Semantic memory activation in individuals at risk for developing Alzheimer disease

M. Seidenberg, PhD
L. Guidotti, MS
K.A. Nielson, PhD
J.L. Woodard, PhD
S. Durgerian, BS
P. Antuono, MD
Q. Zhang, BS
S.M. Rao, PhD

Address correspondence and reprint requests to Dr. Stephen M. Rao, Schey Center for Cognitive Neuroimaging, Neurological Institute, Cleveland Clinic, 9500 Euclid Ave./U10, Cleveland, OH 44195
raos2@ccf.org

ABSTRACT

Objective: To determine whether whole-brain, event-related fMRI can distinguish healthy older adults with known Alzheimer disease (AD) risk factors (family history, APOE ε4) from controls using a semantic memory task involving discrimination of famous from unfamiliar names.

Methods: Sixty-nine cognitively asymptomatic adults were divided into 3 groups (n = 23 each) based on AD risk: 1) no family history, no ε4 allele (control [CON]); 2) family history, no ε4 allele (FH); and 3) family history and ε4 allele (FH+ε4). Separate hemodynamic response functions were extracted for famous and unfamiliar names using deconvolution analysis (correct trials only).

Results: Cognitively intact older adults with AD risk factors (FH and FH+ε4) exhibited greater activation in recognizing famous relative to unfamiliar names than a group without risk factors (CON), especially in the bilateral posterior cingulate/precuneus, bilateral temporoparietal junction, and bilateral prefrontal cortex. The increased activation was more apparent in the FH+ε4 than in the FH group. Unlike the 2 at-risk groups, the control group demonstrated greater activation for unfamiliar than familiar names, predominately in the supplementary motor area, bilateral precentral, left inferior frontal, right insula, precuneus, and angular gyrus. These results could not be attributed to differences in demographic variables, cerebral atrophy, episodic memory performance, global cognitive functioning, activities of daily living, or depression.

Conclusions: Results demonstrate that a low-effort, high-accuracy semantic memory activation task is sensitive to Alzheimer disease risk factors in a dose-related manner. This increased activation in at-risk individuals may reflect a compensatory brain response to support task performance in otherwise asymptomatic older adults. ***Neurology***® **2009;73:612–620**

GLOSSARY

AD = Alzheimer disease; **AFNI** = Analysis of Functional NeuroImages; **ANOVA** = analysis of variance; **AUC** = area under the curve; **BA** = Brodmann area; **BOLD** = blood oxygen level–dependent; **CON** = control; **DRS-2** = Dementia Rating Scale 2; ***DSM-IV*** = *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition; **EM** = episodic memory; **FH** = family history; **FOV** = field of view; **fROI** = functional region of interest; **HRF** = hemodynamic response function; **MCI** = mild cognitive impairment; **MOANS** = Mayo Older Americans Normative Studies; **MR** = magnetic resonance; **MTL** = medial temporal lobe; **NS** = not significant; **RAVLT** = Rey Auditory–Verbal Learning Test; **SM** = semantic memory; **SMA** = supplementary motor area; **SPGR** = spoiled gradient-recalled at steady state; **TE** = echo time; **TR** = repetition time; **VBM** = voxel-based morphometry.

Two well-established risk factors for the late-onset, sporadic form of Alzheimer disease (AD) are the presence of one or both copies of the apolipoprotein E (APOE) ε4 allele and a first-degree family history (FH) of AD.[1,2] Task-activated fMRI studies show that cognitively intact older individuals with AD risk factors (FH, APOE ε4, or both) exhibit a pattern of increased neural activity compared with individuals without AD risk factors.[3] Increased fMRI activity is thought to reflect a compensatory brain response that enables older at-risk individuals to perform at levels equivalent to persons without risk factors.[4]

Supplemental data at www.neurology.org

From the Department of Psychology (M.S., L.G.), Rosalind Franklin University of Medicine and Science, Chicago, IL; Department of Psychology and the Integrative Neuroscience Research Center (K.A.N.), Marquette University, Milwaukee, WI; Foley Center for Aging and Development (K.A.N.), Functional Imaging Research Center (K.A.N., S.D., Q.Z., P.A., S.M.R.), and Departments of Psychiatry (K.A.N.) and Neurology (K.A.N., S.D., Q.Z., P.A., S.M.R.), Medical College of Wisconsin, Milwaukee; Department of Psychology (J.L.W.), Wayne State University, Detroit, MI; and Schey Center for Cognitive Neuroimaging (S.M.R.) and the Cleveland Clinic Lou Ruvo Center for Brain Health (S.M.R.), Neurological Institute, Cleveland Clinic, Cleveland, OH.

Supported in part by grants from the NIH (R01-AG022304, M01-RR00058) and Advancing Healthier Wisconsin Foundation.

Disclosure: Author disclosures are provided at the end of the article.

Most fMRI studies conducted in preclinical populations (mild cognitive impairment [MCI]) use episodic memory (EM) tasks and focus on medial temporal lobe (MTL) activity. As clinical symptoms emerge, EM performance declines and MTL atrophy increases.[5] Not surprisingly, task-activated fMRI findings are inconsistent, with both increased and decreased MTL activation observed.[3]

We examined the effect of FH and APOE ε4 on whole-brain fMRI neural activity in cognitively asymptomatic older adults using a semantic memory (SM) task involving the discrimination of famous from unfamiliar names. This task involves minimal conscious effort and is performed at high accuracy levels. Previously, we demonstrated that cognitively intact older individuals produced increased activity in memory circuits (hippocampus, posterior cingulate, and prefrontal regions) relative to young participants[6]; however, participants were not separated on AD risk factors. Here, we sought to determine whether a low-effort, high-accuracy SM task would demonstrate differential patterns of activation in at-risk individual using a whole-brain analysis.

METHODS

Standard protocol approvals, registrations, and patient consents. This study was approved by the Human Subjects Review Committee of the Medical College of Wisconsin, which oversees the ethical standards of human research being conducted. Written informed consent was obtained from all subjects included in this study.

Participants. Healthy adults between ages 65 and 85 years were recruited from newspaper advertisements. A telephone screen, used to determine study eligibility (see below), was administered to 459 individuals. Of the individuals meeting inclusion/exclusion eligibility criteria (see below), 109 agreed to undergo APOE genotype testing from blood samples, neuropsychological evaluation, and an fMRI scanning session. APOE genotype was determined using a PCR method described by Saunders et al.[7,8] DNA was isolated with Gentra Systems Autopure LS for Large Sample Nucleic Acid Purification (Minneapolis, MN).

From this pool, 3 subgroups of equal sample size (n = 23), carefully matched on demographic variables (sex, age, and education), were formed based on the presence/absence of at least 1 APOE ε4 allele and a family history of dementia. Group 1 (FH+ε4) had a family history of dementia and one or both ε4 alleles (1 ε2/ε4; 21 ε3/ε4; 1 ε4/ε4). Group 2 (FH) had a family history of dementia but did not possess an APOE ε4 allele (6 ε2/ε3; 17 ε3/ε3). Group 3 (controls [CON]) consisted of individuals who reported no family history of dementia and did not possess an APOE ε4 allele (1 ε2/ε3; 22 ε3/ε3). Equal sample sizes were required to avoid biases in the image analyses. As expected, no significant group differences were observed on demographic variables of age, sex, or education (table 1).

Family history was defined as a report of a clear clinical diagnosis of AD in first-degree relatives—parents or siblings (probable AD; 63.2%)—or a reported history of gradual decline in memory and other cognitive functions, confusion, or judgment problems without a formal diagnosis of AD before death. One participant reported a diagnosis of AD in a second-degree relative, with some mild cognitive changes noted in a parent before the parent's death.

Participants were excluded if they reported a history of neurologic disease, medical illnesses, major psychiatric disturbance meeting *DSM-IV* Axis I criteria, a Geriatric Depression Scale score greater than 10, substance abuse meeting *DSM-IV* Axis I criteria, or were currently taking psychoactive medications. Participants were allowed to take cardiovascular drugs. No between-group differences were observed in the percent of participants taking blood pressure medications; FH+ε4 participants were more likely to be taking statins to lower cholesterol levels than were the FH and CON participants (59% vs 25%; $\chi^2 = 4.7$, $p < 0.3$). A blood chemistry screen (thyroid-stimulating hormone, homocysteine, vitamin B_{12}, folate, and creatinine) was not found to be clinically significant in any of the participants. Additional exclusion criteria related to fMRI scanning included pregnancy, weight inappropriate for height, ferrous objects within the body, low visual acuity, and a history of claustrophobia. Only right-handed participants were included based on the Edinburgh Handedness Inventory.[9]

Procedures. Neuropsychological testing and the fMRI scanning were conducted on the same day. Participants were asked to refrain from alcohol use for 24 hours and caffeine use for 12 hours before testing. The neuropsychological test battery consisted of the Mini-Mental State Examination,[10] Mattis Dementia Rating Scale 2,[11] Rey Auditory Verbal Learning Test,[12] Geriatric Depression Scale,[13] and Lawton Activities of Daily Living.[14] All participants received financial compensation.

Functional MRI. The task stimuli consisted of 30 names of famous persons and 30 names of unfamiliar individuals selected from an original pool of 784 names because of a high rate of identification (>90% correct).[15] A trial consisted of the visual presentation of a single name for 4 seconds. Participants were instructed to make a right index finger key press if the name was famous and a right middle finger key press if the name was unfamiliar. Both accuracy (percentage correct) and reaction time (in milliseconds) were recorded; signal detection indexes (A′ and B′′) were calculated to examine discriminability and response bias.[16,17] The 60 name trials were randomly interspersed with thirty 4-second trials in which the participant was instructed to fixate on a single centrally placed crosshair. This was done to introduce "jitter" into the fMRI time course. The imaging run began and ended with 12 seconds of fixation. The total time for the single imaging run was 5 minutes 24 seconds.

fMRI acquisition. Whole-brain, event-related fMRI was conducted on a General Electric (Waukesha, WI) Signa Excite 3.0-T short bore scanner equipped with a quad split quadrature transmit/receive head coil. Echoplanar images were collected using an echoplanar pulse sequence (echo time [TE] = 25 msec; flip angle = 77 degrees; field of view [FOV] = 24 mm; matrix size = 64 × 64). Thirty-six contiguous axial 4-mm-thick slices were selected to provide coverage of the entire brain (voxel size = 3.75 × 3.75 × 4 mm). The interscan interval (TR) was 2 seconds. High-resolution, 3-dimensional spoiled gradient-recalled

Table 1 Group demographics, neurobehavioral testing, and fMRI task performance

	CON (n = 23)		FH (n = 23)		FH+ε4 (n = 23)			
Variable	Mean	SD	Mean	SD	Mean	SD	*p* Value	η^2
Demographics								
Age	71.5	4.3	73.4	4.6	71.0	4.0	NS	0.056
Education	14.1	2.5	14.0	2.2	15.7	3.1	NS	0.081
Sex, women/men	17/6		17/6		17/6		NS	—
Global cognition (DRS-2)								
Total	140.5	2.4	140.5	3.4	140.2	3.8	NS	0.002
Attention	36.6	0.7	36.3	1.0	36.3	0.9	NS	0.014
Initiation/perseveration	36.6	0.9	36.7	0.5	36.6	0.8	NS	0.011
Construction	6.0	0.0	6.0	0.2	6.0	0.2	NS	0.030
Conceptualization	37.2	1.7	37.3	2.1	37.3	1.8	NS	0.002
Memory	24.1	1.0	24.1	1.1	24.0	1.4	NS	0.001
Total MOANS (age and education corrected)	12.1	2.4	12.5	2.4	11.6	2.7	NS	0.022
Mini-Mental State Examination	29.4	0.7	29.3	1.1	29.3	0.9	NS	0.005
Verbal learning								
RAVLT Sum of Trials 1–5	47.7	8.4	50.0	9.3	49.3	8.0	NS	0.012
RAVLT Postinterference Recall	9.3	2.4	9.7	2.7	9.1	2.9	NS	0.008
RAVLT Delayed Recall	9.5	2.2	9.7	3.0	9.5	3.0	NS	0.001
RAVLT Long-Term Percent Retention*	84.5	15.6	78.5	16.3	78.6	18.2	NS	0.029
RAVLT Learning over Trials†	16.7	7.2	17.2	6.6	17.3	7.0	NS	0.002
Depression								
Geriatric Depression Scale	2.5	2.4	2.7	2.8	1.4	1.9	NS	0.032
Activities of Daily Living								
Lawton Scale	4.8	0.4	4.9	0.3	4.8	0.4	NS	0.026
fMRI task performance								
Percent correct–famous names	90.1	9.0	94.1	7.1	92.5	8.7	NS	0.038
Percent correct–unfamiliar names	97.7	3.7	95.8	5.3	96.7	7.3	NS	0.019
Discriminability index (logistic d′)	5.7	1.0	5.8	1.1	6.0	1.4	NS	0.014
Bias index (logistic C)	0.7	0.6	0.3	0.6	0.5	0.6	NS	0.070
Reaction time–famous names, msec	1,324	178	1,236	231	1,282	236	NS	0.028
Reaction time–unfamiliar names, msec	1,636	247	1,637	354	1,598	299	NS	0.004

*Long-Term Percent Retention = (words recalled after 30 min/words recalled on trial 5) × 100.
†Learning over Trials = (words recalled trials 1–5) − (5 × words recalled on trial 1).
CON = control; FH = family history; NS = not significant; DRS-2 = Dementia Rating Scale 2; MOANS = Mayo Older Americans Normative Studies; RAVLT = Rey Auditory–Verbal Learning Test.

at steady state (SPGR) anatomic images were acquired (TE = 3.9 msec; repetition time [TR] = 9.5 msec; inversion recovery preparation time = 450 msec; flip angle = 12 degrees; number of excitations = 2; slice thickness = 1.0 mm; FOV = 24 cm; resolution = 256 × 224). Foam padding was used to reduce head movement within the coil.

Image analysis. Functional images were generated with the Analysis of Functional NeuroImages (AFNI) software package.[18] Each image time series was time shifted to the beginning of the TR and then spatially registered to reduce the effects of head motion using a rigid body iterative linear least squares method. A deconvolution analysis was used to extract a hemodynamic response function (HRF) for famous and unfamiliar names from the time series. HRFs were modeled for the 0- to 16-second period poststimulus onset. Motion parameters were incorporated into the model as nuisance regressors. The HRFs were also transposed so that the value of the HRF at trial onset was zero. Despite the high task accuracy rate (see below), estimation of the HRFs for identification of famous names and rejection of unfamiliar names was restricted to correct trials. Area under the curve (AUC) was calculated by summing the hemodynamic responses at time points 4, 6, and 8 seconds after trial onset. Individual anatomic and functional scans were transformed into standard stereotaxic space.[19] To compensate for normal variation in anatomy across subjects, functional images were blurred using a 6-mm gaussian full-width half-maximum filter.

Spatial extent analysis. This analysis was performed to examine within-group differences in the spatial extent of activation comparing the famous and unfamiliar name conditions. For each group, statistical parametric maps were generated to identify voxels where

the AUC for famous names differed significantly from the AUC for unfamiliar names. An individual voxel probability threshold [$t(22) = 3.12$, $p = 0.005$] was coupled with a minimum cluster volume threshold of 0.731 mL. This combination of individual voxel probability and minimum cluster size thresholds is equivalent to a whole brain family-wise error threshold of $p < 0.05$ based on 3,000 Monte Carlo simulations.[20]

Functional region of interest group analysis. As a follow-up to the voxel-wise analyses, a functional region of interest (fROI) analysis was conducted to evaluate potential group differences in the magnitude of the AUC in functionally active regions. An fROI map was generated by conjoining activated regions identified in the spatial extent analysis (see above) across the 3 groups. Any voxel deemed "activated" by the famous–unfamiliar name subtraction in at least 1 of the 3 groups contributed to the final fROI map. For each participant, an "averaged HRF" was calculated for all voxels within an fROI. AUC (4, 6, and 8 seconds after stimulus onset) served as the dependent variable in a 1-way analysis of variance (ANOVA) to examine group differences in each fROI.

Voxel-based morphometry. Voxel-based morphometry (VBM) was conducted using SPGR anatomic images segmented with SPM 5.[21,22] A cutoff gray matter probability ($p = 0.01$) was used to remove spurious signals at gray matter–white matter boundaries. After transforming anatomic images into Montreal Neurological Institute coordinates using a standard template, a study-specific template was created to normalize subjects into a common stereotaxic space. Modulated, normalized gray matter images were blurred using a 12-mm gaussian filter to compensate for normal variation in anatomy across subjects. A voxel-wise, 1-way ANOVA (unpooled variance across subjects) was used to examine differences in cortical atrophy across the 3 participant groups, using a family-wise error threshold of $p < 0.05$.

RESULTS

Neuropsychological and fMRI task performance. No significant group differences were observed on neuropsychological tests of global cognition, verbal learning, depression, and activities of daily living (table 1). Likewise, no significant group differences were observed on accuracy, discriminability (A′), response bias (B′′), or reaction time for the fMRI task (table 1). Mean accuracy on the fame discrimination task exceeded 90% correct for all 3 groups. The relatively low effect sizes (η^2) suggest that the nonsignificant findings were not influenced by sample size.

Voxel-based morphometry. A 1-way ANOVA identified no brain regions demonstrating significant group differences in gray matter density, a measure of cortical atrophy.

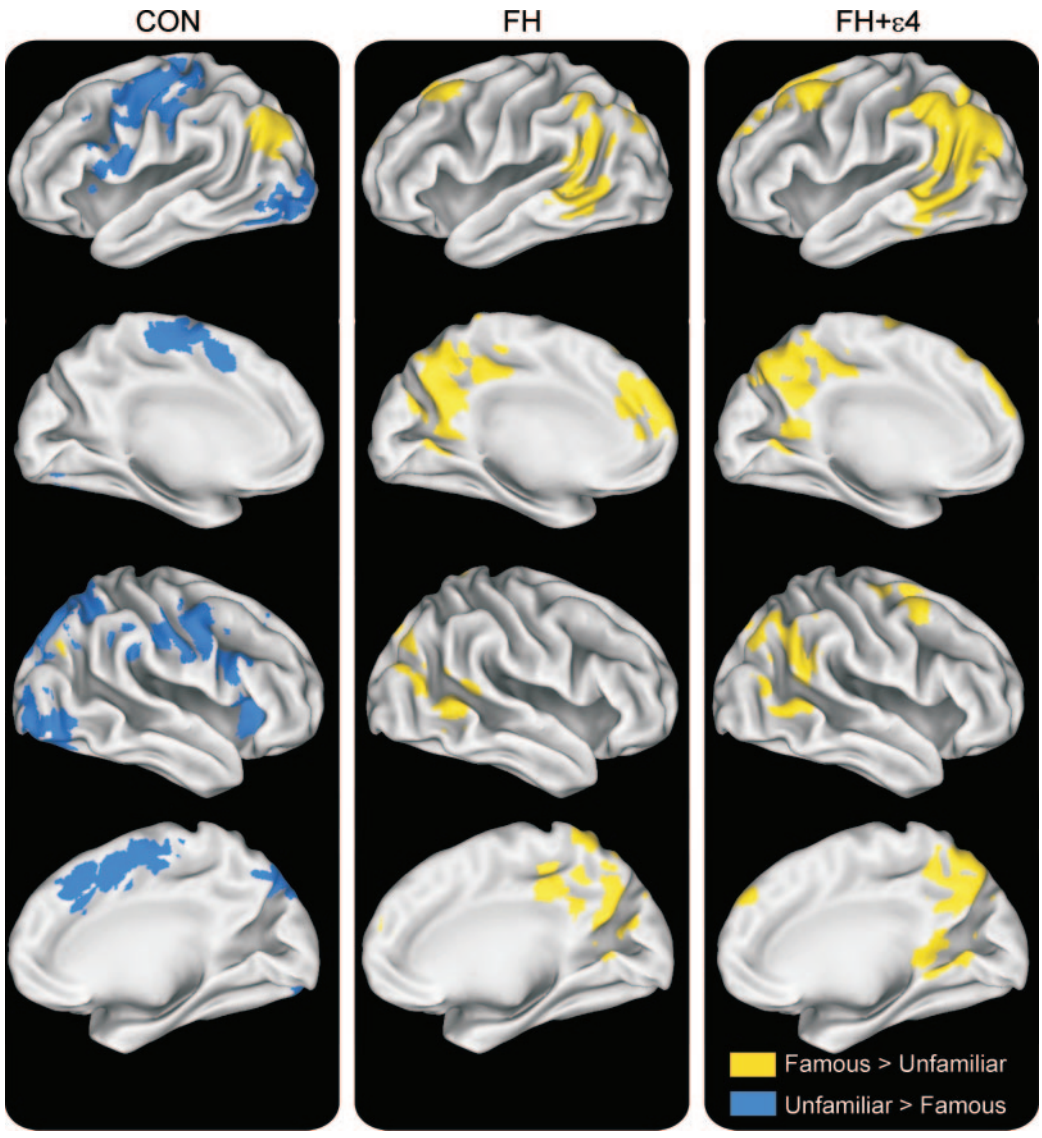
fMRI–spatial extent analysis. Voxels demonstrating significant differences in the AUC for the famous and unfamiliar name stimuli are shown in figure 1 and table 2 for each of the 3 groups (CON, FH, FH+ε4). Both risk groups demonstrated regions with increased magnetic resonance (MR) signal for famous vs unfamiliar names; no regions demonstrated greater activity for unfamiliar than for famous names. In contrast, the CON group showed predominantly increased signal for unfamiliar relative to famous names. Total volume of activation (famous > unfamiliar comparison) was largest in the FH+ε4 group (35.7 mL), intermediate in the FH group (22.4 mL), and smallest in the CON group (6.3 mL). In general, the FH+ε4 group had a larger spatial extent of activation in the same regions activated by the FH group (e.g., posterior cingulate/precuneus, left and right middle temporal gyrus, left inferior parietal cortex; table 2), but also recruited additional areas (e.g., right middle frontal gyrus, right inferior parietal lobule).

fMRI–fROI analysis. A conjunction analysis (see above) identified 21 fROIs (figure 2 and table 3). Eleven regions showed greater blood oxygen level–dependent (BOLD) activity for famous compared with unfamiliar names, and 10 regions showed the opposite pattern (the latter derived entirely from the CON group). Figure e-1 on the *Neurology*® Web site at www.neurology.org shows the averaged famous and unfamiliar HRFs for each participant group for 8 representative brain regions, as well as the HRF derived by subtracting the unfamiliar from famous conditions. Representative AUC estimates derived from the famous–unfamiliar subtraction are presented in the rightmost column of figure e-1.

A 1-way repeated-measures ANOVA performed on the AUC estimates indicated significant group differences in 16 of 21 regions (table 3). Seven of the 11 fROIs exhibiting greater activity for famous than for unfamiliar names demonstrated significant overall group differences, which were then subjected to a post hoc pairwise group comparison. In 4 regions, bilateral precuneus/posterior cingulate, bilateral medial frontal, left angular gyrus, and right middle temporal, the FH+ε4 and FH groups had significantly greater MR signal intensity than the CON group. In one region, right middle frontal, the FH+ε4 group had significantly greater activity than the FH and CON groups. In another region, right inferior parietal/supramarginal gyrus, the FH+ε4 group had significantly greater activity than the FH, which in turn exhibited greater activity than the CON group. Finally, in the bilateral caudate, the CON group had greater activity than the 2 risk groups (FH+ε4 and FH).

Nine of the 10 fROIs exhibiting greater activity for unfamiliar than for famous names demonstrated significant group differences. In 8 of the 10 regions (bilateral supplementary motor area [SMA], left and right precentral, left inferior frontal, right precuneus/angular gyrus, left postcentral, right inferior occipital, left middle occipital), the CON group demonstrated greater activity in response to the unfamiliar

Figure 1 Results of voxel-wise analysis demonstrating significant differences between the famous and unfamiliar name conditions



Results of voxel-wise analysis demonstrating significant differences between the famous and unfamiliar name conditions, conducted separately for each group: control (CON), family history (FH), and family history and APOEε4 (FH+ε4) groups. Yellow = regions showing greater activation to famous than unfamiliar names; blue = regions showing greater activation to unfamiliar than famous names. Brain activation projected on the lateral and medial surfaces of the left and right hemispheres. See table 2 for additional information relating to individual activation foci.

relative to famous name stimuli; the 2 risk groups (FH+ε4 and FH), in contrast, demonstrated equivalent degrees of activation for the 2 types of stimuli within these regions (figure e-1B). In one region, the right insula, this pattern was only observed between the FH+ε4 and CON group.

In contrast, controls showed a consistent pattern, seen in 8 of 10 regions, for increased activity for unfamiliar names compared with famous names. These included bilateral SMA, left precentral and right precentral gyrus, right precuneus, left inferior frontal, left postcentral gyrus, and left inferior occipital gyrus and right insula. The HDR and AUC for several of the regions showing these different patterns are shown separately for the famous, unfamiliar, and famous–unfamiliar contrast in figure e-1.

DISCUSSION Our results indicate that AD risk factors exert a strong influence on patterns of brain activation observed in cognitively intact older individuals. In response to a low-effort, high-accuracy SM task, the FH and FH+ε4 groups demonstrated greater activation in response to famous relative to unfamiliar names, predominantly in the bilateral posterior cingulate/precuneus, bilateral temporoparietal junction, and bilateral prefrontal cortex. Further-

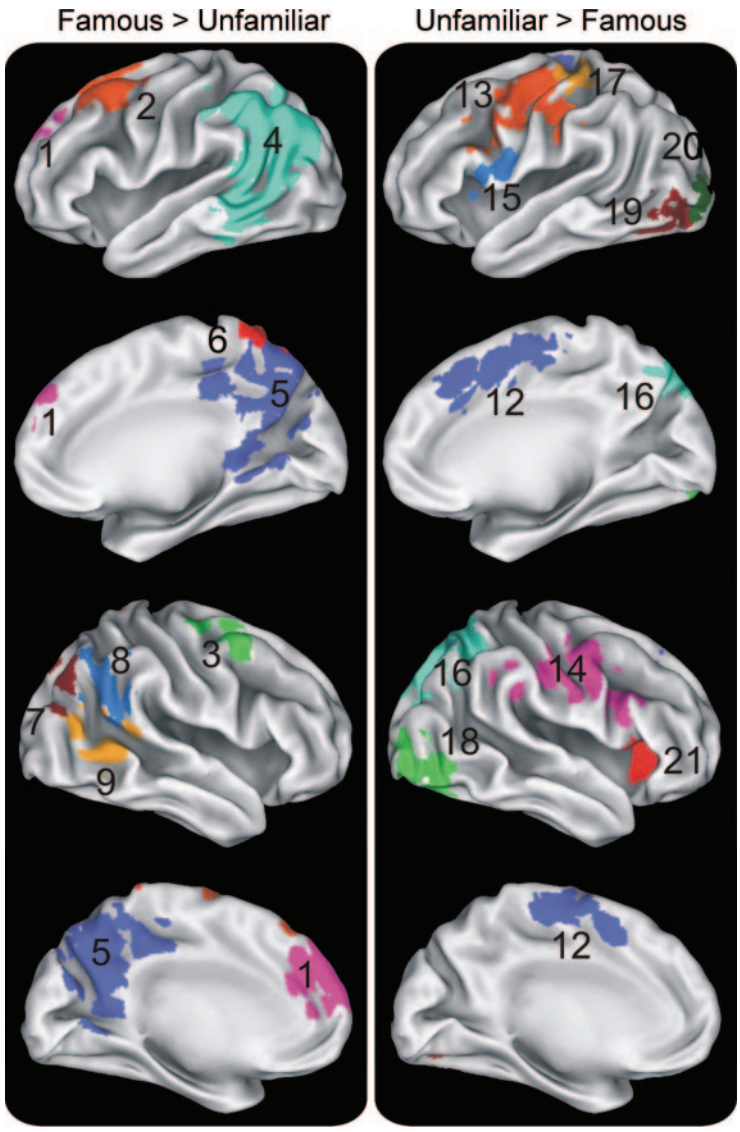
Table 2 Activation foci for famous vs unfamiliar name subtraction

		CON				FH				FH+ε4			
Region	BA	x	y	z	Vol, mL	x	y	z	Vol, mL	x	y	z	Vol, mL
Famous > unfamiliar													
Frontal lobe													
B medial frontal gyrus	8, 9					−7	47	30	3.02	−5	51	40	1.74
R middle frontal gyrus	6									35	1	55	1.04
L middle frontal gyrus	6, 8					−29	19	52	2.02	−27	11	50	3.60
Parietal lobe													
R angular gyrus	19, 39, 40	45	−78	31	0.7	42	−75	32	1.2	39	−71	39	0.8
L angular gyrus, inferior parietal lobule	19, 39	−42	−71	30	4.8								
L inferior parietal lobule	7, 37, 39, 40					−46	−53	49	1.0	−43	−58	31	11.9
R inferior parietal lobule, supramarginal gyrus	40									52	−50	39	1.8
B posterior cingulate	29, 30									2	−51	7	1.7
L precuneus, inferior parietal lobule	19					−34	−75	38	0.9				
B precuneus, L posterior cingulate	7, 23, 30, 31					−1	−52	31	6.6	0	−56	40	7.2
B superior parietal lobule	7					2	−58	65	2.8				
B superior parietal lobule, precuneus	7, 19					2	−82	45	1.2				
Temporal lobe													
L middle temporal gyrus	21, 22, 37					−54	−47	−2	1.7	−57	−49	−5	2.0
R middle temporal gyrus	21, 22, 39					56	−52	10	1.3	59	−59	7	1.9
L superior temporal gyrus, angular gyrus	39					−50	−54	22	0.9				
Subcortical													
R caudate, L cingulate gyrus	—	1	4	20	0.8								
B cerebellum (VIII, IX)	—									3	−55	−43	2.0
Total activation volume					6.3				22.4				35.7
Unfamiliar > famous													
Frontal lobe													
L inferior frontal, precentral gyrus	44	−47	5	12	0.7								
L precentral gyrus	3, 4, 6	−41	−9	43	4.5								
R precentral gyrus	4, 6, 8	49	−4	36	4.3								
B SMA, R medial frontal gyrus	6, 8, 24	3	3	50	8.0								
Parietal lobe													
L postcentral gyrus	1, 3, 4a	−38	−29	55	1.1								
R superior, inferior parietal lobule	7, 19, 39	28	−66	33	10.2								
Occipital lobe													
L inferior occipital gyrus	18	−28	−86	−2	0.8								
L middle occipital gyrus	18, 19	−34	−71	−8	0.9								
Subcortical													
R insula	13	37	17	8	1.1								
Total activation volume					31.6								

CON = control; FH = family history; BA = Brodmann area; vol = volume; B = bilateral; SMA = supplementary motor area.

more, the spatial extent of activated tissue was greater in the FH+ε4 (35.7 mL) than in the FH (22.4 mL) group. Similarly, the magnitude of the fMRI response was significantly greater in the FH+ε4 than in the FH group in 2 right hemisphere regions (middle frontal and supramarginal gyri). In contrast, the

Figure 2 Brain regions used in fROI analysis



Brain regions used in functional region of interest (fROI) analysis (numbers correspond to regions described in table 3). Colors are arbitrarily selected to delineate different regions of interest.

group without risk factors evidenced greater activation in response to unfamiliar than in response to famous stimuli. This pattern of group differences in brain activation could not be explained by demographic variables, cerebral atrophy, verbal EM performance, global cognitive functioning, activities of daily living, or depression.

These findings are generally consistent with the functional recruitment hypothesis of age-related compensatory changes in the fMRI activation patterns of at-risk populations.[5,6,23-26] Previous studies, however, used effortful EM activation tasks. Our study extends the previous work by showing that AD risk factors can exert influence on brain activation patterns even when participants engage in a low-effort and relatively automatic SM task. These findings have practical significance for tracking changes in brain activation longitudinally, because performance on similar SM tasks remains high in MCI and early AD patients.

An additional methodologic advantage of this study was the use of an event-related trial design. Most fMRI studies of at-risk populations have used blocked trial designs, which are not able to eliminate incorrect trials from the HRF estimation. Event-related designs enable removal of incorrect trials from the resulting activation maps. We suspect that one source of inconsistency in the fMRI literature, especially in clinically symptomatic groups (MCI, early AD), results from this confound.

Most studies to date have focused primarily on activation observed within the hippocampus and adjacent MTL regions on EM tasks. This study, as well as others by our group,[6,26] clearly demonstrates that functional recruitment occurs in extrahippocampal regions (posterior cingulate, lateral posterior temporoparietal) in cognitively intact at-risk individuals. Focusing on these neocortical memory circuits mitigates the problems of measuring brain activity solely in the MTL, one of the first regions to demonstrate atrophy in MCI and early AD.[27]

Our findings also suggest that having multiple risk factors (FH and $\varepsilon 4$) may exert a stronger influence on brain activation patterns than having a single factor (FH). This effect has been observed in previous studies,[28-30] although the direction of the altered pattern of activation for the combined risk group has not been consistent. Several methodologic variations between studies might account for the divergent findings.[31]

Controls showed a greater fMRI response for unfamiliar compared with famous names, a pattern opposite to that seen in the 2 at-risk groups. These regions, including the SMA, left and right precentral gyri, left inferior frontal gyrus, right insula, precuneus, and angular gyrus, are frequently activated by language, attentional, and working memory circuits. We speculate that the CON group allocated more resources to rule out unfamiliar names than to identify famous names.

We did not adopt a calibration approach, such as CO_2/O_2 inhalation or a hypercapnic challenge (breath holding),[32] to scale the BOLD response to reduce intersubject variability, a possible study limitation. In addition, we note that a significantly higher percentage of FH+$\varepsilon 4$ subjects were taking statins, suggesting possible cardiovascular group differences that could conceivably influence the BOLD response.

Longitudinal fMRI studies are required to determine whether the differential pattern of SM activa-

Table 3 Group differences derived from functional region of interest analysis

No.	Region	BA	x	y	z	Vol, mL	*p* Value	Group difference
Famous > unfamiliar								
	Frontal lobe							
1	B medial frontal gyrus	8, 9, 32	−6	48	33	4.69	0.01	FH+ϵ4 = FH > CON
2	L medial frontal gyrus	6, 8	−27	14	51	5.27	NS	—
3	R middle frontal gyrus	6	35	1	55	1.04	0.02	FH+ϵ4 > FH = CON
	Parietal lobe							
4	L angular gyrus, inferior parietal lobule	21, 22, 37, 39, 40	−45	−59	26	19.30	NS	—
5	B precuneus, posterior cingulate	7, 23, 30, 31	0	−56	33	14.37	<0.01	FH+ϵ4 = FH > CON
6	B precuneus	7	2	−58	65	2.77	0.03	FH+ϵ4 = FH > CON
7	R angular gyrus	7, 19, 39	42	−74	34	2.33	NS	—
8	R inferior parietal lobule, supramarginal gyrus	40	52	−50	39	1.77	<0.01	FH+ϵ4 > FH > CON
	Temporal lobe							
9	R middle temporal gyrus	21, 22, 37, 39	58	−56	8	2.98	<0.01	FH+ϵ4 = FH > CON
	Subcortical							
10	B cerebellum (VIII, IX)	—	3	−55	−43	2.00	NS	—
11	B caudate	—	1	4	19	0.75	<0.01	CON > FH+ϵ4 = FH
Unfamiliar > famous								
	Frontal lobe							
12	B SMA, R medial frontal gyrus	6, 8, 24, 32	3	2	50	7.96	<0.01	FH+ϵ4 = FH > CON
13	L precentral gyrus	3, 4, 6	−41	−9	43	4.54	<0.01	FH+ϵ4 = FH > CON
14	R precentral gyrus	4, 6	49	−4	36	4.29	<0.01	FH+ϵ4 = FH > CON
15	L inferior frontal, precentral gyrus	44	−47	5	12	0.75	<0.01	FH+ϵ4 = FH > CON
	Parietal lobe							
16	R precuneus, angular gyrus	7, 39, 40	26	−64	42	8.09	<0.01	FH+ϵ4 = FH > CON
17	L postcentral gyrus	1, 3, 4a	−38	−29	55	1.12	<0.01	FH+ϵ4 = FH > CON
	Occipital lobe							
18	R inferior occipital gyrus	18, 19	36	−75	−2	2.09	<0.01	FH+ϵ4 = FH > CON
19	L middle occipital gyrus	18, 19	−34	−71	−8	0.94	<0.01	FH+ϵ4 = FH > CON
20	L inferior occipital gyrus	18	−28	−86	−2	0.75	NS	—
	Subcortical							
21	R insula	13	37	17	8	1.08	0.02	FH+ϵ4 > CON

No. corresponds to numbered regions in figure e-1.
BA = Brodmann area; vol = volume; B = bilateral; FH = family history; CON = control; NS = not significant; SMA = supplementary motor area.

tion observed in this cross-sectional study predicts future cognitive decline and enables the precise tracking of the clinical course during the preclinical phase of AD.

DISCLOSURE

Ms. Durgerian receives salary support from the NIH [NIA R01-AG022304] and Advancing Healthier Wisconsin Foundation; her husband holds patents unrelated to the work described in this publication: US Patent No. 7,244,572 issued on 07/17/2007 and US Patent No. 5115000 issued on 05/19/1992. Dr. Seidenberg received funding support from the NIH [NIA RO1-AG022304 (Coinvestigator) and NINCDS RO1-NS44351 (Coinvestigator)]. He serves as a consulting editor for the *Journal of Neuropsychology*. Dr. Seidenberg receives royalties from a self-report questionnaire that he developed. Ms. Guidotti received a travel award from Rosalind Franklin University. Dr. Nielson serves as a consulting editor for the *Journal of Neuropsychology*; receives research support from the NIH [NIA R01-AG022304 (Coinvestigator and Site PI) and NIOSH T 42 OH008672 (Coinvestigator)], the Medical College of Wisconsin, Marquette University, and the Wisconsin Women's Health Foundation; and has served as an expert witness (consultation only) for Dorsey, Dorsey & Whitney LLP, Minneapolis, MN. Dr. Woodard serves as a consulting editor for the *Journal of Athletic Training*, *Neuropsychology*, and *Aging, Neuropsychology, and Cognition*; has received consultant fees from the University of Oklahoma and the National Rehabilitation Hospital; serves/has served as a neuropsychology consultant for the Atlanta Thrashers Hockey Club, the Chicago Wolves Hockey Club, and the Atlanta Falcons Football Club; and receives research support from the NIH [NIA P01-AG17553 (Program Project Coinvestigator and Co-Project Leader), NIA R01-AG022304 (Coinvestigator), NIMH R21-MH069704 (Co-PI)]. Dr. Antuono serves on the speakers' bureaus of Novartis and Pfizer; receives research support from Elan Pharmaceuticals, Eisai, GlaxoSmith-Kline, the Helen Bader Foundation, and the Advancing Healthier Wisconsin Foundation. Ms. Zhang received salary support from the NIH [NIA R01-AG022304]. Dr. Rao served as founder and chief science officer of Neurognostics, Inc.; serves/has served as Editor of *Neuropsychology*, Associate Editor of the *Journal of the International Neuropsychological Soci-*

ety, and a member of the editorial board of *Brain and Cognition*, *Brain Imaging and Behavior*, *Journal of Clinical and Experimental Neuropsychology*, *Journal of the International Neuropsychological Society*, *Journal of Neurological Rehabilitation*, *Neuropsychology*, *Neuropsychology Review*, and *NMR in Biomedicine*; received royalties from publication of *Neuropsychiatry* (Wolters Kluwer Health, Inc., 2005–2008) and a neuropsychological test (PASAT); received honorarium for serving as journal editor from the American Psychological Association; has served as consultant or on the speakers' bureaus for Biogen Idec, Genentech, Pfizer, EMD Serono, Brintnall & Nicolini, Inc., and the Nationwide Children's Hospital; and has received research support from the NIH [NIA R01-AG022304 (PI) and NINDS R01-NS054893 (Co-PI)], US Department of Defense [PTSD/TBI Research Program W81XWH-08-2-0124 (PI)], CHDI Foundation (PI), Advancing Healthier Wisconsin Foundation (PI), Biogen Idec (PI), and EMD Serono (PI).

Received January 13, 2009. Accepted in final form May 18, 2009.

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