

Activation and baseline changes in functional MRI studies of Alzheimer disease

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Functional MRI (fMRI) with blood oxygenation level dependent (BOLD) contrast¹ has made mapping the regions involved in particular tasks accessible to a large community of neuroscientists. BOLD fMRI can only map differences between brain states, however, so a reference condition, typically resting, is required. Prescribed drugs can alter the resting baseline as can neuronal dysfunction and vascular aging. Since BOLD contrast is closely and nonlinearly related to baseline oxygen extraction, altered baseline state can affect the amplitude of fMRI signals observed during a task.² A minor nuisance in some studies, differences in baseline state can affect the significance and interpretation of activation studies of neurologic disorders.

Early diagnosis of Alzheimer disease (AD) is critical for the better understanding of AD pathophysiology, for testing of prevention and treatment strategies, and ultimately for clinical management. Since early AD first manifests through subtle deficits in cognitive function, fMRI during cognitive tasks may be useful as a challenge test for AD. fMRI studies in patients with AD have generally shown decreased activation during memory tasks, consistent with poor memory function.³ However, in otherwise normal elderly subjects at genetic risk for AD, activation is greater than in controls.⁴ In mild cognitive impairment (MCI), the results are more variable, perhaps suggesting a transition between elevated activity in presymptomatic AD to reduced activity in clinical AD.³

Part of the change in BOLD fMRI during the course of AD may be related to changes in the resting state. Decreased glucose utilization and blood flow have been widely demonstrated in AD, especially in parietal, temporal, and frontal association cortex. Elevated oxygen extraction has also been shown.⁵ This elevated oxygen extraction could lead to increased signal on BOLD

fMRI, for a fixed neuronal and even flow response. Further complicating the picture is the possibility of an altered resting state in AD. Recent work has suggested a default resting state involving the hippocampus, the posterior cingulate, and lateral parietal cortex that is deactivated during most conscious tasks.⁶ This default resting network deactivation appears attenuated in AD, complicating the measurement of reduced functional activity in these regions.

In this issue, Xu et al.⁷ employed an alternative fMRI technique capable of measuring both resting and activated flow to help clarify the relative role of resting state and activation in MCI. This fMRI technique measures blood flow by comparing two images where the signal of inflowing blood is modulated with applied magnetic fields. Because blood water signal is “labeled” in the inflowing arteries, this technique is often referred to as arterial spin labeling (ASL) MRI.⁸ A relatively straightforward theory permits quantification of blood flow in MRI independent physiologic units. The ability to acquire a quantitative baseline measure of flow noninvasively with MRI in just a few minutes may fundamentally alter the information obtained in a routine clinical scan and expand the application of functional imaging assessment to clinical neurology. The technique has a number of other advantages including its noninvasive nature, the lack of exposure to radiation, and the ability to acquire structural images in the same session, allowing for atrophy correction. While the latest ASL techniques are not fully available on commercial scanners, this limitation will likely be addressed within the next 2 years.

In addition to providing a baseline measure of blood flow, the ASL technique has superior sensitivity for slow changes in activity than BOLD,⁹ it can be performed in inferior frontal and temporal regions where magnetic fields are distorted by nearby air-tissue and bone tissue interfaces, and it

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has better intrinsic spatial resolution because of reduced venous contamination. Preliminary indications are that intersubject variance is lower in ASL than in BOLD fMRI. Combination of ASL and BOLD fMRI has been used to quantify changes in oxygen utilization accompanying activation.

Xu et al. applied ASL fMRI to measurement of flow at rest and during a memory task. Their results highlight the complex interaction between baseline and activation changes in MCI. Decreased resting blood flow was demonstrated in parietal and posterior cingulate cortex, consistent with other baseline studies.¹⁰ However, a more significant difference was observed during the memory task in these regions. Additionally, the fractional increase in flow in the right parahippocampus caused by the memory task in normal subjects was not detectable in the subjects with MCI. Overall, all differences between groups during the memory task were greater than at rest, supporting the use of challenge paradigms in studies of AD. The ability to detect parahippocampal differences only after normalizing to baseline flow also illustrates the benefit of measuring both baseline and resting flow.

Additional work will be required to address imperfections of the study design. Most importantly, this study did not differentiate between subjects with MCI who converted to an AD diagnosis and those who did not. Up to 50% of patients with MCI do not convert,¹¹ so the specificity of the findings to AD is uncertain. Longitudinal studies are challenging but critical in the determination of tests that accurately predict progression to dementia. Much could be learned about the nature and evolution of functional changes in AD by the sequential study of resting and activated function in an MCI population over sufficient years to observe conversion to AD in many of the subjects. The combination of ASL

fMRI and volumetric MRI acquired within the same session will allow for both functional and structural measurements of brain pathology. The findings of Xu et al. strongly suggest that this pathway will be fruitful.

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