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APOE e4 polymorphism in young adults is associated with improved attention and indexed by distinct neural signatures

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ABSTRACT

The APOE e4 allele, which confers an increased risk of developing dementia in older adulthood, has been associated with enhanced cognitive performance in younger adults. An objective of the current study was to compare task-related behavioural and neural signatures for e4 carriers (e4+) and non-e4 carriers (e4−) to help elucidate potential mechanisms behind such cognitive differences. On two measures of attention, we recorded clear behavioural advantages in young adult e4+ relative to e4−, suggesting that e4+ performed these tasks with a wider field of attention. Behavioural advantages were associated with increased task-related brain activations detected by fMRI (BOLD). In addition, behavioural measures correlated with structural measures derived from a former DTI analysis of white matter integrity in our cohort. These data provide clear support for an antagonistic pleiotropy hypothesis — that the e4 allele confers some cognitive advantage in early life despite adverse consequences in old age. The data implicate differences in both structural and functional signatures as complementary mediators of the behavioural advantage.

Introduction

Apolipoprotein E (APOE) is a polymorphic protein implicated in mechanisms of neurogenesis, plasticity and repair (Mahley, 1988). In humans, the APOE gene has 3 allelic variants (e2, e3, and e4) that are differentially distributed across the population. The e4 allele, represented in approximately 25% of the population (Mahley, 1988) is a well-established genetic risk factor for Alzheimer's disease (AD) (Rocchi et al., 2003). Independent of dementia risk, the e4 variant of the APOE gene is a significant risk factor for age-related memory failure (Deary et al., 2002). Studies have reported that cognitively healthy older adults (plus 50 years) with the e4 allele are impaired on measures of prospective memory (Duchek et al., 2006), spatial and working memory (Greenwood et al., 2005), episodic memory and attention (Nilsson et al., 2002, 2006). A meta-analysis of 38 studies showing e4-related cognitive deficits in middle-aged and older healthy adults (aged 45–85 years) indicated small but significant impairments in global cognitive performance, episodic memory and executive functioning in e4 carriers (e4+) relative to non-e4 carriers (e4−) (Small et al., 2004). A more recent meta-analysis by Wisdom et al. (2011) confirmed this analysis on a larger body of literature published betweeen 1993 and 2008, with significant deficits emerging on measures of global cognitive skill (e.g. Wechsler Adult Intelligence scale, Mini Mental State exam) and on measures of episodic memory (e.g. auditory verbal lerning tasks of immediate and delayed recall). Although future dementia status may be considered a confounding factor in these studies (Bondi et al., 1999; Bunce et al., 2011); Greenwood et al. (2005) argue that the non-selective nature of the deficits point to a cognitive phenotype, rather than prodromal dementia. Brain imaging studies support these behavioural data. Under fMRI, relative to age-matched non-e4 participants, cognitively intact older adult e4+ show increased blood oxygenation level dependent (BOLD) response to challenging cognitive tasks (Han et al., 2007b; Wishart et al., 2006) including evidence for increased bilateral fronto-temporal activation as the primary compensatory response of older adults to cognitive challenge (Cabeza et al., 2002).

Interestingly, differences in cognitive performance have been reported also between e4+ and e4− in young life, but in this case, these differences have suggested a behavioural advantage for e4+. Some early studies reported that young e4+ are more likely to progress to higher education (Hubacek et al., 2001), and have higher IQs at university age (Yu et al., 2000). In a series of experimental studies that followed, young e4+ were shown to outperform their peers on a range of cognitive tasks, including episodic memory (Mondadori et al., 2007), prospective memory, executive function (Marchant et al., 2010), speed of processing (Han et al., 2007a; Marchant et al., 2010), mental arithmetic (Puttonen et al., 2003) and verbal fluency (Alexander et al., 2007; Marchant et al., 2010). In the Mondadori et al. (2007) study (mean age 22.3), young adult e4+ showed better memory performance and a more rapid decrease in BOLD activity over 3 learning trials, interpreted as more efficient use of memory resources ("smaller neural investment into learning") for e4+. In the Marchant et al. (2010) study, young adults (age range 18–30) showed superior

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cognitive performance across three cognitive domains, and these advantages were not explained by differences in metacognitive strategies.

A key feature of all studies that report advantages in at least one domain is that the e4 genotype did not invariably confer an advantage in all domains tested on the same occasion (Alexander et al., 2007; Han et al., 2007a; Marchant et al., 2010; Mondadori et al., 2007; Yu et al., 2000). This suggests that the benefits are not domain-specific. Possibly the advantage for e4+ may emerge under challenge or perhaps fatigue, but is not specific to selective domains tested in any testing session. Consistent with this interpretation, advantages are usually not detected by studies which use general cognitive ability measures (Ruiz et al., 2010; Turic et al., 2001) or large standard test batteries (Bunce et al., 2011; Jorm et al., 2007). Tuminello and Han (2011) also suggest interactive effects between APOE status and other genetic and environmental risk factors (e.g. birth factors, family history of AD, genetic variations in the MTHFR 677TT allele) may differentiate studies showing contradictory findings in younger populations. These factors, both within and between studies, are likely responsible for the null findings reported in the only meta-analysis of genotype effects on cognition in young people (Ihle et al., 2012b).

The suggestion that the e4 allele confers some cognitive advantage in early life coupled with adverse consequences in old age may provide an example of antagonistic pleiotropy (Han and Bondi, 2008): cognitive advantages in younger adults support higher achievement and greater selection benefits, but may increase susceptibility to memory failure as we enter old age. In line with the compensatory model of cognitive deficits in older adults (Bondi et al., 2005; Bookheimer et al., 2000; Han et al., 2007b) increased (compensatory) brain activation, specifically in frontal regions, may mediate the cognitive advantage in younger adult e4+ (Han and Bondi, 2008). More recently, Tuminello and Han (2011) considered the mixed support for the simple model of frontal compensatory activation in e4+, and suggest that observed regional changes may be flexible and task-determined in younger cohorts, though localised frontally in older adults. Alternatively, Mondadori et al. (2007) suggests e4+ exhibit increased neural efficiency rather than compensatory overactivation, as indicated in their study by decreased neural activity during learning producing a better cognitive outcome. These alternatives need not be mutually exclusive. Both receive support from neuroimaging studies.

Two studies have suggested structural differences between e4+ and e4− that are apparent across the lifespan. Shaw et al. (2007) reported that in a cohort of children and young adults (up to 21 years) there was a significant relationship between the thickness of the entorhinal cortex and APOE genotype, with thickness greatest in e2 carriers and least in e4+ (i.e. 2>3>4). Ruest et al. (under review) reported that while, consistent with results from Filippini et al. (2009) and Dennis et al. (2010) there is no evidence for white or grey matter volumetric differences between genotypes, young adult e4+ did show a significant increase in axial diffusivity obtained from diffusion tensor imaging (DTI) of white matter fibres. The white matter fibres provide a barrier to diffusion of water molecules that results in a preference for diffusion along the direction of the fibre tract (anisotropic diffusion) (Basser and Ozarslan, 2011). DTI uses a second-rank tensor to model diffusion in three orthogonal directions within the tract (axial diffusivity, parallel to the direction of the white matter axons, radial diffusivity, perpendicular to the axons). Decreases in axial diffusivity are associated with axonal damage (Budde et al., 2008, 2009; Deboy et al., 2007; Mac Donald et al., 2007; Sun et al., 2007). Higher fractional anisotropy (FA), an alternative measure diffusion anisotropy and a marker for axon integrity, is associated with higher IQ and more efficient processing of information (Deary et al., 2006). Significantly, axial diffusivity across both e4+ and e4− in the sample correlated with behavioural measures of episodic memory and speed of processing.

Functional imaging studies also report genotype-related differences. In resting state, e4+ show enhanced co-activation in the hippocampus and medial prefrontal cortex, elements of the default mode network (DMN) (Filippini et al., 2009; Westlye et al., 2011) and differences in fronto-parietal and visual networks (Trachtenberg et al., 2012b). Two earlier PET studies (Reiman et al., 2004; Scarmeas et al., 2003), however, reported lower global measures of resting state activation in e4+ within a similar age range (20–35 years). Likewise, functional imaging studies have reported both increased (Dennis et al., 2010; Evans et al., under review; Filippini et al., 2011; Han et al., 2007b; Scarmeas et al., 2005) and decreased (Borghesani et al., 2008) activity in the medial temporal lobe (MTL) in e4+, albeit using different tasks. In most of these studies, the activation differences were reported in the absence of behavioural differences between groups. In a recent study by Evans et al. (under review) e4+ showed increased activation in Brodmann Area (BA) 10 region, relative to e4−, with some associated advantages in their speed-of-response on a prospective memory task. These imaging studies vary in the age range of participants, a potential problem given the age-dependent nature of the functional changes, and in the baseline conditions selected for analysis (Trachtenberg et al., 2012b), further complicating interpretation. One consistent finding is that e4+ recruit the medial temporal lobe during tasks that do not typically require such involvement (Filippini et al., 2009; Trachtenberg et al., 2012a) reminiscent of the compensatory activations reported in older adults.

An objective of the current study was to compare behavioural and neural signatures for e4+ and e4− on measures of attention. Marchant et al. (2010) reported advantages in young adult e4+ on a short battery of cognitive tasks that included a direct measure of sustained attention (the Rapid Visual Information Processing (RVIP) task) and a task with a significant attention requirement (event-related prospective memory (PM)). Even though the sample size was small, e4+ performed better than a corresponding sample of e4− on both of these tasks, with the advantage significant in the PM task. Here we engaged a larger sample of young adults and tested their performance on two tasks of attention; on one task functional neuroimaging data was also acquired.

First, capacity for sustained attention was measured using the RVIP task (adapted from Wesnes and Warburton (1983)). Second, all volunteers completed a covert attention task (adapted from Thiel et al. (2004)) in the scanner. The validity effect, indexed by the covert attention task, measures the ability of the volunteer to reorient attention. It is derived from differences in reaction times (RT) to the occurrence of target items appearing at a cued versus an uncued location. Robustly, participants' responses are faster to targets appearing in a cued location. The reduced RTs correlate with reduced BOLD activity in brain regions associated with the resting state default mode network, encompassing the anterior and posterior cingulate cortex, angular gyrus, middle frontal gyrus and cuneus brain regions (Shulman et al., 1997; Han et al., 2007a, 2007b). Neither attention task is associated with significant hippocampal activation.

We anticipated, based on previous findings, that we would observe significant behavioural advantages for the e4+ relative to e4−, and that these would be mediated by differences in task-related neural activity. The covert attention task is associated with DMN, elements of which show genotype-specific effects in resting state fMRI studies (Filippini et al., 2009; Westlye et al., 2011). Based on previous studies (Filippini et al., 2009; Trachtenberg et al., 2012a) we also anticipate additional brain regions will be recruited by e4+ during task performance, specifically in medial temporal lobes (MTL), and independent of task requirements. Alternatively, genotype differences in neural efficiency could produce improved behavioural outcomes for e4+ in the absence of enhanced brain activations.

As a supplementary analysis, we were able to explore potential correlations between the behavioural data and structural imaging data previously acquired with this cohort of volunteers (reported in Ruest et al., under review). Using diffusion tensor imaging techniques, this structural imaging data recorded significant genotype differences on a measure of whole-brain axial diffusivity, with e4 carriers having a higher mean axial diffusivity index. In previous studies, white matter

integrity has been linked to reaction times (Madden et al., 2004). We therefore anticipated a positive correlation between our behavioural outcome measures and mean axial diffusivity indices in our volunteers.

Materials and methods

Participants

Ninety-eight healthy young participants were recruited (aged 20±2 years, range 18–30, 64 females, 34 males). Volunteers were excluded from the study for untreated high blood pressure, cardiac pathology, a history of psychiatric or neurological illness including the use of psychoactive medication, pregnancy, and presence of metallic implants including bridges and braces, or tattoos above the shoulder.

Volunteers signed written informed consent, following procedures approved by the University of Sussex Schools of Psychology and Life Sciences Research Ethics Committee. Cheek swab samples were collected for DNA analysis from each participant. APOE genotypes were determined by KBiosciences (Hoddesdon, UK; www.kbioscience.co.uk), using their own system of fluorescence-based competitive allele-specific polymerase chain reaction (KASPar). Two APOE single-nucleotide polymorphisms (SNPs) rs429358 and rs7412 allowed identification of the three major APOE alleles (e2, e3 and e4). From the samples, 9 participants were heterozygous e2 and excluded from the study. 50 were identified as e4−, of which 20 were selected randomly as our control group representing the genotype most frequent in the general population (Rebeck et al., 1993). From the remaining 34 volunteers who were e4+, we randomly selected 21 of the group to be participants to enter our experimental group. This group included two participants that were homozygous e4 carriers. Neither volunteers nor the researchers were informed regarding genotype results; the image acquisition and analysis were conducted under double-blind procedures (that is, all preprocessing was completed before group assignment was revealed). Demographics for the final group of 41 individuals who participated in the study are shown in Table 1.

Materials

The National Adult Reading Test, NART (Nelson and Willison, 1991) estimates verbal IQ. Participants read aloud 50 irregular words and errors in pronunciation are recorded.

Immediate free recall provides an episodic memory score. Participants are presented with 20 unrelated words at a rate of one word every two seconds in a computerised sequence; they are then prompted for immediate written recall.

The 6-min RVIP task (Wesnes and Warburton (1983)) is a computerised task. Volunteers monitor a continuous stream of digits, presented at a rate of 80 digits per minute, and press a response button when 3 odd or 3 even digits appear in succession (sequence illustrated in Fig. 1a). Eight such target strings occur in each 1 min block. Correct detections of targets are recorded within a 1500 ms window following the onset of the third digit in the target sequence. Number of correct detections, average latency to correct detections and the number of false alarms (responses to non-targets) are recorded. The original task ran for 10 or 20 min but was adapted here to run for 6 min only.

Table 1
Volunteer characteristics and measures of baseline cognitive performance (standard deviations in parentheses).

Group	Age (years)	Gender	IQ	Episodic memory (recalled words, max 20)
e4+ ($n=21$)	21.4 (2.2)	13 F	113 (4)	9.0 (2.7)
e4− ($n=20$)	20.9 (1.4)	14 F	115 (3)	9.7 (2.9)
t Statistic	$t=0.82$, ns		$t=1.23$, ns	$t=0.81$, ns

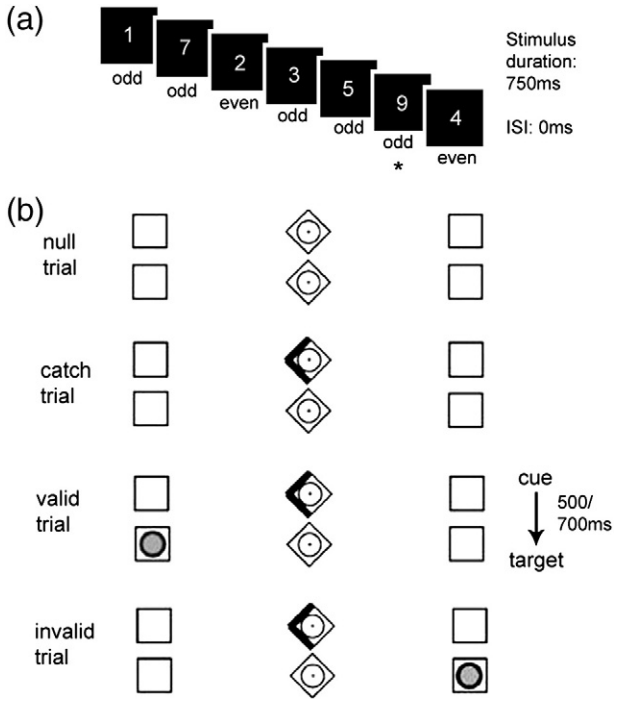

Fig. 1. Schematic representations of the sequence of events in each of the two attention tasks: a) rapid visual information processing, b) covert attention.

The covert attention task (Thiel et al., 2004) is a computerised task. In each trial, participants fixate a small diamond in the center of the screen; after 3000 ms one side of the diamond changes colour, cueing one side of the screen. The target is then displayed to either the left or right of the diamond (sequence is illustrated in Fig. 1b). The cue is predictive in 70% of trials (cue congruent), and incorrect for the remaining 30% of trials (cue incongruent). Participants indicate with a left or right button response which side of the screen the target appears. Half of each of the 184 congruent and 80 incongruent trials occur with a short cue-target interval (500 ms) and half with a longer cue-target interval (700 ms). In addition to the cued trials, 36 catch trials (where the cue was not followed by a target) and 74 null trials (where no cue or target occurred) are included across the session to prevent response habituation. Thus there were 374 trials in total. Trial types occurred randomly with the limitation that only congruent or null trials were shown in the first 5 trials and there were no consecutive null trials. Neutral cue and No cue trials from the original Thiel et al. (2004) version of this task were not included in this adaptation. The paradigm was implemented in cogent 2000 and MATLAB.

Procedure

Genotype analyses were performed by a third party and volunteer call-back was completed under a triple blind procedure ensuring that neither the experimenter nor the volunteer was aware of the genotype result. Recalled volunteers attended 3 sessions.

In an initial session participants completed measures of IQ (National Adult Reading Test, NART (Nelson and Willison, 1991) and episodic memory (immediate verbal free recall), used to assess baseline comparability of groups. These were followed by a 6-min version of the RVIP task. Finally, participants were familiarised with the covert attention task. In two subsequent scanning sessions (approx 1 week apart), volunteers participated in a double –blind pharmacological manipulation, in one session self-administering placebo and in the other, nicotine (as nasal sprays), 18–20 min prior to

Table 2
Performance on RVIP and Covert Attention tasks by genotype. Standard deviations shown in brackets; significant *F* values ($p<0.05$, in all cases indicating superior performance by e4 volunteers) indicated by asterisks.

	RVIP Task			Covert Attention Task		
Group	Mean detections per min (max 8)	Mean false alarms per min	RT (ms) to correct detections	RT (ms) to validly cued trials	RT (ms) to invalidly cued trials	Validity effect (ms)
e4+	5.46 (1.42)	0.46 (0.29)	494 (46)	358 (50)	387 (58)	26 (5.5)
e4−	4.57 (1.15)	0.88 (0.84)	526 (102)	329 (72)	371 (67)	42 (5.36)
F statistic	$F=4.53^*$	$F=4.07$	$F=1.55$	$F=2.24$	$F=0.66$	$F=4.48^*$

imaging. The sessions were identical and their order randomised and counterbalanced.

The pharmacological manipulation was designed to explore the effects of nicotine administration on a prospective memory task completed at 20 min post spray, and is reported in a separate paper (Evans et al., under review). In this report, we consider performance on the covert attention task, which was completed 20 min into the scanning session, 40 min post-spray. Nicotine effects were found to be largely absent at this point in the session, nevertheless analysis was completed using data from the placebo sessions only. Structural and resting state data were acquired after the tasks were completed. After the second session all participants were verbally debriefed and compensated.

Design

Analyses were completed using data from the placebo sessions only; nevertheless, the ANOVA included order of sessions (i.e. whether the placebo session was the first or second session) as a factor. Baseline measures of IQ and episodic memory were compared between genotype.

RVIP task

Number of correct detections, average latency to correct detections and the number of false alarms (responses to non-targets) were analysed separately using ANOVA. Time bin (six levels: minutes 1 to 6) was the within-subject factor; genotype (two levels: e4+, e4−) and session order (two levels: first or second scanner session) the between subject factors.

Covert attention task

Raw reaction times to correct responses were split by condition (cue congruent/incongruent) and by cue-target interval (short — 500 ms /long — 700 ms) with outliers (±3 SD). Difference between mean RTs to the incongruent and congruent conditions constituted the validity effect. ANOVA examined effects of cue-target interval (two levels: short, long), genotype (two levels: e4 carriers, non-carriers), and session order (two levels: first or second scanner session) in a mixed design.

Magnetic resonance imaging protocol

All images were acquired on a Siemens 1.5 T Avanto MRI scanner (Siemens, Erlangen, Germany). High-resolution anatomical images were acquired using a 3D T_1-weighted MP-RAGE sequence, (TR = 1160 ms, TE = 4.44 ms, TI = 600 ms, FOV = 230×230 mm^2, matrix size = 256×256, flip angle = 15°, voxel dimensions of 0.9×0.9×0.9 mm^3, acquisition time = 5 min). Gradient echo B_0 field-maps (used to correct the functional and DTI data) were acquired (TR = 513 ms, TE = 5.78 mm, FOV = 192 mm, matrix size = 64×64, voxel dimensions = 3×3×3 mm^3, acquisition time = 1 min).

fMRI recording and analysis

fMRI datasets sensitive to BOLD contrast were acquired at 1.5 T (Siemens Avanto). To minimise signal artefacts originating from the sinuses, axial slices were tilted 30° from inter-commissural plane. Thirty-six 3 mm slices (0.75 mm interslice gap) were acquired with an in-plane resolution of 3 mm×3 mm (TR = 3300 ms per volume, TE = 50 ms). Images were pre-processed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/). Raw T2-weighted volumes were spatially realigned and unwarped, spatially normalised to standard space and smoothed (8 mm kernel). fMRI data were analysed with the standard hierarchal model approach employed in SPM. For each subject, three trial types (congruent, incongruent, and catch) were modelled in first level design

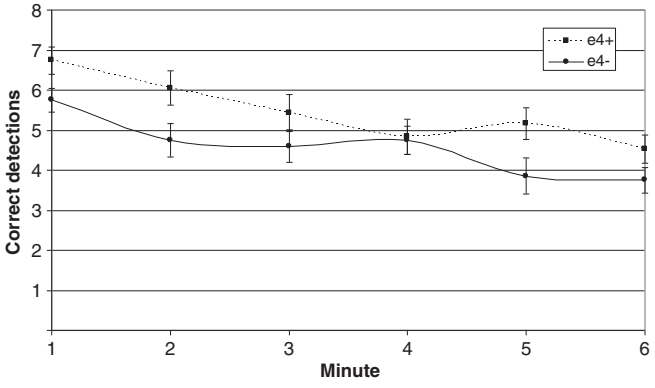

Fig. 2. RVIP task. Mean number of correct detections by genotype across the six 1-min time bins. Error bars show standard errors on the means.

Table 3
Task-related activity. Brain regions showing significantly greater activity following successful detection of target, relative to 'cue-only' condition. The *F* scores are all significant at $p<0.05$ (FWE-corrected).

Cortical region of activation	MNI coordinates			Group *F* value
	x	*y*	*z*	*F*
Parietal				
Left Superior Parietal Lobule (SPL)	−18	−46	66	36.75
Right SPL	6	−42	48	65.43
Left Precuneus	−12	−48	60	48.45
Right Precuneus	18	−72	44	65.42
Frontal				
Right Insula	34	30	0	39.80
Left Area BA4a	−4	−28	46	65.16
Right Area BA6 (SMA)	4	−22	44	57.65
Cingulate				
Right middle cingulate	4	0	38	57.28
Right anterior cingulate cortex (ACC)	2	18	28	40.10
Left ACC	0	20	24	39.59
Visual				
BA17/18	−2	−90	4	93.55
Left fusiform gyrus	−36	−48	−16	38.46

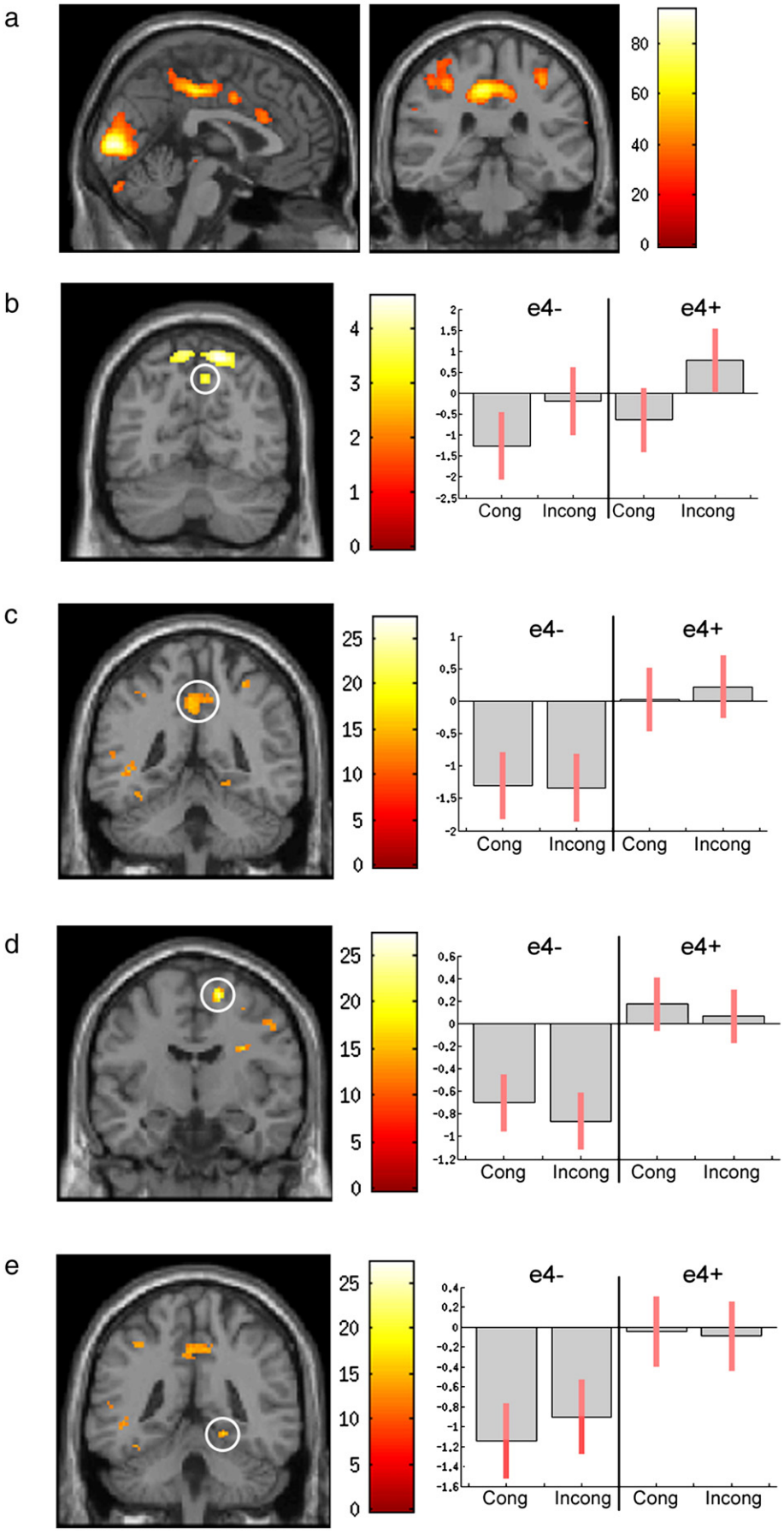
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Table 4
Reorienting activity. Brain regions showing higher responses to the target on incongruent compared to congruent trials. The *t* scores are significant at $p<0.001$ (uncorrected) with a 50-voxel extent threshold.

Cortical region of activation	MNI coordinates			Group *t* value
	x	*y*	*z*	*t*
Right middle frontal gyrus	40	0	45	3.86
Right SPL	16	−72	65	4.61
Left SPL	−18	−74	65	4.3
Right precuneus	6	−68	51	3.84
Right BA6 (SMA)	10	10	73	3.86

Table 5
Genotype-related differences in neural activity. Brain regions showing significantly different activity between e4+ and e4−, following successful detection of target. The *t* scores are significant at $p<0.001$ (uncorrected) with a 50-voxel extent threshold, apart from (*), which was significant at $p<0.05$ (FWE-corrected) following small volume correction for that structure.

Cortical region of activation	MNI coordinates			Group *t* value
	x	*y*	*z*	*T*
Right area 6 (SMA)	16	−10	64	25.59
Left precuneus	−4	−44	40	15.63
Right precuneus	6	−44	44	14.11
Right parahippocampal gyrus (SUB) (*)	20	−42	−10	16.29

matrices which also included 6 movement parameters estimated during pre-processing. For congruent and incongruent trials, we only included trials where correct responses were made (first button response only), and events were time-locked to presentation of the target. Analyses of the task-related network are presented at a threshold of $p<0.05$ family-wise error (FWE) corrected. Genotype differences are reported at $p<0.001$ (uncorrected) with a minimum cluster threshold of 50 voxels. Small volume corrections, (where appropriate, based on the APOE literature) are reported at $p<0.05$ FWE-corrected. Regions of interest were defined using the Wakefield University PickAtlas. Anatomical localisation of clusters was performed using the Talairach Daemon (University of Texas, USA), and the anatomy toolbox for SPM (Eickhoff et al., 2005).

DTI acquisition and analysis

Diffusion-weighted images were acquired using an EPI sequence (TR = 12.4 s, TE = 111 ms, echo spacing = 0.83 ms, FOV = 240 × 240 mm^2, matrix size = 96 × 96, voxel dimensions = 2.5 × 2.5 × 2.5 mm^3, acquisition time = 7 min). Diffusion gradients were applied along 30 non-collinear directions (b_{max} = 1000 s/mm^2). A non-diffusion-weighted ($b\approx0$) volume was also acquired. DTI data were pre-processed using the FMRIB Software Library (FSL) suite (Smith et al., 2004; Woolrich et al., 2009). DTI volumes were realigned using the eddy current correction module, then unwarped using the acquired B_0 fieldmap and the FUGUE tool. The diffusion tensor was calculated using dtifit, yielding a fractional anisotropy (FA) map, a T_2-weighted image free from diffusion weighting (S_0), the 3 eigenvalues of the diffusion tensor $\lambda_{1\text{-}3}$, and a mean diffusivity (MD) map. λ_1 represents axial diffusivity.

Results

Volunteer characteristics and cognitive performance

Independent *t*-tests (two-tailed) revealed no significant differences between the groups on measures of verbal IQ or episodic memory (Table 1).

Rapid visual information processing (RVIP)

Two volunteers were excluded, one from each genotype group, because their accuracy for correct detections was comparable to their false alarm rate. For the remaining 39 volunteers, correct detection rate, latencies and false alarms are presented in Table 2.

Correct detections of target sets

A main effect of time on correct detections ($F(1,37) = 13.58$, $p = 0.001$), reflected a decreasing hit rate over the 6 min of the task. There was no time by genotype interaction ($F(1,37) = 1.25$, $p = 0.271$). Overall, significantly more hits were recorded by e4+ relative to e4− ($F(1,37) = 4.53$, $p = 0.04$) (Fig. 2).

RTs to correct detections

There was no main effect of time on latency ($F(1,36) = 1.43$, $p = 0.24$), no time by genotype interaction ($F(1,36) = 0.51$, $p = 0.48$), and no significant difference in reaction time between e4+/e4− ($F(1,37) = 1.55$, $p = 0.221$).

False alarm rate

e4+ showed a trend towards fewer false alarms over the task ($F(1,37) = 4.07$, $p = 0.051$). There were no effects of time and no time by genotype interactions.

Covert attention task

One volunteer was excluded from this analysis because of an exceptionally high error rate (>40% of trials). After this exclusion, remaining volunteers all exceeded 90% correct performance. Data are shown in Table 2.

Preliminary analyses looking at raw RTs to correct trials revealed no genotype differences, no session order differences, no trial duration effects, and no interactions between factors for RTs to congruent or for RTs to incongruent trials (all $ps > 0.14$).

The validity effect, derived by subtracting RTs to invalidly cued trials from RTs to validly cued trials, was analysed in the same fashion. ANOVA revealed no main effect of spray order ($F(1,37) = 0.872$, $p = 0.356$), and no genotype by spray order interaction ($F(1,37) = 0.399$, $p = 0.532$). A main effect of genotype ($F(1,37) = 4.48$, $p = 0.041$) occurred, with e4+ showing a significantly reduced validity effect compared to e4−.

Covert attention: fMRI analysis

Task-related activations

Across both congruent and incongruent trials, successful detection of the targets was associated with increased activity in parietal, frontal, cingulate and visual areas (see Table 3, and Fig. 3(a)).

Fig. 3. (a) Task-related activation. Brain regions showing significantly greater activity following successful detection of target, relative to 'cue-only' condition. Sagittal section shows activity in BA17/18, precuneus, middle cingulate and anterior cingulate. Coronal view shows activity in precuneus and bilateral SPL. (b) Reorienting activation in right precuneus (circled) and bilateral SPL. Parameter estimates for right precuneus showing differential activity per condition, and generally greater activity in e4+. (c) Bilateral precuneus activity differs according to genotype, on both congruent and incongruent trials. Parameter estimates showing greater activity in e4+. (d) e4+ also show greater activity in right SMA. (e) Outside of the task-related network, only e4+ show activity in the right hippocampal formation, specifically the subiculum.

Reorienting activity

Incongruent trials were contrasted with congruent trials to determine activity specifically associated with reorienting of attention away from the cued direction. This contrast revealed greater activity on incongruent trials in parietal regions, middle frontal gyrus and supplementary motor area (SMA) (see Table 4, and Fig. 3(b)). There were no regions where activity decreased on incongruent trials.

Genotype differences

Across congruent and incongruent trials, a main effect of genotype was observed in SMA, bilateral precuneus and right parahippocampus (see Table 5, and Fig. 3(c),(d),(e)). e4+ showed greater activity in these regions upon detection of the target, and there were no regions where e4+ showed less activity compared to e4−. Also there were no regions showing an interaction between condition (congruent/incongruent) and genotype, indicating that genotype-related differences in activity did not differentiate by condition.

Correlations between behavioural data and structural MRI data

Structural data analyses on this cohort (reported in a separate paper (Ruest et al., under review)) recorded significant genotype differences on a measure of whole-brain axial diffusivity. Pearson correlations (one-tailed) were computed between this measure and the behavioural measures from the covert attention task. Mean RT across all trials correlated with the structural measure in e4+ only (e4+: $r=-0.51$, $p=0.013$; e4−: $r=-0.159$, $p=0.25$). In e4+, the correlation was stronger with RT to incongruent trials ($r=-0.52$, $p=0.011$, 1-tailed) than with RT to congruent trials ($r=-0.47$, $p=0.021$, 1-tailed). Across all participants, the size of the validity effect correlated with axial diffusivity ($r=-0.31$, $p=0.03$, 1-tailed).

Discussion

Behavioural data

The behavioural data reported here demonstrate a clear positive advantage for young adult e4+ over e4− on tests of sustained and covert attention. Furthermore, the mechanism through which this advantage is manifest can be linked to demonstrated neural differences both in structural and functional signatures.

In the RVIP task, e4+ detected more target sets. There was no evidence of a speed/accuracy tradeoff and indeed, e4+ showed a trend towards lower false alarm rates also, compared to e4−. In e4+, better target detection was seen from the outset with the advantage remaining stable across the full 6-min time frame. Both groups showed a comparable fatigue effect.

In the covert attention task, e4+ showed a significantly reduced validity effect, signalling that they were less disadvantaged by invalid cueing. Examining the mean RTs (Table 2) provides some indication of the source of this reduced validity effect. Although there were no significant differences in RT between groups for either trial type, it seems that e4+ achieve a smaller validity effect through a slowing of responses to validly-cued trials, rather than accelerated performance on invalidly-cued trials.

Previous studies have produced inconsistent findings with regard to the APOE genotype effect on cognition in younger adults on measures of memory and attention (Alexander et al., 2007; Han et al., 2007a; Marchant et al., 2010; Mondadori et al., 2007; Yu et al., 2000). This is the first study to measure both sustained and covert attention in young adults in relation to the APOE genotype and the data contribute positive evidence for the notion of antagonistic pleiotropy (Han and Bondi, 2008; Tuminello and Han, 2011). The results contradict the suggestions that the behavioural advantages reported previously reflect underpowered data (Ihle et al., 2012a) or that the effects emerge only when other mediating factors (family history, other genetic mutations; birth factors) are taken into account (Tuminello and Han, 2011). The results are particularly powerful because they demonstrate behavioural advantages in young adult e4 carriers on tasks that consistently show disadvantages in older adults carrying the e4 allele (Greenwood et al., 2000, 2005). The data from the fMRI suggest a possible common mechanism for the observed behavioural effects in young adults on these two attention tasks.

fMRI

Initial analyses focused on task-related activity. Successful detection of targets was associated with widespread activity across parietal, frontal, cingulate and visual areas, relative to trials where only the cue was presented. These activations, associated with shifts of attention from central cue to peripheral target, were broadly consistent with previous work using similar tasks (Gitelman et al., 1999; Perry and Zeki, 2000).

To examine neural activity associated with reorienting, we contrasted congruent and incongruent cue trials and found that activity in parietal regions, middle frontal gyrus and SMA was greater on incongruent trials, consistent with previous imaging findings (Thiel et al., 2004, 2005). Activity was largely lateralised to the right hemisphere, in accordance with reports of greater disengagement deficits in patients with right, rather than left, parietal damage (Losier and Klein, 2001). In the SMA and bilateral precuneus, e4+ showed greater activations although these effects were not specific to reorienting: the parameter estimates in Fig. 3(c) and (d) show that e4+ demonstrate greater activity in these regions across both validly- and invalidly-cued trials. This finding points to a possible explanation of the behavioural differences observed.

Parietal activity is thought to represent top-down attentional control, with activity in precuneus and SPL often associated with attentional shifting and tracking (Culham et al., 1998; Nagahama et al., 1999). Previous work with the covert attention task employed here has shown that greater parietal activity occurs also under conditions where a target is presented without any cueing stimulus (Thiel et al., 2005). This finding supports the notion that parietal activity is enhanced when a target occurs outside the current focus of attention, and that this activity indexes modulation of the attentional spotlight (Vidyasagar, 1999). Other work which aimed to manipulate the size of the attentional field report similar links with parietal activity (Muller et al., 2003; Small et al., 2003) and it seems that it is a widening of the attentional field that drives increased parietal activity. Specifically, increasing the number of targets, but not their complexity, modulates parietal activity (Shim et al., 2010).

Therefore greater bilateral precuneus activity in e4+ regardless of trial type might be due to e4+ approaching target detection with a wider attentional field. This could explain also why behavioural advantages in young e4+ only manifest with certain tasks and conditions. In the covert attention task, a wider attentional spotlight would lead to lesser benefits from validly-cued trials, but a smaller reorienting disadvantage from invalidly cued trials, and this describes the e4+ performance that we observed on this task. In terms of the RVIP task, we postulate that a wider attentional field might occur not just spatially, but also temporally, with e4+ maintaining attention across the time frame required to detect a run of three successive target digits. An ability to integrate information over a wider spatial and temporal window would mean that e4+ rely less on environmental cues to direct their attention, and this would elicit performance advantages on tasks where stimulus-driven strategies are inefficient. Increased levels of parietal activity, promoting greater top-down processing and a wider field of attention in the e4+, also would afford lower reliance on the cue to engage attention. If the source of the cognitive advantage reported here and elsewhere is the application of a wider attentional field, we can anticipate cognitive tasks where this would produce no difference or even a significant disadvantage (e.g. Stroop tasks, episodic recall tasks). This is consistent with previous reports (Dennis et al., 2010; Filippini et al., 2009).

In line with certain other imaging studies (Evans et al., under review; Trachtenberg et al., 2012a), we found that e4+, but not e4−, activated their right MTL during both congruent and incongruent trials. This appears to reflect a generalised tendency in e4+ to activate this region regardless of task demands. Since e4+ seem to overactivate this region also during memory tasks (Bookheimer et al., 2000; Dennis et al., 2010), these findings point to a non-specific compensatory mechanism whose behavioural significance is yet to be established.

Neurobiologically, lowered estimates of cue validity have been associated with enhanced tonic acetylcholine (Ach) activity in attentional cueing tasks (Yu and Dayan, 2005), and cholinergic agonist studies in both animals and humans have confirmed this relationship (Blondel et al., 2000; Han et al., 2007a, 2007b; Phillips et al., 2000; Thiel et al., 2005). Demeter and Sarter (2012) propose that tonic Ach activity levels mediate both top-down attentional control and the engagement of attentional effort 'to stablise or maintain attentional performance'. Using an animal analogue of the RVIP, Sarter's group report that tonic levels of Ach increase with performance demands, and that higher levels correlate with a decrease in the decremental effect of distraction (St Peters et al., 2011). From these data, Demeter and Sarter (2012) suggest that augmentation of tonic levels of ACh may represent a central mechanism for enhancing attentional control and optimising cue dectection. As noted above, enhanced sustained attention and a reduced validity effect was observed in e4+. On this basis, the behavioural advantages we have observed in e4+ could indicate a difference in ACh tonic activity.

Previous imaging work also supports a common interpretation of the behavioural effects. Brain areas where overactivity was seen in e4+ during the covert attention task (bilateral precuneus and SMA) have been linked to RVIP task performance, with greater activity in these regions is associated with a higher hit rate and lower RT (Lawrence et al., 2003).

It is possible, then, that by better recruiting parietal regions, e4+ exercise more top-down control and maintain a higher attentional effort, indexed by a widening of the attentional field both spatially and temporally. This may be linked to an increase in tonic levels of Ach activity — either through baseline differences or as a consequence of greater sensitivity to task demands. We have speculated previously that response to challenge by e4+ may define situations where cognitive differences emerge (Evans et al., under review) and that there may be an association with the integrity of the cholinergic system (Marchant et al., 2010). Greenwood et al. (2000) and Parasuraman et al. (2002) have speculated that reduced cholinergic activity in parietal regions in e4+ older adults mediates the behavioural deficits observed in attention shifting and attention scaling. Support for this view came from an early study by Poirier et al. (1995) reporting a dose-related reduction in cholinergic activity in e4+ older adults. More recently, however, Eggers et al. (2006) reported that for a group of older adults with dementia, cognitive impairment correlated with reduced levels of cortical acetylcholinesterase, but e4+ individuals in fact had significantly higher levels relative to e4−. To our knowledge, no studies have measured tonic ACh levels in younger adults. This is an area that clearly warrants further research.

DTI

In order to draw links with structural connectivity measures, we assessed correlations between behavioural performance and whole-brain axial diffusivity, a measure that differentiated this cohort of e4+ and e4− (Ruest et al., under review). Axial diffusivity is thought to reflect integrity of axonal microstructure, with higher axial diffusivity implying better fibre coherence (Zhang et al., 2007). Here we demonstrate a relationship between axial diffusivity and the size of the validity effect in the covert attention task, across all participants. Those with higher axial diffusivity showed a smaller difference in performance between valid and invalidly cued trials. Higher axial diffusivity likely relates to the functional overactivity discussed above. Studies combining both structural and functional measures have shown positive correlations between indices of white matter integrity and functional activity (Kern et al., 2012; Toosy et al., 2004), and white matter integrity has been linked to reaction times (Madden et al., 2004). Improved white matter integrity in e4+ suggests better communication between brain regions, driving increases in the observed functional activity. The fMRI BOLD signal seems to mainly reflect input activity to an area and localised processing (Logothetis et al., 2001), so more coherent myelination could directly produce an increase in BOLD response. Alternatively, action potentials could influence myelinogenesis during development, since myelination seems to be driven by action potentials in neighbouring neurons (Demerens et al., 1996).

We could find no correlation between performance on the RVIP task and axial diffusivity measures. This might be due to the accuracy measure derived from the task not being sufficiently sensitive to differentiate individuals.

Conclusions

We have shown that e4+ young adults achieve better performance on a rapid visual information processing task, and a reduced validity effect on a covert attention task. We suggest that this may indicate that e4+ individuals operate with a broader attentional field that may for certain tasks promote better cognitive outcomes. This broader attentional field is associated with both enhanced precuneus activity and greater axial diffusivity. We speculate that it may also index genotype differences in cholinergic system activity, for example, higher tonic acetylcholine levels in e4 carriers.

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