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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 non-invasive 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 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.

Keywords

Alzheimer's disease; biomarker; cognitive impairment; dementia; fMRI; functional magnetic resonance imaging

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 non-invasive 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 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

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The author has no actual or potential conflicts of interest related to this article.

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of fMRI studies performed to date have enrolled small, highly selected cohorts within single academic centers.

BOLD fMRI is an indirect measure of neuronal activity, thought to reflect the integrated synaptic activity of neurons via MR signal changes due to changes in blood flow, blood volume, and the blood oxyhemoglobin/deoxyhemoglobin ratio, inferred from measuring changes in blood oxygen level dependent (BOLD) MR signal (Kwong, et al., 1992, Logothetis, et al., 2001, Ogawa, et al., 1990). Task fMRI studies typically compare MR signal during one condition to MR signal during a control task or baseline condition, either in blocks of stimuli (e.g. novel versus familiar stimuli) or in event-related designs (e.g. stimuli that were correctly remembered compared to 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 functional connectivity or fc-MRI. These techniques examine the correlation between the intrinsic oscillations or timecourse 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).

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, Gron, et al., 2002, Hamalainen, et al., 2007, Kato, et al., 2001, Machulda, et al., 2003, Remy, 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 FDG-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).

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 medial temporal lobe (MTL) activation in individuals with MCI compared to 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., 2007, Lind, et al., 2006a, Lind, et al., 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., 2005, Dickerson, et al., 2004, Hamalainen, 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, Filippini, 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.

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., 2010). 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, Pihlajamaki, et al., 2008, Pihlajamaki, et al., 2009).

BOLD fMRI techniques can also be used to investigate spontaneous brain activity and the inter-regional correlations in neural activity during the resting state, clearly documenting that the brain is organized into multiple large-scale brain networks; which persist during sleep and anesthesia (Damoiseaux, et al., 2006, Vincent, et al., 2007). These networks support specific sensory and motor systems, as well as specific cognitive processes (Vincent, et al., 2006). Of particular interest in AD, is the intrinsic connectivity of the default network. Both “seed-based” connectivity and independent component analytic (ICA) techniques have demonstrated robust intrinsic connectivity between cortical nodes of the default network, with somewhat less consistent results in connectivity with the hippocampus. Multiple groups have reported impaired intrinsic functional connectivity in the default network during the resting state in individuals with MCI and AD dementia (Bai, et al., 2008, Greicius, et al., 2004, Rombouts, et al., 2005, Rombouts, et al., 2009, Sorg, et al., 2007) that is greater than the general age-related disruption of large-scale networks (Andrews-Hanna, et al., 2007, Damoiseaux, et al., 2008). A recent study that applied connectivity measures to task fMRI data found that disrupted default network connectivity in MCI subjects was predictive of “conversion” to AD dementia over several years (Petrella, et al., 2011). Another recently developed analytic technique that probes whole brain functional connectivity or “cortical hubs” may also prove useful in AD. Recent studies suggest that the topography of cortical hubs in young subjects overlaps the anatomy of amyloid- β deposition detected on PET amyloid imaging (Buckner, et al., 2009), and that

whole brain connectivity is disrupted in amnesic MCI patients (Bai, et al., 2011, Drzezga, et al., 2011).

The default network regions that demonstrate aberrant task-related fMRI activity and dysconnectivity in MCI and AD dementia correspond to regions with high amyloid burden in AD patients (Buckner, et al., 2009, Buckner, et al., 2005, Klunk, et al., 2004). Recent studies demonstrate evidence of disrupted default network activity during memory tasks (Sperling, et al., 2009) and at rest in cognitively normal older individuals with evidence of amyloid deposition on PET imaging (Hedden, et al., 2009, Sheline, et al., 2009, Sperling, et al., 2009, Drzezga, et al., 2011) suggesting a combination of molecular and functional imaging techniques markers may be particularly useful to track response to trials of anti-amyloid or therapies in preclinical stages of AD (Sperling, et al., 2011).

fMRI, either during cognitive paradigms or during resting state, may hold the greatest potential in the rapid evaluation of novel pharmacological strategies to treat AD. Several studies in healthy young and older subjects suggest that fMRI can detect acute pharmacological effects on memory networks (Kukolja, et al., 2009, Sperling, et al., 2002, Thiel, et al., 2001). To date, only a few small fMRI studies have demonstrated enhanced brain activation after acute or prolonged treatment with cholinesterase inhibitors in MCI and AD, although these studies were not conducted as typical double-blind, placebo-controlled trials (Bokde, et al., 2009, Goekoop, et al., 2004, Rombouts, et al., 2002, Saykin, et al., 2004, Shanks, et al., 2007, Venneri, et al., 2009). There are a number of challenges in performing longitudinal task fMRI studies in patients with AD because as dementia severity increases, individuals are less likely to be able to perform cognitive tasks or to avoid head motion while in the scanner. As mentioned above, resting fc-MRI studies may be more much more feasible in longer term studies in symptomatic stages of AD, although unfortunately, all fMRI techniques are very sensitive to head motion. fMRI has recently been incorporated into a small number of investigator-initiated add-on studies to ongoing Phase II and Phase III trials, which should provide information regarding the potential utility of these techniques in clinical trials.

Additional validation studies of fMRI in at-risk and AD dementia patients are critically needed. The short term reproducibility of BOLD signal changes within young healthy individuals during memory encoding tasks and resting fc-MRI is only moderately high (Meindl, et al., Sperling, et al., 2002, Zuo, et al., 2010) and very few reproducibility studies in older and cognitively impaired subjects have been published to date (Clement and Belleville, 2009, Putcha, et al., 2011). Resting functional connectivity MRI techniques may be particularly advantageous for use in multi-center AD clinical trials and natural history studies, as no special equipment is required, individuals do not have to be able to perform a cognitive task, and a single 6 minute run added to the end of a safety or volumetric MRI protocol may provide reproducible patterns of fMRI connectivity over time and across scanner platforms (Van Dijk and Sperling, 2011). One study suggested that resting connectivity fMRI techniques may even demonstrate a larger “effect size” than task fMRI in at-risk populations (Fleisher, et al., 2009). Longitudinal functional imaging studies are needed to track the evolution of alterations in the fMRI activation pattern over the course of the cognitive continuum from healthy aging to preclinical AD, MCI and ultimately, AD dementia. It is also important to evaluate the contribution of structural atrophy to changes observed with functional imaging techniques in neurodegenerative diseases. Ideally, studies employing combinations of imaging modalities, such as structural MRI, fMRI, FDG-PET and PET amyloid imaging techniques, will serve to further our understanding the interrelationships of these markers and their relative value in tracking change along the clinical continuum of AD (Jack, et al., 2010). Such data may come in part from the Dominantly Inherited Alzheimer Network (DIAN) study of autosomal dominant AD that

incorporates fc-MRI into its standard acquisition and from the continuation of the Alzheimer's Disease Neuroimaging Initiative (ADNI-2) that includes fc-MRI on a limited number of scanners, and in other at-risk cohorts around the world.

In summary, although both task and resting fMRI have been valuable in elucidating the neural basis of AD-related memory dysfunction, additional work to validate fMRI as a potential biomarker for use in clinical trials is critically needed. It is likely that task fMRI may have the greatest utility in early "Proof of Concept" studies, to detect an efficacy signal over a relatively short time frame. Recent work using fc-MRI during the resting state, which does not require special equipment or ability to perform a task, suggests that these techniques may be particularly amenable to use in multi-center clinical trials. As the field moves towards diagnosis and intervention at earlier stages of the AD process, even prior to clinically evident symptoms, the combination of amyloid biomarkers and fMRI may prove increasingly useful to detect evidence of early AD-related brain dysfunction and to monitor response to pharmacological treatment.

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