

Functional Brain Imaging in Dementia: CCCD 2012

Introduction:

Functional brain imaging involves the use of different imaging modalities that provide “on-line” information about the brain activity during the performance of task or at rest. There are several available imaging modalities such as quantitative electro-encephalogram (QEEG), which detects electrophysiological changes, Positron Emission Tomography (PET), which detects glucose and water metabolism and functional Magnetic Resonance Image (fMRI), which detects hemodynamic changes during activities and at rest. In this paper we will summarize the evidence for using fMRI in subjects with pre-clinical and clinical dementia.

Functional MRI technique identifies brain activation/deactivation based on imaging of the endogenous blood-oxygen-level-dependent (BOLD) contrast signal. The BOLD signal is the product of the integrated synaptic activity of neurons via MRI signal changes due to hemodynamic changes, mainly change in oxyhemoglobin/deoxyhemoglobin ratio.

There are mainly two types of studies using fMRI in pre-clinical and clinical dementia:

- 1- Functional activation studies: Increased BOLD signal is usually interpreted as “activation” of the underlying brain areas during a task and negative BOLD response as “deactivation”, which is thought to represent decreases in neuronal activity below baseline levels of activity. Typically, fMRI experiments compare the MRI signal during one cognitive condition to a control condition like viewing familiar objects or to a passive baseline condition like visual fixation. (1-2-)
- 2- Functional connectivity studies (fc-MRI). These techniques examine the correlation between the intrinsic oscillations or time courses of different brain regions (3-).

Brain networks involved in memory function

There is a wide range of cognitive and behavioral domains that can be investigated using fMRI. Memory function remains the most commonly investigated domain because of its early and consistent involvement in Alzheimer’s disease. There is strong evidence to suggest that memory function is subserved by a distributed network of brain regions this includes:

- 1- Medial temporal lobe (MTL) including the hippocampus and adjacent structures, which are central to encoding novel information into a cohesive episodic memory (4-5-6-) and,
- 2- A distributed network of cortical regions functionally connected to the hippocampus. These are referred to as the “default network”, in particular, posterior-medial regions extending from posterior cingulate to precuneus and lateral parietal regions (7-8-9-).

Successful memory formation seems to require coordinated and reciprocal activity between activation in the hippocampal nodes of the MTL system and deactivation in the retrosplenial–parietal nodes (10-). Memory retrieval tasks tend to show task-induced activation in retrosplenial–parietal nodes (11-). Task-

induced activation has also been reported in the posterior cingulate during autobiographical memory retrieval (12-) and metamemory processes, involving the subjective evaluation of memory performance, such as confidence judgments regarding recognition memory (13-).

The areas described above are selectively vulnerable to early AD pathology, with tangle pathology and cell loss predominately in the MTL, and amyloid deposition in parietal regions (14-15-).

Functional MRI studies in clinical and preclinical Alzheimer's disease (AD):

Because of the central role of memory formation in AD most fMRI studies have examined brain activity accompanying an episodic memory task such as: memory encoding and retrieval and self-awareness of memory process. There is emerging interest in fMRI signal in the extended memory networks during memory tasks and in the "resting state" as well. Bellow we summarize fMRI studies in AD, MCI and those asymptomatic people at genetic risk for AD.

1- Medial Temporal Lobe (MTL) fMRI activation during memory encoding tasks:

Because of the central role of MTL structures in memory encoding, these structures have been the focus of majority of fMRI memory encoding activation studies. In patients diagnoses with AD, there is consistent evidence of decreased activation in MTL regions including hippocampus and parahippocampus (16-17-18-19-20-21-22-) and impaired normal suppression of MTL activity to repeated face-name stimuli (22-24-). The findings are more variable in patients at risk for AD designated with Mild Cognitive Impairment (MCI). In these patients there has been studies reporting lesser degree of MTL activation (15-18-24-), others reporting increased activation (26-27-28-29-) and yet others reporting no difference in activation pattern compared to controls (30-). Performance on the memory task seems to affect MTL activation with higher activation when MCI patients were able to perform well on the memory task possibly suggesting increased effort (31-). Johnson et al. 2004 (32-) demonstrated lack of the normal decrease in hippocampal activation with face repetition in MCI patients compared to controls. Two functional MRI studies to date have found that Posterior Cingulate Cortex activity during episodic retrieval is attenuated in MCI patients compared to controls (33-34-) However, another study of episodic retrieval found decreased activity in bilateral frontal regions and left hippocampus instead (35-). Some studies have suggested that a baseline relative hyperactivation of hippocampus and MTL structures on fMRI during memory tasks correlate with the risk of further cognitive decline in MCI patients. (36-37-). It also appears that alterations in hippocampal activation and parietal deactivation over the course of MCI and AD are strongly correlated (38-).

In asymptomatic genetically at risk for AD group, Bookheimer et al (39-) reported that, despite equivalent performance on a verbal paired-associate task, cognitively intact ApoE ϵ 4 carriers showed significantly greater activation, particularly prominent in bilateral MTL regions, compared to non-carriers. Results from subsequent studies stratified by ApoE genotype have been somewhat mixed, with nearly equal number of studies reporting greater activation in ApoE ϵ 4 carriers (40-41-41-43-44-) and decreased activation in ApoE ϵ 4 carriers (45-

46-47-48-49-), compared to non-carriers.

2- Default network activation/deactivation during memory encoding tasks:

“default network” demonstrates markedly abnormal responses during memory tasks in clinical AD patients and in subjects at risk for AD (50-38-51-52-). Although some studies suggested possible compensatory increased in neural activity, particularly in prefrontal regions during memory encoding tasks (53-54-) there is evidence to suggest that regions involved in the so-called “cognitive control network” (dorsolateral prefrontal, posterolateral parietal, anterior cingulate, frontoinsula) are less engaged in AD compared to controls, indicating the contribution of dysfunction in other cortical networks to impaired memory function in AD (55-). In a group ranging from cognitively intact to patients with AD divided to APOE 4 carriers and non-carriers, Pihlajamaki et al 2009 reported that across all subjects, posteromedial and ventral anterior cingulate cortices (key components of the default network) as well as right middle and inferior prefrontal regions demonstrated reduced task-induced deactivation in the ϵ 4 carriers relative to non-carriers. They suggested that altered fMRI activity of the posteromedial areas of the brain default network may be an early indicator of risk for AD. (56-)

3- the default network in “resting-state”:

compared to healthy controls patients with MCI show diminished resting state default mode activity especially in the frontal regions while AD patients show diminished default mode activity in wider spread cortical regions (57-). Similarly, resting state fMRI data has demonstrated alterations in parietal and hippocampal connectivity in MCI and AD (58-). A recent study in young (ages 20–35) ApoE ϵ 4 carriers revealed evidence of both altered default network connectivity at rest and increased hippocampal activation relative to noncarrier (59-).

Functional MRI studies in non-Alzheimer’s dementia:

One potential utility of fMRI is in identifying different pattern of brain activation or resting activities in different forms of dementia. So far there are only few reports that address this issue. For example, Galvin et al investigated functional connectivity in patients with Dementia with Lewy Bodies, AD and cognitively normal controls. They found that Participants with DLB had a functional connectivity pattern for the precuneus seed region that was distinct from AD; both the DLB and AD groups had functional connectivity patterns that differed from the cognitively normal group. In the DLB group, they found increased connectivity between the precuneus and regions in the dorsal attention network and the putamen. In contrast, they found decreased connectivity between the precuneus and other task-negative default regions and visual cortices. There was also a reversal of connectivity in the right hippocampus. (60-). In patients with Fronto-temporal dementia (FTD), Rombouts et al reported a significant decrease in fMRI activation in frontal and parietal cortex, during a parametric working memory task compared to

patients with AD. Frontal regions in patients with FTD showed less linear activation increase with working memory load than in AD. Possibly as a compensation mechanism, the cerebellum showed a stronger increasing response in FTD. (61-).

Advantages and caveats of using fMRI in studying patients with neurodegenerative disorders:

Advantages:

- 1- Functional MRI sessions are non-invasive and do not require injection of radioactive agents. Therefore, can be repeated many times over the course of a longitudinal study
- 2- It has relatively high spatial and temporal resolution,
- 3- The use of event-related designs enables the hemodynamic correlates of specific behavioral events, such as successful memory formation (62-63-) be measured.

Caveats:

- 1- The BOLD fMRI technique is particularly sensitive to even small amounts of head motion.
- 2- 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 (64-65-).
- 3- Disease-related alterations in brain structure may make it difficult to interpret the source of abnormalities in functional data (i.e., hypoactivation may reflect atrophy in addition to primary functional changes).
- 4- Functional neuroimaging measures may also be affected by transient brain and body states at the time of imaging, such as arousal, attention, sleep deprivation, sensory processing of irrelevant stimuli, or the effects of substances with pharmacologic central nervous system activity, which are commonly used in older individuals with cognitive impairment.
- 5- Abnormalities found in fMRI studies of AD patients may be heavily dependent on the type of behavioral task used in the study. Also, the nature of functional abnormalities may depend on whether the activated brain regions are directly affected by the disease, are indirectly affected via connectivity, or are not pathologically affected.
- 6- The ability to perform the task may greatly influence the pattern and degree of fMRI activity, as suggested by event-related subsequent memory studies.
- 7- Although there are now a few studies of fMRI test–retest reliability in young subjects (66-67-68-), reproducibility studies are only beginning to be performed in MCI and AD patients (69-) it is critical to complete further reliability experiments if fMRI is to be used widely in longitudinal or pharmacologic studies.

Conclusions/recommendations:

Despite the relative infancy of the field, there has already been a number of promising fMRI studies in AD, MCI, at risk asymptomatic subjects and in other forms of dementia. This highlights the potential uses of fMRI in both cognitive

neuroscience and clinical spheres of investigation. There are several issues that need to be addressed before fMRI can be used in routine clinical practice (see advantages and caveats above).

At this point we do not recommend routine clinical use of fMRI in investigating patients presenting with cognitive complain.

This tool should continue to be used as a research tool to delineate brain activation/deactivation and resting state patterns in patients presenting with cognitive complaints and in those with diagnosed dementia. this will provide insight into brain networks involved in cognitive and behavioral symptoms in these illnesses.

Potential use for fMRI in the future includes:

- 1- Early detection and longitudinal follow-up of change in brain networks in patients presenting with cognitive complaints. This will aid in confirming diagnoses such as MCI rather than subjective memory impairment, MCI rather than AD.
- 2- Identify patterns of brain activation that predict conversion of MCI to AD.
- 3- Distinguishing between AD and non-AD dementia such as FTD and LBD and aid in the diagnosis of rare and atypical dementia such as Progressive Supraneuclear palsy and Cortico-basal ganglionic degeneration.
- 4- Assess change in brain activation in response to interventions such as cognitive training and pharmacotherapy.
- 5- Map brain activation in various neuropsychiatric and behavioral symptoms in the context of pre-clinical and clinical dementia such as depression, apathy and psychosis, which will help in developing specific treatments for these symptoms.

Finally, there are several excellent reviews on the use of fMRI in patients with pre-clinical and clinical dementia that we utilized in preparing this summary and recommendations, for more details the reader is referred to these reviews. (70-71-72-73-)

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