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Age and Apolipoprotein E ϵ 4 Effects on Neural Correlates of Odor Memory

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Abstract

Alzheimer's disease affects 5.4 million Americans. Evidence suggests that individuals who are positive for the apolipoprotein E ϵ 4 allele are at higher risk for developing the disease. Studies have also shown that the ϵ 4 allele is linked to olfactory decline. Olfactory functioning may be investigated using olfactory event-related potentials (OERPs). The high temporal resolution of OERPs enables an understanding of the neural correlates of olfactory processing and functioning. This study investigated the effects of age, ApoE ϵ 4 status, response type, and electrode site on OERP latency and amplitude during encoding and retrieval in an odor recognition memory task. The 60 participants were equally divided into 3 age groups matched on ϵ 4 status – younger, middle, and older. Odors were presented using a computer-controlled olfactometer. Participants were notified during encoding that this was a task of odor memory. Results indicated differences in OERP activity as a function of age, ApoE ϵ 4 status, response type, and electrode site. These findings highlight the potential of OERPs to distinguish ϵ 4– and ϵ 4+ individuals and to contribute to an earlier diagnosis of AD.

Keywords

Aging; Alzheimer's Disease; event-related potentials; ApoE; odor memory; episodic recognition memory; smell impairment

Alzheimer's Disease

Alzheimer's Disease (AD) currently affects over 5.4 million Americans and is the most common cause type of dementia. One in eight people over 65 years old and nearly half of those over 85 years have been diagnosed with this neurodegenerative condition (Alzheimer's Association, 2012). Due to the rapidly increasing population of older adults, prevalence of AD in the United States is expected to rise, with estimates surpassing 13 million by 2050 (Hebert, Scherr, Bienias, Bennet, & Evans, 2003).

Clinically, AD is characterized by the progressive deterioration of memory, executive function, language and other areas of cognitive function, with particular difficulty encoding new information (McKhann, Knopman, Chertkow, Hyman, Jack, Kawas, et al., 2011). However, definitive diagnosis only occurs at autopsy or biopsy with the histopathological classification of neuritic plaques and neurofibrillary tangles (NIA, 1997). The deterioration begins in the mesial temporal regions, which include the areas critical for olfactory function. Amyloid- β peptide ($A\beta$) accumulates creating amyloid plaques while the microtubule-binding protein tau forms neurofibrillary tangles, and a pathogenic cascade is associated with inflammation, neuronal and synaptic loss and brain atrophy that ultimately leads to AD.

Diagnosis

At the time of clinical diagnosis, irreversible cognitive decline has already occurred. Pharmaceutical medications are available to treat symptoms of AD, yet none have been able to reverse the progression of the disease. Large research efforts to develop a treatment capable of ceasing further AD pathogenesis are in progress. Studies are focusing on therapeutic strategies that include antioxidant therapies, methods targeting heat shock proteins and antibody treatment (Bonda et al., 2010; Frost, Liu, Kleinschmidt, Schilling, Demuth, & Lemere, 2012; Hoshino et al., 2011; Tabira, Matsumoto, & Jin, 2011). Given the pervasiveness of AD and the promise of preventative agents, significant research is necessary to identify tools that will facilitate early detection of AD.

Apolipoprotein E

Apolipoprotein E (ApoE) is a glycoprotein mapped to the proximal long arm of Chromosome 19 (Das et al., 1985; Olaisen, Teisberg, & Gedde-Dahl, 1982). ApoE is responsible for lipid transport throughout the body but in the brain and CSF it also promotes neural growth and repair. There are three common allelic types of ApoE: $\epsilon 2$, $\epsilon 3$ and $\epsilon 4$. The three isoforms are distinguished by minor differences in their amino acid sequences but have a major effect on the structure and function of ApoE. ApoE can also bind to $A\beta$ which induces a pathological β -sheet conformational change in $A\beta$ (Poirier, 1994; Wisniewski & Frangione, 1992) resulting in the formation of neuritic plaques (Strittmatter et al., 1993).

The $\epsilon 4$ allele of apolipoprotein E is the single greatest genetic risk factor for sporadic and familial AD (Bertram, McQueen, Mullin, Blacker, & Tanzi, 2007; Farrer et al., 1997; Roses, 1995; Strittmatter et al., 1993). Homozygotes have a 15-fold increased risk of developing AD while heterozygotes have 3-fold increased risk (Corder et al., 1995; Farrer et al., 1997). Studies show a positive correlation between the number of $\epsilon 4$ alleles and the quantity of neuritic plaques (Kim, Basak, & Holtzman, 2011; Rebeck, Reiter, Strickland, & Hyman, 1993; Schmechel et al., 1993). Research has linked $\epsilon 4$ expression to increased $A\beta$ aggregation in vitro (Buttini et al., 1999; Hatters, Zhong, Rutenber, & Weisgraber, 2006; Mahley & Huang, 2006; Veinsbergs, Everson, Sagara, & Masliah, 2002), impaired $A\beta$ clearance (Deane, et al., 2008), reduced resiliency to oxidative stress (Jofre-Monseny, Minihane, & Rimbach, 2008), increased neuroinflammation (Colton et al., 2004; Lynch et al., 2003) and altered calcium dynamics. Tau, the protein that forms neurofibrillary tangles,

is elevated in individuals with AD who possess the $\epsilon 4$ allele in comparison to the other isoforms of ApoE (Tapiola et al., 1998).

Olfaction and AD

The earliest stages of AD compromise the entorhinal and transentorhinal areas critical to olfactory function. The olfactory bulbs, anterior olfactory nucleus and orbitofrontal cortex are also compromised (Christen-Zaech et al., 2003; Esiri & Wilcock, 1984; Haberly & Price, 1978; Ohm & Braak, 1987; Price, Davis, Morris, & White, 1991; Struble & Clark 1992). Cross modal odor identification tasks demonstrate olfactory impairment in individuals with AD (Morgan, Nordin, & Murphy, 1995; Serby, 1986) and those with mild cognitive impairment (Devanand et al., 2010). Carriers of APOE $\epsilon 4$ without signs of dementia also showed decreased olfactory function (Murphy et al., 1998; Olofsson et al., 2010). Studies show that individuals with poor odor identification performance, particularly those with $\epsilon 4$, were more likely to develop cognitive impairment (Graves et al., 1999; Schubert et al., 2008; Wilson et al., 2007). Thus, olfactory studies improve our understanding the neurodegenerative process of AD and the impact of $\epsilon 4$.

OERP

Assessing olfactory function utilizing olfactory event-related potentials (OERP) reveals impairment in olfactory function in addition to that demonstrated with behavioral tests. Of particular interest, OERPs display sensitivity in identifying individuals with AD (Morgan & Murphy, 2002). Past OERP studies have shown that P3 peaks have increased latencies and decreased amplitudes as people age (Morgan, Covington, Geisler, Polich, & Murphy, 1997; Murphy et al., 1994, 2000; Nordin et al., 1999). This effect is greatly exaggerated in comparison to auditory ERP when measuring OERP in individuals with AD (Morgan & Murphy, 2002). There is also evidence that reductions in an N400-like ERP component in patients with mild cognitive impairment are associated with an increased risk of AD development (Olichney et al., 2008). Significant differences have also been observed in olfactory performance in an olfactory-visual semantic congruency task in persons at genetic risk for AD compared to non-carriers of $\epsilon 4$ (Kowalewski & Murphy, 2012). Individuals with the $\epsilon 4$ allele also show increased latencies and decreased amplitudes of the OERP during retrieval in a cross-modal task of episodic odor/odor name memory (Murphy, Solomon, Haase, Wang, & Morgan, 2009). Because significant differences in ERP peaks in ApoE $\epsilon 4$ carriers have been observed during retrieval of cross-modal episodic memory using odor names, the present OERP study was designed as a novel investigation of the nature of differences in ApoE $\epsilon 4$ carriers during uni-modal odor encoding and retrieval, with the intent to maximally challenge the system in those who may be undergoing early degeneration. And because difficulty in encoding new information into memory is one of the defining characteristics of AD, we were particularly interested in brain response during encoding of odors.

Most episodic memory research has focused on recognition accuracy by comparing hit and false positive responses (Cabeza et al., 2001; Slotnick & Schacter, 2004; Garoff-Eaton et al., 2006), but little is known about the neural networks of rejection accuracy (correct rejections

and misses) (Royet et al., 2011). For example, patients with questionable Alzheimer's disease typically commit more false positive errors compared to healthy age-matched controls for odors. ApoE $\epsilon 4+$ individuals at risk for AD typically show significant deficits in cross-modal odor-recognition memory and odor identification compared to $\epsilon 4-$ individuals (Gilbert & Murphy, 2004; Nordin, & Murphy, 1998; Sundermann, Gilbert, & Murphy, 2007). Specifically, these $\epsilon 4+$ individuals commit more false positive errors in response to olfactory stimuli than do $\epsilon 4-$ individuals (Gilbert & Murphy, 2004). Therefore, false positive errors in tasks of odor memory may be very useful in distinguishing not only patients with probable AD from controls (Nordin & Murphy, 1996), but also in identifying early deficits in recognition memory in those at risk for AD (Gilbert & Murphy, 2004).

Patients with Alzheimer's disease and individuals at risk for AD may be more susceptible to false positive errors than age-matched controls in odor recognition memory tasks due to the role of the mesial temporal lobe in encoding and retrieval of episodic memories (Gilbert & Murphy, 2004). There is fMRI evidence to suggest that perirhinal cortex is preferentially activated during false positive responses during episodic odor recognition memory retrieval (Royet et al., 2011). In cross-modal investigation using odor names for retrieval, $\epsilon 4+$ and $\epsilon 4-$ individuals have demonstrated significantly different intra-class correlations at different electrode sites for misses and false positives, suggesting that differential activity underlies these performance errors, and supporting the hypothesis that $\epsilon 4+$ individuals require greater cognitive processing effort during retrieval in an odor memory task (Murphy et al., 2009).

The present study aimed to investigate whether differences in OERP latency and/or amplitude exist as a function of age, ApoE $\epsilon 4$ status, response type, and electrode site in odor recognition memory tasks. This study is the first to investigate differences during encoding of olfactory information using OERPs and to investigate these effects in middle age. The study is designed to improve our understanding of memory and olfactory processes, and specifically, to determine whether the integrity of the processes underlying odor recognition memory are affected as early as middle age in persons at risk for AD because of the $\epsilon 4$ allele.

Method

Participants

Participants were 60 adults, equally divided into three age groups: 20 younger (18 to 25 years old, mean age = 21.35 years SD = 1.17), 20 middle-aged (45 to 55 years old, mean age = 50.35 years SD = 4.63) and 20 older adults (65 years old and above, mean age = 68.95 years SD = 3.28). Each age group consisted of 10 ApoE $\epsilon 4+$ and 10 ApoE $\epsilon 4-$ and half of each subgroup was female. Participants gave informed consent and were compensated for their time.

Psychophysical and Cognitive Testing

Prior to testing, all individuals were screened for cognitive impairment using the Dementia Rating Scale (DRS) (Mattis, 1976) and for olfactory functioning using the San Diego Odor Identification Test (SDOIT) (Murphy et al., 1994, 2002) and an odor threshold test (Murphy,

1990). All participants with scores indicative of dementia, anosmia, or severe hyposmia (DRS scores lower than 124 out of a maximum of 144, odor ID scores lower than 3 out of a maximum of 8, and odor threshold scores lower than 3 out of a maximum of 9) were excluded from the study. Table 1 displays the results of psychophysical and cognitive testing. ApoE ϵ 4 status was determined by obtaining buccal epithelial cells that were genotyped through the UCSD Alzheimer's Disease Research Center.

Event Related Potential Stimulus Presentation

The study design was composed of 3 components: the first and second were olfactory (encoding, retrieval using odors as cues), and the third, visual (retrieval using odor names as cues). The sequence of odor and visual retrieval conditions was randomized so that half of the participants received the visual retrieval condition first and half received the olfactory retrieval condition first. The olfactory stimuli were presented using a computer-controlled olfactometer that incorporated a number of features from several previously designed olfactometers (Lorig et al., 1999; Lorig, 2000; Morgan et al., 1999; Murphy et al., 1994). Odors were selected on the basis of identifiability from a prior sample of 40 young, middle-aged, and older adults (Kowalewski & Murphy, 2012) after initial selection based on identifiability by older and younger adults from prior studies that included a sample battery of 80 odors. Participants were asked to identify a battery of odors using written multiple-choice options. A subset of the participants reported whether each odor was supra-threshold and iso-intensive when delivered through the olfactometer. The olfactory stimuli included 20 common oil-based odors, consisting of 14 targets (odors presented in Session 1) and six foils (odors not presented in Session 1). Velopharyngeal closure was employed to restrict breathing to the mouth in order to maintain a constant odorant flow rate (Kobal, 1981; Lorig et al., 1999; Thesen & Murphy, 2001). Visual stimuli consisted of odor names presented in size 32 white-colored font on black background on a 15-inch monitor (12.8 inches in width) placed 36 inches in front of the participant at a viewing angle of 20.5 degrees. In all sessions, the stimuli were presented for 200 msec with an interstimulus interval (ISI) of 30 sec.

Participants were notified that this was a task of odor memory and were asked to remember the odors from Session 1 for the subsequent retrieval sessions. In Session 1, 14 different odors were presented to the participant for 200 msec. Each of the stimuli was presented twice for a total of 28 trials. After each presentation, the participant was presented with a pleasantness scale on the monitor and asked to verbally communicate a pleasantness rating of the stimulus on a scale of 0 (least pleasant) to 100 (most pleasant). During the 30-second ISI, the time elapsed between stimuli, a red crosshair on a black screen appeared on the monitor. In Session 2, eight target stimuli (presented in Session 1) and six foil stimuli (not presented in Session 1) were presented three times each in random order for a total of 42 trials with a 30 sec ISI. Participants were given a controller box with a "Yes" and a "No" button and were asked to press the appropriate button corresponding to whether or not they had received the same stimulus in Session 1 immediately after detecting the stimulus. In Session 3, the names of the odors representing the eight targets and six foils from Session 2 were presented visually on the monitor for 200 msec three times each in random order for a total of 42 trials. Participants were again asked to respond using the controller box as to

whether they had been presented with the named stimuli in Session 1. For both Sessions 2 and 3, only responses within five seconds of the stimulus presentations were included for analysis. Stimuli were taken from the same set of stimuli used in Session 1. STIM² (Compumedics, Charlotte, NC) software was used to present and trigger all stimuli and to record participant responses in all sessions.

Electrophysiological Recording

Olfactory and visual ERPs were obtained using Compumedics 64-electrode Ag/AgCl sintered Quik-Cap and QuikCell system amplified using Synamps2 amplifiers and recorded on computer hard disk with the Compumedics Neuroscan software package. Electrode impedances were kept below 10 k Ω . Continuous EEG activity was recorded throughout each session. Subsequently, trials were epoched offline to 500 msec pre-stimulus and 1500 msec post-stimulus. Eye blink activity was recorded and corrected offline with the Neuroscan software using the Ocular Artifact Reduction (OAR) method within the software. Neuroscan's OAR method includes multiple steps. First a scan is made of the continuous pre-epoched EEG for maximum eye movement potentials. Next an average electrooculogram (EOG) artifact response is constructed. Using this average, transmission coefficients are computed by estimating the covariance of the averaged potentials of the ocular channel with the EEG channels. The transmission coefficients (b) were computed using the following equation: $b = \text{covariance}(\text{EOG}, \text{EEG}) / \text{var}(\text{EOG})$. The EOG is subtracted from the EEG channel on a sweep-by-sweep, point-by-point basis in the following manner: $\text{corrected EEG} = \text{original EEG} - b * \text{EOG}$. Trials were then epoched from the continuous EEG data. Individual trials were analyzed for other artifacts with rejection of trials with voltage exceeding $\pm 75 \mu\text{V}$. Trials with no response or a response occurring 5 or more seconds after the stimulus were excluded for Sessions 2 and 3 (Session 1 has no recorded response component). On average, in each retrieval session, three trials per condition (response type) for each participant were excluded from the averaging procedure and data analysis. Each trial was filtered offline .01 to 6 Hz, baseline corrected and averaged for each participant and each of the four possible conditions (hits, correct rejections, false positives and misses).

OERP Data Analysis

Peak amplitude was calculated as the difference between pre-stimulus baseline (averaged over the 500 msec preceding stimulus presentation) and maximum peak amplitude. Latency was determined using latency windows from previous studies (Morgan et al., 1997, 1999) as guidelines for peak components. OERP latency windows for N1 were from 400 to 600 msec, from 500 to 800 msec for P2, from 600 to 1000 msec for N2 and 700 to 1100 msec for P3. In the few individual trial averages in which P2 was not visible, the midpoint of the slope preceding the P3 peak was selected as an estimation. Amplitudes and latencies for all 64 electrodes were calculated and recorded. Midline electrode sites Fz, Cz, and Pz have commonly been used in data analysis, particularly in the olfactory modality, due to their tendency to produce the largest amplitudes for ERPs (Fabiani, Karis, & Donchin, 1986; Karis, Fabiani, & Donchin, 1984; Morgan & Murphy, 2010; Rushby, Barry, & Johnstone, 2002). In the present study, electrode site recordings were averaged over F1/Fz/F2, C1/Cz/C2, and P1/Pz/P2 in order to reduce dependency on single electrodes but still provide

focused analyses of the ERP data. Data recorded from the C1 electrode site for one older $\epsilon 4$ -negative participant and from the P2 electrode site for one older $\epsilon 4$ -positive participant were excluded from the formation of grand averages and performance of analyses due to the presence of artifact in the recording signal.

Results

Multivariate analyses of variance (MANOVA) on mean age and Dementia Rating Scale (DRS), San Diego Odor Identification Test (SDOIT), and odor threshold scores revealed no significant differences between ApoE $\epsilon 4+$ and $\epsilon 4-$ participants in each age group (Table 1). In addition, there were no statistically significant effects of age or ApoE $\epsilon 4$ status on the proportion of correct responses during retrieval using odors ($M = 0.30$, $SD = 0.05$) and odor labels ($M = 0.47$, $SD = 0.04$) as cues, though the effect of ApoE status approached significance at $p = .11$ for odors and $p = .10$ for odor labels (Table 2). OERP latency and amplitude data were analyzed using ANOVA with separate repeated-measures for the encoding (3 age x 2 ApoE x 3 electrode site) and retrieval sessions (3 age x 2 ApoE x 3 electrode site x 4 response type). The Newman Keuls procedure was utilized to perform necessary post hoc analyses to determine differences among means. Significant results from the ANOVA summary tables for each condition are shown in Tables 3–5.

Encoding of odors

Latency—Table 3 shows significant results of the analyses. Note the significant interaction between age and ApoE $\epsilon 4$ status on N1 latency during encoding of odors [$F(2,54) = 3.75$, $p = .03$, $\eta^2 = .12$] (see Table 3). Post hoc analyses revealed that in the younger and middle-aged groups, N1 latencies were longer in $\epsilon 4-$ than $\epsilon 4+$ individuals, but the reverse was true in the older age group.

Age significantly affected P2, N2, and P3 latencies [$F(2,54) = 3.96$, $p = .03$, $\eta^2 = .13$; $F(2,54) = 22.56$, $p < .001$, $\eta^2 = .46$; $F(2,54) = 25.13$, $p < .001$, $\eta^2 = .48$], respectively. Post hoc analyses revealed that P2 and N2 latencies were longer in older than middle-aged and younger participants. P3 latency was longer in both middle-aged and older than younger participants (Figure 1).

There was also a significant effect of $\epsilon 4$ status on N2 and P3 latencies during encoding of odors, collapsing across age groups [$F(1,54) = 5.72$, $p = .02$, $\eta^2 = .10$; $F(1,54) = 10.27$, $p < .01$, $\eta^2 = .16$], respectively. Post hoc analyses revealed that latencies were longer in $\epsilon 4+$ than $\epsilon 4-$ individuals (P3 latency differences shown in Figure 2).

Amplitude—No statistically significant effects of age, ApoE status, electrode site, or their interactions on OERP amplitude were observed during encoding of odors.

Retrieval using odors as cues

Latency—Table 4 shows significant results of the ANOVA for latency and amplitude of ERPs recorded during retrieval using odors. Note that there was a significant interaction between age, response type, and electrode site on P2 latency [$F(12,48) = 2.63$, $p = .01$, $\eta^2 = .10$]. Post hoc analyses revealed that P2 latency was longest during hits in older participants.

Age significantly delayed N2 and P3 latencies [$F(2,48) = 8.58, p < .01, \eta^2 = .27$; $F(2,48) = 13.64, p < .001, \eta^2 = .37$]. Post hoc analyses revealed that latencies were longer in both middle-aged and older than younger participants.

There was also a significant interaction between ApoE $\epsilon 4$ status, response type, and electrode site on N2 latency [$F(6,48) = 3.05, p = .02, \eta^2 = .06$]. Post hoc analyses revealed that N2 latencies during hits, misses, and false positives were longer in $\epsilon 4+$ than $\epsilon 4-$ individuals.

Amplitude—There was a significant effect of response type on N1 amplitude during retrieval using odors as cues, collapsing across age, $\epsilon 4$ status, and electrode site [$F(3,48) = 2.92, p = .04, \eta^2 = .06$]. Post hoc analyses revealed that N1 amplitudes were larger (more negative) during correct rejections and false positives than during hits and misses. No statistically significant effects of age, ApoE status, electrode site, response type, or their interactions on P2, N2, or P3 amplitude were found during retrieval using odors as cues.

Retrieval using odor labels as cues

Latency—Table 5 shows significant results of the ANOVA for latency and amplitude of ERPs recorded during retrieval using odor labels. There was a 3-way interaction between age, ApoE $\epsilon 4$ status, and electrode site on N1 latency during retrieval using odor labels as cues [$F(4,48) = 3.80, p = .02, \eta^2 = .14$]. Post hoc analyses suggested longer N1 latency in $\epsilon 4-$ younger and older participants, but longer latency for $\epsilon 4+$ carriers than non-carriers in the middle-aged group. There was the expected effect of electrode site on P2 latency [$F(2,48) = 13.40, p < .001, \eta^2 = .22$].

Amplitude—There was a significant interaction between age and electrode site on N1 amplitude during retrieval using odor labels as cues [$F(4,48) = 4.74, p = .01, \eta^2 = .17$]. Post hoc analyses revealed that N1 amplitude was largest (most negative) over frontal sites in younger individuals and largest over central sites in middle-aged and older individuals.

There was also a significant interaction between ApoE $\epsilon 4$ status and electrode site on N1 amplitude [$F(2,48) = 3.91, p = .04, \eta^2 = .08$]. Post hoc analyses revealed that N1 amplitude was larger (more negative) in $\epsilon 4+$ than $\epsilon 4-$ individuals (Figure 3).

There was a main effect of electrode site on P2, N2, and P3 amplitudes [$F(2,48) = 8.14, p < .01, \eta^2 = .15$; $F(2,48) = 9.81, p < .01, \eta^2 = .17$; $F(2,48) = 3.90, p = .03, \eta^2 = .08$]. Post hoc analyses revealed that amplitude decreased in the frontal to parietal direction at P2, but increased in the frontal to parietal direction at N2 and P3.

There was a significant interaction between age, ApoE $\epsilon 4$ status, and electrode site on P2, N2, and P3 amplitudes [$F(4,48) = 7.18, p < .01, \eta^2 = .23$; $F(4,48) = 4.85, p < .01, \eta^2 = .17$; $F(4,48) = 3.96, p = .01, \eta^2 = .14$]. Post hoc analyses revealed that P2 amplitude was larger in middle-aged and younger $\epsilon 4-$ individuals than other groups. N2 amplitude was larger in middle-aged $\epsilon 4-$ individuals than middle-aged $\epsilon 4+$ and younger individuals. At frontal electrode sites, P3 amplitude was larger among $\epsilon 4-$ individuals in the younger and middle-

aged groups, whereas at parietal electrode sites, P3 amplitude was larger among $\epsilon 4-$ individuals in the middle-aged and older groups.

There was also a significant interaction between age, ApoE $\epsilon 4$ status, response type, and electrode site on P2 amplitude [$F(12,48) = 2.25, p = .03, \eta^2 = .09$]. Post hoc analyses revealed that P2 amplitude was generally larger for $\epsilon 4-$ than $\epsilon 4+$ individuals in each age group and during each response type. However, P2 amplitude was larger in $\epsilon 4+$ than $\epsilon 4-$ individuals during misses in older participants.

Discussion

Results indicated differences in olfactory and visual ERP latency and amplitude as a function of age, ApoE $\epsilon 4$ status, response type, and electrode site in the odor recognition memory task. These differences were present in the absence of differences in behavioral performance, which illustrates the sensitivity of ERP recording to olfactory processing. The ERP data reflect cognitive processes associated with the recognition memory task and provide useful information about the effects of the variables of interest on the neural correlates of odor recognition memory.

Encoding of odors

The present study provides novel evidence that age and $\epsilon 4$ status have similar effects on OERP latency during encoding of olfactory information. It is worth noting that the N1 and P2 ERP components reflect exogenous (sensory) processes that rely on stimulus qualities (Kotchoubey, 2005).

Murphy and Morgan (2002) reported that OERP latencies negatively correlate with DRS scores in individuals diagnosed with AD during an odor detection task. In the present study, DRS scores of healthy individuals without dementia did not differ as a function of $\epsilon 4$ status. Nonetheless, N1 latency in older participants varied as a function of $\epsilon 4$ status during encoding of odors. This suggests that N1 latency differences during encoding in an odor recognition memory task may be useful in distinguishing older individuals genetically at risk for AD before cognitive and memory impairment are evident.

The N2 ERP component has been associated with visual attention-focusing processes (Luck & Hillyard, 1994), but its role in olfaction is unclear. In the present study, P2 and N2 latencies were longer in older than middle-aged and younger individuals during encoding of odors. This suggests that increasing age may result in longer, less efficient sensory and attention-focusing processes during encoding of olfactory information, especially in the transition from middle to older age.

P3 latency during encoding of odors was delayed in both middle-aged and older individuals in comparison to younger individuals (Figure 1). The P3 component is commonly thought to reflect cognitive processing and can be elicited by responding actively to a target stimulus (Bennington & Polich, 1999; Morgan & Murphy, 2009). This significant finding suggests that the cognitive processes associated with encoding of olfactory information that are reflected by the P3 component are compromised as early as middle age.

N2 and P3 latencies were longer in $\epsilon 4+$ than $\epsilon 4-$ individuals during encoding of odors (Figure 2). Logistic regression revealed that 95% of individuals genetically at risk for AD can be classified based on $\epsilon 4$ status using P3 latency at frontal electrode sites during encoding. Individuals with AD typically demonstrate specific deficits in encoding new information in addition to retrieving previously encoded information. It is possible that those genetically at risk for AD engage in less efficient cognitive processes reflected by the N2 and P3 components during encoding of olfactory information in comparison to $\epsilon 4$ non-carriers. Thus, examining these latency differences during encoding may be useful for distinguishing those at risk for AD before the onset of cognitive and behavioral symptoms of dementia.

Together, these findings demonstrate that encoding processes in odor recognition memory are compromised with increasing age and the $\epsilon 4$ allele. Past research has focused on retrieval processes. These results add novel information from ERP responses to existing evidence that neuropathology occurs in areas critical to memory and olfactory processing as a result of aging and AD (Braak & Braak, 1997; Ohm & Braak, 1987) and that this decline occurs earlier and more progressively in $\epsilon 4+$ individuals at risk for AD. Knowledge of the effects of age and $\epsilon 4$ status on OERP latency and amplitude during encoding may provide insight into the effects of these variables on the neural correlates of retrieval, assuming these processes within odor recognition memory are interdependent. Importantly, using OERPs to investigate encoding mechanisms in odor recognition memory may be useful for identifying those at risk for AD before the manifestation of dementia-related symptoms.

Retrieval using odors as cues

Past OERP studies have investigated the effects of age and $\epsilon 4$ status on OERP latency and amplitude during retrieval in a cross-modal odor recognition memory task using odor labels as retrieval cues. This study is the first to use odors as retrieval cues and to explore and reveal differences in middle age.

P2 latency was longest during hits in older individuals. This finding expands on previous evidence for longer P2 latency with increasing age, by suggesting it is most delayed in the case of older individuals achieving correct recognition of odors. Royet et al. (2011) reported that significant fMRI activity occurs in the hippocampus and parahippocampal gyrus during hits. Clearly, as these areas become compromised with increasing age, the integrity of associated retrieval mechanisms declines.

N2 and P3 latencies varied as a function of age during retrieval using odors as cues. Past studies have reported longer P3 latencies in older versus younger individuals in an odor detection task (Morgan, Covington, Geisler, Polich, & Murphy, 1997; Murphy et al., 1994, 2000). The present study reveals that P3 latency during retrieval in an odor recognition memory task is also delayed in middle age. These effects further suggest that the tendency for increasing age to result in longer, less efficient cognitive processes during retrieval in odor recognition memory may occur as early as in middle age. Thus, increasing age is associated with longer N2 and, significantly, P3 latency during both encoding and retrieval in odor recognition memory. This further supports existing evidence that areas critical to memory and olfactory processing deteriorate with increasing age and for the hypothesis that

retrieval efficiency relies on the integrity of encoding mechanisms. Particularly, these deficits as measured by OERPs are evident beginning in middle age.

N2 latency for hits, misses, and false positives were longer in $\epsilon 4+$ than $\epsilon 4-$ individuals. A trend toward a similar effect for correct rejections did not reach statistical significance. We speculate that $\epsilon 4$ carriers may engage in less efficient attention-focusing processes reflected by the N2 component during retrieval in an odor recognition memory task in comparison to $\epsilon 4$ non-carriers, and that in addition to P3 latency differences (Morgan & Murphy, 2002), N2 latency differences may be useful for distinguishing those at risk for AD.

P3 amplitude varied as a function of the interaction between age and response type during retrieval using odors as cues. In older individuals, P3 amplitude was larger during misses and correct rejections than false positives, suggesting more neuronal recruitment is associated with correct and incorrect rejection of odors. In younger and middle-aged individuals, P3 amplitude was larger during hits than false positives, suggesting these individuals engage in neuronal recruitment to achieve correct recognition of odors.

The grand averages of four individuals within the older age group exhibited a CNV response during false positives in retrieval using odors as cues. This response might reflect brain activity in anticipation of a target stimulus but in which a foil stimulus is presented and is followed by an incorrect recognition response.

These findings further suggest that retrieval processes associated with odor recognition memory decline with increasing age and the $\epsilon 4$ allele. Importantly, seeing that the effects of age and $\epsilon 4$ status vary across response types allows us to acknowledge the possibility that these variables have different effects on distinct subprocesses of retrieval.

Retrieval using odor labels as cues

N1 amplitude was larger (more negative) for $\epsilon 4+$ than $\epsilon 4-$ individuals on average across electrode sites during retrieval using odor labels as cues. According to Vogel and Luck (2000), the N1 ERP component reflects discrimination efforts during a task of focused attention. The tendency for $\epsilon 4+$ individuals to produce larger N1 amplitudes therefore suggests that $\epsilon 4+$ individuals may engage in compensatory neuronal recruitment to make necessary discrimination efforts when using visual stimuli to retrieve encoded olfactory information.

Previous studies have reported larger P2 amplitudes in younger than older individuals (Covington et al., 1999; Morgan et al., 1997). In the present study, P2 amplitude was larger in middle-aged and younger $\epsilon 4-$ individuals than other groups during retrieval using odor labels as cues. Changes in P2 amplitude have been suggested to reflect differences in recall ability due to variance in encoding processes between different individuals (Dunn, 2000). We might speculate that the present findings suggest that as age increases, the semantic networks involved in using visual stimuli (odor labels) to retrieve encoded olfactory information (odors) are compromised, and this decline is amplified in $\epsilon 4$ carriers.

Summary—The present findings improve our understanding of the effects of AD-related risk factors such as increasing age and the $\epsilon 4$ allele on odor recognition memory. Importantly, this study reports novel outcomes providing support for the view that processes critical to memory and olfactory function deteriorate with increasing age, with particular force in $\epsilon 4$ carriers. The findings support the hypothesis that retrieval efficiency in these populations relies on the integrity of encoding mechanisms. Significantly, these deficits as measured by OERPs are evident beginning in middle age. These findings highlight the potential contribution of OERPs toward achieving an earlier diagnosis of Alzheimer's disease years before cognitive and behavioral symptoms of dementia are evident.

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Figure 1.
P3 latency as a function of age during encoding of odors.

Figure 2.
P3 latency as a function of ApoE ε4 status during encoding of odors.

Figure 3.
N1 amplitude as a function of ApoE ε4 status during retrieval using odor labels as cues.

HITS IN OLDER INDIVIDUALS

Figure 4. Grand average waveforms for hit responses by older individuals at midline electrode sites during retrieval using odors versus odor labels as cues.

MANOVA results for age, Dementia Rating Scale, San Diego Odor Identification Test, and odor threshold scores for ApoE e4+ and e4- participants in each age group.

Table 1

	ApoE e4+		ApoE e4−		F	df	p
	M	SD	M	SD			
Younger							
Age	21.00	0.93	21.70	1.42	1.45	1	0.25
DRS	139.13	5.14	141.60	2.27	1.88	1	0.19
Odor ID	7.00	1.07	7.30	0.68	0.53	1	0.48
Odor Threshold	7.69	0.59	7.20	0.96	1.60	1	0.22
Middle							
Age	51.09	5.75	49.60	3.50	0.50	1	0.49
DRS	140.73	2.20	140.60	2.88	0.01	1	0.91
Odor ID	6.27	1.85	6.60	1.35	0.21	1	0.65
Odor Threshold	6.68	1.74	6.85	1.76	0.05	1	0.83
Older							
Age	69.56	4.22	68.33	2.35	0.58	1	0.46
DRS	138.89	7.34	141.67	1.66	1.23	1	0.28
Odor ID	5.11	1.27	5.78	1.99	0.72	1	0.41
Odor Threshold	4.83	1.35	6.17	1.79	3.20	1	0.09

Note: Participants with DRS scores lower than 124 out of 144 and odor identification scores or odor threshold scores of less than 3 were excluded from the study.

Table 2

ANOVA summary table for proportion of correct responses based on age and ApoE e4 status during retrieval using odors and odor labels as cues.

Effect	Retrieval Cue	F	df	p	η^2
Age	Odors	0.20	2,54	0.82	0.01
	Odor labels	1.02	2,54	0.37	0.04
ApoE	Odors	2.71	1,54	0.11	0.05
	Odor labels	2.83	1,54	0.10	0.05
Age x ApoE	Odors	0.61	2,54	0.55	0.02
	Odor labels	1.96	2,54	0.15	0.07

Note: Effects of age and e4 status were not significant predictors of PC scores.

Table 3

ANOVA summary table for significant main and interactive effects of age group, ApoE ε4 allele status, and electrode site on latency of each OERP component during encoding of odors.

OERP Component	Effect	F	df	p	η^2
N1	Age x ApoE	3.75	2,54	0.03	0.12
	Age	3.96	2,54	0.03	0.13
	Site	3.75	2,54	0.03	0.07
N2	Age	22.56	2,54	<.001	0.46
	ApoE	5.72	1,54	0.02	0.10
P3	Age	25.13	2,54	<.001	0.48
	ApoE	10.27	1,54	<.01	0.16

Note: no significant effects on amplitude were detected.

ANOVA summary table for significant main and interactive effects of age group, ApoE ε4 allele status, response type, and electrode site on latency and amplitude of each OERP component during retrieval using odors.

Table 4

OERP Component	Property	Effect	F	df	p	η^2
N1	Latency	Site	4.83	2,48	0.02	0.10
		Age x ApoE	4.58	2,48	0.02	0.17
	Amplitude	Response	2.92	3,48	0.04	0.06
P2	Latency	Age x ApoE	4.43	2,48	0.02	0.16
		Age x Response x Site	2.63	12,48	0.01	0.10
N2	Latency	Age	8.58	2,48	<.01	0.27
		Response x Site	3.36	6,48	0.01	0.07
		ApoE x Response x Site	3.05	6,48	0.02	0.06
P3	Latency	Age	13.64	2,48	<.001	0.37

ANOVA summary table for significant main and interactive effects of age group, ApoE ε4 allele status, response type, and electrode site on latency and amplitude of each visual ERP component during retrieval using odor labels.

Table 5

ERP Component	Property	Effect	F	df	p	η^2
N1	Latency	ApoE x Site	6.45	2,48	0.01	0.12
		Age x ApoE x Site	3.80	4,48	0.02	0.14
	Amplitude	ApoE	5.60	1,48	0.02	0.11
		ApoE x Site	3.91	2,48	0.04	0.08
		Age x Site	4.74	4,48	0.01	0.17
P2	Latency	Site	13.40	2,48	<.001	0.22
		Site	8.14	2,48	<.01	0.15
	Amplitude	Age x ApoE x Site	7.18	4,48	<.01	0.23
		Age x ApoE x Response x Site	2.25	12,48	0.03	0.09
		Site	9.81	2,48	<.01	0.17
N2	Amplitude	Age x Site	3.42	4,48	0.02	0.13
		Age x ApoE x Site	4.85	4,48	<.01	0.17
		Site	3.90	2,48	0.03	0.08
P3	Amplitude	Age x Site	2.85	4,48	0.04	0.11
		Age x ApoE x Site	3.96	4,48	0.01	0.14