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## **Positive effects of cholinergic stimulation favor young APOE ε4 carriers**

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### Abstract

The potential of putative cognitive-enhancing compounds to improve mental processing both in healthy and vulnerable populations is an area of growing interest to scientific and clinical communities. The possible influence of individual genetic differences on efficacy of these compounds has yet to be considered. We sought to investigate the profile of young-adult apolipoprotein E (APOE)  $\epsilon 4$  carriers across cognitive domains given that possession of this gene variant increases risk of developing dementia in later life. We also explored whether APOE genotype interacts with the cognitive enhancer, nicotine. 1mg of the cholinergic agonist nicotine was administered via nasal spray to healthy non-smoking young adults (aged 18-30) with either  $\epsilon 3/\epsilon 3$  (N = 29) or  $\epsilon 4$  (at least one  $\epsilon 4$  allele, N = 27) genotype. Participants were matched on age, sex and IQ, in a placebo controlled, double blind 2 (drug: placebo, nicotine) x 2 (genotype:  $\epsilon 3$ ,  $\epsilon 4$ ) between subjects design. Here we demonstrate that, paradoxically, possession of the  $\epsilon 4$  allele confers a cognitive advantage on tasks mediated by the frontal lobe, and that young carriers of the  $\epsilon 4$  allele show larger cognitive benefit from procholinergic nicotinic stimulation. These results are the first to demonstrate that genetic differences influence the efficacy of a cognitive enhancer.

Keywords: Apolipoprotein E, Nicotine, Prospective Memory, Cognitive Enhancement, Cholinergic System, Cognition

## Introduction

The recent proliferation of research concerning “smart drug” use in normally functioning young adults has identified a number of compounds capable of improving cognitive performance (Farah *et al* 2004). A call has been made for increased research into the factors that may influence the potential for compounds to boost cognition in healthy adults given that usage of these compounds may now be surpassing associated knowledge (Greely *et al* 2008). Thus far compounds that affect different neurotransmitter systems in the brain, different cognitive domains, and different baseline profiles have been explored, but no clear cut indices of efficacy have been achieved for any of these factors (Lanni *et al* 2008).

With this in mind we sought to investigate whether genetic differences might interact with the potential for neuromodulation of cognition by putative cognitive enhancers. The most widely studied genetic variation is that associated with a common polymorphism of the apolipoprotein E (APOE) gene, which results in three alleles ( $\epsilon 2$ ,  $\epsilon 3$ ,  $\epsilon 4$ ). Emerging studies now indicate that young adult  $\epsilon 4$  carriers may comprise a cognitive supergroup (Han and Bondi 2008), and in fact that the well-documented negative consequences of possessing an  $\epsilon 4$  allele (eg greater risk for developing dementia, poorer cognitive aging (Corder *et al* 1993; Saunders *et al* 1993)) may not emerge until after the fifth decade of life (Savitz *et al* 2006). Specifically, recent behavioural studies report that  $\epsilon 4$  carriers in younger life have higher IQs (Yu *et al* 2000), higher educational achievement (Hubacek *et al* 2001), and better performance on certain cognitive tasks (Mondadori *et al* 2007) compared to their non- $\epsilon 4$  peers. Therefore we asked the question: does the  $\epsilon 4$

advantage in healthy young adults reduce or increase the potential for pharmacologic cognitive enhancement?

One such cognitive enhancer, nicotine, acts via cholinergic stimulation. It improves attention and memory performance in younger and older adults without a history of nicotine use (Levin *et al* 2006; Robbins 2002). Additionally, it improves prospective memory (PM) in normally functioning nicotine-naïve young adults (Marchant *et al* 2008; Rusted and Trawley 2006; Rusted *et al* 2005). PM is a type of memory particularly relevant to everyday living and as such is a valuable indicator of real world memory capability against which to test cognitive enhancers. It is engaged when we interrupt an ongoing activity to retrieve and act upon a previously formed intention, and allows us to multi-task successfully through the day. Cognitively healthy older adult  $\epsilon 4$  carriers show poorer PM performance than non- $\epsilon 4$  peers (Driscoll *et al* 2005), suggesting that PM performance is a sensitive index of genetic as well as pharmacologic manipulation. Therefore we chose this task as the primary focus of a study that co-varied genotype ( $\epsilon 3/\epsilon 3$  vs  $\epsilon 4$  carriers) and nicotine administration in normally functioning young-adults.

## **Methods and Materials**

### *Participants*

One-hundred and fifty-six volunteers were recruited from Sussex University. All volunteers met strict criteria for physical and psychological health, were non-smokers (with >5

years abstinence), had a body mass index within the normal range (18-30), and were aged 18-30. APOE genotype was determined by a blood sample or buccal swab. Twenty-seven  $\epsilon 4$  (1  $\epsilon 2/\epsilon 4$ , 2  $\epsilon 4/\epsilon 4$ , 24  $\epsilon 3/\epsilon 4$ ; furthermore referred to as  $\epsilon 4$  carriers) and 29  $\epsilon 3/\epsilon 3$  participants (furthermore referred to as the  $\epsilon 3$  controls) returned for the full study ( $\epsilon 3/\epsilon 3$ 's were chosen as it is normal practice to provide a homogenous control group representing the genotype most frequent in the general population (Rebeck *et al* 1993)). This  $\epsilon 4$  allelic frequency is aligned with population percentages and from other studies (eg Corder *et al* 1993). Forty-four participants were Caucasian, 7 Asian, 1 Black, and 4 participants described themselves as 'mixed ethnicity'. The study was approved by the National Health Service (NHS) - National Research Ethics Service. Written informed consent was obtained, and all participants were reimbursed for their time.

Participants in each group ( $\epsilon 3$ /placebo,  $\epsilon 3$ /nicotine,  $\epsilon 4$ /placebo,  $\epsilon 4$ /nicotine) were matched on age, gender, IQ, and appropriate behavioral and physiological measures (see table 1). Alcohol consumption was measured using the Alcohol Usage Quotient (AUQ; Mehrabian and Russell, 1978), a questionnaire that provides a composite measure based on units of alcohol consumed per week, drinking rate, number of times the participant was drunk in the last six months, and percentage of times the participant gets drunk. Exercise was determined by self-reported number of times the participant exercised per week (Sedentary: <1 day of exercise, Moderate: 1-3 days, Active: 4-5 days, Athletic: >5 days).

*Neuropsychological Assessment*

Spatial Working Memory (Mechaeil, unpublished thesis) was assessed during the familiarization session. Participants were instructed to remember the locations of seven rectangles presented simultaneously for 1 second. After an 8 second delay, one rectangle appeared and participants decided whether the solitary rectangle was in the same location as one of the initial seven rectangles by circling either 'yes' (the rectangle is in the same location as one of the seven presented earlier) or 'no' (the rectangle is not in the same location as one of the seven presented earlier) on a trial-by-trial template. They were allowed 10 seconds to make their decision before the program progressed to the next stimuli. There were 2 practice trials and 16 experimental trials.

The National Adult Reading Test (NART; Nelson and Willison, 1991) provides an estimate of IQ and was administered as part of the baseline battery of tests. Participants are required to read 50 phonetically irregular words aloud and their responses are individually scored as correct or incorrect based on their pronunciation. The total numbers of errors is well correlated with the Wechsler Adult Intelligence Scale-R (Nelson and Willison 1991).

Immediate Verbal Free Recall was measured during the familiarization session and again at the end of the experimental session. Participants were instructed to complete written recall of a 20-word list with each word presented on screen for 2 s with an inter-stimulus interval (ISI) of 1

s. Different lists were used at the different time points, matched on frequency of occurrence, imageability and number of syllables (Rusted 1988).

A verbal fluency task, in which participants generate as many words as possible that begin with a certain letter within 60 seconds, was included to measure ‘executive functioning’.<sup>1</sup> They were given the letters “F”, “A”, and “S”, and the number of unique words for each of these letters were summed and reported in 15-second segments.

Cognitive failures questionnaire (CFQ; Broadbent *et al* 1982) is self-report questionnaire that assesses four different appraisals of cognitive functioning: memory, distractibility, blunders, and naming. Participants are asked to respond to the questions using a 5-point scale (very often, quite often, occasionally, very rarely, never).

Sustained attention was measured using the Rapid Visual Information Processing (RVIP) task (Wesnes and Warburton 1983). Single digit numbers appeared in the middle of the computer screen and participants were instructed to press ‘spacebar’ each time they saw either three odd numbers or three even numbers in a row. Digits were presented for 750 ms with no interstimulus interval. The task lasted continuously for five minutes with five target sequences occurring per minute. Target hits, misses, false alarms, and correct rejections for each minute were entered into a  $d'$  transformation. The  $d'$  transformation minimizes the potential influence of response bias by subtracting the z-transformed false alarm rate from the hit rate; therefore a higher  $d'$  value indicates better performance.



Decision making ability was measured using the ongoing task of the PM paradigm. Participants first completed this task prior to drug administration as a measure of ‘decision making’ ability. They were instructed to sort a deck of 52 playing cards according to suit (Rusted *et al* 2009). Each card image remained on the computer screen for 750 ms with an ISI of 1000 ms (where the back of a playing card was displayed). Therefore participants were allowed 1750 ms from stimulus onset to respond. This task was completed prior to drug administration.

Prospective Memory was measured in the context of the ongoing decision-making task. In addition to completing the decision-making task, participants were told to withhold their suit-sorting responses and press the spacebar key if they saw a number ‘7’ card – the PM target. There were two decks of cards comprising 104 trials in total; with 8 target cards. Therefore, PM targets constituted roughly 4% of trials. Participants received these instructions prior to drug administration and completed the task approximately 15 minutes after using the nasal spray.

### *Design and Procedure*

Participants visited the laboratory 1-7 days prior to the experimental session to become familiar with the nasal spray, complete the spatial working memory task, immediate verbal free recall task, and practice the RVIP task.

Baseline physiological and mood measures were taken at the beginning of the experimental session, followed by instructions and practice of the ongoing decision-making task.

On completion, participants received the added PM instructions. They then self-administered the nasal spray and immediately performed the verbal fluency task, NART, and CFQ. Completion of these tasks required 12-15 minutes, the time necessary for nicotine to reach peak plasma concentration (Schneider *et al* 1996). Physiological and mood measures were again taken. They then completed the ongoing/PM task and then restated the ongoing/PM instructions to confirm compliance. Four participants incorrectly reported these instructions and were removed from analyses of this task. A five-minute version of the RVIP task was then performed, followed by a second immediate verbal free recall task. Final physiological and mood measures were taken. Participants also reported whether they believed they had received nicotine or not, and were subsequently debriefed and discharged from the lab.

### *APOE Genotyping and Data Analysis*

APOE genotype was determined following a standardized protocol using a polymerase chain reaction (PCR)-based assay that employs the Afl III and HaeII restriction enzymes to distinguish among the alleles (Ossendorf and Prellwitz 2000).

### *Statistical Analyses*

Statistical analyses were conducted using Statistical Package of Social Sciences (SPSS 14) software and an alpha level of .05 was used to interpret significant differences in the results. In all cases genotype and drug represented between subjects factors, and time represented the

within subject factor. Pre-nicotine analyses were conducted using independent t-tests (genotype) or a mixed design analysis of variance (ANOVA; genotype x time). Post-nicotine analyses were conducted using between subjects ANOVAs (genotype x drug) or mixed design ANOVAs (genotype x drug x time). Post hoc analyses were performed using independent t-tests with Bonferroni corrections reported when appropriate. Means with  $\pm 1$  standard error of the mean (SEM) are reported.

All of the analyses examining the cognitive measures were run using only Caucasian participants (see supplementary table), and also comparing only  $\epsilon 3/\epsilon 3$  and  $\epsilon 3/\epsilon 4$  participants. The same pattern of results emerged for these smaller groups as those reported in the results section which used the entire sample.

## Results

### *Pre-nicotine Assessments*

$\epsilon 4$  carriers were faster at the ‘decision making’ task (measured in milliseconds, ms;  $472 \pm 8$ ) than  $\epsilon 3$  controls ( $499 \pm 8$ ;  $t_{(54)} = 2.38$ ,  $p = .02$ ), while maintaining equal levels of accuracy ( $t_{(34.52)} = 1.51$ ,  $P = .14$ , equal variances not assumed; figure 1a).

Examination of the verbal fluency task revealed a main effect of time, with participants producing fewer words over the course of the task ( $F_{(3,63)} = 103.44$ ,  $p < .001$ ). There was no

main effect of genotype for overall performance on the 60 second task ( $t_{(22)} = 1.72, p = .1$ ), but there was a time x genotype interaction ( $F_{(3,63)} = 3.18, p = .03$ ).  $\epsilon 4$  carriers ( $19.2 \pm 1.72$ ) produced more words in the first quarter of the task than  $\epsilon 3$  controls ( $14.85 \pm .77; t_{(21)} = 2.5, p = .02$ ), and while they continued to produce more words in each subsequent quarter the differences were not significant (figure 1b).

For the other cognitive tasks administered prior to nicotine administration, no differences were found between gene groups: spatial working memory ( $t_{(53)} = .19, p = .85$ ); immediate verbal recall ( $t_{(54)} = .71, p = .48$ ). Additionally, no differences emerged on any of the factors from the CFQ: memory ( $t_{(54)} = 1.15, p = .25$ ), distractibility ( $t_{(54)} = .4, p = .69$ ), blunders ( $t_{(54)} = .31, p = .76$ ), and naming ( $t_{(54)} = .89, p = .38$ ).

Following nasal spray administration, participants completed the ongoing task of sorting the playing cards by suit but this time with the embedded PM component. The  $\epsilon 4$  carriers were again faster at the ongoing task than  $\epsilon 3$  controls ( $F_{(1,48)} = 5.11, p = .03$ ), with no main effect of drug or interaction (figure 2a). There was a near significant main effect of genotype on levels of accuracy for the ongoing task ( $F_{(1,48)} = 3.87, p = .055$ ), with an additional near significant interaction with drug ( $F_{(1,48)} = 3.41, p = .07$ ; figure 2b). Given the investigative nature of the study, post hoc analyses were conducted. The  $\epsilon 4$ /nicotine group ( $95.24 \pm .84$ ) was significantly more accurate than the  $\epsilon 4$ /placebo group ( $89.21 \pm 1.7; t_{(21)} = 3.1, p = .005$ ), the  $\epsilon 3$ /nicotine group ( $86.73 \pm 2.87; t_{(23)} = 2.55, p = .02$ ), and  $\epsilon 3$ /placebo group ( $88.94 \pm 2.29; t_{(17.55)} = 2.59, p = .02$ , equal variances not assumed). There was no difference between the  $\epsilon 3$ /placebo and  $\epsilon 3$ /nicotine

groups, or  $\epsilon 4$ /placebo and  $\epsilon 3$ /placebo groups. After employing the Bonferroni correction ( $p < .01$ ) the only difference to remain significant was between  $\epsilon 4$ /nicotine and  $\epsilon 4$ /placebo groups.

PM was measured by the number of times the volunteer pressed the spacebar to register the detection of the PM target, regardless of whether they had first made a response to the ongoing task (maximum = 8). No main effects or interactions were found between groups when analyzing reaction time. A main effect of gene was found for PM target percent accuracy ( $F_{(1,48)} = 5.78, p = .02$ ), with  $\epsilon 4$  carriers ( $71.2 \pm 4.8$ ) surpassing  $\epsilon 3$  controls ( $53.45 \pm 5.39$ ). Post hoc analyses indicated that the  $\epsilon 4$ /nicotine group were significantly more accurate than the  $\epsilon 3$ /nicotine group ( $t_{(23)} = 2.77, p = .01$ ), and the  $\epsilon 3$ /placebo group ( $t_{(23.79)} = 2.25, p = .03$ ; equal variances not assumed), but not the  $\epsilon 4$ /placebo group ( $t_{(21)} = 1.39, p = .18$ ; figure 2c). There was no difference between the  $\epsilon 3$ /placebo group and the  $\epsilon 3$ /nicotine group. After employing the Bonferroni correction ( $p < .01$ ) the only difference to remain significant was between  $\epsilon 4$ /nicotine and  $\epsilon 3$ /nicotine groups. Thus not only did  $\epsilon 4$  carriers show superior decision-making and PM performance, this advantage was augmented by the cognitive enhancer, nicotine. In fact, nicotine appeared to benefit only  $\epsilon 4$  carriers.

Sustained attention was measured using the Rapid Visual Information Processing (RVIP) task. A  $d'$  transformation revealed a main effect of time on task ( $F_{(4,208)} = 17.44, p < .001$ ), which was qualified by a three way (time x gene x drug) interaction ( $F_{(4,208)} = 3.95, p = .004$ ). Post hoc analyses revealed that the  $\epsilon 4$ /placebo group were more accurate ( $3.77 \pm .11$ ) than the  $\epsilon 3$ /placebo group ( $3.0 \pm .28$ ) in minute 1, ( $t_{(17.83)} = 2.58, p = .02$ ; equal variances not assumed), and in minute 2, ( $t_{(25)} = 2.4, p = .02$ ). When corrected for multiple comparisons using the Bonferroni post hoc

analysis ( $p < .01$ ), these differences did not remain significant. A Chi square analysis was conducted to identify the number of people who were unable to correctly identify 50% of the targets. Significantly more  $\epsilon 3$  controls recorded 50% or less hits (11 out of 29) than  $\epsilon 4$  carriers (2 out of 27;  $\chi^2_{(1)} = 7.31, p = .007$ ). There was no differential effect of nicotine on this measure. Response times (ms) to correctly identified targets were not differentiated by gene or drug. The results from this task indicate that  $\epsilon 4$  carriers were better able to sustain their attention, and showed an early advantage in accuracy.

Physiological measures and subjective assessments of mood were collected at baseline, following nicotine absorption, and upon completion of the experimental tasks. Mean arterial blood pressure (MAP) increased in a linear fashion over the course of the experiment ( $F_{(2,104)} = 4.85, p = .01$ ). There were no main effects of drug or gene, and no interactions. Heart rate showed no main effects or interactions. Mood was assessed using two standardized measures: the Profile of Mood States (McNair *et al* 1971) and Thayer's measures of alert and tense arousal (Thayer 1978). Both measures registered a decline in arousal/alertness across the time course of the study, independent of gene type or drug condition ( $p$ 's  $< .02$ ). There were no other main effects or interactions. These findings are consistent with previous reports using nicotine nasal sprays (Marchant *et al* 2008).

## Discussion

The potential of putative cognitive-enhancers and of select genetic polymorphisms to boost performance in normally functioning adults is an area of growing interest. We sought to

investigate the extent of the  $\epsilon 4$  advantage in young adults across a broad coverage of cognitive domains, and also, using a double-blind placebo-controlled study, to explore the interactive effect of APOE genotype and the cognitive enhancer, nicotine. The results from these cognitive tasks indicate that possession of an  $\epsilon 4$  allele produces domain-specific advantages rather than a global cognitive advantage. Specifically,  $\epsilon 4$  carriers excelled in decision-making, PM performance and verbal fluency, all tasks that require frontal lobe involvement, but not on spatial memory or word recall. Thus we argue that, early in life, frontally-mediated tasks appear to benefit from possession of an  $\epsilon 4$  allele. Indeed these findings support emerging literature showing cognitive superiority of young  $\epsilon 4$  carriers (Alexander *et al* 2007; Han and Bondi 2008; Mondadori *et al* 2007). In our study, this cognitive superiority was not explained by an alternate hypothesis, namely that  $\epsilon 4$  carriers were consciously compensating for poorer memory skills with metacognitive strategies.  $\epsilon 4$  and  $\epsilon 3$  participants demonstrated similar self-reported abilities in cognitive functioning as measured by the CFQ.

In addition, the manipulation of performance by the introduction of a cognitive enhancer revealed that even though  $\epsilon 4$  carriers already showed a cognitive advantage over their  $\epsilon 3$  counterparts, nicotine potentiated this advantage on measures of decision-making and PM performance. These results indicate the capacity for cognitive performance in young healthy volunteers to be modified both by pharmacologic and genetic factors, and, critically, for those effects to be cumulative. The result is in contrast with recent suggestions (Muller *et al* 2004; Randall *et al* 2005) that cognitive enhancement in younger adults is most likely to be achieved when baseline performance is below average.

Our results, then, add further support for the emerging view that while the  $\epsilon 4$  allele produces detrimental consequences in later life, it in fact confers a cognitive advantage in younger adulthood. These findings support the recent proposition of APOE  $\epsilon 4$  antagonistic pleiotropy (Han and Bondi 2008; Wright *et al* 2003), whereby the  $\epsilon 4$  variant might have contrasting effects across the lifespan. Our results suggest that this labile cognitive profile of  $\epsilon 4$  carriers may be related to and influenced by the integrity of the cholinergic system. Older carriers of the  $\epsilon 4$  allele have significantly less choline (the precursor to acetylcholine) and less choline acetyltransferase (the enzyme involved in converting choline to acetylcholine) activity than matched non- $\epsilon 4$  carriers (Poirier *et al* 1995). These deficiencies certainly contribute to the more rapid cognitive decline in older  $\epsilon 4$  carriers and may explain why, in our study,  $\epsilon 4$  carriers were more receptive to the cholinergic agonist, nicotine. Our findings offer new implications for the antagonistic pleiotropy theory and suggest the possible molecular basis or locus for the opposing effects of APOE across the lifespan. A similar advantage for carriers of the APOE polymorphism from other putative cognitive enhancers would implicate a noncholinergic explanation, however.

Knowing that possession of an  $\epsilon 4$  allele increases susceptibility to dementia and cognitive deterioration in later life, our results raise the question of how long this advantage in younger life might last, and whether cholinergic stimulation in earlier life might delay or hasten this decline. These results thus have implications for the development of cognitive enhancing drugs for healthy individuals and treatment approaches for dementia. Specifically, individual differences may play a significant role in the efficacy of these compounds across the lifespan. This study provides the first study to cross the  $\epsilon 4$  polymorphism with a pharmacological manipulation. The



sample size, while typical of pharmacological manipulation studies, may be considered small in relation to genetic studies. As such, it may be viewed as a preliminary step in the field of gene x drug interaction. It argues firmly, however, for the value of further research into the individual factors that may moderate the effects of putative cognitive modulators across the lifespan.

### **Disclosure/Conflict of Interest**

Naji Tabet has received research grants (unrelated to this study) from Pfizer and Novartis. He also received consultation and/or speaker fees from Pfizer, Eli Lilly, AstraZenca, Shire, Novartis and Lundbeck. Natalie Marchant, Sarah King, and Jennifer Rusted have no potential conflicts of interest to disclose.

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### **Footnotes**

<sup>1</sup> Only data from participants whose first language was English and who were in the placebo condition are reported because this task was conducted during the nicotine absorption phase (making any possible effects of nicotine ambiguous).

**Title and legend to table.**

Table 1. Mean baseline scores for volunteers on measured participant characteristics (standard deviations below). \*Based on data from participants for whom English is their first language. ○Exercise Classifications per week: S=Sedentary (<1 day of exercise), M=Moderate (1-3 days), Ac=Active (4-5 days), At=Athletic (>5 days).

	<b>ε3 controls</b>			<b>ε4 carriers</b>			<b>Total</b>	<b>p values</b>
	Placebo N = 15	Nicotine N = 14	Total N = 29	Placebo N = 12	Nicotine N = 15	Total N = 27		
<b>Age</b>	19.73 1.28	21.21 3.42	20.45 2.61	19.83 1.27	20.33 1.99	20.11 1.69	20.29 2.21	H(3) = 1.11, p = .78
<b>Gender</b>	8M/7F	7M/7F	15M/14F	7M/5F	6M/9F	13M/14F	28M/28F	$\chi^2(3) = 1.00$ , p = .80
<b>Estimated IQ*</b>	105.28 7.76	109.58 8.46	107.04 8.15	105.37 7.52	107.43 4.74	106.52 6.07	106.76 7.04	F(3,46) = .85, p = .47
<b>English First Language</b>	13Y/2N	9Y/5N	22Y/7N	11Y/1N	14Y/1N	25Y/2N	47Y/9N	$\chi^2(3) = 5.6$ , p = .13
<b>Baseline Heart Rate</b>	72.93 18.15	78.93 15.13	75.83 16.74	74.50 11.82	72.60 12.87	73.44 12.21	74.68 14.65	F(3,55) = .55, p = .65
<b>Baseline systolic blood pressure</b>	110.27 15.05	105.00 8.05	107.72 12.26	109.42 10.82	107.87 10.16	108.56 10.28	108.13 11.26	F(3,55) = .58, p = .63
<b>Baseline diastolic blood pressure</b>	55.20 10.56	53.36 6.40	54.31 8.70	49.08 11.26	53.13 6.29	51.33 8.90	52.88 8.84	F(3,55) = 1.1, p = .36
<b>Body Mass Index</b>	24.13 3.41	23.03 3.44	23.60 3.41	21.05 1.85	23.36 2.82	22.33 2.66	22.99 3.11	F(3,55) = 2.48, p = .07
<b>Family Hx of dementia</b>	14N/1Y	13N/1Y	27N/2Y	12N/0Y	12N/3Y	24N/3Y	51N/5Y	$\chi^2(3) = 3.59$ , p = .31
<b>Exercise○</b>	2S/9M/ 3Ac/1At	2S/11M/ 1Ac/0At	4S/20M/ 4Ac/1At	3S/5M/ 4Ac/0At	3S/9M/ 2Ac/1At	6S/14M/ 6Ac/1At	10S/34M/ 10Ac/2At	$\chi^2(9) = 6.56$ , p = .68
<b>Alcohol Use Quotient</b>	47.48 43.59	23.74 23.42	36.02 36.75	37.48 29.39	39.59 28.91	38.65 28.58	37.29 32.80	F(3,55) = 1.33, p = .28

### Titles and legends to figures.

Figure 1. Genotype differences on cognitive measures that require frontal cortex involvement.

Means and error bars indicating S.E.M. are displayed. **a**, Response times (measured in milliseconds) in a decision-making task.  $\epsilon 4$  carriers responded significantly faster than  $\epsilon 3$  controls ( $t_{(54)} = 2.38, p = .02$ ). **b**, The number of words produced using a task of verbal fluency, measured in 15 second segments. All participants declined in word generation over time ( $F_{(3,63)} = 103.44, p < .001$ ), with a time x gene interaction ( $F_{(3,63)} = 3.18, p = .03$ ). This result was driven by  $\epsilon 4$  carriers producing more words in the first 15 seconds ( $t_{(21)} = 2.5, p = .02$ ).

Figure 2. Cognitive measures showing different effects of nicotine on performance by  $\epsilon 4$  carriers and  $\epsilon 3$  controls. Means and error bars indicating S.E.M. are displayed. **a**, Response times (measured in milliseconds) in a decision-making task. The  $\epsilon 4$  carriers were significantly faster than  $\epsilon 3$  controls ( $F_{(1,48)} = 5.11, p = .03$ ). No significant effects of nicotine or interactions were observed. **b**, The  $\epsilon 4$ /nicotine group were more accurate in the decision-making task than all other groups ( $\epsilon 4$ /placebo group:  $t_{(21)} = 3.1, p = .005$ ),  $\epsilon 3$ /nicotine group:  $t_{(23)} = 2.55, p = .02$ ,  $\epsilon 3$ /placebo group:  $t_{(17.55)} = 2.59, p = .02$ ). **c**, Prospective memory (PM) accuracy was measured by the number of correct responses to the PM cue to during the decision-making task.  $\epsilon 4$  carriers showed superior PM accuracy ( $F_{(1,48)} = 5.78, p = .02$ ), specifically the  $\epsilon 4$ /nicotine group was more accurate than the  $\epsilon 3$ /nicotine group ( $t_{(23)} = 2.77, p = .01$ ), and the  $\epsilon 3$ / placebo group ( $t_{(23.79)} = 2.25, p = .03$ ), but not the  $\epsilon 4$ /placebo group ( $t_{(21)} = 1.39, p = .18$ ).

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