Early detection of Alzheimer's disease: An fMRI marker for people at risk?

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A recent study suggests that functional brain imaging combined with behavioral tests can identify preclinical changes that may predict Alzheimer's disease.

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized behaviorally by gradual and eventually devastating memory loss, and cellularly by neuron loss, neuritic plaques and neurofibrillary tangles. Before AD is diagnosed, its hallmark behavioral symptom is a gradual decline in declarative memory—conscious long-term memory for everyday experiences. This memory impairment is thought to result from a slowly progressing neuropathology that occurs first in medial temporal lobe structures critical for declarative memory, and later in frontal, lateral temporal and parietal cortices[1]. Extensive neuropathological damage occurs before clinical diagnosis, so preclinical discrimination between people who will and will not ultimately develop AD is critical for treatment of the disease in its earliest stages[2]. Unfortunately, in humans, we cannot directly detect neuritic plaques and neurofibrillary tangles associated with AD *in vivo*. To gain leverage on this problem, researchers have turned to brain imaging techniques, which may identify preclinical neural changes that predict subsequent AD.

In the August issue of the *New England Journal of Medicine*, Bookheimer and colleagues[3] provide important new data suggesting that functional brain imaging, combined with behavioral measures of memory and genetic indices of increased disease risk, may be particularly sensitive to changes in neural function that presage memory decline and perhaps AD. Increased risk for late-onset AD is associated with the ε4 allele of the apolipoprotein E (APOE) gene[4]. On its own, the presence of the ε4 allele is not a diagnostic test because most AD patients do not carry this allele. Further, in cognitively intact individuals, the ε4 allele is not a strong predictor of whether a person will or will not develop AD, although APOE genotyping may eventually reveal other preclinical markers that accurately predict subsequent AD[2], either on their own or in conjunction with APOE ε4.

Bookheimer and colleagues[3] used functional magnetic resonance imaging (fMRI) of neurologically normal adults (47 to 82 years old) to determine whether neural activation elicited by declarative memory is related to APOE genotype, and whether such activation predicts later memory decline. Before fMRI scanning, behavioral assessment of 16 carriers and 14 noncarriers of the APOE ε4 allele showed that the memory abilities of both groups fell within the normal range for their ages. However, consistent with previous reports that delayed recall is sensitive to memory decline associated with the ε4 allele[5], carriers had marginally worse delayed recall than noncarriers, suggesting early memory decline. Inside the scanner, participants were asked to intentionally memorize seven unrelated word pairs during learning blocks and to generate the second member of the pair in response to the first during recall blocks. For both groups, fMRI revealed memory-related activation in frontal, temporal and parietal structures that show neuropathological changes in AD. Importantly, the magnitude and extent of this activation was greater in ε4 carriers than in noncarriers (Fig. 1) in the left hemisphere, as expected given the involvement of left prefrontal and temporal regions in declarative memory for verbal stimuli[6]. Thus, APOE genotype correlates with functional brain activation patterns in middle-aged and older adults, even when their memory abilities fall within the normal range. This outcome raises the possibility that neural activation related to declarative memory may be a predictive marker for memory decline.

To test this possibility, Bookheimer and colleagues reassessed memory in 14 of their subjects 2 years later. Critically, for one of three memory measures (the Benton Visual Retention test), decreased memory scores over the two-year period were significantly correlated with the initial extent (number of active regions) of left hemisphere fMRI activation. The fMRI marker did not correlate significantly with the other two memory measures, although these other correlations were directionally similar but modest. Thus, with increased sample size or longer follow-up time, the fMRI marker might predict a decline on these measures as well. This caveat notwithstanding, this correlation is the first evidence that changes in functional neuroanatomical activation patterns may precede memory decline.

Individuals with mild AD often demonstrate increased functional activation during cognitive task performance relative to healthy controls[7,8] (although regionally specific activation decreases also have been observed; Corkin *et al.*, *Soc. Neurosci. Abstr.* 23, 193.5, 1997). Similarly, greater memory-related activation in selected brain regions is often observed in nondemented older adults compared to younger adults[9]. Bookheimer and colleagues' findings extend this pattern to preclinical measures in individuals who are genetically at risk for AD, as well as to those who will experience greater memory decline in the next two years. In AD patients and nondemented older adults, increased functional activation is proposed to reflect recruitment of neural and cognitive operations that compensate for a decline in the neural circuitry normally used for task performance[7–9]. Bookheimer and colleagues[3] hypothesize that similar compensatory demands may accompany the asymptomatic stage in the progression toward AD. Greater cognitive and neural effort may offset early neuropathological abnormalities, thus maintaining memory abilities within the normal range. Although regional activation increases may be accompanied by activation decreases in other structures in those with mild AD[10] and in nondemented older adults[9], this pattern was not detected in ε4 carriers in the Bookheimer study. Nevertheless, the convergence of increased magnitudes of neural activation across various groups suggests that compensatory recruitment of additional processing resources may be a common solution to the problem of cognitive and neural abnormalities.

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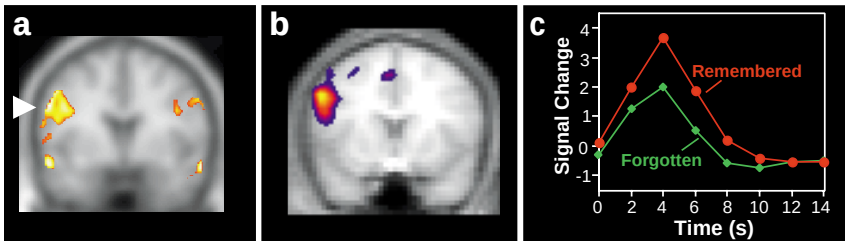

Fig. 1. Functional MRI measures of neural activation associated with verbal declarative memory. (**a**) Bookheimer *et al.* observed greater memory-related activation in multiple neural regions when comparing APOE ε4 carriers relative to noncarriers, including left prefrontal cortex (white arrow)[3]. (**b**) Previous fMRI data indicate that similar regions in left prefrontal cortex show increased activation during verbal learning in healthy, young adults[6]. (**c**) Moreover, in young adults, the magnitude of left prefrontal activation during verbal learning predicts whether the studied item will be subsequently remembered or forgotten. Although not shown, a similar pattern was observed in left medial temporal structures, with ε4 carriers demonstrating greater activation than noncarriers, and with greater activation in young adults predicting superior subsequent memory. Thanks to S. Bookheimer for providing image in (**a**).

Interpretation of the increased memory-related brain activity in ε4 carriers as a marker of neuropathology raises an intriguing paradox when considered alongside functional neuroimaging studies demonstrating that the magnitude of activation during verbal declarative memory formation predicts subsequent memory in young adults[6]. Stimulus items that elicit greater left prefrontal and medial temporal activation during learning tend to be better remembered than those that elicit less activation (Fig. 1). It is possible that a similar relationship between item-by-item measures of activation and subsequent memory also holds during aging regardless of APOE genotype. However, other between-subject data indicate that those young adults who demonstrate greater medial temporal and prefrontal activation during learning tend to show superior subsequent memory[11,12]. These observations support the conclusion that increased activation during memory formation is a marker of more effective engagement of the neural machinery that builds memories, at odds with the view that greater neural activation indicates compensation for early neuropathology. The left prefrontal and medial temporal regions showing activation differences between ε4 carriers and noncarriers appear to overlap with those that predict subsequent memory in younger adults (Fig. 1). A clue to resolving this paradox may come from determining whether between-item and between-individual differences in subsequent memory correlate with the magnitude of activation during encoding in nondemented older adults, as is seen in younger adults. If not, then perhaps the relationship between neural activation during declarative memory formation and subsequent remembering fundamentally shifts at some point during aging.

Bookheimer and colleagues' functional neuroimaging observations complement a burgeoning imaging literature on neural changes in individuals at risk for AD. Structural MRI differences in medial temporal, lateral temporal and cingulate regions are reported to discriminate, with high sensitivity (high 'true positives') and specificity (low 'false postives'), between cognitively intact adults and those with mild memory difficulties who ultimately will be diagnosed with AD three years later[13]. These structural measures also provide modest discrimination between individuals with mild memory deficits who do and do not progress to the point of clinical diagnosis at follow-up[13]. Metabolically, positron emission tomography (PET) reveals decreased resting glucose metabolism in parietal, temporal and frontal regions in middle-aged and older nondemented carriers of the ε4 allele relative to noncarriers[2]. Another PET study shows that, in ε4 carriers, initial metabolic levels in the parietal and posterior cingulate cortices predict the extent of memory decline over the next two years[14]. Bookheimer and colleagues' data demonstrate that functional neuroimaging also predicts the magnitude of memory decline two years later, at least on one memory measure. This observation suggests that this technique can identify neuropathological changes that foretell memory loss, raising the possibility that functional indices may help to discriminate between those who will and will not go on to develop AD. As with metabolic measures[2], however, assessment of the level of discrimination offered by functional measures awaits longer-term follow-up studies, as neither measure has been shown to predict ultimate AD diagnosis either clinically or at autopsy[15]. In addition, future research will determine whether changes in functional activation patterns precede, coincide with, or follow detectable metabolic and structural abnormalities, and whether the predictive value can be increased by using multiple indices.

Although central challenges remain, the results of Bookheimer and colleagues highlight the promise of brain imaging techniques, illustrating the power of integrated approaches that combine functional neuroimaging with behavioral and genetic markers. Their results suggest that fMRI is sensitive to neural changes that precede memory decline. Although this finding alone is not unequivocal evidence for a functional neuroanatomical marker predictive of memory decline, nor evidence that such a marker predicts subsequent AD onset, these data may prove to be a critical step along the road to preclinical detection of Alzheimer's disease.

1. Arriagada, P. V., Growdon, J. H., Hedley-Whyte, E. T. & Hyman, B. T. *Neurology* 42, 631–639 (1992).
2. Rapoport, S. I. *Proc. Natl. Acad. Sci. USA* 97, 5696–5698 (2000).
3. Bookheimer, S. Y. *et al. N. Engl. J. Med.* 343, 450–456 (2000).
4. Saunders, A. M. *et al. Neurology* 43, 1467–1472 (1993).
5. O'Hara, R. *et al. J. Am. Geriatr. Soc.* 46, 1493–1498 (1998).
6. Wagner, A. D. *et al. Science* 281, 1188–1191 (1998).
7. Becker, J. T. *et al. Neurology* 46, 692–700 (1996).
8. Woodard, J. L. *et al. Neuropsychology* 12, 491–504 (1998).
9. Cabeza, R. *et al. J. Neurosci.* 17, 391–400 (1997).
10. Backman, L. *et al. Neurology* 52, 1861–1870 (1999).
11. Alkire, M. T., Haier, R. J., Fallon, J. H. & Cahill, L. *Proc. Natl. Acad. Sci. USA* 95, 14506–14510 (1998).
12. Wagner, A. D., Maril, A. & Schacter, D. L. *J. Cogn. Neurosci.* (in press).
13. Killiany, R. J. *et al. Ann. Neurol.* 47, 430–439 (2000).
14. Small, G. W. *et al. Proc. Natl. Acad. Sci. USA* 97, 6037–6042 (2000).
15. Skoog, I. *N. Engl. J. Med.* 343, 502–503 (2000).