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Working memory deficits in healthy APOE epsilon 4 carriers

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Abstract

Studies on the cognitive effects of *APOE* allele variation in healthy persons have mainly focused on episodic memory performance as most sensitive to genetic effects. The present study focuses on working memory performance, measured both in an experimental paradigm, the AX-Continuous Performance Task (AX-CPT), and in neuropsychological test paradigms of span capacity and interference control. In a highly functioning healthy group (N = 186) of mean age 64.5 years we found evidence of reduced working memory performance in *APOE*

4 carriers, with sex and 4 dose as modifying variables. Several aspects of capacity and control in working memory were affected, while genetic effects were not present for measures of episodic memory. The pattern of results suggests that response inhibition is sensitive to genetic effects. In healthy individuals the broad range of neurobiological mechanisms associated with *APOE* is consistent with effects on non-memory cognitive

subsystems, and gender effects may be modulated by interaction of APOE with myelination, androgen mechanisms, or broad patterns of age-related changes in gene expression.

Keywords: Working memory; Genetics; Gender; APOE; Inhibition

Article Outline

The *APOE* gene is an established risk factor for Alzheimer's disease (AD) with a risk profile skewed towards earlier age of onset in 4 carriers ([Corder et al., 1993] and [Raber et al., 2004]). The normal variation in alleles includes 2, 3, and 4, with 3 as the most frequent. The mechanisms associated with negative central nervous system effects of 4 are complex, and may include both mechanisms specifically related to accelerating AD pathology, and mechanisms broadly related to maintaining and optimizing normal neuronal function (Mahley, Weisgraber, & Huang, 2006). Because of the association of *APOE* with AD risk, and the central role of episodic memory deficit in AD, the focus of research on *APOE* in normal aging has been biased towards episodic memory. *APOE* is associated with episodic memory deficit or rate of decline in healthy non-demented older adults ([Baxter et al., 2003], [Caselli et al., 2004], [Caselli et al., 2007], [Flory et al., 2000], [Mayeux et al., 2001], [Nilsson et al., 2006] and [Small et al., 2004]) but findings are not consistent ([Jorm et al., 2007] and [Luciano et al., 2009]). Double dose of *APOE* 4 is associated with markedly increased risk of AD (Raber et al., 2004) and Caselli et al. (2007) showed that in the 60–69 year group 4 homozygotes declined more than 4 heterozygotes, but in several cognitive domains in addition to episodic memory.

Greenwood, Lambert, Sunderland, and Parasuraman (2005) have argued that in view of the complexity of *APOE* mechanisms affecting cognition it would be misleading to view all cognitive effects

of 4 as evidence of incipient AD, and they argue that in normal aging there is an accumulating effect of inefficient neural repair mechanisms associated with the 4 allele. These changes make the brain more vulnerable to pathological processes, including accumulation of amyloid β42 in AD, but do not cause this process to occur in all 4 carriers. Furthermore, since *APOE* is a vulnerability gene, it may interact with a range of demographic, biological and pathological factors with diverse cognitive consequences. Greenwood and Parasuraman have shown in a series of studies of normal aging that visual attention function is a sensitive indicator of *APOE* 4 effects ([Greenwood and Parasuraman, 2003], [Greenwood et al., 2005], [Greenwood et al., 2000], [Negash et al., 2009], [Parasuraman et al., 2005] and [Parasuraman et al., 2002]).

Studies of association of *APOE* with working memory (WM) are sparse. WM is a cognitive system that keeps information in an active state for shorter time intervals, and allows manipulations of that information in a cognitive work space while the information is protected from interference. A recent review conducted by a broadly representative group of cognitive neuroscience researchers has focused on identifying conceptual and methodological aspects of WM that are ripe for application in individual differences and clinical research (Barch et al., 2009a). They concluded that two sufficiently well defined constructs for such application are *goal maintenance* and *interference control*. The AX-Continuous Performance Task is a prime candidate for measuring goal maintenance, whereas adaptations of the Operation Span task are good candidates for measures of interference control. In the AX-CPT task the instruction is to respond selectively to a target stimulus (X) when the preceding cue is valid (A), otherwise not. A high percentage of trials are of the type A followed by X, thus inducing an expectation of X when A is presented. Critical conditions are AY (the expectation is falsified, and the response must be withheld), and BX (the cue signals a non-target, and response to X, otherwise a potential target, must be withheld). The condition BY (non-target cue and non-target stimulus) is a control condition indicating adherence to the task. Operation Span tasks emphasize maintaining information in storage while performing distracting operations (Conway et al., 2005), whereas other span tasks (Letter–Number span, LN) emphasize restructuring all the information in storage without information loss. Span tasks with combination of storage capacity and processing demands have a long history in clinical research as sensitive and functionally relevant measures of WM (Conway et al., 2005), and Letter–Number span (LN) is an example of a span task which has shown sensitivity to normal genetic variation (Aguilera et al., 2008), to cognitive effects of aging (Emery, Myerson, & Hale, 2007), and to clinical syndromes with working memory deficits (Twamley, Palmer, Jeste, Taylor, & Heaton, 2006).

Stroop Color-Word Interference (Stroop, 1935) performance is not in itself a measure of WM, but may measure a subprocess that is closely related to working memory. Long and Prat (2002) found that low-span participants are more subject to interference in the Stroop task, supporting that inhibitory processes are central to WM as measured in span tasks. Rush, Barch, and Braver (2006) found significant correlations between some parameters of the AX-CPT task (AY errors) and Stroop reaction time. Further development of the Stroop task has included a condition with switching between response criteria (Delis, Kaplan, & Kramer, 2001), further complicating the task and making it a measure of cognitive control more than of inhibition or interference (Barch, Braver, Carter, Poldrack, & Robbins, 2009b). In cognitive neurogenetic research Greenwood et al. (2005), Parasuraman et al. (2005), Mattay and Goldberg (2004), and others, have made efficient use of additional WM paradigms including N-back and visuo-spatial span tasks.

In research focusing on *APOE* and WM, Rosen, Bergeson, Putnam, Harwell, and Sunderland (2002) found that operation span was more negatively affected in 4 carriers than non-carriers in a healthy normal group with mean age 62 years. Digit span and general memory index was not affected. Greenwood et al. (2005) used an experimental paradigm measuring WM for dot locations in a spatial array, and found that accuracy was reduced in healthy 4 homozygotes, but not in

heterozygotes of mean age 57–60. Wishart et al. (2006) found that healthy 3/ 4 participants showed greater fronto-parietal activation in an N-back task than 3 homozygotes. No differences were found in task performance, indicating that increased effort reflected in activation may underlie intact performance. In a study of cognitive control functions measured in the Stroop task Wetter et al. (2005) found that healthy 4 carriers of mean age 75 years made more errors in a task condition including cued switching between response criteria. There is thus evidence that different aspects of WM performance are sensitive to negative effects of 4 allele burden in healthy middle aged and older persons.

Few studies focus on gender as a modifier of genetic effects on cognition. A study by Mortensen and Høgh (2001) found that *APOE* 4 was associated with more rapid cognitive decline in women after the age of 70. Swan, Lessov-Schlaggar, Carmelli, Schellenberg, and La Rue (2005) found significant interaction of gender with APOE in affecting cognitive decline in older healthy participants, with different patterns of cognitive decline in 4 positive males and females. Men with 4 showed greater decline in some measures of executive function and verbal memory compared to those without 4, whereas women with 4 showed greater decline in Trail Making test performance relative to women without the allele. A large-scale study of a healthy population from Western Norway (Lehmann et al., 2006) used a clinical test of attention and memory function, and found a marked gender difference. The adjusted odds ratio (OR) of cognitive impairment in women was shown to be 1.8 for 4 heterozygotes and 1.1 for homozygotes, whereas the adjusted OR in men was 1.1 for 4 heterozygotes and 10.7 for homozygotes.

Recent genetic and neurobiological studies have strengthened the evidence for gender-based modulation of cognition in aging. Raber (2008) reviewed evidence mainly from mice, that a*poE* isoforms interact with androgen receptors, where reduced neuritic sprouting is associated with apoE4. ApoE4 may have a more general detrimental effect on androgen and androgen receptor mediated pathways, and based on studies of genetically modified mice Raber, Bongers, LeFevour, Buttini, and Mucke (2002) suggest that stimulating AR-dependent pathways can reverse apoE4-induced cognitive deficits. A recent study by Berchtold et al. (2008) found that patterns of gene expression in the normal aging brains of humans are sexually dimorphic, with an earlier age of onset for typical age-related changes in males than females. The sixth and seventh decades of life are a period of extensive change in gene expression in superior frontal and postcentral gyri in males, whereas females show a more gradual pattern of change continuing into the eighth decade of life. Age-related changes in gene expression are less pronounced in the hippocampus and entorhinal cortex than in the prefrontal cortex (Berchtold et al., 2008). These findings indicate that gender may be a potentially important modifier of genetic effects on cognition in middle aged participants, and when gene expression patterns change in a direction of less efficient neuronal function or more stress on maintaining normal function, then *APOE* may be a modifying factor. Working memory function is strongly dependent on prefrontal cortex activation (Curtis & D'Esposito, 2004), and is a likely candidate for showing age and gender related variation in neurogenetic studies.

The present study aims to assess the effect of *APOE* 4 genotype on main aspects of working memory, i.e. goal maintenance measured with the AX-CPT context updating paradigm, and storage/interference control measured with the Letter–Number Span Task. Additional neuropsychological tasks related to WM and cognitive control (Stroop Color-

Word Inhibition, and Stroop Color-Word Inhibition/Switching) are included as support for interpreting the results. A verbal list learning test of episodic memory is included to determine if WM and episodic memory show similar sensitivity and pattern of genetic association to *APOE* in a study group of high functioning healthy participants. We will examine effects of gender as a possible modifying factor on gene-cognition relation. Our tentative hypothesis is that sexually dimorphic effects of age-related changes in gene expression may have stronger

impact on cognition in *APOE* 4 carriers, and that cognitive tasks that are more strongly dependent on prefrontal function, in this case WM, will be more affected than cognitive tasks more strongly dependent on the hippocampus, in this case episodic memory.

1. Method

1.1. Participants

Healthy persons in the age range 40–80 years were recruited by newspaper advertisement in the greater Oslo urban area. Exclusion criteria were known neurological or psychiatric illness, other serious illnesses relevant for cognitive function, alcohol or substance abuse, history of learning disorder or failure to complete obligatory basic education. Persons on medication for elevated blood pressure, type 2 diabetes or hypercholesterolemia were included if the treatment was judged to be adequate. Participants were first screened by telephone interview, and the information was cross-checked before start of testing. The Beck Depression Inventory-II (BDI-II, Beck & Steer, 1987) was used as a screening instrument to record depressive symptoms at the time of testing. None of the participants were clinically depressed. The participants were given Vocabulary and Matrix reasoning subtests of the Norwegian version of the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999), which estimates general cognitive abilities. Participants scoring 1SD or more below age adjusted population norm were not included in the study.

In all 187 participants (128 females) were included. Mean age was 62.5 years (SD 10.3, range: 39–79). They had on average 14.4 years (range: 7–20) of general education, and 93% of the participants were right handed. Mean IQ was 120 (range: 86–148) and was unrelated to age or genotype subgroup. Also, males and females did not differ in age, IQ, education or depression scores.

1.2. Genotyping

Genotyping was performed by real-time PCR with allele-specific fluorescence energy transfer probes and melting curve analyses on the LightCycler system (Roche Diagnostics, Mannheim, Germany). DNA was extracted from 300 μl whole blood using MagNA Pure LC DNA Isolation Kit—large volume on the MagNA Pure LC (Roche), eluted and diluted to 1 ml, of

which 5 μl was applied in each assay. Typing of the *APOE*- 2, - 3, and - 4 genotypes was performed using the LightCycler APOE Mutation Detection Kit (Roche). The assay was performed as specified by the supplier, except for scaling down the total assay volume from 20 to 10 μl. The laboratory participates in an external quality assurance program (Equalis, Uppsala, Sweden) that includes *APOE* genotyping. *APOE* data were missing for one person. Frequency of allele combinations is shown in Table 1.

Table 1.

Frequency and gender distribution of APOE allele combinations.

APOE-alleles	Male	Female	*N*
22	0	2	2
23	7	17	24
24	1	7	8
33	30	60	91
34	12	35	47
44	8	6	14
Total	58	127	186

Full-size table

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Genotype frequencies with 35% carriers of at least one 4 allele are in accord with the known high frequency of this allele in the northern European population (Gerdes, 2003).

1.3. AX-Continuous Performance Task (AX-CPT)

We adopted a version of the context updating (AX-CPT) paradigm as described in Braver and Barch (2002). Capital letters were presented visually (red letters on a black background) on a computer screen in a continuous series with the instruction to respond by button press to each letter by signaling a target or non-target response. Targets are defined as the letter X preceded by the letter A (AX trials). Target frequency is 70%, whereas non-target trials are divided equally between AY, BX, and BY trials (10% each). B and Y in this context mean any other letter than A or X. Each letter was presented for 300 ms, and the stimulus onset asynchrony (SOA) was 2000 ms. Non-target stimuli should be indicated by pressing the left-most key on an E-Prime compatible response box with the left index finger, and target stimuli by pressing the right-most key with the right index finger. All stimuli had to be responded to, but only responses in the time window 100–1500 ms after stimulus onset were included in the analysis. The remaining 500 ms period before the next stimulus onset was used for auditory feedback where errors were indicated by a short beep. Participants first performed a practice

block of 20 trials, and then 6 blocks of 50 trials. Stimuli were presented on an EIZO 21-in. CRT monitor, and the experimental paradigm was controlled and responses collected by the E-Prime software ([Schneider et al., 2002a] and [Schneider et al., 2002b]).

1.4. Neuropsychological tests

Letter–Number span from Wechsler Adult Intelligence Scales (WAIS) III (Wechsler, 1997) measures auditory–verbal working memory capacity by requiring participants to reproduce mixed letter–number sequences in sorted order. The length of presented stimulus sequences is progressively increased until a criterion is reached. Color-Word Interference Task (CWIT) from the Delis Kaplan Executive Function System (D-KEFS; Delis et al., 2001) includes simple conditions of color naming and reading, and additionally two critical conditions of Color-Word *Inhibition* (CW-I) and *Switching* between a word and color response according to a visual cue (CW-I/S). California Verbal Learning Test II (CVLT-II) is a measure of episodic memory function (Delis, Kramer, Kaplan, & Ober, 2000). The test involves learning a list of 16 words from 4 semantic categories repeated 5 times, and testing of recall shortly after presentation of an interference list (short-term recall, ST recall) and after a period of 20 minutes filled by other tasks (long-term recall, LT recall). Recognition is tested by requiring an old–new response to a list of orally presented words including same category foils.

1.5. Statistics

We performed repeated-measures ANOVAs of the AX-CPT scores with three conditions (AY vs. BX vs. BY) as the within subject variables, and sex (male vs. female) and *APOE* 4 status as between subject variables. When analysing *APOE* status we performed analyses both with a dichotomized variable (4 carrier vs. non-carrier) and with 4 dose (0, vs.1 vs. 2 alleles). The model for the ANOVAs of Condition × Sex × Genotype was therefore 3 × 2 × 2 factors or 3 × 2 × 3 factors, respectively. Age was entered as covariate. Reaction times to stimulus two (X or Y) were analyzed for correct responses only and based on the mean of median reaction time for each condition limited to responses in the time window of 100–1500 ms post stimulus.

For the neuropsychological variables all scores were standardized, and if necessary the sign was changed so that positive scores indicate better performance. Results for the neuropsychological variables were then analyzed using univariate analysis of variance with *APOE* (carrier status or dose) and sex as independent variables and age as covariate. For the CW-I and CW-I/S conditions of the Stroop CWIT, the simpler conditions (naming and reading) were entered as covariates. Participants made very few errors, and only time to perform the tests was analyzed.

2. Results

The sex distribution of 4 alleles (see Table 1) indicated that relative to number of female and male participants, there was a tendency for more 4 homozygotes among the males ($\chi^2 = 5.86$, $p = .056$). That did, however, have the advantage that the male and female groups had a comparable number of 4 homozygotes (8 and 6, respectively).

Mean accuracy data from AX-CPT was submitted to a repeated-measures ANOVA with Condition, Sex and *APOE* genotype as independent factors as explained above, and Age as

covariate. There was a significant between-subjects effect of Sex ($F(1, 179) = 4.49$, $p < .05$, $\eta^2 = .024$), and a Sex × *APOE* dose interaction ($F(2, 179) = 4.83$, $p < .01$, $\eta^2 = .051$). The within-subjects analysis revealed a two-way Condition × Sex interaction ($F(2, 358) = 5.79$, $p < .01$, $\eta^2 = .031$), and a three-way Condition × Sex × *APOE* dose interaction ($F(4, 179) = 2.42$, $p < .05$, $\eta^2 = .026$). Post hoc analysis (separate one-way ANOVAs with Tukey's HSD for males and females) revealed that the three-way interaction was due to lower

accuracy in AY trials for male *APOE* 4 homozygotes, but no similar effect in females

(see Fig. 1). The data were reanalyzed excluding all carriers of the 2 allele (23, 24), which served to increase the levels of significance in the effects reported, and did not change the pattern of results. Percent accuracy scores are shown for each condition, gender and genotype group in Fig. 1.

Full-size image (29K)
High-quality image (135K)

Fig. 1. Performance accuracy in three different conditions of the AX-CPT task. Male homozygotes perform significantly more poorly than females.

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It is clear from Fig. 1 that the significant interaction effects are caused by the fact that male 4 homozygotes perform worse than all other groups. In general the level of accuracy is between 80 and

90% in all other groups and conditions, whereas male 4 homozygotes perform at 63% accuracy

in the AY condition. Female 4 homozygotes show, if anything, slightly better performance than other groups. Corresponding analyses for reaction time showed no significant effects of *APOE* genotype. Effects of sex and age on reaction time were found, but will not be discussed because they are peripheral to the aim of the study.

Standardized scores for males and females on the LNs and CWIT variables are shown in Table 2.

Table 2.

Standardized (*z*) neuropsychological test scores in sex and APOE 4 dose subgroups.

4 dose	Sex	CW-I	CW-I/S	LNs
0	Female (*N* = 79)	.00	−.07	.04
	Male (*N* = 37)	.18	.15	.26
1	Female (*N* = 42)	.03	−.05	−.27
	Male (*N* = 13)	−.92	−.01	−.34
2	Female (*N* = 6)	.71*	.61	.19
	Male (*N* = 8)	−.18	−.26	−.17

Full-size table

CW-I: Color-Word Inhibition; CW-I/S; Color-Word Inhibition/Switching; LNs: Letter–Number span.

* $p < .05$ of females > males within same task and genotype group.

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For the Letter–Number Span Task there was a significant effect of *APOE* 4 carrier status, but not of dose, on performance ($F(1, 179) = 2.82$, $p < .05$, $\eta^2 = .021$) with 4 carriers performing worse than non-carriers (Fig. 2). It is clear from the figure that the poor performance of 4 heterozygotes contributes strongly to the significant difference.

Full-size image (19K)
High-quality image (65K)

Fig. 2. *Z*-scores of genetic subgroups on the Letter–Number Span Task show that the 4 carriers perform worse than the non-carriers, but there is no dose effect of 4.

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Results for neuropsychological tests of other working memory related functions showed strong effects for the Stroop CW-I task with a significant Sex × *APOE* interaction for both the dichotomous *APOE* 4 variable ($F(1,179) = 3.99$, $p < .05$, $\eta^2 = .022$) and for the 4 dose variable ($F(2,177) = 4.13$, $p < .05$, $\eta^2 = .045$). The results are shown in Fig. 3.

Full-size image (20K)
High-quality image (69K)

Fig. 3. Performance on the Color-Word Inhibition task (CW-I) is adversely affected by APOE carrier status in males, but not in females.

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From Fig. 3 it is apparent that it is the poor performance of male 4 heterozygotes that mainly accounts for the observed findings, and that the significant dose effect is not an indication of progressively increasing deficit with increased 4 burden. The very good performance of female 4 carriers is consistent with their superior performance also on other tasks. The CW-I/S variable showed no significant genetic effects of *APOE* or interaction with sex.

Results for episodic memory variables are shown in Table 3. Separate analyses for each test condition showed significant main effects of Sex on Learning ($F(1, 181) = 8.47$, $p < .01$, $\eta^2 = .051$); short-term recall ($F(1, 181) = 5.18$, $p < .05$, $\eta^2 = .030$) and on long-term recall ($F(1, 181) = 4.70$, $p < .05$, $\eta^2 = .028$).

Table 3.

Standardized (*z*) episodic memory test scores in sex and APOE 4 dose subgroups.

Group		**Memory test condition**				
4 dose	**Sex**	**Learning**	**ST recall**	**LT recall**	**Recognition hits**	**Recognition FA**
0	Female	.11*	.11	.09*	.07	.10
	Male	−.31	−.23	−.30	−.21	−.23
1	Female	.04	−.04	−.07	−.20	.02
	Male	−.26	−.09	−.10	.14	.00

Group		Memory test condition				
4 dose	Sex	Learning	ST recall	LT recall	Recognition hits	Recognition FA
2	Female	.92**	1.09**	1.04*	.68	.56
	Male	−.29	−.39	−.04	.38	−.14

Full-size table

ST = short term, LT = long term, FA = false alarms.

** $p < .01$.
* $p < .05$ of females > males within same task and genotype group.

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Effects of *APOE* 4 dose or interaction of Sex and *APOE* 4 dose were non-significant ($p > .10$ for all analyses), but we note the very high performance level in female

4 homozygotes. The data were reanalyzed excluding all carriers of the 2 allele, which did not change the pattern of uniformly insignificant results.

3. Discussion

We found a negative effect of *APOE* 4 carrier status on working memory measured with tasks reflecting a range of WM aspects including goal maintenance, storage capacity and interference control. The effects differed in degree of complexity of other factors modifying

the effect of 4, in that the Letter–Number Span Task showed poorer performance in

4 carriers and no gene dose effect. The AX-CPT task showed a specific effect of 4 only in male homozygotes and only in one specific task condition (withholding response to a non-target preceded by a target cue). Results from the Stroop CW-I task indicated that problems in

response inhibition (color-word conflict) were present in the male 4 carriers, and may

have contributed to their WM task performance. More general cognitive control problems (Stroop CW-I/S task) could not be shown for the 4 carriers.

The LNs task does not allow for analysis of cognitive sub-components of task performance, whereas the AX-CPT task is designed for this purpose. The general reduction in performance of the LNs task in *APOE* 4 carriers thus allows several interpretations, whereas interpretation of AX-CPT performance is more constrained. Interpretation of performance in this task rests on the pattern of results for AY trials (target cue followed by non-target) and BX trials (non-target cue followed by target). Previous factor analytic studies ([Barch et al., 2009a] and [MacDonald et al., 2005]) have shown that the AY condition of the task may reflect an underlying factor of response preparation. Control of response conflict is an aspect of the Stroop Color-Word Task (MacLeod and MacDonald, 2000), so the finding that male 4 carriers also have problems with the Stroop task supports this interpretation. Rush et al. (2006) found a significant correlation of AY accuracy and Stroop reaction time in their study, supporting common functional aspects. Imaging studies have indicated that tasks involving updating of task relevant information and interference resolution have overlapping activation foci in dorsomedial prefrontal cortex (Derrfuss, Brass, Neumann, & von Cramon, 2005) and probably share processing resources. Inhibitory control may be a common factor to CW-I and AX-CPT, contributing to the present results. This would also be consistent with previous studies of *APOE* 4 effects on attention mechanisms ([Espeseth et al., 2006] and [Greenwood and Parasuraman, 2003]) indicating that the balance of engagement/disengagement of visual attention is adversely affected by 4.

We found no effect of *APOE* 4 on episodic memory, consistent with several previous studies in cross-sectional samples ([Jorm et al., 2007] and [Luciano et al., 2009]). These finding do not rule out the possibility that higher rates of decline in episodic memory in 4 carriers may be found in longitudinal studies ([Caselli et al., 2004] and [Caselli et al., 2007]).

Variable patterns of dose effects of *APOE* 4 on different measures within a study group are found in some studies ([Reinvang et al., 2005] and [Greenwood et al., 2005]) including the present. It may be the case that while *APOE* 4 shows additive allele effects in relation to AD risk and some cognitive tasks, other tasks may show effects best explained by non-additive models known from quantitative genetics (Falconer and Mackay, 1996). Epistasis of *APOE* with other genes with more specific effects on working memory and attention subfunctions is another likely source of variation ([Espeseth et al., 2006], [Goldberg and Weinberger, 2004] and [Parasuraman et al., 2005]). Variation in the *COMT* allele has been demonstrated to affect WM performance in several previous studies ([Barnett et al., 2008], [Goldman et al., 2009] and [Mattay and Goldberg, 2004]) including AX-CPT performance (Macdonald, Carter, Flory, Ferrell, & Manuck, 2007). The results for the Letter–Number Span Task are consistent with the findings of Rosen et al. (2002), obtained with a different version of a span task, and indicate an 4 carrier effect. The AX-CPT on the other hand shows an effect only in 4 homozygotes. Greenwood et al. (2005) found an 4 carrier effect on attention tasks and no dose effect, whereas working memory performance was only affected in 4 homozygotes. Assuming that Stroop CW-I is more attention related, while AX-CPT is a WM measure,

that is also the result in the present study, with the added observation that it is only males who show the effect.

Since both reduced span task performance and reduced AX-CPT performance are common findings in cognitive aging research ([Braver and Barch, 2002], [Emery et al., 2007] and [Paxton et al., 2008]), one might consider that *APOE* 4 carriers show an increased rate of cognitive aging which may be found earlier in sensitive tasks of working memory, and only at a later age in episodic memory performance. Two observations speak against this interpretation. Firstly, we used age as covariate in all statistical analyses so that the findings reported are age independent within the age range studied (39–79). However only 15% of the group was aged 50 or younger, so if the relevant changes happen around age 50 or earlier, the age correction may not have captured this change. The second observation is that the pattern of *APOE* and sex related changes observed in AX-CPT and Stroop CW-I performance is not typical of age-related changes as described in the literature. Previous studies using the AX-CPT paradigm to assess cognitive changes in normal aging have revealed a pattern of findings characterized by *higher* accuracy of older than of younger participants in AY trials combined with increased reaction time in BX trials (Braver and Barch, 2002). If the effect of *APOE* 4 is to accelerate the normal aging process, then we would expect to see the same pattern in 4 carriers. This is not the case, since the main finding of the present study is a *reduction* in accuracy on AY trials, with no significant effect on BX trials. Further studies of normal cognitive aging have revealed that more than one cognitive strategy is available to participants, termed proactive and retroactive (Paxton et al., 2008). In the proactive strategy there is a strong reliance on the expectation set up by the cue (A or non-A), whereas in the retroactive strategy the emphasis is on observing the probe (X or non-X) and then retrieve and validate the cue. Older participants tend to favor a retroactive strategy, but with practice they may shift to a more proactive strategy (Paxton, Barch, Storandt, & Braver, 2006). The present findings of increase in AY errors in the male 44 subgroup is an indication of an overreliance on a proactive strategy, however they do not seem to reap the possible benefit of this strategy in terms of a faster response to BX trials. Winjevoll (2009) has studied age effects on AX-CPT performance using the present paradigm, and found that the pattern of age-related changes in an age range from 20 to 80 is a linear increase in AY errors. Although the pattern of results for male 4 homozygotes does not fit with the normal aging pattern reported by Braver and Barch (2002), it is consistent with an accentuated pattern of normal aging changes observed in an expanded adult lifespan sample including the present study group.

The finding that males were selectively vulnerable in our study is a novel result. There may be several reasons why this has not been reported in earlier studies. Most important is probably the previous lack of a plausible neurobiological mechanism for interaction of gender and autosomal genes with cognitive function in the older population. The number of 4 carriers and especially 4 homozygotes in the healthy population is small, and lack of statistical power may preclude analysis of gender subgroups in most studies unless highly prioritized. The group studied by Caselli et al. (2007) included 45 4 homozygotes, but they decided to focus on age as the primary strategy for subgrouping, which would make further analysis of sex subgroups difficult. Previous neuropsychological studies of 4 carriers that have reported gender associated findings ([Burkhardt et al., 2006], [Mortensen and Høgh, 2001] and [Swan et al., 2005]) have reported variable patterns of decline in males and females, including findings that closely parallel those in our study. Swan et al. (2005) found greater decline in CW-I test scores in male 4

carriers than non-carriers, but the same difference was not found in females. The participants were older than in the present study.

Recent evidence from neuroanatomy, neurogenetics and neurophysiology has considerably strengthened the basis for interpretation of gender effects in the aging brain and possible genetic modifiers including *APOE*. Gender differences in proportions of neurons, glial cells and myelinated fibers have been reported ([Marner et al., 2003] and [Pelvig et al., 2008]). Sex differences are somewhat larger for glial cells (oligodendocytes) and for myelinated fiber length than for neuron number, and age-related loss is greater for myelinated nerve fibers than for neurons

(Marner et al., 2003). *APOE* 4 shows association with reduced white matter and myelin integrity ([Bartzokis et al., 2006] and [Bartzokis et al., 2007]), and further research may explore white matter integrity measured with diffusion tensor imaging (DTI) as a neurobiological source for gender and *APOE*-related cognitive differences.

Recent studies have found that age-related changes in gene expression occur earlier in males than females (Berchtold et al., 2008), and these differences are most pronounced in the sixth and seventh decade of life. It is not known if the *APOE* gene shows age or sex related change in gene expression, but cognitive effects may involve interaction of *APOE* with other genes showing such changes. The pattern of sexually dimorphic alterations in gene expression described by Berchtold et al. (2008) includes a broad range of genes, with a three-fold increase in changes in males over females. Genes related to energy metabolism and protein generation are specifically downregulated in males, while females show a higher frequency of upregulated genes and more specific changes in genes related to neuronal morphogenesis. These changes happen primarily later in life in females. The regions of the brain evidencing these changes are the same in both sexes. Relating these observations to possible effects of *APOE*, cerebral energy metabolism as measured with fluoro-deoxy-glucose (FDG) positron emission tomography (PET) has been shown to be reduced in healthy *APOE*

4 carriers ([Reiman et al., 2005] and [Rimajova et al., 2008]). The regionally specific pattern of reduction includes areas relevant for working memory performance (prefrontal, parietotemporal, and cingulate cortex), but so far sex differences have not been focused on in these studies.

The studies of *APOE* effects on androgen receptors (Raber, 2008) derive mainly from mice, but holds promise for treatment of cognitive reduction in aging. Berteau-Pavy, Park, and Raber (2007) studied salivary testosterone in a healthy old group, and found the level increased in male but not in

female 4 carriers. They speculate that the increase may be a compensatory response serving to maintain normal function. This interpretation is contradicted by Burkhardt et al. (2006), who found an interaction between testosterone levels and *APOE* in healthy cognitively normal males. For tests of

executive functions, but not for tests of episodic memory, 4 carriers with high testosterone levels

performed worse than 4 carriers with low testosterone levels. The composite measure of executive function they reported included the LNs task as well as the CWIT. The opposite pattern of

results was found in 4 non-carriers, indicating that testosterone supplementation may be

beneficial for this group, but not for 4 carriers.

This is the first study to directly compare effects of *APOE* allele combination on working memory and episodic memory using well established and validated working memory paradigms. The results indicate that in a generally high functioning group reduction in working memory may be a sensitive sign of reduced cognitive function in selected subgroups

of *APOE* 4 carriers. It is not surprising that 4 homozygotes are most vulnerable in

view of evidence for increased AD risk and earlier onset of cognitive decline in this group ([Caselli et al., 2004], [Caselli et al., 2007], [Corder et al., 1993] and [Raber et al., 2004]). Recent studies of cognitively normally functioning participants ([Reiman et al., 2009] and [Small et al., 2009])

have further shown that 4 carriers, and especially homozygotes, show increasing accumulation of β amyloid in the brain after age 60. We cannot rule out that increased load of AD pathology in older participants contributes to the present results. Our results may also do not rule out an interpretation of

accelerated aging effects on aspects of working memory in *APOE* 4 carriers. The fact that the findings are still significant when adjusted for age effect, however, indicates that they can reasonably be interpreted as evidence of an *APOE*-related cognitive phenotype which is present in the adult

middle aged and older population. Evidence that *APOE* 4 has effects on brain function and cognitive processing even in young adults, where pathology is unlikely supports the possibility of such a cognitive phenotype ([Reiman et al., 2004] and [Scarmeas et al., 2005]).

Limitations of the present study are mainly that selective recruitment may have affected the

results. The study group of females, including the 4 homozygotes, is a very highly functioning group who perform better than males on a range of tasks, especially memory tasks. We would point out, however, that males and females do not differ in IQ or education, and that it is the pattern of interactions, with reduced performance in males on selective task parameters, that are of interest. Also, a large population-based Norwegian study with more than 2000 participants (Lehmann et al., 2006) found a marked difference in performance between

male and female 4 homozygotes, but not of heterozygotes. The gene expression studies (Berchtold et al., 2008), showed not only earlier onset but also greater variation in age-related gene expression patterns in males. That indicates that there may be great variation in performance in males, and that generalization to middle aged males as a group is uncertain. The effect sizes observed are generally small, and indicate that *APOE* is only one among several influential factors. Epistasis, the interactive effects of several genes (Phillips, 2008 P.C. Phillips, Epistasis—The essential role of gene interactions in the structure and evolution of genetic systems, *Nature Reviews Genetics* **9** (2008), pp. 855–867. **Full Text** via CrossRef | View Record in Scopus | Cited By in Scopus (30)Phillips, 2008), is a likely source of variation, and further progress may depend on addressing polygenetic causality in large samples.

We conclude that the results are consistent with the general hypothesis that presence of *APOE*

4 serves to modulate restorative or degenerative processes that are otherwise active in healthy, normal study groups. In normal aging these processes affect working memory and attention more than they do episodic memory (Buckner, 2004). The recent evidence of gender specific neurobiological effects on androgen mechanisms, myelin fiber length, and gene expression in the 6th and 7th decade of life, give biological plausibility to our finding that *APOE* may affect working memory differently in males and females.

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