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Olfaction in Aging and Alzheimer's Disease: Event-Related Potentials to a Cross-Modal Odor Recognition Memory Task Discriminate ApoE $\epsilon 4+$ and ApoE $\epsilon 4-$ Individuals

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Abstract

Alzheimer's disease (AD) is a devastating neurodegenerative condition that affects more than 5 million Americans. Currently, a definitive and unequivocal diagnosis of AD can only be confirmed histopathologically via post-mortem autopsy, demonstrating the need for objective measures of cognitive functioning for those at risk for AD. The single most important genetic risk factor of AD is the Apolipoprotein E (ApoE) $\epsilon 4$ allele. The present study investigated olfactory and cognitive processing deficits in ApoE $\epsilon 4$ positive individuals using a cross-modal recognition memory task and an objective electrophysiological measure, the event-related potential (ERP). Ten $\epsilon 4+$ individuals (5 M, 5 F, M = 75.1 yrs) and ten age and gender-matched $\epsilon 4-$ individuals (5 M, 5 F, M = 71 yrs) sequentially encoded a set of 16 olfactory stimuli and were subsequently shown names of odors previously presented (targets) or not (foils). EEG activity was recorded from 19 electrodes as participants distinguished targets from foils using a two-button mouse. P3 latencies were significantly longer in $\epsilon 4+$ individuals and intra-class correlations demonstrated differential activity between the two groups. These findings are consistent with a compensatory hypothesis, which posits that non-demented $\epsilon 4+$ individuals will expend greater effort in cognitive processing or engage in alternative strategies and therefore require greater activation of neural tissue or recruitment of different neural populations. The findings also suggest that cross-modal ERP studies of recognition memory discriminate early neurocognitive changes in ApoE $\epsilon 4+$ and ApoE $\epsilon 4-$ individuals and may contribute to identifying the phenotype of persons who will develop Alzheimer's Disease.

Keywords

Aging; Alzheimer's Disease; ApoE $\epsilon 4$; Olfaction; Olfactory Impairment; Smell; Recognition Memory

Introduction

Alzheimer's disease (AD) is a devastating neurodegenerative condition that affects more than 5 million Americans. Since 1980, the prevalence of AD in America has nearly doubled making it the most common form of dementia, accounting for 50-60% of dementia related cases. Current estimates suggest that by 2050, more than 13 million Americans will suffer from this debilitating disorder.¹

Diagnostic Criteria

Both the NINDS-ADRDA and the DSM-IV diagnostic criteria for AD include progressive and global cognitive impairment in two or more cognitive areas including memory. Attempts to diagnose the disorder in a living person using physiological tests are imperfect. Therefore, a definitive and unequivocal diagnosis of AD can only be confirmed histopathologically via post-mortem autopsy. As pharmacological and other interventions become available, distinguishing very early those individuals who will go on to develop AD will be very important for targeted treatment; hence, efforts to identify these individuals are keen. The current study was designed to investigate a new method for targeting these individuals using evoked brain potentials.

Risk Factors

A number of risk factors for AD have been identified with the most obvious being age,^{1,2} a decreased reserve capacity of the brain resulting from reduced brain size, low educational and occupational attainment, low mental ability in early life, and reduced mental and physical activity during later life,^{3,4} head trauma,⁵ and Down's syndrome.^{6,7}

The single most important genetic risk factor is the allelic variant apolipoprotein E (ApoE) $\epsilon 4$.⁸ The ApoE $\epsilon 4$ allele increases the risk of developing AD by three times in heterozygotes and by fifteen times in homozygotes.^{9, 10}

ApoE $\epsilon 4$

ApoE is a key lipoprotein found in the brain as well as the cerebral spinal fluid (CSF).^{11,12} It has been mapped in the human genome to the proximal long arm of Chromosome 19.^{13,14} ApoE normally functions as a cholesterol transporter in the brain¹² but it also abnormally binds to soluble and insoluble forms of B-amyloid¹⁵ and the $\beta A4$ peptide, which is the primary component of neuritic plaques.¹⁶ As shown by Poirier,¹⁷ the ApoE $\epsilon 4$ allele is less efficient than other ApoE alleles in the reuse of membrane lipids and neuronal repair. ApoE has also been found to contribute to the formation of neurofibrillary tangles (NFTs).¹¹

ApoE mRNA, which plays a compensatory role in neuronal sprouting and synaptogenesis in the central nervous system, is reduced in the hippocampus in AD.¹⁵ Tau, the main component of NFTs, is elevated in the CSF of AD patients who possess at least one copy of the $\epsilon 4$ allele compared to those without the $\epsilon 4$ allele.¹⁸ Soininen and Riekkinen¹⁹ showed a positive association between the number of $\epsilon 4$ alleles and the increased deficit of acetylcholine-containing neurons in the brains of AD patients.

Prior research into global cognitive functioning and ApoE allele genotype has been inconclusive. A number of studies have shown that the $\epsilon 4$ allele predicted cognitive decline²⁰⁻²⁶ and $\epsilon 4+$ persons perform poorly on tests of processing speed, delayed free recall, and semantic long term memory.²⁷ However, performance is not impaired on all tests²⁸⁻³⁰ and some have reported no difference in cognitive decline between the different allelic variants of ApoE.^{31,32}

Olfaction and AD

AD produces neuropathological changes in peripheral and central areas of the brain that process olfactory information. The first stage in the neurodegenerative progression of AD occurs in the entorhinal and trans-entorhinal areas critical to olfactory information processing.^{33,34} The olfactory bulbs, anterior olfactory nucleus, and orbitofrontal cortex are all also affected by AD.^{34,35} This pathology motivates the investigation of olfactory functioning in individuals in the beginning stages of AD. The olfactory deficits observed in AD include decreases in odor threshold sensitivity,³⁶⁻³⁸ odor identification,³⁹⁻⁴² odor memory,^{43,44} odor fluency,⁴⁵ and olfactory event-related potentials.⁴⁶

Deficits in olfactory functioning have also been associated with those at risk for AD. Wilson (this volume) discusses elegantly the olfactory impairment in persons with mild cognitive impairment, an important risk factor for AD. He and his group have also shown a significant relationship between olfactory impairment and neuroanatomical bases of AD. Olfactory deficits are clearly associated with the ApoE $\epsilon 4$ allele. Physiologically, a post-mortem study showed ApoE was localized in an increased number of olfactory receptor neurons becoming more pervasive in the olfactory epithelium of individuals with AD compared to non-AD individuals.⁴⁷ Behaviorally, Bacon et al.³⁶ demonstrated that in the first year of their AD diagnosis, $\epsilon 4+$ individuals had inferior odor threshold sensitivity. Murphy et al.⁴² showed that even in nondemented elderly individuals, those with the $\epsilon 4$ allele showed impaired odor identification, and Calhoun-Haney and Murphy⁴⁸ found significant decline in odor identification in $\epsilon 4+$ individuals who did not yet show significant declines in DRS, suggesting that changes in olfactory function may predict later overall decline.

Memory

Neuroimaging and electrophysiological studies have revealed several different brain regions involved in encoding and retrieval of episodic memory. These studies demonstrated that neural activity is observed in different brain regions depending on a number of conditions, e.g., depth of encoding,⁴⁹ sensory modality,⁵⁰ and task set.⁵¹

Recognition Memory and ApoE

A number of studies have shown significant deficits in odor recognition memory and odor identification in $\epsilon 4+$ individuals.⁵²⁻⁵⁴ They also commit more false positive errors in response to olfactory stimuli than $\epsilon 4-$ individuals.⁵² A false positive error is defined as erroneously choosing a new stimulus (foil) as a member of the original stimulus set (target). Analysis of false positive errors and poor performance on odor recognition memory tasks may be useful ways to distinguish between normal older individuals and those at risk for developing AD.

ERP Components

Early components of the ERP waveform, N1/P2, represent exogenous sensory mechanisms that have been associated with psychophysical measures of olfactory functioning, e.g., odor threshold sensitivity.^{57,58} Later components of the ERP waveform, especially P3, represent endogenous mechanisms such as stimulus classification speed as well as cognitive attending and evaluation of stimuli.^{59,60} P3 latency is correlated with performance on neuropsychological tests that measure memory and cognitive processing speed.⁶¹ P3 amplitude is proportional to the amount of neural resources allocated to a given task.^{62,63} P3 latency increases and P3 amplitude decreases as individuals age.^{57,58,64,65} Wetter and Murphy⁶⁶ also demonstrated that ApoE $\epsilon 4+$ individuals performing an oddball task show abnormally increased P3 latency and decreased P3 amplitude. These findings suggest the potential of EEG measures for assessing cognitive functioning and more specifically recognition memory in $\epsilon 4+$ individuals.

However, to date, an ERP recognition memory study using a cross-modal odor recognition task (presenting olfactory stimuli during encoding and visually presenting names of those same odors during recognition) has never been employed to investigate differences in cortical activation in ApoE $\epsilon 4+$ and $\epsilon 4-$ individuals. This was our aim.

Methods

Participants were 20 non-demented older adults, 10 who were $\epsilon 4+$ (5 M, 5 F, M = 75.1 years, SD = 8.3) and 10 who were $\epsilon 4-$, age- and gender matched (M = 71 years, SD = 6.1). All gave informed consent.

Psychophysical and Neuropsychological Measures

Psychophysical measures included the San Diego Odor Identification Test,⁷⁰ measures of verbal fluency including letter and category fluency, and tests of odor fluency.⁴⁵ The odor threshold test³⁷ screened for potential anosmia or severe hyposmia.

Neuropsychological measures included the California Odor Learning Test (COLT),⁷¹ the Dementia Rating Scale (DRS),⁷² and the Mini Mental State Exam (MMSE).⁷³ These measures assess participants' global cognitive functioning, cognitive impairment, and odor learning, recall, and recognition memory abilities.

Electrophysiological Data Collection

Electroencephalographic (EEG) activity was recorded with an electrode cap from 19 electrode sites, FP1/2, Fz, F3/4, F7/8, Cz, C3/4, T7/8, Pz, P3/4, P7/8, and O1/2, for 2000 ms, including a 100 ms pre-stimulus baseline; amplified via a Grass RPS 197 amplifier system; filtered (0.1 30 Hz band pass, 6 dB octave/slope); and digitized at 256 Hz. Data were averaged off-line using in-house software to reject artifactual responses of $\pm 150 \mu\text{V}$ and a regression analysis based EOG correction procedure to remove any remaining artifact.⁷⁴ Neuroscan software was used to calculate intra-class correlations.

Procedure

The experimental paradigm used in this study is identical to the paradigm used in a parallel fMRI study investigating cross-modal recognition memory for odors,⁶⁹ and is based on a design of Stark and Squire.⁵⁰ Stimuli were presented in 3 blocks, each with 72 trials. During encoding, participants were presented with 16 familiar odors from the California Odor Learning Test.⁷¹ Each was presented for 5 sec, with a 15 sec inter-stimulus interval.

During EEG recording, every 4 sec participants were presented with words displayed on a computer screen that corresponded to names of odors previously presented (targets) or not (foils), followed by a fixation cross. Participants distinguished targets from foils using a two-button mouse.

Hypotheses

The purpose of the proposed study was to examine whether ApoE $\epsilon 4+$ and $\epsilon 4-$ individuals exhibit differences in the neural allocation of resources during a cross-modal recognition memory task. We analyzed P3 latency and intra-class correlations of activity at each electrode site. We hypothesized differences in ERP data as a function of allele status: Longer P3 latencies, and differences in activity in ApoE $\epsilon 4+$ individuals, dependent on response type.

Results

Psychophysical and Cognitive Functioning Tests

Multivariate analyses of variance (MANOVA) on age, years of education, category fluency, odor fluency, letter fluency, mean odor threshold, SDOIT, DRS, and MMSE scores demonstrated no significant differences between groups (Table 1). In particular, analyses demonstrated no significant difference in odor threshold scores between ApoE $\epsilon 4+$ and $\epsilon 4-$ participants. This finding suggests that $\epsilon 4+$ and $\epsilon 4-$ participants had similar sensory functioning and therefore, similar potential to encode the olfactory stimuli. This result was not surprising since participants were screened to exclude participants with anosmia or severe hyposmia.

P3 Latency

Olfactory ERP studies have focused almost exclusively on the Fz, Cz and Pz electrode sites and thus, to place the data in the context of the literature, we first conducted ANOVA on midline electrode sites (Table 1). ANOVA of P3 latency showed that latency was significantly delayed in ApoE $\epsilon 4+$ individuals [$F(1,18) = 9.6$, $p < .05$, $\eta^2 = .35$] (Figure 1).

Intra-class Correlations

To investigate differences in activity between groups intra-class correlations of the positive area measured from 525-675 msec post stimulus from ApoE $\epsilon 4+$ and $\epsilon 4-$ participants were examined at each electrode sites and for each response type. The 525-675 msec post-stimulus response epoch was used in order to capture the epoch during which the P3s for the participants were generated (See Fig. 1). The intra-class correlation expresses the degree of overlap and related variability between two waveforms. The statistic is generated by

comparing two ERP waveforms, taking into account both waveshape and absolute voltage values. Correlation values below .44 ($p < .05$) indicated statically significant differences in amplitude (See Table 3). As illustrated in Table 3, there were significant differences in activity between groups. Intra-class correlations for each of the response types are given in Figure 2, with blue indicating the largest differences between groups and red indicating greatest similarity between groups. The topographical maps in Figure 3 illustrate the group differences in P3 amplitude, with warmer colors indicating greater amplitude.

Discussion

This study was designed to investigate whether EEG correlates of cross-modal odor recognition memory discriminate between $\epsilon 4+$ and $\epsilon 4-$ individuals. The results support significant differences between $\epsilon 4+$ and $\epsilon 4-$ individuals in P3 latency and in intra-class correlations of activity.

Psychophysical and Cognitive Functioning Tests

No significant differences were found in psychophysical and cognitive functioning test scores between $\epsilon 4+$ and $\epsilon 4-$ participants, suggesting that participants had similar olfactory functioning supporting similar sensory encoding of the olfactory stimuli. Participants with anosmia or serious hyposmia were screened out using the odor threshold test, thus this result is not surprising.

P3 Latency, & Intra-Class Correlations

P3 Latency—The original hypothesis that $\epsilon 4+$ participants would demonstrate longer P3 latencies than $\epsilon 4-$ participants was supported. This is the first report of longer latencies in a cross-modal odor recognition memory task. Latency differences have been observed in ERP studies using oddball tasks;^{75,66} however, this is the first observation that a cross-modal odor recognition memory task discriminates between $\epsilon 4+$ and $\epsilon 4-$ individuals. Longer P3 latencies in $\epsilon 4+$ individuals are consistent with the theory that $\epsilon 4+$ individuals demonstrate slower cognitive processing than normal older adults and are at risk for subsequently developing AD.

Amplitude & Intra-class Correlations—Figure 3 illustrates the differences in P3 amplitude between $\epsilon 4+$ and $\epsilon 4-$ participants at the different electrode sites.

Intra-class correlations were employed in order to compare waveshape and voltage values at each individual electrode site between $\epsilon 4+$ and $\epsilon 4-$ participants. These correlations were generated for each response type using a 525 675 milliseconds post stimulus response epoch to capture the epoch during which the P3s for the participants were generated (See Fig. 1). For correct rejection responses, $\epsilon 4+$ and $\epsilon 4-$ participants showed significant differences in intra-class correlations in electrode sites over frontal (F3, F4, F7, F8, Fp1, Fp2) and temporal areas (T7, T8). This effect was also observed when evaluating hit responses (F3, F4, F7, F8, T7, T8, Fp1). The $\epsilon 4+$ and $\epsilon 4-$ individuals showed significantly different intra-class correlations at a number of electrode sites for false positive responses (CZ, F4, F7, F8, T7, T8, Fp2) and misses (FZ, CZ, PZ, F7, F8, C3, T8, Fp1, Fp2), suggesting that differential

activity underlies these performance errors (See Table 3 and Figure 2). These findings are consistent with the compensatory hypothesis that $\epsilon 4+$ individuals expend greater effort in cognitive processing in a cross-modal odor recognition memory task than $\epsilon 4-$ individuals. This increased effort observed in $\epsilon 4+$ individuals requires activation of a greater area extent of neural tissue, or an increased firing rate within a given area, or a larger number of neurons recruited to perform the task. This pattern of correlations is also compatible with the hypothesis that $\epsilon 4+$ individuals may engage in different strategies in order to perform the task. Preliminary data from our laboratory using fMRI are also consistent with these hypotheses.⁷⁶

These findings are complemented by anatomical studies that have demonstrated that $\epsilon 4+$ individuals experience greater temporal atrophy than $\epsilon 4-$ individuals.^{77,78} Finally, intra-class correlations lend further support to neuropsychological studies that suggest false positive responses were able to discriminate between $\epsilon 4+$ and $\epsilon 4-$ individuals.^{52,79}

Conclusion

ApoE $\epsilon 4+$ individuals demonstrated significantly longer P3 latency than $\epsilon 4+$ individuals and differential activity for all response types. Differential activity in ApoE $\epsilon 4+$ and $\epsilon 4-$ individuals, demonstrated by the intra-class correlation coefficients, is consistent with a compensatory hypothesis, which posits that $\epsilon 4+$ individuals expend greater effort in cognitive processing and therefore require greater activation of neural tissue during retrieval attempts. Finally, in accordance with previous ERP and fMRI studies involving odor familiarity, participants exhibited greater positive area in electrode sites over the right hemisphere in comparison to the left hemisphere. These findings suggest that cross-modal ERP studies of recognition memory in ApoE $\epsilon 4+$ and $\epsilon 4-$ individuals are a useful measure for indexing functional brain integrity, for understanding the neurocognitive changes associated with the ApoE $\epsilon 4$ allele, and for discriminating between brain response in $\epsilon 4+$ and $\epsilon 4-$ individuals.

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Figure 1.
P3 latency for ApoE $\epsilon 4+$ and $\epsilon 4-$ participants.

Figure 2.
Intra-Class correlations for electrode sites for the four response types for ϵ_4+ and ϵ_4- individuals. Blue indicates the greatest differences between groups and red the highest correlations between groups.

Figure 3. P3 amplitude for the four response types for $\epsilon 4+$ and $\epsilon 4-$ individuals. Warmer colors indicate greater amplitude.

Table 1

MANOVA Results for Psychophysical and Cognitive Function Tests

Dependent Variables	ApoE ε4+		ApoE ε4−		df	F	Sig.
	Mean	SD	Mean	SD			
Age	75.13	8.34	71.00	6.14	1	1.27	.28
Education (Years)	14.38	2.61	14.63	2.26	1	.04	.84
Category fluency score	44.50	9.61	45.38	6.97	1	.04	.84
Odor fluency score	17.13	8.18	12.75	8.88	1	1.05	.32
Letter fluency score	40.00	12.97	37.88	6.71	1	.17	.69
Odor threshold score	5.69	2.07	5.38	1.85	1	.10	.76
SDOIT Score	5.25	1.04	4.00	2.00	1	2.47	.14
DRS	140.63	2.77	142.25	3.45	1	1.07	.32
MMSE	27.00	2.73	26.13	2.75	1	.41	.53

Table 2ANOVA Results Comparing P3 Latency for ApoE ϵ 4+ and ApoE ϵ 4– Participants

Effect	df	P3 Latency		
		F	Sig.	η_p^2
Allele Status (AS)	1	9.59	.01	.35
Site (S)	2	17.63	.00	.50
Response (R)	3	1.18	.32	.06
R X AS	3	.53	.62	.03
S X R	6	.88	.46	.05
S X R X AS	6	.57	.64	.03

Table 3

Intra-class correlations at the 19 electrode sites, comparing brain response in $\epsilon 4+$ and $\epsilon 4-$ individuals during the four memory response types: correct rejections, false positives, hits and misses respectively.

Electrode Site	Correct Rejections: Correlation (r)	False Positives: Correlation (r)	Hits: Correlation (r)	Misses: Correlation (r)
Fz	.95	.93	.61	.18 *
Cz	.94	.25 *	.89	.26 *
Pz	.89	.62	.92	.34 *
F3	.28 *	.54	.17 *	.50
F4	.29 *	.42 *	.30 *	.64
F7	.00 *	.17 *	.01 *	.08 *
F8	.07 *	.13 *	.01 *	.32 *
C3	.58	.50	.65	.41 *
C4	.35 *	.82	.63	.87
T7	.29 *	.30 *	.18 *	.56
T8	.13 *	.29 *	.18 *	.19 *
P3	.73	.66	.75	.80
P4	.68	.96	.91	.96
P7	.60	.71	.72	.98
P8	.78	.67	.60	.76
FP1	.10 *	.73	.12 *	.03 *
FP2	.01 *	.06 *	.47	.11 *
O1	.74	.51	.95	.68
O2	.80	.71	.95	.75

* Correlations that indicate significantly different responses are indicated by.