Imaging Memory Encoding in Mild Cognitive Impairment (MCI) using fMRI

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Abstract

Episodic memory declines with age and is the most prominent and earliest domains of cognitive impairment in Alzheimer’s disease (AD). To further improve our understanding of the pathophysiological mechanisms behind the memory decline seen in AD this thesis used functional magnetic resonance imaging (fMRI) to investigate the neuronal activity during successful encoding in cognitively intact individuals (controls) and individuals diagnosed with mild cognitive impairment (MCI). Individuals with MCI are considered to be at risk of AD, with a yearly conversion rate of 15-20%, and likely harbor early AD pathology, particularly in the posteromedial cortex (PMC). The main goal of this thesis was to investigate whether the MCI individuals would demonstrate altered functional memory processes, particularly in the hippocampus and PMC, as compared to healthy control subjects. In accordance with the hypothesis, the results demonstrated that MCI subjects failed to show deactivation in the PMC compared to healthy controls. In addition, although both the groups demonstrated significant bilateral activation in the hippocampus, the MCI showed a paradoxical hyperactivation in the hippocampus compared to the controls. These results are consistent with previous studies and suggest a possible compensatory mechanism in the MCI subjects, most likely due to accumulation of AD pathology. The current results are potentially very important because it marks the memory processes in the PMC and the hippocampus as an early indicator of dysfunction, indicating that testing memory function with fMRI could provide a useful diagnostic marker that may be used to identify individuals in a preclinical (that is, asymptomatic) stage of AD.

Keywords: Alzheimer’s disease, Episodic memory, Functional magnetic resonance imaging, Hippocampus, Mild Cognitive impairment, Posteromedial cortex, Activation, Deactivation.
Preface

I am Gokulraj Prabhakaran and this thesis was a part of my Master studies in Medical Imaging at the Royal Institute of Technology (KTH), Sweden. This work was a part of an fMRI project carried out at Karolinska Institutet (KI) to study and identify functional markers for early diagnosis of Alzheimer’s disease (AD) under the supervision of Dr. Patrizia Vannini and Dr. Katarina Howner. Identifying and investigating these functional markers will have a very significant impact in understanding the neural mechanisms behind the development of neurodegenerative disorders and have both diagnostic and therapeutic values. The thesis work aims at identifying such markers with the help of fMRI in individuals diagnosed with Mild Cognitive Impairment (MCI); a preclinical phase to AD, by investigating the neural correlates behind episodic memory encoding using a face-name association task.

I would like to take this opportunity to thank and express my sincere gratitude to both my supervisors at KI; Patrizia Vannini and Katarina Howner for trusting me with this thesis work on the first place and for the support and guidance they have given me through the course of this thesis work.

I would also like to thank my supervisor at KTH, Dmitry Grishenkov and my examiner, Mats Nilsson for their valuable comments and positive criticism which helped me a lot with both my thesis report and presentation.

I would also like to thank SMILE lab, Huddinge for providing me with the resources necessary for the successful completion of my thesis work.

Finally I would like to thank my parents, my brother and all my friends for all their continued love and encouragement throughout my life.
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<th>Description</th>
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<tr>
<td>AD</td>
<td>Alzheimer’s disease</td>
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<tr>
<td>BA</td>
<td>Brodmann area</td>
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<td>BOLD</td>
<td>Blood oxygenation level dependent</td>
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<tr>
<td>CBF</td>
<td>Cerebral blood flow</td>
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<tr>
<td>CBV</td>
<td>Cerebral blood volume</td>
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<tr>
<td>CMRGlc</td>
<td>Cerebral metabolic rate for glucose</td>
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<td>CMRO2</td>
<td>Cerebral metabolic rate of oxygen</td>
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<tr>
<td>DICOM</td>
<td>Digital imaging and communications in medicine</td>
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<td>DMN</td>
<td>Default mode network</td>
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<tr>
<td>DSM</td>
<td>Diagnostic and Statistical Manual of Mental Disorders</td>
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<td>EPI</td>
<td>Echo-planar imaging</td>
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<tr>
<td>FHIT</td>
<td>Forgotten hit</td>
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<tr>
<td>FMISS</td>
<td>Forgotten miss</td>
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<tr>
<td>fMRI</td>
<td>Functional magnetic resonance imaging</td>
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<tr>
<td>GLM</td>
<td>General linear model</td>
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<tr>
<td>GUI</td>
<td>Graphical user interface</td>
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<tr>
<td>ICD</td>
<td>International Classification of Diseases</td>
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<tr>
<td>IPL</td>
<td>Inferior parietal cortex</td>
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<tr>
<td>MCI</td>
<td>Mild cognitive impairment</td>
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<td>MFG</td>
<td>Medial frontal gyrus</td>
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<tr>
<td>MNI</td>
<td>Montreal neurological institute</td>
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<tr>
<td>MR</td>
<td>Magnetic resonance</td>
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<tr>
<td>MTL</td>
<td>Medial temporal lobe</td>
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<td>NINCDS-ADRDA</td>
<td>National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association</td>
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<tr>
<td>OEF</td>
<td>Oxygen extraction fraction</td>
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<tr>
<td>PIB-PET</td>
<td>Pittsburgh compound B - Positron emission tomography</td>
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<td>PMCI</td>
<td>Progressive mild cognitive impairment</td>
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<td>PMC</td>
<td>Postero medial cortex</td>
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<td>ReML</td>
<td>Restricted Maximum Likelihood</td>
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<tr>
<td>RHIT</td>
<td>Remembered hit</td>
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<tr>
<td>RMISS</td>
<td>Remembered miss</td>
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<tr>
<td>ROI</td>
<td>Region of interest</td>
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<tr>
<td>SFG</td>
<td>Superior frontal gyrus</td>
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<td>SMCI</td>
<td>Stable mild cognitive impairment</td>
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<td>SPL</td>
<td>Superior parietal cortex</td>
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<td>SPM</td>
<td>Statistical parametric mapping</td>
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<td>STG</td>
<td>Superior temporal gyrus</td>
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<td>TR</td>
<td>Repetition time</td>
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References
1. Introduction

1.1 Background

1.1.1 Episodic memory

Memory can be defined in a simple way as the ability to perceive information and remember it so that it can be recalled later, when needed. This successful recollection of information is possible by means of two memory processes; encoding and retrieval. *Encoding* is the process by which new information, either visual, acoustic or by any other senses is stored as memories and *retrieval* is the process by which the encoded memory is recalled. Memories can be broadly classified into declarative (sometimes referred to as explicit memory) and non-declarative memory (sometimes referred to as implicit memory). Declarative memory attributes to the memories which require conscious control to recollect it and it is broadly classified into two types; episodic memory, the memory of personal or autobiographical experiences and semantic memory, the memory of facts. Non-declarative memory or procedural memory does not require conscious control and intention to recall it, for example riding a bicycle.

1.1.2 Using functional MRI to investigate the neuronal correlates of episodic memory

One way to investigate the neuronal correlates of memory processing is by means of *functional magnetic resonance imaging (fMRI)*, a technique which uses the relationship between the brain activity and the local cerebral blood flow. Specifically, the technique uses the oxygen concentration in the blood as an indirect marker or a contrast of the underlying neuronal activity in a brain region activated during a task. That is, an increase in the neuronal activity in a brain region results in a subsequent surge of blood flow to the region. This increase in blood flow causes higher blood oxygen concentration in the region resulting in an increase in the MR signal intensity. The functional images obtained from fMRI therefore represent these MR signal intensities (indirectly the neuronal activity) at every voxel of the brain across the time course of the scan. These images can be used to create *activation* and *deactivation* maps by using statistical programs.

Previous fMRI studies have demonstrated that successful memory processes consists of multiple sub-processes involving several large-scale neuronal networks and requires coordinated patterns of activity among them. Of these, the activation of the hippocampus and adjacent medial temporal lobe (MTL) structures and the regions in the prefrontal cortices have been demonstrated to be crucial for intact episodic memory (Squire et al., 1992; Alvarez and Squire 1994). Although existing episodic memory models supports the predominant role of the hippocampus, MTL structures and prefrontal cortices in successful encoding of information, recent functional imaging studies have implied that the deactivation of the posteromedial parietal regions also plays a major part in successful episodic memory functions (especially the
precuneus, the posterior cingulate and retrosplenial cortex regions) (Vannini et al., 2011; Miller et al. 2008a; Sperling et al., 2009). These posteromedial parietal regions form a part of the default mode network (DMN), and the function of these regions have been found to be active during rest but suspended while the individual is involved in an active cognitive function (Buckner et al., 2008). Thus, deactivation maps during an episodic memory fMRI task represent the brain regions showing greater activity at rest compared to when the individual is performing the task, whereas activation maps represent the brain regions showing greater activity while performing a task compared to the same brain regions at rest. Although the underlying reason for these deactivations is still unclear, one theory suggests that the observed deactivations may be considered as an outcome of redistribution of neuronal resources necessary for successful cognitive performance and has thus been termed ‘beneficial deactivation’. For instance, previous fMRI studies investigating episodic memory encoding have shown deactivation patterns in the PMC and the level of deactivation in these regions has been linked to the performance of the encoding task (Daselaar et al. 2004; Miller et al. 2008a).

1.1.3 Using fMRI to study functional changes during episodic memory in aging and Alzheimer’s disease

Episodic memory declines with age (Bäckman et al., 1999) and is one of the earliest and prominent domains of cognitive impairment in Alzheimer’s disease (AD) (Welsh et al., 1991). Investigating the neuronal networks involved in episodic memory encoding and the alterations in the functioning of these networks associated with development of AD symptoms might prove to be of potential importance in identifying markers for an early diagnosis of AD. The study presented in this thesis employed fMRI to investigate the neuronal networks engaged during successful episodic encoding of a face-name association task and the alterations in these networks that occur in individuals diagnosed with mild cognitive impairment (MCI). Mild cognitive impairment is a condition considered to be the prodromal phase to AD in which the individuals start to experience a lesser degree of deterioration in normal cognitive function, but do not meet diagnostic guidelines set in the DSM-IV by American Psychiatric Association, 1994 or ICD-10 by World Health Organization, 1992 for dementia and by NINCDS-ADRDA; for probable Alzheimer's disease (AD) (McKhann et al., 1984). Individuals diagnosed with MCI belong to a diverse group with reference to both displaying clinical symptoms of MCI and progression to AD. Studies have shown a progression rate of 10 – 15 % annually to AD in a greater number of MCIs (Tierney et al., 1996; Petersen et al., 1999) and this group of MCIs are called as progressive MCI (PMCI), however some MCI individuals do not progress to AD for a long time after being diagnosed with MCI; grouped as non-progressive or stable MCI (SMCI). Given the high risk of progression in individuals with MCI, identifying markers that might predict which ones will develop AD in the future is really important.

Previous fMRI studies in older adults have demonstrated failure to suppress activation in the DMN, and this failure in the ability to deactivate has been linked to subsequently poorer memory
performance (Miller et al., 2008a). Individuals in the early stages of AD have also demonstrated similar kind of inability to suppress activation in the DMN during memory encoding (Lustig et al., 2003). In addition to the functional changes observed in the PMC with cognitive decline, fMRI studies have also demonstrated functional alterations in the hippocampus in patients with AD (Sperling et al., 2003) which have showed significant decreased hippocampal activation compared to healthy control subjects. However, previous studies investigating the hippocampus function in a memory encoding task in MCI have found the MCI exhibiting paradoxical increased activation in the hippocampus compared to control and AD subjects (Dickerson et al., 2005; Dickerson et al., 2008; Hämäläinen et al., 2007) suggesting a phase of hippocampal hyperactivation in the prodromal stage of AD.

1.1.4 Linking functional changes to Alzheimer’s disease pathology

Interestingly, the same regions which exhibit alterations in functional deactivation in older individuals and AD patients and the brain regions that are most susceptible to early accumulation of amyloid plaques (Klunk et al., 2004) – a pathological hallmark of AD overlap. For instance, recent studies have found evidence of amyloid deposition in 20 to 50% of cognitively normal older individuals (Pike et al., 2007; Bennett et al., 2006) which suggests that the pathophysiological changes may start way ahead before the clinical symptoms of AD begin to develop. In addition, previous studies have shown that older adults with intact cognitive function with increased amounts of amyloid demonstrate altered functional activity during the memory processes as compared to older adults with reduced levels of amyloid deposition (Vannini et al., 2012, Vannini et al., 2013). In particular, when comparing young individuals with cognitively normal older individuals, Vannini et al., (2012) demonstrated that older adults with high amyloid concentration showed decreased ability to deactivate the PMC as compared to young subjects as well as older adults with low amounts of amyloid. These findings are congruent with results from other studies which have shown less deactivation in the PMC in subjects at different levels of cognitive impairments (MCI and AD) as compared to young individuals (Sperling et al., 2003; Lustig et al. 2003). Similarly, the observed hyperactivation of the hippocampus in MCI subjects to that of of the controls (Dickerson et al., 2005) and AD patients (Celone et al., 2006; Dickerson et al., 2008) has been suggested to serve as a compensatory mechanism due to the accumulation of AD pathology. For instance, in a longitudinal study of MCI subjects Miller et al., (2008b) found a correlation between the degree of hyperactivation to the rate of cognitive decline, such that individuals with greater hippocampal hyperactivation at baseline had increased the rate of cognitive decline after follow-up.

In sum, the above mentioned findings are potentially very important because it marks the memory processes in the PMC and the hippocampus as a very early indicator of dysfunction of the memory network which might be related to amyloid pathology. Furthermore, these studies suggests that testing memory function with fMRI could provide a useful diagnostic marker of dysfunction that could be used in conjunction with amyloid imaging and other tests to identify
individuals in a preclinical (that is, asymptomatic) stage of AD.

1.2 Overall goal and specific aims

The current work presented in this thesis, builds on these previous findings and aims to validate the hypothesis that altered functional memory processes in the PMC in older adults (Vannini et al., 2012; 2013) is an early indicator of progressive decline towards AD dementia due to increased amyloid pathology. The overall goal of the proposed study was to perform an fMRI study of memory processes during successful encoding in healthy individuals and patients diagnosed with MCI, to provide us with much more knowledge and understanding of the pathophysiological mechanisms behind the memory decline linked with AD. The results from this study will be critical in order to validate if the functional alterations that have been previously observed in cognitively normal older individuals can be used to better discriminate normal age-related changes from pathological neurodegenerative processes.

By studying two groups (Controls and MCI), using a face-name associative memory encoding task at a 3 T magnetic field strength, the following aims were set up:

**Aim 1.** To investigate differences in deactivation patterns in the PMC during successful episodic memory encoding in MCI and controls.

**Rationale:** Given that previous studies have demonstrated pathological (i.e. amyloid deposition) changes starts occurring years even before clinical symptoms of AD begin to appear and the association between these pathological change and functional alterations during episodic memory encoding in cognitively normal older adults (Vannini et al., 2012, 2013), we hypothesize that the MCI subjects (who are said to be in a prodromal phase of AD) would show less deactivation than the controls in the PMC.

**Aim 2.** To investigate differences in activation patterns in the hippocampus during successful episodic memory encoding in MCI and controls.

**Rationale:** Given that previous studies have demonstrated a paradoxical increased activation in the hippocampus region during encoding in MCI subjects as compared to controls (Dickerson et al., 2005, 2008; Miller et al., 2008b; Hämäläinen et al., 2007; ) the findings from this thesis work were expected to show that the MCI subjects would demonstrate similar hyperactivation in the hippocampus as compared to the controls.
2. Materials and Methods

2.1 Participants

A total of 12 subjects took part in the study, consisting of 7 control subjects (mean age: 52.7 years; Male/Female: 2/5) and 5 subjects diagnosed with MCI (mean age: 68.8 years; Male/Female: 3/2) (recruited from the Memory Clinic, Karolinska University Hospital). There was no statistical difference in age between the groups (t=1.54; p=0.076). All subjects that participated in the study were native Swedish speakers. For all subjects, standard MRI exclusion criteria were used, (for e.g. pacemaker, claustrophobic subjects, metal implants). Informed written consents were obtained from every subject participating in the experiment.

2.2 Functional Magnetic Resonance Imaging (fMRI)

Functional magnetic resonance imaging is an MRI technique which employs the relationship between the brain activity in a region and the cerebral blood flow changes associated with the neuronal activity in that region. The technique is based on 1) Increase in the local cerebral blood flow in a brain region when it is activated and 2) Difference in the magnetic properties between the oxygenated and deoxygenated blood in those brain regions, also called the Blood Oxygenation Level Dependent (BOLD) signal (Ogawa et al., 1990). An overview of the principle behind fMRI is shown in Fig 2.1. In order to understand how this signal is generated it is important to study the physiological and the metabolic processes taking place in the neurons which is described more in detail below.

Information transfer within the brain takes place by means of electrical impulses or action potentials traversing between the billions of neurons (the basic functional unit of the brain). These action potentials depend on the membrane potential of the neuronal cells and are generated by means of a disturbance or depolarization of this membrane potential. The membrane potential of a cell is determined by the ionic distribution across the cell membrane and its permeability to different ions. A change in the distribution of the different ions within or outside the cell may give rise to an increase or decrease in the membrane potential and when this reaches a certain threshold it results in an action potential. These electrical impulses are transferred from one neuron to another by means of connections, i.e. synapses, with the help of neurotransmitter molecules creating neural circuits within the brain. Neuronal activity is the overall term used to describe these processes. This activation of the neurons must be followed by the restoration of ionic distribution both intracellular and extracellular and also the repacking of the neurotransmitter molecules which is an energy consuming process. This energy is provided by means of metabolism of glucose into carbon dioxide and water in the presence of oxygen i.e. oxidative phosphorylation. Hence a local demand of oxygen is created in the region of neural activity in the brain and the required oxygen is provided by means of increased local cerebral blood flow.
An increased neuronal activity in the brain results in an increase in the cerebral blood flow (CBF), volume (CBV), metabolic rate of glucose (CMRGlc) and a moderate increase in the cerebral metabolic rate of oxygen (CMRO2). The decrease in oxygen extraction fraction (OEF), the ratio of oxygen used by the brain to the oxygen supplied to the brain is used to measure the functional response to a task. That is, a decrease in the OEF increases the ratio of oxygen in the venous (deoxygenated) blood. There is a difference in the magnetic properties between the oxygenated and deoxygenated blood (i.e. oxygenated blood is less prone to distortion because of its iso-magnetic nature whereas deoxygenated blood is paramagnetic which gives rise to distortions). Since the blood gets a little more oxygenated after activation it results in a small increase in the intensity of the MR signal. This increase in signal intensity is named the BOLD response and forms the basis of fMRI.

![Fig 2.1 Overview of the principle behind fMRI signal](image)

### 2.3 Experimental Task

The paradigm used in the fMRI experiment is a Swedish version of an event related face-name association task used in previous studies (e.g. Vannini et al., 2011) and created using *E-prime* software. The experiment consisted of two sections, encoding and a retrieval part and there were a total of 4 encoding and 4 retrieval runs alternating with each other.

The encoding runs consisted of presenting the subjects with color pictures of human faces against a black background. Below each face, a fictional first name was displayed in white as shown in Fig 2.1a. To enhance attention and facilitate encoding of the face-name stimuli, subjects were asked to choose if they thought the face and the name pair were a good match (Namnet passar - Name fits the face) or not (Passar inte - Name does not fit the face) (Sperling et al., 2003). Each encoding run consisted of a total of 20 face-name pairs which were shown to the subject 3 times (EN1, EN2, EN3). The 20 face-name pairs were grouped into 5 groups with 4 face-name pairs in each group and each stimuli was displayed for a period of 2.75 seconds. Each encoding run consisted of 20 face-name pair stimuli that were shown to the subject 3 times (EN1, EN2, EN3). Each stimuli was displayed for a period of 2.75 seconds. Between each face-name stimuli, a white fixation cross centered against a black background was displayed and the participants were asked to focus on the fixation point.
Each encoding run was succeeded by a retrieval run which consisted of two tasks, a cued recall task and a forced-choice recognition task. In the cued recall task (Fig 2.1b) the subjects saw the same color pictures of the faces used during encoding and had to indicate if they ‘Remembered’ (Kommer ihåg) or had ‘Forgotten’ (Glömt) the name associated with it. Each cued recall stimuli was displayed for 5.25 seconds followed by a fixation cross and subsequently by a forced-choice recognition task (Fig 2.1c) for 3.25 seconds. In the forced choice recognition task the subjects saw the same pictures of faces and below the face, two names were displayed for the subjects to choose the correct name for the face. Although the results presented in this thesis focuses on the functional activity during encoding, the behavioral response given by the subjects during retrieval was used to categorize the face-name encoding stimuli. Fig 2.1d displays the experimental design of the face-name association task for one encoding and retrieval run.

2.4 E-Prime

E-Prime software was used to program the experimental design. Since the experiment was originally an English version (Vannini et al., 2011) with American first names these names were exchanged with Swedish first names – thereby creating a Swedish version of the paradigm. E-prime was also used to run the experiment in the fMRI scanner and to record behavioral data from each subject, e.g. the subject’s behavioral response (remember, forgotten, hit and miss) and response time for each stimuli. E-Prime is really advantageous for neuroimaging experiments because of its timing accuracy in milliseconds, both while presenting the stimulus as well as
collecting the response, and its ability to be connected and synchronized with external devices such as fMRI.

Fig 2.1d fMRI experimental paradigm for one encoding and retrieval run. Each encoding run displays 20 face-name pairs divided into five sets with four stimuli in each set for a total of 3 times (EN1, EN2, EN3) followed by the cued recall task (CR) and forced choice recognition (FCR) task during the retrieval run. The figure above is an example of how the stimuli’s were presented during encoding and retrieval runs using one set of 4 face-name pairs.

E-Studio is the section of E-Prime used to design and create experiments using a graphical user interface (GUI) window. This was achieved by means of several pre-programmed objects called E-objects which form the basic building blocks of the experiment. The GUI window is divided into four parts.

1. Structure Window - Displays the structure of an experiment
2. Toolbox Window - Consists of different objects required to design the experiment
3. Properties Window - Displays the properties of selected objects.
4. Workspace - Is where the experiment is built.

The basic structure of any E-Prime experiment is based on top level hierarchy and procedure is the most important E-object in the experiment and it is where all the events of an experiment are
sequenced. It provides the construct for the experiment. The basic structure of an E-Prime experiment is constituted by the following three procedures.

- **Session Procedure** is the highest level in the hierarchy and it is used to determine the order of events in the experiment. That is, the experiment can have only one session procedure where all other events are placed.

- **Block Procedure** comprises the different subsets of the experiment as individual blocks. An experiment can contain one or more blocks depending on how complex it is. In this experiment, only one block procedure was used. Thus every encoding and retrieval runs were programmed as individual programs rather than merging all the runs as individual blocks in the same program. In total, 8 different session procedures (4 encoding and 4 retrieval runs) were created in the experiment.

- **Trial Procedure** is the lowest level in the structural hierarchy of the E-Prime experiment and is where the stimuli (i.e. each face-name pairs and the fixation cross) are presented to subjects.

The structure of the E-prime experiment for one encoding run is shown in Fig 2.3. The experiment starts with an image display object (Start) which displays a fixation cross to the subject in the scanner until it receives a trigger signal from the fMRI scanner. The trigger signal provides timing synchronization between the start of the scanner and the E-prime experiment. EncProc is the trial procedure where the real experiment takes place. The two image display objects ‘Fixation’ and ‘FaceNamePair’ in the EncProc are responsible for presenting the fixation cross and the face-name pairs to the subjects. The properties of these image display objects and the stimuli’s (images) displayed by it were set using the property window of their respective objects and also with the help of a ‘List’ object (TrialList), Fig 2.4. This list was used to sequence the stimuli that had to be displayed by the image objects in the EncProc (Fixation column in the list holds the images presented by the object ‘Fixation’ and the FaceName column holds the images displayed by the object ‘FaceNamePair’). The presentation duration of these stimuli are also determined by the TrialList. The image display object in the EncProc fetches these information from the TrialList and performs the experiment. The EncProc displays a fixation stimuli followed by a face-name stimuli according to sequence listed in the TrialList and this procedure loops around until all the stimuli have been displayed. The data logging property in the objects was used to create a log of the various timing parameters in the experiment and the subject’s response during the stimuli. Responses were collected by means of a serial response box connected to the laptop running E-prime. Thus, behavioral response for each stimuli and the response time were collected and stored in the data logging property. Fig 2.5 displays the structure of the E-prime experiment for one retrieval run.
As described above, separate session procedures were designed and run for each encoding and retrieval run. Thus, one individual data file for every run included details of the experiment such as the stimuli onset and duration, as well as behavioral response and reaction time for each stimuli. *E-DataAid* was used to open these data files and to convert and export the data into a format compatible for statistical analysis of the data. Multiple data files from different runs and different subjects were merged as a single large file by using *E-Merge* - making it easier and reducing the time to analyze the large sets of data files the experiment created.

### 2.5 fMRI Acquisition

Functional images were obtained by means of T2* weighted gradient *echo-planar* imaging sequence sensitive to the BOLD signal, using a Siemens 3 Tesla Magnetom Trio scanner, with an 8 channel head coil, located at the Karolinska University Hospital in Huddinge. For every participant, a total of eight functional runs were collected and 145 time points or functional scans were acquired for every run with a repetition time (TR) of 2000 milliseconds. Each functional scan consisted of thirty coronal slices acquired by interleaved acquisition with an interslice distance of 1 mm per scan. Scan time for one run lasted for 4 minutes and 50 seconds and the total scan time for one subject was approximately 36 minutes.
2.6 Data Acquisition Setup

The whole data acquisition setup consisted of two systems coupled together; the fMRI system and E-prime system (Fig 2.6). The fMRI system located outside the scanner room consisted of a computer which was used to select and set up sequences in the experiment. This computer also collected the functional images. To prevent the radio frequency waves from outside environment to mix with those of the MR scanner, the scanner room is surrounded by RF shield (also known as faraday cage). The E-prime system was a laptop running E-prime and was used to run the face-name association task. The E-Prime system was connected to a projector and the experiment was projected on a small screen placed at the scanners rear side, which was viewed by the subject inside the scanner by a mirror system placed in the head coil. Since timing is very important in neuroimaging experiments it was necessary that both the scanner and the E-prime experiment started at the same time. This was achieved by means of programming the E-prime experiment to start with a trigger signal from the scanner. The E-prime system was also connected with a serial response box which was used to collect the responses made by the subjects. The subjects were provided with a two button response pad connected to the serial response box to select their responses.

2.7 fMRI Preprocessing

The functional scans were in DICOM format and had to be converted to Nifty or .nii format in order to be used in statistical analysis. This conversion was performed using the software MRJcron. The functional data was then preprocessed using Statistical Parametric Mapping (SPM 8; Welcome Department of Cognitive Neurology; www.fil.ion.ucl.ac.uk). As the scope of this thesis work was to study only the functional activity during encoding, only the functional images obtained during the encoding section of the fMRI experiment were subjected to preprocessing and further analysis. However the behavioral data of the retrieval part from the E-prime data were used to design the statistical model for analysis of the functional encoding data. That is, the encoding data was filtered to only include events when the subjects said that they remembered the name to the face (cued recall) and subsequently selected the correct name during the forced choice recognition task (remembered hit).
The preprocessing steps were as follows:

2.7.1 **Slice timing correction** It is important to perform slice timing correction in event related experiments using Echo Planar imaging scanner in which slices are obtained throughout the repetition time (TR) as timing differences between acquired slices in an image might result in a possible shift of time between data on a slice to its adjacent slices. Thus, slice timing correction was done to assign all the slices within a functional image volume to the same point by sinc interpolation.

2.7.2 **Realignment** was used to eliminate the motion artifacts within and between different sessions in each subject. The first image volume was used as reference volume and all the other time series images within the subject were aligned with respect to the reference image using a least square minimization and a 6-parameter (rigid body) transformation. All the realigned images were resliced voxel by voxel and a mean resliced image for all the sessions were obtained. Realignment also creates a .txt file for each session with the realignment parameters (See Fig 2.7 ) which consists of 6 columns, first 3 representing the translation parameters (X, Y and Z) and the other 3 representing the rotational parameters (Pitch, Roll and Yaw) which was later used during statistical analyses.

2.7.3 **Normalization** was performed to transform the functional images from all the subjects into the same 3D space. This step is very important in order to compare data across all the subjects included in the experiment. A standard SPM8 EPI template was used as the reference image to which all the realigned images across all the session were matched and then resliced into 3 x 3 x 3 mm$^3$ in Montreal Neurological Institute (MNI) space as shown in Fig 2.8a and 2.8b.

2.7.4 **Smoothing** A Gaussian kernel of 8mm full width half maximum was used to remove noise from the functional images and also to reduce the inter subject spatial differences.

2.8 **fMRI statistical analysis**

Statistical analysis of the data included first and second level analysis using SPM8. First level analyses were performed for every subject seperately to look at within subject results and second level analyses were performed to look at between subject results.
2.8.1 First level statistical analysis consists of the following steps:

- Specification of the first level statistical model
- Estimation of the model
- Specification of contrasts

2.8.1.1 First level statistical model Specification and Estimation

Statistical analysis models are based on the General Linear Model (GLM) approach.

\[ Y = A\beta + E \]

Where,

\( Y \) is the observed data; In this case it was the time series BOLD signal images; i.e. the functional images from the scanner.
\( A \) is the GLM design matrix comprising of different parameters responsible for the observed data \( Y \).
\( \beta \) is the matrix defining the contribution of each parameter included in the design matrix to the observed data.
\( E \) is the error matrix showing the difference between the observed data and the data predicted by \( A\beta \).

The structure of the design matrix reflects the nature of the experiment and the hypothesis that is being tested. The design matrix models the different conditions that needed to be involved in the model to verify a hypothesis. These conditions were classified based on the behavioral responses the subjects gave during the retrieval part of the experiment; i.e. during the cued recall (‘Remembered’ or ‘Forgotten’) and forced choice recognition (‘Hit’ or ‘Miss’) resulting in four possible conditions: remembered hit (RHIT), remembered miss (RMISS), forgotten hit (FHIT) and forgotten miss (FMISS). Since the aim of this thesis work was to investigate the role of hippocampus and PMC in successful encoding across controls and individuals with...
MCI, only the face-name stimuli which fell into the category of the condition (RHIT) during EN1 (i.e. the first time the images were shown to the subject) were considered. Onsets of the face-name stimuli associated with the condition RHIT were also included in the design matrix. Since this is an event related experiment the duration was set to zero in the design matrix. Every condition file has to have a name, duration and onsets of the stimuli’s associated with the condition.

A first level model was created for each subject to investigate individual activated and deactivated regions during successfully remember (RHIT) in the first encoding trial (EN1). The design matrix for encoding thus included the stimuli with the condition ‘RHITEN1’. The translation and rotational parameters that were obtained during the realignment of functional images during image preprocessing were also added as regressors to the model. Fig 2.9 displays the design matrix for one subject across the encoding trials. Each row in the design matrix represents a functional scan i.e. time series images from the scanner and the column represents the conditions and regressors included in the model. The parameters of these models were estimated by classical approach using Restricted Maximum Likelihood (ReML) in order to reduce the difference between the observed data Y and the predicted data A. Estimation of the model creates a vector of voxel by voxel estimates of how much a particular condition or parameter in the model contributes to the observed data i.e. the BOLD images which is termed as the beta-weight estimates of that particular condition. These beta-weight estimates are saved as beta images by the SPM and every condition has its own beta image where each voxel gives the beta-weight for that particular condition at that voxel.

2.8.1.2 Contrast Specification

After creating and estimating the first level model, simple T-contrasts were performed. Contrast specification was done to investigate regions of the brain i.e. the voxels that were activated or deactivated only during a successful encoding of the face-name stimuli (RHIT). These contrasts are specified as vectors and they are defined by weighting the conditions assigning different values like 1, 0 and -1 as weights depending on what is being looked for.

To look at an activation effect due to a particular condition the weight for that condition is assigned to 1 and the rest of the conditions are assigned as 0. In the same way, to look for the deactivation due to a particular condition, the weight of that condition is assigned as -1.

In this thesis work, only the regions that activated and regions that deactivated during successful encoding ‘RHIT’ were investigated and the contrast created to look for these effects was specified for each subject by comparing it with baseline, i.e. the activity during the control condition; i.e. fixation cross ‘Fix’. Thus to study which regions that activate in the brain during successful encoding of face-name pairs, the contrast (RHITEN1>Fix) was created by assigning of a weight of ‘1’ set to the condition ‘RHITEN1’ and ‘0’ for all other conditions. Similarly to study which regions that deactivate during successful encoding, a contrast (Fix>RHITEN1) was created by assigning ‘RHITEN1’ a weight of ‘-1’ and the rest of the conditions ‘0’. See Fig 2.10a and 2.10b for the contrasts created to look at activation (RHITEN1>Fix) and deactivation (Fix>RHITEN1 during successful encoding of the face-name task.
The contrast (RHITEN1>Fix) identifies voxels activated during successful encoding and creates a contrast image with weighted parameter estimates (.con images). SPM creates the contrast images by giving the beta image of each condition the weight defined for that condition during contrast specification and making a weighted sum of all the conditions. These contrast images were used as inputs during the 2nd level group analysis. In addition to the contrast images, SPM also returns images representing the voxel by voxel estimates of every individual parameter (Beta images) and a T-statistic (spmT00*.img) image with T values across the entire brain. T values are calculated as a function of ratio between explained variances in a model (beta parameters, movement artifacts from the realignment) to that of unexplained variances (random noise). The contrast (RHITEN1>Fix) identifies voxels activated during successful encoding and creates a contrast image with weighted parameter estimates (.con images).
and these contrast images obtained from the 1st level analysis for every subject were used for the 2nd level analysis.

**2.8.2 Second level statistical analysis**

Second level analysis was performed to study the hippocampal activation and PMC deactivation during successful encoding at a group level. Similar to the first level analysis, second level statistical analysis also comprises of statistical model specification, estimation and contrast specification. The individuals contrast images obtained from the 1st level analysis (both RHITEN1>Fix & Fix>RHITEN1) were placed in two groups; controls and MCI subject groups. One sample and two sample t-test were performed using SPM8.

**2.8.2.1 One sample t-tests** were performed to identify all the brain regions that activated or deactivated during encoding in each group separately. One sample t-test works on the principle of ‘null hypotheses’ which states that the mean value of one group of subjects is equal to zero (here zero can be considered to be the mean of the fixation). Similar to the first level t-statistic analysis, a statistical model was created for one sample t-test as well with the contrast images from the first level analysis as the inputs to the design matrix. To identify the regions that activated in the control group during successful encoding, the contrast images from the first level contrast RHITEN1>Fix across all the control subjects were used. A simple t-contrast was specified by assigning a weight of ‘1’ to all the input images and the one sample t-test returns the mean activation across the group. The deactivated regions in the control group were investigated by using opposite first level contrast images Fix>RHITEN1 of all the subjects. Similarly, one sample t-tests to investigate the mean activation and deactivation for
the MCI subjects were also performed. The output files from the one sample t-test comprise of a contrast image, T-Statistic and beta images along with statistic table providing the voxel and cluster information. All the statistical maps were created with a threshold of uncorrected p-value <0.05 and an extent threshold of 10 voxels.

2.8.2.2 Two Sample t-tests were done to study the mean difference between the controls and the MCI group in regard to activation or deactivation patterns in the brain. Two sample t-test does this by testing the ‘null hypothesis’ that the mean of both groups are identical to one another. The design matrix for the two sample model was defined using two columns, one for each group with their respective first level contrast images as shown in Fig 2.11a (here, controls were considered as group 1 and MCI subjects as group 2). After estimating the two sample statistical model, t-contrasts were specified to investigate the differences between the groups. For example to look for regions that had a greater activity in the control subjects compared to that of MCI subjects (Control > MCI), a t-contrast [1 -1] was used. To look for the opposite effect (Controls<MCI) i.e. the regions showing greater activity in MCI subjects than the controls, the opposite contrast [-1 1] was specified. (Fig 2.11b) - t-contrast created to look at Controls > MCI. The first level images from the contrast RHITEN1>Fix were used as the input to demonstrate the activation differences and the images from the contrast Fix>RHITEN1 were used to investigate the deactivation differences between the groups. Two sample statistic images and tables were also created by SPM. All of the statistical maps were created with a threshold of p-uncorrected<0.05 and an extent threshold of 10 voxels.

Fig 2.11a: Design matrix of a 2 sample t-test. It consists of 2 columns, Group1 and Group2. Group1 comprises of the 1st level contrast images of control subjects and Group 2 with the contrast images of MCI subjects

Fig 2.11b: Contrast specified to look at Controls > MCI with a t-contrast [1 -1]. To investigate the regions that showed greater activation in the controls than MCI the 1st level contrast images from the contrast RHITEN1>Fix were used and to investigate the regions of greater deactivation in controls the images from the other 1st level contrast Fix>RHITEN1 were used.

2.9 Region of interest analysis

To further investigate the signal intensity in each subject group an additional region of interest (ROI) analyses was performed with respect to the results from the two sample t-test. Based on the a priori hypothesis that the hippocampus and the PMC would show the most difference
between the groups, ROIs in these regions were selected for further examination. To investigate the signal intensity during deactivation, the beta-weights for the contrast Fix>RHITEN1 were extracted for all the PMC ROIs and all the subjects. Similarly, to investigate the signal intensity during activation the beta-weights for the contrast RHITEN1>Fix for all the hippocampus ROIs were extracted. Independent two sample t-tests of the beta-weights for each subject group were then performed for each ROI to further examine the difference between the groups. We are aware that these analyses are bit circular, given that the ROIs were selected based on analyses investigating the differences between the groups using a whole-brain approach. However, the main purpose of the ROI analyses were to determine the direction of the signal intensity in each group and confirm the between-group results obtained using the whole-brain approach.
3. Results

3.1 fMRI memory task performance

Table 1 displays the behavioral results of the groups based on the performance of the subjects during the retrieval task (cued recall and forced choice recognition). As presented above the face-name pairs were classified into four categories; Remembered Hit (RHIT), Forgotten Hit (F_HIT), Remembered Miss (RMISS), Forgotten Miss (FMISS) and the mean percentage of the subject groups for each of the classes was calculated. In accordance to previous studies (Vannini et al., 2011, 2012), the control subjects were able to perform the task well, with a high percentage of RHITs (77.3%). The MCI subjects also performed the task well with a mean percentage of RHITs (61.2%). The groups did not show significant statistical difference (p>0.05) in their memory performance across any of the conditions.

Table 1: Behavioral Results

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>MCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Hits</td>
<td>87.6(12.1)</td>
<td>75.2(14.4)</td>
</tr>
<tr>
<td>RHIT</td>
<td>77.3(25.4)</td>
<td>61.2(21.0)</td>
</tr>
<tr>
<td>F_HIT</td>
<td>1.0(15.3)</td>
<td>1.3(17.2)</td>
</tr>
<tr>
<td>RMISS</td>
<td>4.2(5.5)</td>
<td>6.5(2.7)</td>
</tr>
<tr>
<td>FMISS</td>
<td>1.9(4.1)</td>
<td>4.5(6.9)</td>
</tr>
</tbody>
</table>

Table 1: Mean percentage and Standard deviation (SD) for the behavioral results; RHIT: remembered hit; F_HIT: forgotten hit; RMISS: remembered miss; FMISS: forgotten miss. No statistical difference was observed between the groups.

3.2 One-Sample t-test

To investigate the brain regions involved in successful encoding, one sample t-tests (SPM8) were performed for the control and MCI group separately. The results from these analyses are presented below.

3.2.1 Deactivation during successful encoding

The one sample t-test on the control subjects revealed significant deactivation in multiple brain regions in the DMN, especially in the parietal regions (Fig 3.1 A). Significant deactivation was observed in the PMC specifically in the precuneus bilaterally (BA 7) extending into the posterior cingulate (BA 31), superior parietal lobe (SPL, BA 5) and inferior parietal lobes (IPL, BA 40). In addition, significant deactivation was also observed in the superior frontal gyrus (SFG, BA 8), superior temporal gyrus (STG, BA 22/41) and anterior cingulate gyrus. MCI subjects did not reveal much significant deactivation in the PMC except a few regions in the precuneus (BA 7) and posterior cingulate (Fig 3.1 B) from the one sample t-test. However, significant deactivation was observed in the SFG (BA 6/9), medial frontal gyrus (MFG, BA9).
Fig 3.1 Statistical parametric maps obtained from one sample t-tests demonstrating deactivation in the PMC during successful encoding (Fix>RHITEN1) in control subjects (A) and MCI subjects (B).

Fig 3.2 Statistical parametric maps obtained from the one sample t-test showing the brain regions which demonstrate brain regions in the hippocampus that are activated (RHITEN1>Fix) during successful encoding in control subjects (A) and MCI subjects (B).

3.2.2 Activation during successful encoding

The one sample t-tests revealed that both subject groups showed significant clusters of activation in the hippocampus and the para hippocampal gyrus (BA 28) regions as well as in the occipital lobe (BA 18/19). In addition, the control subjects showed several activation clusters in the frontal lobes (BA 8/13/46) which was not observed in the MCI subjects. Fig 3.2 demonstrates the activations in the hippocampus and para hippocampus during successful encoding in controls and MCI subjects respectively.

3.3 Two-Sample t-test And Region of interest analysis

In order to identify the differences in the deactivation and activation patterns between the two subject groups, a series of two sample t-tests were performed. ROI analyses of the PMC and the hippocampus were also performed to further investigate the signal intensity in each group. The results from these analyses are presented below.
3.3.1 Differences in the deactivation patterns during successful encoding

The two-sample t-tests (Controls < MCI) revealed no regions in the PMC showing greater deactivation by the MCI subjects than the controls. In contrast, control subjects demonstrated greater deactivation as compared to the MCI subjects (Controls > MCI) in several brain regions in the PMC (Fig 3.3); Posterior cingulate (MNI coordinates: x=-4, y=-49, z=32); Precuneus (MNI coordinates: x=11, y=-55, z=11); Precuneus (MNI coordinates: x=8, y=-55, z=47); Inferior parietal lobe (MNI coordinates: x=53, y=-46, z=53). The PMC ROIs and the mean beta-weights for each group are shown in Fig 3.3. Independent two sample t-tests of the extracted beta weights from the PMC ROIs revealed a significant difference between the group’s beta weights, demonstrating increased deactivation in the controls as compared to MCI subjects. The location of the voxels showing peak deactivation difference from the two sample t-test; their ‘T’ values (magnitude of the difference in deactivation); p-value; mean beta weights of these clusters are specified in Table 2 (A).

3.3.2 Differences in the activation patterns during successful encoding

Two sample t-test (Controls > MCI) did not reveal any areas in the hippocampus demonstrating increased activation in the control subjects as compared to the MCI. In contrast, the two-sample t-test (Controls < MCI) revealed that the MCI subjects demonstrated greater activation in hippocampus bilaterally (x=-31, y=-22, z=-11) and (x=17, y=-34, z=-1) (MNI coordinates)(Fig 3.4). Beta-weights were extracted from the hippocampus and the mean beta-weights are plotted in Fig 3.4. Independent two sample t-tests of the extracted beta weights from the hippocampus ROIs revealed a significant difference between the group’s beta weights for hippocampus bilaterally, demonstrating increased activity in MCI as compared to that of control subjects. The location of the voxels showing peak activation difference from the two sample t-test; their ‘T’ values (magnitude of the difference in activation); p-value; mean beta weights of these clusters are specified in Table 2 (B).

### Table 2

<table>
<thead>
<tr>
<th>Anatomical Region</th>
<th>BA</th>
<th>MNI Coordinates x y z</th>
<th>T-value</th>
<th>P-value</th>
<th>Beta-weights Controls</th>
<th>Beta-weights MCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>(A) Deactivation –Successful Encoding (Fix&gt;RHITEN1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Precuneus</td>
<td>7</td>
<td>11 -55 11</td>
<td>3.95</td>
<td>0.001</td>
<td>-0.72 ± 0.57</td>
<td>5.08 ± 1.89</td>
</tr>
<tr>
<td>Inferior parietal lobe</td>
<td>40</td>
<td>53 -46 53</td>
<td>3.41</td>
<td>0.003</td>
<td>-4.5 ± 0.75</td>
<td>-0.49 ± 1.38</td>
</tr>
<tr>
<td>Posterior cingulate</td>
<td>31</td>
<td>-4 -49 32</td>
<td>2.68</td>
<td>0.011</td>
<td>-4.0 ± 0.84</td>
<td>0.61 ± 2.11</td>
</tr>
<tr>
<td>Precuneus</td>
<td>7</td>
<td>8 -55 47</td>
<td>1.95</td>
<td>0.039</td>
<td>-3.6 ± 0.69</td>
<td>-0.17 ± 2.56</td>
</tr>
<tr>
<td>(B) Activation –Successful Encoding (RHITEN1&gt;Fix)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hippocampus</td>
<td>17</td>
<td>-34 -1</td>
<td>2.88</td>
<td>0.002</td>
<td>2.03 ± 0.92</td>
<td>7.37 ± 1.97</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>-31</td>
<td>-22 -11</td>
<td>2.06</td>
<td>0.026</td>
<td>0.87 ± 0.57</td>
<td>2.49 ± 0.70</td>
</tr>
</tbody>
</table>

Notes:  Regions of interest obtained from the two sample t test; regions showing greater deactivation in controls than MCI (A) and regions showing greater activation in MCI than controls (B) during successful encoding in the face-name association task; Brodmann areas (BA); MNI coordinates in millimeters; statistical threshold value (T); p value from the two-sample t-test; Mean beta-weights and standard error.
Whole brain analysis

Region of interest analysis

Fig 3.3. Statistical parametric maps from two-sample t-tests displaying regions which showed greater deactivation in controls as compared to MCI subjects during successful encoding. Lighter the color, greater the difference in deactivation between the groups.

Fig 3.3. Mean beta weights extracted from ROIs in the PMC with standard error bars. * p<0.05; ** p<0.01 and *** p<0.001.
Whole brain analysis

Region of interest analysis

Fig 3.4. Statistical parametric maps from two-sample t-tests displaying regions which showed greater activation in MCI compared to control subjects during successful encoding. Darker the color, greater the difference in activation between the groups.

Fig 3.4. Mean beta-weights extracted from the hippocampus and standard error bars. * p<0.05; ** p<0.01 and *** p<0.001.
4. Discussion

The results from this master thesis work illustrates the importance of a proper functioning of the neural networks in the PMC (deactivation) and the hippocampus (activation) for successful encoding of episodic memory. The findings indicate a significant difference in functional responses in both the hippocampus and the PMC between the control and the MCI groups during face-name pair encoding. In the PMC, the control subjects demonstrated extensive deactivation in several regions whereas the MCIs displayed failure in deactivating the PMC region during successful encoding. Both the control and MCI groups exhibited significant activation in the hippocampus bilaterally, however the MCI subjects showed greater activation (hyperactivation) compared to the controls in the hippocampal region.

The observed deactivation pattern in the PMC in the control subjects are in conformity with several previous studies (Vannini et al., 2011, 2012; Daselaar et al., 2004; Miller et al., 2008a) demonstrating the importance of beneficial deactivation in the PMC for successful encoding. These findings support the role of the PMC during encoding and demonstrate the importance of deactivation of this regions for successful memory performance. The vulnerability of the PMC to early amyloid deposition (Klunk et al., 2004) has been illustrated by several studies how the deposition of Aβ plaques could hinder the PMC from deactivating during encoding (Vannini et al., 2012; Sperling et al., 2009) by comparing deactivation pattern of older individuals with and without high amyloid burden. Similar kind of deactivation patterns in the PMC has been observed in subjects at different levels of cognitive impairments (MCI and AD) (Sperling et al. 2003; Lustig et al. 2003). Deposition of Aβ plaques is considered to be a hallmark pathology in AD (Hardy and Selkoe 2002) and with several findings suggesting an early onset of pathophysiological changes in the neural networks prior to the onset of clinical symptoms of AD. Considering these findings, one plausible interpretation of the reduced deactivation observed in the MCI patients is that it is caused by amyloid deposition. The results from this thesis work holds support to the above hypothesis by demonstrating a significant decrease in functional response in PMC by MCI subjects in comparison to the control subjects because of its inability to deactivate this region effectively due to pathological conditions linked with development of neurodegenerative diseases.

The result of the activation pattern from this study during successful encoding has demonstrated significant bilateral activation in the control group which is in accordance with findings from earlier studies (Vannini et al., 2011, 2012; Sperling et al., 2003) and the MCI group demonstrated hyperactivation bilaterally in the hippocampus than that of the controls. One potential reason for this hyperactivation might be the need for additional neuronal resources by the memory networks due to accumulation of AD pathology - a compensatory mechanism suggested by physiologic studies of animal models (Stern et al., 2004). Recent studies have also suggested that the DMN and the MTL network might function as a coupled with one another as a single large network and the association between them is very essential for a better memory function (Buckner et al., 2005; Daselaar et al., 2006). These findings have gained support from several studies that have found functional alterations in this network in MCI and patients in the early stages of AD may lead to functional disassociation between
these two networks (Lustig et al., 2003). The results of deactivation patterns from this study also provide evidence of significant alterations in the neural correlates in the DMN by the difference in their ability to deactivate between the two groups. The finding from this study suggests that the MCI subjects, with failure to modulate functional response for ‘beneficial deactivation’ of the PMC tends to hyperactivate the hippocampus adding further evidence to the compensatory mechanism theory for a successful memory performance and this was justified by the performance of the MCI group in the face-name association task i.e. 61.2% of Remembered hits which is above chance. These finding extends support to previous fMRI studies which have demonstrated the significance of hippocampus hyperactivation for successful encoding by the MCI group (Dickerson et al., 2005, 2008; Miller et al., 2008b) and its functional association with the neural correlates in the PMC.

Alterations in the functional activity observed in the MCI subjects, i.e. hyperactivation in the hippocampus and failure to deactivate the PMC may prove to be of significant importance in understanding the development of cognitive decline in neurodegenerative disorders. Functional MRI has the potential to detect these functional alterations early in the course of AD, before any significant structural changes have occurred, thus providing us with a possible functional biomarker to detect AD early. The biggest limitation of this thesis work is the sample size of only 7 cognitively normal adults and 5 MCI subjects; however the results from this thesis work nonetheless aids to demonstrate and improve our understanding about the neuronal networks associated with memory function in normal subjects and functional alterations in these networks with neurodegenerative diseases. Future fMRI studies involving subjects across the continuum of cognitive decline with neurodegenerative disease (including individuals with mild AD) and normal aging will help us validate these findings of functional alterations with cognitive impairment. In addition, multimodal studies, combining this fMRI task with amyloid imaging (as assessed with PiB-PET) will provide further insights into the relation between these functional alterations and AD pathology in these individuals. In summary, the findings from the current study provide us with further knowledge about the role of PMC and hippocampus for successful episodic memory function and may provide us with further insights into identifying early functional markers to the cognitive impairment seen in AD.
5. Conclusion

The results from this thesis work demonstrate the neural underpinnings (especially in the hippocampus and PMC) of memory function in normal subjects and patients with memory dysfunction related to functional alterations in MCI subjects. The MCI subjects were found to show significant difference in the functional activity in both the hippocampus (hyperactivation) and the PMC (inability to deactivate) compared to that of the control subjects, suggesting that these functional alterations may serve as potential early diagnostic markers in identifying individuals at risk of developing possible AD.
References


SPM 8; Welcome Department of Cognitive Neurology; www.fil.ion.ucl.ac.uk


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