

The potential of functional MRI as a biomarker in early Alzheimer's disease

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Abstract

Functional magnetic resonance imaging (fMRI) is a relative newcomer in the field of biomarkers for Alzheimer's disease (AD). fMRI has several potential advantages, particularly for clinical trials, as it is a noninvasive imaging technique that does not require the injection of contrast agent or radiation exposure and thus can be repeated many times during a longitudinal study. fMRI has relatively high spatial and reasonable temporal resolution, and can be acquired in the same session as structural magnetic resonance imaging. Perhaps most importantly, fMRI may provide useful information about the functional integrity of brain networks supporting memory and other cognitive domains, including the neural correlates of specific behavioral events, such as successful versus failed memory formation.

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1. Functional MRI as a biomarker in early Alzheimer's disease

Functional magnetic resonance imaging (fMRI) is a relative newcomer in the field of biomarkers for Alzheimer's disease (AD). fMRI has several potential advantages, particularly for clinical trials, as it is a noninvasive imaging technique that does not require the injection of contrast agent or radiation exposure and thus can be repeated many times during a longitudinal study (Atri et al., 2011). fMRI has relatively high spatial and reasonable temporal resolution, and can be acquired in the same session as structural magnetic resonance imaging (MRI). Perhaps most importantly, fMRI may provide useful information about the functional integrity of brain networks supporting memory and other cognitive domains, including the neural correlates of specific behavioral events, such as successful versus failed memory formation (Brewer et al., 1998; Miller et al., 2008a; Sperling et al., 2003b; Wagner et al., 1998). However, there are very limited published data on

fMRI test-retest or cross-scanner platform reproducibility, or correlation with longitudinal clinical outcome, and the majority of fMRI studies performed to date have enrolled small, highly selected cohorts within single academic centers.

2. BOLD fMRI techniques

Blood oxygen level dependent (BOLD) fMRI is an indirect measure of neuronal activity, thought to reflect the integrated synaptic activity of neurons via magnetic resonance (MR) signal changes due to changes in blood flow, blood volume, and the blood oxyhemoglobin/deoxyhemoglobin ratio, inferred from measuring changes in BOLD MR signal (Kwong et al., 1992; Logothetis et al., 2001; Ogawa et al., 1990). Task fMRI studies typically compare MR signal during 1 condition with MR signal during a control task or baseline condition, either in blocks of stimuli (e.g., novel vs. familiar stimuli) or in event-related designs (e.g., stimuli that were correctly remembered compared with those that were forgotten). In addition to functional activation studies, there has been considerable interest in the intrinsic connectivity of brain networks during the resting state using BOLD fMRI techniques, often referred to as

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functional connectivity or fc-MRI. These techniques examine the correlation between the intrinsic oscillations or time course of BOLD signal between brain regions, and have revealed a number of brain networks that demonstrate coherence in the spontaneous activity of distributed nodes (Vincent et al., 2006).

3. fMRI studies in AD dementia

The majority of fMRI studies in AD dementia utilized episodic memory tasks to focus on the pattern of fMRI activation in hippocampus and related structures in the medial temporal lobe (MTL). These studies consistently report decreased hippocampal or parahippocampal activity during the encoding of new information (Golby et al., 2005; Grön et al., 2002; Hämäläinen et al., 2007; Kato et al., 2001; Machulda et al., 2003; Rémy et al., 2004; Rombouts et al., 2000; Small et al., 1999; Sperling et al., 2003a). AD-related alterations in the pattern of fMRI activation in neocortex have also been reported. A recent quantitative meta-analysis of both fMRI and fluorodeoxyglucose (FDG)-positron emission tomography (PET) memory activation studies of AD identified several regions as being more likely to show greater encoding-related activation in healthy older individuals than in persons with Alzheimer dementia (Schwindt and Black, 2009). These regions include the hippocampal formation, ventrolateral prefrontal cortex, precuneus, cingulate gyrus, and lingual gyrus. Interestingly, evidence of increased neural activity, particularly in prefrontal regions, has been observed in persons with AD dementia during task performance (Celone et al., 2006; Grady et al., 2003; Sperling et al., 2003a; Wierenga et al., 2011).

4. fMRI studies in “at-risk” subjects

Task fMRI studies in individuals at risk for AD dementia, including subjects with mild cognitive impairment (MCI) and genetic-at-risk have yielded much less consistent findings. Several studies have reported decreased MTL activation in individuals with MCI compared with healthy persons (Johnson et al., 2006; Machulda et al., 2003; Petrella et al., 2006; Small et al., 1999). A number of studies in symptomatic individuals at risk for AD dementia have also reported decreased MTL activity (Borghesani et al., 2008; Lind et al., 2006a, 2006b; Mondadori et al., 2007; Smith et al., 1999; Trivedi et al., 2006), but other studies report increased MTL activity in both individuals with MCI (Celone et al., 2006; Dickerson et al., 2004, 2005; Hämäläinen et al., 2007; Heun et al., 2007; Kircher et al., 2007) and in asymptomatic persons with genetic or family history risk factors (Bondi et al., 2005; Bookheimer et al., 2000; Filipini et al., 2009; Fleisher et al., 2005; Han et al., 2007; Quiroz et al., 2010; Seidenberg et al., 2009; Smith et al., 2002; Wishart et al., 2004). A common feature of the studies reporting increased fMRI activity is that these studies primarily included subjects who were still able to perform the

fMRI tasks reasonably well. In particular, some event-related fMRI studies found that the hyperactivity was observed specifically during successful memory trials, providing support for the early hypothesis that the increased activity may serve as a compensatory mechanism in the setting of early Alzheimer pathology (Dickerson and Sperling, 2008; Sperling et al., 2009). However, more recent work also suggests that the hyperactivity may be a harbinger of impending hippocampal failure and rapid clinical decline (Sperling et al., 2010). Cross-sectional studies suggest that the hyperactivity may be present only at early stages of MCI followed by a loss of activation as cognitive impairment worsens which is similar to the pattern seen in individuals with Alzheimer dementia (Celone et al., 2006). Longitudinal clinical follow-up studies suggest that hyperactivity at baseline is a predictor of both rapid cognitive decline (Bookheimer et al., 2000; Dickerson et al., 2004; Miller et al., 2008b) and loss of hippocampal function (O'Brien et al., 2010).

The mechanistic underpinnings of MTL hyperactivation remain unclear. Potential mechanisms that may contribute to this phenomenon include cholinergic or other neurotransmitter upregulation (DeKosky et al., 2002); aberrant sprouting of cholinergic fibers (Hashimoto et al., 2003), inefficiency in synaptic transmission (Stern et al., 2004), increased calcium influx or excitotoxicity (Busche et al., 2008; Palop et al., 2007), or alterations in glutamatergic receptor (Rammes et al., 2011). Further research to determine the specificity of hyperactivation to stage of disease and task performance, the relationship to baseline perfusion and metabolism, and the association with imaging markers of molecular pathology, including amyloid deposition and neurotransmitter systems, is clearly needed to elucidate this phenomenon.

5. Functional alterations in large scale networks

Both lesion studies and functional imaging evidence suggests that memory function is subserved by a network of brain regions that involves the hippocampal memory system and a set of cortical regions, including the precuneus, posterior cingulate, lateral parietal, lateral temporal, and medial prefrontal regions. Collectively known as the “default network,” these regions typically decrease activity during memory encoding and other cognitively demanding tasks focused on processing of external stimuli (Buckner et al., 2008; Raichle et al., 2001). These default network regions that typically demonstrate beneficial deactivations during encoding actually activate during successful memory retrieval (Daselaar et al., 2006; Vannini et al., 2011). Interestingly, a consistent failure to modulate default network activity during encoding has been reported in both AD dementia and in individuals at risk for AD (Celone et al., 2006; Fleisher et al., 2009; Lustig et al., 2003; Petrella et al., 2007; Pihlajamäki et al., 2008; Pihlajamäki et al., 2010).

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