Chapter 19

Functional MRI in Alzheimer's Disease

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1. Introduction

Alzheimer's disease (AD) is the most common form of dementia affecting millions of people worldwide. AD results in progressive brain atrophy, memory loss and widespread neurologic deterioration. The first AD-related neuropathological changes appear in the medial temporal lobe (MTL) memory structures already years prior to the manifestation of clinical dementia. Atrophy of the MTL structures as revealed by structural magnetic resonance imaging (MRI) is nowadays considered to be a valid diagnostic marker at the mild cognitive impairment stage, although structural imaging findings may be somewhat nonspecific. "Mild cognitive impairment" (MCI) is in fact one of the recent concepts to describe the possible prodromal state of AD, that is a stage between healthy aging and full-blown clinical AD, for example in terms of neuropathological, imaging and cognitive changes.

Despite extensive research, the fundamental neural basis of memory impairment characteristic to early AD is still largely unknown. Particularly, the relationship between β-amyloid (Aβ) pathology and alterations in memory function remains to be fully elucidated. During recent years, clinical functional MRI (fMRI) has provided tools to investigate the neural underpinnings of AD-related cognitive alterations and thus novel insights into the pathognomonic changes in the MTL structures and related whole-brain memory networks. The ultimate clinical goal of fMRI research is to develop means to reliably define alterations in brain function related to the earliest symptoms of AD before development of significant irreversible structural damage. Since the MTL memory structures are known to be the site of early neuropathological alterations (e.g., neurofibrillary tangles) in AD, previous fMRI studies have largely focused on investigating this particular region of the brain. FMRI during tasks probing episodic memory encoding, which is the cognitive function most characteristically impaired in early AD, is of particular interest.

In this chapter, we will summarize previous studies demonstrating changes in task-related fMRI activity, primarily focusing on memory tasks, as well as studies investigating resting state fMRI findings in clinical AD patients compared to healthy elderly individuals. In a nutshell, fMRI studies in AD patients have demonstrated hypoactivation of the MTL structures during memory task performance, whereas studies in elderly individuals with MCI have reported both increased and decreased MTL responses depending on the severity of the cognitive impairment and underlying structural atrophy. Additionally, recent fMRI findings in MCI and AD patients are beginning to reveal functional abnormalities between the MTL and posteromedial regions such as posterior cingulate and precuneal cortices. In addition to MCI and clinical AD, we will also review recent advances in our understanding of the neuroimaging correlates of cognitively intact elderly subjects at increased risk to develop AD in terms of carrying the apolipoprotein E ε4 (*APOE* ε4) allele.

The long asymptomatic or minimally symptomatic phase of AD provides a potential period for early therapeutic interventions to slow down – and perhaps ultimately prevent – the progression to clinical dementia. Large-scale worldwide multimodal imaging studies on reliable predictors of AD are on-going. There is great hope that imaging of the MTL memory structures and related whole-brain networks would facilitate early diagnosis of AD and other dementias as well as improve treatment options of these devastating diseases in the near future.

2. Alzheimer's disease

AD was originally described in 1907 by the German physician Alois Alzheimer (Alzheimer, 1907; Maurer et al., 1997). Today it is the most common form of dementia in the elderly (Bookmayer et al., 1998). AD is a progressive neurodegenerative syndrome which typically begins with insidious impairment of episodic memory (*i.e.*, memory for past personal experiences in a particular spatial and temporal context).

The most common form of AD is often termed sporadic or late-onset AD as opposed to the relatively rare early-onset forms of the disease (Tanzi & Bertram, 2001). For late-onset AD, the main known genetic risk factor is the *APOE* ε4 allele in chromosome 19 (Bertram et al., 2007; Saunders et al., 1993). Neuropathologically, the disease is characterized by the accumulation of extracellular deposits of Aβ plaques, intracellular neurofibrillary tangles (NFTs) consisting of hyperphosphorylated tau protein, and brain atrophy with regional synaptic, neuronal, and axonal loss (Braak & Braak, 1991). Interestingly, as opposed to the NFT pathology, at the early stages of the disease, Aβ accumulation is often modest within the MTL memory structures but more pronounced, for example, in the posteromedial cortices of the brain. Presentation and clinical course of the AD syndrome can, however, be very variable. Accordingly, AD can be heterogeneous in terms of genetic background (Bertram et al., 2007), response to treatment (Kaduszkiewicz et al., 2005) as well as neuropathological and neuroradiological patterns (Henry-Feugeas, 2007; Jagust et al., 2008**;** Jellinger, 2002).

The diagnosis of AD relies on clinical judgement. Perhaps the most widely used criteria for defining AD were developed by the National Institute of Neurological and Communicative Disorders and Stroke / Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA; McKhann et al., 1984). A recent proposal for new research criteria for AD suggests that various biomarkers could be used as supportive features in the diagnostics to improve the specific identification of AD as early as possible (Dubois et al., 2007; Dubois et al., 2010). According to this suggestion, the diagnosis of AD requires meeting the core criterion of significant episodic memory impairment together with at least one or more of the supportive biomarker criteria. Hippocampal atrophy as revealed by structural MRI is one of the most widely documented supportive biomarkers of AD, in addition to abnormal cerebrospinal fluid (CSF) Aβ and tau findings, and a specific pattern of temporoparietal hypometabolism as indicated by [^{18}F]fluorodeoxyglucose positron emission tomography (FDG-PET). Currently, a diagnosis of *definite* AD can, however, only be done by *post mortem* neuropathological evaluation.

The concept of MCI (mild cognitive impairment) refers to subjects with cognitive impairment beyond that expected for their age and education but who are not demented (Petersen et al., 1999; Petersen et al., 2001; Petersen et al., 2004; Petersen et al., 2009; Winblad et al., 2004). During recent years, MCI has had a number of definitions. Diagnostic criteria for the amnestic subtype of MCI widely used during recent years are as follows: 1) memory complaint, preferably corroborated by an informant; 2) objective memory impairment; 3) normal general cognitive function; 4) intact activities of daily living; and 5) not demented (Petersen et al., 2001). Persons who present with amnestic MCI have an increased risk of developing clinical AD with an annual conversion rate of 12 – 15 %, in contrast to 1 – 2 % risk of conversion in healthy elderly individuals (Petersen et al., 1999). Not all subjects with MCI progress to dementia / AD, but a high number of MCI subjects remain stable or may even revert back to normal during follow-up (Ganguli et al., 2004; Gauthier et al., 2006; Larrieu et al., 2002; Petersen, 2004). As noted above, however, a lively discussion on revisions of the MCI / AD diagnostic criteria is on-going among researchers and clinicians.

3. Methodological basis for fMRI in AD

During the past fifteen years, fMRI – together with complementary imaging modalities and sophisticated data analysis methods – has proved to be a very useful tool in investigating the neural basis of intact human memory and other higher cognitive functions. Activation of the hippocampal and parahippocampal regions of the MTL during successful memory encoding has been demonstrated in several fMRI studies in healthy young subjects (Brewer et al., 1998; Pihlajamäki et al., 2003; Sperling et al., 2003b; Stern et al., 1996; Wagner et al., 1998;). These human fMRI findings strongly support the notion that the MTL structures are critical for encoding new events into long-term memory (Eichenbaum, 2000; Mesulam, 1998; Squire & Zola-Morgan, 1991).

Clinical fMRI research into the pathophysiology of age-associated neurodegenerative diseases has become established more recently. Neuroimaging tools such as fMRI provide *in*

vivo methods to investigate the integrity of the resting human brain as well as mapping neural networks supporting higher cognitive functions (*e.g.*, memory). fMRI is non-invasive, radiation-free and offers a combination of good spatial and reasonable temporal resolution. Nowadays, the most widely used fMRI technique to measure hemodynamic changes related to underlying cellular activity is based on imaging of the endogenous blood-oxygen-level-dependent (BOLD) contrast (Kwong et al., 1992; Ogawa et al., 1992). In a nutshell, the relative decrease in the amount of deoxygenated hemoglobin enhances the MRI signal locally in brain areas activated during a particular cognitive task. In addition to observed increases in BOLD signal in "activated" brain areas, it has recently been shown that negative BOLD responses are also related to underlying neural activity and originate in decreases in neuronal activity below spontaneous activity in "deactivated" brain regions (Logothetis et al., 2001; Shmuel et al., 2006).

Typically, fMRI experiments compare the BOLD signal during one cognitive condition (*e.g.*, encoding novel pictures) to a control task (*e.g.*, viewing familiar pictures) or to a passive baseline condition (*e.g.*, visual fixation on a cross-hair). This can be done in a "block design" paradigm, in which stimuli of each cognitive condition are grouped together in blocks lasting 20–40 s, or in "event-related" paradigms, in which single stimuli from several different conditions are interspersed.

In addition to functional activation studies, there has recently been considerable interest in studying the baseline activity, or the "default mode" activity, of the resting human brain using FDG-PET and various fMRI techniques (Buckner et al., 2005; Gusnard & Raichle, 2001). It is very interesting that the same brain areas which show high default mode activity and predilection for task-induced fMRI deactivation responses have also demonstrated the earliest hypometabolic changes in AD in previous FDG-PET studies as well as early accumulation of Aβ pathology in recent molecular PET studies using a tracer called [11C]Pittsburgh Combound B, or PIB (Buckner et al., 2005; Cavanna & Trimble, 2006; Klunk et al., 2004; Minoshima et al., 1997; Nestor et al., 2003).

Taken together, fMRI based on BOLD contrast offers a unique, safe and widely available technique for the study of intact human cognition as well as alterations in neuronal function related to healthy aging and dysfunction related to neurodegenerative diseases such as AD.

4. FMRI activation studies

4.1. FMRI activation studies in AD and MCI patients

The hallmark of early AD is the inability to form new enduring episodic memories. At the same time, mild AD patients typically present with neuropathological changes such as synaptic alterations, selective neuronal loss and neurofibrillary tangles in the MTL structures (Braak & Braak 1991; Gomez-Isla et al., 1997; Hyman et al., 1984; Kordower et al., 2001; Scheff et al., 2006; Scheff et al., 2007). In addition to the critical role of the MTL, successful memory formation is thought to require a carefully synchronized interplay between the

MTL and large-scale neural networks (Buckner et al., 2005; Eichenbaum, 2000; Lavenex & Amaral, 2000; Mesulam, 1998; Squire & Zola-Morgan, 1991; Suzuki, 2007; Tulving & Markowitsch, 1998).

Given the prominence of MTL pathology and structural atrophy in early AD, the pioneering fMRI studies on AD focused on investigating alterations in hippocampal activation during various episodic memory tasks (Kato et al., 2001; Machulda et al., 2003; Rombouts et al., 2000; Small et al., 1999; Sperling et al., 2003a). To date, there are several fMRI studies, which have consistently reported diminished or absent MTL activation in AD compared to healthy elderly controls (Fig. 1), during encoding numerous different types of novel stimuli such as faces, face-name pairs, line-drawings, scenes, and geometric shapes (Dickerson et al., 2005; Golby et al., 2005; Grön & Riepe, 2004; Hämäläinen et al., 2007; Kato et al., 2001; Machulda et al., 2003; Pariente et al., 2005; Remy et al., 2005; Rombouts et al., 2000; Small et al., 1999; Sperling et al., 2003a).

Subjects with amnestic MCI (Petersen et al., 2001; Petersen et al., 2009) are an important group to investigate, as they are at increased risk for developing dementia, AD in particular. Consonant with the notion of clinical heterogeneity, results of fMRI studies in MCI subjects relative to controls and AD patients have been variable, findings of hippocampal activation ranging from hyperactivation during encoding (Dickerson et al., 2004; Dickerson et al., 2005; Hämäläinen et al., 2007; Kircher et al., 2007; Woodard et al., 2009**;** Yassa et al., 2010) to hypoactivation both during encoding and retrieval tasks (Johnson et al., 2006a; Machulda et al., 2003; Mandzia et al., 2009; Petrella et al., 2006). In addition to the heterogeneity of the MCI population, some of the diversity of fMRI results in MCI subjects may be explained by differences in subject selection criteria and the level of clinical severity and underlying MTL atrophy, fMRI paradigms and their difficulty as well as functional imaging and data analysis methods. The mechanistic underpinnings of the observed MTL hyperactivation still remain unclear. In addition to pathological changes in cellular, synaptic or neurotransmitter activity, for example, multiple non-neural factors (such as resting hypoperfusion and metabolism) may also confound the interpretation of BOLD fMRI results in MCI and AD. Typically MCI subjects with significantly impaired memory have, however, similar to AD patients, shown decreased hippocampal activity compared with controls (Machulda et al., 2003; Petrella et al., 2006).

Interestingly, there is also evidence of increased MTL activity in AD patients during specific contrasts, primarily involving the brain response to repetitive stimuli. Golby et al. (2005) reported impaired fMRI repetition suppression paralleled by more MTL activation in AD patients than in older controls during processing of repeated scenes. Another recent study provided evidence that the normal suppression of MTL activity to repeated face-name pairs as compared to visual fixation is impaired in AD (Pihlajamäki et al., 2008). Similar findings have been reported in individuals with amnestic MCI (Johnson et al., 2004). Failure of the hippocampus and surrounding MTL cortices to discriminate familiar from novel information at encoding has also been related to both poor associative recognition memory and poor performance in neuropsychological tests of episodic memory across a range of age and cognitive impairment (Pihlajamäki et al., 2011).

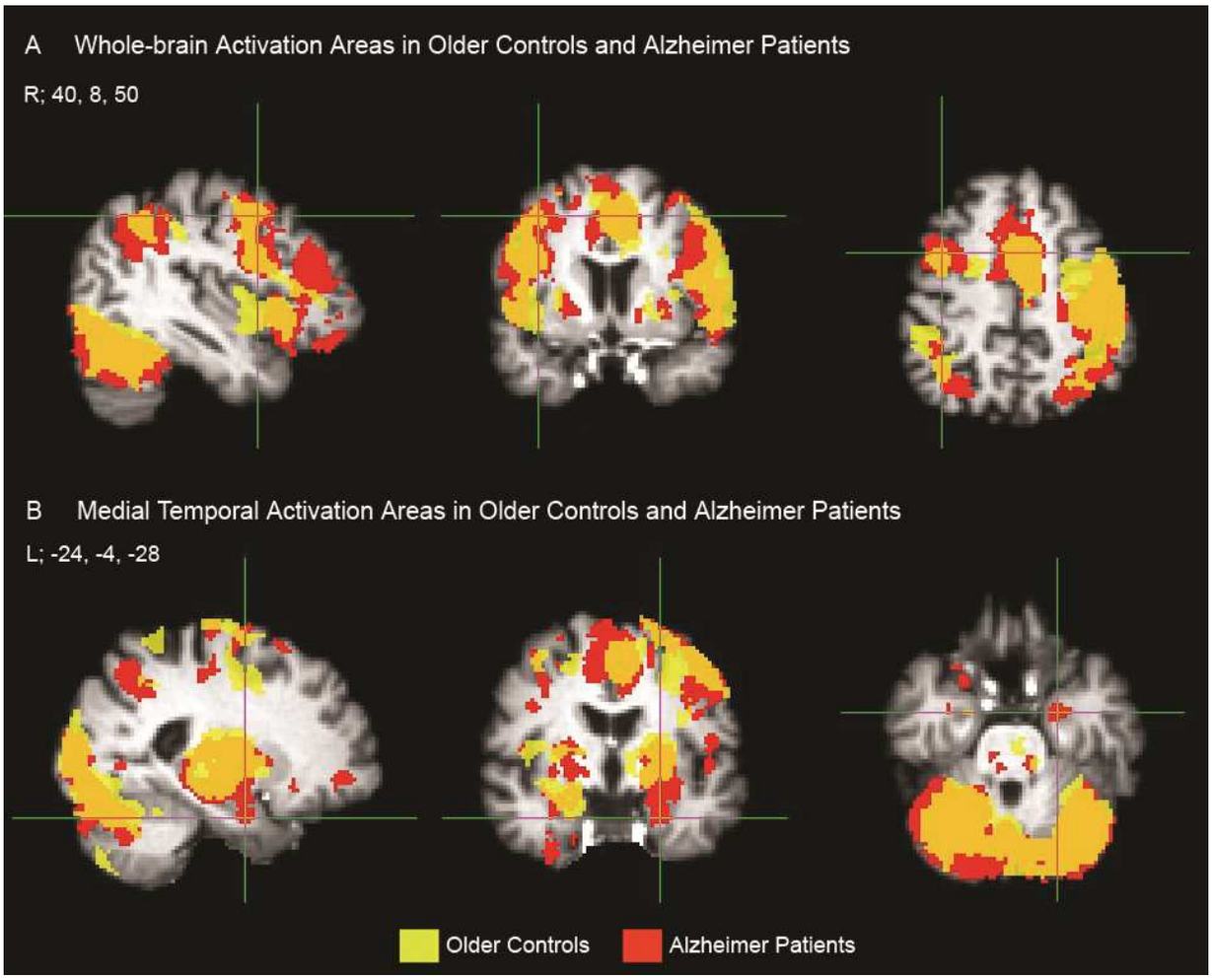

Figure 1. Increased fMRI activity in neocortical (A) and medial temporal (B) brain areas during processing of repeated face-name stimuli in patients with Alzheimer's disease (in red) relative to healthy older control subjects (in yellow). A: Crosshair is located in the right (R) prefrontal cortex, MNI coordinate: 40, 8, 50; B: Crosshair is located in the left (L) anterior hippocampus, MNI coordinate: -24, -4, -28.

As mentioned above, not only the hippocampus but also whole-brain neural networks interconnected with the MTL, are critical for higher cognitive functions such as episodic memory formation (Buckner et al., 2005; Eichenbaum, 2000; Mesulam, 1998). It can be hypothesized that – as opposed to focal changes in the MTL only – multiple nodes within these networks and their mutual interconnectivity are affected at the earliest stage of AD (Scheff et al., 2006; Selkoe, 2002). A recent meta-analysis (Schwindt & Black, 2009) of both fMRI and FDG-PET memory activation studies of AD identified several cortical regions as being more likely to show greater encoding-related activation in controls than in AD patients, including the ventrolateral prefrontal, precuneal, cingulate and lingual cortices. On the other hand, in addition to consistent findings of decreased MTL activation during novel encoding memory tasks, several groups have found evidence of increased fMRI or PET activation in neocortical brain regions, such as frontal and parietal cortices in mild AD patients compared to controls (Grady et al., 2003; Sperling et al., 2003a; Pariente et al., 2005; Celone et al., 2006). This may represent a compensatory process in the setting of MTL dysfunction.

In summary, previous fMRI studies in AD patients, compared to healthy elderly individuals, have reported decreased MTL activity during processing of novel versus repeated information (Dickerson et al., 2005; Golby et al., 2005; Rombouts et al., 2000; Sperling et al., 2003b). These findings of decreased hippocampal activity when comparing novel to repeated stimuli in AD or MCI patients are, in fact, likely to be explained at least to some degree by failure of hippocampal repetition suppression to repeatedly presented stimuli as reviewed above (Golby et al., 2005; Johnson et al., 2004; Pihlajamäki et al., 2008; Pihlajamäki et al., 2011). There is also converging evidence that AD patients show increases in brain activity to compensate for cognitive difficulties in brain regions such as frontal areas that are pathologically less affected than the MTL at the early stages of the disease (Braak & Braak, 1991; Johnson & Albert, 2000; Lehtovirta et al., 1996). Future studies combining multiple imaging modalities such as various structural and functional MRI techniques and PIB-PET imaging (Klunk et al., 2004) are likely to expand our knowledge of the relationships between cognitive impairment, neuropathological changes and alterations in functional imaging patterns.

4.2. FMRI activation studies in *APOE* ε4 carriers

Several experiments in cognitively intact elderly control subjects have demonstrated that elderly individuals are able to activate their hippocampus during successful associative encoding largely to the same degree as young subjects (Miller et al., 2008a; Rand-Giovannetti et al., 2006; Sperling et al., 2003a; Sperling et al., 2003b), although age-related alterations in fMRI activity during normal aging have also been reported (Cabeza et al., 2004; Daselaar et al., 2006a, Daselaar et al., 2006b**;** Dennis et al., 2007). It has been suggested that age-related changes in memory performance may primarily be due to alterations in cortical regions or in the connectivity between the MTL and neocortical regions.

Similarly to MCI subjects, results of fMRI studies comparing activation in *APOE* ε4 carriers at risk for AD versus their non-carrier counterparts have been diverse. Increased hippocampal and cortical activation has been reported during tasks such as encoding novel and repeated pictures or face-name pairs, encoding and retrieval of word-pairs, a letter fluency task, and an auditory verbal *n*-back working memory task, and has usually been interpreted to reflect compensatory neural mechanisms (Bondi et al., 2005; Bookheimer et al., 2000**;** Burggren et al., 2002; Dickerson et al., 2005; Fleisher et al., 2005; Han et al., 2007; Pihlajamäki & Sperling, 2009; Smith et al., 2002; Wishart et al., 2006). At the same time, several studies have demonstrated reduced functional brain activity in the MTL and other brain areas in cognitively normal ε4 carriers (Borghesani et al., 2007; Lind et al., 2006; Smith et al., 1999; Trivedi et al., 2006). Several of the above mentioned studies have carefully matched the study groups regarding age, gender and cognitive performance. It is difficult to draw firm conclusions of the ε4 effects on BOLD fMRI activation pattern. In the most recent large-scale fMRI studies, more complex patterns of alterations in brain activation differentially affected by *APOE* ε4 and family history of AD have been suggested (Bassett et al., 2006; Johnson et al., 2006). Longitudinal fMRI testing of subjects at genetic risk for AD would likely be informative, optimally in combination with metabolic FDG- and molecular PIB-PET imaging to

improve our understanding of the temporal sequence of events early in the course of prodromal AD.

4.3. FMRI in prediction of cognitive decline

Since some of the MCI subjects will remain stable and some will progress to dementia over time, great interest has been focused on attempts to identify the features predicting future conversion from MCI to clinical AD. As reviewed above, previous cross-sectional fMRI studies in subjects with MCI / prodromal AD have reported variable results, ranging from MTL hypoactivation to hyperactivation compared to cognitively normal elderly individuals. It has been hypothesized that subjects in early phases of prodromal AD may present a short period of paradoxical hippocampal hyperactivation, which is then followed by loss of hippocampal activation along with progressive cognitive decline. FMRI studies with clinical follow-up data on MCI subjects have reported that increased MTL activity at baseline in MCI compared to elderly control subjects may indicate higher likelihood of subsequent cognitive decline (Dickerson et al., 2004; Miller et al., 2008b). Similar findings of a temporary period with abnormally enhanced MTL activity during a preclinical stage of AD have been reported in *APOE* ε4 carriers relative to non-carriers (Bookheimer et al., 2000).

Recently, one longitudinal fMRI study (O'Brien et al., 2010) demonstrated both the highest hippocampal activation at baseline and the greatest loss of hippocampal activation during follow-up in cognitively impaired subjects with the most rapid decline during the follow-up period. The authors concluded that cognitive decline is associated with loss of hippocampal activation and suggested that fMRI may prove valuable in tracking very early progression of brain dysfunction on the trajectory towards clinical AD but prior to the point of irreversible neuronal loss and significant macroscopic atrophy. Thus, it seems that there may be a temporary phase of abnormal MTL hyperactivity along the course of MCI to clinical AD, which may in turn be an indicator of compensatory neural mechanisms recruited in MCI subjects in order to keep memory performance close to the level of cognitively normal elderly subjects. Around the conversion from MCI to clinical AD, the ability to compensate for the MTL pathology is lost, which is then seen as poor task performance and disrupted hippocampal fMRI activity. In other words, hippocampal hyperactivity observed in some previous fMRI studies during the progression of MCI to clinical AD may be a compensatory phenomenon, but it may also be a harbinger of impending hippocampal failure.

5. FMRI resting state studies in AD, MCI and *APOE* ε4 carriers

In addition to task-related fMRI activation studies primarily focusing on the MTL function, recent functional imaging studies have demonstrated AD-related alterations in the so called brain "default mode", or resting state activity. The default mode of the human brain was originally identified by its consistent activity increases during passive task states as compared to a wide range of goal-directed activation tasks (Buckner et al., 2008; Gusnard & Raichle, 2001; Mazoyer et al., 2001; Raichle et al., 2001; Shulman et al., 1997). Regions of the

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default network show high resting glucose metabolism and blood flow relative to other brain regions as well as coordinated low frequency fluctuations in states of relative rest (Buckner et al., 2008; Minoshima et al., 1997; Raichle et al., 2001; Shulman et al., 1997). Anatomically, the key default mode regions consist of the posteromedial and lateral parietal regions as well as midline and lateral frontal regions. Interestingly, the same default mode regions which are upregulated at rest appear to be suppressed during various cognitive activities, including intentional encoding of new memories (Pihlajamäki et al., 2008; Rombouts et al., 2005a; Shulman et al., 1997). Deactivation of key nodes of the default mode network, in coordination with hippocampal activation, seems in fact to be a prerequisite for successful memory encoding (Daselaar et al., 2004; Miller et al., 2008a; Weissman et al., 2006).

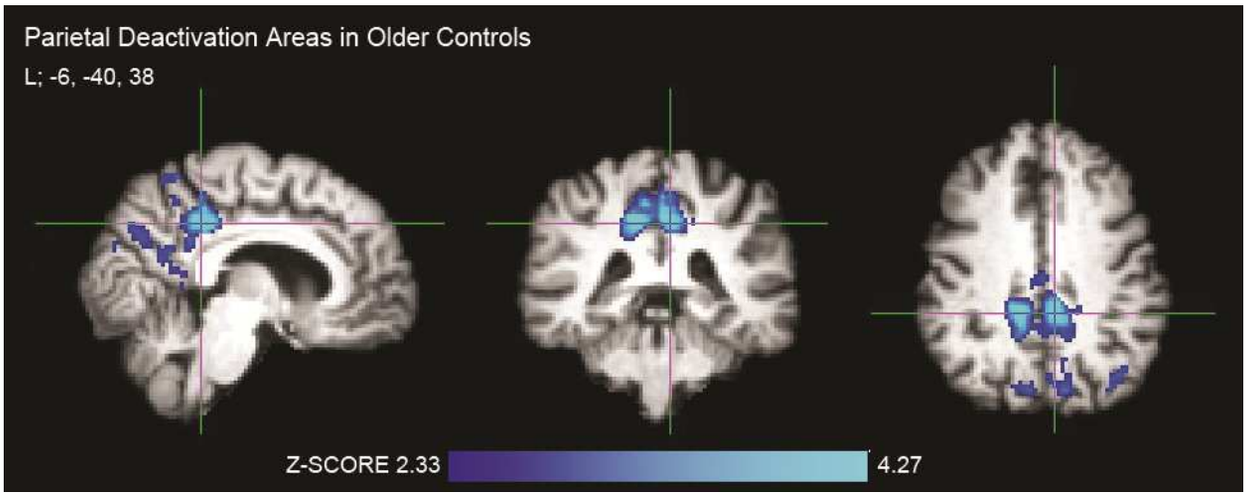

Figure 2. FMRI deactivation areas during processing of repeated face-name stimuli in healthy older subjects (in blue). Crosshair is located in the left (L) posterior cingulated cortex, MNI coordinate: -6, -40. 38.

Previous FDG-PET studies in clinical AD patients and older individuals at risk for AD have revealed hypometabolism of the posteromedial and other association cortical regions (Herholz et al. 2002; Minoshima et al. 1997; Mosconi et al. 2008b; Rapoport 1991; Reiman et al., 1996). In recent fMRI studies of AD, corresponding brain default mode regions have been found to demonstrate an abnormal fMRI task-induced deactivation pattern (Greicius et al., 2004; Lustig et al., 2003; Petrella et al., 2007a; Petrella et al., 2007b; Pihlajamäki et al., 2008; Rombouts et al., 2005a; Rombouts et al., 2005b). Predilection of the posteromedial core regions of the default network to demonstrate task-induced deactivation (*i.e.*, relative decreases in the BOLD fMRI signal) during paradigms requiring attention to external stimuli has been consistently demonstrated in both young and old healthy subjects (Fig. 2) using a multitude of cognitive stimuli and both fMRI and PET imaging modalities (Buckner et al., 2005, 2008; Cavanna & Trimble, 2006; Daselaar et al., 2004; Fransson & Marrelec, 2008; Gusnard et al., 2001; Mazoyer et al., 2001; Miller et al., 2008a; Otten & Rugg, 2001; Raichle et al., 2001; Shulman et al., 1997). In other words, the relative decreases in fMRI signal normally observed in the default mode regions in healthy subjects performing a cognitive task are not

seen in AD patients, or may even be reversed to a paradoxical activation response (Grady et al., 2006; Lustig et al., 2003; Miller et al., 2008a; Otten & Rugg, 2001).

Recent fMRI studies have also revealed alterations in the deactivation pattern in elderly individuals at risk for AD by virtue of their *APOE* e4 genotype or evidence of MCI. The pattern of fMRI task-induced deactivation seems to be progressively disrupted along the continuum from normal aging to MCI and to clinical AD and more impaired in ε4 carriers than in non-carriers (Persson et al., 2008; Pihlajamäki et al., 2009). It is likely that the pathologically affected MCI or AD brain (Selkoe, 2002; Tanzi, 2005) is no longer capable of "turning off" the default mode activity during focused cognitive processing as it should in order to optimally recruit other networks – such as the hippocampal memory network or the frontoparietal attentional network – for task performance (Eichenbaum, 2000; Mesulam, 1998; Miller et al., 2008a; Weissman et al., 2006). This finding is consonant with recent studies in healthy young and elderly adults demonstrating that the ability to suspend default mode activity during goal-directed cognitive tasks, *i.e.* to reallocate neurocognitive resources to those brain regions optimal for the task performance, may be critical for successful cognitive performance (Daselaar et al., 2004; Grady et al., 2006; Miller et al., 2008a; Otten & Rugg, 2001; Weissman et al., 2006). Posteromedial cortical regions of the default mode network not only overlap topographically with the pattern of FDG-PET hypometabolism but also with the distribution of the fibrillar Aβ deposition in AD (Buckner et al., 2005). Recent PIB-PET studies, the tracer PIB labeling Aβ plaques (Edison et al., 2007; Klunk et al., 2004), have suggested that the posteromedial cortical areas of high default mode activity may in fact be among the earliest sites of Aβ pathology in AD (Mintun et al., 2006). Thus, functional (as well as structural) imaging studies focusing on this region are pathobiologically very relevant when searching for potential early markers of prodromal AD.

In MCI and AD patients, alterations observed in the fMRI deactivation pattern of the posteromedial cortices (Greicius et al., 2004; Lustig et al., 2003; Petrella et al., 2007a; Petrella et al., 2007b; Pihlajamäki et al., 2008; Rombouts et al., 2005a; Rombouts et al., 2005b) may also reflect remote effects of the MTL pathology and atrophy. The MTL, which is thought to be responsible for the episodic memory deficits observed in amnestic MCI and AD and is known to present the earliest neurofibrillary changes and neuronal and synapse loss, is strongly interconnected to the posteromedial nodes of the default network (Braak & Braak, 1991; Gomez-Isla et al., 1997; Hyman et al., 1984; Insausti et al., 1987; Kordower et al., 2001; Leichnetz, 2001; Suzuki & Amaral, 1994). It is also possible that local structural atrophy of the underlying posteromedial brain regions may explain some of the findings of altered fMRI deactivation (Greicius et al., 2004; Lustig et al., 2003; Petrella et al., 2007a; Petrella et al., 2007b; Pihlajamäki et al., 2008; Rombouts et al., 2005a; Rombouts et al., 2005b).

A more recent imaging approach, that is the functional connectivity MRI (fcMRI), identifies brain systems via intrinsic functional (activity) correlations (Damoiseaux et al., 2006; Fox & Raichle, 2007; Greicius et al., 2003; Greicius & Menon, 2004). Recent fcMRI studies in healthy young subjects have demonstrated the consistency of the resting state networks in the human brain and have also corroborated the findings of altered task-induced deactivation in MCI and AD relative to controls (Celone et al., 2006; Sorg et al., 2007; Supekar et al., 2008;

Wang et al., 2007; Zhou et al., 2008). As an example, functional connectivity between the posteromedial and MTL cortices has been reported to be impaired even in MCI subjects relative to healthy elderly controls (Sorg et al., 2007; Zhou et al., 2008). Resting state fcMRI between the MTL and posteromedial cortices has also been demonstrated to reflect underlying structural connectivity as revealed by diffusion tensor imaging. Future studies investigating the relations between, for example, the fMRI task-induced activation / deactivation, resting fcMRI and PIB-PET amyloid imaging findings will further expand our understanding of the role of the Aβ pathology and impaired default mode network function in the pathogenesis and cognitive symptomatology of AD.

6. Conclusions and future directions of fMRI in AD

There have been a number of promising clinically relevant imaging studies targeting brain functional alterations in AD, MCI and subjects at-risk for AD relative to normal aging. Functional imaging during memory paradigms has shown evidence of specific alterations in the MTL and related whole-brain memory networks that may be able to differentiate the process of very early AD from normal aging. The greatest potential of functional imaging most likely lies in the study of very early stages of dementias, at the point of emerging neuronal dysfunction without significant macroscopic brain atrophy. In the context of early diagnostics of AD, the most interesting and challenging target group to be investigated continues to be the elderly subjects with subtle memory impairment as these subjects would still have preserved brain function and thus scope for therapeutic interventions. Recent revisions of the criteria for AD and MCI strongly emphasize the use of imaging biomarkers in future clinical diagnostics of these disorders. Structural MRI evaluation of the hippocampus is already widely used as a supportive biomarker for AD diagnosis.

The past two decades have seen remarkable advances in our understanding of the pathophysiology of neurodegenerative dementias. As reviewed above, fMRI has many potential advantages in studying patients with cognitive impairment. FMRI can be acquired on a standard clinical magnet during the same session as structural imaging. Because it is non-invasive and subjects are not exposed to radiation, fMRI can be safely repeated many times over the course of longitudinal studies. Perhaps the greatest potential advantage of fMRI is that we can image patients with memory disorders while they are attempting to do the type of cognitive process that is causing them difficulty in their daily living. The use of event-related designs enables investigation of the hemodynamic correlates of specific behavioral events, such as successful long-term memory formation.

There are, however, several challenges in performing fMRI studies in patients with neurodegenerative dementias. It is likely that fMRI will remain quite problematic in examining patients with more severe cognitive impairment. High-field fMRI with optimized imaging parameters can offer spatial resolution as high as in the order of 1 mm, or even less. This is, however, currently not realistic with demented patients as the technique is sensitive to head motion. Inherently, the signal-to-noise ratio of BOLD signal changes between activation and

baseline conditions is low, which necessitates repeated measurements and thus leads to relatively long scanning sessions. There is a need for continued technical advances, such as real-time motion correction and high-speed acquisition, to fully realize the potential of this technology in dementia research. Also, if the patients are not able to adequately perform the cognitive task, one of the major advantages of fMRI activation studies is lost. Differences in task performance between patient and control groups complicate data interpretation, as the ability to perform the task may greatly influence the pattern and degree of observed fMRI activity. Resting state fMRI can, however, be performed with less co-operative subjects and is thus better applicable to imaging more severely impaired patients.

It is important to remember that BOLD fMRI is an indirect measure of neuronal activity. The BOLD fMRI signal, and neurovascular coupling linking cellular activity to hemodynamic changes, is likely to undergo changes during healthy aging and during AD-related pathological processes. Some of the changes that may occur even in healthy elderly subjects include, for example, increased atherosclerosis. In AD, the presence of Aβ in the cerebral vasculature, together with altered neurotransmitter activity, impairs synaptic, neuronal and glial function, and may thus lead to attenuated BOLD response. Both increased and decreased BOLD fMRI responses have, however, been reported in MCI and AD and MCI compared to elderly controls, which does not support the view of attenuation of the BOLD signal solely due to vascular reasons (Golby et al., 2005; Grady et al., 2003; Sperling et al., 2003a). The alterations in BOLD activity reported in AD also appear to be quite regionally specific and dependent on the nature of the cognitive task, thus making it relatively unlikely that the changes observed in fMRI studies represent global pathophysiological alterations in neurovascular coupling.

In terms of using fMRI in longitudinal or pharmacological studies, it is critical to complete further validation experiments. The reproducibility of BOLD signal changes within young healthy individuals during memory encoding tasks across separate days is reported to be reasonable (Sperling et al., 2002; Harrington et al., 2006). However, reproducibility of task-related or resting state fMRI activity in older and cognitively impaired subjects has not yet been well established. More longitudinal functional imaging studies are needed to track the evolution of alterations in the fMRI activation / deactivation pattern over the course of the cognitive continuum from healthy aging to AD. It is also important to evaluate the contribution of structural atrophy to changes observed with functional imaging. A combination of structural MRI, fMRI and other functional and molecular imaging techniques such as PIB-PET may eventually serve as a valuable method for the *in vivo* detection of AD prior to clinical dementia, at the point when disease modifying therapies would likely be most efficacious.

In summary, despite technical challenges, there have been a number of promising fMRI studies in elderly individuals with prodromal AD. Neuroimaging, and in particular BOLD fMRI has produced invaluable information and will likely enable even deeper understanding of the human brain function both in health and disease in the future. Carefully designed future studies using multimodal imaging are hoped to yield us new tools that aid in the early identification of subjects likely to develop dementia. Further longitudinal studies are

needed to track the evolution of brain functional alterations over the course of the cognitive continuum from healthy aging to clinical dementias such as AD, and perhaps also the pharmacological efficacy for novel disease-modifying therapies.

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