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Putting attention in the spotlight: The influence of *APOE* genotype on visual search in mid adulthood

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Abstract

The Apolipoprotein E e4 allele is associated with greater cognitive decline with age, yet effects of this gene are also observed earlier in the lifespan. This research explores genotype differences (e2, e3, e4) in the allocation of visuospatial attention in mid-adulthood. Sixty-six volunteers, aged 45-55 years, completed two paradigms probing the active selection of information at the focus of attention (a dynamic scaling task) and perceptual capacity differences. Two methods of statistical comparison (parametric statistics, Bayesian inference) found no significant difference between e4 carriers and the homozygous e3 group on either the dynamic scaling or perceptual load task. E2 carriers, however, demonstrated less efficient visual search performance on the dynamic scaling task. The lack of an e4 difference in visuospatial attention, despite previous suggestion in the literature of genotype effects, indicates that select attentional processes are intact in e4 carriers in mid-adulthood. The association of e2 genotype with slower visual search performance complicates the premised protective effects of this allele in cognitive ageing.

Keywords: *APOE*, Cognitive Aging, Alzheimer's disease, Attention, Visuospatial, Mid-adulthood

1. Introduction

The Apolipoprotein E (*APOE*)¹ gene is associated with individual differences in cognitive ageing. The three allelic variants (e2, e3, and e4) differ in prevalence, estimated at 12%, 60% and 23% of Caucasian populations respectively (Raber, Huang, & Ashford, 2004). While homozygous e3 carriers are considered the population norm, possession of an e4 allele increases risk of Alzheimer's disease (AD) (Corder et al., 1993; Farrer et al., 1997). In addition, negative effects of carrying an e4 allele are reported in a number of domains in healthy aging (65 years and older), including global cognition, episodic memory, attention, and executive function (Berteau-Pavy, Park, & Raber, 2007; Espeseth et al., 2006; Marioni et al., 2015; Packard et al., 2007; Reinvang, Winjevoll, Rootwelt, & Espeseth, 2010; Staehelin, Perrig-Chiello, Mittrache, Miserez, & Perrig, 1999; for reviews see: Small, Rosnick, Fratiglioni, & Bäckman, 2004; Wisdom, Callahan, & Hawkins, 2011). Of interest, the e2 variant is suggested to offer some protection against pathological ageing (Farrer et al., 1997; Lippa et al., 1997; Wilson, Bienias, Barry-Kravis, Evans & Bennett, 2002), but fewer studies have considered the effects of this allele in healthy cognitive ageing, with reported effects limited to tasks engaging memory (Helkala et al., 1996; McFall et al., 2015; Wilson et al., 2002).

Carriers of the e4 allele demonstrate subtle cognitive differences earlier in the lifespan, but at present genotype differences observed prior to 65 years of age lack consistency (for reviews see: Ihle, Bunce, & Kliegel, 2012; Lancaster, Tabet, & Rusted, 2017; Rusted & Carare, 2015; Salvato, 2015). A likely factor in this inconsistency is the cognitive process under study, with the strength of genotype effects premised to vary by cognitive domain. To date, many studies have explored the association between *APOE* and episodic memory, in line with the prevalence of memory loss in dementia. A meta-analysis, however, found attention differences to be a more reliable marker of preclinical dementia than measures of delayed recall (Twamley, Ropacki, & Bondi, 2006). Hence, we predict attention may be a more sensitive marker than episodic memory of cognitive decline from mid-adulthood, facilitating the early identification of those shifting to a disadvantageous trajectory of cognitive ageing.

Here we explore *APOE* genotype differences in visual search, defined as the efficient deployment of selective attention to a relevant target within the visual scene (Awh, Vogel, & Oh, 2006). Selective attention is often analogised to a 'spotlight', conceptualised as a gradient of heightened processing surrounding a central fixation; with individuals able to shift this spotlight across the visual scene (Posner, 1980). Greenwood & Parasuraman (2004) argue selective attention is characterised by an additional ability to scale the breadth of this attentional 'spotlight' on the basis of top-down information. Selective attention and working memory are sometimes viewed as overlapping constructs, with working memory acting as an interface for the active maintenance and manipulation of information at the forefront of attention (Awh et al., 2006; Chun, 2011; Cowan, 1999; Gazzaley & Nobre, 2012). Hence,

¹ **Abbreviations:** Analysis of variance (ANOVA), Apolipoprotein E (*APOE*), Alzheimer's Diseases (AD), Bayes factor (*B*), Blood pressure (BP), Body mass index (BMI), Independent variables (IV), Irrelevant distractor (ID), National Adult Reading Test (NART), No distractor (ND), Response time (RT), Simple response time (SRT), Standard deviation (SD).

early genotype differences should be considered in the context of the expected pattern of age-related decline in both of these processes.

The dynamic scaling paradigm (Greenwood & Parasuraman, 1999) probes individual differences in the ability to adjust the breadth of attentional ‘spotlight’ during visual search. Participants’ attention is guided to a region of the visual scene by a spatial cue presented before the search array. This cue facilitates visual search by indicating where the target stimulus will appear, if present, hence promoting greater perceptual processing at this location (Hawkins, Goyal, & Sergio, 2015). The size of the cue varies across trials, with smaller cues (encompassing fewer stimuli from the visual array) providing more localised target information. Decreasing cue size is associated with shorter search response times (RTs), indexing the benefit of dynamically restricting attentional focus on the basis of this top-down information. The greatest benefit of spatial cueing is observed on conjunction search trials, characterised by a target letter being distinct in a combination of features, as opposed to feature or ‘pop-out’ trials where the target is identifiable by one feature (i.e. colour) (Parasuraman, Greenwood, & Alexander, 2000).

Performance on the dynamic scaling paradigm shows sensitivity to both age-related change, and pathological change associated with AD (Parasuraman et al., 2000). In adults aged 65-74 years, more localised spatial cues clearly benefit the efficiency of visual search, however, this effect is reduced in a sample of healthy older adults, aged 75-85 years, and is present only following the most localised spatial cue for a group with AD (Parasuraman et al., 2000). Hence it is interpreted that the spatial flexibility of attentional focus is sensitive to age-related decline.

The dynamic scaling task has also been used to explore *APOE* genotype effects in late-mid adulthood. In comparison to both a homozygous e3 group and an e2 group, e4 carriers aged 50 years and older demonstrated reduced benefit of smaller, more localised spatial cues (Greenwood, Sunderland, Friz & Parasuraman, 2000). Additionally, in a population of healthy adults (mean age 60 years), homozygous e4 carriers showed significant declines in the use of spatial cueing across three years (Greenwood, Sunderland, Putnam, Levy, & Parasuraman, 2005). This pattern was not seen in heterozygous e4 carriers, or non-carriers. These results suggest that e4 carriers demonstrate a profile of accelerated ageing, with comparable reductions in the spatial flexibility of attentional focus seen in this group and adults aged 75 years and older. Therefore, reduced visuospatial attentional scaling may be a sensitive marker for those in the initial stages of cognitive decline.

APOE genotype differences have also been reported using variants of the Posner spatial cueing task (Posner, 1980). While visual search paradigms probe the selection of information within attentional focus, this task provides an index of both the efficiency of attentional shifts across the visual field and the ability to process information at the periphery of the attentional ‘spotlight’. On trials of the Posner spatial cueing task, a directional spatial cue is presented prior to target onset, which guides attention to one half of the visual scene. The majority of cues are valid, leading to more efficient perceptual processing of the visual target. Some trials however, contain invalid cues; these trials are associated with a cost to the speed of target identification as following target onset in the periphery, attentional focus must be disengaged from the incorrect location and shifted across the visual scene (Pesce & Bösel, 2001; Posner & Petersen, 1989).

In agreement with e4 carriers demonstrating a profile of accelerated ageing in visuospatial attention, e4 carriers aged 41-85 years, and 50 years and older respectively, showed greater cost of invalid cueing to target item location (Greenwood et al., 2000; Greenwood et al., 2005). This was interpreted by the authors as representing deficits in the reorientation of attentional focus across the visual scene, similar to the behavioural profile shown by those in the early stages of AD on this task (Parasuraman, Greenwood, Haxby & Grady, 1992). In a group of middle-aged adults, aged 43-58 years, however, no genotype differences in attentional shifting were observed (Evans et al., 2014), questioning at what point in the lifespan e4 detriments in visuospatial attention emerge. Indeed, in a sample of young adults, aged 18-30 years, e4 carriers showed reduced cost of invalid cueing compared to homozygous e3 carriers, suggesting this group are less disadvantaged by directing their attention to an incorrect region of the visual scene (Rusted et al., 2013). This may represent e4 carriers approaching the task with a larger 'spotlight' of perceptual attention, allowing for greater processing of targets in the periphery. Of note, reports of differential *APOE* genotype effects across age-groups may reflect changing gene expression over the lifespan, rather than contradictions across research reports (Han & Bondi, 2008).

The overarching aim of this research is to establish if there are *APOE* genotype differences in the allocation of selective attention during visual search in mid-adulthood. The study administers two complementary tasks; the dynamic scaling paradigm (Greenwood & Parasuraman, 1999) (used previously), and a perceptual load task (Forster & Lavie, 2007). Whilst the dynamic scaling task probes the active selection of information at the locus of attention, the perceptual load task explores another important determinant of selection attention: perceptual capacity. Together these tasks provide a broad investigation of differences in attentional 'spotlight' processes during visual search.

Over the past two decades a large body of evidence supporting Load Theory has highlighted that the involuntary allocation of attention to irrelevant information depends on the availability of perceptual capacity (Lavie, Hirst, de Fockert, & Viding, 2004; Lavie, 1995; for review see: Lavie, 2005; 2010). Load Theory accommodates both early and late selection accounts of attention, with selection at the stage of perception defined as early and post-perceptual selection as late (Benoni & Tsal, 2013; Lavie et al., 2004). Load theory suggests that information will be attentionally processed until our fixed perceptual capacity limit is reached, after which point task-irrelevant information will be passively filtered out (early selection). When the limit of perceptual capacity has not been reached, attentional control mechanisms are applied to bias processing of goal-relevant stimuli in cases where the distractor has reached attentional awareness (late selection). This theory has been supported by measures of distractor processing in healthy adults (Forster & Lavie, 2007, 2008). A consistent cost of peripheral distractor presence has been found in visual search trials of low perceptual load. This cost is eliminated in trials of high perceptual load, as there is no capacity left to process the distractor. The level of load in which the cost disappears is indicative of the perceptual attentional capacity.

Recruiting individuals from a narrow age-range (45-55 years) we sought to avoid any potential influence of preclinical pathological change. The study explores two possibilities: whether visuospatial attention is sensitive to accelerated ageing in e4 carriers, indicated by either a reduction in perceptual capacity or in the spatial flexibility of 'spotlight' mechanisms;

or alternatively, whether, as in early adulthood, e4 carriers differentially approach visual search with a broader ‘spotlight’ of perceptual attention that persists into mid-adulthood.

In line with previous research using the same dynamic scaling paradigm (Greenwood et al., 2000; Greenwood et al., 2005), e4 carriers are expected to show less efficient attentional scaling on this task, consistent with reduced spatial flexibility of attentional ‘spotlight’ mechanisms. Carriers of the e3 and e2 alleles are expected to show equal benefit of increasingly localised spatial cues on the dynamic scaling paradigm, indicative of an efficient use of attentional scaling. Detrimental effects of e4 status may be absent, however, due to the younger group included here compared with previous research (Greenwood et al., 2000, 2005).

Like dynamic scaling, the perceptual load task has demonstrated sensitivity to cognitive ageing. In healthy older adults (aged 65-79 years), distractor compatibility effects were significantly reduced between low (set size: one stimulus) and mid (set size: four stimuli) levels of perceptual load. By contrast, distractor effects were still present on trials of mid perceptual load in young adults, although both age groups showed an elimination of distractor effects on trials with high perceptual load (set size: six stimuli) (Maylor & Lavie, 1998). The elimination of distractor processing at a lower level of perceptual load is consistent with an age-related reduction in perceptual capacity. If e4 carriers were demonstrating a profile of accelerated ageing on this task, by mid-adulthood this group may show no distractor effects on mid-perceptual load trials (i.e. showing the reduced capacity found in older adults in Maylor & Lavie’s (1998) study). If, however, the widened attentional ‘spotlight’ suggested by performance on the Posner spatial cueing task in younger adults (Rusted et al., 2013) persists into mid-adulthood, distractor cost may persist on trials of higher perceptual load in e4 carriers. As the effect of e2 status is less commonly studied, no predictions are made for this genotype group.

2. Method

2.1 Participants.

One hundred and sixty-five healthy adult volunteers (aged 45-55 years), recruited through advertisement at local universities, clubs and community centres, completed the initial screening phase of the study. Volunteers were required to be non-smokers and fluent in English. Furthermore, volunteers were screened for a history of vascular health problems, untreated high blood pressure (BP), psychoactive medication use, or recorded neurological/psychiatric condition within the past 5 years.

The initial screening allowed for prior collection of a genotype sample from each volunteer. Screening procedures followed Human Tissue Authority (HTA) procedures, and the full study followed a protocol approved by the research ethics committee of the school of Psychology and Life Sciences, University of Sussex. All procedures were in accordance with the Helsinki declaration. Volunteers first provided written informed consent, including acknowledgment that the results of the genotype analysis would not be made available to them, before DNA was collected by buccal swab. Genotyping followed triangulated anonymization procedures, with two anonymized codes used per sample. Samples were analysed to determine *APOE* gene variant by LGC Genomics (Hertfordshire, www.lgcgroup.com/genomics). A

fluorescence-based competitive allele-specific polymerase chain reaction determined the combination of three major *APOE* alleles (e2, e3, and e4) based on two *APOE* single nucleotide polymorphisms (rs429358, rs7412).

Sixty-six volunteers completed the experimental phase of the research. Post-screening, invitation to participate was pseudo-random to ensure a suitable sample size in each genotype group, rather than selection being representative of the expected frequencies of each allele within the population. The distribution of genotypes within the sample was as follows: 16 e2 carriers (1 e2/e2; 15 e2/e3), 26 homozygote e3 carriers, and 25 e4 carriers (17 e3/e4; 7 e4/e4). Throughout the study both the participant and the experimenter were kept blind to genotype information. Characteristics of the final sample are shown in Table 1.

2.2 Materials.

2.2.1 Demographics and baseline cognitive measures.

Medical history, medication use and general state of health were assessed using a shortened version of the Nuffield Medical History Questionnaire. Additionally, baseline measures of IQ (National Adult Reading Test (NART)(Nelson & Willison, 1991)), working memory (backwards digit-span), and simple response time (SRT) were obtained. To index response time (RT), participants were required to make a keyboard response as soon as possible following presentation of a stimulus on screen. Response time was averaged over 48 trials, excluding RTs more than 3 standard deviation (SD) away from the mean.

2.2.2 The dynamic scaling task.

The dynamic scaling task (Greenwood & Parasuraman, 2004) required participants to search for a pink T within a 15 letter array (5 across x 3 down), and make a speeded response as to whether the target letter is present ('2' keyboard response) or absent ('6' keyboard response). Before each array is presented, a black box cues where the target may or may not appear.

In total, the task consisted of 240 trials split randomly into 3 blocks. In each trial, a central fixation cross was presented for 1000ms, followed by a cue for 500ms prior to the onset of the letter array. The letter array and the cue were then presented simultaneously until a response was detected. The array could appear on either the right (120 trials) or left (120 trials) of the fixation cross, and consisted of the characters T, G, and N presented in either pink, blue or green. Letter-colour combinations of non-target items in the array were generated randomly, following constraints of the search type (conjunction, feature) for that trial.

The task had 3 IVs integrated into its design: search type, cue size and cue validity. Search trials were split into feature search (120 trials), where the target letter is the only pink letter in the display, and conjunction search (120 trials), where the participant searched for the pink 'T' among an array of letters of the same type ('T') and colour (pink). Physical cue size varied across trials, encompassing either 1, 3, 9, or 15 letters from the search array, with 60 trials at each size of cue. Cues were classed as valid (200 trials) or invalid (40 trials) depending on whether the target letter was enclosed within. An example trial of the dynamic scaling task is presented in Figure 1.

2.2.3 The perceptual load task.

The perceptual load task (Forster & Lavie, 2007; 2008) is a visual search paradigm including two independent variables (IVs): perceptual load (low, high and medium) and distractor presence (blank, capture).

Participants were required to indicate the presence of either an 'X' or an 'N' target letter in each trial, by making a '0' key press response for X and '2' key press response for N. Each trial initiated with the presentation of a central fixation cross for 500ms, followed by the presentation of a stimuli display for 200ms. Each stimuli display consisted of 6 white letters, one of which was always a target letter, arranged circularly on a black background. Identity of target letter and position of target within circle was counterbalanced across trials. Participants were requested to respond as quickly and accurately as possible. An auditory tone was used to provide feedback for incorrect responses or if no response was made within 2000ms.

Perceptual load was manipulated across trials. In trials of low perceptual load (set size 1), non-target letters in the stimulus display consisted of small 'O's. In trials of medium perceptual load (set size 4) there was 1 target letter, 3 non-target letters and 2 small 'O's in the stimulus display. In trials of high perceptual load (set size 6), in addition to the target, there were 5 non-target letters in the display. Non-target letters consisted of 'H', 'K', 'Z', 'M', 'W'; chosen to be similar to target letters in angular shape. 720 trials were presented in 12 blocks of 60, with each block containing trials of a single level of perceptual load. Each participant completed 4 repetitions of a counterbalanced perceptual load sequence. In addition, participants completed a practice block for each level of perceptual load, with feedback on performance accuracy provided. An accuracy level of 65% was required for participants to proceed to experimental trials to ensure each participant was able to perform the task above chance level (50%).

Trials were classified according to whether a task-irrelevant distractor image (Spongebob, Spiderman, Superman, "Pokemon", Donald duck and Mickey) was presented in the periphery of the screen. 10% of trials featured a distractor image and were hence considered 'capture' trials, whilst 90% of trials had no distractor, and so were considered 'blank'. An example of distractor trial can be seen in Figure 1. Participants were instructed to ignore the distractors, as these would impede their performance.

2.3 Procedure

Volunteers selected from the screening phase took part in a single study session. First, demographic and health measures including age, family history of dementia, height, weight, and BP were collected. A measure of systolic and diastolic blood pressure was collected whilst seated, using an automatic arm-cuff machine on the right arm. Participants then completed a selection of experimental tasks and questionnaires in a fixed order.

2.4 Analysis

Differences in demographics and baseline cognitive performance were analysed between genotype groups (e2, e3 and e4) using a series of one-way analysis of variances (ANOVAs)

for continuous variables, and chi-squared tests for categorical measures (gender, family history).

For each experimental task data was first analysed using parametric statistics, then using Bayesian statistics. All three genotype groups were compared using parametric statistics; following this, if there was suggestion of a genotype difference, separate analyses were run comparing e4 carriers and e2 carriers individually to the e3 group. Bayesian statistics independently compared e2 and e4 genotype groups to homozygote e3 carriers.

Bayesian statistics were included to establish the strength of evidence for either the null (H_0) or alternative hypothesis (H_1). A Bayes factor (B) of > 3 indicates substantial evidence for H_1 , whereas a B of $< 1/3$ indicates substantial evidence for H_0 . A B in the range $1/3 - 3$ indicates the data may be insensitive for distinguishing between the two hypothesis (Dienes, 2014). B s were modelled from 3 distributions in the current analysis. Directional predictions were modelled from a half-normal distribution ($B_{H(0, x)}$), with x representing the prior estimate of effect size. Non-directional predictions were modelled from a normal distribution ($B_{N(0, x)}$), with x representing half the prior effect size. In addition, when all effects in a specified range were equally likely B s were modelled as a uniform distribution ($B_{U(0, x)}$), with x representing the maximum expected effect.

2.4.1 The dynamic scaling task.

2.4.1.2 Overall task performance.

Accuracy and median RTs for each search type (feature, conjunction) and cue size (1, 3, 9, 15 letter stimuli) were analysed for valid trials. Across all volunteers, a repeated measures ANOVA (search type x cue size) was completed for search RTs. The slope of attentional scaling (an index of RT change with decreasing cue size) was used to probe this interaction further using Bayesian inference, with a greater scaling slope predicted for conjunction trials compared to feature search trials. The prior effect size was based on the feature and conjunction scaling slopes reported in a late-mid age homozygous e3 group (Greenwood et al., 2000).

2.4.1.2 Genotype effects.

To explore genotype differences in RT a mixed ANOVA with cue size (1, 3, 9, and 15 letter stimuli) as the within-subject factor and genotype (e2, e3, e4) as the between-subject factor was conducted for both feature and conjunction search trials. Individual Bonferroni-adjusted t -tests were used to probe significant effects of genotype where present, comparing e4 and e2 carriers to the e3 group. A B for the Genotype x Cue Size interaction was modelled from the current data for both feature and conjunction search trials (see Dienes (2014) for further explanation of using Bayesian statistics to explore interactions). The population interaction effect (effect of cue size in group 1- effect of cue size in group 2) was modelled as a uniform distribution for each search type, varying from 0 (i.e. when both groups show an equivalent effect of cue size) and the maximum effect of cue size reported for the two groups (i.e. when one group demonstrates an effect of cue size, and one group demonstrates no effect). In addition, following a significant Genotype x Cue Size interaction (indicated by parametric statistics), B s were computed for each post-hoc comparison. Prior effect sizes were based on

previously reported genotype differences (Greenwood et al., 2000). It was predicted that e4 and e2 carriers would demonstrate greater search RTs at cue size 3 and 1. All other predictions were non-directional.

The scaling slope for conjunction search trials was compared between genotype groups using a one-way ANOVA. Again, individual Bonferroni adjusted *t*-tests were used to probe significant effects of genotype where present, comparing e4 and e2 carriers to the e3 group. For the Bayesian analysis of scaling slope on conjunction search trials, no directional prediction was made for an e2 difference, however, e4 carriers were predicted to show a reduced slope compared to the e3 group. Prior effect sizes were estimated from the genotype differences in slope reported in Greenwood et al., (2000).

A one-way ANOVA was used to test genotype differences in accuracy. There was no directional prediction for a genotype difference in accuracy, hence *B*s were modelled from a normal distribution. The prior effect size was based on the maximum difference in accuracy previously reported (Greenwood et al., 2000).

2.4.2 The perceptual load task.

RTs less than 100ms or more than 3000ms were removed prior to analysis. Mean RT for correct trials and accuracy were considered separately. Mixed 3 x 3 x 2 ANOVAs were performed on both RTs and accuracy, with genotype (e2, e3, e4) as the between-subjects factor, and perceptual load (low, mid, high) and distractor (blank, capture) as the within-subjects factors. Interactions were probed using Bonferroni-adjusted *t*-tests.

2.4.2.1. Bayesian analysis

Bayesian analysis of the main effect of perceptual load followed the same approach for RTs and accuracy. For blank trials, a *B* for each pairwise comparison of perceptual load was modelled from a half normal distribution, based on the prediction that RTs would increase and accuracy decrease with increasing perceptual load. The neutral distractor condition in young adults² (set size 1, 4 and 6) was used for prior effect sizes (Maylor & Lavie, 1998).

The Load x Distractor interaction was analysed by calculating a *B* for the difference in distractor cost, defined as the difference between blank and capture trials, for all pairwise comparisons of perceptual load. For RTs, the prior effect size was based on the difference in irrelevant distractor cost between trials of low (set size 1) and high (set size 6) perceptual load (Experiment 2b: Forster & Lavie, 2008). In addition, the presence of RT distractor costs at each level of perceptual load was probed, modelled as a half normal distribution with a prior effect size based on the maximum distractor cost reported in Experiment 2b; Forster & Lavie (2008). Perceptual load differences in distractor cost for task accuracy were modelled from a full-normal distribution, as load was not predicted to modulate distractor effects.

² The effect of perceptual load in our dataset, both for RT and accuracy, more closely resembled the effect reported in young adults than the older group included in Maylor and Lavie (1998). Hence this group was used for the prior. Recalculating the *B*s with prior effect sizes based on the older population did not change the results.

Multiple *B*s for the Load x Distractor x Genotype interaction were computed to assess the strength of evidence for distractor costs at each level of perceptual load in each genotype group. For both RTs and accuracy, prior effect sizes were again based on Experiment 2b, Forster & Lavie (2008).

3. Results

3.1 Demographics & baseline cognitive measures.

No genotype difference was found across demographic measures ($p > .05$). Furthermore, no group differences were found in WM span, or SRT ($p > .05$). The demographic and baseline characteristics of each genotype group are shown in Table 1.

Table 1. *Demographics and performance on baseline cognitive measures*

| Measure | Genotype Group | | |
|-----------------------|----------------|----------------|----------------|
| | e2 | e3 | e4 |
| <i>n</i> | 16 | 26 | 24 |
| Age | 50.44 (3.58) | 49.04 (2.68) | 49.17 (3.07) |
| Gender (% female) | 75 | 73 | 63 |
| Family History (%Yes) | 25 | 35 | 54 |
| Education | 17.22 (3.24) | 17.23 (3.13) | 17.85 (4.32) |
| NART | 119.06 (2.84) | 118.56 (2.93) | 116.87 (4.62) |
| BMI | 24.02 (3.44) | 26.24 (4.37) | 25.15 (3.78) |
| Systolic BP | 115.63 (7.55) | 118.23 (8.47) | 115.00 (8.76) |
| Diastolic BP | 77.31 (9.99) | 81.77 (10.63) | 79.13 (7.77) |
| SRT (ms) | 272.24 (44.15) | 265.24 (32.39) | 266.90 (27.84) |
| Digit-span | 4.31 (1.30) | 4.19 (1.50) | 4.00 (1.65) |

Notes: Mean (SD). Body mass index (BMI)

3.2 Dynamic scaling task.

3.2.1 Overall task performance.

Accuracy on task was consistently high, with scores ranging from 84% to 100% (Mean=97%) correct across valid trials. Accuracy of one volunteer was below chance (43%) on this task, and so their data was removed prior to analysis.

Across participants, median RTs were significantly longer for conjunction search trials than feature search trials, $F(1,63)=458.19$, $p < .001$, $\eta^2_p = .879$. A significant effect of cue size, $F(1.99, 125.65)=202.53$, $p < .001$, $\eta^2_p = .763$, was also found, with RTs decreasing as a function of smaller cue. There was a Search type x Cue size interaction, $F(1.99, 125.65)=115.73$, $p < .001$, $\eta^2_p = .648$, shown in Figure 2. This was driven by a greater slope of RT decrease with reducing cue size for conjunction search trials ($b=15.44$) than feature search trials ($b=3.98$), $t(64)=-14.83$, $p < .001$, $B_H(0, 7.5) = 8.09374E+46$.

3.2.2 Genotype differences.

No significant genotype difference was found for accuracy across valid trials, $F(2, 61)=.979$, $p=.381$. Both the e2 to e3 comparison ($B_N(0, 2.35)=.97$) and the e4 to e3 comparison ($B_N(0, 2.35)=.95$) are insensitive for determining a genotype difference in accuracy.

For feature search trials, there was a significant main effect of cue size on RT, $F(2.26, 137.82)=50.81$, $p<.001$, $\eta^2_p=.454$, but the main effect of genotype ($p=.243$) and the interaction between genotype and cue size ($p=.290$) were both non-significant. Bayesian analysis of the Genotype (e2, e3) x Cue Size (1, 3, 9, 15 letters) interaction provides anecdotal support for H0: $F(3, 117)=.56$, $p=.646$, $\eta^2_p=.014$, $B_U(0, 56.80)=.57$. Data was insensitive for determining a Genotype (e4, e3) x Cue size (1, 3, 9, 15 letters) interaction, $F(3, 141)=1.98$, $p=.120$, $\eta^2_p=.040$, $B_U(0, 74.13)=1.58$.

Search RTs and the slope of attentional scaling on conjunction search trials are shown in Table 2. There was a significant main effect of both cue size, $F(2.04, 124.50)=213.26$, $p<.001$, $\eta^2_p=.778$, and genotype, $F(2, 61)=3.69$, $p=.031$, $\eta^2_p=.108$, on conjunction search RTs. The effect of genotype was driven by e2 carriers responding significantly slower than the e3 group ($p=.042$). In addition, there was a significant Genotype x Cue Size interaction, $F(4.08, 124.50)=2.53$, $p=.043$, $\eta^2_p=.077$. The comparison of e2 and e3 genotype groups provide sensitive support for a Genotype x Cue Size interaction, $F(3, 117)=4.53$, $p=.005$, $\eta^2_p=.104$, $B_U(0, 279.67)=4.33$. The comparison of e4 and e3 genotype groups provide sensitive support for no Genotype x Cue Size interaction, $F(3, 141)=.239$, $p=.869$, $\eta^2_p=.005$, $B_U(0, 221.70)=.26$.

Results of the post-hoc analysis of genotype differences at each cue size on conjunction search trials are shown in Table 3 (Bonferroni corrected $\alpha=.006$). E2 carriers demonstrated significantly longer RTs than the e3 group at cue size 15 ($p=.004$, $B_N(0, 30)=4.32$). There was also support for this group showing significantly longer RTs at cue size 1 ($p=.068$, $B_H(0, 60)=3.47$). E4 carriers did not significantly differ in search RTs from the e3 group at any cue size ($p>.006$) however; data appears insensitive for supporting either the null or alternative hypothesis.

To further probe the interaction between genotype group and cue size on conjunction trials, the slope of change in RT with reducing cue size was considered. At trend level there was an effect of genotype, $F(2, 63)=2.66$, $p=0.78$, driven by the difference between the e3 and e2 groups ($p=.035$; $B_N(0, .1)=1$). The genotype difference between e3 and e4 carriers was non-significant, ($p=.525$; $B_N(0, 1.75)=1.07$). Genotype differences in slope are also shown in Figure 3.

Table 2. For each genotype group, RT (ms)(SD) to detect target presence and the slope of attentional scaling is shown.

| Genotype | Cue size | | | | Slope |
|----------|----------|----------|----------|----------|-------|
| | 1 | 3 | 9 | 15 | B |
| e2 | 537 (73) | 612 (74) | 696 (80) | 817 (85) | 18.80 |
| e3 | 484 (73) | 565 (75) | 646 (80) | 691 (85) | 13.83 |

| | | | | | |
|----|----------|----------|----------|----------|-------|
| e4 | 481 (73) | 563 (75) | 654 (80) | 703 (85) | 14.93 |
|----|----------|----------|----------|----------|-------|

Note: Cue size represents the number of letter stimuli encompassed within each spatial cue

Table 3. *p* values and *B*s for the post hoc comparisons of the Genotype x Cue Size interaction for conjunction search trials

| Genotype group comparison | Cue Size | | | | |
|---------------------------|----------|-------------------|-------------------|---------------------|-------------------|
| | 1 | 3 | 9 | 15 | |
| e2 and e3 | <i>p</i> | .068 | .114 | .156 | .004 |
| | <i>B</i> | $B_H(0, 60)=3.47$ | $B_H(0, 65)=2.27$ | $B_N(0, 22.5)=1.14$ | $B_N(0, 30)=4.32$ |
| e3 and e4 | <i>p</i> | .899 | .932 | .748 | .687 |
| | <i>B</i> | $B_H(0, 45)=.39$ | $B_H(0, 35)=.53$ | $B_N(0, 2)=1$ | $B_N(0, 2.5)=1$ |

Note: Bonferonni corrected alpha=.006. *B*'s <1/3 or >3 or sensitive.

3.3 The perceptual load task.

Performance on this task is shown according to genotype group in Table 4.

3.3.1 RT.

Assumptions of sphericity were violated so a Greenhouse-Geisser correction was applied for the main effect of perceptual load. With increasing perceptual load, RTs significantly increased, $F(1.27, 78.62)=352.16$, $p<.001$, $\eta^2_p=.850$. The Bayes analysis supports a sensitive increase in RT with increasing perceptual load (low to mid : $B_H(0, 118)= 9.80017E+90$; low to high: $B_H(0, 230)= 1.54409E+92$; mid-high: $B_H(0, 52)= 2.93020E+22$).

The main effect of distractor was significant, $F(1, 62)=17.81$, $p<.001$, $\eta^2_p=.223$, with RTs longer for capture trials than blank trials. Sphericity was again violated for the interaction between perceptual load and distractor presence, so degrees of freedom were corrected using a Huynh-Feldt correction ($\epsilon=.92$). A significant interaction between perceptual load and distractor presence was found, $F(1.84, 113.98)=8.55$, $\eta^2_p=.223$. This interaction is shown in Figure 4, and was driven by there only being a main effect of distractor presence at low-load, Bonferonni corrected $\alpha = .017$, $t(64)=-8.87$, $p<.001$, $B_H(0, 61)= 1.03191E+16$. At mid and high perceptual load the effect of the distractor was eliminated ($p>.017$; mid: $B_H(0, 61)= .29$; high: $B_H(0, 61)= .16$). Distractor cost was reduced at both mid ($B_H(0, 50)= 573.01$), and high levels of perceptual load ($B_H(0, 50)= 292.22$) compared to low perceptual load. There was no difference between the distractor cost at mid and high perceptual load ($B_H(0, 50)= .23$).

The main effect of genotype was non-significant ($p=.262$) as were all interactions between genotype, perceptual load and distractor ($p>.05$). All 3 genotype groups show a sensitive distractor cost on trials of low perceptual load (e2: $B_H(0, 61)= 86169$, e3: $B_H(0, 61)= 356206$, e4: $B_H(0, 61)= 43112$), however, there suggestion of no distractor cost at mid (e2: $B_H(0, 61)= .74$, e3: $B_H(0, 61)= .50$, e4: $B_H(0, 61)=.14$) and high levels (e2: $B_H(0, 61)=.97$, e3: $B_H(0, 61)=.39$, e4: $B_H(0, 61)=.17$) of perceptual load, with sensitive nulls reported in the e4 group.

3.3.2 Accuracy.

Perceptual load again violated assumptions of sphericity, so a Greenhouse-Geisser correction was applied. Accuracy significantly decreased as perceptual load increased, $F(1.46, 91.08)=71.62, p<.001, \eta^2_p=.536$. The Bayes analysis supports a sensitive decrease in accuracy with increasing perceptual load (low to mid: $B_H(0, .05)=157.06$; low to high: $B_H(0, .01)=1.86562E+22$; mid-high: $B_H(0, .07)=1.60033E+21$).

The main effects of distractor and genotype on task accuracy were both non-significant, as were all interaction terms ($p>.05$). Bayesian analysis indicated data was insensitive for detecting a change in distractor cost on accuracy with increasing perceptual load ($B_N(0, .03) < 1/3$ and > 3). The perceptual load x distractor x genotype interaction approached significance, $F(4, 124)=2.11, p=.084, \eta^2_p=.064$, but further examination using pairwise comparisons revealed no significant differences ($p>.05$). Data was insensitive for detecting a distractor cost in task accuracy at each level of load when separately considered between genotype groups ($B_N(0, .03) < 1/3$ and > 3)

Table 4. Mean RT (ms) and accuracy (proportion of trials correct) on the perceptual load task, presented by genotype group, with SD shown in brackets.

| Genotype | Load | | ND | ID | Cost |
|----------|------|----------|-----------|-----------|---------|
| e2 | Low | RT | 552 (48) | 579 (63) | 27 (21) |
| | | Accuracy | .93 (.04) | .94 (.05) | |
| | Mid | RT | 770 (69) | 780 (69) | 10 (40) |
| | | Accuracy | .89 (.07) | .89 (.07) | |
| | High | RT | 827 (81) | 829 (81) | 2 (48) |
| | | Accuracy | .82 (.09) | .79 (.12) | |
| e3 | Low | RT | 524 (42) | 542 (42) | 19 (18) |
| | | Accuracy | .93 (.05) | .92 (.07) | |
| | Mid | RT | 716 (100) | 724 (101) | 8 (27) |
| | | Accuracy | .90 (.07) | .91 (.07) | |
| | High | RT | 780 (132) | 788 (134) | 8 (34) |
| | | Accuracy | .83 (.11) | .82 (.11) | |
| e4 | Low | RT | 549 (85) | 573 (90) | 24 (23) |
| | | Accuracy | .94 (.04) | .94 (.05) | |
| | Mid | RT | 750 (121) | 749 (126) | -1 (38) |
| | | Accuracy | .90 (.07) | .88 (.12) | |
| | High | RT | 825 (156) | 826 (160) | 1 (28) |
| | | Accuracy | .83 (.10) | .82 (.13) | |

Notes: ND= no distractor, ID= irrelevant distractor, Cost = ID-ND

4. Discussion

This study sought to explore how *APOE* genotype influences performance on visuospatial search paradigms in mid-adulthood. Both of the experimental tasks administered here sensitively demonstrated the variation in cognitive performance appropriate to within-task manipulations, supporting the theoretical underpinnings of these paradigms. Of interest, distractor effects were eliminated at both mid and high levels of perceptual load, supporting a reduction in perceptual capacity in a mid-age cohort, an age-range that has not previously been tested (Maylor & Lavie, 1998).

The two tasks included here were selected to investigate if e4 carriers show attentional ‘spotlight’ differences during visual search in mid-adulthood. E4 carriers, however, demonstrated comparable performance to the homozygous e3 group on both the dynamic scaling task and the perceptual load task. This provides no support for the risk factor being associated with either a less responsive ‘spotlight’ mechanism in mid-adulthood, or a widened perceptual window of attention. Carriers of the less commonly studied e2 allele, however, did show performance disadvantages. This group were slower overall to detect the target on conjunction search trials in the dynamic scaling task, with sensitive differences confirmed on trials including both the maximum and minimum size of spatial cue. These results are not consistent with the simple view that e2 status is protective against cognitive ageing, whilst e4 status is disadvantageous.

In contrast to Greenwood and colleagues’ (2000, 2005) findings, our mid-age e4 carriers showed no difference in the ability to modify attentional ‘spotlight’ in light of top-down information. This does not support a trajectory of accelerated ageing being present by mid-adulthood. Failure to replicate this earlier finding may in part be accounted for by differences in sample selection, highlighting a methodological concern in the existing mid-age *APOE* literature (Lancaster et al., 2017). The age-range of participants’ included in Greenwood et al.’s (2000) study was wider, and as a consequence of including older individuals, later-life e4 disadvantages may have impacted overall group differences. The narrow age range included here (aged 45-55 years) importantly, precludes the potential confound of preclinical pathological change. Furthermore, while Greenwood et al. (2000) selected individuals on the basis of an immediate family history of AD, family history of AD was not a selection criterion of the current study meaning the sample may be more representative of a healthy ageing population. In addition, the tightly controlled age-range included here acknowledges the expectation that expression of *APOE* genotype effects is not constant across the lifespan.

Performance on the perceptual load task was equivalent between *APOE* genotype groups, supporting intact perceptual attention in mid-age e4 carriers. Distractor effects were absent in all three genotype groups on trials of both mid and high perceptual load, suggesting reductions in perceptual capacity, comparable to those seen in an older group (aged 65-79 years) (Maylor & Lavie, 1998), occur by mid-adulthood regardless of genotype. Future research could apply the present perceptual load paradigm to test whether young e4 carriers might show this reduction at an earlier point. Previous research reported e4 genotype differences on the Posner spatial cueing task in both young (Rusted et al., 2013) and older adults (Greenwood et al., 2000; Greenwood et al., 2005), perhaps indicating a difference in the breadth of attentional ‘spotlight’. No genotype differences on this task, however, were found in a group of similar age (43-58 years) to the current participant sample (Evans et al., 2014). This may suggest that in mid-adulthood at least, there is little effect of *APOE* genotype on breadth of perceptual attention. One explanation for why no genotype differences in perceptual threshold were seen could be that task sensitivity was poor - load increased in jumps of one item, four items, and six items; a more gradual increase in load may have improved sensitivity to any subtle genotype differences.

Overall, the present results suggest that relative to the e3 population ‘norm’, e4 carriers show equivalent attentional scaling and perceptual capacity in mid-adulthood, countering the argument that the e4 genotype represents a detrimental cognitive phenotype right across the

lifespan. There is some support in the literature for an age x *APOE* interaction, with several studies identifying the end of the 5th decade as a point when detrimental performance effects of *APOE* e4 emerge (Caselli et al., 2009; Jochemsen, Muller, van der Graaf, & Geerlings, 2012; Marioni et al., 2015; Shin et al., 2014). It would seem behavioural performance is preserved in e4 carriers up until 5th decade despite evidence for structural and functional changes prior to this (e.g Dowell et al. 2016; Trachtenberg et al., 2012a; 2012b). Given the reported attentional detriments in a late-mid age sample (Greenwood et al., 2000; 2005a; 2005b), research probing additional factors that may mediate the emergence of decline in this genotype, is important. In respect of the antagonistic pleiotropy position (Han & Bondi, 2008), if the effects of this gene are transitioning from advantages in young adulthood, to disadvantages in later life, the absence of genotype differences recorded here are consistent with a transitioning stage in which the allele is exerting neither a positive nor a negative effect of cognition. Stronger evidence of dissociative effects with longitudinal data across the age span is needed, however, to substantiate this model.

Contrary to expectations, the current study reported performance disadvantages in carriers of the premised ‘protective’ e2 allele. Although cognitive effects of e2 in mid-adulthood have not been well characterised to date, Greenwood and colleagues (2000; 2005) included an e2 group, and found no performance differences on the dynamic scaling task. Again, our results may differ due to discrepancy in population selection. Our results suggest that e2 carriers are approaching the visual search paradigms differently, showing less efficient visual search strategies.

In line with the differential performance of e2 carriers seen in this task, neural data has suggested both e2 and e4 carriers show corresponding differences in function BOLD response compared homozygous e3 carriers (Trachtenberg et al., 2012a; 2012b). Despite equivalent performance on both an episodic memory and Stroop task, both e2 and e4 groups showed overlapping profiles of over-activation in a mid-age group (Trachtenberg et al., 2012a), and similar profiles in a resting-state connectivity analysis (Trachtenberg et al., 2012b). These results, again, confuse the clear dichotomy between cognitive risk and variants of the *APOE* gene, and support the need for further profiling that directly compares all three variants across a wider age span.

There are limitations in the current study. The sample size of each genotype group, in particular the number of e2 carriers, completing the behavioural paradigms was relatively small. However, Bayesian analysis was used to confirm the sensitivity of both e4 equivalence and e2 differences in cognitive performance. Further, although overall group performance on the perceptual load task replicated those suggested by perceptual load theory, standard deviations were large, and this may have reduced sensitivity of the task for detecting genotype differences.

4.1 Conclusions

The results suggest that in healthy mid-age individuals, carrying the e4 variant of *APOE* is not associated with disadvantaged performance on dynamic scaling and perceptual load measures of visuospatial attention, despite the established detrimental effects of this gene in older adults. Attentional ‘spotlight’ differences did not emerge as a potential marker of cognitive decline in this ‘at-risk’ group. Carriers of the e2 allele showed performance disadvantages on

the measures tested here, stressing the need to consider all three variants of *APOE* individually when assessing its impact on cognition. The distinction between 'protective' e2 and 'detrimental' e4 status is not as clear-cut as supposed, and longitudinal studies of how both of these variants impact the trajectory of cognitive ageing is a vital next step.

Figures:

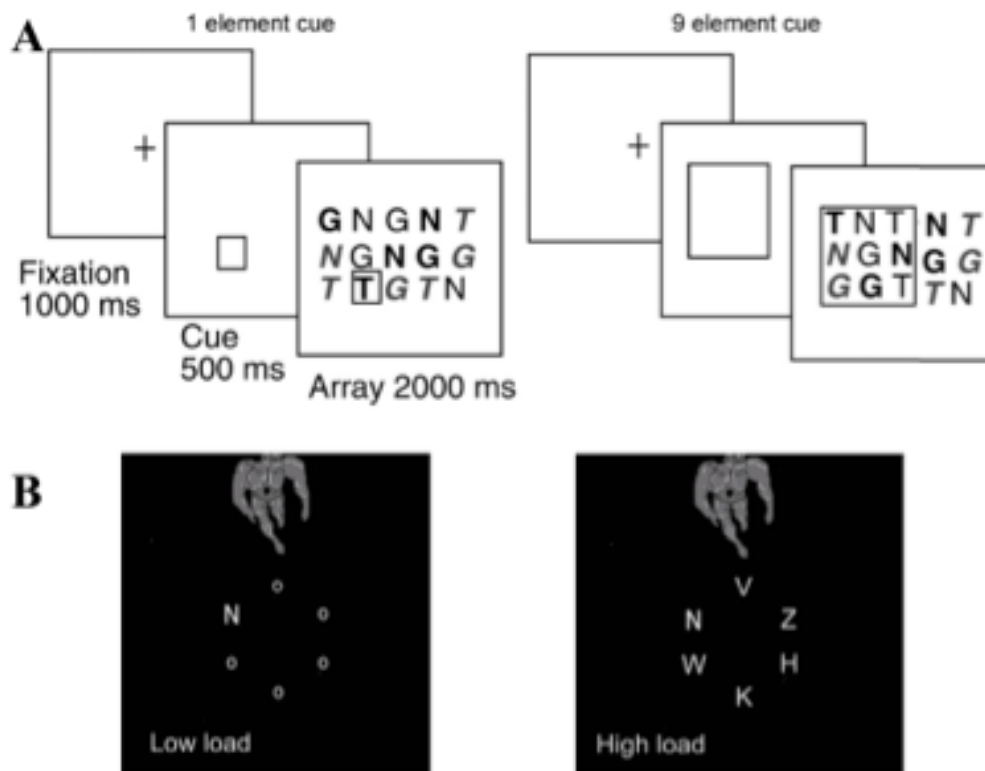


Figure 1. A representation of experimental tasks: A) The dynamic scaling task showing two conjunction search trials with spatial cues encompassing 1 and 9 search array stimuli respectively, B) The perceptual load task with example low and high load distractor trials. Note- the distractor is an example rather than the actual cartoon stimuli used in task.

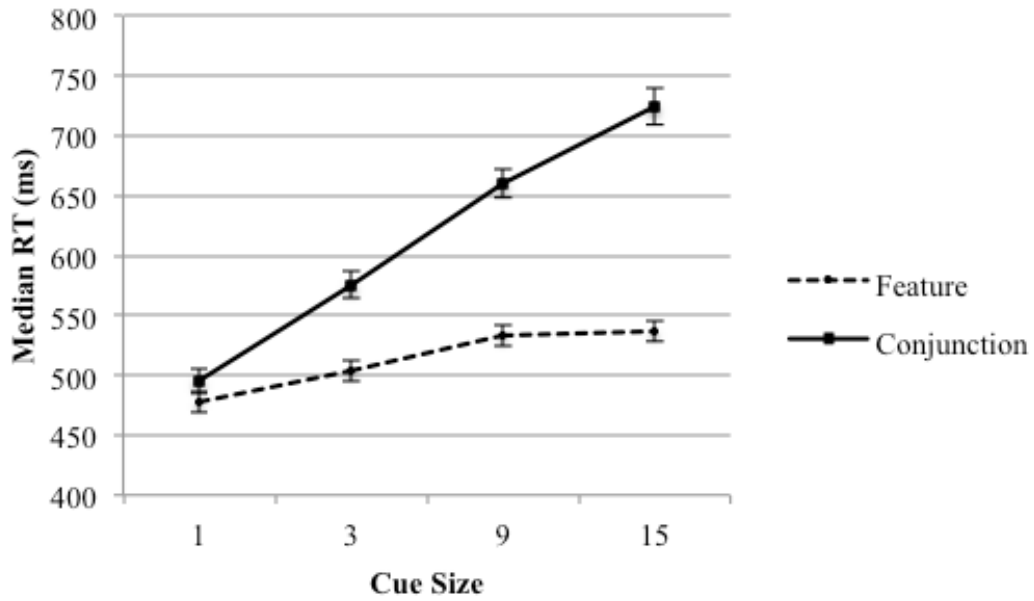


Figure 2. Median response time for each cue size presented by search type.

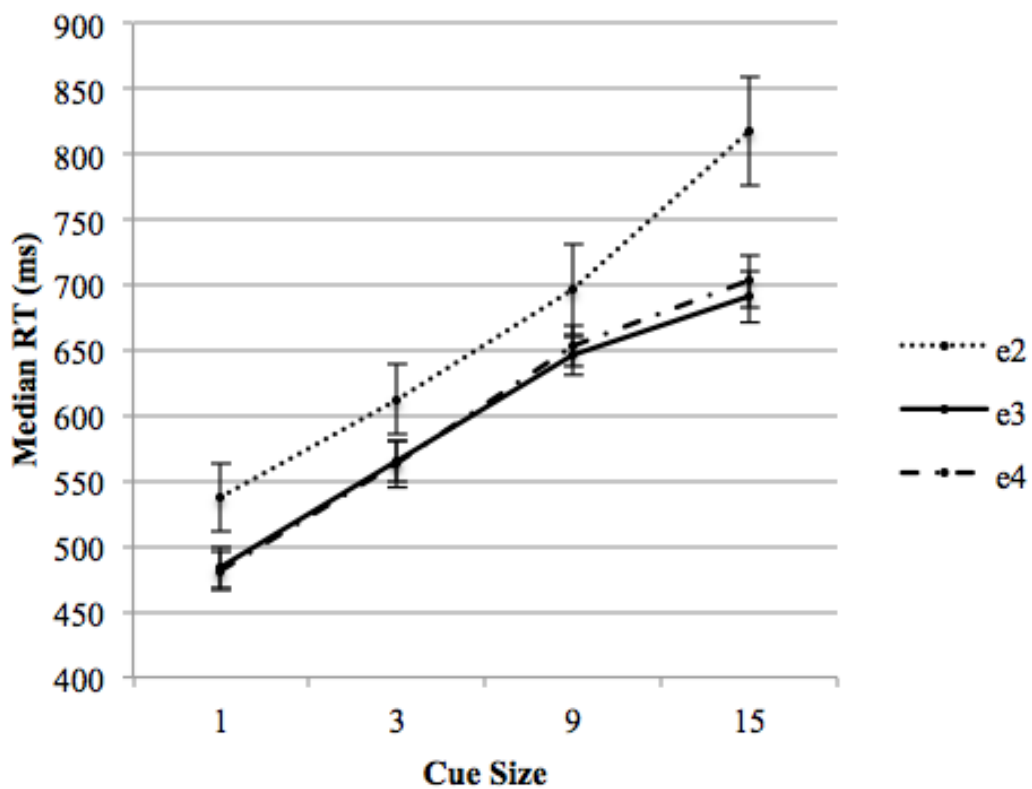


Figure 3. Benefit of reducing cue size on RT for conjunction search trials by genotype group.

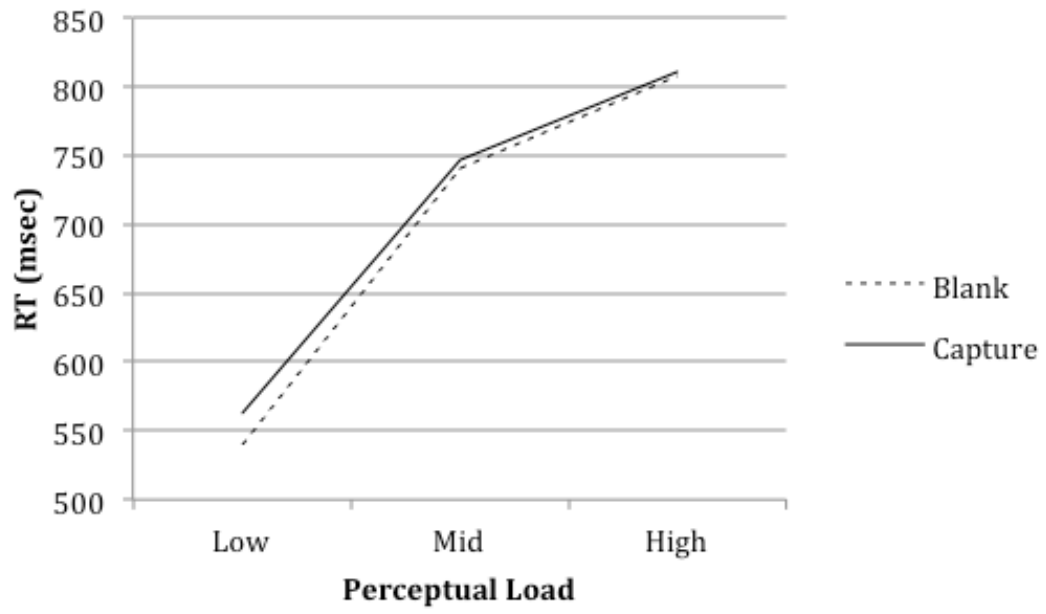


Figure 4. The interaction between perceptual load and distractor presence on RTs.

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