (table 3, fig 2). Groups with or without one ε4 allele showed an overlap between the control group and ε4 homozygous group. An asymmetry between right and left temporofrontal coherence was found in the control as well as in all three diagnostic subgroups, with a tendency to higher values on the right side.

Discussion

This study showed that the APOE ε4 allele influences electrophysiological variables in the group of patients with Alzheimer's disease with the same severity of the disease. Interestingly, the most prominent effects were found in coherence measures. Slowing of EEG, as assessed by the ratio of alpha and theta absolute power, did not vary significantly across the three patient subgroups. This indicates that, once the disease is developed, the APOE ε4 allele does not influence EEG slowing, which is an indicator of the severity of the disease. This is in accordance with some studies which reported little variation in progression of Alzheimer's disease depending on APOE genotype.[29–31]

However, patients homozygous for the ε4 allele were clearly separated from patients with other genotypes and controls by coherence measures. Groups with and without one ε4 allele did not differ significantly from the controls or the homozygotes indicating that there might be a gene dose effect influencing electrical connectivity in Alzheimer's disease. In this study we used a model of bipolar electrode combinations designed by Leuchter and collaborators, covering the projection of major cortical association pathways and providing a profile of coherence changes between multiple brain regions.[20 26] These authors have postulated that patients with Alzheimer's disease have selective disconnection of long corticocortical fibres represented by trans-rolandic pathways. Patients with vascular dementia would have more pronounced damage in pre-rolandic and post-rolandic complex association pathways, assessed by measures of frontal and visual coherence, described in our study as occipitoparietal coherence, because of mainly periventricular tissue destruction. They supported their hypothesis with evidence for an association between periventricular white matter hyperintensities and lowered mean coherence in pre-rolandic and post-rolandic electrode sets.[32]

In our study we found that the Alzheimer's disease group taken as a total sample was significantly different from the controls in the coherence mediated mainly by post-rolandic association networks represented by temporoparietal and occipitoparietal coherence. Absence of changes in coherence mediated by long corticocortical connections and represented by fronto-occipital coherence might be due to the fact that we analysed different frequency bands. In Leuchter's study the 16 Hz

Table 3 Coherence measures in the diagnostic subgroups

Coherence measures	*Controls*	*AD group 0 (no ε4 allele)*	*AD group 1 (one ε4 allele)*	*AD group 2 (two ε4 alleles)*	*F value (3,55)*	*P value*
Frontal:						
Right	0.39 (0.34 to 0.44)	0.43 (0.36 to 0.50)	0.38 (0.32 to 0.45)	0.35 (0.27 to 0.43)	1.00	0.40
Left	0.43 (0.37 to 0.48)	0.42 (0.35 to 0.49)	0.34 (0.28 to 0.39)	0.35 (0.24 to 0.46)	2.11	0.11
Fronto-occipital:						
Right	0.39 (0.34 to 0.45)	0.35 (0.29 to 0.41)	0.34 (0.27 to 0.40)	0.40 (0.31 to 0.49)	1.13	0.34
Left	0.39 (0.35 to 0.43)	0.35 (0.29 to 0.40)	0.32 (0.27 to 0.37)	0.37 (0.29 to 0.46)	1.41	0.25
Temporo-frontal:						
Right	0.61 (0.55 to 0.67)	0.49 (0.43 to 0.55)	0.51 (0.45 to 0.57)	0.44 (0.39 to 0.48)	6.44	0.001
Left	0.39 (0.35 to 0.42)	0.36 (0.32 to 0.41)	0.33 (0.30 to 0.36)	0.34 (0.30 to 0.37)	2.22	0.09
Temporo-parietal:						
Right	0.69 (0.65 to 0.73)	0.66 (0.58 to 0.73)	0.60 (0.55 to 0.66)	0.53 (0.43 to 0.63)	5.10	0.003
Left	0.70 (0.65 to 0.75)	0.64 (0.55 to 0.73)	0.63 (0.57 to 0.69)	0.51 (0.45 to 0.57)	5.10	0.003
Occipito-parietal:						
Right	0.63 (0.57 to 0.70)	0.61 (0.51 to 0.71)	0.54 (0.49 to 0.59)	0.45 (0.33 to 0.56)	4.06	0.01
Left	0.62 (0.56 to 0.69)	0.59 (0.48 to 0.70)	0.58 (0.51 to 0.65)	0.40 (0.32 to 0.49)	4.80	0.005

Values are means (95 % CIs). AD=Alzheimer's disease.

frequency band was used. Our choice of alpha frequency band coherence was based on our previous work, in which we found the only significant changes in coherence measures in that frequency band in patients with Alzheimer's disease compared with the controls.[14] Furthermore, our study population was younger and only mildly to moderately demented according to the mean MMSE score.

However, when the Alzheimer's disease group in Leuchter's study was subcategorised according to the presence or absence of periventricular white matter hyperintensities, the first group had lower mean frontal and occipitoparietal coherence which approached values obtained in the group with multiinfarct dementia.

Interestingly, when our group of patients with Alzheimer's disease was subcategorised according to their APOE genotype, only patients homozygous for the ε4 allele were significantly different in post-rolandic coherence measures: right and left temporoparietal coherence, and left occipitoparietal coherence. There was a clear preference for left side changes in occipitoparietal coherence in our sample of patients with Alzheimer's disease homozygous for APOE ε4. This agrees with the findings of Leuchter *et al* that left sided periventricular white matter hyperintensities had a greater effect on left occipitoparietal and frontal coherence. This is in line with previously mentioned findings, as the APOE ε4 allele does not seem to be a risk factor uniquely associated with Alzheimer's disease, but may increase the risk for cerebrovascular disease as well.[33 34] The amyloid angiopathy which is often associated with Alzheimer's disease may be the neuropathological substrate for chronic ischaemic changes, myelin loss, and white matter hyperintensity on MRI.[35] Occurrence of white matter changes has been reported in senile

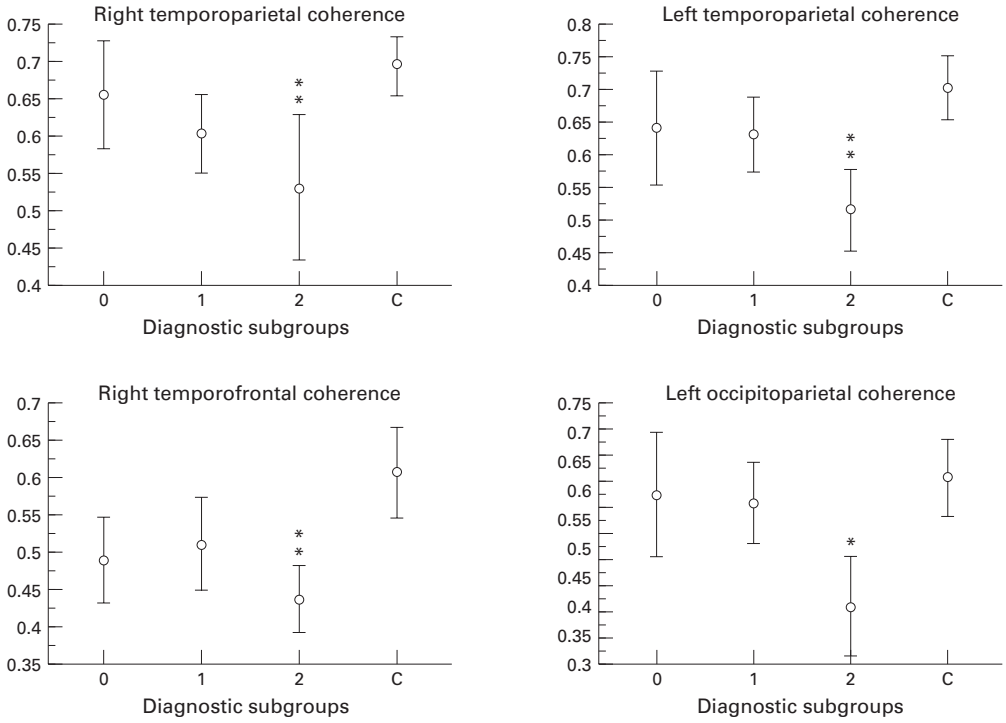

*Figure 2 Differences in the EEG coherence among the studied groups. 0= Alzheimer's disease group without ε4 allele; 1=group with one ε4 allele; 2= group with two ε4 alleles, C= controls. Circles indicate means, bars 95% confidence intervals. * P<0.01; ** P<0.005; ***P<0.001.*

onset Alzheimer's disease.[36] Although our study population is classified as presenile onset, the APOE ε4 isoform may accelerate the pathogenetic process which takes place in the white matter. It would be interesting to see whether decreases in electrical connectivity in patients homozygous for APOE ε4 follow or even precede these structural changes disclosed by MRI.

Alternatively, disconnection of functionally related cortical areas may occur at the cortical level, due to the death of pyramidal neurons that are the source as well as the target of long corticocortical projections.[37] Our finding of decreased right temporofrontal coherence may well fit in with this model. It is interesting to note that higher coherence values were found for the right temporofrontal coherence throughout the study population. This asymmetry might have functional relevance and make these networks more critical for the process of selective disconnection.

In our previous study we found that temporoparietal coherence taken together with alpha and theta power was a discriminant variable between patients with Alzheimer's disease and controls, but it lost discriminant power when patients with Alzheimer's disease were compared with subjects with mild cognitive impairment.[14] These findings indicated that decreased electrical connectivity might be an early change in the subclinical stage of the disease. It would be interesting to see whether the same electrophysiological pattern is present in groups of patients with mild cognitive impairment subcategorised according to their APOE genotype. Positive findings would provide further support for the hypothesis that APOE ε4 is a risk factor for Alzheimer's disease, and that it is associated with altered functional connectivity.

In conclusion, the present findings show that the APOE ε4 allele seems to be associated with selective decreases in functional connectivity in patients with Alzheimer's disease, as assessed by EEG coherence. Further investigation is required to determine whether this reflects the presence of subclinical vascular changes as coexisting aetiologic factors in the development of clinical symptoms of Alzheimer's disease.

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