Published in final edited form as:

Neurology. 2008 May 13; 70(20): 1898–1904. doi:10.1212/01.wnl.0000312288.45119.d1.

Altered fMRI activation during mental rotation in those at genetic risk for Alzheimer disease

Michael A. Yassa, MA, Guillermo Verduzco, BA, Catherine Cristinzio, MS, and Susan Spear Bassett, PhD

Department of Psychiatry and Behavioral Sciences, Johns Hopkins Medical Institutions, Baltimore, MD.

Abstract

Objective: This study was undertaken to examine differential functional MRI patterns in those at genetic risk for Alzheimer disease (AD), specifically investigating parietal lobe activation, a brain region with changes noted in the early stages of AD.

Methods: This study uses functional MRI to investigate blood oxygenation level dependent changes in the parietal lobe in a high-risk sample of 18 asymptomatic offspring of autopsy-confirmed AD cases, compared to 15 matched controls. The cognitive activation paradigm was a mental rotation task, which requires individuals to rotate three-dimensional cube stimuli to judge their similarity.

Results: We found no differences in either reaction time or performance accuracy between groups. However, the at-risk individuals showed increases in activation in the right superior parietal lobule (BA 7), the right insula (BA 13), the right middle frontal gyrus (BA 10), and the right inferior frontal gyrus (BA 47).

Conclusions: We present evidence for a compensatory mechanism for those at increased risk for Alzheimer disease (AD). This study examines and confirms parietal changes with increased risk for late-onset AD, despite normal cognitive performance. Added to the previous findings from this group, these results demonstrate the sensitivity of functional imaging measures to brain changes that are not yet reflected in cognitive performance, which may ultimately serve as an important indicator of disease.

Since pathologic changes most likely start years or even decades before the manifestation of clinical symptoms in Alzheimer disease (AD), functional brain imaging of unaffected offspring of confirmed AD cases provides a means of studying the earliest brain changes associated with risk for the disease. From functional studies of mildly affected patients with AD, several brain regions demonstrate changes early in the disease process. The question is whether functional alterations are evident prior to the development of clinical symptoms and prove predictive of conversion to AD. The medial temporal lobe (MTL), a region critical for memory function, is implicated early in the course of AD. Our group has now shown increased activation in the MTL among asymptomatic individuals at elevated risk for AD using an episodic memory paradigm.¹ Further, it appears that distinct patterns of activation among those at risk are associated with genetic findings reported by our group.²⁻⁴ In addition to changes in the MTL, results of positron emission tomography (PET) studies in patients with early AD reveal

Address correspondence and reprint requests to Dr. Susan Spear Bassett, Department of Psychiatry and Behavioral Sciences, Johns Hopkins Medical Institutions, Johns Hopkins Hospital, Phipps 300, 600 North Wolfe Street, Baltimore, MD 21287 E-mail: sbassett@jhmi.edu.

Disclosure: The authors report no conflicts of interest.

Supplemental data at www.neurology.org

significant cerebral glucose hypometabolism in parietal cortical regions,⁵⁻⁷ positing the parietal lobes as yet another locus where functional changes may precede clinical symptoms.

The purpose of the present study, therefore, was to assess parietal changes in an asymptomatic sample that is at genetic risk for late-onset AD (by having one autopsy-confirmed affected parent, and at least one more affected first-degree relative), using fMRI. For this purpose, we chose a task involving mental rotation (also known as mental imagery). Mental rotation has been frequently studied in perception and cognition research.⁸ In functional imaging studies, tasks involving mental rotation demonstrate robust and consistent activation in the parietal cortex.⁹⁻¹³ We hypothesized that individuals at familial risk for AD would demonstrate increased activation in parietal regions compared to a matched sample of healthy controls during performance of this task. We also hypothesized that these brain changes would be present before changes in cognitive performance are evident.

METHODS

Sample selection

At-risk participants in this study are enrolled in an ongoing study of preclinical disease markers in a sample of individuals at genetic risk for development of late-onset AD. These individuals come from families initially enrolled at Johns Hopkins University as part of the NIMH Alzheimer's Disease Genetics Initiative. Those enrolled have a parent with autopsy-confirmed AD and at least one additional first-degree relative with a clinical diagnosis of probable AD, are at least 50 years of age, and are free of memory impairment, memory complaints, or treatment for cognitive impairments. Control participants, also free of memory impairment, cognitive complaint, or treatment, screened negative for the presence of a first-degree relative with AD or suspected dementia. A full description of this study, which has been approved by the Johns Hopkins Institutional Review Board, can be found in our previous publication.¹ Included here are data from a subset of the overall sample, 18 right-handed at-risk and 15 right-handed control subjects, matched on age, sex, and education, who completed the fMRI task outlined below. Prior to scanning, individuals completed measures of anxiety and depression.^{14,15} In addition, all participants were administered a cognitive battery which included the Mini-Mental State Examination and the North American Adult Reading Test from which estimated IQs were computed.^{16,17} All participants provided written informed consent.

Scan acquisition

Data were acquired on a 1.5 Tesla Philips Intera-NT system (Philips Medical Systems, Best, The Netherlands) at the F.M. Kirby Functional Imaging Research Center (Kennedy Krieger Institute, Baltimore, MD). The system is equipped with Galaxy gradients (66 mT/m at 110 mT/m/sec). A sagittal localizer scan was collected to pinpoint the exact location of the brain. Functional scans were collected using echoplanar imaging (EPI) and a blood oxygenation level dependent (BOLD) technique with repetition time (TR) = 1,500 msec, echo time (TE) = 39 msec, flip angle = 90 degrees, field of view (FOV) 240 mm² in the xy plane, and matrix size = 64 × 64. Twenty-seven axial slices were acquired with a 3.5 mm thickness and an interslice gap of 0.5 mm (used to reduce the possibility of obtaining artifacts in the images due to incomplete echo digitization) oriented parallel to the anterior-posterior commissure line. Functional scanning was performed in a single session with 300 time points. Total functional acquisition time was 7.5 minutes. A high-resolution whole-brain anatomic scan was also obtained using a T1-weighted, three-dimensional magnetization prepared rapid acquisition gradient echo sequence with the following parameters: TR = 8.6 msec, TE = 3.9 msec, FOV = 240 mm, flip angle = 8 degrees, matrix size = 256 × 256, slice thickness = 1.5 mm, 124 slices.

fMRI paradigm

Participants were presented with a mental rotation challenge, using three-dimensional cube stimuli. Participants viewed the stimuli in pairs and were instructed to press one button if the two stimuli were either the same or could be rotated to look the same (congruent), and to press the other button if the two objects were different or could not be rotated to look the same (incongruent). Trials that involved rotation used a 20-, 40-, or 90-degree rotation (randomly assigned), to prevent subjects from developing a degree-specific mapping strategy. The incongruent stimulus pairs appeared as mirror images of each other, upon completing the required rotation. The different stimulus pairs were identical to each other, except one of the stimuli was missing a cube (figure 1). The task was programmed using the E-prime programming environment (E-prime 1.1; Psychology Software Tools, Inc., Pittsburgh, PA). The task consisted of 80 trials with unique stimuli, evenly divided among “same,” “different,” “congruent,” and “incongruent” stimulus types. Twenty additional null event trials (fixation) were interspersed throughout the task. The stimulus order was completely randomized and interstimulus intervals were jittered between 5, 6, and 7 seconds. All subjects underwent a computerized practice session with similar stimuli before scanning, with practice sessions continuing until the participant demonstrated task comprehension. The instructions were explained again once the participant was inside the scanner. Behavioral responses were recorded using an MR-compatible serial response button box.

Data preprocessing

Data preprocessing was conducted on a Windows XP Professional workstation. Statistical Parametric Mapping (SPM99, Wellcome Department of Imaging Neuroscience, University College, London, UK) was used, under the MATLAB 6.1 (The Mathworks, Sherborn, MA) programming environment. Slice timing correction was conducted using an intermediate slice (#13) as the reference slice, and sinc-interpolation. Motion correction was conducted using a six-parameter affine transformation (three translations and three rotations in x, y, and z axes), followed by reslicing using a “windowed” sinc-interpolation. Twelve parameter affine transformation and nonlinear deformation using $7 \times 8 \times 7$ basis functions and medium nonlinear regularization were conducted to warp each subject's data into standard stereotaxic space. Template space was defined by SPM's standard EPI template (Montreal Neurologic Institute, McGill University, Montreal, Canada). Data were resliced to isotropic voxels (2 mm^3) using trilinear interpolation, and spatially smoothed with a full-width at half-maximum isotropic Gaussian kernel of 8 mm^3 .

Statistical modeling and analysis

A voxel-based general linear model was fit to each subject's time series, within the framework of Statistical Parametric Mapping (SPM99). Data were modeled as event-related, and convolved with SPM's canonical hemodynamic response function to account for the lag between stimulation and the BOLD signal. The model was estimated using SPM's standard ordinary least squares. Stimulus onset times and corresponding reaction times were used to define two conditions, ROTATION and NO-ROTATION. The former condition consisted of the trials in which subjects were required to perform a mental rotation (whether it was a match or a non-match), whereas the latter consisted of trials in which they were required to match the stimuli without rotation (same or different). The contrast of interest subtracted activation during the NO-ROTATION condition from the ROTATION condition, in order to isolate task-relevant activation (i.e., rotation) from task-irrelevant activation (i.e., motor, visual).

Analysis of within-group activation using one-sample *t* tests was conducted to determine the individual group activation patterns and ensure the task produced the expected parietal lobe activation in both groups.

In addition, a two-group comparison was conducted to compare the at-risk group with the control group using an analysis of covariance, to control for possible confounding effects of age, sex, handedness, education, anxiety, depression, and APOE ϵ 4 status. Voxel-wise threshold for inference and visualization was set to $p = 0.001$, uncorrected, with a cluster-extent threshold of $k = 20$ voxels. The coordinates of voxels that survived the statistical threshold were produced in MNI space and converted to Talairach space to facilitate anatomic labeling, which was conducted using the Talairach Daemon software with an adaptive gray matter search range of 5mm³. Labels were manually checked with the Talairach and Tournoux atlas.

Behavioral data recorded from the task included mean reaction time and accuracy for each of the task conditions. These scores were compared using an independent samples t test in SPSS version 15.0 (Statistical Package for Social Sciences; SPSS Inc., Chicago, IL).

RESULTS

The at-risk and control participants did not differ in age, education, gender, or APOE4 status, nor were there any significant differences in cognition, anxiety, or depression (table 1). Analysis of within-group activation using one-sample t tests revealed the expected task-related activation in the parietal lobes in both groups. However, the at-risk group showed much more extensive activation. Controls showed uni-lateral activation in the superior temporal, superior frontal, and parietal lobes when contrasting the non-rotate and rotate trials. The at-risk group showed a greater degree of activation in these regions as well as others including the occipital lobe (table 2, figure e-1 on the *Neurology*[®] Web site at www.neurology.org).

The two-group analysis of covariance, with age, sex, handedness, education, anxiety, depression, and ApoE ϵ 4 as covariates, revealed significantly increased activation in the right inferior frontal gyrus (BA 47), the right middle frontal gyrus (BA 10), the right insula (BA 13), and the right superior parietal lobule (BA 7) in the at-risk group compared to the control group. Talairach coordinates and statistical values are presented in table 3 and images in figure 2. The reverse comparison did not show any decreased activation in the at-risk group compared to the controls. Comparison of the groups' behavioral data revealed no significant differences in performance. Reaction time and accuracy were similar between groups during all task conditions, demonstrating the task was being performed at comparable levels (table e-1).

DISCUSSION

This study presents an investigation of brain activation in asymptomatic offspring of autopsy-confirmed late-onset familial AD cases, in response to a spatial cognitive challenge. We report evidence that subjects in this high-risk sample are capable of performing as well on this task as their matched controls, but are activating specific cerebral loci to a greater extent. Familial risk status appears to be associated with increased activation in the parietal region as hypothesized, as well as the insula and frontal regions during mental rotation, providing further evidence that genetic risk for AD is associated with modifications in brain function, and that increased activation, especially in the prefrontal cortex, seems to be part of compensatory network.

There is some recent evidence that patients with AD perform poorly on mental rotation tasks, which may be due to pathologic changes in the parietal lobe that manifest as deficits in spatial processing.¹⁸ However, changes in cerebral blood flow as a function of cognitive load may be a characteristic preclinical marker in cases where AD symptoms have not yet manifested. While there has been report of decreased activation among individuals at risk for AD, our results are consistent with the majority of findings from other neuroimaging studies that report increases in brain activation in individuals at risk for AD, in spite of normal cognitive

performance.¹⁹⁻²⁴ These findings lend further support to the hypothesis that increased brain activation acts in a compensatory fashion to bring performance on cognitive challenges to the baseline of healthy controls. Additional neural resources may be required to complete the task in order to compensate for neuronal loss.^{25,26}

Increased activation in the inferior and middle frontal gyri (Brodmann areas 47 and 10) in at-risk subjects may be part of a prefrontal compensatory network, previously implicated in functional imaging research with AD cases.^{25,27} A recent investigation also found that the right inferior pre-frontal lobe was activated to a higher extent in patients with AD than controls in response to a subtraction task, compared to various other regions with decreased activation.²⁸ It is possible that prefrontal compensatory mechanisms are not task specific and respond similarly with increased neural activity to a variety of cognitive challenges.²⁹ It has been proposed that distributed interactions between the parietal and frontal regions represent circuitry related to spatial attention.²⁹ Thus increased activation in the frontal lobe, a brain region that does not usually show early pathology in AD, may reflect decreased functioning within the circuit. Further research is needed to elucidate the role of the prefrontal cortex in modulating cognitive performance in cases where the primary processing cortices are compromised.

Activation in the superior parietal lobule (SPL) in response to a mental rotation task has been extensively documented.^{11,30-33} Increased SPL activation during rotation was expected in this high-risk sample, and illustrates that individuals at risk for AD recruit more neural resources in the parietal lobe to resolve this spatial cognitive challenge than healthy controls.

Increased activation in the insula in the at-risk sample was a somewhat unexpected finding. Although its exact involvement in this type of task is unclear, previous research using similar tasks has demonstrated activation in the insular cortex with PET and fMRI.^{30,34} There is some recent evidence suggesting that the insula may be involved in spatial attention to mental representations. A recent fMRI study, using a spatial attention and working memory task to test whether it is possible to shift attention to locations within mental representation in working memory, found brain regions that were specific to the orienting of spatial attention, including the posterior parietal cortex, the insula, and the lateral and medial frontal cortices.³⁵ This suggests that the insula may play an auxiliary role in mental rotation, one that deals with the orienting of attention. The absence of increased insula activity when the at-risk group is examined independently suggests they have a sustained increase in insular activity across all conditions. This further supports the notion that the heightened insular activity may reflect the orienting of spatial attention. Further, structural MRI and cerebral volumetry studies of AD report local gray matter loss in the insula.³⁶⁻³⁹ Thus it is possible that overactivation in the insula makes up for mild neuronal loss in the same area. Finally, although increased insular activation has been associated with elevated anxiety,⁴⁰ that does not provide an explanation for the activation seen in the current study. Clearly this heightened insular activation requires further investigation.

This study lends support to the hypothesis that asymptomatic individuals at risk for familial late-onset AD recruit more widespread neural activity than healthy individuals to resolve a spatial cognitive challenge. This provides further evidence that genetic risk for AD is associated with modifications in brain function, and that increased activation, especially in the prefrontal cortex, seems to be part of a compensatory network.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

Funding for this work was provided by the National Institute on Aging, NIH (PI: Susan Bassett; AG16324).

GLOSSARY

AD, Alzheimer disease
 BOLD, blood oxygenation level dependent
 CES-D, Center for Epidemiologic Studies Depression Scale
 EPI, echoplanar imaging
 FOV, field of view
 MMSE, Mini-Mental State Examination
 MTL, medial temporal lobe
 PET, positron emission tomography
 SPL, superior parietal lobule
 TE, echo time
 TR, repetition time.

REFERENCES

1. Bassett SS, Yousem DM, Cristinzio C, et al. Familial risk for Alzheimer's disease alters fMRI activation patterns. *Brain* 2006;129:1229–1239. [PubMed: 16627465]
2. Bassett SS, Avramopoulos D, Fallin D. Evidence for parent of origin effect in late-onset Alzheimer disease. *Am J Med Genet* 2002;114:679–686. [PubMed: 12210287]
3. Bassett SS, Kusevic I, Cristinzio C, et al. Brain activation in offspring of AD cases corresponds to 10q linkage. *Ann Neurol* 2005;58:142–146. [PubMed: 15984011]
4. Bassett SS, Avramopoulos D, Perry RT, et al. Further evidence of a maternal parent-of-origin effect on chromosome 10 in late-onset Alzheimer's disease. *Am J Med Genet B Neuropsychiatr Genet* 2006;141:537–540. [PubMed: 16741936]
5. Pietrini P, Furey ML, Alexander GE, et al. Association between brain functional failure and dementia severity in Alzheimer's disease: resting versus stimulation PET study. *Am J Psychiatry* 1999;156:470–473. [PubMed: 10080567]
6. Drzezga A, Riemenschneider M, Strassner B, et al. Cerebral glucose metabolism in patients with AD and different APOE genotypes. *Neurology* 2005;64:102–107. [PubMed: 15642911]
7. Mosconi L, Sorbi S, de Leon MJ, et al. Hypometabolism exceeds atrophy in presymptomatic early-onset familial Alzheimer's disease. *J Nucl Med* 2006;47:1778–1786. [PubMed: 17079810]
8. Shepard RN, Metzler J. Mental rotation of three-dimensional objects. *Science* 1971;171:701–703. [PubMed: 5540314]
9. Gauthier I, Hayward WG, Tarr MJ, Anderson AW, Skudlarski P, Gore JC. BOLD activity during mental rotation and viewpoint-dependent object recognition. *Neuron* 2002;34:161–171. [PubMed: 11931750]
10. Podzebenko K, Egan GF, Watson JD. Widespread dorsal stream activation during a parametric mental rotation task, revealed with functional magnetic resonance imaging. *Neuroimage* 2002;15:547–558. [PubMed: 11848697]
11. Vingerhoets G, de Lange FP, Vandemaele P, Deblaere K, Achten E. Motor imagery in mental rotation: an fMRI study. *Neuroimage* 2002;17:1623–1633. [PubMed: 12414300]
12. Buckner RL. Memory and executive function in aging and AD: multiple factors that cause decline and reserve factors that compensate. *Neuron* 2004;44:195–208. [PubMed: 15450170]
13. Podzebenko K, Egan GF, Watson JD. Real and imaginary rotary motion processing: functional parcellation of the human parietal lobe revealed by fMRI. *J Cogn Neurosci* 2005;17:24–36. [PubMed: 15701237]
14. Spielberger, CD.; Gorsuch, RC.; Lushene, RE. Manual for the State Trait Anxiety Inventory. Consulting Psychologists Press; Palo Alto, CA: 1970.

15. Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. *Appl Psychol Meas* 1977;1:385–401.
16. Folstein MF, Folstein SE, McHugh PR. “Mini-mental state”: a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12:189–198. [PubMed: 1202204]
17. Uttl B. North American Adult Reading Test: age norms, reliability, and validity. *J Clin Exp Neuropsychol* 2002;24:1123–1137. [PubMed: 12650237]
18. Lineweaver TT, Salmon DP, Bondi MW, Corey-Bloom J. Differential effects of Alzheimer's disease and Huntington's disease on the performance of mental rotation. *J Int Neuropsychol Soc* 2005;11:30–39. [PubMed: 15686606]
19. Bookheimer SY, Strojwas MH, Cohen MS, et al. Patterns of brain activation in people at risk for Alzheimer's disease. *N Engl J Med* 2000;343:450–456. [PubMed: 10944562]
20. Burggren AC, Small GW, Sabb FW, Bookheimer SY. Specificity of brain activation patterns in people at genetic risk for Alzheimer disease. *Am J Geriatr Psychiatry* 2002;10:44–51. [PubMed: 11790634]
21. Smith CD, Andersen AH, Kryscio RJ, et al. Women at risk for AD show increased parietal activation during a fluency task. *Neurology* 2002;58:1197–1202. [PubMed: 11971086]
22. Dickerson BC, Salat DH, Greve DN, et al. Increased hippocampal activation in mild cognitive impairment compared to normal aging and AD. *Neurology* 2005;65:404–411. [PubMed: 16087905]
23. Mondadori CR, Buchmann A, Mustovic H, et al. Enhanced brain activity may precede the diagnosis of Alzheimer's disease by 30 years. *Brain* 2006;129:2908–2922. [PubMed: 17012294]
24. Trivedi MA, Schmitz TW, Ries ML, et al. Reduced hippocampal activation during episodic encoding in middle-aged individuals at genetic risk of Alzheimer's disease: a cross-sectional study. *BMC Med* 2006;4:1. [PubMed: 16412236]
25. Grady CL, McIntosh AR, Beig S, Keightley ML, Burian H, Black SE. Evidence from functional neuroimaging of a compensatory prefrontal network in Alzheimer's disease. *J Neurosci* 2003;23:986–993. [PubMed: 12574428]
26. Dickerson BC, Salat DH, Bates JF, et al. Medial temporal lobe function and structure in mild cognitive impairment. *Ann Neurol* 2004;56:27–35. [PubMed: 15236399]
27. Ouchi Y, Yoshikawa E, Futatsubashi M, Okada H, Torizuka T, Kaneko M. Activation in the premotor cortex during mental calculation in patients with Alzheimer's disease: relevance of reduction in posterior cingulate metabolism. *Neuroimage* 2004;22:155–163. [PubMed: 15110005]
28. Xie S, Xiao JX, Gong GL, et al. Voxel-based detection of white matter abnormalities in mild Alzheimer disease. *Neurology* 2006;66:1845–1849. [PubMed: 16801648]
29. Naghavi HR, Nyberg L. Common fronto-parietal activity in attention, memory, and consciousness: shared demands on integration? *Conscious Cogn* 2005;14:390–425. [PubMed: 15950889]
30. Kosslyn SM, DiGirolamo GJ, Thompson WL, Alpert NM. Mental rotation of objects versus hands: neural mechanisms revealed by positron emission tomography. *Psychophysiology* 1998;35:151–161. [PubMed: 9529941]
31. Thomsen T, Hugdahl K, Ersland L, et al. Functional magnetic resonance imaging (fMRI) study of sex differences in a mental rotation task. *Med Sci Monit* 2000;6:1186–1196. [PubMed: 11232158]
32. Richter W, Somorjai R, Summers R, et al. Motor area activity during mental rotation studied by time-resolved single-trial fMRI. *J Cogn Neurosci* 2000;12:310–320. [PubMed: 10771414]
33. Jordan K, Wustenberg T, Heinze HJ, Peters M, Jancke L. Women and men exhibit different cortical activation patterns during mental rotation tasks. *Neuropsychologia* 2002;40:2397–2408. [PubMed: 12417468]
34. Kucian K, Loenneker T, Dietrich T, Martin E, Von Aster M. Gender differences in brain activation patterns during mental rotation and number related cognitive tasks. *Psychology Science* 2005;47:112–131.
35. Lepsien J, Griffin IC, Devlin JT, Nobre AC. Directing spatial attention in mental representations: Interactions between attentional orienting and working-memory load. *Neuroimage* 2005;26:733–743. [PubMed: 15955482]
36. Foundas AL, Leonard CM, Mahoney SM, Agee OF, Heilman KM. Atrophy of the hippocampus, parietal cortex, and insula in Alzheimer's disease: a volumetric magnetic resonance imaging study. *Neuropsychiatry Neuropsychol Behav Neurol* 1997;10:81–89. [PubMed: 9150507]

37. Rombouts SA, Barkhof F, Witter MP, Scheltens P. Unbiased whole-brain analysis of gray matter loss in Alzheimer's disease. *Neurosci Lett* 2000;285:231–233. [PubMed: 10806328]
38. Karas GB, Burton EJ, Rombouts SA, et al. A comprehensive study of gray matter loss in patients with Alzheimer's disease using optimized voxel-based morphometry. *Neuroimage* 2003;18:895–907. [PubMed: 12725765]
39. Karas GB, Scheltens P, Rombouts SA, et al. Global and local gray matter loss in mild cognitive impairment and Alzheimer's disease. *Neuroimage* 2004;23:708–716. [PubMed: 15488420]
40. Etkin A, Wager TD. Functional neuroimaging of anxiety: a meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. *Am J Psychiatry* 2007;164:1476–1488. [PubMed: 17898336]

A. Congruent - No rotation

B. Incongruent- No rotation

C. Congruent - Rotation

D. Incongruent - Rotation

Figure 1. Rotate stimuli conditions

The figure represents the task conditions and example stimuli. During the “no rotation” trials, subjects view either an identical pair of cube stimuli or a pair in which one stimulus is missing a cube. During the “rotation” trials, subjects view either a congruent pair that can be rotated to fit each other, or an incongruent pair, which when rotated look like mirror images of each other.

Figure 2. Activation differences between at-risk subjects and controls during rotation trials
 Statistical parametric maps demonstrating increased activation in at-risk subjects compared to control subjects during rotation trials. Differences are shown on SPM maximum intensity projections (top) and on several transverse slices of the MNI standard template (bottom).

Table 1

Sample characteristics

Variable	At risk (n = 18)	Controls (n = 15)	p Value
Age, y, mean $\pm$ SD	61.2 $\pm$ 7.9	62.5 $\pm$ 7.5	0.648
Sex (M:F)	8:10	6:9	0.797
Education, y, mean $\pm$ SD	15.7 $\pm$ 2.6	14.1 $\pm$ 3.1	0.119
MMSE, mean $\pm$ SD	28.4 $\pm$ 1.5	27.7 $\pm$ 2.4	0.297
Estimated IQ, mean $\pm$ SD	111.4 $\pm$ 7.7	108.1 $\pm$ 7.5	0.222
CES-D, mean $\pm$ SD	6.8 $\pm$ 6.4	6.8 $\pm$ 6.0	0.988
State Trait Anxiety Index, mean $\pm$ SD	29.8 $\pm$ 9.0	34.3 $\pm$ 9.8	0.187
APOE (no ε 4: ε 4)	14:4	15:0	0.059

MMSE = Mini-Mental State Examination; CES-D = Center for Epidemiologic Studies Depression Scale.

Table 2

Within-group increases in activation

Voxel	Max T	Talairach				Eye	Label	BA
		x	y	z				
Significant activation clusters in at risk								
207	5.67	30	10	12	R	Clastrum/putamen	—	
978	5.07	46	−58	40	R	Inferior parietal gyrus	40	
	4.69	51	−44	21	R	Superior temporal gyrus	13	
	3.92	57	−43	4	R	Middle temporal gyrus	19, 22, 37	
134	5.01	38	50	−1	R	Middle frontal gyrus	10, 11	
45	4.88	22	−16	−9	R	Parahippocampal	35	
29	4.71	−40	−80	−1	L	Inferior occipital	18, 19	
36	4.66	20	3	68	R	Superior frontal gyrus	6	
101	4.29	−22	−18	69	L	Precentral gyrus	6	
88	4.16	50	23	−5	R	Inferior frontal gyrus	47	
32	4.14	42	−30	−14	R	Fusiform gyrus	20	
20	4.11	22	−38	59	R	Postcentral gyrus	5	
34	4.05	−30	11	23	L	Inferior frontal gyrus	9	
58	3.96	38	−8	−11	R	Temporal lobe	21	
36	3.95	28	−69	−27	R	Cerebellum—pyramis	—	
34	3.75	−24	−36	13	L	Caudate tail	—	
28	3.7	55	−11	13	R	Precentral gyrus	43	
Significant activation clusters in controls								
158	4.8	32	−4	−1	R	Putamen/claustrum	—	
79	4.59	−8	0	68	L	Superior frontal gyrus	6, 8	
21	4.3	−34	−4	37	L	Precentral gyrus	6, 4	
22	4.11	48	7	21	R	Superior temporal gyrus	38	
55	3.46	−22	−29	47	L	Parietal lobe— postcentral	3	

Height threshold (p) = 0.00001, uncorrected. Cluster-wise voxel threshold $k = 20$. Coordinates in Talairach and Tournoux space (1988).

BA = Brodmann area.

Table 3
Increases in activation in the at-risk group compared to controls

Cluster size	Talairach coordinates					L/R	Anatomic label	Brodmann area
	Z	Max T	x	y	z			
21	3.94	4.60	53	27	-1	R	Inferior frontal gyrus	47
85	3.93	4.59	30	14	14	R	Insula	13
37	3.63	4.15	38	52	1	R	Middle frontal gyrus	10
	3.53	4.01	44	47	5	R	Middle frontal gyrus	10
21	3.42	3.85	28	-58	53	R	Superior parietal lobule	7
	3.38	3.79	22	-67	57	R	Superior parietal lobule	7
	3.34	3.74	24	-63	57	R	Superior parietal lobule	7

Max T results are significant at $p < 0.001$, with a cluster-wise threshold of 20 voxels.