

An fMRI Stroop Task Study of Prefrontal Cortical Function in Normal Aging, Mild Cognitive Impairment, and Alzheimer's Disease

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Abstract: Severe cortex lesions in the hippocampal, parahippocampal and medial temporal lobe (MTL) of Alzheimer's disease subjects have been observed by functional magnetic resonance imaging (fMRI) during memory task performance. To date, fMRI technology has not been used to investigate the frontal lobe function of Alzheimer's subjects. This study determines if fMRI can be used to assess altered prefrontal cortex activity during Stroop task performance in subjects with mild cognitive impairment (MCI) and Alzheimer's disease (AD). Functional magnetic resonance imaging (fMRI) was performed on 9 healthy elderly controls, 9 subjects with mild cognitive impairment and 10 patients with Alzheimer's disease, to examine the prefrontal changes in fMRI activation in relation to the Stroop color-word paradigm. In comparison with controls, MCI subjects showed distinctly increased cortex activity including: the dorsal anterior cingulate, bilateral middle and inferior frontal gyri, bilateral inferior parietal lobule, and the bilateral insular. In contrast, AD subjects exhibited decreased fMRI responses in the regions of the prefrontal cortex listed above. These results imply two different neurophysiological characteristics of MCI and AD. In MCI, a compensatory activity of the prefrontal cortex is observed, whereas in AD a dysfunction of the prefrontal cortex is indicated.

Keywords: Alzheimer's disease, Mild cognitive impairment, Stroop task, fMRI.

1. INTRODUCTION

Dementia is a syndrome consisting of a number of symptoms including: loss of memory, judgement and reasoning, as well as changes in mood, behaviour and the ability to communicate. In many countries, Alzheimer's disease (AD) is the most common type of dementia, with rates increasing exponentially from age 65 [1]. AD is a progressive, degenerative disease of the brain, causing serious impairment to thinking and memory. Mild cognitive impairment (MCI) is a transitional stage between normal aging and AD [2, 3]. Individuals with MCI have, by definition, memory impairment; however, their general cognitive function is normal and their capacity to perform the activities of daily life remains uncompromised.

In previous research, fMRI has been used to observe severe functional lesions in the cortex of AD patients when they performed working memory and visual spatial tasks [4-6]. Although there is evidence of executive processes lesions for AD patients [7, 8], no functional imaging study to date has used fMRI technology to investigate the frontal lobe function of AD patients. The Stroop task is a typical paradigm from cognitive neuroscience, designed to probe attentional and executive phenomena. The Stroop task is an excellent tool to study the function of the prefrontal cortex using fMRI [9, 10]. In our previous studies we have found that AD and MCI subjects exhibited longer reaction time and a higher percentage of incorrect responses during the Stroop color-

word task in comparison to control subjects. In fMRI studies, our group has used an event-related Stroop paradigm, involving the infrequent presentation of mismatched color-word stimuli, to identify the neural correlates of the Stroop effect. This present study aims to determine whether changes and difference in prefrontal cortex activity during the Stroop color-word task could be detected in MCI and AD patients using fMRI imaging.

2. SUBJECTS AND METHODS

Ten AD patients (5 males and 5 females, mean age 66 years, range 54-69 years) and nine MCI patients (5 males and 4 females, mean age 63 years, range 52-67 years) were recruited from the neurology department of Xinqiao Hospital. The clinical diagnosis of probable AD was made by a senior neurologist according to the criteria of the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, IV). All AD patients had undergone neurological, neuropsychological and structural neuroimaging evaluation. Cognitive performance was evaluated through neuropsychological tasks that included: Mini Mental State Examination (MMSE), Clinical Dementia Rating (CDR), California Verbal Learning Test (CVLT II), Rey figure, Logical Memory, verbal and categorical fluency, Boston Naming Task, and digit span. Disease severity was assessed according to the Clinical Dementia Rating scale (Morris et al, 1993), and cognitive status was expressed, independently from the Clinical Dementia Rating, by the Mini-Mental State Examination (MMSE) (Folstein et al, 1975) scores. Participants were excluded if the mini mental state examination (MMSE) was less than 12, the CDR score was greater than 2.0, or there was a history of brain injury or alcoholism. The pa-

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tients with MCI had subjective memory complaints and showed an impairment greater than 1.5 SD from the mean of healthy controls in at least one memory test in the absence of dementia or significant functional loss [1, 2]. The MMSE scores were ≥ 25 in all cases, with the mean MMSE scores being 26.4, ranged 25 to 28. The onset of the disease was below 70 years of age in all patients with AD and MCI. The past or present use of medication to treat AD and mild cognitive impairment was not a criterion for exclusion. Nine volunteers (4 males and 5 females, mean age 65 years, range 57-68 years) with well documented normal cognitive performance, and no known nervous system diseases, were recruited as the healthy controls. At the time of inclusion, all normal subjects were free of medication that could noticeably affect brain function, and none of them had received an acetylcholinesterase inhibitor. The three groups did not differ significantly in age [$\chi^2=4.13$, $df=2$, $p> 0.05$]. All of the participants were right-handed. Each participant gave written informed consent to participate in the study. Details regarding the patients and control volunteers are provided in the Table 1.

The stimuli of the Stroop task were presented on a projector screen, which was mounted onto the patient's bed in the MR scanner. An angled mirror, positioned above the subjects' eyes, provided a full view of the screen. Subjects performed the incongruent Stroop color-word task [8, 11]. The color-word stimuli consisted of a random presentation of three color names (red, green, or blue) presented in one of these three colors. The words were approximately 6 mm x 15 mm and were presented individually against a black background. In the test, subjects were presented with a list of the words "red", "green", and "blue"; however, the ink color of the words was discordant with the presented word (for example, the word "red" printed in blue ink). Then, subjects were asked to say the color of the ink and ignore the word's semantic meaning (for example to respond "blue" instead of "red", considering the case of the previous example). No color names or presentation colors were ever repeated consecutively. Each stimulus was presented for 1250 msec, with an interstimulus interval of 350 msec with 2-3 runs of 60 stimuli presented. The control task consisted of a solid white cross centered on the black background. Subjects practiced, speaking aloud, with the task for one or two runs before scanning. Prior to scanning, all participants were fitted with MRI-compatible corrective lenses to correct for refractive errors, and were trained to perform the stroop task several times. In order to minimize head movement during the scan, the subjects were asked to respond silently to the Stroop task presented when within the scanner. Following scanning, performance was assessed as a measure of reaction time and the percentage of incorrect responses to the stimuli [11, 12].

All images were taken with a Siemens Sonota 1.5 Tesla MR scanner. The subject's head was immobilized using a vacuum pillow and a helmet that was mounted onto the same platform. Twenty T1-weighted axial slices (TE=13 msec, TR=500 msec, field of view=40x40 cm, 256x192 data matrix) were obtained parallel to the anterior-post commissure, which was identified with the aid of a sagittal localizer anatomical image [13]. The functional image data were acquired with an echo-planar imaging sequence (64 x 64 matrix, 220 x 220cm field of view, echo time (TE) 40 ms, volume repeti-

tion time (TR)3000 s, flipangle 90°). High-resolution structural imaging of the whole brain was performed with 3D gradient-echo, T1-weighted sequence, with the following parameters: 256 x 256 matrix, inversion time (TI) 50.5 s, TE 56.3 ms, TR 511.7ms, flip angle 11° . Image processing and analyses were performed with Analysis of Functional Neuro-Images (AFNI) software [14]. The fMRI data was slice time-corrected. Echo planar images were coregistered to the image that minimized image translation and rotation relative to all other images. Data was motion corrected for three translational directions and three possible rotations [15]. Runs with motion in excess of 1.5 mm displacement and 2 degrees rotation were rejected. Corrected images were spatially filtered using a Gaussian filter with a full width half maximum of 3 mm. The block design time-series was convolved to account for the ideal hemodynamic response function. For each voxel, a correlation coefficient was calculated, indicating the strength of relationship between the subjects' BOLD signal and the target reference function. The resulting correlation coefficient for each subject was then compared with a value of zero at each pixel using an unpaired *t*-statistic. These *t*-maps were thresholded at a *P* value < 0.01 and a cluster filter of nine adjacent pixels. After functional and anatomical images for each participant were transformed into the Talairach and Tournoux coordinate system [16], the group composite *t*-maps for fMRI signal change associated with the Stroop task were obtained.

3. RESULTS

The Stroop color-word task performance of AD patients showed a higher percentage of incorrect responses (mean=9.36% [SD=14.13%]) and longer reaction time (mean=678.32msec [SD=155.39]) than those of the MCI group (mean=5.31% [SD=6.21%], $\chi^2=4.59$, $df=1$, $p<0.05$; mean=595.03 msec [SD=157.21], $\chi^2=4.26$, $df=1$, $p<0.05$), which were also higher and longer than those of the control group (mean=4.31% [SD=10.58%], $\chi^2=6.6$, $df=1$, $p<0.05$; mean=528.41 msec [SD=97.55], $\chi^2=4.9$, $df=1$, $p<0.05$). Different prefrontal activations were observed in the three group following the presentation of Stroop color-word stimuli. The control and MCI subjects showed activations of the dorsal anterior cingulate, bilateral middle and inferior frontal gyri, bilateral inferior parietal lobule and bilateral insular. In comparison to control subjects, MCI patients demonstrated distinctly increased prefrontal cortex activation. In contrast, most of the activation in AD patients consisted of the right middle and inferior frontal gyri, and the bilateral inferior parietal lobule. AD patients exhibited decreased fMRI responses in the regions of the prefrontal cortex. AD, MCI and the control subjects were clearly distinguished by differences in brain activation (Fig. 1, Table 2).

4. DISCUSSION

The Stroop color-word task is a common paradigm in cognitive neuroscience used to probe attentional phenomena, such as the selection of processing and the inhibition of habitual responses [17]. Since its introduction in 1935, the Stroop color-word task has been a classic measure of frontal lobe function [9]. Successful performance requires a focus of attention on task-relevant processes, while inhibiting atten-

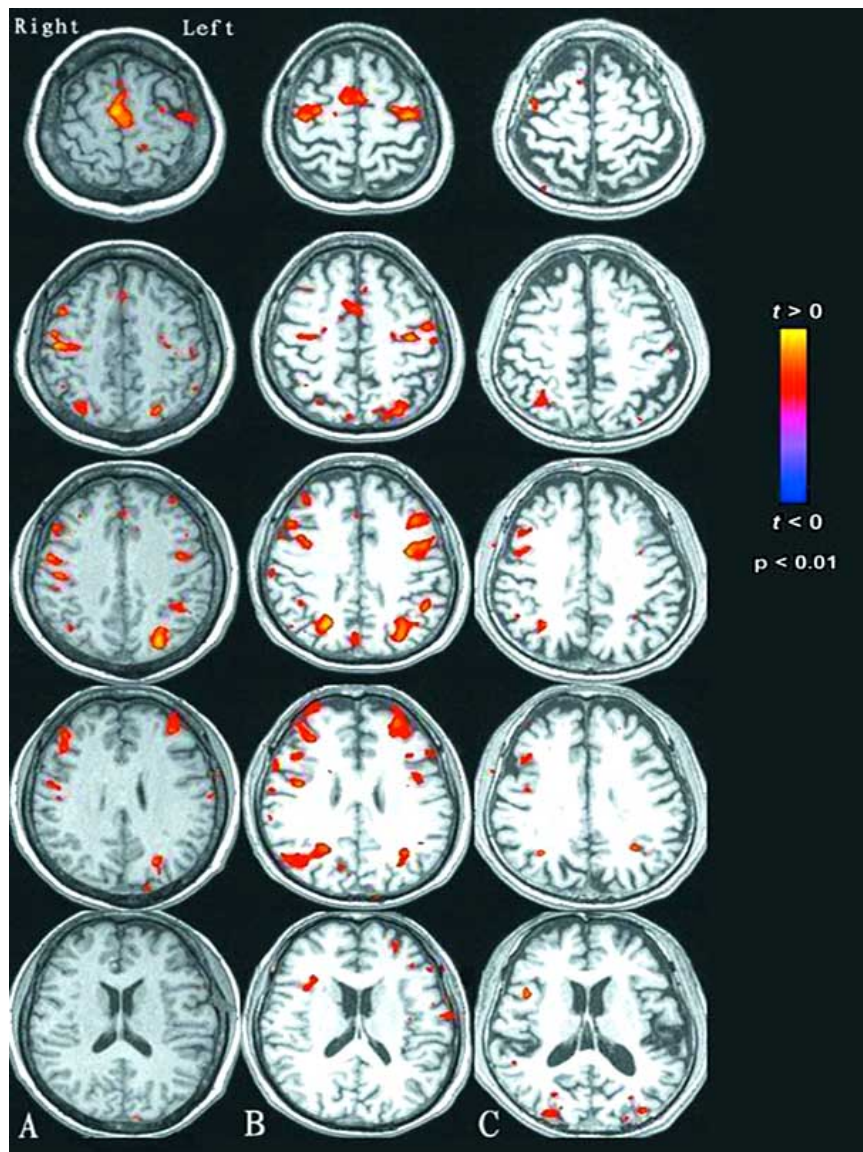


Fig. (1). Brain activation of Alzheimer's disease, MCI and control subjects following presentation of Stroop color-word task stimuli. From left to right: (A) Control subjects (N=9); (B) MCI patients (N=9); (C) Alzheimer's disease patients (N=10). During Stroop color-word task stimulation, MCI subjects showed distinctly increased cortex activation, including the dorsal anterior cingulate, bilateral middle and inferior frontal gyri, and bilateral inferior parietal lobule. AD subjects exhibited decreased fMRI responses in the regions of the prefrontal cortex listed above. Yellow coloured regions represent a more activated state than the red coloured regions.

tion on those which are task-irrelevant. Several studies have utilized the Stroop task and modified Stroop task [18-20] to explore executive processes. In this task, the subject is instructed to name the color of the ink of an incongruent color-word stimulus. Because reading is a more automatic cognitive process than color naming, subjects must resolve cognitive interference to arrive at the correct answer.

Past investigations have reported attentional deficits and cognitive biases in AD [7]. It has been found that AD patients produced significantly larger Stroop interference effects than control subjects, and that the severity of dementia significantly influenced Stroop task performance [8]. In this study, task-related brain activities of the prefrontal cortex were largely decreased in AD patients compared with those of the control subjects. In the prefrontal cortex, brain regions

implicated in conflict monitoring and cognitive control have been identified to be activated by the Stroop paradigm [11, 12]. These findings suggest dysfunction occurs in these brain regions in AD. Until now MCI has been thought to be an accelerated form of normal aging, and no study has found executive control function impairment during Stroop performance [21]. In our study, compared with AD patients and control subjects, MCI patients showed distinctly increased cortex activation, including the dorsal anterior cingulate, bilateral middle and inferior frontal gyri and the bilateral inferior parietal lobule. These findings suggests that an efficient compensatory activity occurs in the prefrontal cortex of subjects with MCI. In investigations of memory, a number of fMRI studies in patients with AD have identified decreased activation of hippocampal and parahippocampal regions in

Table 1. Selected Participants Characteristics

Groups	AD	MCI	Controls
N	10	9	9
Age	65.8(6.1)	63.4(4.6)	65.2(7.2)
Female/male	5/5	4/5	5/4
Education(years)	6.8(2.7)	7.2(3.1)	7.1(4.6)
MMSE	16.7(2.6)	26.4(4.2)	28.8(0.9)

Table 2. Regional Brain Activity in Alzheimer's Disease, MCI and Control Subjects Following Presentation of Incongruent Stroop-Color Word Task Stimuli ^a

Groups	Brain Regions	Talairach Coordinates (x, y, z)	Size (mm ³)
Alzheimer's Disease	Right parietal cortex (inferior parietal lobule)	-52,-59,27	835
	Left parietal cortex (inferior parietal lobule)	51,-62,25	449
	Dorsal Anterior cingulate	9,12,14	337
	Right prefrontal cortex(inferior and middle frontal gyri)	-31,41,22	1289
	Left prefrontal cortex(inferior and middle frontal gyri)	32,24,33	554
MCI	Right parietal cortex (inferior parietal lobule)	-49,-26,28	3268
	Left parietal cortex (inferior parietal lobule)	51,-38,25	2412
	Dorsal Anterior cingulate	3,11,27	3623
	Right prefrontal cortex(inferior and middle frontal gyri)	-20,-0,56	4819
	Left prefrontal cortex(inferior and middle frontal gyri)	24,8,48	4951
	Left insula/inferior frontal gyrus	31,26,5	1512
	Right insula/inferior frontal gyrus	-31,21,5	1786
Basal ganglia	8,-11,9	525	
Controls	Right parietal cortex (inferior parietal lobule)	-35,-70,28	637
	Left parietal cortex(inferior parietal lobule)	33,-71,32	1016
	Dorsal Anterior cingulate	6,13,36	2852
	Right prefrontal cortex(inferior and middle frontal gyri)	-43,22,37	3821
	Left prefrontal cortex(inferior and middle frontal gyri)	42,20,39	3458
	Left insula/inferior frontal gyrus	30,25,8	1257
	Right insula/inferior frontal gyrus	-31,23,13	1196
Basal ganglia	-12,-4,3	461	

^a Coordinates listed identify approximate x, y, and z coordinates based on the average center of mass for an activity. Negative x values indicate the right side of the brain, negative y values indicate brain posterior to the anterior commissure, and negative z values indicate brain regions inferior to the plane defined by the anterior and posterior commissures.

comparison with control subjects during episodic encoding tasks [22, 23]. Using a face-name associative paradigm, Petrella *et al.* found no difference between MCI and controls in MTL activation during encoding, but observed left hippocampal hypoactivation in MCI during the retrieval condition [24]. Using an item based old/new recognition retrieval paradigm, Johnson *et al.* also found right hippocampal hypoactivation in MCI patients compared to controls [25].

The most robust between-group activation difference was observed in the dorsal anterior cingulate and bilateral dorsolateral prefrontal cortex between AD and control subjects. The difference was attributed to decreased prefrontal activity in AD patients. The anterior cingulate cortex (ACC) has often been hypothesized to play an important role in cognitive control. The ACC's specific role in cognitive control is to detect conflict between simultaneously active, competing

representations, and to engage the dorsolateral prefrontal cortex (DLPFC) to resolve the conflict [26]. The level of activation of ACC and DLPFC also seems to reflect the degree of detection and control of conflict [27]. Experimental evidence from both monkey and human studies indicates that the anterior cingulate and dorsolateral prefrontal cortex are important, not only for memory buffering to permit "on-line" processing, but also for inhibition of "prepotent" habitual responses [28, 29]. Activations in the dorsolateral prefrontal cortex have been obtained in other experiments which induce a conflict between process or response tendencies [30]. Individuals with impaired impulse control have demonstrated prefrontal cortex dysfunction [31-34], which has been observed during Stroop task performance [35]. Lesions of the prefrontal cortex could result in impaired performance in the Stroop task [36]. Some human diseases, such as schizophre-

nia, which involves dorsolateral prefrontal and anterior cingulate abnormalities, result in impairments in attentional conflict paradigms [37-39].

The present study is the first fMRI study of the prefrontal cortex of AD and MCI subjects. We found that the activation of the prefrontal cortex by the performance of the Stroop task was different in normal elderly subjects, AD patients, and MCI patients. A dysfunction of the prefrontal cortex was observed in AD patients, whereas an efficient compensatory mechanism was observed in MCI subjects. These findings suggest differences in the neurophysiological mechanisms of the prefrontal cortex amongst the different phases of cognitive impairment.

This study presents some limitations. In order to minimize head movement during the scan, we asked subjects to silently respond to the presented Stroop task while within the scanner. Consequently, task compliance and behavioral performance during the scan could not be measured. Future investigations should address the limitations of this present study by using larger, more diverse sample groups, and by correlating on-line Stroop task performance with measures of brain activity.

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