fMRI and SAGE Test Evaluation of pre-Mild Cognitive Impairment (pre-MCI)

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Introduction: Mild Cognitive Impairment (MCI) is characterized by impaired memory and preserved activities of daily living. fMRI shows increased medial temporal lobe (MTL) activation during memory tasks in MCI patients as compared to lower activation in normal and dementia controls. Recent research has investigated patients with cognitive decline that is insufficient for MCI criteria, but who also appear to be at increased risk for developing MCI and dementia, known as pre-MCI. We compared pre-MCI subjects with matched normal controls using fMRI memory, visual, verbal, and problem solving tasks in an attempt to improve early identification of pre-MCI subjects.
Methods: Right-handed, English speaking pre-MCI patients were age and education matched with normal controls. Each subject completed the National Adult Reading Test (NART) and the Self-Administered Georcognitive Examination (SAGE). fMRI scanning was performed on a 3 T Achieva Philips scanner using an Invivo IFIS-SA fMRI System. Four cognitive tasks were performed during and after fMRI imaging testing: [1] Attention, [2] Verbal fluency, [3] Visuospatial problem solving (VPS), and [4] Memory. Single subject and group functional analysis was performed.
Results: Sixteen subjects (8 pre-MCI, ages 66–82y, and 8 matched normal controls) participated. Pre-MCI subjects showed numerically worse cognitive performance on the verbal fluency, problem solving and attention tasks than controls. While performing these tasks, pre-MCI subjects had reduced activation in the visual cortex during the attention task and in the frontal cortex during the verbal fluency task.
Conclusions: While more research is needed, specific fMRI activation tasks appear to differentiate pre-MCI from normals and may aid both in the initial identification of pre-MCI and possibly in follow-up evaluations looking for progression to dementia.

Keywords: fMRI, SAGE, Mild Cognitive Impairment (MCI), Alzheimer's Disease (AD)

Introduction

Our studies will involve the use of tasks developed to identify functional areas of the brain associated with visual, language and cognitive functions. Sensitivity of each task will be determined by the probability that the targeted region will be activated for individuals with pre-Mild Cognitive Impairment.

The first applications of magnetic resonance imaging (MRI) to mapping brain function were reported in 1991 [1]. Called functional MRI (fMRI), the technology has several advantages over nuclear medicine approaches to brain function mapping, including minimal discomfort, no need to use ionizing radiation or other invasive procedures, easy correlation with anatomical images, and excellent spatial and temporal resolution.

MCI is characterized by impaired memory and preserved activities of daily living [2,3]. This may relate to impairments seen in the functional abilities of these patients. fMRI revealed decreased medial temporal lobe (MTL) activation during memory tasks in MCI patients as compared to controls [5]. This has been utilized to examine the effect of treatment with cholinesterase inhibitors on brain functioning in-vivo in MCI, revealing a significant increase in fMRI activation on memory tasks with treatment [6,7], despite only modest effects on task performance in some cases [6]. Some studies demonstrate significant dissociations in fMRI activation and task performance in MCI [8]. Therefore, fMRI might be more sensitive than task performance to changes associated with treatment.

In order to identify patients at the earliest possible stage of MCI, recent research has investigated patients with memory decline that is insufficient for MCI criteria, who also appear to be at increased risk for developing MCI and dementia, termed as pre-MCI [4]. It will be important to better understand the fMRI activation patterns in such patients in order to establish its utility as a marker for treatment response. However, memory might not be the optimal task for this purpose due to conflicting results, showing that MCI patients have increased rather than decreased fMRI activation during memory tasks [9]. Our preliminary results have shown a decrease in fMRI activation with cholinesterase inhibitor treatment in tasks where performance is preserved, in contrast to treatment related increases reported previously with memory tasks [6,7]. Therefore, we wish to compare pre-MCI patients to normal control patients for fMRI activation during memory tasks and various non-memory tasks. We propose that the non-memory tasks will be more sensitive for detecting a group difference than the memory task activation, and might therefore be better for use as treatment response markers. Therefore, we will compare subjects diagnosed with pre-MCI with age, education level and IQ-matched controls using fMRI. We also hope to gain a better understanding of how to further optimize therapies.

Objectives

To use fMRI to identify and compare functional areas of the brain associated with visual, language and cognitive functions for subject populations that include patients with pre-mild cognitive impairment.

Material and methods

Eight right-handed, native English speaking pre-MCI subjects with memory loss but intact activities of daily living, and 8 age, education level and IQ-matched controls without memory loss took part in this study. The diagnose was made based on the criteria defined by Storandt et. al. [4] Data from these subjects will serve as pilot data, from which a power analysis can be derived for planning a larger study. Handedness was assessed through the Edinburgh Handedness Test. Each participant completed the National Adult Reading Test (NART; 10) the results from which provide an estimate of full scale IQ, verbal IQ, and performance IQ. This is a standard method tool which ensured each subject had the mental capacity to understand the research study. Participants in the pre-MCI study performed the Self Administered Geriatric Evaluation [14] and provided information for the ADCS-ADL scale (an activities of daily living scale; 11).

The tasks included the Visuospatial Problem Solving (VPS) Task, the Attention task, the Verbal Fluency (Letters) task and the Memory task. The subject was prepared using the fMRI Scanning Instructions and Task Details guide. They were shown examples of the VPS Task to familiarize themselves with the task that may be new to them. Upon completion of scanning, the subjects completed the tests to evaluate performance outside the scanner. The VPS task latency was measured, along with memory recall and verbal fluency criteria using the post-scan response forms.

Exclusion criteria was applied for the following conditions:

- Subjects who have any type of bioimplant activated by mechanical, electronic or magnetic means (e.g. cochlear implants, pacemakers, neurostimulators, biostimulators, electronic infusion pumps, etc.);
- Subjects who have any type of ferromagnetic bioimplant that could potentially be displaced or damaged;
- Subjects who have cerebral aneurysm clips;
- Subjects who may have shrapnel embedded in their bodies (such as from war wounds), metal workers and machinists (potential for metallic fragments in or near the eyes), severe auto accident victims;
- Subjects who are pregnant or suspect they may be or have become pregnant. If reasonable doubt exists, beta-HCG testing will be utilized for confirmation at no cost to the subject;
- Subjects who exhibited noticeable anxiety and/or claustrophobia;
- Subjects who cannot adhere to the experimental protocols for any reason, or have an inability to communicate with the researchers;
- Minors;
- Prisoners.

During the fMRI data collection all subject populations had to perform tasks utilizing visual, language, and cognitive functions, as well as cognitive flexibility. The aim of each of the presented tasks was to activate the area of the brain responsible for responding to that task. This allowed comparisons between subject groups in which areas of the brain are utilized for these tasks and evaluate the extent to which each area of the brain is utilized during these tasks. The statistical comparison of scans in the active and the resting states is the research component of fMRI. Visual tasks aimed to activate the visual cortex and stimuli including letters, patterns, photographs, and pictures. Language tasks aimed to activate language areas of the brain involving generating words. Cognitive and cognitive flexibility tasks included tests of memory, problem solving, attention, and decision making.

Visual stimuli were presented through projection on a white screen. Auditory stimuli were presented through magnet compatible headphones. When tasks required a non-verbal response from the subjects they made their responses using a two button press key pad which is also compatible with the magnet. This key pad was linked to a computer in the control room where these responses were registered and collected. This yields behavioral data (their response choice and reaction time) which was analyzed in a statistical software package (e.g. SPSS).

Functional imaging was accomplished using the BOLD (blood oxygen level dependent contrast) technique. First, the brain slices containing the regions of interest was located using a low-resolution scan. Next, high-resolution scans of the entire brain were made for anatomic registra-

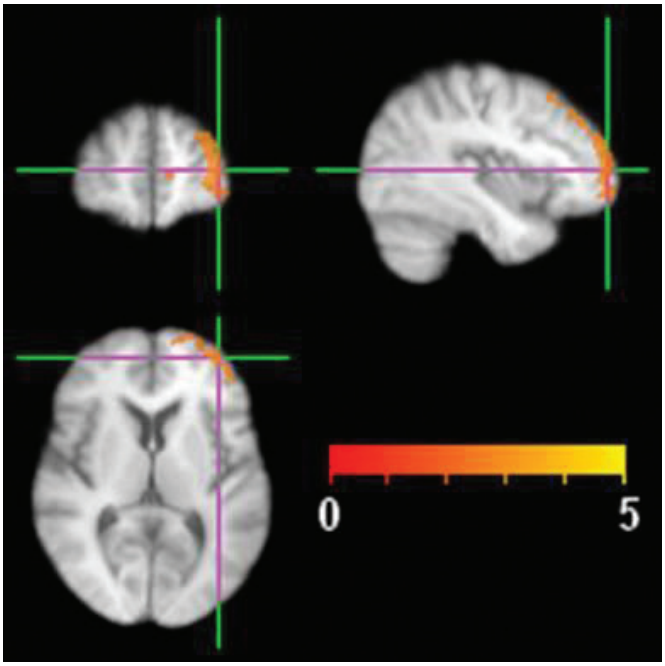

Fig. 1. Visuospatial Problem Solving – Statistically obtained activation map

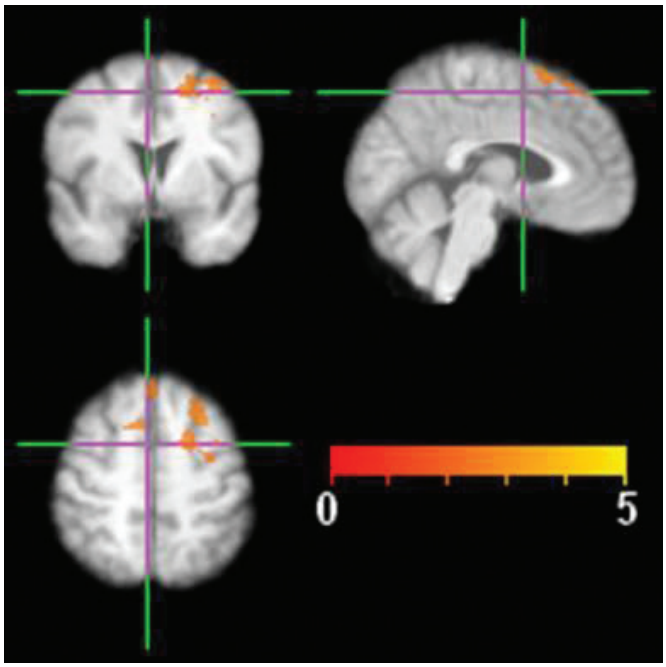

Fig. 2. Word generation – Statistically obtained activation map

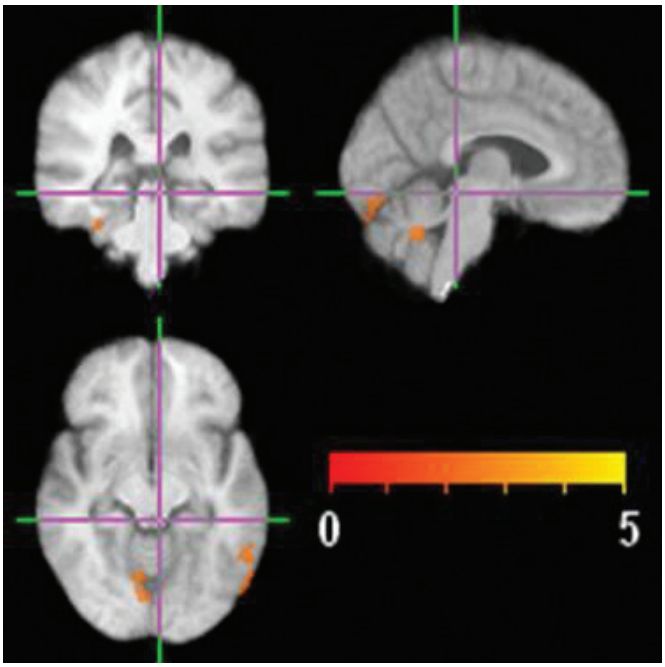

Fig. 3. Attention tasks – Statistically obtained activation map

tion of the functional image data. Then fMRI using echo-planar imaging (EPI) was completed for 28 axial slices with 80 images of each slice gathered for each of the sessions above. Image processing of the fMRI data consisted of a voxel by voxel correlation analysis to determine the activated cortex using the Analysis of Functional Neuro Images software (AFNI) [12] and FMRIB Software Library (FSL) [13] software packages. Both these software packages are widely used and accepted for analysis of fMRI data. The function of these programs is to statistically compare the images during a task to the images during rest in order to determine what brain regions are activated by the task. Voxels are found to be significant if their signal increases and decreases can be correlated with the stimulus. Activated voxels were overlaid on the anatomical image to generate an activation map.

The FDA classified MRI at or below a 1.5 Tesla as well as a 3 Tesla field as a device with non-significant risk, including (i) body exposure to static magnetic fields, (ii) exposure to time-varying magnetic fields, (iii) effects of absorption of energy from radio waves, (iv) hazards from acoustic noise, (v) electrical and mechanical hazards and (vi) some subjects may feel claustrophobic. Magnetic fields were the standard clinically used 1.5T, or the commonly used research strength of 3 T. As is common for routine clinical MRI exams, use of earplugs reduced minimal hazard due to acoustic noise from the MRI system. Throughout the entire procedure the subject was in constant communication with the investigators via a two way audio system linked between the magnet room and the control room being able to speak to investigators at any time during the procedures if they experienced concerns or difficulties.

Table I. Visio Spatial Problem Solving Test Score – Subjects

Pre MCI Subject	1	2	3	4	5	6	7	8
Visio Spatial Problem Solving Test Score (1–4)	1	3	2	1	2	3	1	2

Table II. Visio Spatial Problem Solving Test Score – Control group

Pre MCI Subject	1	2	3	4	5	6	7	8
Visio Spatial Problem Solving Test Score (1–4)	3	3	3	1	1	1	2	3

Statistical Analysis and Quantification of Results

Behavioral data

Data collected from the subject's responses to the tasks presented was statistically compared between participant groups and between drug conditions within groups using ANOVA. Individual t-tests were done to examine individual comparisons.

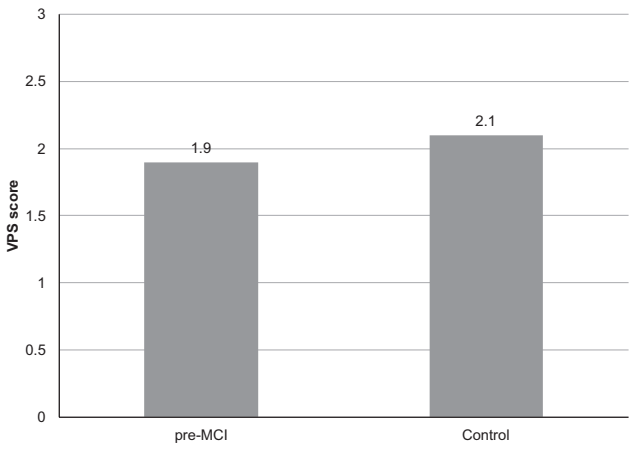

Fig. 4. VPS average values for pre-MCI patients and control group

Table III. SAGE Score for pre MCI Patients

Subjects	1	2	3	4	5	6	7	8
SAGE test	15	22	13	15	17	19	12	20

Table IV. SAGE Score for Control Group

Control	1	2	3	4	5	6	7	8
SAGE test	18	22	22	22	22	22	22	19

Imaging data

Image processing of the fMRI data consisted of a voxel by voxel correlation analysis to determine the activated cortex using both AFNI [12] and FSL [13]. These software packages employed regression and correlation analyses, in order to determine in which areas of the brain the magnetic resonance signal correlates with the task performance. Both these software programs are widely used and accepted for analysis of fMRI data. The function of these programs is to statistically compare the images during a task to the images during rest in order to determine what brain regions are activated by the task. Voxels are found to be significant if their signal increases and decreases can be correlated with the stimulus. Activated voxels were overlaid on the anatomical image to generate an activation map (Fig. 1, fig.2 and fig. 3).

Results

Sixteen subjects (8 pre-MCI – ages 66–82y, and 8 matched normal controls) participated.

Pre-MCI subjects showed numerically worse cognitive performance on the problem solving test (Table I and II and Fig 4) verbal fluency, and attention tasks than controls. While performing these tasks, pre-MCI subjects had reduced activation in the visual cortex during the attention task and in the frontal cortex during the verbal fluency task.

SAGE test was used for this study in order to diagnose pre MCI patients. The score obtained at this test qualified our patients for pre MCI as long as they do not show any impairment in activities of daily living.

Discussions

fMRI is a noninvasive method of detecting alteration in brain functioning with a higher spatial resolution than pet scan or SPECT.

fMRI examines changes in blood oxygenation level dependent (BOLD) signal intensity being an indirect method of measuring neural activity (Matthews et al., 2004).

fMRI meta-analysis study done recently by Yamasaki et al. shows variable results from hyperactivation to hypoactivation of the medial temporal lobe (MTL) because of two factors: ability of subjects to perform tasks during the test (Maculda et al.) and different degrees of cognitive impairment between normal aging and dementia (Hamalainen et al.).

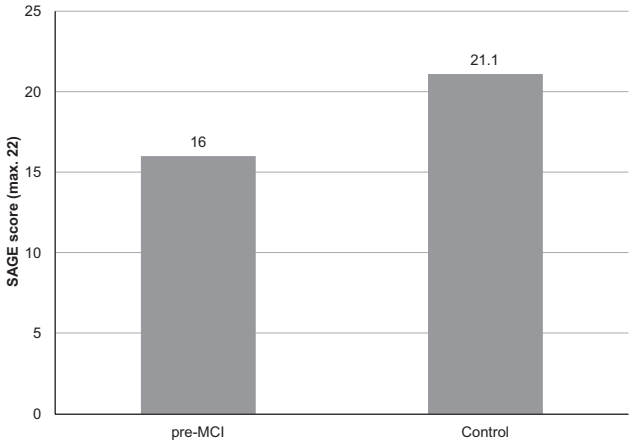

Fig. 5. SAGE test – average score

FMRI studies done with healthy young and elderly adults showed similar activation patterns (Yamasaki et al.)

Visuospatial dysfunction in MCI patients investigated by numerous fMRI studies is linked to Alzheimer's disease (AD) related neuropathological changes (Thulborn et al.).

The current study showed a decrease in frontal cortex activation during memory tasks and occipitoparietal activation during visuospatial orientation.

SAGE test is a sensitive method to evaluate executive function of the brain in patients with pre MCI being used as a screening tool in fMRI pilot study. The test results of 8 pre MCI patients and a matched control group by gender, age and education level with no cognitive complaints and no positive signs in neurological exam, showed differences in orientation, verbal fluency and problem solving capacity. (Table III, IV and Fig. 5).

While more research is needed, specific fMRI activation tasks appear to differentiate pre-MCI from normals and may aid both in the initial identification of pre-MCI and possibly in follow-up evaluations looking for progression to dementia (Table I, II and Fig. 4).

Conclusions

This study will help us better understand the effect of treatment on the brain in pre-MCI subjects. We will also gain a better understanding of how to further optimize therapies.

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