NEURAL CORRELATES OF SELECTIVE ATTENTION IN COGNITIVELY NORMAL OLDER ADULTS, PATIENTS WITH MILD COGNITIVE IMPAIRMENT AND PATIENTS WITH MILD ALZHEIMER'S DISEASE

by

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Abstract

It is well established that people experience a decline in cognitive functions, such as selective attention (SA), as they get older. SA is the ability to focus on task-relevant information and suppress task-irrelevant information. The Stroop task has been used to assess SA. In the current study, the neural correlates of SA were investigated using functional MRI-Stroop task with cognitively normal older adults (NC), patients with amnestic Mild Cognitive Impairment (aMCI) and patients with mild Alzheimer's disease (AD).

The current study reanalyzed previous master student's data, due to the disagreement in analyzing the data. In the fMRI data analysis, the contrast of correct responses in the naming incongruent color (SC) condition minus correct responses in the reading incongruent word (RW) condition (SC-RW) in series 2a and 2b was reanalyzed using an event-related analysis.

The current Stroop experiment was in a block design with four series: series 0, series 1, series 2a and 2b. In behavioral analysis, the performance of the word-reading task was expected to be significantly better than the color-naming task in series 1, series 2a and 2b because the belief that reading incongruent color word was always an easier task than the color-naming task. The results from behavioral analysis showed that significant more errors were made in reading incongruent color words in series 2a and 2b than in series 1. In the functional MRI data analysis, although brain activation associated with inhibition was expected in the contrast of SC-RW of series 2a & 2b, the results did not show any brain activation. The unexpected results could be due to the RSE that was elicited by the

task switching paradigm of series 2a and 2b. The results suggest that the current Stroop task adapted from the Stroop Neuropsychological Screening Test may not yield a Stroop interference effect of sufficient magnitude to be detected with fMRI in the contrast of SC-RW of series 2a and 2b.

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List of Abbreviations

ACC	Anterior cingulate cortex
AD	Alzheimer's disease
aMCI	Amnestic mild cognitive impairment
BOLD	Blood oxygenation level dependent
CCRT	Cued choice reaction time
CRT	Choice reaction time
DLPFC	Dorsolateral prefrontal cortex
FDR	False discovery rate
fMRI	Functional magnetic resonance imaging
FWE	Family-wise error
IFG	Inferior frontal gyrus
IPL	Inferior parietal lobule
ISI	Interstimulus interval
MFG	Middle frontal gyrus
NC	Normal control
PFC	Prefrontal cortex
PI	Proactive interference
Pre-SMA	Pre-supplementary motor area
RSE	Reverse Stroop effect
RT	Reaction time

RW	Read incongruent color word
SVC	Small volume correction
SA	Selective attention
SC	Name incongruent color word
SNST	Stroop Neuropsychological Screening Test
SPL	Superior parietal lobule
SPM	Statistical parametric mapping
SPSS	Statistical Package for the Social Sciences
SRT	Simple reaction time task
TSI	Task-set inertia
WM	Working memory

Chapter 1 Introduction

The Canadian population continues to age at an accelerated pace. The median age of Canada's population was 39.5 years in 2009, compared to 26 years in 1971. By the end of 2030s, the senior population aged 65 and over will be nearly one-quarter of Canada's population (statistics Canada). This enormous growth of the senior population requires a dramatic re-allocation of health care resources. Older adults are the most vulnerable group to be affected by dementia.

Behavioral research has found a general age-related decline in cognitive functions, such as attention (Craik & Salthouse, 2008). Attention is not a unified term. There are several subtypes of attention, such as selective attention (SA), sustained attention, and divided attention (Perry & Hodges, 1999). SA has been studied the most in basic research (Parasuraman & Haxby, 1993; Townsend, Adamo & Haist, 2006). SA is the ability to suppress task-irrelevant information so that task-relevant information could be performed (Spieler et al., 1996). The Stroop task (Stroop, 1935) is one of the tools most often used for measuring SA and has been regarded as the gold standard for assessment of SA (McLeod, 1991). Many studies have used it in conjunction with neuroimaging techniques to study the neural correlates of SA.

Several brain regions are involved in the performance of the Stroop task in normal older adults. Two general areas have been suggested to be involved in the performance of the Stroop task in normal older people: the prefrontal cortex (PFC) (e.g., inferior frontal gyrus (IFG)) and the parietal regions, such as superior parietal lobule (SPL) (e.g., Milham et al., 2002). PFC activation has been observed in inhibitory control tasks in

several neuroimaging studies (e.g., Garavan et al., 1999; Konishi et al., 1998a, b, 1999). Several imaging studies of attentional control have revealed a frontoparietal network, which proposed functional and structural connections between the PFC and the parietal regions (Melcher & Gruber, 2006; Miham et al., 2002).

The purpose of the current study was to use Stroop-fMRI to investigate the neural correlates of SA in a normal control group (NC), in Alzheimer's disease patients (AD) and in amnestic Mild Cognitive Impairment patients (aMCI), as well as the neural correlates of the erroneous responses that occur mostly in mild AD patients by fMRI using an adaptation of the Stroop task.

Chapter 2 Literature Review

The Stroop Task

Standard Stroop Color-Word Test

The standard Stroop Color-Word Test, sometimes called the Serial Color-Word Test was first conducted as Stroop's Experiment 2 (Stroop, 1935). In this experiment, there were two tests. One test was a naming color test (NC), whereas the other was a naming color of word test (NCWd). Subjects were asked to name the color of solid squares in the NC test. In the NCWd test, subjects were asked to name the color of the word where the color of the ink and the word were different (e.g., the word "green" was printed in "red") (Stroop, 1935; MacLeod, 1991).

The time to name the incongruent color words was 47 s longer than for solid-color squares, showing a significant interference effect in the performance of NCWd test. Stroop (1935) concluded that the amount of interference was reflected in the different reaction times on these two types of tests. The difference in the time for naming the color of words and the color of squares was expressed as the interference of conflicting word stimuli upon naming colors. The interference indicated by Stroop is now known as the Stroop interference effect (Stroop, 1935; MacLeod, 1991).

Congruency Effects/Stroop facilitation

If the color word that is incongruent to the ink color (e.g., the word red printed in green, respond green) could slow down the performance of color naming, then the color word that is congruent to the ink color (e.g., the word red printed in red, respond red) could speed up the performance of color naming (MacLeod, 1991). Many Stroop studies

have confirmed this Stroop facilitation phenomenon since the congruent case was first investigated (MacLeod, 1991). Duncan-Johnson and Kopell (1980, 1981) found reliable facilitation in the congruent condition and strong interference in the incongruent condition relative to the neutral control (name the color of a string of X). In Dunbar and MacLeod's (1984) study, they obtained little facilitation in the congruent condition when the words were turned upside down and backward. But they found a large interference in the incongruent condition.

Dyer (1973a) observed 26 ms of facilitation for the congruent condition compared with naming the color in a control condition (name the color of a string of X), and 48 ms of interference in the incongruent condition. In Dyer's (1973b) another study, he found significant interference (179 ms) and facilitation (55 ms) when compared with naming the color in a control condition. Glaser and Glaser (1982) obtained 16 ms of facilitation and 72 ms of interference using the XXXX-type control. Based on Stroop facilitation studies, it could be concluded that congruency between the irrelevant color word and the ink color often produces facilitation. However, there is usually much less facilitation than the corresponding interference in the incongruent condition when compared with naming the color in a controlled condition, such as naming a string of X (MacLeod, 1991).

The degree of interference

In a standard Stroop color-word paradigm, the amount of interference could be manipulated by changing the task-irrelevant feature of the stimuli (Egner & Hirsch, 2005). The more meaningful the irrelevant word, the more interference it causes. That is to say, when subjects are asked to name the ink color, minimal interference of color

naming is observed if irrelevant verbal stimuli are unrelated to the concept of the color (e.g., name the color of a string of Xs). As the word is more semantically similar to the concept of the incongruent color, the more interference is obtained (MacLeod, 1991). The interference is the greatest when subjects are asked to name the ink color when the stimulus is an incongruent color word (color word red printed in green). The interference is the least when the color word is congruent with its ink color (facilitation). When the task-irrelevant stimulus is a string of X, the interference of naming the color ink is intermediate between incongruent color words and congruent color words (McLeod, 1991; Egner, & Hirsch, 2005)

It is clear that incongruent color-word trials require a higher degree of selective attentional ability than neutral trials (identify the color of a string of X). Congruent color-word trials have lower attentional requirements relative to the neutral and incongruent trials because word identity can facilitate naming the ink color. Therefore, Stroop task performance is influenced by the ability of color words to impair color identification (Milham et al., 2002).

Stroop Neuropsychological Screening Test

The Stroop task has been used as an experimental measure in psychological studies for a long time, and has been adapted for clinical neuropsychological use (MacLeod, 1991). The Stroop Neuropsychological Screening Test (Trenerry et al., 1989) is one of the versions of the Stroop test that has been used in clinical work. Max Trenerry's Stroop (1989) includes two tasks: Color Task and Color-Word Task. Each word stimulus is printed in an incongruent ink color. There are 112 color words in each task. In the Color

Task, subjects are first asked to read the color words as fast as possible followed by the performance of the Color-Word task. In the Color-Word task, subjects are instructed to name the ink color as quickly as they can. Subjects have two minutes to complete each task. The score for each task is the number of correct responses minus incorrect responses within two minutes. Only the score from Color-Word Task is used for interpretation purposes.

The Reverse Stroop Effect (RSE)

A reverse Stroop effect (RSE) is when the color interferes with the word-reading (MacLeod, 1991). The first report of the RSE was by Stroop (1935, Experiment 3). Stroop's (1935) third experiment was called "The Effects of Practice upon Interference." There were four tasks for the experiment: "Read color word" printed in black (RCNb), "read color word" where the word and the ink color were different (RCNd), "name color of solid squares" (NC), and "name color of ink" where the color ink and the word were different (NCWd).

Thirty-two subjects were instructed to perform the RCNb test on the first day. The RCNd test was given the next day and the 13th day to obtain a measure of the interference developed by the practice on the NC and NCWd tests. The RCNd test was also given on the 14th day to get a measure of the effect of a day's practice upon the newly developed interference. On day 3 and day 12, subjects were instructed to perform the NC test. From day 4 to day 11, subjects were asked to perform the NCWd test for 8 days (Stroop, 1935).

Over the practice days of NCWd test, time to perform the NCWd test decreased from 49.6 s to 32.8 s. This result indicated that interference of the word upon the ink color

reduced with practice but was not eliminated (Stroop, 1935; Atkinson et al., 2003). The experiment also explored the development of interference of color stimuli upon reading color words after the practicing NCWd test. Comparing day 2 and day 13 of the RCNd test result, the time spent on the test increased from 19.4 s to 34.8 s, indicating that there was an increase in the interference of conflicting color stimuli upon reading words. However, this newly developed interference was transient. On day 14 of the RCNd test, the time on the performance of the task decreased to 22 s (Stroop, 1935). Since Stroop's experiment, others have been successful in producing a stable reverse Stroop effect and its existence is now widely accepted (MacLeod, 1991).

The RSE is usually not observed in most cases (Atkinson et al., 2003; Ruff et al., 2001). This is also noticed in Stroop (1935) first experiment. In this experiment, the effect of the interference of color stimuli upon reading color words where ink color and word are different was examined. There were four cards in the experiment, with two control-condition cards and two experimental condition cards. Five color words red, blue, green, brown, and purple were used for both control-condition and experimental condition cards. In the control condition (RCNb task), the word stimuli were in black ink, while in the experimental condition (RCNd task), the color words were printed in an incongruent color. Half number of the subjects was in the order of Control 1, Experimental 2, Experimental 1, Control 2, and half was in the reverse order. Subjects were instructed to read the words aloud as quickly as possible.

The results showed that on average subjects spent 2.3 s longer on reading the color words on the RCNd task. But this increase was not significant (Stroop, 1935). Stroop

(1935) concluded that the interference of color stimuli upon reading words was not significant enough when compared with reading words that were printed in black. However, a RSE could be readily elicited in at least three contexts with a vocal response (Blais & Besner, 2007).

First, a RSE could be yielded when subjects have extensive practice in color naming before the word-reading task. However, the RSE does not last long after the word-reading task is completed (Stroop, 1935, Experiment 3). Second, a RSE could be obtained by reducing the readability of the color words, such as making the word much smaller so that it is hard to identify (Melara & Mounts, 1993), or the color word is printed upside down or backward (Dunbar & MacLeod, 1984, Experiment 4). Nevertheless, a review from MacLeod (1991) reported that the RSE from these studies was not reliable as the tasks were so different from the basic Stroop task. Third, a RSE could be observed when subjects are required to switch between color naming and word reading tasks (Allport et al., 1994; Allport and Wylie, 1999).

Task switching

The behavioral effects of task switching have been used to study executive control processes (e.g., Allport, Styles & Hsieh, 1994; Meiran, 1996; Rogers & Monsell, 1995). In such studies, participants are asked to perform two or more simple tasks. In one condition, participants are asked to switch between the tasks on successive trials. In another condition, participants are asked to perform the same task on successive trials. The switch costs usually result both in terms of the increase of reaction time and the number of errors when the two conditions are compared (Monsell, 2003).

The measurement of switch costs is believed to reflect the executive control processes that are engaged when subjects switch between two or more competing tasks (e.g., Wylie & Allport, 2000; Meiran, 1996; Rogers & Monsell, 1995). Several theories have been proposed to explain the switch cost mechanism. Task carry-over is one of the theories that are well established as an important contributor to switch costs (Monsell, 2003).

The task carry-over theory – Task-set inertia hypothesis (TSI hypothesis)

Allport and colleagues (e.g., Allport et al., 1994; Allport & Wylie, 2000) have suggested that switch costs represent an interference effect caused by a carryover of the previous task set into switch trials. In other words, the previous active task set is carried over into the switch trial and thus causes the interference of the switch trial that is previously inhibited. In Allport and his colleagues' (1994) experiment 5, participants were asked to perform switching tasks. One task was to read the incongruent color words (word blue was printed in green); while the other task was to name the incongruent color ink.

Typically participants have little difficulty in reading incongruent Stroop stimuli, and find it hard to name the incongruent color ink (Stroop, 1935; MacLeod, 1991). However, the experiment from Allport and his colleagues' paper (1994) produced a surprising result. A large incongruity effect was found not only on the reaction time for color-naming trials, but also on the reaction time for word-reading trials. The experiment showed that the reaction time for word-reading trials were slower following the performance of color-naming trials when compared to the reaction time of word-reading

trials in pure blocks. In the study, Allport et al. (1994) did not detect a reliable switch cost for color-naming trials during the switch tasks when compared to the reaction time of color-naming trials in pure blocks. The results indicated that there was an asymmetric switch cost, which was more associated with word-reading task.

Later experiments have supported this asymmetric switch cost (Allport & Wylie, 2000; Wylie & Allport, 2000). In these experiments, they found a switch cost for color-naming trials. However, the cost was much smaller than the switch cost for word-reading trials. In another example, Meuter and Allport (1999) found an analogous finding when bilingual subjects were asked to name digits in their dominant and non-dominant languages. They reported that subjects were slower to name digits in their second language on non-switch trials. But on switch trials, subjects became slower in naming digits with their first language.

The finding that larger switch costs for a better learned, easier and more dominant task is difficult to explain. Allport et al. (1994) proposed the task-set inertia hypothesis to explain this paradoxical finding. They hypothesized that a form of proactive interference (PI) arising from the performance of a previous competing task was a major contributor to switch costs in reaction time. Proactive interference is defined as the lost of current information (word-reading in this case) that is due to the interference of previously learned, similar information (color-naming) (Allport et al., 1994). Allport and his colleagues (1994) suggested that these PI effects resulted from task-set inertia. They believe that when subjects are performing the color-naming task, the inhibition of the word-reading process may be required. This inhibition will be carried on to a switch trial

where word-reading is now appropriate. This persisting inhibition delays the generation of the word-reading response (Allport et al., 1994).

Furthermore, during the word-reading switch trials, because color-naming is still activated, information relevant to the color-naming task interferes with word-reading trials, which leading to a RSE, resulting in a large switch cost. In the word-reading task, the requirement to suppress color naming is absent because word-reading is a more automatic and easier task. Hence, there is no carryover of inhibition during the performance of color-naming switch trials. As a result, a small or absent switch cost is found in color-naming trials (Allport et al., 1994).

Aging and the Stroop task

One of the first studies to address Stroop interference in healthy older adults was a life-span study conducted by Comalli, Wapner, and Werner (1962). They found an increased Stroop interference with aging in people from age 65 to 80 years. This finding is confirmed by other Stroop studies which indicate a larger Stroop effect for normal older adults when compared with younger adults (e.g. Hartley, 1993; Panek, Rush & Slade, 1984). However, some studies argue that an age-related increase in Stroop interference is a result of slowed processing in older adults (Verhaegen & De Meersman, 1998; Uttl & Graf, 1997).

In a meta-analysis of 20 behavioral studies on the Stroop interference effect, Verhaegen and De Meersman (1998) found no significant differences in interference effect between younger and older adults. They suggested that the apparent age-associated increase in the Stroop effect is due to general slowing. Although there are contradictory

findings in interpreting the Stroop interference effect in older adults, the results of many studies are consistent with the inhibition theory of cognitive aging. Older adults consistently produce a disproportionate increase in interference in comparison with younger adults when interference proportions are computed (e.g. Comalli et al., 1962; Panek et al., 1984; Dulaney & Rogers, 1994).

Alzheimer's disease (AD)

Dementia, which first affects the higher-level cortical functions of the brain, is a common disease in older adults (Jorm, 1987; Petersen, 2000). Alzheimer's disease (AD) is the most common type of dementia, which is one of the leading causes of death in the older population (Petersen, 2000). Age is the strongest risk factor for AD. Although AD can occur in young population, the incidence increases dramatically with advancing age (Cummings, 2004; Bachman, et al., 1993; Fillenbaum, et al., 1998; Ott, et al., 1998; Rocca, et al., 1998).

AD is a progressive and fatal neurodegenerative brain disorder (Cummings, 2004). People with AD initially show memory deficits, which is regarded as the hallmark of the disease (Belleville, Chertkow & Gauthier, 2007). A defect in delayed verbal recall is an early sign of the memory problem (Welsh, et al., 1991). The core features of AD diagnosis are that there are significant impairments in memory and at least one other cognitive domain, such as language, orientation, and abstract thinking. These impairments lack of other explanations for the decline and significantly interfere with people's day-to-day functional activities (Petersen, 2000; Dickerson & Sperling, 2008).

Amnestic mild cognitive impairment (aMCI)

Individuals who ultimately develop AD likely will pass through a period of amnestic MCI (aMCI) (Petersen, & Morris, 2005). Amnestic MCI is considered to be a transitional stage between normal aging and mild AD (Petersen, 2000; Morris, et al., 2001). People with aMCI are consistently shown to have a high risk for developing AD (Petersen, 2000). The progression rate from MCI to AD is in the range of 10% to 15% per year, compared with normal older adults who convert to AD at a rate of 1% to 2% per year (Petersen, et al., 1999). In the current study, the term MCI refers to aMCI.

Individuals who have MCI have a memory deficit greater than other healthy adults of the same age and sex who have a similar educational background. However, these memory impairments do not interfere with basic activities of daily living. The diagnosis of MCI is clinical. The characteristic of people with MCI in clinic includes subjective memory impairment corroborated by an informant, objective memory impairment, normal general cognitive function, normal activities of daily living and not demented (Petersen, 2000). Usually, persons with MCI become aware of their forgetfulness. Neuropsychological testing is used in assessing objective memory impairments in MCI. The cutoff score for the performance of the test is generally set at about 1.5 standard deviations below the average performance of individuals with similar age and education on standard memory tests, such as California Verbal Learning Test (CVLT) (Petersen et al., 1995; Petersen et al., 1999; Petersen, 2000).

Interdependence of attention and working memory (WM)

Attention control plays a crucial role in the organization, management, and completion of complex cognitive activities. Attention is usually involved when the tasks cannot be performed automatically, or when the tasks are demanding (Norman & Shallice, 1984). Attentional control can be regarded as an executive process used to focus attention on relevant information and inhibit irrelevant information (Engle, 2002; Smith & Jonides, 1999). Many studies indicate that attention is responsible for the performance of WM tasks (Conway & Kane, 2001; Engle, 2001, 2002; Engle, Kane, & Tuholski, 1999).

WM temporarily holds the information that is required to carry out complex cognitive tasks. WM is engaged in many executive processes, such as the selection, initiation, and termination of information-processing functions, such as encoding, storing, and retrieving data. Baddeley and Hitch (1974; Baddeley, 1986, 1993) suggested a WM model that emphasized the importance of the interaction of attentional control and memory maintenance in order to perform complex cognitive tasks.

It is clear that attention and WM are mutually dependent functions (Baddeley, 1986; Wagner, 1999). WM is essential to attention processes for the selection of task-relevant actions as it temporarily holds information for current goals or behaviors. In turn attention can further help in prioritizing the order of the contents of WM (Milham et al., 2002). The interdependence of attention and WM presents a challenge in understanding the etiology of cognitive deficits associated with aging (Salthouse, 1996). Researchers need to verify whether an impairment is due to WM function, or is due to changes in

attentional function when they are studying age-related declines in performance on WM tasks (Milham et al., 2002).

The relationship between WM and attention can be understood in the context of inhibitory control. Inhibition processes prevent the actions of an inappropriate response that is elicited by potentially attention-capturing stimuli (Bjorklund & Harnishfeger, 1995). Current models of attention state that SA is responsible for inhibitory functions (e.g., Posner & Dehaene, 1994; MacDonald et al., 2000; Neill, 1977; Tipper, 1985).

Studies of age-related cognitive change suggest that the decrease in WM with age is related to the decline of selection processes. In other words, WM processes become increasingly affected by task-irrelevant information with aging (West, 1999a; May et al., 1999). West (1999a) found that older adults were more susceptible to the presence of a visual distractor than younger adults when older adults attempted to remember the location of a target stimulus. West (1999a) concluded that the reduced speed of performance in older adults was due to the decreased ability to inhibit irrelevant information.

Several studies have suggested that age-related decline in inhibitory function results in the increased ability of irrelevant information to disrupt WM processes (Milham et al., 2002; West, 1999a; May et al., 1999; May et al., 1995). Hasher and Zacks (1988) stated that older people have decreased ability to prevent the entrance of irrelevant information into WM, to suppress irrelevant information within working memory, and to inhibit improper responses. It is apparent that the study of inhibitory control is essential for understanding age-related decline in WM. Additionally, it has been suggested that

inhibitory processes not only interact with WM, but they also play a role in organizing cognitive performance in various domains of cognition (Clark, 1996; Kok, 1999).

Attention control in persons with AD and MCI

Although impaired memory has been well accepted as the clinical feature of both MCI and AD, extensive evidence has suggested that deficits in attentional control are an important feature of the cognitive deterioration in patients with MCI and early AD (Spinnler, 1991; Balota & Faust, 2001; Della Sala & Logie, 2001; Perry & Hodges, 1999). Perry & Hodge (1999) believe that apart from memory deficits, attention is the first non-memory function to deteriorate. The idea of very early attentional deficits challenges the previous notion that only memory is impaired in early AD and MCI.

Clinical observations of patients with early AD reveal that they often complain of having great difficulties in carrying out everyday tasks. These tasks include shopping for different items in different stores, keeping track of conversations with multiple persons, driving in heavy traffic or managing finances (Shallice & Burgess, 1991; Alberoni et al., 1992; Belleville, Chertkow & Gauthier, 2007). Attentional control plays an essential role in performing these daily tasks. These observations posit that the impairment of attention functions could be an early feature of AD (Belleville, Chertkow & Gauthier, 2007; Perry & Hodges, 1999). Studies of attentional control also show deficits of attention in persons with MCI. In an attentional study, performance on speed and planning was worse in persons with MCI than in normal older adults, but better than AD patients (Goldman et al., 1999).

Perry et al. (2000) indicated that not all subtypes of attention were equally impaired in early AD. He pointed out that the attentional tasks involving response inhibition, target selection or switching were particularly affected in early AD. In Perry and Hodges' (1999) comprehensive review, they suggested that facilitatory functions of attention, such as detecting targets, were relatively preserved in early AD. On the contrary, mild AD patients were more impaired in coping with interference tasks (Perry & Hodges, 1999). It is believed that deficits of response inhibition could be used as an early feature for clinical diagnosis of early AD (Perry & Hodges, 1999).

Inhibitory control in patients with AD and MCI

Inhibitory control is a fundamental component of SA (Tipper, 1985; Neill et al., 1995). The Stroop task is one of the most used tools to study inhibition (McLeod, 1991). The Stroop task is very sensitive to AD, even at very early stages: Patients in early stages of AD show a larger Stroop effect when compared with healthy older adults (Grady et al., 1988; Haxby et al., 1990; Spieler et al., 1996; Koss et al., 1984; Fisher et al., 1990). This has been evidenced in the Stroop study of Spieler et al. (1996). In their study, it was found that compared with healthy older adults, patients with AD made more intrusions errors when naming incongruent color words (Spieler et al., 1996). These studies suggest the impaired inhibition in early AD.

Although many studies have proposed inhibition deficits in early AD, little is known about how early the inhibition impairment occurs in the development of AD (Belanger, Belleville & Gauthier, 2010). MCI is considered as the prodrome to AD (Petersen & Morris, 2005). Increasing evidence has supported the presence of deficits of inhibitory

control using the clinical Stroop test (Kramer et al., 2006; Belanger, Belleville & Gauthier, 2010; Li et al., 2009).

Functional Magnetic Resonance Imaging (fMRI)

Stroop-fMRI design paradigms

The key concept of the fMRI images is functional contrast. The images distinguish between active and non-active areas of the brain. The functional contrast is usually based on the proportion of deoxygenated hemoglobin in the blood. The magnitude of the change in deoxygenated hemoglobin concentration leads to compare whether a region is active or inactive (Huettel, Song & McCarthy, 2004).

Take the Stroop task as an example. It is well established that people have longer reaction time to name the incongruent color ink (Stroop, 1935; MacLeod, 1991). Cohen and his colleagues (1990) demonstrated an important finding in pure blocks of the Stroop tasks using their model: the cost of incongruent trials is greater than the benefit of congruent trials when compared with neutral trials. The model shows that incongruent Stroop stimuli have the largest interference. In other words, incongruent Stroop stimuli make the highest selective attentional demands. The comparison between incongruent Stroop stimuli with either neutral stimuli or congruent color stimuli will give the magnitude of the Stroop interference effect (Cohen et al., 1990). Therefore, modern Stroop-fMRI studies use the contrast of either (naming incongruent color)-(naming color) in neutral condition or naming incongruent color-naming color in a congruent condition to manipulate attention level. These contrasts in turn give the activated brain areas that are associated with inhibition (Milham et al., 2002; Pardo et al., 1990).

A word-reading condition is sometimes included in Stroop-fMRI studies (Atkinson et al., 2003). The words used in these studies are printed in black. Although the task is different for the two types of stimuli, the magnitude of the Stroop effect could still be detected in the contrast of (naming incongruent color)-(reading words printed in black) as there is no conflict between the word and the ink color of words printed in black (Atkinson et al., 2003). In the current study, the Stroop paradigm was different from a typical Stroop-fMRI study. The word-reading condition was included where the word was incongruent with its color. Previous work suggests that the reaction time in reading incongruent Stroop stimuli is not different from reading color words that are printed in black (Stroop, 1935). However, when the task of reading incongruent Stroop stimuli is switching with the task of naming incongruent Stroop stimuli, the difficulty level for reading incongruent Stroop stimuli would be higher than when it is performed in pure blocks (Allport et al., 1994; Wylie & Allport, 2000; Allport & Wylie, 2000).

Neuroimaging studies of attention

As the importance of the interdependence of attention with WM has become more evident, a great number of studies have focused on investigating the neural correlates of SA/inhibitory control. Initial lesion studies have indicated that left frontal lobe pathology results in poor performance in the Stroop task (Perret, 1974). Studies also found that both individuals with left and right cerebrovascular accidents and AD have low scores on the Stroop test (Trenerry et al., 1989; Binetti et al., 1996; Pachana et al., 1996). In Aine and Harter's (1984a, 1984b) study of evoked potentials, they claimed that left hemisphere was more associated with the Stroop interference.

Many studies have used the Stroop task in conjunction with fMRI technique to study brain regions that are engaged in inhibitory control (e.g., Zysset et al., 2007; Langenecker et al., 2004; Pardo et al., 1990). In such studies, it has been proposed that several brain regions are involved in the performance of the Stroop task (e.g., Pardo et al., 1990; Bench et al., 1993; Langenecker et al., 2004). The dorsolateral prefrontal cortex (DLPFC) and the parietal regions are the most commonly observed activated areas in inhibitory control studies. These areas are believed to be responsible for selecting and maintaining task-relevant representations (e.g., Banich et al., 2000a, 2000b; Banich et al., 2001; Milham et al., 2002; Langenecker et al., 2004).

Previous lesion and imaging studies have revealed the role of the DLPFC in attention (Casey et al., 1997; Pujol et al., 2000; Banich et al., in press). Significant activation in prefrontal regions in incongruent color-naming trials as compared to neutral trials has been found and the activation of the DLPFC becomes more prominent with increasing attentional demands in younger adults (Banich, 1997; Banich et al., 2000).

Studies have also suggested that the prefrontal cortex (PFC) may play a role in maintaining an attentional set (Rainer, 1998; Rogers & Monsell, 1995). A study in monkeys revealed that lateral prefrontal cortex appeared to be activated while monkeys were anticipating a choice in a delayed paired associate task (Rainer et al., 1999). In a switching task study, a reliable activation in the DLPFC and associated areas was found while individuals were switching from one task to another (Rogers & Monsell, 1995). Another PET study also found a reliable activation in the left DLPFC while participants

were required to switch between shape and color tasks as compared to performing only one of the tasks (Meyer et al., 1997).

Several studies have suggested that activation of the DLPFC and the parietal regions co-occurs to maintain an attentional set (e.g., Banich et al., 2000a, 2000b; Cabeza & Nyberg, 2000). Studies have suggested that the parietal regions are involved in attentional control and visual selection (Milham et al., 2002; Thornton & Raz, 2006). Several researchers have illustrated the existence of both structural and functional connectivity between DLPFC and parietal cortex (e.g., Morecraft et al., 1993; Cabeze et al., 1997), which further supports a possible interdependence of these regions in maintaining an attentional set (Milham et al., 2002).

Several neuroimaging studies have found age-related brain activation changes within the PFC and parietal regions during the performance of attentional tasks (e.g., Banich et al., 2000b; Cabeza & Nyberg, 2000; Milham et al., 2002). One Stroop-fMRI study reported activation differences between younger and older adults, predominantly in frontal regions. The younger adults showed greater activation in left middle frontal gyrus (MFG), and superior parietal lobule (SPL); while older adults had greater activation in bilateral inferior frontal gyri (IFG) (Milham et al., 2002). However, the result of greater activation in younger adults than older adults is not consistent with some of the studies (e.g., Cabeza et al., 1997; Nielson et al., 2002). In summary, Stroop-fMRI studies have revealed various frontal and parietal regions that are associated with inhibitory control processes.

Many inhibitory studies using the Stroop task also have demonstrated the activation of the anterior cingulate cortex (ACC) (e.g., Pardo et al., 1990; Carter et al., 1995). A PET study showed a robustly active ACC during the performance of the Stroop task (Pardo et al., 1990). Another study also showed the activated ACC in the contrast of naming incongruent color and neutral word (Taylor et al., 1997). However, the finding of an activated ACC during inhibitory tasks is not consistent. Taylor et al. (1997) did not observe the ACC activation when the taboo words (e.g. shit) were compared with incongruent color-naming words. The cognitive functions of the ACC are debatable. Two major roles of the function of the ACC have been proposed: a) Detecting of response conflict (e.g., Barch, 1999; Carter et al., 2000) and b) monitoring for errors that result from failure to overcome response conflict (Gehring et al., 1993; Dehaene et al., 1994). Event-related fMRI studies have revealed enhanced activation in the ACC during error trials as compared to correct trials (Kiehl et al., 2000; Menon et al., 2001). Other neuroimaging studies have found increased activity in the ACC during cognitive tasks that induce response conflict, such as the Stroop task (e.g., Carter et al., 1995; Carter et al., 2000).

The current project

The goal of the present study was to investigate the neural correlates of selective attention with a Stroop task using fMRI with normal older adults, patients with amnestic MCI and patients with mild AD. All data have been obtained from a previous Stroop-fMRI block-design study that was conducted by the former master student Jen Bowes. In her study she also investigated the neural correlates of SA. This was done using the main

contrast of correct responses in the say color condition (SC) – correct responses in the read word condition (RW) (SC-RW). Brain activation associated with inhibition in this contrast was expected as the believe that color-naming task required greater SA and reading incongruent color word was always an easier and more automatic task than the color-naming task. The contrast of SC-RW was expected to give a magnitude of Stroop interference.

In her study, she found brain activation in the contrast of SC– RW with a block analysis. In the fMRI data analysis, she combined series 1 with series 2a & 2b in the contrast of SC - RW to examine the brain activation associated with inhibition. The results were reported from uncorrected p-value 0.05 level. Uncorrected p-value 0.001 was first applied to each subject, and then the uncorrected p-value was changed to 0.05 for the multiple comparisons in each group. The reason the uncorrected p-value was changed to 0.05 was that no activation was found when uncorrected p-value 0.001 was applied to each group. I do not agree how she analyzed the data. First, the paradigm of series 1 was different from the paradigm of series 2a & 2b. Thus, I do not think series 1 should be combined with series 2a & 2b in the contrast of SC-RW. Second, the use of uncorrected p-value 0.05 was very liberal and false positives were very likely to be involved. I also reanalyzed the contrast of SC-RW in series 2a & 2b using uncorrected p-value 0.001, and no activation was found in this contrast.

I am really interested in finding out the reasons of the absent brain activation in the contrast of SC-RW in series 2a & 2b. Therefore, in the current study, 1) I did the behavioral analysis to look at the number of erroneous responses in each condition in

series 1, series 2a and 2b. Series 1 was analyzed separately from series 2a and 2b because of the paradigm differences. 2) I reanalyzed the contrast of SC-RW in series 2a and 2b using an event-related analysis. The reason to use an event-related analysis is that it allows the analysis of individual responses. In the block analysis, incorrect responses could not be separated from correct responses within a block. These incorrect responses within the block could add variability and resulted in the absent brain activation in the contrast of SC-RW in series 2a and 2b. In the current study, we were also interested in the neural correlates of the incorrect responses and this was done by the contrast of incorrect responses – correct responses in the RW condition of the AD group. I expected to observe activation of the ACC. The NC group was not included because there were not enough incorrect responses to do the individual comparison. The MCI group was not included due to its small size. 3) I believed the existence of the RSE in the RW condition in series 2a and 2b and the absent brain activation in the SC-RW in series 2a and 2b could be due to the RSE. Therefore, in the current study in order to examine the existence of the RSE, two more contrasts were conducted using a block analysis: correct responses in the RW condition- rest and correct responses in the SC condition-rest.

Chapter 3 Methods

All behavioral and functional MRI data were obtained from previous master student Jen Bowes' study. Please refer to Jen Bowes' thesis that was submitted to Queen's University for the detail of the study methods.

Participants

The current study included healthy older adults (NC), patients with amnestic mild cognitive impairment (aMCI), and patients with mild Alzheimer's disease (AD). The control group was recruited from the community. Patients with aMCI and mild AD were recruited from the outpatient memory disorders clinic in Kingston, ON. Twenty-one normal adults, 19 participants with mild AD and 9 participants with aMCI were recruited for the current study. All participants were screened using a battery of neuropsychological tests before going into the MRI machine: Mini-Mental State Examination (MMSE), the Montreal Cognitive Assessment (MoCA), the Mattis Dementia Rating Scale (DRS) and the Stroop test. Participants were provided informed consent before undergoing any study procedure. The study protocol and procedures were approved by Queen's University Research Ethics Board.

Inclusion criteria: All subjects were volunteers between the ages of 50 and 85 years, and were proficient in English. Before performing the Stroop task in the MRI machine, all subjects needed to perform a battery of neuropsychological tests to ensure they were eligible to the study. All subjects from the MCI group and NC group should be able to comprehend and complete a battery of neuropsychological tests including the MMSE, MoCA, the Mattis Dementia Rating Scale (DRS), the California Verbal

Learning Test (CVLT), and the Stroop test. Subjects from mild AD group should be able to perform MoCA, MMSE, DRS and the Stroop test.

In the NC group, subjects with a MMSE ≥ 26, MoCA ≥ 26, DRS ≥ 123, CVLT verbal recall sub-scores higher than 1.5 SD below the average performance of individuals with similar age and education were included as cognitive normal adults. The diagnosis of aMCI was based on Peterson's criteria (Peterson, et al. 1999), and was confirmed by the geriatrician of the outpatient memory clinic. Subjects with MMSE ≥ 26, MoCA ≥ 20, DRS ≥ 123, CVLT with at least two verbal recall sub-scores equal to or lower than 1.5 SD below the mean, with a normal general cognitive function after being matched for age, sex, and years of education were included in the aMCI group. The diagnosis of AD was confirmed by the geriatrician of the outpatient memory clinic as well. In the AD group, subjects with a score on MoCA between 15 and 26 were included.

Exclusion criteria: Subjects who were not able to perform the Stroop test were excluded from the study. Subjects who had history of neurological disorders other than cognitive impairment or dementia, psychiatric disorders, acute illness, color blindness, macular degeneration were excluded from the study. Participants with implanted metallic objects, pacemaker, metallic valves, surgical pins, stents, aneurysm clips, prosthesis or other implants were excluded due to high magnetic field in the MRI.

Functional MRI Stroop task

The Stroop task used in the current study was an adaptation of the Stroop Neuropsychological Screening Test (Trenerry et al., 1989; Bowes, 2009). Participants were asked to either read the incongruent color words or name the incongruent color

words, for example, a color word blue that is printed in red (see figure 1). If the subject is asked to read the word, the answer would be blue; if the subject is asked to name the color, the answer would be red. There were four color word stimuli used in the Stroop-fMRI experiment: green, blue, red and tan. These color words used in the current Stroop task were the same as they were in the Stroop Neuropsychological Screening Test. Participants were allowed to name the color tan as either yellow or brown. Participants' verbal responses were marked as correct, incorrect (name the color instead of reading the words or read the word instead of naming the color; or incorrect responses that were not due to interference: i.e. during the color-naming task: word blue in red ink with a response of tan), missed (no responses to the word stimuli) and corrected responses (participant initially said an incorrect response but was able to correct themselves). (i.e.,

The Stroop experiment had a block design with four runs: series 0, series 1, series 2a and series 2b. Subjects were instructed to either "read the word" (RW) or "name the color ink" (SC) prior to each task block. There were 16 word-stimuli in each task block, and each word was presented for 1.75 seconds on the screen with no inter-stimulus interval. Each task block was 28-sec long and was separated by a 14-second rest period during which time either a fixation cross or instructions for the subsequent block (RW, or SC) was provided in writing.

There were four task blocks in series 0 where the color word stimuli were presented in black ink and participants were instructed to read the word. There were eight task blocks in series 1, series 2a and series 2b. The color words in each block were presented in an incongruent color (e.g., the word "blue" printed in red ink). In series 1, participants

were instructed to read the color words for the first four blocks followed by naming the ink color for the next four blocks. In series 2a and series 2b, each task block alternated between read the color word and name the color ink. Figure 2 presents the Stroop-fMRI experimental paradigm.

BLUE **GREEN** **TAN** **RED**

Figure 1. fMRI-Stroop task. When subjects were instructed to read the word, the answers were blue, green, tan and red; when subjects were instructed to say the color, the answers were red, blue, green and tan.

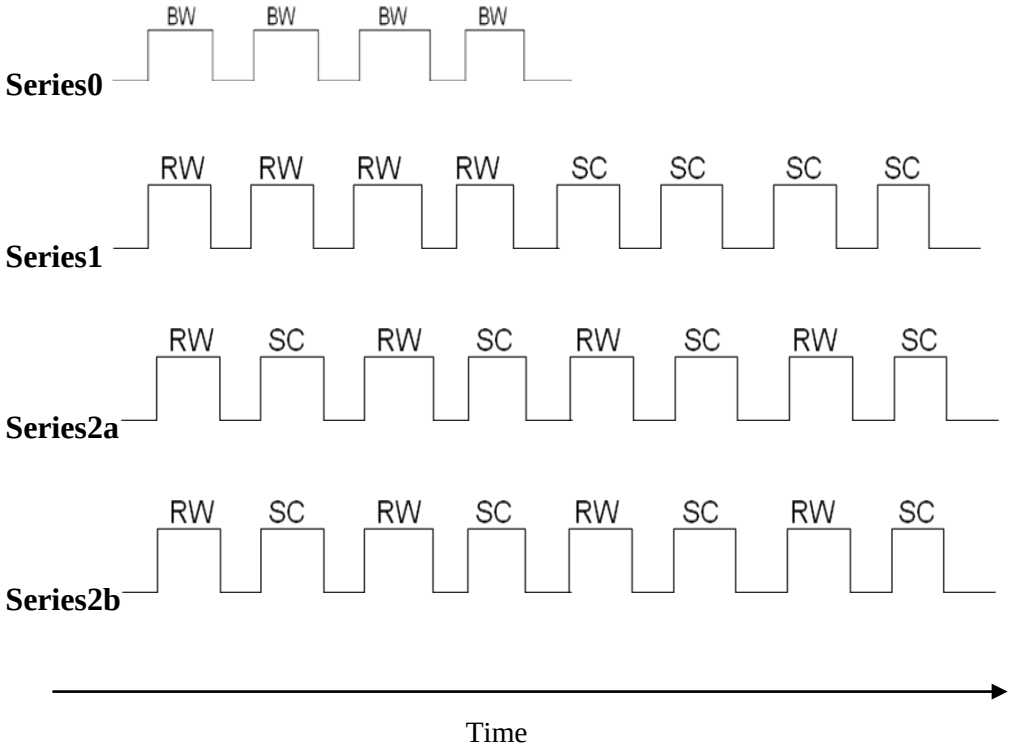


Figure 2. Stroop-fMRI experimental paradigm.

Data Analysis

Stroop-fMRI task behavioral data analysis

The behavioral data analysis was performed using Statistical Package for the Social Sciences (SPSS), version 17.0. (SPSS Inc., Chicago, IL). Data for the behavioral analysis

was collected from 21 normal control (NC) subjects, 9 mild cognitive impairment patients (MCI), and 19 Alzheimer's disease patients (AD). Responses of series 1, series 2a and 2b were included in the behavioral analysis. Participant's verbal responses were categorized as correct, incorrect, corrected, or missed. Incorrect, corrected and missed responses were regarded as erroneous responses, and were included for the behavioral analysis. The task paradigm of series 1 was different from the paradigm of series 2a and 2b because in the later two series the two tasks were alternating. Therefore, erroneous responses from series 1 were analyzed separately from erroneous responses from series 2a and 2b. Non-parametric analysis of K-independent sample test, K-related sample test and 2-related sample test were conducted. The behavioral analyses were held to a significance criterion of $p \leq 0.05$.

Stroop-fMRI task functional data

The functional data were analyzed using Statistical Parametric Mapping (SPM5; Wellcome Department of Cognitive Neurology, University College London, UK, www.fil.ion.ucl.ac.uk/spm/spm5/html).

In the current study, only series 2a and 2b were used for the fMRI data analysis. In the behavioral analysis, corrected, incorrect and missed responses were included as the erroneous responses in series 1, series 2a & 2b. Different from the behavioral analysis, only the incorrect responses that were due to interference (i.e., name color instead of reading the words) were included in the fMRI data analysis as the erroneous responses. An event-related analysis was used. When the stimuli were selected for the SPM5 analysis, the time when the stimulus was presented on the screen was selected and

entered to the SPM5. Every first stimulus of the task block started at 10 seconds after block onset, and every 1.75 seconds thereafter.

Two contrasts were conducted for each participant in series 2a and 2b using an event-related analysis. The first contrast was between the trials eliciting correct responses in the SC condition and those in the RW condition. This is in order to reveal areas that were associated with the Stroop interference effect as explained in the introduction word-reading is a much easier and more automatic task to perform than the color-naming task in most cases. Thus, areas associated with inhibition are expected to be revealed in the contrast of SC-RW. The contrast of RW-SC was also examined. Two subjects' data from the NC group and two from the MCI group were discarded as the data could not be performed using SPM5. Therefore, 19 NC subjects, 19 AD patients and 7 MCI patients' data were used in the contrast of SC-RW and RW-SC.

A second contrast was intended to reveal the neural correlates of the incorrect responses in the RW condition, by contrasting incorrect responses with correct responses of series 2a and 2b. Data from 13 AD patients were included in this contrast as there were not enough incorrect responses to do the individual comparison in the NC group. The MCI group was also not included due to its small sample size. All the contrasts were calculated on individual data and then combined in a random effects analysis for each group.

A block analysis was also conducted to examine the contrasts of SC-RW and RW-SC of series 2a and 2b. The current Stroop experiment was designed as a block experiment. The results from the block analysis are a check to ensure that the event-

related analysis was correctly implemented. Even though the previous study of Bowes (Bowes, 2009) examined the contrast of SC-RW using a block analysis, the contrast of SC-RW in her study was across series 1, 2a and 2b. The contrast of RW-SC of series 2a and 2b was also not performed in her study. The current fMRI data analysis did not combine series 1 with series 2a and 2b in the contrast of either SC-RW or RW-SC as the paradigm of series 1 was different from paradigm of series 2a and 2b. Some subjects were not included as they had errors in either the entire blocks of the RW condition or the SC condition so that the contrasts of SC-RW and RW-SC could not be conducted. Therefore, functional MRI data used for the block analysis in the contrast of SC-RW and RW-SC of series 2a and 2b included 19 NC subjects, 15 AD patients and 8 MCI patients.

A block analysis of contrasts of RW-rest and SC-rest was conducted as well from series 2a & 2b. The contrasts of task-rest of the current study were different from Bowes' (Bowes, 2009) previous study. In her study, she conducted contrasts of task-rest in series 0 and in series 1, 2a and 2b. The purpose of having the contrast of task-rest in her study was to look at the differences of the brain activation between each group (the NC and AD group). In the current study, the contrast of task-rest was to look at if the areas that are associated with inhibition could be observed in series 2a and 2b.

A *p* threshold of 0.001, uncorrected for multiple comparisons was used for each individual participant. The individual contrasts were then combined into a 2^{nd} level group analysis. A one-sample *t*-test with a *p* threshold of 0.001 uncorrected for multiple comparisons was applied for each (NC, MCI, and AD) group. The results were reported from the column of cluster-level with $p \leq 0.05$, corrected for multiple comparison, as well

as $p \leq 0.001$ level, uncorrected from the voxel-level. Anatomical Automatic Labeling (AAL) toolbox (Tzourio-Mazoyer et al., 2002) was used to identify the anatomical locations.

I also applied region-of-interest (ROI) analysis using small volume correction (S.V.C.) in the contrast of RW-SC, SC-RW, RW-rest and SC-rest. An a priori hypothesis for the expected activated areas included inferior frontal gyrus (IFG), middle frontal gyrus (MFG), pre-supplementary motor area (pre-SMA), inferior parietal lobule (IPL), and superior parietal lobule (SPL). A number of studies have suggested that these areas are associated with inhibitory control (e.g., Milham et al., 2002; Langenecker et al., 2004; Nielson et al., 2002). The results from S.V.C. were reported from the voxel-level of family-wise error (FWE) with $p \leq 0.05$. The sphere locations were selected from other studies of inhibition and included right IFG with the coordinate 30, 30, -12 (Langenecker et al., 2004), left IPL with the coordinate -48, -42, 30 (Milham et al., 2002)

Chapter 4 Results

1. Results from behavioural analysis

1.1 Series 1 results

Most of the subjects made 4 or fewer errors out of 64 responses on the word-reading task of series 1. In the NC group, only one subject made 1 error in the RW condition of series1. Only three subjects (2 AD patients, and 1 MCI patient) made more than 30 errors in reading color words of series 1, each of whom made on average 36 errors during the word-reading task out of 64 responses (see figure 3). A non-parametric K-independent sample test was performed in series 1 RW condition across the three groups. The result revealed a significant group difference ($X^2 = 8.13$, $p < 0.05$). This result indicates that few individuals from the AD and MCI group made more errors than the NC group in the performance of the RW condition of series 1.

All subjects on average made more errors in the SC condition than in the RW condition of series 1 (see figure 3 and 4). A non-parametric 2-related sample test was performed in each group between the medians of the SC condition and the RW condition. The result revealed a significant difference of the number of erroneous responses between the SC condition and the RW condition in each group (paired SC-RW: Z_{NC}=-2.94, $p<0.05$; Z_{MCI}=-1.96, $p=0.05$; Z_{AD}=-2.54, $p<0.05$). The result indicates that all subjects experience more difficulty on the color-naming task than the word-reading task of series 1. The magnitude of the Stroop effect could be measured in the contrast of SC-RW. When the number of erroneous responses in the contrast of SC-RW in series 1 of the NC group was compared with the number of erroneous responses in the contrast of

SC-RW of the AD and MCI groups, the NC group made fewer errors than both the MCI and the AD group. A non-parametric K-independent sample test on the median of the contrast of SC-RW across the three groups revealed that there is a significant difference among the three groups in the difference in the number of errors between the SC condition and the RW condition in series 1 (X^2=11.97, $p<0.05$). The result suggests that the NC group performs better on the color-naming task than the AD and the MCI group. Both the AD and the MCI group have more difficulty in inhibiting more automatic word-reading responses during the color-naming task.

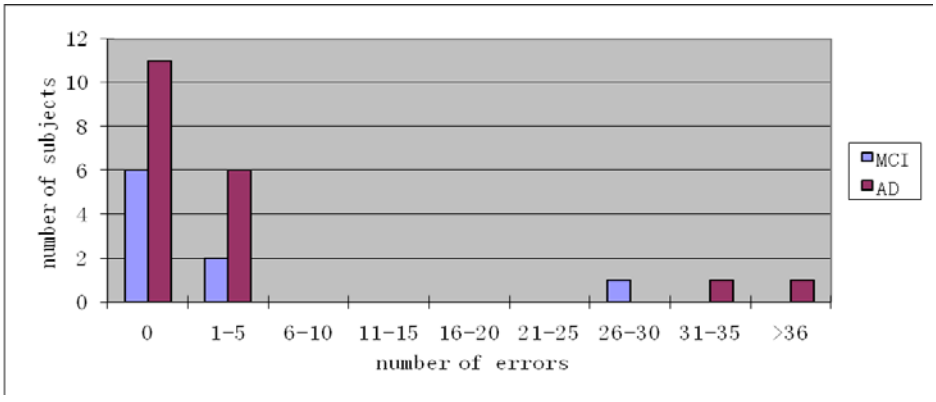


Figure 3. Histogram of number of subjects of the MCI and the AD groups in each error range in the RW condition of series 1.

Figure 4. Histogram of number of subjects of the NC, MCI and the AD groups in each error range in the SC condition of series 1.

1.2 Series 2a and 2b results

In the switching paradigm of series 2a and 2b, the number of errors of the RW condition increased when compared to series 1 (see figure 3, 5 & 6). In the NC group, two subjects made more than 5 errors in the RW condition of series 2a and 2b (see figure 6). The errors made by the two subjects covered almost the entire block. The possible reason could be due to the loss of the word-reading task goal. A non-parametric K-related sample test revealed a significant difference of the number of errors in the RW condition among the three series in each group ($X^2_{NC}=10.29$, $p<0.05$; $X^2_{MCI}=9.59$, $p<0.05$; $X^2_{AD}=17.79$, $p<0.001$). All groups perform better in the RW condition of series 1 than in series 2a and 2b. Although the number of errors of the RW condition increased dramatically in series 2a and 2b, the numbers of errors of the SC condition of series 2a and 2b did not increase significantly when compared to series 1 in neither the NC nor the MCI group. A non-parametric K-related sample test did not show a significant difference in the number of errors of the SC condition among the three series in the NC and the

MCI group (X^2_{NC}=1.72, p=0.42; X^2_{MCI}=0.40, p=0.82). In the AD group the mean number of errors of the SC condition of series 2b ($\bar{X}$ =7.74) was less than series 2a ($\bar{X}$ =11.89) and series 1 ($\bar{X}$ =12.84). A non-parametric K-related sample test revealed a significant difference in the number of errors of the SC condition among the three series in the AD group (X^2_{AD}=9.70, p<0.05).

In order to look at whether the performance of the color-naming task was better than the word-reading task in series 2a and 2b, the number of erroneous responses of the RW condition was compared with the SC condition. A non-parametric two-related sample test was conducted in each group and revealed that there was no significant difference in the number of erroneous responses between the two conditions of series 2a and 2b (paired SC-RW: Z_{NC}=-0.052, p=0.96; Z_{MCI}=-0.771, p=0.44; Z_{AD}=-1.83, p=0.067). The results suggest that the amount of the Stroop interference in the contrast of SC-RW of series 2a and 2b could not be observed.

In the switching task paradigm of series 2a and 2b, the NC group performed better than the MCI and the AD group in both the word-reading and the color-naming tasks (see figure 5-8). A non-parametric K-independent sample test was conducted in the RW condition across the three groups and revealed a significant group difference (X^2=13.68, p≤0.001). Similarly, a non-parametric K-independent sample test in the SC condition across the three groups also revealed a significant group difference (X^2=21.13, p<0.001). The results suggest that MCI and AD patients have more difficulty in shifting attention than the NC group.

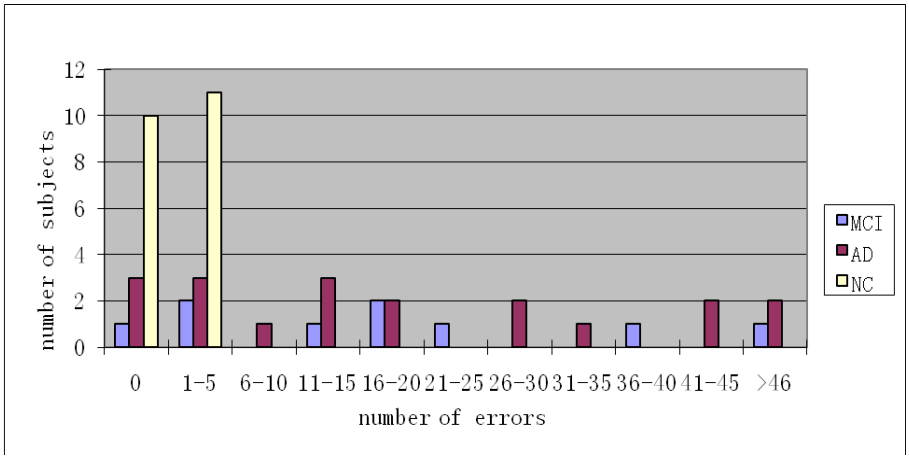


Figure 5. Histogram of number of subjects of the NC, MCI and the AD group in each error range in the RW condition of series 2a.

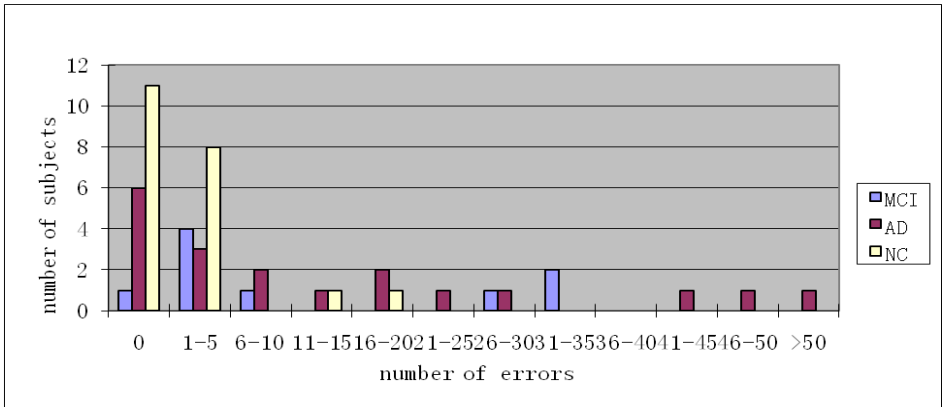


Figure 6. Histogram of number of subjects of the NC, MCI and the AD group in each error range in the RW condition of series 2b.

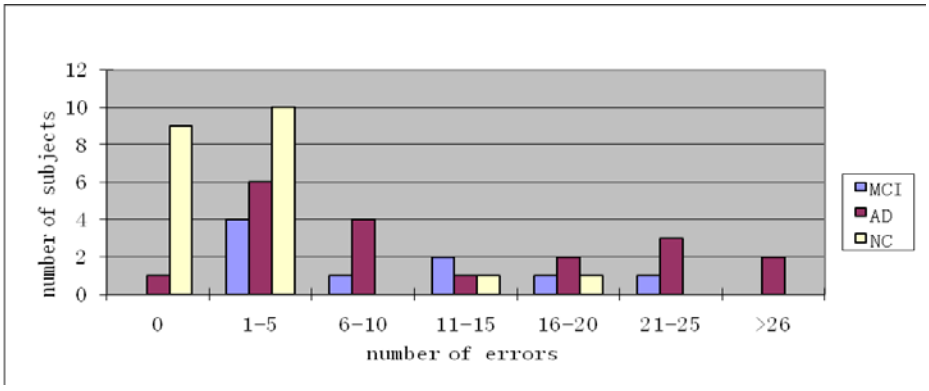


Figure 7. Histogram of number of subjects of the NC, MCI and the AD group in each error range in the SC condition of series 2a.

Figure 8. Histogram of number of subjects of the NC, MCI and the AD group in each error range in the SC condition of series 2b.

2. Stroop-fMRI task-related brain activation

Only series 2a and 2b were used for the fMRI data analysis. No activation was found in the contrast of SC-RW in neither the NC group nor the AD group using either block or event-related analyses. This finding is in line with the behavioural analysis, which suggests that the magnitude of the Stroop interference may not be observed in the contrast of SC-RW in the switching paradigm of series 2a and 2b when the number of erroneous responses between the RW condition and the SC condition were compared. The contrast of RW-SC was conducted to see if any activation could be found using both analyses.

Event-related analysis and block analysis in the contrast of RW-SC of series 2a and 2b in the NC group

Both the event-related and the block analyses displayed similar activated regions in the RW-SC contrast (see table1 and 2, figure 9 A and B). The similar brain activation between the two analyses could be due to superposition and was explained in discussion. These areas included right inferior frontal gyrus (IFG), left middle frontal gyrus (MFG), left inferior parietal lobule (IPL), angular gyrus and middle temporal gyrus (MTG).

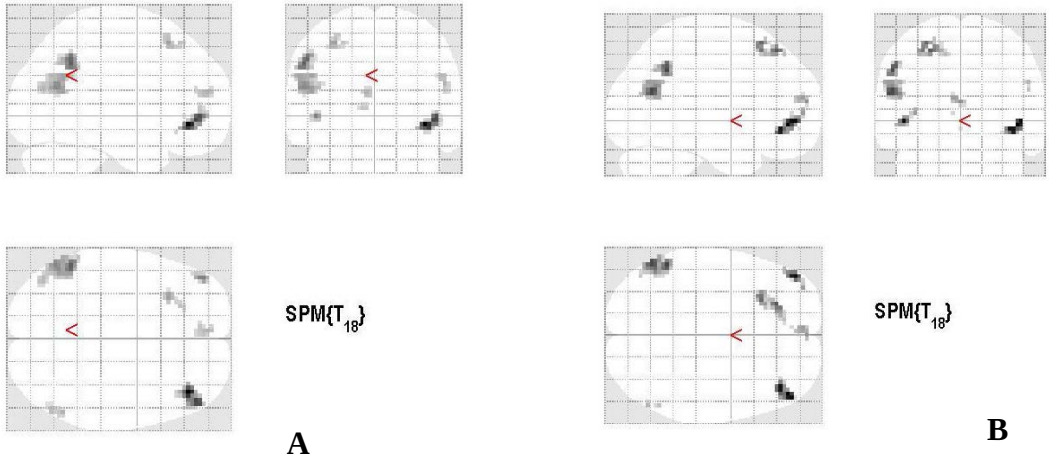


Figure 9 A) Activated areas in the contrast of RW-SC in the NC group using an event-related analysis. **B)** using a block analysis.

Table 1. Significantly activated regions in the NC group using an event-related analysis in RW-SC contrast of series 2a and 2b. A cluster-level significance threshold was employed with $p<0.05$, corrected. Foci marked with a * are significant at the $p<0.001$ level uncorrected for multiple comparisons. Foci marked with a ** are significant at the $p<0.05$ level corrected under family-wise error (FWE) for multiple comparisons after small volume correction (S.V.C.). Sphere location 30 30 -12 (Langenecker et al., 2004); sphere location -48 -42 30 (Milham et al., 2002).

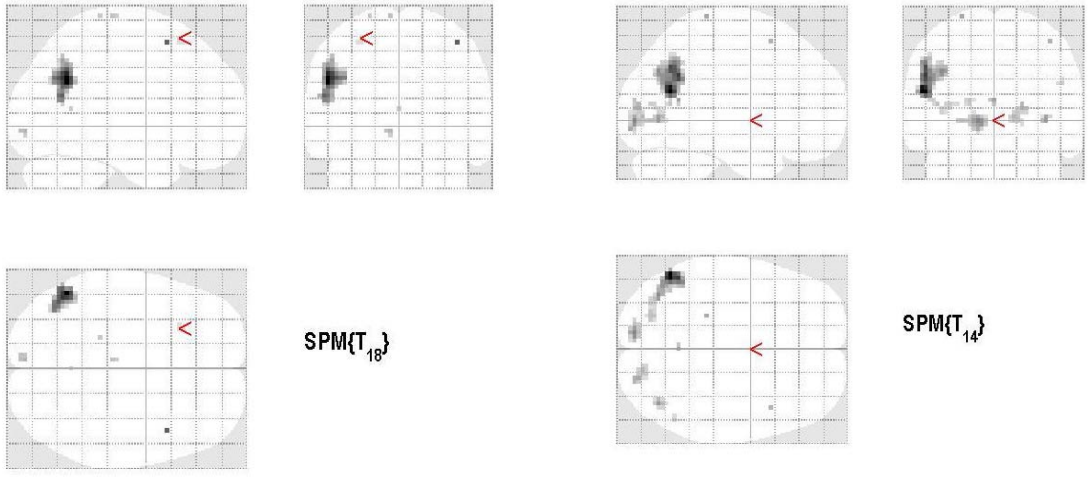
Region	**Cluster size**	**Side**	**Z**	**x y z**	**Sphere Size (mm)**	**Sphere Location x y z**	**p-value**
Orbitalis IFG		R	4.20	39, 39, -6	25	30, 30, -12	0.015**
Triangular part of IFG		R	3.67	45, 45, -3	25	30, 30, -12	0.042**
Inferior parietal lobule		L	3.75	-54, -51, 39	15	-48, -42, 30	0.016**
			3.51	-54, -60, 24			0.040**
Middle frontal gyrus		L	3.43	-30, 24, 54			0.000*
			3.25	-24, 33, 54			0.000*
Angular gyrus	133	L	3.43	-48, -54, 30			0.006
Middle temporal gyrus	133	L	3.54	-54, -63, 21			0.006
	133		3.32	-45, -72, 21			

Table2. Significantly activated regions in the NC group using a block analysis in RW-SC contrast of series 2a and 2b. A cluster-level significance threshold was employed $p<0.05$, corrected. Foci marked with a * are significant at the $p<0.001$ level uncorrected for multiple comparisons. Foci marked with a ** are significant at the $p<0.05$ level corrected under family-wise error (FWE) for multiple comparisons after small volume correction (S.V.C.). Sphere location 30 30 -12 (Langenecker et al., 2004); sphere location -48 -42 30 (Milham et al., 2002).

Region	**Cluster size**	**Side**	**Z**	**x y z**	**Sphere size (mm)**	**Sphere location x y z**	**p-value**
Orbitalis IFG		R	3.43	42, 36, -9	15	30, 30, -12	0.020**
Orbitalis IFG		R	3.67	39, 39, -6	15	30, 30, -12	0.039**
Middle frontal gyrus		L	3.44	-27, 24, 60			0.000*
Inferior parietal lobule		L	3.52	-54, -51, 39	15	-48, -42, 30	0.031**
Angular gyrus	84	L	3.24	-48, -57, 30			0.037
Middle temporal gyrus	84	L	3.18	-45, -72, 21			0.037

Event-related analysis and block analysis in the contrast of RW-SC of series 2a and 2b in the AD group

Similar brain activation was also found in the AD group using both analyses, which could be explained by superposition as well. Both the event-related and the block analysis showed common activated regions including left angular gyrus, left MTG, left IPL and MFG (see figure 10 A and B, table 3 and 4). The activation of the IFG was not observed in the AD group.



A **B**

Figure 10 A) Activated areas in the contrast of RW-SC in the AD group using an event-related analysis.**B)** using a block analysis.

Table3. Significantly activated regions in the AD group using an event-related analysis in RW-SC contrast of series 2a and 2b. A cluster-level significance threshold was employed $p \leq 0.05$, corrected. Foci marked with a * are significant at the $p \leq 0.001$ level uncorrected for multiple comparisons.

Region	**Cluster size**	**Side**	**Z**	**x y z**	**p-value**
Angular gyrus	134	L	3.97	-51, -57, 30	0.05
Middel temporal gyrus	134	L	3.60	-54, -60, 21	0.05
Inferior pariental lobule	134	L	3.33	-48, -60, 45	0.05
Middle frontal gyrus		R	3.61	42, 15, 57	0.000*
Middle frontal gyrus		L	3.10	-27, 24, 60	0.001*

Table4. Significantly activated regions in the AD group using a block analysis in RW-SC contrast of series 2a and 2b. A cluster-level significance threshold was employed p≤0.05, corrected. Foci marked with a * are significant at the p≤0.001 level uncorrected for multiple comparisons.

Region	**Cluster size**	**Side**	**Z**	**x y z**	**p-value**
Middle temporal gyrus	172	L	4.12	-54, -60, 21	0.011
Angular gyrus	172	L	3.86	-51, -54, 33	0.011
Inferior parietal lobule	172	L	3.79	-51, -60, 39	0.011
Middle frontal gyrus		R	3.34	42, 15, 57	0.000*

Event-related analysis and block analysis in the contrast of RW-SC of series 2a and 2b in the MCI group

Very few activated areas were found in the MCI group. Neither analysis showed any expected activated regions, such as IFG, IPG and MFG (see figure 11A and B). The small amount of activation found in the MCI group may be due to its small size.

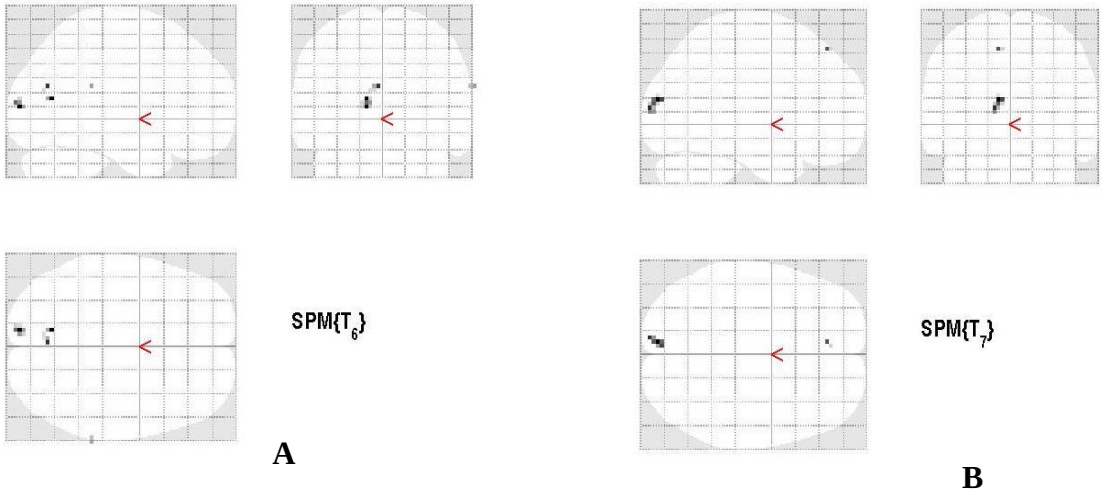


Figure 11 A) Activated areas in the contrast of RW-SC in the MCI group using an event-related analysis. **B)** using a block analysis.

Event-related analysis and block analysis in the contrast of SC-RW in the MCI group

The expected activated areas were not found in either the block and event-related analyses (see figure 12A and B). Little activation was found using both analyses.

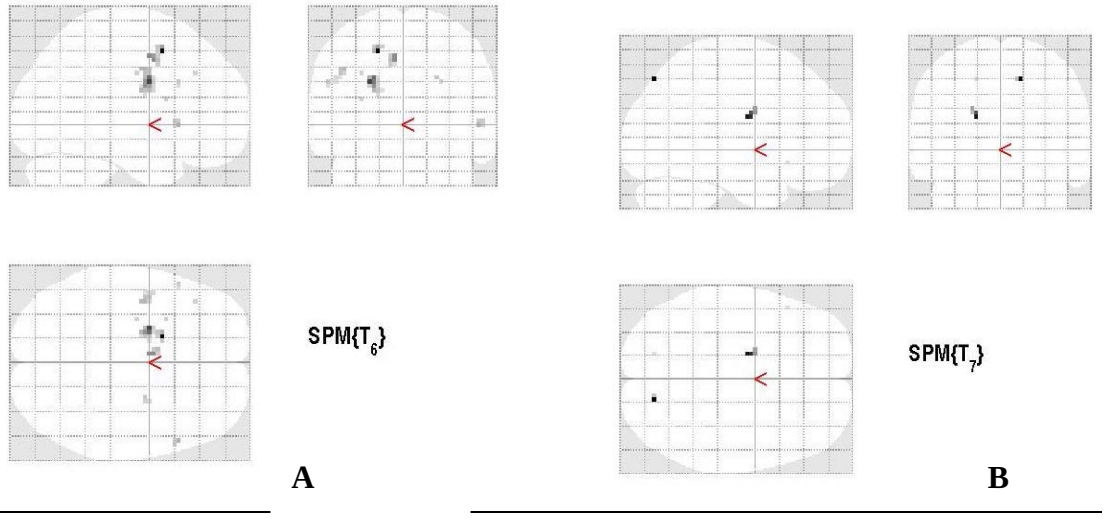


Figure 12 A) Activated areas of the contrast of SC-RW in the MCI group using an event-related analysis. **B)** using a block analysis.

Block analysis: contrast of RW-rest and of SC-rest of series 2a and 2b in the NC group

The number of erroneous responses in the RW condition of series 2a and 2b increased significantly in comparison with series 1. The increased number of erroneous responses on the word-reading task was believed to be due to the reverse Stroop effect (RSE) elicited by the task switching paradigm of series 2a and 2b. The RSE is the competition of incongruent color that slows down the word reading (Wylie & Allport, 2000; MacLeod, 1991). If the RSE exists in the RW condition of series 2a and 2b, the areas associated with inhibitory control would be expected to be observed. Therefore, I assumed that the activated areas associated with inhibition could be observed in the contrast of task-rest (SC-rest and RW-rest). Similar activated areas were found in both the contrasts of RW-rest and SC-rest in the NC group (see figure 13A and B, table 5 and

6). These areas included left pre-SMA, bilateral MFG, left IFG, left IPL and left SPL. Figure 13 showed dropouts, which was due to one subject's data error. This subject was not excluded as the error was found after the group analysis.

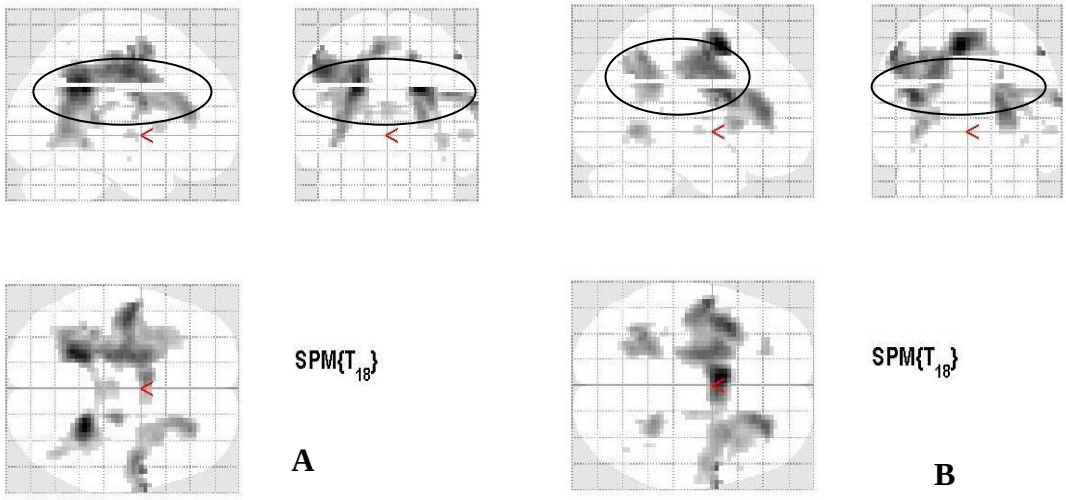


Figure 13 A). Activated areas in the contrast of RW-rest in the NC group using a block analysis. **B)** Activated areas in the contrast of SC-rest in the NC group using a block analysis.

Table5. Significantly activated regions in the NC group using a block analysis in RW-rest contrast of series 2a and 2b. A cluster-level significance threshold was employed $p \leq 0.05$, corrected. Foci marked with a * are significant at the $p \leq 0.001$ level uncorrected for multiple comparisons.

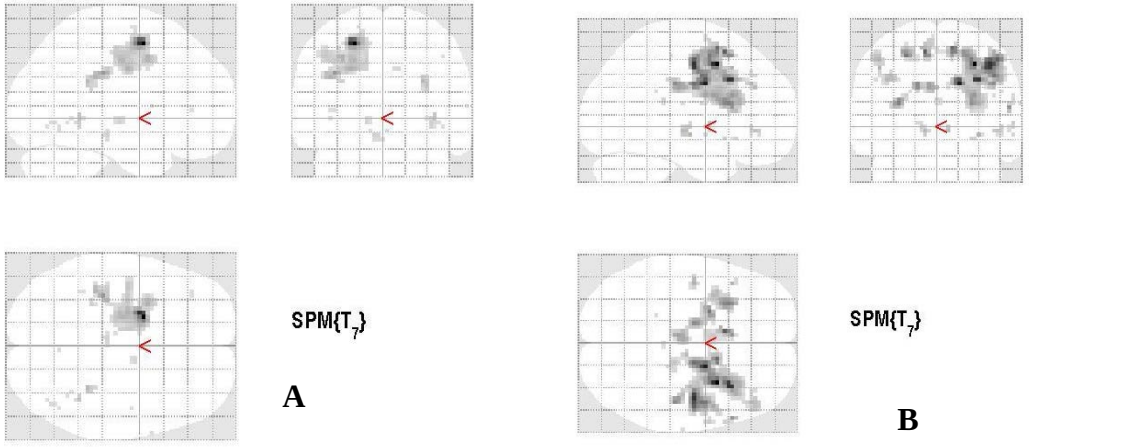
Region	**Cluster size**	**Side**	**Z**	**x y z**	**p-value**
Precentral	820	L	4.67	-45, -9, 42	0.000
	216		3.71	-45, -3, 27	0.004
Postcentral	324	R	4.18	66, 3, 21	0.000
Middle frontal gyrus		R	4.23	54, 0, 51	0.000*
Opercularis IFG	216	L	3.63	-36, 3, 27	0.004
Pre-SMA		L	4.11	-6, 3, 57	0.001*
			4.03	-6, 6, 54	0.001*
Inferior parietal lobule		L	3.59	-27, -42, 45	0.000*
Superior parietal lobule		L	3.61	-18, -59, 44	0.000*
			3.09	-30, -54, 60	0.001*

Table6. Significantly activated regions in the NC group using a block analysis in SC-rest contrast of series 2a and 2b. A cluster-level significance threshold was employed p≤0.05, corrected. Foci marked with a * are significant at the p≤0.001 level uncorrected for multiple comparisons.

Region	**Cluster size**	**Side**	**Z**	**x**	**y**	**z**	**p-value**
Pre-SMA	899	L	4.94	-6	6	57	0.000
Precentral	899	L	4.40	-51	-3	51	0.000
	500	R	4.17	66	3	21	0.000
Triangular part of IFG	288	L	4.57	-39	12	24	0.000
		R	3.19	54	21	6	0.001*
Insula	288	L	3.81	-30	18	6	0.000
Inferior parietal lobule	162	L	4.03	-30	-51	48	0.008
Superior parietal lobule		L	3.63	-27	-60	45	0.000*
Orbitalis IFG		L	3.13	-39	15	-12	0.001*
Middle frontal gyrus		L	3.93	-24	3	50	0.000*
		R	4.35	54	3	51	0.000*

Block analysis: contrast of RW-rest and of SC-rest of series 2a and 2b in the MCI group

In the MCI group, the contrast of SC-rest showed more activated areas than RW-rest contrast, such as the pre-SMA and IFG (see table 7, and 8).



14 A). Activated areas in the contrast of RW-rest in the MCI group using a block analysis. **B)** Activated areas in the contrast of SC-rest in the MCI group using a block analysis.

Table7. Significantly activated regions in the MCI group using a block analysis in RW-rest contrast of series 2a and 2b. A cluster-level significance threshold was employed p≤0.05, corrected. Foci marked with a * are significant at the p≤0.001 level uncorrected for multiple comparisons.

Region	**Cluster size**	**Side**	**Z**	**x**	**y**	**z**	**p-value**
Superior frontal gyrus	387	L	5.12	-21	3	54	0.000
Middle frontal gyrus	387	L	3.84	-30	6	45	0.000

Table8. Significantly activated regions in the MCI group using a block analysis in SC-rest contrast of series 2a and 2b. A cluster-level significance threshold was employed p≤0.05, corrected. Foci marked with a * are significant at the p≤0.001 level uncorrected for multiple comparisons.

Region	**Cluster size**	**Side**	**Z**	**x**	**y**	**z**	**p-value**
Middle frontal gyrus	844	R	4.75	30	9	48	0.000
		L	4.10	-24	3	54	0.000*
			3.62	-45	21	45	0.000*
	30		3.57	-39	9	36	0.019
(pre) SMA		L	3.28	-6	0	51	0.044*
			4.25	-9	15	57	0.000*
Precentral	844	R	4.49	42	-9	48	0.000
Triangular part of IFG		R	3.87	57	21	15	0.000*
			3.26	60	15	21	0.001*
			3.45	48	39	-3	0.000*
Orbitalis IFG		R	3.25	30	24	-9	0.001*
Opercularis part of IFG		L	3.54	-36	6	39	0.000*

<u>Block analysis: the contrast of RW-rest and of SC-rest of series 2a and 2b in the AD group</u>

Compared to the NC group, the AD group showed less brain activation in both contrasts (see figure 15A and B). Both the pre-supplementary motor area (pre-SMA) and superior parietal lobule (SPL) were found in both contrasts. Both the AD and the NC group showed similar activated areas, such as pre-SMA, SPL in both contrasts.

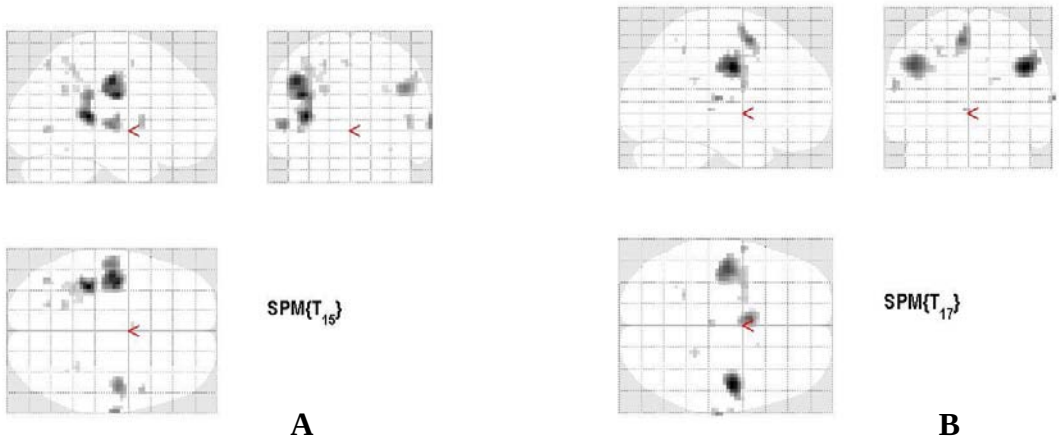


Figure 15 A). Activated areas in the contrast of RW-rest in the AD group using a block analysis. **B)** Activated areas in the contrast of SC-rest in the AD group using a block analysis.

Table9. Significantly activated regions in the AD group using a block analysis in RW-rest contrast of series 2a and 2b. A cluster-level significance threshold was employed $p \leq 0.05$, corrected. Foci marked with a * are significant at the $p \leq 0.001$ level uncorrected for multiple comparisons.

Region	**Cluster size**	**Side**	**Z**	**x**	**y**	**z**	**p-value**
Superior temporal gyrus	142	L	4.36	-36	-33	12	0.019
Postcentral	228	L	4.17	-45	-15	39	0.003
Opercularis IFG		R	3.40	48	12	9	0.000*
Pre-SMA		L	3.27	-3	3	54	0.001*
Superior parietal lobule		L	3.33	-21	-66	54	0.000*
			3.32	-21	-51	48	0.001*
Inferior parietal lobule		L	3.34	-36	-45	51	0.000*
			3.18	-39	-51	60	0.001*

Table10. Significantly activated regions in the AD group using a block analysis in SC-rest contrast of series 2a and 2b. A cluster-level significance threshold was employed $p \leq 0.05$, corrected. Foci marked with a * are significant at the $p \leq 0.001$ level uncorrected for multiple comparisons.

Region	**Cluster size**	**Side**	**Z**	**x**	**y**	**z**	**p-value**
Precentral	130	R	4.20	45	-9	36	0.037
Postcentral	221	L	3.83	-45	-12	39	0.006
Pre-SMA		L	3.74	-6	6	57	0.000*
Superior parietal lobule		L	3.27	-24	-48	48	0.001*
			3.10	-30	-54	57	0.001*

Event-related analysis in the contrast of incorrect responses-correct responses in the RW condition of series 2a and 2b in the AD group

Another contrast of the study was to investigate the neural correlates of the incorrect responses. This was achieved by using the contrast of incorrect responses – correct responses. Several studies have found the activation of the anteior cingulate cortex (ACC) during the error detection (e.g., Swick & Turken, 2002). Thus, in the contrast of incorrect responses-correct responses, the activation of the ACC is expected. However, no activation was found in this contrast.

Chapter 5 Discussion

The current study investigated the neural correlates of selective attention (SA) using a Stroop task with normal older adults (NC), patients with mild cognitive impairment (MCI) and patients with mild Alzheimer's disease (AD). This was done using two contrasts in an event-related analysis. The first contrast was to examine the neural correlates of the Stroop interference effect by subtracting correct responses in RW incongruent condition from correct responses in SC incongruent condition of series 2a and 2b (SC-RW). The second contrast was to investigate the neural correlates of the incorrect responses from the RW condition by subtracting correct responses from incorrect responses of series 2a and 2b in the AD group. The two contrasts, however, failed to show expected activated areas. The results from the first contrast of SC-RW, failed to show any activated areas in either the NC or the AD group using both the block and event-related analysis. The second contrast did not show any brain activation using an event-related analysis.

In the behavioural analysis of series 1, series 2a and 2b, the results were also unexpected. More erroneous responses were found in the RW condition of series 2a and 2b than in series 1 across the three groups. The difference of the number of erroneous responses between the RW condition and the SC condition of series 2a and 2b were not significant across the three groups. These results were consistent with the current Stroop paradigm of series 2a and 2b not revealing a Stroop interference effect in the fMRI contrast of SC-RW. The reason could be due to the reverse Stroop effect (RSE) elicited

by the switching between the color-naming task and the word-reading task in series 2a and 2b.

Behavioural analysis

Little RSE found in the RW condition of series 1

The paradigm of series 1 was analogous to the Stroop Neuropsychological Screening Test (SNST) (Trenerry et al., 1989) where subjects were asked to read the incongruent Stroop stimuli (e.g., the word blue printed in green) followed by naming the incongruent Stroop stimuli. Reading words of series 1 was not as difficult as color-naming for most of the subjects judging by the number of erroneous responses. Participants had more difficulty in the color-naming task and performed better in word-reading task in series 1.The results indicate that the RSE is not robust when the word-reading task is performed first in the absence of color-naming trials. The Stroop interference may have been observed in the contrast of SC-RW of series 1.

RSE in series 2a and 2b

The paradigm in series 2a and 2b was a task switching in the two conditions. A switching cost results from the RSE was observed, judging by the number of errors in these two series. All subjects made significantly more errors in the word-reading task in either series 2a or 2b than in series 1. The results could be due to the task-switching paradigm. Several lines of evidence suggest that task switching can affect the behavioral performance. Reliably longer response times and higher error rates have been observed in task-switching blocks than in single-task blocks by a number of researchers (e.g.Allport et al., 1994; Rogers & Monsell, 1995; Wylie & Allport, 2000).

When the number of erroneous responses across the two conditions of series 2a and 2b was compared, the difference of the number of erroneous responses between the two conditions was not significant in any of the three groups. This result indicates that in series 2a and 2b subjects not only experience difficulty in naming the colors but also in reading words. The RSE was observed in the RW condition in series 2a and 2b as subjects named the color during the word-reading task. The finding of the RSE from series 2a and 2b is consistent with the conclusion of Allport et al. (1994), which states that substantial RSE can be elicited when tasks are switched between color naming and word reading. The results suggest that the amount of the Stroop interference in the contrast of SC-RW of series 2a and 2b may not be observed.

The level of difficulty in terms of the number of erroneous responses changed dramatically in the word-reading task when subjects were required to switch between the word-reading task and color-naming task in comparison with the word-reading task performed in pure blocks. However, in terms of the number of erroneous responses in the color-naming task, the difficulty level did not change significantly between task switching condition and non-task switching condition. This result shows an asymmetrical switch cost with a larger cost towards to the word-reading task than the color-naming task. This finding is consistent with the task-set inertia (TSI) hypothesis (Allport et al., 1994). When subjects perform the color-naming task, they have to strongly suppress the word-reading task. This suppression continually persists in the word-reading trials, which results in a longer response time to read the color words (Allport et al., 1994; Wylie and Allport, 2000). In the current study, the incongruent Stroop stimuli were presented every

1.75s, the fast changing stimulus rate may not give subjects enough time to react in the word task, thus resulting in a large number of erroneous responses in switch tasks.

Inhibitory deficits of the MCI and AD group in the Stroop task

Both MCI and AD patients exhibited significantly more errors than the NC group in the contrast of SC-RW of series 1. The results demonstrate that compared with the NC group, the MCI and the AD group have impaired inhibitory control of more automatic word-reading responses. The finding further demonstrates that both MCI and AD patients have trouble controlling complex behaviour and perseverations as they have great difficulty using inhibitory strategies to suppress irrelevant responses (Amieva et al., 2004; Belleville et al., 2008). This finding is consistent with a large body of literature on inhibitory deficits that was found in early AD and MCI patients (e.g., Amieva et al., 2004; Belleville, Rouleau & Van der Linden, 2006; Belanger et al., 2010).

Task switching capacities in the MCI and the AD group

A larger switch cost in the AD and the MCI group than the NC group was found when comparing the number of erroneous responses in either word-reading task or color-naming task of series 2a and 2b. Both the AD and MCI group had significant more errors than the NC group in either condition of series 2a and 2b. The results demonstrated that both AD and MCI patients have deficient switching capacities when compared with normal older adults. They made more color naming intrusions (name color instead of reading words) during word-reading task and more word reading intrusions (read word instead of naming color) during color-naming task of series 2a and 2b than the NC group.

The higher number of erroneous responses from the AD and the MCI group than the NC group in series 2a and 2b reflect the difficulty to respond to a new task set. This phenomenon could be compared to the perseverative errors that AD and MCI patients encountering in the Wisconsin Card Sorting Test, which are considered to reveal the difficulty in learning the new rules (Amieva et al., 2004; Bondi et al, 2002; Kramer et al., 1994). AD and MCI patients have an impairment in shifting attention from one task to another when compared with normal older adults. The paradigm of series 2a and 2b allowed us to relate our findings to the existing literature on switching tasks in AD and MCI patients.

The behavioural results from series 1, series 2a and 2b add further support that both the AD and the MCI group have impairments in shifting attention and in inhibition in comparison with the NC group. Although a memory deficit is an essential part in diagnosis of MCI (Petersen et al., 1999), the results of behavioural analysis from the current study also suggest that MCI patients have deficits in executive functions, such as inhibition and shifting attention. In Perry and his colleagues' (2000) study, they have suggested that MCI patients were very vulnerable to response inhibition and attention switching. A study from Traykov et al. (2007) also supports this view, where they reported deficits in inhibition and in task switching capacities on MCI patients using the Stroop test and Wisconsin Card Sorting Task respectively.

fMRI data analysis

The behavioral analysis has shown that the word-reading task is much harder for subjects in the task switching condition (series 2a and 2b) than in the non-task switching

condition (series 1) across the three groups. The absence of activation in the contrast of SC-RW of series 2a and 2b may be due to the involvement of the RSE in the RW task. These results suggest that the adaptation of the Stroop Neuropsychological Screening Test (SNST) implemented here may not be suitable for the investigation of the Stroop effect. The following will discuss the findings from fMRI data analysis.

Event-related and block analysis in the NC and the AD groups in the contrast of RW-SC of series 2a and 2b

No activation was found in the contrast of SC-RW using both analyses in the NC and the AD group. The activation of the dorsolateral prefrontal cortex (DLPFC) and parietal areas was observed in the contrast of RW-SC using both analyses in both groups. Several possible reasons could explain this finding based on the literature review of the function of the DLPFC and the parietal regions.

The involvement of the DLPFC becomes more prominent in task performance when selection of the task-relevant information requires more effort compared to the task-irrelevant information. On the other hand, an increase in the DLPFC activation would not be observed when the task-relevant information is processed more automatically than the task-irrelevant information (Banich et al., 2000). If the word-reading task of series 2a and 2b is still performed more automatically as it was in series 1, the activated area of the DLPFC would not be observed in the contrast of RW-SC. Therefore, the activated area of the DLPFC (inferior frontal gyrus (IFG) and middle frontal gyrus (MFG)) in the contrast of RW-SC in the NC group may suggest that subjects were exerting more effort in performing the word-reading task in the task switching paradigm.

The attentional control is not limited to only the DLPFC. The parietal cortex may work in association with prefrontal cortex to impose attention control (e.g., Banich et al., 2000b; Cabeza & Nyberg, 2000). A number of studies have suggested that the parietal cortex plays a role in maintaining sustained attention and attention shifts (e.g., Bench et al., 1993; Banich et al., 2000b; Chelazzi & Corbetta, review, 2000). The activated DLPFC and parietal regions in the contrast of RW-SC may indicate that more effort might be required to maintain the goal of the word-reading task than the color-naming task of series 2a and 2b. The behavioural data have shown that there is a larger switching cost to the word-reading task than the color-naming task in series 2a and 2b, consistent with the "task-set inertia" (TSI). Therefore, subjects may need more attention to maintain the word-reading task-set. The activation of the DLPFC and the parietal regions may reveal that these areas may help to maintain the goal of word-reading task set within working memory (Banich et al., 2000a, b, 2001).

Activation of the parietal regions is associated not only with attention control, but also with word reading processes (Brunswick et al., 1999; Buchel et al., 1998; Shaywitz et al., 1998). Several Stroop studies have found regions of the parietal lobe are responsible for word-related processing (Banich et al., 2000a, b; 2001). The left inferior parietal region has been reported as more active when viewing or naming words as compared to pictures (Price, 1998).The activated inferior parietal lobule found in the contrast of RW-SC in the current study could also indicate that subjects require more effort to process word-reading in the RW condition than in the SC condition.

Block analysis in the contrast of tasks – rest in the NC and AD group in series 2a, 2b

Many Stroop-fMRI studies have suggested that the IFG, MFG and parietal regions are associated with inhibition (e.g., Petersen et al., 1999). In the contrast of RW-rest in the NC group, activation in the DLPFC (IFG and MFG), inferior and superior parietal lobule were found, and were also observed in the SC-rest contrast. This result may indicate the existence of inhibition of color in series 2a and 2b in the RW condition. In other words, the result from the contrast of RW-rest may suggest that subjects experience the RSE in the RW condition of series 2a and 2b. Greater attentional demands are required to perform the word-reading task, while ignoring the color. The IFG has been implicated in inhibition in many neuroimaging studies (e.g., Garavan et al., 1999; Konishi et al., 1998a, b, 1999). The region of the IFG has been reported in both older adults and younger adults during inhibitory control tasks (e.g., Nielson et al., 2002). It has been suggested that the IFG plays an important role in resolving interference across inhibitory paradigms (Langenecker et al., 2004). The observation of the activated area of the IFG in the RW-rest contrast in the NC group may suggest the evidence of the existence of the RSE in series 2a and 2b.

Like the NC group, the AD group activated predominantly the brain areas in the left hemisphere. This result is in line with the finding that the left hemisphere is responsible for the resolution of the interference of the tasks that are more dependent on verbal mechanisms (e.g., Mead et al., 2002; Jonides & Smith, 1999; Perret, 1974). Many neuroimaging studies with the Stroop task have also revealed predominant recruitment of left-sided brain areas (e.g., Zysset et al., 2007; Perret, 1974; Jonides & Smith, 1999). The

activation of the left pre-SMA, IFG, and left parietal regions in the contrast of RW-rest in the AD group may also reflect greater attentional demands in performing the RW task.

Both the AD and the NC group exhibited the activation of pre-SMA in both contrasts of SC-rest and RW-rest. Pre-SMA activation has been identified to play a critical role in response to inhibition and has been observed in many Stroop studies (Garavan et al., 1999; Humberstone et al., 1997). It is believed that the pre-SMA activation helps to overcome interference by selecting task-relevant information (Volz et al., 2003; Gehring & Taylor, 2004). A clinical study has also provided additional evidence of the importance of pre-SMA in response inhibition. A person with a bilateral tumor in this region had severe inhibitory deficits on a go/no-go task until the tumor was removed (Leimkuhler & Mesulam, 1985). The RSE involves the competition between color-naming and word-reading (e.g., Wylie & Allport, 2000; Allport et al., 1994; Allport & Wylie, 1999). The observance of the activation in the pre-SMA area may also suggest the existence of the RSE in the RW condition of series 2a & 2b.

Issues with the current analysis

1). Issues using the rest period as the baseline in the contrast of RW-rest and SC-rest

Although activation of the areas of the IFG, MFG, and parietal regions was observed in the contrast of RW-rest in both the NC and the AD group, we cannot conclude that these areas are the regions that are associated with inhibitory control as observed in other inhibitory studies. In an fMRI experimental design, using rest period as baseline is not recommended. This is because during the non-task condition period, subjects will naturally think about various things, such as how they are doing in the experiment, or

when the experiment will be finished (Huettel et al., 2004). In addition the rest period is a very low level control. Although similar activation pattern was found in both the contrasts of RW-rest and SC-rest of the NC group, the similar brain activation could be due to various factors, such as visual stimulus, color processing or speech production. Therefore, we cannot conclude that regions, such as IFG, MFG, observed in the task-rest contrast of series 2a and 2b are those areas that are associated with inhibition. The contrast of RW-rest thus could not really confirm the existence of the RSE in the RW condition of series 2a and 2b.

Due to the issues of using rest period as baseline, what should have been done is to have a new contrast to compare between series 1 and series 2a and 2b in order to examine the existence of the RSE in the RW condition of series 2a and 2b. The switching task of series 2a and 2b was believed to elicit the RSE in the RW condition; while the RSE was not robust in the RW condition of series 1. In order to identify the existence of the RSE in the RW condition of series 2a and 2b, the contrast could be proposed as SC-RW from series 2a and 2b as compared to SC-RW from series 1 [$(\text{SC-RW})_1 - (\text{SC-RW})_{2a2b}$]. More activation would be expected in this new contrast. We would expect to see less activation in the contrast of SC-RW in series 2a and 2b because of the RSE in the RW condition. More activation would be expected in the contrast of SC-RW in series 1 as little or no RSE should be observed in the RW condition. The activation observed in this new contrast could suggest the existence of the RSE in the RW condition in series 2a and 2b. Lastly, the results should be reported from voxel-level with corrected p value.

2). Problem using the 0.001 uncorrected p value for multiple comparison

In the current study, part of the fMRI results was reported from voxel-level with $p \leq 0.001$, uncorrected for multiple comparisons. The uncorrected p value can enhance the possibility of false positives in fMRI data (Bennett et al., 2009). An interesting study of dead salmon from Bennett and his colleagues (2009) found activation in the salmon's brain using p uncorrected <0.001. When the study used the false discovery rate (FDR) and family-wise error (FWE) for multiple comparisons, no activated brain areas were found. The study argued that multiple comparisons correction should be used for fMRI data analysis in order to prevent false positives. Most of the results from the current study were reported using uncorrected, p=0.001 level. False positives with this threshold may be involved. Therefore, the results may not be valid as the possibility of activated areas observed in the current study may not actually exist with corrected multiple comparisons. Thus, the results should have used corrected multiple comparisons, such as family-wise error, for fMRI data.

Event-related analysis in the contrast of incorrect responses-correct responses in the RW condition in the AD group

The result of the contrast did not show any activation in the area of the ACC. Two possible reasons could contribute to it.

1) The proper event-related design

First, the event-related analysis used in the current study may not be suitable for the block design. The basic idea of the event-related fMRI design is that the processes of interest can be generated transiently by brief stimulus events. In most event-related designs, each event is separated in time from the previous event. The time period between

successive stimuli is called interstimulus interval (ISI), which can range from about 2s to 20s depending on the goals of the experiment. The purpose of the ISI is to allow the hemodynamic response to return to baseline. In an event-related design, the different conditions of the events are usually presented in a random order as well. Unlike the event-related design, a block design allows many stimuli of the same condition consecutively presented within a task block (Huettel et al., 2004).

The event-related analysis used in the current block design may not be appropriate because each event was presented in a very short interval (1.75s) and the events of the SC condition and the RW condition were not presented in a random order. The absence of the ISI/ short interval between successive stimuli in the current study may not allow us to look at the transient change of the interesting stimuli, which are incorrect responses in this case. Therefore, the comparison of incorrect responses with correct responses may not be appropriate.

In the contrast of RW-SC of series 2a and 2b of the NC group, similar brain activation was found by the event-related analysis and to block analysis. If the event-related analysis is not appropriate for the block design, how can we explain the similar activation pattern found in the contrast of RW-SC using the two analyses? The following will explain the reason.

The principle of the hemodynamic response in a block design is superposition, which states that the summation of the independent responses to the inputs is equivalent to the total response to a set of inputs. The hemodynamic response to two successively presented identical stimuli is equal to the sum of the individual responses. As more and

more stimuli are presented in succession, each contributes to the total hemodynamic response until the end of the block (Huettel et al., 2004). Most subjects in the NC group only made scattered erroneous responses within a block (1-4 errors/block). Two of the subjects made more errors. However, the erroneous responses covered the whole block and were discarded as a whole block. When correct responses are selected in both conditions in the event-related analysis, the sum of the hemodynamic response of correct responses is equal to the sum of the hemodynamic response of a block. Thus, the results of the contrast of RW-SC in both analyses in the NC group yielded similar brain activation pattern.

On the other hand, only incorrect responses of series 2a and 2b were selected from the AD group. The incorrect responses sometimes come with a cluster of 5 to 7; sometimes the whole block was incorrect responses; sometimes the incorrect responses were scattered randomly (1 to 4 incorrect responses) within a block. When incorrect responses were selected across the blocks in the RW condition, several issues could appear: 1) the hemodynamic response of selected incorrect responses cannot return to baseline due to very short interval between successive events (Huettel et al., 2004); 2) the hemodynamic response of selected incorrect responses may be contaminated by the stimuli before the incorrect responses within a block. The responses preceding the incorrect responses could be correct responses, missed or corrected responses. Different responses before the incorrect responses could affect the hemodynamic response of the incorrect responses. These issues could account for the reason that current blocked design is not suitable for the event-related analysis.

2) The components of the inhibition performance

When reviewed the behavioural data of the erroneous responses in both the RW and SC conditions across the group in series2a and 2b, it is noteworthy that some of the time the erroneous responses covered the entire block. Some of the time the erroneous responses occurred in the middle of the block or happened towards the end of the block. When reviewed their audio-tape, the majority of their erroneous responses were due to their confusion of what task they were asked to perform. These results indicate that the loss of the goal maintenance may partially contribute to the erroneous responses.

Recent theoretical models have proposed that inhibition performance consists of two components: the ability to resist interference and the ability to maintain the task goal (Braver et al., 2008; Kane & Engle, 2003). The interference effect is the competition that occurs between two processes that are activated by contradictory information. In a Stroop task, naming colors of incongruent trials induces interference due to the competition between the word and the color. This competition will eventually be resolved with a longer response time. Goal maintenance is the ability to maintain a task-specific goal. It is believed that if the task goal is not activated sufficiently, it will fail to block the responses in a context where they are irrelevant to the task, hence leading to interference effects. Therefore, both active maintenance of specific task-related goals and interference resolution are required in order to successfully perform inhibition tasks (Cohen & Servan-Schreiber, 1992; Kane & Engle, 2003).

Studies have suggested that interference resolution and goal maintenance may be more interdependent when the task is more complex (Belanger et al., 2010). In the

context of a Stroop task, name the color in pure blocks of incongruent trials requires little challenging to goal maintenance. This is because the inappropriate goal (read the word) is never reinforced since it leads to errors. On the other hand, a large goal-maintenance capacity will be required in the context of a Stroop task that includes a large proportion of congruent trials. This is because congruent trials favor goal loss by promoting a word-reading strategy. As a result, subjects experience a larger Stroop effect in the mixed blocks than in the pure blocks (Logan et al., 1984).

The current study of series 2a and 2b involved two tasks of word reading and color naming in an alternating order. In addition to the requirement of interference resolution in the tasks, the goal maintenance of a specific task is also required in series 2a and 2b. The goal maintenance of a specific task allows subjects to update task-set information at the beginning of each block in order to successfully perform required tasks. The ability to rapid update of task-set information is critical for allowing participant to react quickly to the next required task (Braver et al., 2003). In the current study, either by behavioural data or audio-tape, the loss of goal maintenance in the AD group has been observed. Therefore, both components of goal maintenance and interference resolution were required in the current study in order to perform successfully in both tasks. The impairment of either component would lead to the failure of the task performance.

A number of studies and computational models have suggested that interference resolution and goal maintenance are distinct processes in contribution to inhibition performance. Different brain areas may be involved in processing these two different components (Kane & Engle, 2003). In the current study, the selection of incorrect

responses whether these were due to goal loss or resulted from deficits of interference resolution was not categorized. The function of the ACC as indicated earlier has been suggested to associate with conflict response or errors detection that results from failure to overcome interference resolution (Gehring et al., 1993; Dehaene et al., 1994). The deficits of the goal maintenance in AD patients have been observed in Belanger and her colleagues' study (2010). If the majority of the incorrect responses were due to the deficits of the goal maintenance in the current study, the activation of the ACC might not be observed. The absence of the activation in the ACC may be due to the involvement of the goal maintenance processes in the current study.

Conclusion

The results from both behavioural analysis and fMRI data analysis show that the contrast of SC-RW of series 2a and 2b does not reveal the amount of the Stroop interference effect. A reverse Stroop effect (RSE), which is elicited by the switching task paradigm of series 2a and 2b, might be the reason for the absent brain activation. Although the current Stroop paradigm of series 2a and 2b was not appropriate for the detection of the amount of the Stroop interference effect, it still allowed us to relate our findings to the existing literature on the RSE.

Behavioural results add further support that both the AD and MCI group have more impairment in shifting attention and inhibition in comparison with the NC group. Not only interference resolution was impaired in the AD group, deficits in goal maintenance were also observed when compared to the NC group. In conclusion, both behavioural analysis and functional data analysis indicate that the paradigm of series 2a and 2b used in the current study is inappropriate to yield a Stroop interference effect in the contrast of SC-RW.

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