Available online at www.sciencedirect.com
ScienceDirect
Biological Psychology 75 (2007) 229–238
BIOLOGICAL PSYCHOLOGY
www.elsevier.com/locate/biopsycho

The contribution of apolipoprotein E alleles on cognitive performance and dynamic neural activity over six decades

D.M. Alexander [a,b,c,*], L.M. Williams [d,e], J.M. Gatt [d,e], C. Dobson-Stone [f,g,h], S.A. Kuan [d], E.G. Todd [f], P.R. Schofield [f,g,h], N.J. Cooper [a], E. Gordon [a,d,e]

[a] *Brain Resource Company and Brain Resource International Database, PO Box 737, Broadway, NSW 2007, Australia*
[b] *Faculty of Information Technology, University of Technology Sydney, PO Box 123, Broadway, NSW 2007, Australia*
[c] *Laboratory for Perceptual Dynamics, RIKEN BSI, 2-1 Hirosawa, Wako-shi, Saitama 351-0198, Japan*
[d] *Brain Dynamics Centre, Westmead Millennium Institute and Western Clinical School, University of Sydney, Acacia House, Westmead Hospital, NSW 2145, Australia*
[e] *Psychological Medicine, Western Clinical School, University of Sydney, Westmead Hospital, New South Wales 2145, Australia*
[f] *Garvan Institute of Medical Research, 384 Victoria Street, Darlinghurst, NSW 2010, Australia*
[g] *Prince of Wales Medical Research Institute, Barker Street, Randwick 2031, Australia*
[h] *University of New South Wales, New South Wales 2052, Australia*

Received 18 October 2006; accepted 8 March 2007
Available online 16 March 2007

Abstract

Neuroimaging shows brain-functional differences due to apolipoprotein E (*APOE*) polymorphisms may exist decades before the increased risk period for Alzheimer's disease, but little is known about their effect on cognition and brain function in children and young adults. This study assessed 415 healthy ε2 and ε4 carriers and matched ε3/ε3 controls, spanning ages 6–65, on a range of cognitive tests. Subjects were also compared on a new dynamical measure of EEG activity during a visual working memory task using alphabetical stimuli. ε4 subjects had better verbal fluency compared to ε3, an effect that was strongest in 51–65 year-olds. No ε4 deficits in cognition were found. In 6–15 year-olds, there were differences in total spatio-temporal wave activity between ε3 and ε4 subjects in the theta band, approximately 200 ms post-stimulus. Differences in brain function in younger ε4 subjects and superior verbal fluency across the entire age range suggest that the *APOE* ε4 allele is an example of antagonistic pleiotropy.

Keywords: Apolipoprotein E; Development; Electro-encephalogram; Spatio-temporal waves; Cognition; Verbal fluency

1. Introduction

Little research has looked at the effects of apolipoprotein E (*APOE*) alleles on brain function and cognition at ages prior to the onset of increased risk for Alzheimer's diseases (AD). If differences in brain function for *APOE* ε4 in the pre-elderly are paralleled by a pattern of subtle cognitive deficits, this would suggest a direct link between differences in brain function in the pre-elderly and predisposition to AD after age 65. If, however, *APOE* ε4 does not confer subtle cognitive deficits in the pre-elderly, the specific differences in brain function in the pre-elderly may not be related to predisposition to AD, or only indirectly related via factors that arise during the period of increased risk (e.g. cumulative brain insult interacting with poorer brain repair mechanisms; level of post-retirement activity; or risk of cardiovascular disease).

A number of studies have shown that the ε4 allele of the *APOE* gene is associated with cognitive decline in the elderly (Helkala et al., 1995; Fillenbaum et al., 2001; Wilson et al., 2002; Den Heijer et al., 2002; Hofer et al., 2002) and confers a pre-disposition for Alzheimer's disease (Corder et al., 1993; Rebeck et al., 1994; Kuusisto et al., 1994; Smith et al., 1998). Not all studies have found agreement on the effects of *APOE* on cognitive decline in the non-demented elderly (Smith et al., 1998; Small et al., 2000; Cohen et al., 2001; Klages and Fisk, 2002; Winnock et al., 2002; Marquis et al., 2002; Kim et al., 2002; Pendleton et al., 2002), and several authors have suggested that studies finding cognitive decline in the general elderly population may be conflating these effects with onset of

* Corresponding author at: Laboratory for Perceptual Dynamics, RIKEN BSI, 2-1 Hirosawa, Wako-shi, Saitama 351-0198, Japan.
E-mail address: dalex@brain.riken.jp (D.M. Alexander).

0301-0511/$ – see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.biopsycho.2007.03.001

AD (Pendleton et al., 2002; Kim et al., 2002; cf. Hofer et al., 2002).

A number of studies have used electro-encephalogram (EEG) measures to study the effects of the *APOE* ε4 allele on brain function in normal aging, AD and mild cognitive impairment (MCI). The methods have included power spectra (Lehtovirta et al., 1996, 2000), event-related potentials (ERPs; Green and Levey, 1999; Wetter and Murphy, 2001; Reinvang et al., 2005) and coherence (Jelic et al., 1997). Only a few studies have assessed the effects of the *APOE* ε4 allele on brain function in healthy, young adults. PET and fMRI studies have shown that compared to non-ε4 carriers, *APOE* ε4 carriers have reduced activity in the posterior cingulate, parietotemporal and frontal cortex while in the resting state (Reiman et al., 2004, 2005); and elevated activations in the left middle temporal and right transverse temporal gyri, and reduced activations in the right superior temporal and left fusiform gyri during a non-verbal memory task (Scarmeas et al., 2005). These studies suggest that differences in brain function, related to *APOE* ε4, are present decades before the elevated risk for AD arises (Reiman et al., 2005; Scarmeas et al., 2005).

A few studies have looked at the effects of *APOE* alleles on cognition in children and young adults. While some studies demonstrated no effects (Deary et al., 2002; Turic et al., 2001; Kutner et al., 2000; Reiman et al., 2004; Scarmeas et al., 2005), others have found evidence of better cognitive performance in ε4 carriers (Yu et al., 2000; Puttonen et al., 2003; Hubacek et al., 2001; Wright et al., 2003; Oria et al., 2005). According to Wright et al. (2003), the *APOE* ε4 allele may be an example of antagonistic pleiotropy, having a net benefit during development despite being associated with disease in the elderly. There is some evidence that the ApoE ε4 isoform of the lipoprotein plays a neuroprotective role in development (Ohkubo et al., 2001; Zetterberg et al., 2002; Wright et al., 2003; Oria et al., 2005).

This study utilized subjects from Brain Resource International Database (Gordon, 2003; Gordon et al., 2005), whose performance was measured on a range of cognitive tests that tap major brain networks, including tests of reaction time, sensory-motor integrity, verbal memory, working memory, executive function and verbal fluency. This study also utilized a new measure of spatio-temporal wave activity in the EEG (Alexander et al., 2006c). This wave activity is the cortical equivalent to waves on a pond spreading from a dropped stone. Specifically, the measure detects episodes of smoothly propagating waves of electrical activity, detectable by the EEG array at the scalp. These waves arise in an event-related fashion, and over a range of frequencies. A number of studies have shown spatio-temporal wave activity in scalp EEG to be task/activity dependent, including working memory (Sauseng et al., 2002), listening to auditory tones (Ribary et al., 1991), resting states (Ito et al., 2005) and sleep (Massimini et al., 2004). EEG wave activity has been shown to be closely related to the pattern of event-related potential (ERP) amplitudes (Alexander et al., 2006b,d) and ERP latencies across the scalp (Alexander et al., 2006c).

Spatio-temporal wave measures have been shown to predict cognitive performance in elderly subjects with subjective memory complaints (Alexander et al., 2006a), and at the other end of the age spectrum, to differentiate children with attention deficit/hyperactivity disorder from controls (Alexander et al., 2006b) and show correlations of $r > 0.5$ with symptom factors in adolescents with first episode psychosis (Alexander et al., 2006d). In each of these studies, the measured effect sizes for spatio-temporal wave activity were at least as large as the effect sizes for either EEG power or ERP amplitudes. The *increased sensitivity* of the wave measure to group differences therefore makes the wave measure suitable to the study of differences in *APOE* alleles, whose effects on brain function in the pre-elderly are likely to be subtle. The present study also measured the global power of the EEG across the scalp to provide a direct comparison with the measures of global spatio-temporal wave activity in the EEG.

There is sufficient evidence that brain function differs from early adulthood in *APOE* ε4 subjects to expect brain function differences to be evident in younger subjects. The present research therefore attempted to reproduce findings of consistent differences between pre-elderly *APOE* ε3 and ε4 subjects using the global measures of EEG activity. The EEG data from a working memory task was chosen for analysis because this task requires active processing, storage of information and sustained attention; and working memory tasks have previously been shown to differentiate young adult ε4 carriers from ε3 subjects on measures of brain function (Scarmeas et al., 2005). On the basis of the limited literature on *APOE* alleles and cognition in children and young adults, we hypothesized that brain-functional *differences* due to *APOE* ε4 would not amount to cognitive *deficits* in the pre-elderly.

2. Methods

2.1. Participants

Brain imaging, neuropsychological and genetic data from 415 healthy Caucasian subjects were used in this study, ranging in age from 6 to 65 years (223 males, 192 females). The subjects participated in the standardized testing procedures of the Brain Resource International Database (BRID; Gordon, 2003; Gordon et al., 2005). All subjects gave written informed consent prior to participation, and local ethics committees for each participating laboratory approved all experimental procedures. Subjects were recruited from general metropolitan New York, Rhode Island, Nijmegen, Sydney and Adelaide. Subjects were required to refrain from caffeine, alcohol and smoking for at least 2 hours prior to testing. Subjects were screened via telephone interview using strict and standardized exclusion criteria: subjects participating in the study did not report an existing neurological disorder; physical brain injury; trauma-induced unconsciousness within the last 5 years; severe impediment to vision, hearing, or hand movement; personal history of addiction to drugs; diagnosis of any psychological disorder; or any other serious medical disorder.

2.2. Genetics acquisition

APOE genotyping was performed on 508 subjects of European ancestry. DNA was extracted from cheek swab samples by a standard proteinase digestion and chloroform extraction procedure. PCR amplification of participant DNA was undertaken using primers 5′-TCCAAGGAGCTGCAGGCGGCGCA-3′ and 5′-ACAGAATTCGCCCCGGCCTGGTACACTGCCA-3′ in a standard reaction containing 2.5 mM $MgCl_2$ and 10% dimethyl sulphoxide. Amplified fragments were digested with the restriction enzyme *Hpa*II and digests were separated on 4% agarose gels. Genotypes were scored twice independently by two researchers. The ε2/ε3/ε4 polymorphism is composed of two C/T single-

Table 1
Detailed breakdown of subject numbers

	Age group				Total
	6–15 years	16–30 years	31–50 years	51–65 years	
APOE group					
ε2	15	13	12	9	49
ε3 (matched to ε2)	28	28	27	13	96
ε4	32	26	20	13	91
ε3 (matched to ε4)	66	50	42	21	179
Total	141	117	101	56	415

Detail breakdown of subjects in this study, by age and *APOE* group. For the cognitive analysis, all 415 subjects were used in a single ANCOVA. For the analysis of EEG measures, ε4 subjects were compared directly to their age and gender matched, ε3, control groups.

nucleotide polymorphisms, rs429358 and rs7412: ε2 = rs429358 T and rs7412 T; ε3 = rs429358 T and rs7412 C; ε4 = rs429358 C and rs7412 C. Genotype frequencies for rs429358 were not statistically in Hardy–Weinberg equilibrium (TT, 401/508 = 78.9%; TC, 94/508 = 18.5%; CC, 13/508 = 2.6%; $\chi^2 = 6.34$, d.f. = 2, $p = 0.042$). Every care was taken to ensure accuracy of genotyping and we interpret this deviation from Hardy–Weinberg equilibrium as a chance finding. Genotype frequencies for rs7412 were in Hardy–Weinberg equilibrium (TT, 2/508 = 0.4%; TC, 66/508 = 13.0%; CC, 440/508 = 86.6%; $\chi^2 = 0.081$, d.f. = 2, $p = 0.960$). An additional test was carried out to ensure that allelic frequencies did not differ by country of testing ($\chi^2 = 0.882$, d.f. = 4, $p = 0.927$).

2.3. Subject selection

Of the subjects genotyped for *APOE* status, 415 were used to form three *APOE* status groups: ε2 ($n = 49$, comprising 2 ε2/ε2 and 47 ε2/ε3 subjects), ε4 (n = 91, comprising 13 ε4/ε4 and 78 ε3/ε4 subjects), and ε3 ($n = 275$ ε3/ε3 controls, age and gender matched to the ε2 and ε4 groups). There were 14 subjects with ε2/ε4 genotype that were not examined in this study. For the purposes of statistical analysis of *APOE* status by age interactions, the 415 subjects were divided into four age-bands: 6–15, 16–30, 31–50, and 51–65 years. A detailed breakdown of subject numbers by *APOE* group and age group is given in Table 1.

2.4. Cognitive tasks

Subjects were seated in a sound and light attenuated room, controlled at an ambient temperature of 22 °C behind a touch screen monitor, and were assessed on a profile of cognitive (neuropsychological) domains. A complete description of the test battery can be found elsewhere (Gordon et al., 2005). This battery of tests has good test–retest reliability (Williams et al., 2005), validity (Paul et al., 2005) and established norms (Clark et al., 2006) and a lack of cross-cultural differences (Paul et al., 2007). A brief description of the tests that showed significant results in this study is provided below.

Visual working memory. This task consisted of a series of letters (B, C, D or G) presented to the subject on the screen (for 200 ms), separated by an interval of 2.5 s. If the same letter appeared twice in a row, the subject was asked to press buttons with the index finger of each hand. Speed and accuracy of response were equally stressed in the task instructions. There were 125 stimuli presented in total, 85 being non-target letters and 20 being target letters (i.e., repetitions of the previous letter). The task was designed to assess working memory and attention processes. For this task, the non-target trials were analysed using EEG measures. During non-target trials, the subject is required to actively update and store their memory representation.

Word generation. This first part of this test involved the participant naming as many words as possible, in the space of a minute, which begin with a certain letter (F, A and then S). Participants were instructed not to use proper nouns, nor to make variations on the same word stem (for example, 'run' and 'running'). The score on this part of the test was the average number of words produced per letter. The FAS task measures phonetic fluency. In the second part of this test, the subjects were asked to name as many animals as possible in 1 min. The animal naming task measures semantic fluency.

Executive maze task. The subject was presented with a grid (8 × 8 matrix) of circles on the computer screen. The object of the task was to find the hidden path through the grid, from the beginning point at the bottom of the grid to the end point at the top. The subject was able to navigate around the grid by pressing arrow keys. The subject was presented with one tone (and a red cross at the bottom of the screen) if he/she made an incorrect move, and a different tone (and a green tick at the bottom of the screen) if he/she made a correct move. Each time the subject did the task, the maze was the same. The purpose of the task was therefore to assess how quickly the subject learns the route through the maze and his/her ability to remember that route.

2.5. Electroencephalographic data acquisition

Participants were seated in a sound and light attenuated room, controlled at an ambient temperature of 22 °C. EEG data were acquired from 26 channels: Fp1, Fp2, F7, F3, Fz, F4, F8, FC3, FCz, FC4, T3, C3, Cz, C4, T4, CP3, CPz, CP4, T5, P3, Pz, P4, T6, O1, Oz and O2, according to the 10–20 electrode international system, using a QuikCap with Ag/AgCl sintered electrodes and QuikGel (NuAmps, Compumedics, Abbotsford, Vic., Australia). Data were referenced to a virtual ground and re-referenced to linked mastoids offline. Horizontal eye-movements were recorded with electrodes placed 1.5 cm lateral to the outer canthus of each eye. Vertical eye movements were recorded with electrodes placed 3 mm above the middle of the left eyebrow and 1.5 cm below the middle of the left bottom eye-lid. Skin resistance was <5 and >1 kΩ for all electrodes. A continuous acquisition system was employed, with a sampling rate of 500 Hz. A low pass filter with an attenuation of 40 dB per decade above 100 Hz was employed prior to digitization. EEG data were visually screened by a technician (blind to group membership) during acquisition for artefacts and changes in subject alertness. EEG data were EOG corrected offline (Gratton et al., 1983).

2.6. Phase gradient measures and global power

The EEG data from the visual working memory task (non-target trials) were analysed using measures of spatio-temporal waves and global power. In previous studies, spatio-temporal waves measured at the scalp had *long spatial-wavelength* and showed smooth changes in phase across the scalp – *smooth phase gradients* – at each time sample (Ribary et al., 1991; Sauseng et al., 2002; Massimini et al., 2004; Ito et al., 2005). These properties were explored in detail in Alexander et al. (2006c). Comparisons to surrogate data showed that during episodes of spatio-temporal waves measurable at the scalp, the waves have long spatial wavelength compared with the size of the scalp. Across multiple electrodes, the phase values at a given time sample and frequency could therefore be assigned an unambiguous spatio-temporal ordering – the relative phases – from the phase-leading site to the most phase-lagged site. The presence of a smooth phase gradient in the pattern of relative phases was shown to coincide with the presence of spatio-temporal waves (Alexander et al., 2006c). The measure of spatio-temporal waves in the present study makes use of these properties of long spatial wavelength and smooth phase gradients to detect the waves.

The method for measuring long wavelength activity, via phase gradients, is discussed in detail elsewhere (Alexander et al., 2006c). In brief, the phases at each electrode site were estimated using two-cycle Morlet wavelets. The phases were estimated for 30 logarithmically spaced frequency bands between 0.2 and 32 Hz and at 10 ms intervals between −200 and 800 ms within each trial, where zero is the time of stimulus onset. For each time sample and at each frequency, the phases at each electrode were converted into relative phases by referencing the phases relative to the phase-leading electrode.

The spatial patterns of relative phases were assessed using three phase gradient basis functions. These basis functions are smoothly changing gradients across the scalp. The three basis functions consist of an anterior–posterior basis function, a peripheral–central basis function and a right–left basis function (see Alexander et al., 2006c, Fig. 2). Linear combinations of these phase gradient

basis functions enable a wide range of smoothly changing patterns of phase gradient to be characterized, each having the property of having only one minimum or only one maximum. The amount of variance explained in the pattern of relative phases across the scalp by the phase gradient basis functions is given by

$$\sigma^2_{M\Psi} = \rho(M\Psi, \Psi)^2$$

where $M\Psi$ is the linear combination of basis functions that gives the best fit, Ψ the pattern of relative phases across the scalp, ρ the correlation function, and $\sigma^2_{M\Psi}$ is the amount of variance explained (Alexander et al., 2006c). The expression for $M\Psi$ is

$$M\Psi = \rho(B_{AP}, \Psi)^2 B_{AP} + \rho(B_{PC}, \Psi)^2 B_{PC} + \rho(B_{RL}, \Psi)^2 B_{RL}$$

where B_{AP}, B_{PC}, and B_{RL} are the basis functions described earlier.

The measure $\sigma^2_{M\Psi}$ can be taken as the amount of spatio-temporal wave activity conforming to the properties described in the previous paragraphs, hereafter termed *wave activity. Global power* in the EEG was measured at the same frequencies and times as the long wavelength measure of EEG. The power at each electrode was computed using the same Morlet wavelets, and the logarithm of this value averaged over electrodes to produce the mean log power over the scalp at each time and frequency (Alexander et al., 2006c). Further details of the calculation of wave measures can be found in the methodological paper Alexander et al. (2006c), including the method for calculating phase and power at arbitrary times and frequencies and the method for calculating relative phases. This latter paper also deals explicitly with a number of other methodological issues including the effects of volume conduction, choice of number of cycles in the Morlet wavelet and the relationship of the wave measures to power measures.

2.7. Statistical analysis of cognitive and EEG variables

All cognitive variables were analysed using the Statistical Package for Social Sciences (SPSS v.14) ANCOVA procedure. For the analysis of cognition, all 415 subjects were compared within a single ANCOVA. A goal of the study was to assess the impact of *APOE* alleles on cognition. Therefore, the only main effect term included in the model was *APOE* status. Where main effects for *APOE* status were observed, planned contrasts were used to indicate which groups differed from each other. For the cognitive variables, we assessed the interactions of *APOE* alleles with age and the interactions of *APOE* alleles with gender. Due to the finding that *APOE* status can influence educational achievement (Hubacek et al., 2001), all statistical analyses involving cognitive variables covaried for years of education. Age was also controlled for to reduce associated error variance, and due to known nonlinear effects of age on a number of the cognitive variables, a nonlinear age term (age^2) was also used as a covariate. Since use of control variables may produce spurious results, a conservative approach was taken in the reporting of cognitive differences. The main ANCOVA procedure was repeated with no covariates. *APOE* main effects and interactions were only included in the results if they also were significant in this secondary ANOVA. Planned contrasts on the effects of *APOE* within particular age groups did not use covariates. Additional testing was undertaken to ensure that there were no effects for country of origin. Separate ANCOVAs were carried out using country as a covariate, and to test for *APOE* by country interactions on the cognitive variables.

Another goal of the present study was to confirm previous findings of differences in brain function for *APOE* variants. The focus of this analysis was on differences that persist over a broad range of ages. Brain function was measured using global measures of EEG activity, which provide a matrix of time by frequency data-points. To simplify interpretation of these analyses, the ε4 group was only compared directly to its specific age and gender matched, ε3, control group; the ε2 group was only compared directly to its specific age and gender matched, ε3, control group (see Table 1). The differences between the *APOE* groups (ε2 versus ε3 or ε4 versus ε3) on the EEG measures were explored using one-way ANCOVA tests for each time and frequency point sampled, controlling for age. This entails a large number of statistical tests (one for each of the 3000 time/frequency points for both of the EEG variables). To avoid type I errors, the multiple ANCOVA results were only included as being statistically significant if they were significant at the $p < 0.05$ level, over 20 contiguous time and/or frequency points (Alexander et al., 2006a). The same analyses were carried out using multiple *t*-tests, that is, without controlling for age. Planned contrasts on the effects of *APOE* within particular age groups also did not use covariates.

To verify those results that passed the criterion of 20 contiguous time/frequency points significant at the $p < 0.05$ level, an additional testing procedure was carried out, similar to the Statistical Parametric Mapping procedure used in fMRI studies. Subjects' group labels were randomly re-assigned, while preserving group sizes. For each analysis, 1000 random re-assignments of subjects' group labels were carried out; the number and size of contiguous significant regions were collated at the frequency band of interest (4–8 Hz in the present results). A significant region of a given size (for example, 67 contiguous points) was required to occur with a probability of $p < 0.05$ in order to be included as significant in the results.

3. Results

The mean ages (S.D.) for the different groupings were [ε2] = 30.5 (17.6), [ε3] = 27.7 (16.2), [ε4] = 27.4 (16.3), [6–15] = 11.7 (2.7), [16–30] = 22.9 (4.5), [31–50] = 40.5 (6.1), [51–65] = 56.7 (3.9), [female] = 29.9 (17.0), and [male] = 26.2 (15.6). A frequency histogram of subject age is given in Fig. 1, showing an even sampling of ages except for older children/younger adolescents, who were slightly over-represented in this sample. ANOVA for age and years of education demonstrated no significant main effects or interaction effects of either *APOE* group or gender on these variables.

3.1. Cognitive variables

Significant main effects of *APOE* status were found on tests involving phonetic fluency and semantic fluency (the FAS and animal naming tasks; see Table 2). Planned contrasts revealed that this was due to ε4 subjects demonstrating superior performance compared to ε3 subjects ($p = 0.002$ for phonetic fluency; $p = 0.009$ for semantic fluency). When analysed by separate age groups, only the 51–65 year-olds demonstrated a statistically significant effect ($p = 0.015$ for phonetic fluency; $p = 0.023$ for semantic fluency). Fig. 2 shows the estimated marginal means of the verbal fluency tasks, organized by *APOE* status and age-band. These graphs show that the ε4 group scored consistently higher on the verbal fluency tasks than the ε3 group, in *all* age-bands. These results are interpreted as superior phonetic and semantic fluency in ε3 versus ε4 groups across the lifespan, although the effect was clearly strongest in the 51–65 year-olds. By contrast, the ε2 group did not show a

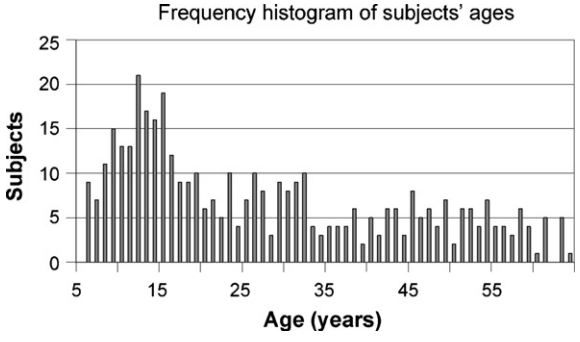

Fig. 1. The number of subjects as a function of age.

Table 2
Cognitive variables used in the study, *APOE* group estimated marginal means, standard errors and significant *APOE* status results

Dependent variable	Mean (S.E.)			Source	d.f.	F	p	η_p^2
	ε2	ε3	ε4					
Digit span forward: total score	6.54 (0.43)	6.79 (0.27)	6.59 (0.33)					
Digit span reverse: total score	4.21 (0.35)	4.57 (0.22)	4.53 (0.27)					
Verbal interference (stroop)	12.52 (0.68)	11.49 (0.42)	11.80 (0.52)					
Word generation: average number of words for the letters F, A and S	14.00 (0.70)	13.56 (0.44)	15.29 (0.54)	*APOE*	2	5.67	0.004	4.0%
Word generation: number of animal names	23.54 (1.22)	22.28 (0.76)	24.71 (0.94)	*APOE*	2	3.57	0.029	2.6%
Verbal memory: total number of words recalled in presentations 1–4	31.03 (1.11)	32.08 (0.69)	33.12 (0.86)					
Verbal memory: number of words recalled from original list after delay	7.50 (0.44)	7.66 (0.28)	8.10 (0.34)					
Working memory: average reaction time	520.74 (21.70)	518.42 (13.57)	521.45 (16.77)					
Working memory: total number of errors	2.97 (0.66)	3.19 (0.41)	2.80 (0.51)					
Choice reaction time: average reaction time	805.8 (73.4)	761.0 (45.9)	772.8 (56.7)					
Executive maze: time to complete maze without error	217,289 (16,697)	224,940 (10,438)	199,539 (12,907)					
Executive maze: number of trials to complete maze without error	9.70 (0.77)	8.90 (0.48)	8.50 (0.60)	*APOE* × age	6	2.67	0.016	5.6%
Executive maze: total number of errors	41.96 (5.09)	44.85 (3.18)	35.59 (3.94)					
Switching of attention test: time to complete alphanumeric sequence	50,723 (3,486)	54,533 (2,179)	49,800 (2,694)					

List of all cognitive measures used in this study; *APOE* group estimated marginal means and standard errors (controlling for effects of age and years of education) and significant results. The measures are part of the standard testing procedure of the Brain Resource International Database, and details on the tasks and measures can be found elsewhere (Gordon et al., 2005; Paul et al., 2005). There were significant main effects for phonetic fluency (FAS score) and semantic fluency (animal naming). On these tasks the *APOE* ε4 groups performed better than the *APOE* ε3 groups in all age-bands. Statistical significance level is indicated by the p value, and effect size by η_p^2 (partial eta-squared). See Table 1 for a detailed breakdown of the 415 subjects used in this analysis. All scores which are expressed as times are given in seconds.

consistent relationship to the ε3 group for the verbal fluency tasks in different age-bands.

There were significant interactions between *APOE* status and age group for the number of trials completed in the maze task ($p = 0.016$). Fig. 2 also indicates that the largest mean difference for the number of maze trials completed was for 51–65 year-olds, in which ε2 subjects took more trials to successfully complete the maze task compared to ε3 or ε4 subjects. Planned contrasts revealed that both the ε3 and ε4 groups performed better than the ε2 group in this 51–65 age range ($p = 0.035$ and $p = 0.013$, respectively). There was an additional difference between the ε3 and ε4 groups in the 16–30 age range ($p = 0.022$), in which the ε3 subjects showed superior performance. The ANCOVA results revealed no *APOE* status main effects or *APOE* status by age group interactions for the remaining cognitive variables, including working memory, verbal memory, and reaction time measures.[1] Controlling for country of testing did not alter any of the substantive results, nor were there any *APOE* by country interactions for any of the cognitive variables. An additional analysis of cognitive variables using ANOVA (that is, without covariates such as age and years of education) produced the same outcomes for cognitive variables as the results reported here.

[1] There was also a significant interaction between *APOE* status and age group for total time to complete the maze task. However, this variable had a skewed distribution, which when corrected via a logarithmic transform, caused the significant interaction to become non-significant. This result is therefore not included in the main table of results.

3.2. EEG variables

Grand-average time by frequency plots for global measures of EEG activity are shown in Fig. 3. There were significant differences for the ε4 subjects and their matched ε3 controls on the wave activity measure ($\sigma^2_{M\Psi}$), when age was used as a covariate. The region of significant difference was centred on 200 ms, 4.8 Hz, indicated in Fig. 3A, middle panel. However, when age was not used as a covariate, this result failed to meet the criteria of 20 contiguous time/frequency points at $p < 0.05$. Planned contrasts of wave activity results indicated that the youngest age grouping (6–15 year-olds) made the predominant contribution to the observed difference in lower theta band wave activity in ε4 subjects. This is illustrated in Fig. 3A, right panel. When analysed separately, the 6–15 year-old group showed significant differences in this region, passing all the criteria for significance set in out in Section 2. This is illustrated in Fig. 3B. The region of significant difference overlapped with the peak in theta wave activity in *APOE* ε3 controls (middle panel), which was diminished in the *APOE* ε4 group in these younger subjects (left panel).

There were no significant differences between the ε2 subjects and their matched ε3 control group on either of the global EEG measures. For the ε4 subjects and their matched ε3 control group, there were no significant differences for the EEG measure of global power. Controlling for country of testing did not alter the results on EEG measures, nor were there any *APOE* by country interactions for these variables.

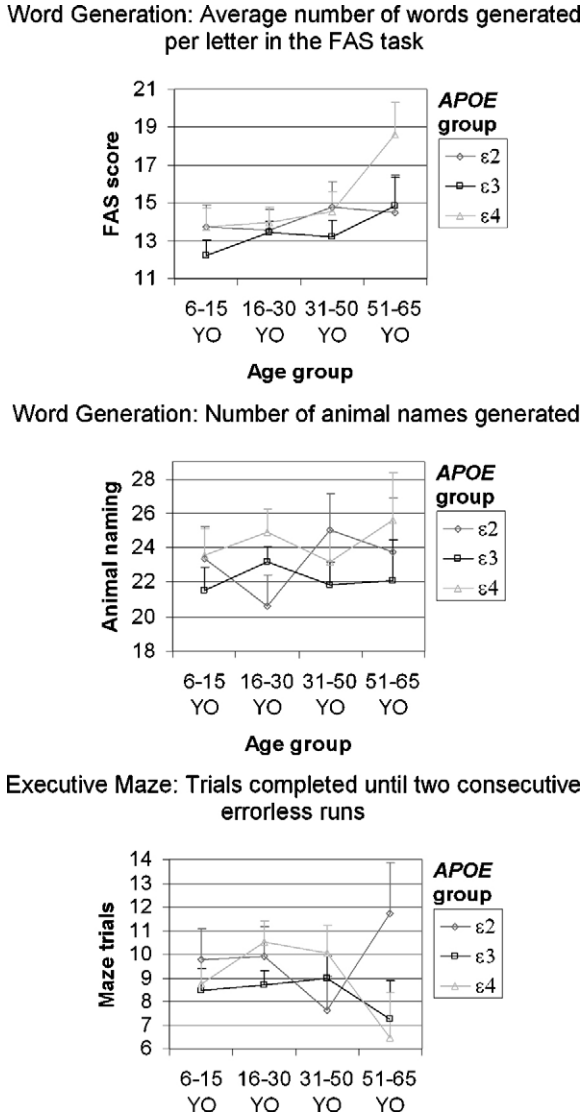

Fig. 2. Estimated marginal means for cognitive tests that showed significant ANCOVA results involving *APOE* status, controlling for age and years of education. For each mean, the standard error of the estimate is shown as an error bar. For FAS score and animal naming, there were significant main effects for *APOE* status. Planned contrasts revealed that this was due to better performance in the ε4 compared to the ε3 group ($p = 0.002$ for phonetic fluency; $p = 0.009$ for semantic fluency), and the graphs indicate clear differences between ε3 and ε4 subjects in all age groups. The graph for number of maze trials completed shows that the significant age × *APOE* interaction was mainly due to a larger number of maze trials attempted in ε2 subjects in the age-band 51–65 years compared to ε3 and ε4 subjects.

4. Discussion

There are two central findings in the present research. This is the first study to show systematic brain-functional differences for *APOE* alleles in children and adolescents using the EEG. Similarly, this is the first study to show that for a wide age-range, *APOE* ε4 confers a small benefit to semantic and phonetic fluency and is neutral in its effects on other cognitive tests. Taking the two central findings together, the results of the study suggest that while there may be brain-functional differences between ε4 and ε3 subjects, these differences cannot necessarily be equated with *deficits* in the non-elderly populations (cf. Reiman et al., 2004).

The first finding is that global measures of EEG activity, designed to detect the presence of long spatial wavelength travelling waves, are able to distinguish ε4 subjects from ε3 subjects. The difference is only apparent in the age group 6–15 years in the present study. These findings in relation to dynamical EEG activity support previous findings showing differences between ε4 and ε3 subjects in either young or mature adults (Reiman et al., 2004, 2005; Scarmeas et al., 2005).

The second finding is that for phonetic fluency (FAS task) and semantic fluency (animal naming), ε4 subjects performed better than ε3 subjects across all age-bands studied, although the effect sizes were small. The battery of cognitive tests revealed no other differences in cognitive performance between *APOE* groups, across a broad range of measures. The large subject numbers in the present study, and consequent gains in statistical power, enable confidence in the findings of no cognitive differences for most tests. Similarly, the findings in relation to a small advantage for verbal fluency can also be taken with confidence. The wide range of tests employed in this study also enables a degree of confidence in the finding of no cognitive disadvantages for pre-elderly *APOE* ε4 carriers.

Previous cognitive findings in relation to elderly are in contrast with the findings of the effects of *APOE* ε4 on children and young adults. The results for the elderly are not entirely consistent, but the overall trend is that *APOE* ε4 has a negative impact on cognition in old-age, possibly independently of conversion to AD (Helkala et al., 1995; Fillenbaum et al., 2001; Wilson et al., 2002; Den Heijer et al., 2002; Hofer et al., 2002; Smith et al., 1998; Small et al., 2000; Cohen et al., 2001; Klages and Fisk, 2002; Winnock et al., 2002; Marquis et al., 2002). The previous findings for children and young adults are also not entirely consistent, but the overall trend is that *APOE* ε4 has a small but positive influence on cognition.

In 2 year-olds, ε4 carriers had significantly higher scores on the Mental Development Index of the Bayley Scale than those without ε4 alleles (Wright et al., 2003). This study also found that ε4+ status conferred a protective effect on children with high lead exposure. An analogous finding is that the *APOE* ε4 allele had a protective effect on visual working memory and semantic fluency[2] (measured at age 10) in Brazilian shanty-town children with a large number of diarrhoea episodes in the first two years of life (Oria et al., 2005). However, two other studies have found no effects for the *APOE* ε4 allele in children, on reasoning skills at age 11 (Deary et al., 2002), and on IQ scores at 6–15 years of age (Turic et al., 2001). In young adults, several studies with small subject sets (17–26 subjects) have found no effect of the *APOE* ε4 allele on neuropsychological test scores (Kutner et al., 2000; Reiman et al., 2004; Scarmeas et al., 2005), whereas two other studies using larger subject sets (57 and 134) have found that the *APOE* ε4 allele was associated with higher IQ scores (Yu et al., 2000) and better mental

[2] Animal and food naming.

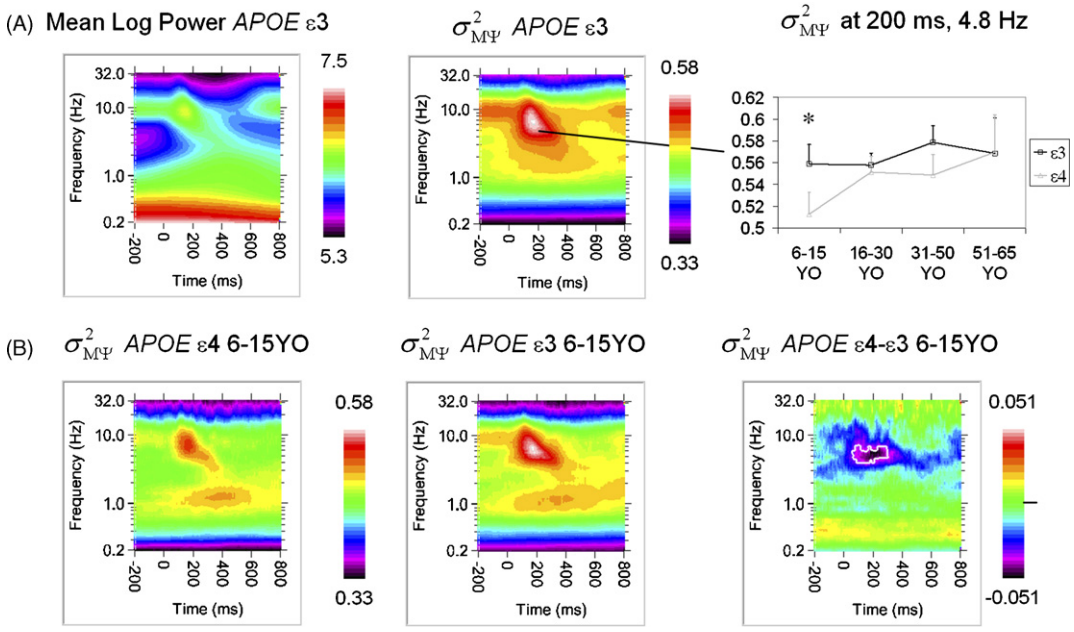

Fig. 3. Results for the global measures of EEG activity. For each of the colour plots, the scale of values is shown next to the plot. For the line graph, the conventions are the same as Fig. 2; that is, the horizontal axis shows the age group and the vertical axis shows the values of the relevant variable (wave activity in this case). (A) Left: grand-average time by frequency plot, for the ε3 subjects, of global power (mean log power). There were no significant differences between any of the *APOE* groups on this variable. Middle: grand-average time by frequency plot, for the ε3 subjects, of the wave activity measure, $\sigma^2_{M\Psi}$. The region in the vicinity of the line terminus at ∼4.8 Hz, 200 ms was significantly different for the ε3 vs. ε4 group, when age was used as a covariate. However, when age was not controlled for, this difference did not fulfil the criterion of 20 contiguous time/frequency points at $p < 0.05$. Right: the wave activity values for each age group at 4.8 Hz, 200 ms, indicating the largest differences were for the 6–15 year-old age group. The asterisk indicates that only the 6–15 year-olds differed significantly at this particular time/frequency point, when the age groups were analysed separately. (B) Left: grand-average time by frequency plot of the wave activity measure, $\sigma^2_{M\Psi}$, for 6–15 year-old ε4 subjects during the working memory task, non-target trials. The plot shows a peak in mean wave activity at approximately 170 ms, 8 Hz. Middle: grand-average time by frequency plot of the wave activity measure, $\sigma^2_{M\Psi}$, for 6–15 year-old ε4 subjects during the Working Memory task, non-target trials. The plot shows a peak in mean wave activity at approximately 170 ms, 6.7 Hz. Right: multiple *t*-test comparisons revealed that there was a significant difference between 6–15 year-old ε4 subjects and their matched ε3 controls at ∼200 ms in the theta band for wave activity. The significant region is indicated by the thin white boundary, and encompasses the frequency range of 4–6.7 Hz. The minimum *p*-value within this region was $p = 0.012$.

arithmetic performance (Puttonen et al., 2003). Another study sampled 1% of the population (366 subjects) in a district of the Czech Republic, in a cohort for whom education was practically equally accessible to all socio-economic groups (Hubacek et al., 2001). Carriers of the *APOE* ε4 allele were significantly more likely to have attained higher education than other allelic groupings. Two studies of healthy middle-aged subjects found negligible differences between ε4+ and ε3 subjects (Helkala et al., 2001; Sager et al., 2005).

Integration of previous findings in various age-bands is problematic due to the limited number of cognitive measures used in some studies, and the variety of measures across studies. Further, the employment of small sample sizes may have reduced the power in detecting genuine effects in some of the previous studies. However, taken together with the results of the present study, the studies on *APOE* ε4 and cognition show there is an age-dependent relationship that differs at either end of the age spectrum (Puttonen et al., 2003). According to Wright et al. (2003), the *APOE* ε4 allele is an example of antagonistic pleiotropy. This means that despite its association with a terminal illness in the elderly population, the net benefit during neurodevelopment keeps the ε4 variant common in the population.

While the potential mechanisms by which *APOE* ε4 increases risk to AD are well explored, its action during neurodevelopment has become a matter of increasing scientific interest (Cooper and Howell, 1999; Bothwell and Giniger, 2000; Herz and Beffert, 2000; Beffert et al., 2004). The protein ApoE is unique among lipoproteins in its involvement in the recovery response of injured nerve tissue (Poirier and Sevigny, 1998). After binding with cholesterol, ApoE is taken up by ApoE receptors and incorporated into cell membrane structures and myelin (Yankner, 1996; Teter et al., 1999). Cholesterol metabolism plays a major role during neurodevelopment in neurite outgrowth and synaptogenesis (Beffert et al., 1998; Dietschy and Turley, 2001; Mauch et al., 2001) and the ApoE ε4 isoform is associated with higher levels of serum cholesterol during early development (Herrmann et al., 1994; Tammi et al., 2000) and binds to cholesterol with equal or greater affinity than ε3 (Weisgraber et al., 1982). While the ApoE ε4 isoform has been associated with less efficient repair of neurons and synapses and a reduction in the outgrowth of neurons (Mahley, 1988; Strittmatter et al., 1994; Nathan et al., 1994; Pitas et al., 1998; Jordan et al., 1998; Tolar et al., 1999), the ApoE ε4 isoform (but not ε3) activates a cascade involving the cell protective gene *Bcl*-2 (Ohkubo et al., 2001). Significantly higher rates of embryonic spontaneous abortion have been found for *APOE* ε3 compared to *APOE* ε4, suggesting a neuroprotective role in very early development (Zetterberg et al., 2002).

Two features of the subject population are worth underlining: the exclusion criteria of physical brain injury and the subjects' age distribution. *APOE* ε4 has been implicated in deficient brain repair mechanisms (Friedman et al., 1999; Kutner et al., 2000; Crawford et al., 2002). It is unlikely, however, that the brain injury exclusion criterion would influence the prevalence, in the sample, of the small, cumulative-type brain insults derived from activities such as contact sports. The other feature of the subject population worthy of note is the prevalence of older children and young adolescents (see Fig. 1). In previous studies, positive effects on cognition for the ε4 allele have been found in subject populations for either children or young adults (Wright et al., 2003; Oria et al., 2005; Yu et al., 2000; Puttonen et al., 2003; Hubacek et al., 2001). In this study, however, the positive effects of the ε4 allele on semantic and phonetic fluency were consistent across all age-bands studied (see Fig. 2), and there were no significant age by *APOE* status interactions for verbal fluency measures. It therefore seems unlikely that the present positive results for verbal fluency are due to the specific age profile of the subject population.

Studies of brain function in relation to *APOE* ε4 have been few and largely confined to elderly populations with AD or MCI (Lehtovirta et al., 1996, 2000; Jelic et al., 1997; Green and Levey, 1999; Wetter and Murphy, 2001; Reinvang et al., 2005). This study has shown brain-functional differences related to *APOE* status in children and adolescents. The results support previous findings of consistent brain-functional differences between *APOE* ε4 and ε3 subjects, for both young and mature adults (Reiman et al., 2005; Scarmeas et al., 2005). In this study, the measure of brain function that differentiated the groups detected spatio-temporal waves in the EEG. Potential mechanisms underlying long wavelength activity in the EEG are discussed in Alexander et al. (2006c).

The observed differences between ε3 and ε4 subjects in wave activity were confined to the theta band in the working memory task, and therefore likely involve differences in memory-related processes. Theta band activity is considered to be critically involved in cortical memory function and hippocampal function (Buzsaki et al., 1994; Nelson, 1995; Sauseng et al., 2002). For example, high post-stimulus theta power is associated with better performance on a working memory task (Klimesch, 1999; Klimesch et al., 2004). In this study, however, the wave activity difference occurred in the absence of differences in global EEG power. This suggests wave measures of EEG activity were more sensitive to genetic differences than was global EEG power, in the absence of performance differences on the working memory task.

In the present results, the timing of the group difference in wave activity, at ∼200 ms and approximately coincident with the N2 ERP, suggests the increased wave activity in ε3 subjects may be related to response selection (Snyder and Hillyard, 1976; Pritchard et al., 1986) rather than working memory storage. This finding is similar to the Klimesch et al. (2004) finding that phase-locking in the alpha and theta bands is related to N1/P2 amplitude and working memory performance. However, the present result involves a pattern of *global* phase organization coincident with the N2 ERP, and arises in the *absence* of performance differences on the working memory task. Therefore, the exact significance of this finding, in terms ERP components, remains unclear.

Brain-functional differences were only found in the youngest age group in this study, 6–15 year-olds. By contrast, the group differences in relation to verbal fluency were largest in the oldest age group, 51–65 year-olds. This latter finding has relevance to previous studies showing increased left parietal and decreased inferotemporal activation during a letter fluency task, in a population of subjects at risk for AD with average age in the early 50's (Smith et al., 1999, 2002). These findings were interpreted by the authors as indicative of subclinical neuropathology. The present finding of improved verbal fluency in ε4 subjects aged 51–65 suggests that interpretations of subclinical neuropathology, in the absence of even subtle deficits on the relevant task, may not always be warranted.

It is a plausible working hypothesis that brain-functional differences apparent during early adulthood in *APOE* ε4 subjects are directly related to the brain-functional differences giving rise to predisposition to AD (Smith et al., 1999; Reiman et al., 2005; Scarmeas et al., 2005). On the evidence available, however, a simple and direct relationship between brain function characteristics associated with the *APOE* ε4 allele in the pre-elderly, and cognitive decline in the elderly, still appears an open question. If, indeed, the *APOE* ε4 allele is an example of antagonistic pleiotropy, then brain-functional differences seen in the pre-elderly may be due, in part, to the *benefits* of *APOE* ε4 during neurodevelopment (Zetterberg et al., 2002; Wright et al., 2003; Oria et al., 2005). This latter hypothesis helps explain the high prevalence in the population (∼25%) of the ε4 allele.

Acknowledgements

JMG and SAK are supported by an ARC-linkage grant (LP0455104) held by LMW and PRS (LP0455104). LMW holds a Pfizer Senior Research Fellowship. CDS is supported by a European Molecular Biology Organisation post-doctoral fellowship (ALTF 166-2004). PRS holds an NHMRC Senior Principal Research Fellowship (no. 157209). We thank the Brain Resource International Database (under the auspices of BRAINnet, scientific division of the Brain Resource Company) for use of subject data. We thank the participants who gave their time to this study.

References

Alexander, D.M., Arns, M.W., Paul, R.H., Rowe, D.L., Cooper, N., Esser, A.H., Fallahpour, K., Stephan, B.C., Heesen, E., Breteler, R., Williams, L.M., Gordon, E., 2006a. EEG markers for cognitive decline in elderly subjects with subjective memory complaints. Journal of Integrative Neuroscience 5, 49–74.

Alexander, D.M., Trengove, C., Clark, C.R., Clark, S., Kohn, M.R., Williams, L.M., Gordon, E., 2006b. Apparent travelling waves in scalp EEG reveal a decrease in slow-wave activity for ADHD across several experimental paradigms. Clinical EEG and Neuroscience 37 (2), 144–145.

Alexander, D.M., Trengove, C., Wright, J.J., Boord, P.R., Gordon, E., 2006c. Measurement of phase gradients in the EEG. Journal of Neuroscience Methods 156, 111–128.

Alexander, D.M., Flynn, G., Williams, L.M., Boord, P., Gordon, E., 2006d. First Episode Psychosis and direction of wave propagation at 1 Hz in the EEG. Proceedings of the Australian Society for Psychiatric Research Annual Meeting, Sydney, December 6–8, Acta Neuropsychiatrica 18 (6), 240.

Beffert, U., Danik, M., Krzywkowski, P., Ramassamy, C., Berrada, F., Poirier, J., 1998. The neurobiology of apolipoproteins and their receptors in the CNS and Alzheimer's disease. Brain Research Reviews 27, 119–142.

Beffert, U., Stolt, P.C., Herz, J., 2004. Functions of lipoprotein receptors in neurons. Journal of Lipid Research 45, 403–409.

Bothwell, M., Giniger, E., 2000. Alzheimer's disease: neurodevelopment converges with neurodegeneration. Cell 102, 271–273.

Buzsaki, G., Bragin, A., Chrobak, J.J., Nadasdy, Z., Sik, A., Hsu, M., Ylinen, A., 1994. Oscillatory and intermittent synchrony in the hippocampus: relevance to memory trace formation. In: Buzsaki, G., Llinás, R.R., Singer, W., Berthoz, A., Christen, Y. (Eds.), Temporal Coding in the Brain. Springer-Verlag, Berlin, pp. 145–172.

Clark, C.R., Paul, R.H., Williams, L.M., Arns, M., Fallahpour, K., Handmer, C., Gordon, E., 2006. Standardized assessment of cognitive functioning during development and aging using an automated touchscreen battery. Archives of Clinical Neuropsychology 21 (5), 449–467.

Cohen, R.M., Small, C., Lalonde, F., Friz, J., Sunderland, T., 2001. Effect of apolipoprotein E genotype on hippocampal volume loss in aging healthy women. Neurology 57, 2223–2228.

Cooper, J.A., Howell, B.W., 1999. Lipoprotein receptors: signaling functions in the brain? Cell 97, 671–674.

Corder, E.H., Saunders, A.M., Strittmatter, W.J., Schmechel, D.E., Gaskell, P.C., Small, G.W., Roses, A.D., Haines, J.L., Pericak-Vance, M.A., 1993. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science 261, 921–923.

Crawford, F.C., Vanderploeg, R.D., Freeman, M.J., Singh, S., Waisman, M., Michaels, L., Abdullah, L., Warden, D., Lipsky, R., Salazar, A., Mullan, M.J., 2002. APOE genotype influences acquisition and recall following traumatic brain injury. Neurology 58, 1115–1118.

Deary, I.J., Whiteman, M.C., Pattie, A., Starr, J.M., Hayward, C., Wright, A.F., Carothers, A., Whalley, L.J., 2002. Cognitive change and the APOE epsilon 4 allele. Nature 418, 932.

Den Heijer, T., Oudkerk, M., Launer, L.J., van Duijn, C.M., Hofman, A., Breteler, M.M., 2002. Hippocampal, amygdalar, and global brain atrophy in different apolipoprotein E genotypes. Neurology 59, 746–748.

Dietschy, J.M., Turley, S.D., 2001. Cholesterol metabolism in the brain. Current Opinion in Lipidology 12 (2), 105–112.

Fillenbaum, G.G., Landerman, L.R., Blazer, D.G., Saunders, A.M., Harris, T.B., Launer, L.J., 2001. The relationship of APOE genotype to cognitive functioning in older African-American and Caucasian community residents. Journal of the American Geriatrics Society 49, 1148–1155.

Friedman, G., Froom, P., Sazbon, L., Grinblatt, I., Shochina, M., Tsenter, J., Babaey, S., Yehuda, B., Groswasser, Z., 1999. Apolipoprotein E-epsilon4 genotype predicts a poor outcome in survivors of traumatic brain injury. Neurology 52, 244–248.

Gordon, E., 2003. Integrative neuroscience. Neuropsychopharmacology 28 (Supplement 1), S2–S8.

Gordon, E., Cooper, N., Rennie, C., Hermens, D., Williams, L.M., 2005. Integrative neuroscience: the role of a standardized database. Clinical EEG and Neuroscience 36, 64–75.

Gratton, G., Coles, M.G., Donchin, E., 1983. A new method for off-line removal of ocular artifact. Electroencephalography and Clinical Neurophysiology 55, 468–484.

Green, J., Levey, A.I., 1999. Event-related potential changes in groups at increased risk for Alzheimer disease. Archives of Neurology 56, 1398–1403.

Helkala, E.L., Koivisto, K., Hanninen, T., Vanhanen, M., Kervinen, K., Kuusisto, J., Mykkanen, L., Kesaniemi, Y.A., Laakso, M., Riekkinen Sr., P., 1995. The association of apolipoprotein E polymorphism with memory: a population based study. Neuroscience Letters 191, 141–144.

Helkala, E.L., Lakka, T., Vanhanen, M., Tuomainen, T.P., Ehnholm, C., Kaplan, G.A., Salonen, J.T., 2001. Associations between apolipoprotein E phenotype, glucose metabolism and cognitive function in men. An explorative study in a population sample. Diabetic Medicine 18, 991–997.

Herrmann, W., Hanf, S., Kaffarnik, H., Motzny, S., Reissner, J., Steinmetz, A., 1994. The influence of apolipoprotein E polymorphism on plasma concentrations of apolipoprotein B and A-I during the first year of life. Pediatrics 93, 296–302.

Herz, J., Beffert, U., 2000. Apolipoprotein E receptors: linking brain development and Alzheimer's disease. Nature Reviews Neuroscience 1, 51–58.

Hofer, S.M., Christensen, H., Mackinnon, A.J., Korten, A.E., Jorm, A.F., Henderson, A.S., Easteal, S., 2002. Change in cognitive functioning associated with apoE genotype in a community sample of older adults. Psychology and Aging 17, 194–208.

Hubacek, J.A., Pitha, J., Skodova, Z., Adamkova, V., Lanska, V., Poledne, R., 2001. A possible role of apolipoprotein E polymorphism in predisposition to higher education. Neuropsychobiology 43, 200–203.

Ito, J., Nikolaev, A.R., van Leeuwen, C., 2005. Spatial and temporal structure of phase synchronization of spontaneous alpha EEG activity. Biological Cybernetics 92, 54–60.

Jelic, V., Julin, P., Shigeta, M., Nordberg, A., Lannfelt, L., Winblad, B., Wahlund, L.O., 1997. Apolipoprotein E epsilon4 allele decreases functional connectivity in Alzheimer's disease as measured by EEG coherence. Journal of Neurology, Neurosurgery and Psychiatry 63, 59–65.

Jordan, J., Galindo, M.F., Miller, R.J., Reardon, C.A., Getz, G.S., LaDu, M.J., 1998. Isoform-specific effect of apolipoprotein E on cell survival and beta-amyloid-induced toxicity in rat hippocampal pyramidal neuronal cultures. Journal of Neuroscience 18, 195–204.

Kim, K.W., Youn, J.C., Jhoo, J.H., Lee, D.Y., Lee, K.U., Lee, J.H., Woo, J.I., 2002. Apolipoprotein E epsilon 4 allele is not associated with the cognitive impairment in community-dwelling normal elderly individuals. International Journal of Geriatric Psychiatry 17, 635–640.

Klages, J., Fisk, J.D., 2002. The relation between APOE status and neuropsychological memory test performance: an analysis of the Canadian Study of Health and Aging. Brain and Cognition 49, 201–204.

Klimesch, W., 1999. EEG alpha and theta oscillations reflect cognitive and memory performance: a review and analysis. Brain Research Reviews 29, 169–195.

Klimesch, W., Schack, B., Schabus, M., Doppelmayr, M., Gruber, W., Sauseng, P., 2004. Phase-locked alpha and theta oscillations generate the P1–N1 complex and are related to memory performance. Cognitive Brain Research 19, 302–316.

Kutner, K.C., Erlanger, D.M., Tsai, J., Jordan, B., Relkin, N.R., 2000. Lower cognitive performance of older football players possessing apolipoprotein E epsilon4. Neurosurgery 47, 651–657.

Kuusisto, J., Koivisto, K., Kervinen, K., Mykkanen, L., Helkala, E.L., Vanhanen, M., Hanninen, T., Pyorala, K., Kesaniemi, Y.A., Riekkinen, P., 1994. Association of apolipoprotein E phenotypes with late onset Alzheimer's disease: population based study. British Medical Journal 309, 636–638.

Lehtovirta, M., Partanen, J., Kononen, M., Soininen, H., Helisalmi, S., Mannermaa, A., Ryynanen, M., Hartikainen, P., Riekkinen Sr., P., 1996. Spectral analysis of EEG in Alzheimer's disease: relation to apolipoprotein E polymorphism. Neurobiology of Aging 17, 523–526.

Lehtovirta, M., Partanen, J., Kononen, M., Hiltunen, J., Helisalmi, S., Hartikainen, P., Riekkinen Sr., P., Soininen, H., 2000. A longitudinal quantitative EEG study of Alzheimer's disease: relation to apolipoprotein E polymorphism. Dementia and Geriatric Cognitive Disorders 11, 29–35.

Mahley, R.W., 1988. Apolipoprotein E: cholesterol transport protein with expanding role in cell biology. Science 240, 622–630.

Marquis, S., Moore, M.M., Howieson, D.B., Sexton, G., Payami, H., Kaye, J.A., Camicioli, R., 2002. Independent predictors of cognitive decline in healthy elderly persons. Archives of Neurology 59, 601–606.

Massimini, M., Huber, R., Ferrarelli, F., Hill, S., Tononi, G., 2004. The sleep slow oscillation as a traveling wave. Journal of Neuroscience 24, 6862–6870.

Mauch, D.H., Nagler, K., Schumacher, S., Goritz, C., Muller, E.C., Otto, A., Pfrieger, F.W., 2001. CNS synaptogenesis promoted by glia-derived cholesterol. Science 294, 1354–1357.

Nathan, B.P., Bellosta, S., Sanan, D.A., Weisgraber, K.H., Mahley, R.W., Pitas, R.E., 1994. Differential effects of apolipoproteins E3 and E4 on neuronal growth in vitro. Science 264, 850–852.

Nelson, C.A., 1995. The ontogeny of human memory: a cognitive neuroscience perspective. Developmental Psychology 31, 723–738.

Ohkubo, N., Mitsuda, N., Tamatani, M., Yamaguchi, A., Lee, Y.D., Ogihara, T., Vitek, M.P., Tohyama, M., 2001. Apolipoprotein E4 stimulates cAMP response element-binding protein transcriptional activity through the extracellular signal-regulated kinase pathway. Journal of Biological Chemistry 276, 3046–3053.

Oria, R.B., Patrick, P.D., Zhang, H., Lorntz, B., Castro Costa, C.M., Brito, G.A., Barrett, L.J., Lima, A.A., Guerrant, R.L., 2005. APOE4 protects the cognitive development in children with heavy diarrhea burdens in Northeast Brazil. Pediatric Research 57, 310–316.

Paul, R.H., Lawrence, J., Williams, L.M., Richard, C.C., Cooper, N., Gordon, E., 2005. Preliminary validity of ''integneuro'': a new computerized battery of neurocognitive tests. International Journal of Neuroscience 115, 1549–1567.

Paul, R.H., Gunstad, J., Cooper, N., Williams, L.M., Clark, C.R., Cohen, R.A., Lawrence, J.J., Gordon, E., 2007. Cross-cultural assessment of neuropsychological performance and electrical brain function measures: additional validation of an international brain database. International Journal of Neuroscience 117 (4), 549–568.

Pendleton, N., Payton, A., van den Boogerd, E.H., Holland, F., Diggle, P., Rabbitt, P.M., Horan, M.A., Worthington, J., Ollier, W.E., 2002. Apolipoprotein E genotype does not predict decline in intelligence in healthy older adults. Neuroscience Letters 324, 74–76.

Pitas, R.E., Ji, Z.S., Weisgraber, K.H., Mahley, R.W., 1998. Role of apolipoprotein E in modulating neurite outgrowth: potential effect of intracellular apolipoprotein E. Biochemical Society Transactions 26, 257–262.

Poirier, J., Sevigny, P., 1998. Apolipoprotein E4, cholinergic integrity and the pharmacogenetics of Alzheimer's disease. Journal of Neural Transmission Supplementum 53, 199–207.

Pritchard, W.S., Brandt, M.E., Shappell, S.A., O'Dell, T.J., Barratt, E.S., 1986. No decrement in visual P300 amplitude during extended performance of the oddball task. International Journal of Neuroscience 29, 199–204.

Puttonen, S., Elovainio, M., Kivimaki, M., Lehtimaki, T., Keltikangas-Jarvinen, L., 2003. The combined effects of apolipoprotein E polymorphism and low-density lipoprotein cholesterol on cognitive performance in young adults. Neuropsychobiology 48, 35–40.

Rebeck, G.W., Perls, T.T., West, H.L., Sodhi, P., Lipsitz, L.A., Hyman, B.T., 1994. Reduced apolipoprotein epsilon 4 allele frequency in the oldest old Alzheimer's patients and cognitively normal individuals. Neurology 44, 1513–1516.

Reiman, E.M., Chen, K., Alexander, G.E., Caselli, R.J., Bandy, D., Osborne, D., Saunders, A.M., Hardy, J., 2004. Functional brain abnormalities in young adults at genetic risk for late-onset Alzheimer's dementia. Proceedings of the National Academy of Sciences of the United States of America 101, 284–289.

Reiman, E.M., Chen, K., Alexander, G.E., Caselli, R.J., Bandy, D., Osborne, D., Saunders, A.M., Hardy, J., 2005. Correlations between apolipoprotein E epsilon4 gene dose and brain-imaging measurements of regional hypometabolism. Proceedings of the National Academy of Sciences of the United States of America 102, 8299–8302.

Reinvang, I., Espeseth, T., Gjerstad, L., 2005. Cognitive ERPs are related to ApoE allelic variation in mildly cognitively impaired patients. Neuroscience Letters 382, 346–351.

Ribary, U., Ioannides, A.A., Singh, K.D., Hasson, R., Bolton, J.P., Lado, F., Mogilner, A., Llinas, R., 1991. Magnetic field tomography of coherent thalamocortical 40-Hz oscillations in humans. Proceedings of the National Academy of Sciences of the United States of America 88, 11037–11041.

Sager, M.A., Hermann, B., La Rue, A., 2005. Middle-aged children of persons with Alzheimer's disease: APOE genotypes and cognitive function in the Wisconsin Registry for Alzheimer's Prevention. Journal of Geriatric Psychiatry and Neurology 18, 245–249.

Sauseng, P., Klimesch, W., Gruber, W., Doppelmayr, M., Stadler, W., Schabus, M., 2002. The interplay between theta and alpha oscillations in the human electroencephalogram reflects the transfer of information between memory systems. Neuroscience Letters 324, 121–124.

Scarmeas, N., Habeck, C.G., Hilton, J., Anderson, K.E., Flynn, J., Park, A., Stern, Y., 2005. APOE related alterations in cerebral activation even at college age. Journal of Neurology, Neurosurgery and Psychiatry 76, 1440–1444.

Small, B.J., Graves, A.B., McEvoy, C.L., Crawford, F.C., Mullan, M., Mortimer, J.A., 2000. Is APOE–epsilon4 a risk factor for cognitive impairment in normal aging? Neurology 54, 2082–2088.

Smith, C.D., Andersen, A.H., Kryscio, R.J., Schmitt, F.A., Kindy, M.S., Blonder, L.X., Avison, M.J., 1999. Altered brain activation in cognitively intact individuals at high risk for Alzheimer's disease. Neurology 53, 1391–1396.

Smith, C.D., Andersen, A.H., Kryscio, R.J., Schmitt, F.A., Kindy, M.S., Blonder, L.X., Avison, M.J., 2002. Women at risk for AD show increased parietal activation during a fluency task. Neurology 58, 1197–1202.

Smith, G.E., Bohac, D.L., Waring, S.C., Kokmen, E., Tangalos, E.G., Ivnik, R.J., Petersen, R.C., 1998. Apolipoprotein E genotype influences cognitive 'phenotype' in patients with Alzheimer's disease but not in healthy control subjects. Neurology 50, 355–362.

Snyder, E., Hillyard, S.A., 1976. Long-latency evoked potentials to irrelevant, deviant stimuli. Behavioral Biology 16, 319–331.

Strittmatter, W.J., Weisgraber, K.H., Goedert, M., Saunders, A.M., Huang, D., Corder, E.H., Dong, L.M., Jakes, R., Alberts, M.J., Gilbert, J.R., 1994. Hypothesis: microtubule instability and paired helical filament formation in the Alzheimer disease brain are related to apolipoprotein E genotype. Experimental Neurology 125, 163–171.

Tammi, A., Ronnemaa, T., Viikari, J., Jokinen, E., Lapinleimu, H., Ehnholm, C., Simell, O., 2000. Apolipoprotein E4 phenotype increases non-fasting serum triglyceride concentration in infants—the STRIP study. Atherosclerosis 152, 135–141.

Teter, B., Xu, P.T., Gilbert, J.R., Roses, A.D., Galasko, D., Cole, G.M., 1999. Human apolipoprotein E isoform-specific differences in neuronal sprouting in organotypic hippocampal culture. Journal of Neurochemistry 73, 2613–2616.

Tolar, M., Keller, J.N., Chan, S., Mattson, M.P., Marques, M.A., Crutcher, K.A., 1999. Truncated apolipoprotein E, ApoE causes increased intracellular calcium and may mediate ApoE neurotoxicity. Journal of Neuroscience 19, 7100–7110.

Turic, D., Fisher, P.J., Plomin, R., Owen, M.J., 2001. No association between apolipoprotein E polymorphisms and general cognitive ability in children. Neuroscience Letters 299, 97–100.

Weisgraber, K.H., Innerarity, T.L., Mahley, R.W., 1982. Abnormal lipoprotein receptor-binding activity of the human E apoprotein due to cysteine–arginine interchange at a single site. Journal of Biological Chemistry 257, 2518–2521.

Wetter, S., Murphy, C., 2001. Apolipoprotein E epsilon4 positive individuals demonstrate delayed olfactory event-related potentials. Neurobiology of Aging 22, 439–447.

Williams, L.M., Simms, E., Clark, C.R., Paul, R.H., Rowe, D., Gordon, E., 2005. The test–retest reliability of a standardized neurocognitive and neurophysiological test battery: ''neuromarker''. International Journal of Neuroscience 115, 1605–1630.

Wilson, R.S., Bienias, J.L., Berry-Kravis, E., Evans, D.A., Bennett, D.A., 2002. The apolipoprotein E epsilon 2 allele and decline in episodic memory. Journal of Neurology, Neurosurgery and Psychiatry 73, 672–677.

Winnock, M., Letenneur, L., Jacqmin-Gadda, H., Dallongeville, J., Amouyel, P., Dartigues, J.F., 2002. Longitudinal analysis of the effect of apolipoprotein E epsilon4 and education on cognitive performance in elderly subjects: the PAQUID study. Journal of Neurology, Neurosurgery and Psychiatry 72, 794–797.

Wright, R.O., Hu, H., Silverman, E.K., Tsaih, S.W., Schwartz, J., Bellinger, D., Palazuelos, E., Weiss, S.T., Hernandez-Avila, M., 2003. Apolipoprotein E genotype predicts 24-month bayley scales infant development score. Pediatric Research 54, 819–825.

Yankner, B.A., 1996. Mechanisms of neuronal degeneration in Alzheimer's disease. Neuron 16, 921–932.

Yu, Y.W., Lin, C.H., Chen, S.P., Hong, C.J., Tsai, S.J., 2000. Intelligence and event-related potentials for young female human volunteer apolipoprotein E epsilon4 and non-epsilon4 carriers. Neuroscience Letters 294, 179–181.

Zetterberg, H., Palmer, M., Ricksten, A., Poirier, J., Palmqvist, L., Rymo, L., Zafiropoulos, A., Arvanitis, D.A., Spandidos, D.A., Blennow, K., 2002. Influence of the apolipoprotein E epsilon4 allele on human embryonic development. Neuroscience Letters 324, 189–192.