

Functional Connectivity During Recognition Memory in Individuals Genetically at Risk for Alzheimer's Disease

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Abstract: The medial temporal lobes (MTL) and frontal cortex have been shown to subserve memory processes. Neurodegenerative diseases, such as Alzheimer's disease (AD), disrupt the neuronal networks that underlie memory processing. The $\epsilon 4$ allele of the apolipoprotein E gene is a genetic risk factor for AD and is associated with decrements in memory and in olfactory function. The present study utilized EQS, a structural equation modeling software program, to examine differences in the neuronal networks between non-demented $\epsilon 4$ carriers and $\epsilon 4$ noncarriers during a cross-modal olfactory recognition memory paradigm. Prior to fMRI scanning, participants were presented with 16 odors. During two scans, participants discriminated between names of odors presented before scanning (targets) or not presented (foils). The results indicate significant connections between bilateral frontal lobes and MTL for $\epsilon 4$ carriers when they misidentified a foil as a target. When $\epsilon 4$ noncarriers correctly identified a target, there were greater associations between the amygdala, MTL, and right frontal lobe; these associations also modeled the brain's response when $\epsilon 4$ noncarriers misidentified a foil as a target. During memory retrieval, affective cues may facilitate retrieval in $\epsilon 4$ noncarriers relative to $\epsilon 4$ carriers. Last, no model was found that best represented the functional network used by $\epsilon 4$ carriers when they correctly identified a target, which may reflect variability of neuronal recruitment within this population. *Hum Brain Mapp* 34:530–542, 2013. © 2011 Wiley Periodicals, Inc.

Key words: fMRI; olfaction; apolipoprotein E4; aging; neuroimaging; medial temporal lobe

INTRODUCTION

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Memory impairment is one of the most predominant cognitive complaints associated with healthy aging. In particular, deficits in declarative memory have been consistently documented [Allen et al., 2002; Nilsson et al., 1997; Nyberg et al., 1996]. Declarative memory is comprised of episodic memory (memory for facts and events that relies on context) and semantic memory [memory for facts; Mitchell, 1989; Tulving, 1972]. Brain regions within the medial temporal lobe (MTL; e.g., the hippocampal and parahippocampal gyri) and the prefrontal cortex (PFC) are involved in encoding and retrieval of episodic memories [Dolan and Fletcher, 1999; Eichenbaum, et al., 2007;

Lepage et al., 2000; Rugg et al., 2002; Stark and Squire, 2000; Tulving et al., 1994]. Increased activation within the PFC in older adults is associated with a compensatory mechanism, such that, increased memory performance is associated with increased activation in the PFC [Cabeza et al., 2002; Grady et al., 2005].

Healthy aging is also associated with impairment in sensitivity to odors [Murphy, 1983; Nordin et al., 1995], odor identification [Doty et al., 1984; Murphy, 1983, 2002] and olfactory memory, in recall and recognition [Murphy et al., 1998, 1997; Nordin and Murphy, 1998]. Brain regions within the MTL have been shown to be structurally and functionally involved in olfactory processing and olfactory memory performance. More specifically, anatomical studies of rodents and primates [Carmichael et al., 1994; Critchley and Rolls, 1996; Price et al., 1985], patients with mesial temporal lobe excision [Zatorre and Jones-Gotman, 1991], and human neuroimaging experiments [Cerf-Ducastel and Murphy, 2001, 2003, 2006, 2009; Dade et al., 1998; Kettenmann et al., 1997; Li et al., 2010; Royet et al., 1999; Savic et al., 2000; Wang et al., 2005; Zald and Pardo, 2000] have all shown consistent involvement of the entorhinal cortex, piriform cortex, amygdala, hippocampus, and orbitofrontal cortex in olfactory processing.

Neurodegenerative processes, such as Alzheimer's disease (AD), also show similar, but more profound, decrements in memory and olfactory processing. Specifically, previous studies have demonstrated significant reductions in memory [Bondi et al., 2003; Salmon et al., 1989], olfactory identification [Serby, 1986; Wilson et al., 2009], odor sensitivity [Murphy et al., 1990], and olfactory memory [Murphy et al., 2002; Niccoli-Waller et al., 1999; Nordin and Murphy, 1998] in AD relative to healthy aging. In addition, a number of recent studies have documented reduced brain activation in response to olfactory stimuli in AD, within the primary olfactory cortex (piriform cortex) and higher order olfactory/cognitive processing regions (hippocampus, insula), [Li et al., 2010; Wang et al., 2010].

The $\epsilon 4$ allele of the apolipoprotein E (ApoE) gene is a genetic risk factor for the development of AD [Corder et al., 1993; Saunders et al., 1993]. There are three different isoforms of ApoE, the $\epsilon 2$, $\epsilon 3$, and $\epsilon 4$ allele. Behaviorally, healthy older adults with the $\epsilon 4$ allele ($\epsilon 4$ carriers) show greater cognitive decline (i.e., in episodic memory) relative to those without the $\epsilon 4$ allele [$\epsilon 4$ noncarriers; Bartres-Faz et al., 1999; Bondi et al., 1995; Carmelli et al., 2000; Small et al., 2004]. Prior to a general decline in cognitive functioning, $\epsilon 4$ carriers demonstrate declines in odor identification [Calhoun-Haney and Murphy, 2005; Graves, 1999; Murphy et al., 1998; Olofsson et al., 2010] and olfactory memory performance [Gilbert and Murphy, 2004].

The $\epsilon 4$ allele is associated with neuropathological changes in AD [Namba et al., 1991; Poirier et al., 1993]; the MTL is the initial anatomical location of pathological changes. In particular, prior to detectable cognitive changes, brain degeneration occurs within the entorhinal cortex, transentorhinal area, hippocampus, periamygdala,

anterior olfactory nucleus, and olfactory bulbs [Braak and Braak, 1991, 1996; Christen-Zaech et al., 2003; Dickson, 2001; Esiri and Wilcox, 1984; Juottonen et al., 1998; Price et al., 1991; Struble and Clark, 1992]. These anatomical changes within the MTL are important given the projections from the olfactory inputs (i.e., olfactory bulb) to the entorhinal cortex and subsequently to the hippocampus [Insausti et al., 2002] and the functional role of these regions in olfactory processing and memory function [Eichenbaum et al., 2007; Rugg et al., 2002; Squire et al., 2004].

Age-related differences in brain activation have been reported during encoding and retrieval of episodic memory. Relative to young adults, older adults have shown reduced activation in the left prefrontal cortex and MTL during encoding [Grady et al., 1999]. During retrieval, older adults show bilateral activation in the prefrontal cortex relative to young adults who show lateralized right prefrontal activation [Cabeza et al., 2002; Rugg et al., 1996]. Neuroimaging research examining episodic memory performance between $\epsilon 4$ carriers and noncarriers has produced mixed results. Previous studies have reported increased activation in $\epsilon 4$ carriers within memory processing regions, relative to $\epsilon 4$ noncarriers [Bookheimer et al., 2000; Han et al., 2007]; whereas, others have reported reduced activation [Lind et al., 2006]. These variable findings may be a function of disease progression and task related demands.

Working memory is the ability to store and manipulate information while performing cognitive tasks. Similar to working memory paradigms in other sensory modalities [Owen, 1997], Dade et al. reported involvement of the bilateral orbitofrontal cortices during an olfactory working memory task [2001]. Activation within this region has been shown to decrease with age during a task of working memory [Mitchell et al., 2006]. We have documented similar deactivation in working memory regions in healthy older adults during olfactory recognition memory [Cerf-Ducastel and Murphy, 2009]. Conversely, brain activation during auditory verbal working memory in $\epsilon 4$ carriers was increased relative to $\epsilon 4$ noncarriers [Wishart et al., 2006].

With regard to semantic processes, it has been consistently documented that the left lateral prefrontal cortex (BA 47 and BA 45) is involved in semantic memory [for review see Martin and Chao, 2001]. Furthermore, it has been suggested these regions facilitate the maintenance and retrieval of semantic information [Nyberg, 2002]. Interestingly, in healthy young adults, reading words with strong olfactory associations is associated with brain activation in the piriform cortex and amygdala [Gonzales et al., 2006]. Results within our laboratory have shown age-related effects within olfactory brain regions during an olfactory recognition memory paradigm that are more robust than age effects in brain regions involved in memory processes, suggesting age effects are more pronounced in olfactory regions [Cerf-Ducastel and Murphy, 2009].

The aforementioned studies have provided invaluable information regarding neural substrates of olfactory and memory processing. For many of these studies, the examination of spatial and temporal characteristics of the BOLD (blood oxygenated level dependent) response in neuronal populations was analyzed using univariate statistics [Baldettini et al., 1993; Friston et al., 1995]. This type of data analytic approach (subtraction paradigm) assumes that different and separate brain regions are engaged during different cognitive processes, that is, the brain regions are statistically considered functionally independent [Horwitz, 1995]. However, anatomical interconnections underlie brain function and therefore, disconnections between associated regions result in functional deficits [Levy et al., 2004; for a review see Buckley, 2005]. For example, the production of specific functions (i.e., recognition memory) is a result of the involvement of several cortical areas (i.e., hippocampus, frontal cortex, and parahippocampus) and a disruption between their anatomical connections results in impairment [amnesia; for a review see Eichenbaum et al., 2007; Yonelinas et al., 2005]. Functional connectivity is a multivariate data analytic technique that assumes functional networks underlie specific cognitive processes [covariance paradigm; Horwitz, 1995] and provides increased sensitivity by examining the interregional relationships within the brain [Friston et al., 1994; Horwitz et al., 1998; McIntosh and Gonzalez-Lima, 1994]. Anatomical interconnections underlie brain function and therefore, disconnections between anatomically associated regions result in functional deficits [Levy et al., 2004; for a review see Buckley, 2005].

In normal aging, brain activation in anterior hippocampus during episodic memory was associated with activation in the dorsolateral prefrontal cortex, which is in contrast to young adults who demonstrated significant associations between the anterior hippocampus and ventral prefrontal regions [Grady et al., 2003]. These findings suggest that healthy older adults recruit different neural networks during memory processing. In $\epsilon 4$ carriers with mild memory impairment, Bartrés-Faz et al. [2008] found significant associations between the hippocampus and other cortical (anterior cingulate) and subcortical (caudate) regions. Interestingly, differences in functional connectivity are observed in young adult $\epsilon 4$ allele carriers, suggesting changes in neural networks engaged in memory processing are present early in the lifespan of individuals genetically at risk for AD [Dennis et al., 2010].

The aim of the present experiment was to utilize multivariate analysis to generate and test a model of functional connectivity to elucidate differences in the cortical substrates of olfactory recognition memory processing between nondemented $\epsilon 4$ carriers and $\epsilon 4$ noncarriers. Based on aforementioned experiments, the following regions were included in the functional models of olfactory recognition memory: anterior hippocampus, parahippocampus, amygdala, piriform cortex, and orbitofrontal cortex. It is hypothesized that the best fitting models of functional connectivity subserving olfactory recognition

memory will differ for $\epsilon 4$ carriers and $\epsilon 4$ noncarriers. Specifically, individuals who are $\epsilon 4$ carriers will demonstrate greater recruitment of the frontal cortex and the relationships within MTL structures will be less robust relative to $\epsilon 4$ noncarriers, despite equivalent task performance.

METHODS

Thirty-nine nondemented healthy older adults, ranging in age from 64 to 88 years ($M = 72.56$, $SD = 7.07$), participated in the study after giving informed consent. Subjects received monetary compensation. The Institutional Review Boards both at San Diego State University and the University of California, San Diego approved the research. Each participant was genotyped for the ApoE $\epsilon 4$ allele. Individuals with at least one $\epsilon 4$ allele were classified as $\epsilon 4$ carriers and individuals without the $\epsilon 4$ allele were classified as $\epsilon 4$ noncarriers. In the $\epsilon 4$ noncarrier group there were 2 individuals with $\epsilon 2/\epsilon 3$ and 19 individuals with $\epsilon 3/\epsilon 3$. In the $\epsilon 4$ carrier group there were 2 individuals with $\epsilon 2/\epsilon 4$, 12 individuals with $\epsilon 3/\epsilon 4$, and 4 individuals with $\epsilon 4/\epsilon 4$. Each subject completed an fMRI scan conducted on a 3T GE whole body scanner and three psychophysical/neuropsychological sessions.

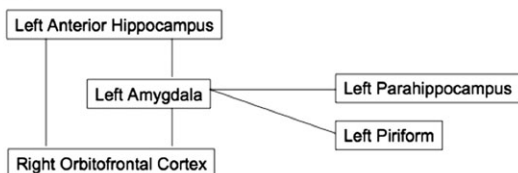
Psychophysical and Neurocognitive Assessment

The first session consisted of chemosensory assessment for ageusia and anosmia with taste threshold and odor threshold tests [Cain et al., 1983; as modified in Murphy et al., 1990] and odor identification [Murphy et al., 2002]. Potential participants with odor thresholds below 3 or odor identification below 3 were excluded to ensure adequate olfactory function. Exclusionary criteria also consisted of a history of head trauma, upper respiratory infection or allergies within the prior 2 weeks [Harris et al., 2006]. Last, the dementia rating scale [Mattis, 1988] was administered to ensure that groups were matched on neurocognitive functioning and to exclude those whose scores entered the clinically impaired range.

Scanning Procedure and Parameters

Prior to scanning, participants were presented with 16 familiar odors corresponding to List A of the California odor learning test [COLT; Murphy et al., 1997]. The odors have been previously shown to be familiar, easily identifiable, and iso-intense [Murphy et al., 1997]. The presentation of odors was randomized and the odors were presented sequentially; participants were asked to close their eyes and concentrate on the odor. During the scan, participants were presented with labels of odors and their task was to decide if the label was an odor that was presented to them prior to the scan (target) or if it was not presented [foil; Cerf-Ducastel and Murphy, 2006, 2009]. Approximately 10 min elapsed between the presentation of the olfactory stimuli and the recognition memory task performed in the scanner.

Model A



Model B

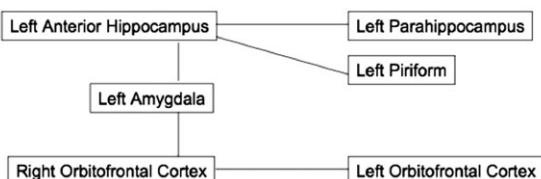


Figure 1.

Schematic figure depicting two a priori hypothesized models of functional connectivity during an olfactory recognition memory task. For Figures 1 and 2: Connections represent associations among brain regions and do not specify causal relationships.

Each participant completed two functional runs (6 min each) and a structural run. The functional runs began and ended with a 36-s baseline period that consisted of a fixation cross in the center of the screen. Following the initial baseline, were eight 36-s periods where the names of odors presented before scanning (targets) or not presented (foils) were displayed. Target periods included the presentation of seven targets and two foils; Foil periods consisted of seven foils and two targets. Participants discriminated between targets and foils using a button box; pressing 1 if they recognized the odor as having been presented before the scan and 2 if not. This paradigm was derived from Stark and Squire [2000a,b]. A program written in Matlab was used to present, collect and calculate performance based on the response of the participant. In the present experiments, responses were classified as the following: hits [H, participant correctly identified a target as being previously presented (old)] and false positives (FP, participant incorrectly identified a foil as being old).

Imaging was conducted on a 3T general electric (GE) excite “shortbore” scanner. Functional images were collected first using a standard gradient echo EPI pulse sequence to acquire T2*-weighted functional images [30 axial slices, Field of view (FOV) = 25 cm, resolution $4 \times 4 \times 4 \text{ mm}^3$, repetition time (TR) = 4 s echo time (TE) = 30 ms, flip angle = 90°], followed by a structural image, acquired using a high-resolution T1-weighted whole-brain FSPGR sequence (FOV = 25 cm, resolution $1 \times 1 \times 1.3 \text{ mm}^3$, TR = 16 s, TE = 4.4 ms, flip angle = 18°). See Cerf-Ducastel and Murphy [2009] for further detail regarding the methods employed.

fMRI Data Processing

Functional data were processed and analyzed using AFNI (analysis of functional neuroimage) software [Cox, 1996]. Preprocessing consisted of: motion correction, temporal and spatial smoothing, automasking, and data normalization. Individual data were normalized by transforming the imaging data to standardized coordinates to fit the Talairach coordinate system [Talairach and Tournoux, 1993].

While the data were collected as a block design, they were analyzed in an event-related fashion. This allowed us to model brain activation that corresponded to individual performances (rather than assuming the targets and foils were correctly identified during their presentation). At the individual level, deconvolution was applied to the first and second runs, separately, which estimated the impulse response function (IRF) based on the participants individualized performance. More specifically, two 1D files were created for each participant that corresponded to performance on the task (i.e., hits and false positives), this file was then convolved with the data to identify areas involved during memory processing.

The average fit coefficients, an index that represents how well the paradigm covaries with the brain activation, corresponding to the regions included in the connectivity model were extracted from the Talairach and Tournoux database implemented in AFNI [Cox, 1996] and inputted into EQS [Bentler and Wu, 1995], a structural equation modeling program. This method has been previously employed to examine functional connectivity networks [Stricker et al., 2006].

Model Specification

Two empirically based target models of functional connectivity were identified, a priori, based on the literature and on previous examination of group data using one-sample t-tests (Fig. 1; Model A and Model B). Given that the current task requires semantic processing, it was hypothesized that neuronal networks would be recruited within the left hemisphere. Previous findings suggest the right prefrontal cortex is engaged during memory retrieval [Tulving et al., 1994]. However, research also suggests that activation in the bilateral frontal cortices during memory retrieval may facilitate task performance in older adults [Rugg et al., 1996]. Given that the present task demands require working memory, it was hypothesized that the frontal cortex would be engaged during the present task [Dade et al., 2001]. As such, activation was also modeled in the right frontal cortex in Model A, and in the right and left frontal cortices in Model B.

Research has shown that emotional aspects of stimuli may aid in memory processes. Recent research examining the connections among emotional processing regions in primates has yielded a more comprehensive understanding of how emotionally laden information is processed

within the brain [Ghashghaei et al., 2007; Höistad and Barbas, 2008]. Specifically, direct connections between the OFC and hippocampus and indirect connections of these regions via the amygdala have been documented. Human neuroimaging experiments examining the brain areas activated during recognition memory have reported consistent activation within regions similar to those found in the rodent and nonhuman primate literature, namely the prefrontal cortex and MTL [Eichenbaum et al., 2007; Lepage et al., 2000; Ranganath et al., 2004; Stark and Squire, 2000; Wais et al., 2006]. In Model A, a direct path from the hippocampus to the frontal cortex was specified. In both models, an indirect relationship from the left anterior hippocampus to the right orbitofrontal cortex via the left amygdala was specified.

In response to olfactory processing, anatomical experiments in rodents and primates have demonstrated direct connections from the olfactory inputs (i.e., olfactory bulb) to the entorhinal cortex and subsequently to the hippocampus [Insausti et al., 2002]. Furthermore, anatomical and functional connections have been identified among the entorhinal, piriform, amygdala, hippocampus, lateral, and ventrolateral orbitalfrontal cortex [Carmichael et al., 1994; Critchley and Rolls, 1996; Price et al., 1985]. Additionally, there are anatomical projections between regions involved in processing olfactory information and odor recognition memory [Carmichael et al., 1994; de la Rosa-Prieto et al., 2008; Insausti et al., 2002; Price et al., 1985]. As such, direct paths from the left anterior hippocampus to the left parahippocampus and left piriform cortex were specified. Additionally, direct paths were specified from the left amygdala to the left parahippocampus and the left piriform cortex.

While there are multiple statistical methods available for examining functional connectivity, the present study employed maximum likelihood (ML) estimation to estimate the unknown parameters, which allows for an empirical analysis of the degree of fit between the hypothesized model and observed data. In particular, the Satorra-Bentler scaled test statistic was used because of its previously demonstrated stable evaluation of small sample sizes with both normal and nonnormal data [Bentler and Yuan, 1999; Curran et al., 1996; Hu et al., 1992]. After applying the model to the data, the Lagrange multiplier test was examined, which determines the magnitude of model fit improvement, if the paths were freely estimated. In other words, the Lagrange multiplier test was used to determine whether adding or removing paths would result in an increase of model fit. If a path was added or removed the model was reestimated.

Group Analysis

A path analysis was conducted using EQS which examined the associations among brain regions in response to performance on the crossmodal recognition memory para-

digm for $\epsilon 4$ carriers and $\epsilon 4$ noncarriers. Model fit was evaluated statistically using the Satorra-Bentler scaled chi-square index, which assesses the discrepancy between observed and hypothesized variance/covariance matrices, in other words, how well the hypothesized model fits the data. Nonsignificant chi-square values indicate that the observed data fits the hypothesized model. Additionally, the comparative fit index [CFI; Bentler, 1990] and the root mean square error of approximation [RMSEA; Steiger, 1990] are reported. The CFI compares the hypothesized model to a null model that specifies no factors. CFI values range from 0 to 1, values greater than 0.90 indicate an adequate model fit. The RMSEA is a parsimony adjusted fit index that adjusts the model fit by weighting indices of fit by the number of parameters estimated, thereby rewarding models that are more parsimonious. RMSEA values less than 0.08 indicate an acceptable model. However, research has shown that when the sample size is smaller than 250, RMSEA is more likely to reject a true model [Hu and Bentler, 1999]. Given the small sample size in the current study, the presence of non-significant chi-square values and CFI values greater than 0.90, were considered to indicate an adequate model.

RESULTS

Demographics

Two-way factorial analysis of variance (ANOVA) tests were performed to examine potential differences in demographic characteristics [dependent variables: age, education, dementia rating scale, odor identification, odor and taste threshold] of male and female, $\epsilon 4$ noncarriers and $\epsilon 4$ carriers. Using an alpha level of 0.001 to evaluate homogeneity assumptions, Levene's homogeneity of variance test was not statistically significant. There were no significant differences in demographic variables between groups nor were there any significant interactions (Table I).

Olfactory Recognition Memory Performance

Four between subjects one-way analysis of variance (ANOVA) tests were conducted to examine differences in olfactory recognition memory performance (hits and false positives) between $\epsilon 4$ carriers and $\epsilon 4$ noncarriers (Table I). There were no significant differences between groups for FP; however, there were significantly more hits for $\epsilon 4$ carriers relative to $\epsilon 4$ noncarriers.

Path Analysis

Marida's coefficient suggests that the data sets for $\epsilon 4$ carriers and $\epsilon 4$ non-carriers are normal (normalized estimate: 1.63 and 1.29, respectively). In addition, data for $\epsilon 4$ carriers and $\epsilon 4$ non-carriers were within normal limits

TABLE I. Demographics and olfactory recognition performance in E4 carriers and E4 noncarriers

	Mean (SD)				F		Significance <i>P</i> > 0.05
	E4 carriers		E4 noncarriers		Gender	ε4 status	
	♂ (<i>n</i> = 9)	♀ (<i>n</i> = 9)	♂ (<i>n</i> =10)	♀ (<i>n</i> =11)			
Demographics							
Age (yrs)	73 (7.7)	72.4 (8.9)	69.6 (3.7)	75 (7.1)	1.14	0.035	<i>P</i> > 0.05
Education (yrs)	15.5 (3.5)	15.2 (3.5)	15.4 (2.6)	15 (3.5)	0.000	0.046	<i>P</i> > 0.05
Olfactory Threshold	4.3 (1.7)	5.8 (1.6)	5.5 (1.8)	5 (1.4)	0.854	0.045	<i>P</i> > 0.05
OID	5 (1.5)	5 (1.8)	4.7 (1.2)	5.8 (1.4)	1.36	0.293	<i>P</i> > 0.05
DRS	139.4 (3.5)	138.7 (5)	140.6 (2)	138 (4.1)	0.191	0.024	<i>P</i> > 0.05
Olfactory recognition							
RUN 1							
Hits	22.7 (5.3)		18.52 (5.3)		6.1		<i>P</i> = 0.018
False positives	12 (4.1)		11.38 (4.9)		0.18		<i>P</i> > 0.05
RUN 2							
Hits	21.81 (4.9)		18.29 (6)		3.7		<i>P</i> > 0.05
False positives	12.13 (3.9)		10.85 (5)		0.7		<i>P</i> > 0.05

♂ = males, ♀ = females, SD = standard deviation, yrs = years, OID = odor identification test, DRS = dementia rating scale.

with respect to kurtosis and skewness, further suggesting that the data are normally distributed. The current experiment employed a crossmodal paradigm, where olfactory stimuli were presented prior to the scan and verbal labels corresponding to olfactory stimuli were presented in the scanner. It is possible that connectivity could vary from the first run and the second run based on the fact that in the first run, the foils were novel and on the second run the foils were no longer novel. Therefore, data were analyzed separately for Run 1 and Run 2.

Model A

During the first run, when ε4 noncarriers correctly identified a target odor (hits), Model A fit well statistically, $\chi^2 = 5.85$, *P* = 0.3209 and descriptively (CFI = 0.979, RMSEA = 0.09, Fig. 2). In terms of the relations specified within the model, the direct effect from the left anterior hippocampus to the right orbitofrontal cortex was not statistically significant ($\beta = -0.296$, *P* > 0.05). However, all other standardized path coefficients were large and statistically significant (values ranged from 0.83 to 0.89). During the second run, when ε4 non-carriers had a hit, Model A fit well statistically, $\chi^2 = 8.67$, *P* = 0.1236, but not descriptively (CFI = 0.804, RMSEA = 0.191). This finding may be due in part to the nonsignificant relationships between the right frontal lobe (ROFC) the left MTL structures (amygdala and anterior hippocampus). During the first and second runs, when ε4 carriers made a hit response, Model A did not fit well statistically ($\chi^2 = 14.54$, *P* < 0.05, $\chi^2 = 3.41$, *P* < 0.05, respectively) or descriptively (CFI = 1.00, RMSEA = 0.000, CFI = 0.22, RMSEA = 0.335, respectively). Interestingly, when examining the Lagrange multiplier test, no model was identified for the hits condition in ε4 carriers during either run.

During the first and second runs, when ε4 noncarriers incorrectly identified a novel odor as being old (false positives), Model A fit well statistically ($\chi^2 = 7.159$, *P* = 0.21, $\chi^2 = 8.61$, *P* = 0.13, respectively) and descriptively (CFI = 0.936, RMSEA = 0.147, CFI = 0.855, RMSEA = 0.19, respectively). Similar to the hits condition for ε4 noncarriers, during both runs, the direct relationship between the left anterior hippocampus and the right orbitofrontal cortex was not significant. All other standardized path coefficients were moderate to large and statistically significant (values ranged from 0.68 to 0.84). When ε4 carriers had false positive response during the first and second runs, Model A did not fit well statistically ($\chi^2 = 20.05$, *P* < 0.001; $\chi^2 = 14.18$, *P* < 0.01, respectively) or descriptively (CFI = 0.592, RMSEA = 0.421; CFI = 0.811, RMSEA = 0.339, respectively).

Model B

When ε4 noncarriers made a hit response during the first and second runs, Model B did not fit well statistically ($\chi^2 = 38.44$, *P* < 0.01; $\chi^2 = 33.86$, *P* < 0.01, respectively) or descriptively (CFI = 0.476, RMSEA = 0.377; CFI = 0.319, RMSEA = 0.345, respectively). Furthermore, during a hit response for first and second runs of ε4 carriers, Model B did not fit well statistically ($\chi^2 = 26.77$, *P* < 0.01; $\chi^2 = 19.66$, *P* < 0.05, respectively) or descriptively (CFI = 0.198, RMSEA = 0.314; CFI = 0.588, RMSEA = 0.238, respectively).

When ε4 noncarriers made a false positive response during the first and second runs, Model B did not fit well statistically ($\chi^2 = 17.74$, *P* < 0.05, $\chi^2 = 36.42$, *P* < 0.05, respectively) or descriptively (CFI = 0.829, RMSEA = 0.197, CFI = 0.033, RMSEA = 0.363, respectively). When ε4 carriers made a false positive response for the first run, Model B fit well statistically ($\chi^2 = 10.5593$, *P* = 0.39) and

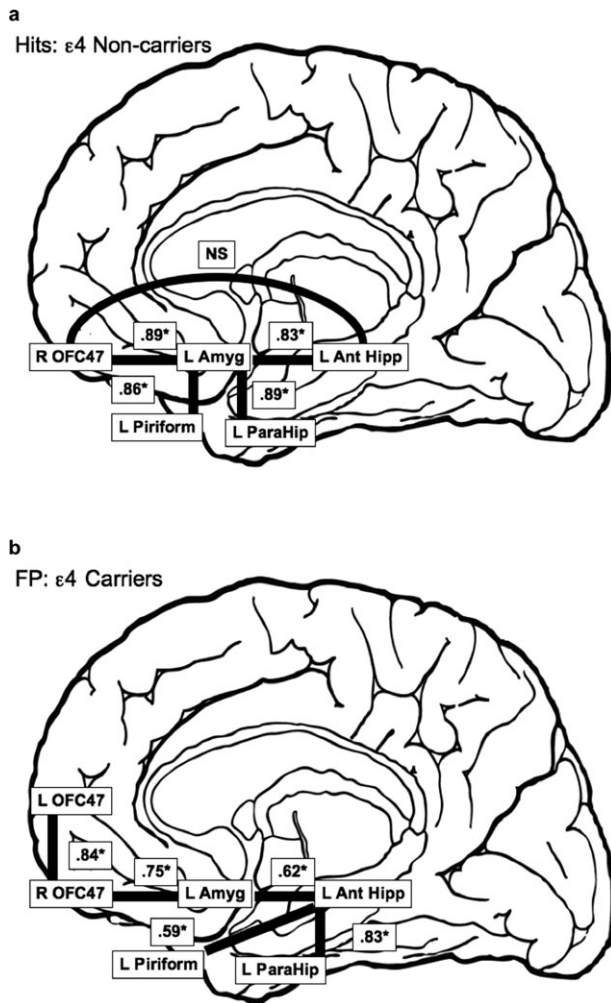


Figure 2.

Schematic illustration of the best fitting models, and their associated standardized path coefficients, for (a) $\epsilon 4$ non-carriers during hits and (b) for $\epsilon 4$ carriers during false positives (FP). Note: NS = non-significant, * = significant standardized path coefficient, R = right, L = left, OFC47 = orbitofrontal cortex brodmann area 47, Amyg = amygdala, Ant Hipp = anterior hippocampus, ParaHip = parahippocampus.

descriptively (CFI = 0.986, RMSEA = 0.057; Fig. 2). All standardized path coefficients were moderate to large and statistically significant (values ranged from 0.59 to 0.84). However, during the second run, when $\epsilon 4$ carriers made a false positive response, Model B did not fit well statistically ($\chi^2 = 24.75, P < 0.05$) or descriptively (CFI = 0.824, RMSEA = 0.304).

DISCUSSION

The present study utilized EQS, a structural equation modeling software program, to elucidate differences in the

neuronal networks between nondemented $\epsilon 4$ carriers and $\epsilon 4$ noncarriers during a cross-modal olfactory recognition memory paradigm. While there are many different data analytic approaches available for the examination of functional connectivity models, the present study employed the Sattora–Bentler scaled test statistic, which was used in the present analysis because of its stable evaluation of small sample sizes with both normal and nonnormal data [Bentler and Yuan, 1999; Curran et al., 1992; Hu et al., 1992]. Model A and Model B indicated significant connectivity between frontal cortex and MTL structures during a cross modal olfactory recognition memory task in $\epsilon 4$ carriers and $\epsilon 4$ noncarriers (Fig. 2a,b). These findings are in accordance with a number of previously published experiments documenting the involvement of the frontal cortex [Nyberg et al., 2000; Rugg et al., 1996; Tulving et al., 1994] and MTL [Cerf-Ducastel and Murphy, 2006, 2009; Eichenbaum, et al., 2007; Stark and Squire, 2000] during memory retrieval.

Model A fit well statistically and descriptively for $\epsilon 4$ noncarriers during the hit condition (Fig. 2a). However, Model B did not fit well for $\epsilon 4$ noncarriers during the false positive condition. Given the good model fit for hits in $\epsilon 4$ noncarriers, we decided to apply the Model A to the false positive condition. Interestingly, this model fit well statistically and fit fairly well descriptively. This suggests that $\epsilon 4$ noncarriers engage the same functional network for both hits and false positives. Contrary to $\epsilon 4$ noncarriers, the Model A did not fit well for $\epsilon 4$ carriers during the hits condition. In fact, utilizing the Lagrange multiplier test did not yield a single adequately fitting model, of those investigated, for hits in the $\epsilon 4$ carriers. The failure to find an adequately fitting model for hits in $\epsilon 4$ carriers could have resulted from a number of different factors such as the type of statistical approach employed, sample size, and greater variability in the functional networks recruited by $\epsilon 4$ carriers during correct identification of previously presented stimuli. In addition, although speculative, the failure to find a cohesive functional connectivity model, may be a function of the prodromal neuropathological processes that are associated with the presence of the $\epsilon 4$ allele, which first disrupt connections between structures that subserve memory functioning [e.g., entorhinal cortex and hippocampus; Braak and Braak, 1997; Corder et al., 1993; Price et al., 1991; Saunders, et al., 1993]. The present cohort of $\epsilon 4$ carriers may compensate for prodromal neuropathological changes by recruiting additional neuronal networks to perform at a level that is equivalent to that of $\epsilon 4$ noncarriers and those $\epsilon 4$ carriers who have not undergone the neuropathological processes associated with the $\epsilon 4$ allele. In fact, $\epsilon 4$ carriers with mild memory dysfunction [Bartres-Faz et al., 2008] and without memory dysfunction [Bondi et al., 2005] and individuals diagnosed with probable Alzheimer’s disease [Becker et al., 1996; Stern et al., 2000] have been shown to compensate for neuropathological changes by engaging different neuronal networks during memory performance. On the other hand, one could also

hypothesize that $\epsilon 4$ carriers may be implementing different cognitive processes to perform the same task (e.g., responses based on familiarity rather than recognition), which may be related to deficits in encoding, resulting in the engagement of different neuronal networks [Grady et al., 1995]. In addition to $\epsilon 4$ allele status, other factors have been shown to moderate fMRI brain activation, such as family history of AD [Seidenberg et al., 2009] and physical exercise [Smith et al., 2011]. In the present experiment, it is possible that these factors could be contributing to the variability in the hit model for $\epsilon 4$ carriers.

In the present study, the rate of false positive responses did not significantly differ between $\epsilon 4$ carriers and $\epsilon 4$ noncarriers. However, when $\epsilon 4$ carriers misidentify an odor as being previously presented, MTL structures as well as bilateral frontal lobes are positively associated (Fig. 2b); this model does not fit $\epsilon 4$ noncarriers. As stated above, the false positive performance in $\epsilon 4$ non-carriers is associated with significant connectivity among right frontal lobe and MTL structures. Interestingly, there are a number of associations that differ between the false positive model for $\epsilon 4$ carrier and noncarriers. For example, the $\epsilon 4$ carrier false positive model does not specify connections between right frontal cortex and anterior hippocampus, amygdala and piriform, or amygdala and parahippocampus. As such, this model may reflect disassociations among brain regions associated with prodromal changes in $\epsilon 4$ carriers [Filippini et al., 2009]. The significant associations between bilateral frontal lobes may reflect compensatory recruitment in $\epsilon 4$ carriers. A number of studies have shown a positive association between bilateral PFC activation and memory performance [Bondi et al., 2005; Cabeza, 2002; Cabeza et al., 2002; Grady, 2001; Wisheart et al., 2006], which may be specific to episodic memory encoding and retrieval [Burggren et al., 2002]. Whereas, others have demonstrated an inverse relationship between bilateral PFC activation and memory performance [Duverne et al., 2009; Logan et al., 2002; Morcom et al., 2007], suggesting that greater activation does not necessarily facilitate memory performance.

One could speculate that the differences in the functional connectivity between $\epsilon 4$ carriers and noncarriers in the present study are related to cross modal olfactory recognition memory task on two levels, sensitivity and difficulty. Given that the primary olfactory regions are the initial sites of neuropathological changes associated with AD, a task that engages these regions may be particularly sensitive to prodromal neuronal changes in $\epsilon 4$ carriers. On the other hand, differences in functional connectivity may also be related to the high task demands required during olfactory recognition performance [Frank et al., 2011]. Previous studies have found that high task demands are associated with increased prefrontal activation [Grady et al., 1996]. It is also possible that different combinations of the $\epsilon 4$ allele, $\epsilon 2/\epsilon 4$, $\epsilon 3/\epsilon 4$, $\epsilon 4/\epsilon 4$ would result in differential performance and differential connectivity at various stages of the incipient disease process, a topic for future studies.

Nevertheless, the current results suggest that $\epsilon 4$ carriers engage different neural networks during olfactory recognition memory relative to $\epsilon 4$ noncarriers.

Activation within the amygdala, for $\epsilon 4$ noncarriers (hits and false positives) was positively associated with activation in the hippocampus, frontal lobe, piriform, and parahippocampus. Interestingly, the direct path between the hippocampus and frontal cortex was not significant. At the group level, in $\epsilon 4$ carriers, amygdala activation was associated with activation in the hippocampus and frontal lobe during false positives [Murphy et al., to be submitted]. The amygdala has been shown to be involved in processing the emotional saliency of stimuli [Fitzgerald et al., 2006] and the right prefrontal cortex (PFC) has been implicated in the retrieval of episodic memories [Buckner et al., 1996; Lepage et al., 2000]. A number of recent studies conducted by Barbas et al. have identified robust reciprocal connections between the frontal cortices and the amygdala, as well as connections among the amygdala and other MTL structures (e.g., entorhinal and perirhinal cortices) in rhesus monkeys [Ghashghaei et al., 2007; Höistad and Barbas, 2008]. It has been suggested that these connections may aid in memory formation and retrieval and help to establish reward related contingencies. In fact, previous studies have reported amygdala activation is associated with better memory performance in individuals diagnosed with Alzheimer's disease [Grady et al., 2001]. As such, affective cues and the subsequent recruitment of the amygdala may facilitate olfactory memory retrieval.

Despite good model fit for data collected during the first run, data collected during the second run did not fit well for Model A in $\epsilon 4$ noncarriers during hits and false positives and for Model B in $\epsilon 4$ carriers during false positives. This suggests that different functional networks are recruited for novel olfactory labels relative to previously presented olfactory labels. While the exact mechanism cannot be parsed out in the present experiment, a number of studies have found differential activation in response to novel versus familiar stimuli. The present findings are consistent with the hemispheric encoding/retrieval asymmetry model proposed by Tulving et al. [1994] that posits the left PFC is differentially recruited during the retrieval and encoding of novel information. Logan et al. [2002] have reported similar findings, such that greater association between left PFC and left anterior hippocampus may be related to the encoding of foils during the first trial. The present findings may also be associated with differential involvement of the hippocampus and parahippocampus as a result of stimulus novelty [Johnson et al., 2008]. Taken together, the current results may reflect the use of different retrieval strategies for novel versus familiar labels or it may be the result of the second run requiring greater cognitive demands (e.g., discriminating targets from old foils). In other words, the lack of significant model fit in the second run, may reflect a transition from encoding novel aspects of previously encoded olfactory information to familiarity based memory processes.

The fact that different functional connectivity models fit well for $\epsilon 4$ carriers and noncarriers during olfactory recognition memory task performance may be better understood by conceptualizing the present findings in the context of what is known regarding the default mode network. The default mode network is comprised of an anatomical substrate that is active when individuals are not engaging external stimuli [Raichle et al., 2001; for a review see Buckner et al., 2008]. Research has shown that over the life-span, deactivation within the default mode network was reduced in older adults relative to middle-aged and younger adults, suggesting an age-dependent inability to filter out information that is irrelevant to the task [Grady et al., 2006; Stevens et al., 2008]. Recently, Beason-Held et al. [2009] have shown that the default mode network is relatively stable in normal aging, while studies examining disease processes have found a disruption within the network during task performance [Frings et al., 2009; Persson et al., 2008]. Specifically, nondemented $\epsilon 4$ carriers had significantly reduced deactivation in the default mode network relative to nondemented $\epsilon 4$ noncarriers [Persson et al., 2008]. Other studies have explored differences in default network of disease states by examining resting state BOLD networks. In particular, differences in resting state connectivity between $\epsilon 4$ carriers and noncarriers have been reported within the frontal, temporal, and parietal lobes [Fleisher et al., 2009; Sheline et al., 2010]. In addition, Sheline et al. [2010] also reported differences in resting state connectivity among the MTL (e.g., hippocampus, parahippocampus), anterior cingulate, hypothalamus, and occipital cortex. These findings are congruent with the present study and suggest that during memory processing, $\epsilon 4$ carriers recruit from other neural networks as a means of compensation for less efficient processing.

In conclusion, the present findings have shown that a task that places demands on olfactory, semantic, and episodic networks is capable of revealing differential functional connectivity between individuals genetically at risk for AD relative to those who are not. Furthermore, the findings highlight the potential role of early neurodegenerative changes on cognition in individuals genetically at risk for AD. In the future, differential functional connectivity during memory processing may be useful in contributing to the prediction of incipient dementia. Understanding preclinical markers of AD may help to identify those who would be targets of pharmaceutical interventions designed to delay the progression to dementia and subsequently improve the lives of the afflicted.

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