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Functional MRI in the early diagnosis of Alzheimer's disease: is it time to refocus?

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EXPERT REVIEWS

"…there is an urgent need to develop sensitive markers … to facilitate detection and/or monitoring of early brain changes suggestive of AD."

Alzheimer's disease (AD), a progressive neurodegenerative disorder associated with disruption of neuronal function and gradual deterioration in cognition, function and behavior, is the most common cause of dementia in the elderly, affecting approximately 2–4 million individuals in the USA and more than 30 million worldwide [1,2]. The progression of AD is gradual, with the average patient living 8–10 years after onset of symptoms. With the growth of the older population in developed nations, the prevalence of AD will undoubtedly rise over the next 50 years. The annual cost of the disease in the US alone, including medical, long-term and home care, as well as loss in productivity, is currently estimated at US$100 billion [3]. In addition to the substantial financial burden, the psychological and emotional burden on patients and their families is even greater. Currently, definitive diagnosis of AD requires a postmortem examination of the brain for characteristic plaques and tangles, which effectively form the 'gold standard'. In the absence of this information, clinical diagnosis of probable AD is based primarily on memory impairment early in the degenerative progression that later expands to multiple cognitive domains [1,4,5].

With the recent availability of several effective pharmaceutical agents for treatment of AD symptoms, along with several new agents undergoing clinical trials, we are entering a new age in the treatment of AD [6]. Current consensus statements have emphasized the need for early recognition; thus, there is an urgent need to develop sensitive markers that may serve as adjuncts to current clinical and neuropsychological tests to facilitate detection and/or monitoring of early brain changes suggestive of AD. Such markers may also facilitate early-intervention studies to prevent or slow disease progression [1,2]. Conventional structural neuroimaging, including MRI, has long played a supportive role in the diagnosis of memory disorders and is recommended for the routine evaluation of AD. However, functional imaging modalities that demonstrate physiologic changes in the brain, including PET and functional MRI (fMRI), also have the potential to enable identification of more subtle pathologic changes earlier during the disease course and, therefore, may have equal or greater potential in comparison with structural imaging modalities [1]. Prognostic neuroimaging studies will be beneficial in the search for markers that help to predict future status [7]. The new paradigm in diagnostic screening tools will therefore include testing for genetic, neuropsychological, imaging and vascular risk factors.

This is reflected in a proposal for new diagnostic criteria for probable AD [8], a modification that would require the core criteria of memory impairment plus one or more supportive features. These features include:

- The presence of medial temporal lobe (MTL) atrophy
- An abnormal cerebrospinal fluid biomarker
- A specific pattern on functional neuroimaging with PET showing reduced

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glucose metabolism or increased uptake of well-validated amyloid binding ligands

- Familial genetic mutations (presenilin 1 and 2, amyloid precursor protein)

Measurement of the structural integrity and rate of atrophy in the MTL and its subregions, including the hippocampus [9–11] and entorhinal cortex [12,13], has proven useful as a clinical aid. However, measurement of atrophy in the MTL is currently not standardized (and therefore is susceptible to methodological differences) and MTL atrophy is not unique to AD [14]. Thus, while MTL atrophy may be a useful supportive feature for current diagnosis, it is important to note that structural changes in AD are preceded by cellular changes, including synaptic dysfunction [1]. As such, functional neuroimaging has the potential to elucidate brain changes earlier in the degenerative progress when memory loss is nascent, yet before structural damage has occurred. This is an important consideration for MTL regions because once atrophy has been detected, patients may not be able to achieve the maximum benefit from an intervention.

> "...functional neuroimaging has the potential to elucidate brain changes earlier in the degenerative progress when memory loss is nascent, yet before structural damage has occurred."

Functional MRI research has been conducted in AD, mild cognitive impairment (MCI) or otherwise at-risk patients. Studies typically measure increased signal or 'activation' from the whole brain, but activation and/or 'deactivation' (a reduction in signal) in specific regions may have the most promise for diagnostic purposes. A substantial number of fMRI studies have focused on the MTLs due to the reasons mentioned above. Another region demonstrating early functional abnormalities is located in the posterior midline cortices of the posterior cingulate, precuneus and retrosplenial areas, collectively termed the posteromedial cortex (PMC). Initial PET studies looking at glucose metabolism have reported hypometabolic regions including frontal, temporal, parietal and posterior cingulate cortex in AD and MCI patients compared with control subjects. These regions overlap with those found to be tonically active during rest and are termed the 'default mode network' [15–17]. Of these regions, there is evidence [18–21] that strong metabolic differences occurring in the PMC may have diagnostic and predictive value in AD and MCI patients. An intriguing overlap exists between the patterns of hypometabolism observed in resting PET studies and the pattern of increased uptake of amyloid binding ligands [22], which may be worthy of consideration with respect to patient monitoring. This overlap also matches regions found using fMRI that show impaired task-related deactivation [7,23,24] and resting network differences [25,26]. The advantages of fMRI are well known and include its noninvasive nature, greater capacity for longitudinal follow-up owing to the lack of ionizing radiation, and relative ease of use and availability as a clinical technique [1]. Here we discuss the use of fMRI in the diagnosis of AD and AD risk.

MTL activation: powers, pitfalls & possibilities

A preponderance of the literature on memory and brain function focuses on the role of the MTLs. This is due, in large part, to seminal reports of memory loss after hippocampal lesions in humans [27] and animals [28]. Additional evidence from functional neuroimaging studies strongly implicates the structures of the MTL (including the hippocampus, amygdala and parahippocampal gyrus) in mnemonic processes. Neurophysiological and high resolution fMRI studies further suggest that within the MTL, subfields of the hippocampus and parahippocampal gyrus (including the cornu ammonis fields, dentate gyrus, subiculum, entorhinal and perirhinal cortices) may support dissociable aspects of memory (e.g., encoding, retrieval, recollection and familiarity). However, analysis of the function of these substructures with fMRI is limited to imaging centers with advanced technological and computational capability. For the sake of simplicity, we will presently consider the MTL as a generic memory structure.

A number of fMRI studies have linked activation in MTL regions to successful memory formation, maintenance and retrieval across a variety of tasks and stimuli [29,30]. Because memory deficits (both subjective and objective) are used in the neuropsychological assessment of AD and MCI, the MTL is a logical starting place to probe for a potential functional marker of disease. However, the aforementioned structural atrophy in the MTL with progression to AD creates a conundrum of sorts for fMRI studies: alterations in signal between groups may be a result of tissue loss rather than activation strength. Ruling out this possibility requires detailed tracing of anatomical structures within the MTL and extraction of the signal from those regions of interest. This time-consuming process may not be possible in large sample size studies or clinical trials. Finally, for those fMRI studies that do not employ anatomical tracing, there is a risk that the normalization techniques commonly used for group analyses will incorrectly classify tissue as MTL, especially the anterior regions, as the disease further progresses [31].

Nevertheless, a common finding in studies of healthy subjects compared with AD or MCI patients is decreased MTL activation in the patients [25,32–39]. The interpretation is typically that reduced activation in this region corresponds to the memory deficits exhibited by these patients. However, this interpretation is complicated by a number of studies that have found increased MTL activation in MCI patients relative to healthy subjects [37,40–43] as well as healthy older adults at genetic risk for AD versus those not at risk [44,45]. The interpretation of this increased activation, or 'hyperactivation', is that early in the progression of AD, there is a period of compensatory brain change, enabling patients to maintain function. This hyperactivation period is then followed by a decrease in activation.

An important caveat of these findings is that the cognitive range of patients and other demographic variables, as well as the specific tasks and analyses used, tend to be unique to each study. For example, family history may interact with APOE status to influence activation [45]. Additionally, measuring the extent of activation as opposed to the magnitude of activation may yield different findings. This problem is compounded by the fact that statistical thresholds in neuroimaging are not standardized and often lowered to investigate the MTL. Regardless of these pitfalls, findings of generalized decrease of MTL function with more severe disease states suggest there is value in fMRI measurements. However, evidence for early phase hyperactivation suggests that the use of MTL activation as a marker of disease progression would be problematic, due to the difficulty in distinguishing MCI patients who are in a 'declining' phase from normal patients, as both may show similar levels of activation (inverted U-shape problem).

PMC deactivation: metabolic marker, cognition coordinator

Evidence from PET studies of AD, MCI and normal older adults provides the strongest support for investigation of the PMC (comprised of the precuneus, posterior cingulate, and retrosplenial cortex and spanning Brodmann areas 7, 23, 26, 29, 30 and 31) as a functional marker of disease. The connection between the PMC, the default mode network of the brain, and AD suggests that a fundamental change may occur in patients regarding the transitions between momentary cognitive states. The default mode has been suggested to reflect intrinsic cognitive operations as well as unfocused monitoring of the external environment [46,47]. Increased glucose metabolism occurs in a network of regions consistently identified in resting PET scans [48]. Furthermore, patients in a persistent vegetative state show reduced metabolism in the PMC that returns to nearly normal after the patient recovers consciousness [49]. Finally, in a PET study measuring cerebral blood flow under increasing doses of propofol, a general anesthetic, PMC measures decreased as the anesthetic dose increased. Thus, the PMC is a key node of the default mode network with important connections to the resting physiological state of the brain and the state of consciousness.

A prominent view of the role of this network is that it facilitates the allocation of cognitive resources once a task or environmental focus is introduced by deactivating the tonically active regions. Thus, the greater the deactivation in a region such as the PMC during an active task, the greater the cognitive benefit [50,51]. Alterations in AD and MCI patients in default network regions, including the PMC have been reported using model-free fMRI analyses (independent components analysis and resting connectivity) [26,37,52–54] and by modeling task-dependent deactivation in the brain [7,23,24]. In model-free analyses, ongoing fluctuations in fMRI signal in the PMC are compared, whereas in task-dependent analyses the PMC is deactivated during the task of interest relative to baseline fixation and/or a simpler task.

The consistent observation across these studies is similar to that of the MTL findings: the more severe the disease status, the poorer the response. In our findings across a sample of controls, MCI and AD patients [24], activation level in the PMC, but not the MTL, correlated with performance on the California Verbal Learning Test (CVLT), a standardized neuropsychological memory measure [55]. In terms of PMC activation level, we found robust deactivation in controls, less robust deactivation in MCI and activation in AD patients (Figure 1). In a subsequent analysis of this data, we categorized the MCI patients as 'nonconverter' or 'converter' to AD, based on longitudinal follow-up visits. PMC activation level from the baseline fMRI scan indicated that nonconverters were more similar to controls, while converters were more similar to AD patients (Figure 1) [7]. Another study found 'hyperdeactivation' of the PMC in the mildest MCI group [37], relative to controls, conflicting with the overall linear pattern we found. Differences in data analysis and patient samples may account for this discrepancy. Celone *et al.* used a model to explicitly test for nonlinear group differences. Their overall MCI sample may be less impaired compared with our sample, as it is based on subjective rather than objective assessments of memory impairment. Indeed, the CVLT-delay scores of MCI subjects in our study were substantially worse (mean ± standard deviation = 5.2 ± 2.6) than even the more impaired MCI group (8.3 ± 4.7) in their study. However, further support for the relation between deficient PMC function and increased disease risk comes from a PET study that found hypometabolism in the PMC in cognitively normal young adult subjects at genetic risk (APOE4 homozygotes) for AD [21].

"An important caveat of these findings is that the cognitive range of patients and other demographic variables, as well as the specific tasks and analyses used, tend to be unique to each study."

Similar to the findings of PMC hypometabolism in PET, perfusion arterial spin labeling (ASL) MRI has also recently demonstrated differential hypoperfusion in MCI [56,57]. Because the output of ASL perfusion is similar to the absolute values of cerebral blood flow obtained in PET studies, this technique is also likely to provide promising biomarkers and further insight into the earliest neural changes associated with AD. Together, these findings from PET and MRI studies raise the intriguing prospect that the PMC is a zone of confluence for metabolic and functional disturbances, and pathological effects found in AD and MCI. If indeed the PMC displays consistent and reliable effects based on well-studied physiological changes, this region may ultimately prove to be the more suitable fMRI marker for diagnostic purposes.

Future perspective

The ultimate goal of using new technology for diagnosis of dementia is not to replace other techniques, but to add to the consistency and reliability of established indicators across a spectrum of tests. In the case of AD and MCI, neuropsychological and structural imaging evaluation, and occasionally PET metabolic markers (typically to rule out other dementia variants) are the most common tests employed today in screening and follow-up of patients with, or at risk for, AD. We believe that in the future, diagnostic testing and treatment monitoring will also take advantage of quantitative structural, pathologic and physiologic imaging, including PET imaging with amyloid- and tau-binding radioligands, and MRI with BOLD-fMRI, diffusion tensor imaging, and ASL-perfusion, as well as genetic markers such as presenilin, APP, APOE4 and SORL1.

Functional MRI techniques typically rely on the use of tasks and cognitive subtraction principles. Factors such as the stimuli, presentation timing and performance during these tasks can greatly influence imaging results and subsequent interpretation. Therefore, a standardized and simple task with normative data, which could be implemented at MRI facilities worldwide, would be of great service to the field, enabling multicenter studies, large clinical trials and powerful meta-analyses. In the absence of such a task, probing resting or default networks may have an immediate advantage over task-based fMRI. Patients do not need any instructions (beyond 'eyes open' or 'eyes closed'), no stimuli need to be presented and the typical duration is only 5 min (plus 5 min for a high resolution structural scan). These advantages over task-based fMRI greatly increase the likelihood of patient compliance and multicenter studies. Furthermore, examination of spontaneous activity via fluctuations in fMRI may provide more fundamental insights into intrinsically correlated brain networks and may be more tightly linked to electrophysiological measurements of coherence and neuronal synchrony [58,59].

A practical implementation we envision is a task and/or resting fMRI exam which would yield a 'score' for the PMC and other brain regions. The patient's score can then be referenced to a normative range (spanning from healthy older adults

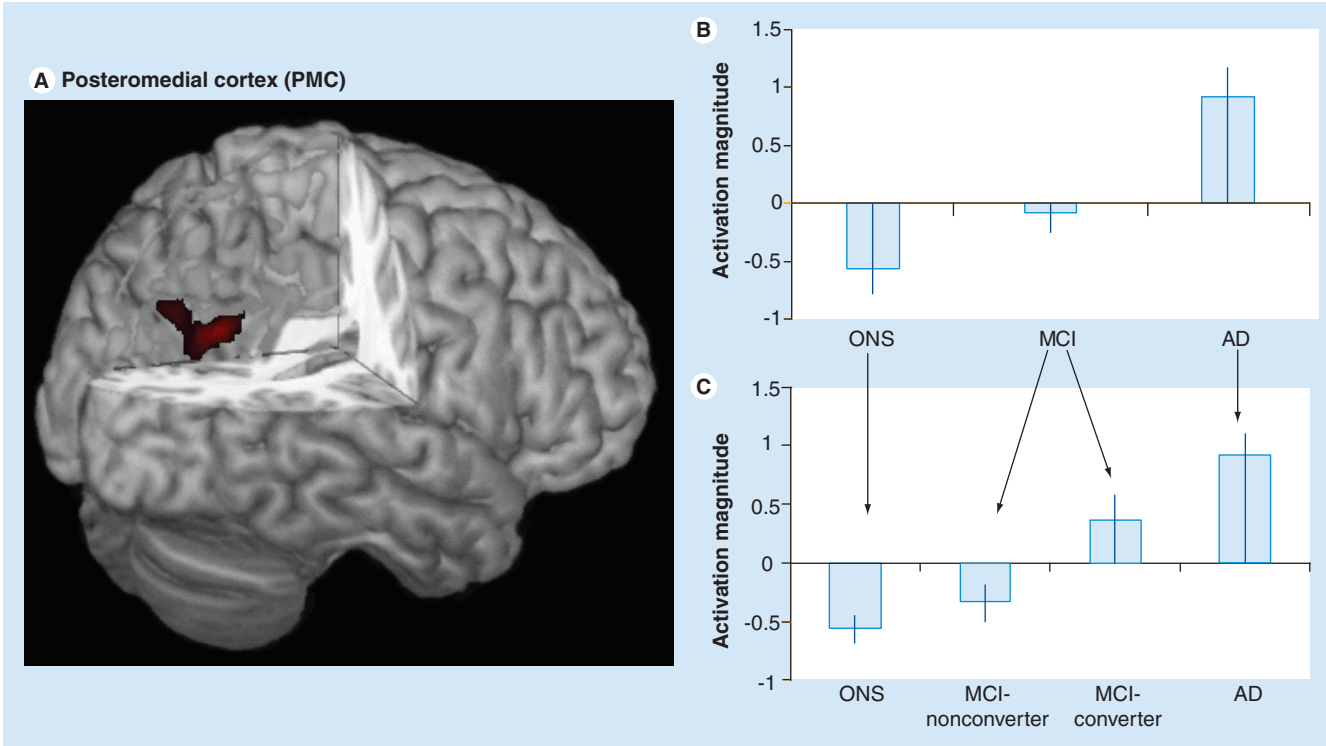

Figure 1. (A) The functional region of interest in the posteromedial cortex (PMC) used in our studies is shown in red and overlaid on a 3D canonical T1-weighted brain template image with posterior cortex cutout. **(B)** Activation magnitude parameter estimate (with standard error bars) in the PMC region **(A)**. In this region, parameter estimates for activation magnitude demonstrated a lesser-to-greater activation from control (ONS), to MCI to AD subjects. **(C)** Activation magnitude parameter estimate (with standard error bars) in the PMC region **(A)**, demonstrating a continuum from control (ONS), to MCI-nonconverter, to MCI-converter to AD. There were statistically significant ($p < 0.05$) differences between all groups with the exception of the control and MCI-nonconverter group, and the AD and MCI-converter group. An overall pattern of negative activation magnitude in the control and MCI-nonconverter groups and positive activation magnitude in the AD and MCI-converter groups is evident. AD: Alzheimer's disease; MCI: Mild cognitive impairment; ONS: Older normal subject.

through to fully progressed AD), placing them along a continuum, similar to other medical assessments (e.g., growth charts used for infants and blood chemistry ranges). This score, in addition to structural, genetic and neuropsychological information, will be used to more accurately formulate a personal risk profile to assess diagnostic status, treatment potential and need for patient monitoring (Figure 2 illustrates a schematic of the role of functional imaging). Currently, secondary prevention in conversion from MCI to AD is a more realistic target, as primary prevention in cognitively normal at-risk patients is more problematic owing to potential hyperactivation in patients with genetic AD risk and the mildest MCI. Longitudinal studies will help to isolate the specific patterns associated with increased risk.

Although we have highlighted the investigation of specific brain regions, it is most likely that investigation of complete brain networks will most thoroughly explain changes associated with AD. The strength of connectivity between the PMC and the MTL may prove to be another useful metric [52,53] for clinical purposes. As we have previously hypothesized [7,24], underlying changes in behavior may be a result of functional and/or structural disconnection of PMC/MTL circuitry. It is possible that disruption of MTL regions results in both the metabolic and functional differences observed in the PMC. Assessing the disruption of such a functional circuit, with the fullest array of tools possible, will yield remarkable new insights into AD. As we stand at the threshold of a new era of functional circuit imaging in AD, we predict significant contributions will be made to both diagnosis and treatment of this debilitating disease.

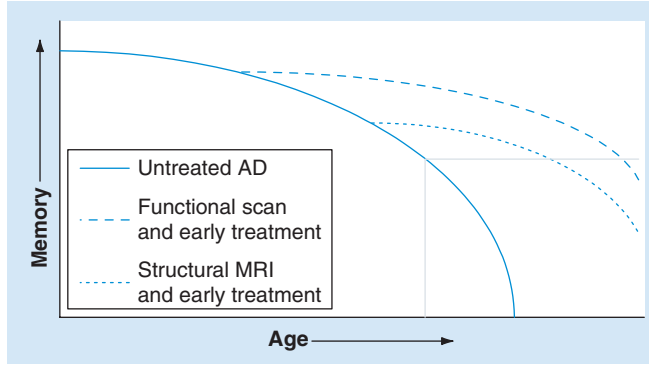

Figure 2. Graph showing the potential role of functional and structural imaging in AD diagnosis and treatment. The unbroken line represents the untreated natural progression, the dashed line represents earlier treatment based on structural MRI and the dotted line represents earlier treatment based on functional MRI. The gray box in the bottom right corner represents the onset of AD.
Modified with permission from one provided by Dr Gary Small.
AD: Alzheimer's disease.

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