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Cognitive control and memory in healthy ApoE-ε4 carriers with a family history of Alzheimer's disease

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A major risk factor for late-onset Alzheimer's type dementia (DAT) is the carriage of the ε4 allele of the apolipoprotein E (ApoE) gene. Identifying cognitive deficits in healthy ApoE-ε4 carriers is valuable in order to develop interventions to prevent them from developing DAT. Existing evidence about cognitive deficits in the domains of episodic memory and cognitive control specific to ApoE-ε4 is contradictory.

The objective of our research was to assess episodic memory and cognitive control in healthy ApoE-ε4 carriers.

Cognitively healthy ApoE-ε4 carriers (13 ε4/ε4 heterozygotes) and noncarriers (22 ε3/ε3 homozygotes), who were matched on age and family history of DAT, were compared on episodic-memory and cognitive-control tasks. Episodic-memory tasks were verbal and visual recognition tasks with a systematic variation of distractor-to-target similarity. Executive functions were assessed by a task for updating working memory, an inhibition task, and a switching task. Working-memory capacity was also assessed.

The results showed that executive functions were generally not impaired in the carriers, but carriers showed a specific increase in accuracy-related switch costs. Working-memory capacity was not reduced in the carriers. In the domain of episodic memory, the carriers were found to make more errors with phonetic distractors in the verbal episodic-memory task. They also tended to make more errors with visually dissimilar distractors in the visual episodic-memory task.

The results are indicative of an episodic-memory deficit specific to the carriage of ApoE-ε4. This deficit may be driven either by deficits in storage or by deficits in the encoding of the to-be-remembered material. Contradictory results concerning the presence of an episodic-memory deficit obtained in previous studies may stem from small effect sizes, the use of specific materials, and the employment of attention-intensive encoding strategies. The carriers also showed a switching deficit that possibly is related to difficulty in retrieving task rules from episodic memory. Existing empirical contradictions concerning the presence of an executive deficit in carriers may in part depend on the extent

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to which tasks used to assess an executive deficit draw on the switching function. In this study, there was no general executive deficit in the carriers of ApoE-ε4.

Keywords: apolipoprotein E, Alzheimer's type dementia, episodic memory, cognitive control, executive functions, working memory, attention, task switching

Introduction

Dementia of the Alzheimer's type (DAT) is a progressive neurodegenerative disease that severely affects the quality of life of patients and their relatives. As the general population becomes older in the developed countries, more people are prone to the development of DAT. This increase in patients suffering from DAT places heavy costs on medical systems. It also places heavy costs on the patient's relatives in terms of both money and emotional involvement. It is therefore important not only to continue to search for effective treatment of already fully developed DAT but also to look for early indicators of DAT that would allow the application of preventive interventions. In this respect it may be valuable to consider the various risk factors that increase the probability of developing DAT.

A major risk factor for late-onset DAT is carriage of the ε4 allele of the apolipoprotein E (ApoE) gene (Raber, Huang, & Ashford, 2005). The carriage of this allele is associated with a highly increased probability (four- to ten-fold, according to various estimates) of DAT. As DAT is characterized by various cognitive deficits, finding cognitive deficits in healthy carriers of ApoE-ε4 could help in the development of interventions that could prevent their cognitive decline. Research on cognitive deficits in healthy ApoE-ε4 carriers has so far brought contradictory results, with some studies but not others finding such deficits (Wisdom, Callahan, & Hawkins, 2011). Two cognitive domains of specific importance for the study of possible accelerated cognitive decline in ApoE-ε4 carriers are episodic memory and cognitive control. The assessment of the integrity of episodic memory is important because episodic-memory impairments are a hallmark of DAT and Alzheimer's disease. Cognitive control is important because of the enormous role frontally mediated executive functions play in the regulation of behavior and because their degradation during age-related cognitive decline may be disproportionately large.

It has been shown that carriers of the ApoE-ε4 allele may exhibit some cognitive shortcomings in the domain of episodic memory (De Blasi et al., 2009). However, it has also been shown that episodic memory may be not affected by the carriage of ApoE-ε4 (Quintas et al., 2014). Better episodic memory in young, healthy carriers compared with noncarriers has also been reported (Mondadori et al., 2007). There is evidence that cognitive control may be negatively affected in carriers (Allain, Etcharry-Bouyx, & Verny, 2013). However, there is also evidence that ApoE-ε4 carriers show no deficits in cognitive control compared with noncarriers (Bondi, Salmon, Galasko, Thomas, & Thal, 1999) or even outperform controls in cognitive-control tasks (Marchant, King, Tabet, & Rusted, 2010). Contradictory conclusions about the presence and nature of possible cognitive deficits in the domains of episodic memory and cognitive control made by previous studies warrant the accumulation of additional empirical evidence about the functioning of these cognitive domains in healthy ApoE-ε4 carriers.

The aim of this study was to assess possible cognitive deficits in episodic memory and cognitive control in a sample of healthy ApoE-ε4 carriers and in a control sample of ApoE-ε3 carriers. The samples were matched on age and family history of DAT, as these two factors are important contributors to the risk of DAT. Episodic memory was assessed by a verbal and a visual recognition task. Typically, when assessing episodic memory in ApoE-ε4 carriers, recall tasks are used. Our use of a recognition task was motivated by the fact that recognition is usually easier than recall and thus possible differences in recognition performance would be indicative of a pronounced difference in memory abilities between carriers and noncarriers. Our study also differs from previous studies through a systematic variation of distractor-to-target similarity, which allows for a more precise analysis of a possible episodic-memory deficit in the carriers than simply stating the presence of such a deficit. The present study also extends previous studies of memory in ApoE-ε4 carriers by including a measure of working-memory capacity as working memory is important for daily functioning and is negatively affected by progressing age. The present study stands out from other studies of cognitive functioning in ApoE-ε4 carriers because it for the first time assesses all three basic executive functions — inhibition, switching, and working-memory updating — identified by Miyake and colleagues (2000).

Method

Subjects

The sample of ApoE-ε4 carriers consisted of 13 subjects (9 female and 4 male) carrying one ApoE-ε4 allele and one ApoE-ε3 allele. The control sample of ApoE-ε3 homozygotes consisted of 22 subjects (17 female and 5 male). The groups did not differ significantly in age (45.5 years vs. 47.5 years, $p>0.5$). All subjects had a close relative (a parent, a sister, or a brother) diagnosed with DAT. The subjects were recruited among relatives of patients of the Mental Health Research Center of the Russian Academy of Medical Sciences (Moscow). All subjects were not demented as revealed by a clinical interview and by performance on Luria's neuropsychological test battery and the Mini Mental State Examination (scores over 25). Subjects gave informed consent to participate in the study according to the ethical regulations of the Center.

Tasks

Four executive tasks and two episodic-memory tasks were given to the subjects. The cognitive-control tasks spanning three executive functions — inhibition, switching, and working-memory updating — were adapted from Miyake et al. (2000). A complex working-memory span task — the operation-span task — was also used to assess executive functioning. Complex working-memory tasks that combine storage of information with processing of a secondary cognitive task are a de facto standard (Conway et al., 2005) in assessing working-memory capacity, which spans the boundary between memory and cognitive-control domains. The episodic-memory tasks were typical recognition memory tasks used in numerous experi-

ments and included a verbal-memory task and a visual-memory task. The details on each task are given below.

Antisaccade task. The antisaccade task was adapted from Miyake et al. (2000) and was used to assess inhibition. A fixation cross was presented in the center of the screen for 500 ms. A rectangle serving as a distractor was presented for 225 ms in the left or right half of the screen (side randomly selected). After that, an arrow pointing left or right was presented in the opposite half of the screen for 150 ms. The task of the subjects was to indicate the direction of the arrow with a button press. They were explicitly instructed not to look at the distractor. There were 4 training trials and 100 test trials with all combinations of arrow location and direction presented equally, often in a truly random sequence.

Switching task. The switching task was adapted from Miyake et al. (2000) and was used to assess the effectiveness of rapid switching between tasks. The screen was divided into four quadrants. A letter-digit pair was subsequently presented in each quadrant starting with the upper right quadrant. If the letter-digit pair was presented in the upper right or lower left quadrant, the subject had to indicate whether the letter was a consonant or a vowel with a button press. When the letter-digit pair was presented in the other two quadrants, the task was to identify whether the digit was even or odd. The subjects had thus to alternate between a letter-categorization task and a digit-categorization task. Each letter-digit pair was presented for at most 5000 ms. There were 8 training trials and 100 test trials.

N-back task. The n-back task is commonly used to assess the updating of working memory (Owen, McMillan, Laird, & Bullmore, 2005). A pseudorandom sequence of digits was presented to the subjects, who had to indicate whether the presented digit matched the digit presented two trials before (2-back). Each digit was presented for 500 ms, and a response was awaited for at most 2500 ms. There was a training sequence of 10 digits with 3 critical events, and a test sequence of 62 digits with 15 critical events.

Operation span. This task is used to test working memory function (Conway et al., 2005). The subjects were presented with a letter to be remembered and an arithmetic equation to be verified. After a set of letter-equation pairs was presented, the letters were to be recalled in the correct order. The set sizes varied from 2 to 6. Working-memory capacity was estimated to be the length of the largest sequence of letters that could be reproduced without errors in the correct order. Letter-equation pairs were presented for 6000 ms.

Verbal episodic-memory task. The task was modeled after the Rey Auditory-Verbal Learning Test. A list of 14 words had to be memorized. The memorization phase preceded the presentation of the executive-function tasks. The list was presented three times with each word presented for 4000 ms and pronounced aloud by the subject. After the subject performed the executive-function tasks, a recognition test was given. In the recognition test, the 14 "old" words were intermixed with distractor words. Half the words were phonetically similar to the studied words, and the other half were semantically similar to them. Each distractor was similar to a different word from the studied list.

Visual episodic-memory task. This task was adapted from the Visual Reproduction I and II subtests of the Wechsler Memory Scale IV. Five abstract geometrical drawings had to be memorized. The drawings were presented for 6000 ms each be-

fore the performance of the executive-function tasks. A recognition test was given after the memorization test for the visual-memory task. In the recognition test, the studied drawings were mixed with 5 "close" and 5 "far" distractors. Close distractors were drawings that differed from the studied drawings only in small detail. Far distractors resembled the studied drawing only distantly.

Data analysis

The performance of the ε4-carrier group and the ε3-carrier group on the experimental tasks was compared with the *t*-test for independent samples. All tests were two-sided. A significance level of 0.05 was used. Results significant at 0.1 were also considered given the exploratory nature of this study.

Results

Descriptive statistics for all tasks are presented in Table 1. The results for the cognitive-control tasks are reported first, followed by the results for the episodic-memory tasks.

Table 1. Descriptive statistics for cognitive-performance indicators in the group of ApoE-ε4 carriers (ε4) and noncarriers (ε3)

Task	ApoE status				*p* level
	ε4 (*N*=13)		ε3 (*N*=22)		
	M	SD	M	SD	
Antisaccade					
RT	658	182	664	125	$p>0.1$
Accuracy	75.1	16.5	76.2	16.2	$p>0.1$
Task switching					
No switch RT	1139	269	1222	330	$p>0.1$
No switch accuracy	93.3	7.6	90.5	13.9	$p>0.1$
Switch RT	1628	500	1730	380	$p>0.1$
Switch accuracy	87.8	9.5	89.3	12.6	$p>0.1$
Switch cost, RT	489	269	508	292	$p>0.1$
Switch cost, accuracy	5.5	4.6	1.2	5.9	$p<0.05$
N-back	88.8	6.2	88.7	5.8	$p>0.1$
Operation span	3.5	0.53	3.8	0.74	$p>0.1$
Verbal memory					
Accuracy, old	99.0	2.5	99.4	2.0	$p>0.1$
Accuracy, semantic	97.8	5.4	96.1	6.5	$p>0.1$
Accuracy, phonetic	93.4	9.4	98.1	5.0	$p<0.1$
Visual memory					
Accuracy, old	95.0	12.6	94.6	12.9	$p>0.1$
Accuracy, close	61.5	23.5	67.4	20.3	$p>0.1$
Accuracy, far	72.7	23.4	83.1	14.4	$p>0.1$

Note. RT = reaction time.

There were no significant differences between the carrier and the noncarrier group on the antisaccade task (RT, $t(33)=0.12$, $p>0.1$; accuracy, $t(33)=2.0$, $p>0.1$). For the switching task, the groups did not differ either in the no switch trials (RT, $t(33)=0.77$, $p>0.1$; accuracy, $t(33)=-0.67$, $p>0.1$) or in the switch trials (RT, $t(33)=0.68$, $p>0.1$; accuracy, $t(33)=0.36$, $p>0.1$). Differences in the switch costs (that is, differences in performance in the no switch and switch trials) were analyzed, as switch costs are the main indicator of switching performance in the task-switching studies. The groups did not differ in RT-related switch costs ($t(33)=0.19$, $p>0.1$). Accuracy-related switch costs were significantly higher in the carrier group ($t(33)=-2.2$, $p<0.05$). The carriers made 5.5% more errors in the switch trials than in the no switch trials. The noncarriers made only 1.2% more errors in the switch trials.

Accuracy in the working-memory updating task, n-back, was not different in the two groups ($t(33)=-0.06$, $p>0.1$). The groups also did not differ in working-memory (operation) spans ($t(33)=1.06$, $p>0.1$).

For the verbal episodic memory, the groups did not differ in correct recognition of the "old" words ($t(33)=0.55$, $p>0.1$) and in correct rejections of semantic distractors ($t(33)=-0.79$, $p>0.1$). There was a strong numeric tendency for the carriers to make more false recognitions of phonetic distractors. Their false-alarm rate in this case was 6.6% vs. 1.9% for the noncarriers. This difference was marginally significant ($t(33)=1.9$, $p<0.1$).

For the visual episodic-memory task, the groups did not differ in correct recognition of the old drawings ($t(33)=-0.1$, $p>0.1$) and in correct rejections of the visually close distractors ($t(33)=0.76$, $p>0.1$). There was a large numeric tendency for the carriers to make more false recognitions of visually far distractors. The carriers made 27.7% errors in this case, while the noncarriers made only 16.9% errors. This difference, however, missed being marginally significant ($t(33)=1.63$, $p=0.11$).

Discussion

In this study we assessed possible cognitive deficits in a group of healthy ApoE-ε4 carriers and noncarriers with a family history of DAT. For the investigation the domains of episodic memory and executive functions were chosen as these are often affected in DAT — a condition closely associated with the presence of the ApoE-ε4 allele. The rationale for this study was to try to find cognitive indicators that would distinguish carriers from noncarriers. Such indicators can be very valuable for the early identification of persons with an increased risk of developing DAT. On this basis preventive measures can be applied to reduce the severity of the developing DAT.

The results obtained show that the carriers seemed to have no general executive deficit. The ε4 carriers performed well on the attention-demanding antisaccade task, thus showing no deficit in inhibition — a fundamental executive function. They also performed well on the n-back task, thus showing no deficit in another basic executive function — working-memory updating. They had complex working-memory spans statistically indistinguishable from those of the noncarriers. One notable exception was the switching task. The carriers had larger error-related switch costs. Increasing switch costs are characteristic of nonpathological cognitive aging. Such a specific increase in switch costs may be indicative of normal aging in

the carriers, whose rate exceeded that of the noncarriers. These results may resolve the apparent empirical contradiction revealed by previous studies regarding the presence of executive-function deficits in the carriers of ApoE-ε4. The ambiguity of results concerning executive deficits in the carriers may stem from the fact that different studies employ different executive tasks. If a task employed requires extensive use of switching, then an executive deficit may be reported. If a task does not depend on the switching function, an executive deficit may not be found.

The overall performance of the episodic-memory tasks was also almost indistinguishable between the carriers and the noncarriers. However, the carriers made more errors with phonetic distractors in the verbal episodic-memory task. Long-term memory is believed to be based on semantic coding, while confusion with phonetically similar material is more typical for short-term memory (Conrad, 1964). One explanation for the observed effect is that carriers use phonological coding in long-term memory instead of semantic coding. Semantic memory is known to be impaired in Alzheimer's disease (Rogers & Friedman, 2008). This impairment may be grounded in the semantic network's being damaged in Alzheimer's disease (Flanagan, Copland, Chenery, Byrne, & Angwin, 2013). Semantic coding may not be reliable in carriers, and thus only the phonological representations of the studied words are used to support performance of the memory task.

Another explanation for the obtained effect is that the carriers encoded not the semantic but the phonetic features of the to-be-remembered word ("shallow encoding"). In the recognition phase of the test, semantic distractors were correctly rejected by the carriers because they differ from the target words phonetically. Phonetic distractors were not rejected because they were confused with the phonetic trace left in long-term memory. The noncarriers fully stored a semantic representation and thus had no difficulty in rejecting phonetic distractors that were also semantically different from the target words. Therefore, our data indicate that carriers may not have a problem with retention of material but they may have a problem with deep processing and encoding of the studied words. This, in turn, indicates that possible episodic-memory problems in carriers are rooted in attention deficits.

The results obtained in the visual episodic-memory task give some support to this explanation. Although statistically not significant, the carriers' false-alarm rate for visually far distractors was substantially higher than that of the noncarriers. Far distractors resemble the target items very roughly, and it should not be hard to distinguish them from the targets unless only a vague trace of the target is left in memory. This is exactly what seems to have been the case with the carriers. The noncarrier group had fewer problems with correctly rejecting this type of distractor. Both groups had considerable difficulty correctly rejecting close distractors, which differ from the targets only in fine detail. The results concerning episodic memory obtained in this study help to resolve the contradictions concerning the presence of an episodic-memory deficit revealed by previous studies. It shows that a possible episodic-memory deficit in carriers is small in size (and thus requires large samples to be detected), occurs only with some types of distractors, and may be dependent on the employment of attention-intensive encoding. These conditions make it probable that an episodic-memory deficit remains undiscovered in many studies (and may even be reversed if, for example, elaborated encoding strategies are consciously employed by carriers).

The failures in episodic memory in the ApoE-ε4 carriers described above contrast with the complete absence of failures in their working memory. Neither updating of working memory during the performance of the n-back task nor the combined storage and processing during the performance of the operation-span task was impaired in the carriers. This result indicates that only long-term memory, not memory in general, is negatively affected by the presence of the ApoE-ε4 allele. Current memory theories usually present long-term memory and working memory as separate systems with different psychological mechanisms underlying each. Long-term episodic memory and working memory are also usually thought of as being supported by different neuroanatomical systems, with episodic memory associated with medial-temporal hemispheric structures and working memory being prefrontally mediated. This distinction of long-term and working memory is thus evident in the distinct effects of the ApoE-ε4 presence on them.

It is, however, possible that working-memory functions are jointly realized through long-term and short-term memory mechanisms (Unsworth & Engle, 2007). This is the case when the amount of the information to be held in working memory exceeds its strongly limited capacity (that is, if more than 3 or 4 items are to be held). As storage requirements clearly exceed these limitations in the operation-span task, it is interesting to see why this does not lead to a breakdown in operation-span performance in carriers. It may be that the reduced effectiveness of long-term memory in carriers is compensated for by the increased effectiveness of their primary memory, which allows for immediate storage and speeded access to the retained items. Such compensation may be shown, for example, by demonstrating that there is a reduced primacy effect during working memory in carriers compared with noncarriers.

Following this line of reasoning we can suggest that the carriers have more-developed executive functions than the noncarriers. This suggestion is permissible in the light of our findings that no general executive deficit was found in the carriers. However, task-switching effectiveness was significantly reduced in the carriers, a finding that disproves the idea of a general executive advantage in the carriers. Task switching is an important executive function that has generated a lot of research. The main conclusion from these studies is that task switching involves an active executive reconfiguration process. Efficiency of task switching decreases because of a number of factors, one of which is aging (Kray & Lindenberger, 2000). It has also been shown that switching efficiency is reduced in people with beginning DAT, contrary to other indicators of executive functioning (Fernandez-Duques & Black, 2008). Other studies also show that task-switching performance is a promising indicator of early-stage DAT (Hutchinson, Balota, & Duchek, 2010) and pathological cognitive aging in general (Duchek et al., 2009). Thus, an increased cost of task switching may be associated with cognitive deficits during DAT, and its association with the presence of the ApoE-ε4 allele may also not be incidental.

Although task switching is usually understood as an executive function clearly separated from long-term memory, the actual deficit underlying task-switching impairments in carriers may be closely related to memory. DeJong (2000) hypothesized that an important aspect of task switching is loading the rules of the new task into working memory from long-term memory. Accordingly, there are two types of task-switching trials. In some trials, access to long-term memory and retrieval of rules

is successful, and there is no extra slowing of reaction time. In other trials, memory access fails and new task rules cannot be activated immediately; this failure requires repeated memory access. As a result, reaction times become longer. Such a mixed distribution of reaction times produces the overall increase in reaction times that is a characteristic of task-switching trials. Similar inferences can be drawn about the emergence of switch costs measured with accuracy data. Thus, an apparent executive deficit in carriers may turn out to be a long-term memory deficit.

Conclusion

Episodic memory and executive functions were assessed in a sample of cognitively healthy ApoE-ε4 carriers and noncarriers with a family history of Alzheimer's disease. The carriers were found to make more errors with phonetic distractors in a verbal episodic-memory task. They were also found to make more errors with visually dissimilar distractors in a visual episodic-memory task. These results are indicative of a general episodic-memory deficit driven either by deficits in storage or by deficits in encoding the to-be-remembered material. Contradictory results concerning the presence of an episodic-memory deficit obtained in previous studies may stem from small effect sizes, the use of specific materials, and the employment of attention-intensive encoding strategies. In our research, executive functions were generally not impaired, a finding that casts doubt on the assumption that there is an executive deficit in ApoE-ε4 carriers. However, task-switching performance was impaired in the carriers. Existing empirical contradictions concerning the presence of an executive deficit in carriers may in part depend on the extent to which tasks used to assess an executive deficit draw on the switching function. The switching deficit may also be related to difficulty in retrieving task rules from episodic memory. Deficits in episodic memory and task switching could be valuable indicators of early cognitive deficits in healthy ApoE-ε4 carriers.

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