Cortical regions involved in proactive control of task-set

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I certify that all material in this thesis which is not my own work has been identified and that no material has previously been submitted and approved for the award of a degree by this or any other University.

Signature:…….

Abstract

This thesis is about what happens in the brain when people switch between tasks. Each task requires a particular assembly of cognitive processes, an orientation of attention and set of rules relating action to input — a "task-set". The research reported used a task-cueing paradigm to study preparatory control of task-set. On each trial a stimulus (a coloured shape) was preceded by a verbal task-cue specifying which task to do (judge the shape or the colour of the stimulus). Reaction time and error rate increase on trials when the task changes relative to trials on which it does not. When the cue stimulus interval (CSI) is increased, this "switch cost" is reduced, indexing a process of task-set reconfiguration in which top-down control is employed to reconfigure the task-set parameters. Effective reconfiguration may also be indicated by a reduction in the "response congruence effect" — poorer performance on stimuli mapped to different responses for the two tasks than for stimuli mapped to the same response. I present six experiments using transcranial magnetic stimulation (TMS), a technique for interfering briefly and harmlessly with neuronal activity in a small region of cortex, to address the question of which brain regions contribute to anticipatory control of task-set as indexed by these behavioural measures.

To help guide the selection of candidate brain regions, I first present a review and meta-analysis of neuroimaging studies of task-switching in the literature. Many fMRI studies, comparing brain activation on task-switch and -repeat trials have been published. Some have also tried to isolate activations related specifically to pro-active control of task-set. The activations reported are quite inconsistent over studies. I used a quantitative meta-analysis technique to identify which brain regions are most consistently found by studies reporting switch minus repeat contrasts and which may be specifically important for preparation on switch trials.

The experiments examined the effect of stimulating several regions during the long cue-stimulus interval of a task-cueing paradigm, relative to control conditions. A first pair of experiments suggests an important role in proactive task-set control for two regions in dorsal medial frontal cortex, the supplementary motor area (SMA) and an area known as pre-SMA, though the former region appeared to contribute to reducing the switch cost while the latter appeared to reduce the effects of response congruence. In a further three experiments, I examined the role of the right intra-parietal sulcus (rIPS); this appears to

play a crucial role in preparation for a task-switch but not post-stimulus task-set reconfiguration. In a final experiment, I used TMS guided by fMRI activations in the same participants to study the effects of stimulation over the left inferior frontal junction (IFJ). The results indicate that a region just anterior to the left IFJ is specifically important for preparing for a switch trial. I discuss the roles that may be played by these three regions in task-set control.

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The expertise and guidance given by my supervisors Stephen Monsell and Aureliu Lavric have been essential throughout my project and allowed me to make significant and invaluable steps in my understanding of experimental psychology and cognitive neuroscience. Their passion for cognitive science has been a great inspiration.

I want to acknowledge the important contributions of some of my fellow PhD students in cognitive psychology; Charlotte Forrest, Felice van ‘t Wout, Hannah Filmer and Heike Elchlepp, who besides being great friends, have always been interested in my projects and helped me on numerous occasions with feedback, expertise and morale. In particular my extensive discussions with Charlotte have helped me to order my thoughts and improve my thesis.

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Declaration

The research reported in this thesis was carried out at the University of Exeter between October 2007 and August 2011 and was supervised by Prof. Stephen Monsell and Dr. Aureliu Lavric.

This dissertation has not been submitted, in whole or in part, for any other degree, diploma or qualification at any university. Chapters 3 and 5 are articles that will be submitted to scientific journals. Chapter 3 will be submitted to NeuroImage by Stevens, T., Monsell, S. and Lavric, A. I conducted the meta-analysis, wrote the first draft and prepared the figures and tables. My coauthors have edited the manuscript. Chapter 5 will be submitted to the Journal of Cognitive Neuroscience (besides the pilot study) by Stevens, T. and Monsell, S. I conducted the experiments, wrote the first draft and prepared the figures and tables. My coauthor has edited the manuscript.

Tobias Stevens
Exeter, August 2011.

Chapter 1: General introduction

1.1 Executive control

Our ability to exert control over our actions in accordance with internal goals is crucial to normal human behaviour. Information coming from the outside world can cause us to respond automatically and unintentionally. However, throughout our daily lives many of the things we do find their origin, not merely in these outside influences, but in the interaction between outside information and our internal goals and intentions. Our brain is thought to house mechanisms of cognitive control that allow us to initiate the appropriate actions and alter routine behaviour in order to reach our goals as well as ignore outside influences and distractors if necessary (Aron, 2007; Desimone & Duncan, 1995; Miller & Cohen, 2001; Tipper, 2001)

The need for cognitive control mechanisms in order to explain human behaviour is illustrated by cases of impaired control in people with brain damage. People with damage to the frontal lobe, in particular, seem to experience problems with organising their behaviour in a coherent and goal directed manner. For example, people with damage to the medial frontal cortex sometimes exhibit "utilisation behaviour" which is characterized by an inability to avoid performing habitual actions to irrelevant stimuli – e.g. when walking through a corridor they might open doors they pass, even though these are irrelevant to their current task and goals (Nachev, Kennard, & Husain, 2008)

Norman and Shallice (1980) suggested that action selection was driven by two separate components: a lower level component which overcomes interference through lateral inhibition between well learnt action schemas which drive routine behaviour, and a higher level component, called the Supervisory Attentional System (SAS) which is thought to regulate the lower level components in goal directed and non-routine behaviour, by actively selecting or inhibiting action schemas. What the nature of the SAS is however remained unexplained. Understanding the different functionalities underlying this executive system has been one of the greater challenges in contemporary cognitive psychology (Monsell & Driver, 2000). Among the proposed functions are management of working memory, inhibition of unwanted behaviour, controlling or dividing the focus of attention and coordinating the concurrent performance of multiple tasks by performing them simultaneously or voluntarily switching between them.

1.2 Mental set shifting

The focus of this thesis is our ability to switch flexibly between task-sets, especially the preparatory control of task-set, and the brain regions that are involved in these control processes. Task-set refers to the set of mental resources and its organisation and tuning that allow the brain to perform a particular task appropriately. When the task to be performed changes as a function of external cues, internal changes in priority, or both, the task-set needs to be altered accordingly (Monsell, 2003). Introspection suggests that we can get a task-set ready well in advance of the environmental events to which we will respond, such as when we get ready to catch a ball or name a face.

The exact processes required to change task-set are still unclear, and will almost certainly depend in part on the particular task transitions required, but they may include re-orienting attention between stimulus modalities, locations, dimensions, or features, updating the contents of procedural working memory (e.g. activating relevant S-R -rules or procedures, suppressing previously relevant rules or procedures), preparing relevant effector systems and monitoring for and dealing with conflict. Task-set and action are closely related, but are not the same. What determines which action is selected in any context results from an interplay of external cues and internal conditions (Monsell, 2003). "Task-set" describes the internal conditions that need to be established for a particular stimulus in a particular context to result in an appropriate action, one consistent with current goals and current input, performed with adequate speed and accuracy.

Several kinds of paradigms have been developed to study human task switching. Neuroimaging research using these paradigms has begun to give some idea of which brain regions become particularly active in situations where task-set needs to be changed. I will first review the behavioural paradigms, some of the phenomena revealed and their theoretical interpretation. Then I will review evidence from the neuroimaging and neuropsychological literature on which brain regions are associated with task-set control, as a prelude to my own studies. These studies were aimed at identifying which brain regions are consistently reported by the imaging literature through a quantitative meta-analysis and I attempted to interfere with task-set preparation and task switching using transcranial magnetic stimulation (TMS) of some of these regions.

1.3 Task-switching paradigms

All these paradigms are designed to compare performance on trials on which the same task was performed on the previous trial (task-repeat trials) to performance on trials where the task is different from the last one (task-switch trials), other things being equal. Some of these paradigms also allow manipulation of the time available for preparation between when the participant knows what task is to be performed and the arrival of the stimulus to which he/she must respond, thus potentially isolating the effects of active endogenous control in preparation for performance of a task from processes required to execute the task and also to deal reactively with conflict due to limitations in top-down control.

In the last 15 years three such paradigms have largely replaced Jesild's (1927) classic paradigm in which he compared the duration of blocks of single task trials with blocks in which participants alternated between two tasks. Jersild's comparison does not make a distinction between switch costs and mixing costs (see below) and keeping track of the sequence of tasks requires more working memory engagement in the alternating blocks than in the single task blocks (Monsell, 2003).

Alternating runs. Rogers and Monsell (1995) used runs of fixed length in the two tasks (e.g. AABBAABB....). There are usually external cues to help the participant know where they are in the sequence, so that the task to be performed on the next trial (and subsequent trials) is always completely predictable. Hence switch and repeat trials are essentially identical apart from the identity of the task on the previous trial. Responses on switch trials are slower than responses on repeat trials: there is a task-switch cost (Rogers & Monsell, 1995). It is possible to vary the time in between trials (the response-stimulus interval), which varies the time available for preparation (as the participant always knows what the next task will be); a longer RSI reduces the switch cost (Rogers & Monsell, 1995). There are also other ways of testing predictable switching -- e.g. presenting pairs or triples of stimuli with forewarning of the sequence of tasks required (e.g. Allport, Styles & Hsieh, 1994; Goschke, 2000) - but these are little used.

Intermittent instruction. In this paradigm, introduced by Gopher and colleagues (Gopher, 1996; Gopher, Greenshpan, Armony, Human, & Ergon, 1996) a task cue or instruction is given followed by a run of trials of variable length, until the next cue display interrupts the sequence. That cue may specify the same or different task as in the previous

run. The interruption slows the response on the first trial of a run (there is a "restart cost"), but this effect is larger when the task changes, which provides a measure of the task-switch cost.

Task-cueing. In this paradigm (Shaffer, 1965, Sudevan & Taylor, 1987, Meiran, 1996), the task to be performed on each trial, though constrained to a small set (usually two or three), is not known until a task cue presented concurrent with or shortly before the stimulus. Varying the time between task cue and stimulus controls the time available for preparation. The standard comparison is between task-switch and task-repeat trials, often as a function of cue-stimulus interval (CSI); a longer CSI typically reduces the switch costs.

Unlike the alternating runs paradigm, the cued-task switching paradigm allows for separate manipulation of the cue-stimulus interval and the response-cue interval, which is important because of the possibility of passive decay over time of the mind-state that generated performance on the previous trials. Unlike the intermittent cueing paradigm, the cueing paradigm allows one to change or repeat the task on each trial and each trial is the same in format. In the experiments presented in this thesis, I use the task-cueing paradigm. The ability to independently manipulate the CSI allows me to specifically target task-set preparation (see below) using TMS and stimulation can be applied during the CSI in the same way on each trial.

1.4 The behavioural phenomena of task-switching

A rich history of switching experiments has revealed several interesting behavioural phenomena. Switch trials have consistently larger average reaction times and higher error rates than repeat trials. This difference in performance efficiency is called the task-switch cost (and we can distinguish between the RT cost and the error cost of a switch). When one increases the length of the cue stimulus interval (CSI) in a task-cueing experiment or the response-stimulus interval in a predictable switching experiment, the difference in reaction time between switch and repeat trials is reduced (Meiran, 1996; Monsell 2003; Rogers & Monsell, 1995). This reduction in switch cost (RISC) effect suggests that one can prepare for the next stimulus by performing at least some of the processes required to change task-set prior to stimulus onset, thus removing some of the processing overhead associated with

a task switch that would otherwise prolong post-stimulus processing. But preparation almost never eliminates switch cost, which become asymptotic when the preparation time (CSI or RSI) reaches somewhere between 0.5 and 1.0 sec (Monsell, 2003; Monsell & Mizon, 2006). This persistent component of the switch cost, apparently immune to preparation, has been termed the "residual cost" (Rogers & Monsell, 1995; Monsell, 2003).

Besides these transient task switch costs, the need to be ready to switch has an additional global effect on reaction time. Repeat trials in a block consisting of both switch and repeat trials, have longer average reaction times than when presented in a single task block. This is referred to as the "mixing cost".

In a task switching paradigm with two tasks, stimuli afford a response in both tasks (bivalent) or just one (univalent). For example in a paradigm where the participant switches between identifying the colour or shape of objects, a bivalent stimulus could be a “blue circle”. This stimulus has two possible answers, namely “blue” in the colour naming task and “circle” in the shape naming task. An example of one type of univalent stimulus could be a “black circle” (if black is never used as a response in the colour task) which is then only associated with the shape task. Another type of univalent stimulus would be in an experiment in which the stimuli are composites of two objects (e.g. a digit and a letter, or a face and a word), and only one of the objects is present.

A bivalent stimulus can be congruent or incongruent. In the example of a blue circle, the stimulus could be incongruent if the response “blue” required pressing a different response key than the response “circle”. Another stimulus from this set could be congruent, for example, if the response key for blue is the same as for triangle, then the blue triangle is a congruent stimulus. In task switching studies, incongruent stimuli take longer to respond to than congruent stimuli (Roger & Monsell, 1995). This congruence effect is similar to other "response conflict" phenomena, such as the Stroop effect and the Simon effect, with the difference that it is not pre-existing familiarity but recent exercise of the alternative S-R mapping that causes it to compete. As an indicator that the irrelevant task is not completely suppressed, it provides another index of the overhead involved in task-switching. Moreover, although the congruence effect is usually somewhat larger on switch trials (Roger & Monsell, 1995), as one might expect if task-set is less well established on a switch trial, it is much more persistent than the transient switch cost: it is still robust

several trials after the transient effect of a task switch (Monsell, Sumner & Waters, 2003). If preparation is effective in engaging the appropriate task-set (or suppressing the competing one), one would expect the congruency effect to reduce with preparation. The data on this are somewhat mixed, but there are a number of demonstrations that the congruence effect can reduce with preparation (Kiesel et al., 2010; Monsell & Mizon, 2006).

Another important observation is that congruent bivalent stimuli can take longer to respond to than univalent stimuli (Rogers & Monsell, 1995; Steinhauser & Hubner, 2007). This has been interpreted as evidence that the currently irrelevant but recently activated task-set can cause competition at the level not only of S-R rules (explaining the congruence effect) but also at the level of whole task-sets. Congruent stimuli may benefit from response facilitation, but also activate competing task sets, while univalent stimuli activate only one task-set: the balance of these effects is under some conditions sufficient to disadvantage the congruent stimuli.

There are however some behavioural findings that shed some doubt on the notion that preparation reduces the switch costs by preparing the new task-set in advance. For example, Schuch and Koch (2003) used a task-switching paradigm in which participants were shown a digit and had to judge whether the stimulus was odd or even or greater or smaller than 5, by responding with a button press. They included a CSI manipulation; in the short CSI condition the interval was 0 ms so there was no time to prepare and in the long CSI condition the interval was 1000 ms to allow for task-set preparation. On 25% of trials, a tone signalled participants to withhold their response. When a go-trial followed a go-trial of a different task, participants showed the normal behavioural switch costs. However, when a no-go trial was followed by a go-trial of a different task, there were no switch costs. So when the other task was not actually executed (by making a manual response), there were no behavioural consequences of switching, even if there had been time to prepare on the previous trial. Whatever was prepared during the CSI of the first trial did not seem to affect the following trial. One possible explanation is that there was no task-set preparation on the first trial and if the switch costs are caused by the need to change task-set or overcome competition between task-sets, then the task-set must have been implemented after the stimulus. Alternatively, the no-go signal could have inhibited any prepared task-

processes. This latter account is supported by the fact that the reaction times on a go-trial following a no-go trial are typically slow. This could be because on the no-go trial, the irrelevant task-set was inhibited during the CSI and the relevant task-set was inhibited when the no-go signal was presented. Recent work by Los and Van der Burg (2010) however show that under certain circumstances (e.g. increasing the time between no-go signal and the stimulus) the reaction times on the go trial following a no-go trial can be fast.

1.5 Theories of preparation

Following critique from Logan and Bundesen (2003) and others, Monsell and Mizon (2006) further specified conditions under which they argued it was safe to interpret the RISC effect as a measure of top-down control. Logan and Bundesen (2003) suggested that the switch costs and the RISC effect were a consequence of confounding task-switching with cue switching. In a series of experiments using two cues per task (in a digit classification paradigm; "odd/even", "high/low") they observed a substantial difference between trials on which the cue switched but not the task and trials on which the cue and task remained the same. Additionally, only a small difference was found between trials on which both cue and task switched and trials on which the cue switched but not the task. The observed difference between a change of cue and a repeat of both cue and task also reduced with preparation. This suggested that the switch costs and the RISC effect were the result of the need to process the new cue and that, when given time, this could be done before stimulus arrival. Mayr and Kliegl (2000) used a colour/shape task and found that the switch costs consisted of an approximately equal share of task switching and cue switching. In response Monsell and Mizon (2006) showed that even when using 2 cues per task, with adequate motivation, the switch costs and RISC effect were still observed. Additionally they showed that the RISC effect becomes more robust when the chance of a switch trial is reduced (they show that for example 1/4 switch trials results in a robust RISC effect). Monsell and Mizon argue that when the switch probability is high, participants tend to prepare for a switch on each trial, whereas if this probability is low, they are more likely to refrain from preparation until a cue tells them otherwise.

The precise nature of the top-down control processes thought to underlie the RISC effect is still an open question. There are two leading ideas that could both to some extent account for both switch costs, the RISC effect and the residual switch costs. An idea postulated by Allport et al. (1994) suggests that the switch costs are the result of interference caused by the lingering activation of the previously activated task-set (task-set inertia). This either needs time to passively decay, be inhibited or resolved in some other fashion. Providing extra time between the task-cue and the stimulus would allow for this the passive decay or inhibition of the old task-set, consequently reducing the switch costs. One of the main sources of evidence for this account was the observation that when switching between two tasks that are different in familiarity (e.g. the Stroop effect), switch costs were bigger when switching to the more familiar task, suggesting that this task had received more inhibition to overcome its interfering influence on the execution of the less familiar task. When switching back to the familiar task, it has consequently become less accessible. These asymmetric switch costs have been carefully studied in recent years but although they are observed in many experiments (Allport & Wylie, 2000; Meuter & Allport, 1999; Sinai, Goffaux, & Phillips, 2007; Yeung & Monsell, 2003b), results from for example, Yeung and Monsell (2003) and Bryck and Mayr (2008) suggest that the asymmetric switch costs are not fully due to inhibition (Vandierendonck, Liefooghe, & Verbruggen, 2010). For example, Yeung and Monsell (2003) showed that the asymmetric switch costs could be reversed. In their first experiment they increasingly delayed the onset of the familiar task in a Stroop switching task, by manipulating the time between displaying the colour and displaying the word. In Experiments 2 and 3 they removed the overlap between the response sets of the tasks. In both situations it became harder to switch to the less familiar task instead of to the familiar, which is difficult to explain through a pure inhibition account.

However, if the lingering activation of the old task-set was the sole contributor to the switch cost, then increasing RSI, while not increasing CSI, should also lead to a reduction in switch costs. Meiran (1996) showed that when CSI is not confounded by RSI, a RISC effect is still observed.

Another account of the origin of the switch costs and the RISC effect is the idea of task-set reconfiguration. This refers to the need to alter the task-set (or aspects of the task-

set) to successfully execute the new task. As mentioned previously, a task-set is thought to consist of various task-set parameters that need to be reconfigured when the tasks changes (Logan & Gordon, 2001; Monsell, 2003; Vandierendonck, et al., 2010).

Some frequently mentioned candidates for such task-parameters are the need to re-bias the attentional stream to process the appropriate stimulus feature/dimension/object, stimulus-response relationships and possibly the inhibition of possible sources of future conflict, such as components of the irrelevant task-set (Meiran, 1996, Vanndierendonck et al., 2010). For example, in the case of a paradigm requiring people to either judge the shape of a stimulus or the colour of a stimulus; participants may need to change the visual dimension they are focusing on when switching from one task to the other. If it is possible to do this in advance of the stimulus, switch related response latencies are likely to be reduced (Meiran, 2000; Meiran, Kessler, & Adi-Japha, 2008). A second example of a task-set parameter could be the need to alter the mappings from the stimuli and the manual responses. Response incongruent bivalent stimuli, for example, require a different manual response depending on the task context. When the task changes, the participants might be able to reconfigure these relationships in advance of the stimulus and consequently reduce the reaction time.

Any account of what processes underlie the RISC effect, must be able to account for the residual switch costs. The idea of task-set reconfiguration provides an explanation for the switch costs and the RISC effect, but the residual switch cost potentially forms a problem for the reconfiguration account. This is because the residual cost suggests that the task-set cannot be fully reconfigured when provided, in advance, with the new task information. A two stage model was suggested by Rogers and Monsell (1995) which proposed that a part of the task-set cannot be reconfigured without stimulus information. The residual switch costs are also often attributed to interference from the previous task-set carrying over from the earlier trial (i.e. task-set inertia) (Monsell, 2003). Additionally, the association between the stimulus and the irrelevant task-set could cause associative retrieval of the irrelevant task-set, potentially causing task-set interference after stimulus presentation (Monsell, 2003).

An interesting explanation of the residual switch costs is the “failure to engage” account first postulated by De Jong (2000). De Jong showed that the reaction time

distribution of prepared switch trials could be modelled as a mixture of the reaction times from prepared repeat trials and unprepared switch trials (not allowing for a preparatory benefit in repeat trials). Apparently extra preparation time does not lead to a lower reaction time on every switch trial. He showed that the residual costs could be the consequence of averaging over fast and slow switch trials. His findings support the idea that preparation is either successful or not or that there is at least a considerable variability in the degree of preparation. Possibly, when the new task is not successfully prepared, the reconfiguration processes needs to be performed after stimulus onset (similar to trials without the ability to prepare). The existence of this pattern in task-switching data was later confirmed by the re-analysis of new and previous data by Nieuwenhuis and Monsell (2002).

One of the most commonly held views at this time is that the RISC effect reflects a process of task-set preparation consisting of the reconfiguration of various task-set parameters and possibly the inhibition of possible causes of interference such as the irrelevant task-set or components of this task-set. In this thesis I will assume this account of the origin of the RISC effect.

1.6 Neural correlates of task set control

Recent years have seen a large number of neuroimaging articles on task-set control published. In the next sections, I will review the imaging literature that has studied the differences in brain activations between switch and repeat trials, and then studies that have used fMRI to try to isolate preparatory processes in the scanner. The latter have employed different strategies to identify regions of the brain that might host processes which can proactively prepare the brain for a new task context. Based on the account of origin of the RISC effect, suggested before, these regions are thought to host the neural processes related to reconfiguring task-set by activating the relevant task-set parameters (or potentially inhibiting the irrelevant ones).

I will then focus on a number of regions implicated by these studies and discuss what their potential role in task-set reconfiguration could be.

These preliminary reviews will be followed in Chapter 3 by a quantitative statistical meta-analysis to determine which of these areas are consistently activated by switch minus

repeat contrasts as well as by studies that try to isolate preparatory activations. As a result, I will be able to offer a more precise picture of which locations seem to be associated with a switch-repeat contrast and/or preparation for a task and hence are candidate regions for exploration with TMS.

1.7 Brain regions associated with a switch of task

Table 1.1 Results from 18 switch minus repeat contrasts.

	DL/VL PFC	MFC	Premot	Insula	SPL/IPL	Precun	Thal/Put	Cereb	Occ	Anterior frontal	Tempo
Number of studies reporting this region	11/18	14/18	4/18	5/18	12/18	5/18	4/18	3/18	4/18	2/18	5/18
Brass 2004	X	X	X								
Erickson 2005					X	X					
Kimberg 2000					X						
Sylvester 2003	X	X			X	X	X				
Hyafil 2009		X					X	X	X	X	X
Rubia. 2006	X	X	X	X	X		X		X		
Yeung 2006		X			X	X					
Braver 2003	X	X			X						
Chiu 2009		X									
Gu 2008	X	X	X	X	X				X	X	X
Liston 2006	X	X	X		X						
Luks 2002	X	X		X							
Ruge 2005	X				X						
Smith 2004	X	X		X	X		X				X
Sohn 2000	X	X		X					X		
Badre 2006	X	X			X						
Jamadar 2010a					X	X		X			X
Jamadar 2010b					X	X		X			X

In the imaging literature, the term "task-switching" has been used in a variety of ways. Here I define a task switching paradigm as one in which there are at least 2 tasks and the

participant does one task per trial. On any given trial, the participant is required to make a perceptual or semantic judgement (e.g., identify the colour or shape or a stimulus, classify a letter as consonant or a vowel, etc.) which can be the same ('repeat' trial) or different ('switch' trial) as the task on the previous trial. Each judgement outcome is associated with a (typically manual) response (e.g., pressing of buttons or moving a joystick in a particular direction). The most common way of employing fMRI to study task switching is to have subjects perform a task-switching paradigm in the scanner and contrast the BOLD signal on switch trials with that on repeat trials, analogous to calculating reaction time switch costs. This reveals the difference in brain activity on switch compared to repeat trials.

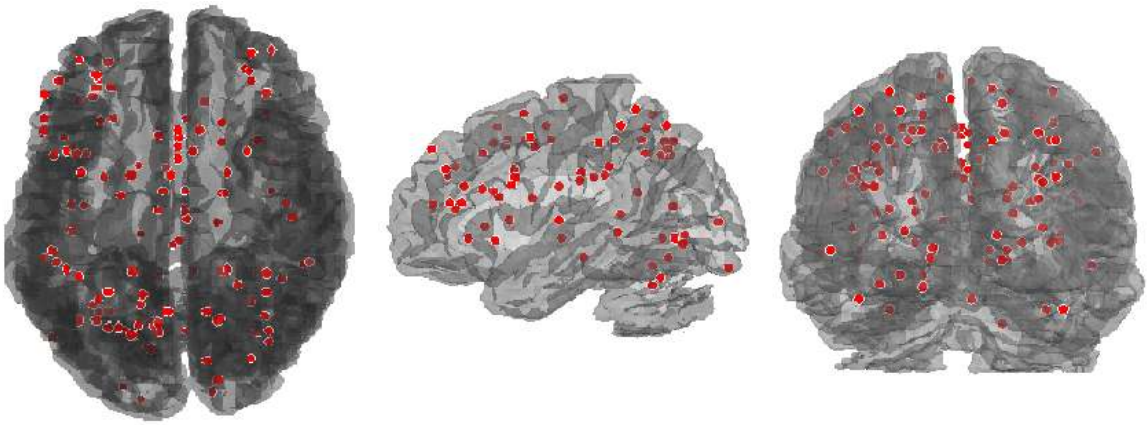


Figure 1.1 Peaks from switch minus repeat contrasts reported by 18 articles (see Table 1.1).

To my knowledge there have been 18 imaging studies reporting a switch minus repeat whole brain contrast in a task-switching paradigm, according to the definition given above. Figure 1.1 (and Table 1.1) shows the reported peaks of activation in these studies for the switch minus repeat contrast. Each point represents the location of the peak within a volume of activation varying in size (number of voxels). The results of these contrasts show great variability and involve many different brain regions. I will illustrate these experiments, with four typical studies and summarize the results of all 18 below.

Kimberg, Aguirre and D'Esposito (2000) used a number and letter task, similar to the one used by Rogers and Monsell (1995). A display divided into four quadrants (in a 2 by 2 grid) was shown to nine participants. Depending on where the stimuli were presented (above or below), the participants had to judge whether the digit was odd or even or the letter was a vowel or a consonant. Successive stimuli were presented in successive

clockwise loci, so that the task switched every two trials. There was a 20s delay between each trial and the next, to accommodate the BOLD signal. The switch-repeat[1] contrast shows a small extra activation in the left superior parietal lobule.

Yeung, Nystrom, Aronson and Cohen (2006) identified individual task-related brain regions in the scanner using single task blocks and then looked at their activation in mixed-task blocks. Mixed blocks consisted of runs of four trials preceded by a cue specifying the task for that run. On each trial, participants saw a face with a word superimposed. They were asked to determine whether the face was male or female or whether the word had two syllables or not. Contrasting switch trials with repeat trials, they found switch-related activity, which was not task specific, in the anterior cingulate cortex (ACC), insula, posterior cingulate, pre-SMA and parietal regions[2].

Rubia al. (2006) used a modified version of the task used by Meiran (1996). In this task a dot appears in one of the quadrants of a 2 by 2 grid. In the middle of the grid, a double headed arrow was presented either horizontally or vertically. The direction of the double arrow indicated whether the participant had to assess whether the dot was up or down or left or right in the grid. The grid with the arrow was presented for 200 ms, after which the dot appeared for another 1400 ms. Participants had to respond as fast as possible after the dot was presented. The authors compared different age groups and different paradigms. I consider only the data from the adult participants , for whom the event-related switch minus repeat contrast shows peak activations in the post-central and inferior parietal gyrus bilaterally extending into the right premotor and inferior frontal cortex as well as the right dorsolateral prefrontal cortex (DLPFC), the ACC and occipital gyrus bilaterally.

Hyafil, Summerfield and Koechlin (2009) let participants switch between responding to a word or to an arrow. The words were the directional words “left”, “right”, “up” and “down”. The words were superimposed on the arrows. The task cue was the colour of the stimulus —either green or red. Their study primarily looked at congruency effects, but here

[1]Switch minus repeat contrasts are contrasts in which the event related BOLD signal during a task switch trial is contrasted with the signal from task repeat trials. This contrasts isolates brain regions which are more active when switching tasks as opposed to repeating trials and does not specifically look at preparatory processes. Some of these studies have an interval between the cue and the stimulus, and some do not, so, it is possible these contrasts could include switch related preparatory activity.

[2] Interestingly, switch related activity related to the currently irrelevant task — in fusiform gyrus and inferior frontal sulcus (IFS) for the face task (face>word), in inferior temporal gyrus and IFG for the word task (word>face) — correlated with the switch costs suggesting that at least part of the switch costs was due to overcoming task-set level and/or response level interference from the previous task set — evidence for task-set intertia.

I include their data from switch minus repeat contrast. Switch specific activations were found in the posterior and anterior cingulate cortex, pre-SMA/SMA, the anterior PFC bilaterally as well as areas in the occipital and temporal lobe.

Preliminary summary

Examination of the whole set of 18 studies shows that two or more report switch-related activations in the dorso-lateral prefrontal cortex (DLPFC), ventro-lateral prefrontal cortex (VLPFC), medial frontal cortex (MFC), pre-motor areas, insula, superior and inferior parietal lobule (SPL, IPL), precuneus, thalamus, putamen, cerebellum, frontopolar cortex, and regions in temporal and occipital lobes. Hippocampus, caudate nucleus and post-central gyrus were reported in only one study. These results suggest there is a wide array of brain regions activated by a change of task (or more activated relatively to a task repeat). The area's most commonly activated by a task switch seem to be around the inferior and middle frontal gyrus, the medial frontal cortex, pre-motor areas, superior and inferior parietal lobule and precuneus. Further on in this chapter I will focus on several of these regions and review why these regions could be involved in task-set reconfiguration. In the discussion section on imaging studies of preparatory activity (see below), I will outline a number of possible reasons why the imaging literature reports so variable a set of different peak activations.

1.8 Studies attempting to image preparatory processes

As mentioned earlier, the RISC effect - the reduction in switch cost as the preparation time increases up to about a second - can be seen as a measure of endogenous task set control. Using fMRI to image brain activity associated with the preparation effect could reveal which regions of the brain host the mental operations which prepare/reconfigure other brain processes to successfully perform the changed task when the stimulus appears. However, implementing this idea is far from easy, for (at least) four reasons.

First, successful task preparation seems to take of the order of one second only. Because of the low temporal resolution of the BOLD signal in fMRI, it is difficult to separate the BOLD signal resulting from brain activity in the cue-stimulus interval of 0 to

2.0 sec typical of the behavioural research, from the signal resulting from post-stimulus activity. But using very long preparation intervals (as in the Kimberg and D'Esposito study mentioned above) is also problematic: the effect of a brief epoch of task-set preparation may be diluted by other activity during a long interval; participants may for example have to engage in extra maintenance activity to hold onto their prepared state, or postpone preparation until later into the interval.

A second problem is that there is likely to be other preparatory activity, not specific to task-set preparation, in the cue-stimulus interval. A century of research on foreperiod effects on performance in experiments involving just one RT task has shown that a warning signal that conveys only the information that a stimulus is imminent reduces RT, with an optimal preparation interval of about half a second (Posner,1975; Niemi & Näätanen, 1981; Nobre, Correa and Coull, 2007). Brain activity associated with preparation for stimulus-processing and or motor processing is reflected in the "readiness potential" (Brunia & Damen, 1988). Typically in task-cueing experiments, RTs on repeat trials show substantial improvement with preparation, albeit not as much as on the task-switch trials. This could reflect either generic preparation, or the occurrence even on task-repeat trials of some degree of task-set preparation, or both.

A third problem is that even if preparatory activity associated with task-set preparation per se can be isolated, there is the usual problem of determining whether it is the source of control or the target of control.

A fourth problem is that advance preparation in the cueing paradigm is an option, not compulsory: for the most part the cue remains present until the stimulus and even if it does not, the subject may just encode the cue, but wait to engage in task-set reconfiguration until the stimulus appears. In RT experiments we rely on the emphasis on minimising RT to encourage preparation, but nevertheless motivation and effort are required. Rogers and Monsell (1995) found that in their alternating runs experiments, unpredictable trial to trial variation in RSI was sufficient to discourage preparation, as indexed by abolition of the RISC effect seen with a constant interval in an otherwise identical experiment. Participants' willingness to engage in advance preparation may be quite vulnerable to -- for example -- the noise, anxiety, and general strangeness of being tested in the scanner.

And finally, almost every fMRI study uses 50% switches and repeats – according to Monsell and Mizon (2006) this distribution is not optimal for separating trials on which participants do and do not prepare for a task change (see section 1.5).

A number of imaging studies have attempted to solve the problem of separating cue- and stimulus-related activity in recent years. They have applied a variety of strategies to isolate cue-related activity. The downside however is that the paradigm often becomes unnaturally slow or the stimulus is omitted on some trials to try to induce preparation on a trial with no contamination from stimulus processing.

Some of these studies did not find a reliable difference in cue-related activations between switch and repeat trials (e.g. the interaction between preparation and switching) and report the cue related activations pooled over switch and repeat trials. This of course means, that for a lot of the results of the various studies we cannot be sure that they are involved in task-set reconfiguration or that they perform a more general preparatory function. Because not finding a switch related difference could be due to relative differences between the activation of particular regions it can be difficult to distinguish between the BOLD signal of a switch trial and that of a repeat trial. Therefore, when a study only finds preparatory activations when pooling over switch and repeat trials, the results could be seen as "narrowing down" the possible TSR related brain regions.

Table 1.2 shows the studies that have tried to isolate preparatory activations. They are sorted into two groups; studies that did find switch specific preparatory activations and studies that did not and consequently reported preparation related activations pooled over switch and repeat trials. I will discuss a number of them below.

Sohn and Carlson (2000) increased the length of the CSI to accommodate separation of cue and stimulus related activity. In trials lasting 18s, 2 stimuli were presented 5 seconds apart. Participants saw a letter and a number and depending on the colour on the stimulus either determined whether the letter was a consonant or a vowel or determined whether the number was odd or even. Sohn and colleagues manipulated the availability of task-foreknowledge between block. In the foreknowledge condition the participants knew that the task changed or remained the same between the first stimulus to the second stimulus. Hence the first stimulus acted as a cue for the task to be performed to the second stimulus. The scans in between the first and the second stimulus were analysed for preparatory

activity. The results of a contrast between foreknowledge trials and trials in which the next task was not known revealed activations in the parietal lobe (inferior parietal lobule), motor cortex, caudate nucleus, thalamus, lateral prefrontal cortex (inferior frontal gyrus) and temporal lobe. As mentioned before however, the long CSI might introduce maintenance processes or otherwise dilute effects of task-set preparation.

An interesting approach was used by Luks, Simpson, Feiwell and Miller (2002). They manipulated the informative content of the cue in an odd/even, high/low task switching paradigm. Informative cues indicated which task was to be performed on the trial (red and blue diamonds), neutral cues (green diamonds) did not give any information regarding the task. The targets were coloured red or blue, indicating the tasks as well. The cue manipulation resulted in 3 cue conditions, namely informative switch, informative repeat, and a neutral condition and four target conditions, namely informed switch and repeat and neutral switch and repeat. Participants were faster on repeat trials than on switch trials and faster on informed trials than on neutral ones. There was no significant interaction. The imaging results of informative cues contrasted with neutral cues (pooled over switch minus repeat) show MFC activations (posterior ACC and left pre-SMA) as well as the left insula. Pre-SMA and insular activations were also found when contrasting target activation on switch trials with repeat trials overall. Bilateral DLPFC (middle frontal gyrus/ inferior frontal sulcus) activations were found for the informative switch and repeat cues as well as neutral cue trials, when contrasting them with baseline, but not when informative cues were contrasted with neutral ones. DLPFC was also active in the neutrally cued switch and repeat trials following target presentation, but not in the overall switch-repeat contrast. Parietal activations were found bilaterally in the informative cue conditions and neutrally cued target conditions, but only when contrasted with baseline (not in the informative cue-neutral cue or switch-repeat contrasts). These data suggest that the MFC becomes active when task information is available before stimulus presentation on both switch and repeat trials. DLPFC is activated in all cue conditions and after target presentations on switch trials when there is no information to prepare. The behavioural data do suggest that people prepare in the informed conditions, suggesting the MFC activation is specifically linked to preparation. The results however were not properly corrected for FWE and they used a long CSI (2.5-5s).

A related approach has been used by Brass and Von Cramon (2004). They used a task switching paradigm with two cues (two tasks and two cues per task). On each trial two cues would follow one another. On some trials, the second cue would be different from the first but indicate a different task (task meaning switch) and on other trials it indicated the same task (cue-switch). Contrasting trials on which the cue and its task meaning changed with trials on which cue changed without a change of task meaning showed activations in the left inferior frontal junction (IFJ), the right IFG and right IFS.

Manipulation of information of cue content in a study done by Jamadar, Hughes, Fulham, Michie and Karayanidis (2010) showed greater activations for informative cues (informing the participant of the upcoming task) over non-informative cues (task-neutral cues) in the posterior cingulate cortex, cuneus and the superior and middle temporal gyrus as well as parahippocampal gyrus. This contrast was pooled over switch and repeat trials and showed distinctly different regions to be involved than earlier studies manipulating cue content.

Contrasting task-informative cues with neutral cues is a potentially interesting way of isolating preparatory activations. Activations, bigger on informed trials than on uninformed trials, would reflect whatever is different, e.g the ability to prepare. Neutral cues however could potentially be qualitatively different from task-cues. Over time for example, processing of the neutral cue could become very brief and processing of task-cue could entail things like cue-interpretation (which task does this cue indicate?) or goal retrieval, of which one can argue that it is not strictly a part of the task-set reconfiguration process.

In their earlier work Brass and Von Cramon (2002) used a cued task switching paradigm in which on certain trials the cue was not followed by a stimulus. This way one could measure cue related activity using fMRI without being confounded by stimulus related activity. A contrast between cue-only trials and null-events (pooled over switch and repeat trials) showed activations in the bilateral IFJ, precentral gyrus, middle and medial frontal gyrus, insula, IFG, IPS, IPL, SPL, precuneus, middle temporal gyrus, cingulate gyrus and several regions in the occipital cortex.

The use of cue-only trials has several limitations however. The omission of the stimulus on certain trials could discourage participants to prepare. This could also lead to a

consistent BOLD response (e.g. surprise, sudden inhibition of prepared functions) which would get entangled with the BOLD signal of preparatory processes on these trials. The latter could contaminate the activity measured on cue-only trials with non preparatory activity, which is difficult to predict.

Several others have used a similar approach. Shi, Zhou, Muller and Schubert (2010) used a paradigm in which participants switched between judging the gender or colour of a picture (both were binary classifications). They also used cue-only trials to measure cue related activity in the scanner and found the medial superior frontal gyrus (pre-SMA) to be more active during the preparation interval of a switch than of a repeat trial. Madden et al. (2010) had participants switch between judging whether the meaning of a word was manmade or natural, or large or small. Extra switch-related activity on cue only trials was found in the supramarginal gyrus, precuneus, medial temporal gyrus, middle frontal gyrus, insula, precentral gyrus, IPL, thalamus and the cerebellum.

Innovations in fMRI techniques have made it easier in recent years to distinguish between events close in time. Gruber, Karch, Schlueter, Falkai and Goschke (2006) used an interscan interval of 1.5s and a CSI of 0, 500 ms, 1000 ms and 1500 ms to distinguish between cue and stimulus related activations. Contrasting cue with target related activity (pooled over switch and repeat trials) showed activations in the IFJ, IPS, extrastriate cortex, right IFG, left frontal eye field and lateral occipito-temporal sulcus.

Table 1.2 An overview of imaging results from studies which attempted to isolate preparatory activations in a cued task switching paradigm.

	DL/VL PFC	SPL IPL	MFC	Precun	Insula	Premot	Temp	Occ	Thal
Switch>Repeat									
Brass et al. 2004	X								
Ruge et al. 2005	X	X	X		X				
Slagter et al. 2006		X				X			
Chiu et al. 2009		X							
Shi et al. 2009			X						
Madden et al. 2010	X	X	X	X	X		X		X
Bunge et al. 2003		X	X		X				
Number of studies reporting this region	3/7	5/7	4/7	1/7	3/7	1/7	1/7	0/7	1/7
Pooled									
Sohn et al. 2000	X	X					X		X
Luks et al. 2001	X	X	X		X				
Brass & Von Cramon 2002	X	X	X	X			X	X	
Forstmann et al. 2005	X	X	X	X	X	X			X
Sakai & Passingham 2003	X	X	X				X	X	
Gruber et al. 2006	X	X						X	
Ruge et al. 2009	X	X	X	X	X	X			
Jamadar et al. 2010							X		
Number of studies reporting this region	7/8	7/8	5/8	3/8	3/8	2/8	4/8	3/8	2/8

A number of studies found preparatory activations which reliably differed between switch and repeat trials (Switch>Repeat group) an others found no switch minus repeat difference in preparatory activations and reported preparatory activations pooled over switch and repeat trials (Pooled group).

1.9 Conclusions about the preparatory network

Studies reporting the preparation by switch interaction, report activations (2 studies or more) in the superior and inferior parietal lobule, the dorso and ventro-lateral prefrontal cortex (in particular inferior frontal gyrus and middle frontal gyrus), medial frontal cortex and the insular cortex (See Table 1.2).

Preparation pooled over switch and repeat trials showed activations in the superior and inferior parietal lobule, the dorso and ventro-lateral prefrontal cortex (in particular inferior frontal gyrus and middle frontal gyrus), medial frontal cortex the insular cortex, precuneus, premotor cortex, thalamus and regions in the temporal and occipital cortex.

As in the case of the switch minus repeat contrasts described earlier, many regions sensitive to these preparation contrasts have been reported in both left and right hemispheres and there is considerable overlap in the regions associated with preparation effects or overall switch-repeat contrasts.

There could be several reasons for the large number of brain regions identified by studies of task-set preparation and the substantial variability between different studies:

- It could be the case that a large number of regions are involved in task-set reconfiguration — especially when we bear in mind that active regions may be either source or target of control (or both).
- Another problem is the level of statistical control used by the imaging studies. Many of the articles report regions using an uncorrected statistical threshold, so some of the regions reported could be due to Type 1 error. Wager, Lindquist and Kaplan (2007) estimate the Type 1 error rate in the imaging literature to be 10-20% of the reported peak activations. One of the reasons that many studies report at lenient statistical thresholds is because, when fully corrected for family wise error (FWE), the types of contrast reviewed here reveal no or small activations.
- A third possible reason for the variety between studies is the different paradigms, pairs of tasks, and contrasts used (even though the contrasts in the switch minus repeat review were very similar). One might expect the target areas in particular (and perhaps the source areas) to vary with the type of processing required by the tasks switched between, and the overlap in processing between the two tasks.

The various papers on task set preparation employ different contrasts to bring out cue-related activations. In order be more confident about which regions are involved in task-set reconfiguration, I conducted a quantitative meta-analysis, reported in Chapter 3. This analysis computes which regions are consistently activated across a number of studies,

in the hope that this will identify regions in a way less vulnerable to statistical lenience and differences between paradigms and contrasts.

1.10 Neuropsychology of task-set control

Damage to the frontal lobes has been found to have a profound influence on our ability to exert cognitive control over our behaviour (Norman & Shallice, 1980). Mecklinger, Von Cramon, Springer and Von Cramon (1999) studied 18 patients with brain damage by letting them switch between two visual classification tasks. Switch costs were higher for patients with left frontal brain damage than for right frontal brain damage. Closer analysis showed that this effect was specifically strong for patients with left frontal damage that had language or speech problems. Patients with damage to the right side of the brain showed an increased congruence effect in comparison with patient with left sided lesions. Rogers, Sahakian, Hodges, Polkey, Kennard et al. (1998) studied 12 patients with frontal lobe damage using an alternating runs paradigm similar to that used by Rogers and Monsell (1995). They found that left sided patients showed larger switch costs in trials with larger interference from the irrelevant task. Aron, Monsell, Sahakian and Robbins (2004) used an alternating-runs switching paradigm to study a large sample of patients (N=36) with left or right frontal lobe damage. The stimuli consisted of a letter string ("left", "right" or "XXXX") presented inside a left pointing arrow, a right pointing arrow or a rectangle. The tasks were to press a left or right key depending on the direction of the arrow (left, right) or the word it contained (“LEFT” or “RIGHT”); the irrelevant value was congruent or incongruent for bivalent stimuli or neither for univalent stimuli, presented inside the shape of a left arrow, a right arrow or a rectangle. The task switched predictably every 3 trials, and position in a run was signalled by dividing the screen into three sectors and presenting successive stimuli in successive locations clockwise, with a response-stimulus interval (RSI) of either 100 ms or 1500 ms. Both left and right frontal patients showed larger switch costs than controls. Patients with a lesion to the left frontal cortex showed higher switch costs in the shorter RSIs than patients with a right sided lesion and controls. A volumetric analysis showed that the degree of damage to the left medial frontal gyrus was specifically related to the inability to exert task-set control as measured by larger switch costs at both

short and long RSI's. Patients with a lesion to the right frontal cortex had notably longer RTs on switch trials which required overcoming Stroop-like interference from the previous task. They also showed greater error rates for incongruent trials versus congruent trials than controls and left sided patients. The authors argue that the left frontal lobe plays an important role in top-down control of task-set and that the right frontal lobe and in particular the right pars opercularis plays a crucial role in inhibiting the competing response.

Shallice, Stuss, Picton, Alexander and Gillingham (2008) used a cueing paradigm similar to the one used by Meiran et al. (1996) to study patients with frontal lobe damage. The task consisted of a square equally divided in four sub-squares. A dot would appear in one of the sub-squares on each trial and the tasks were to either indicate whether the dot was in the upper part or lower part of the main square or in left or the right part. Patients with damage to the superior medial frontal lobe had larger switch costs. Lesions to the inferior medial lobe resulted in more errors. The authors suggest that the medial frontal cortex plays an important role when a response cannot be made on the basis of a standard well learned action schemata but when a new task-set needs to be activated via a mechanism of top down control in order to make the right response (i.e. a process of task-set reconfiguration). Additionally, patients with damage to the left DLPFC showed more errors in the early stage of the experiment, suggesting that they had difficulties learning the rules.

1.11 Potential functions of candidate regions

In this section I have selected a number of regions that are regularly linked to switching or task-set preparation in the imaging literature. Here I review other ideas and evidence, especially from neuropsychological data and other paradigms, concerning their potential role during preparatory task-set reconfiguration.

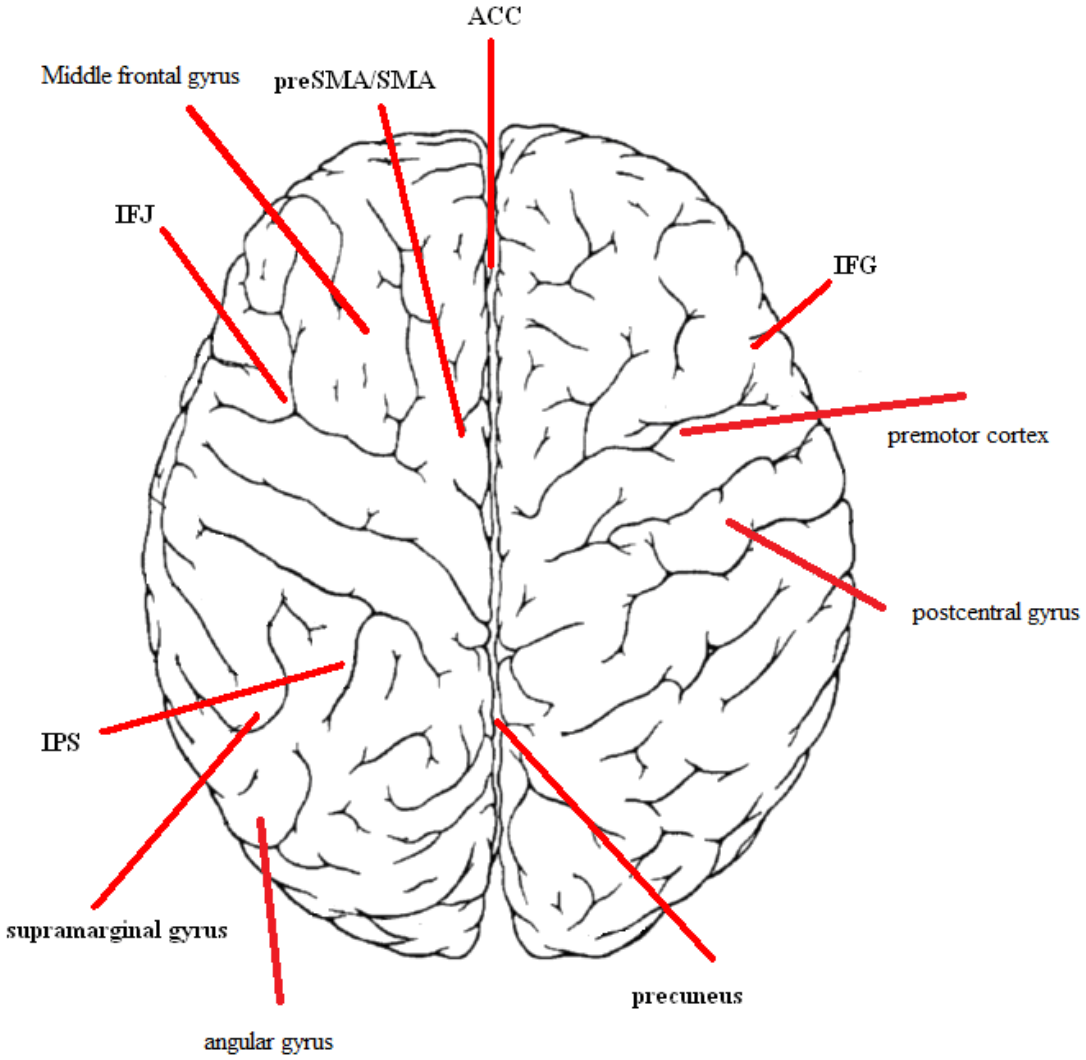


Figure 1.2 Brain regions that are implicated in task switching

Prefrontal cortex

The frontal cortex is thought to represent abstract tasks or situational contexts that guide the selection of attention and appropriate behaviours (Banich et al., 2000; Desimone & Duncan, 1995; Miller & Cohen, 2001; Wager, Jonides, & Reading, 2004), a broad function that would appear to include task-set reconfiguration.

Task switching studies in patients and task-switching imaging studies have greatly contributed to our understanding of frontal lobe functions. The DLPFC, VLPFC and MFC

have been associated with other related control paradigms, among which are interference paradigms like the Stroop and flanker tasks as well as working memory paradigms (Duncan & Owen, 2000; Nee, Wager, & Jonides, 2007; Wager & Smith, 2003). MacDonald, Cohen, Stenger, & Carter (2000) used a Stroop task-cueing paradigm in which the stimulus was a coloured word, and the cue indicated whether the word or the colour should be named. By making the interval between cue and stimulus 12.5 seconds, they were able to measure the BOLD signal after the cue, without stimulus related activity. They found left DLPFC activity (middle frontal gyrus) to be specifically related to preparing for the less familiar colour naming task as opposed to word reading. This suggests that the left DLPFC is involved in task-set preparation, with more intense preparation to enable the less familiar task and/or in anticipation of Stroop-like interference. In contrast ACC was found to be more active in incongruent trials in comparison to congruent trials, supporting the idea that the ACC is important for conflict detection. (Although participants had to switch between these tasks, switch related activations were not mentioned, and were presumably unreliable.)

A closer analysis of the task switching and preparation imaging literature by plotting all reported activations in a "glass brain" (see Figure 1.1) as well as patient studies suggest that certain regions in the left DLPFC, VLPFC bilaterally, MFC and superior parietal cortex are repeatedly reported and seem to be particularly important for TSR. In the next part of the review, I will focus in particular on the region surrounding the IFS on the border of DLPFC and VLPFC (also referred to as the IFJ), the pre-SMA, ACC, premotor cortex, right inferior frontal gyrus and a number of parietal regions (See Figure 1.2).

The region surrounding the left inferior frontal sulcus.

The region named by Brass et al. (2005) the "inferior frontal junction" is located at the crossing of the inferior precentral sulcus and the inferior frontal sulcus near the anterior border of the pre-motor cortex. Both the left and the right IFJ regions are often implicated in switch minus repeat contrasts as well as in studies looking at preparation. The location of the left IFJ region places it on the intersection between the premotor cortex, important language areas and DLPFC regions, important for working memory (Brass, 2005)

A meta-analysis of the imaging literature by Wager (2003) showed the left IFJ to be important for updating in working memory and found evidence for a left hemispheric dominance in verbal working memory. Working memory has often been thought to play a vital role in task-set reconfiguration; the activation/suppression of S-R rules and or task-goals can be conceptualised as loading the required rules/goals into some form of procedural working memory (Kieras and Meyer, 2000). Liefooghe, Barrouillet, Vandierendonck and Camos (2008) ran a series of four behavioural experiments in which participants were presented with a series of digits (Experiment 1). In the pure list condition participants either did a parity task or a magnitude judgment. In the mixed condition the participants had to alternate between the tasks. At the start of each list a consonant was presented. At the end, the consonants had to be recalled in the correct order. They showed that recall performance was reduced when the number of task switches was increased. Increasing the working memory load during switching however did not increase the switch costs. This suggests that processes underlying our ability to switch between tasks also play a role in working memory. These results as well the fact that this region is frequently associated with both task switching and updating in working memory, suggests that the left IFJ is the possible host for the working memory contribution to task-set reconfiguration.

Its location close to Broca's area also is also consistent with a possible role of language in task-set control. It has been suggested that inner speech plays a role in regulating task-set. Mecklinger et al. (1999) showed that patients with lesions to the left frontal lobe that had problems with speech and/or language had increased switch costs during a task switching task as opposed to patients with right sighted lesions and patients with left sited lesions without speech or language problems. During a cued task-switching paradigm this could take the form of verbal self instruction of the task after cue presentation. Miyake, Emerson, Padilla and Ahn (2004) used articulatory suppression to suppress verbalisation (at a phonological level) during switching. They showed that when using cues that did not literally depict the task (e.g. "c" instead of "colour") the switch costs increased, while articulatory suppression did not affect trials with full word cues. In the letter condition, generating the task name in inner speech could arguably play a more important role in activating the correct task-set than in the condition in which the full task name is provided externally. Goschke (2000) had participants say an irrelevant word, the

name of the current task ("letter", "colour") or nothing during the cue-stimulus interval. He found that saying an irrelevant word impaired participants' ability to prepare for a task switch, whereas the other manipulations did not. These results suggest that verbal processes could play an important role in task switching, this provides one potential rationale for the contribution of the left IFJ in task set control.

Brass, Derrfuss, Forstmann and von Cramon (2005) suggests that the region located near the IFJ combines information coming from the premotor, verbal processes and working memory domains when task-set representations are updated. However, the concept of task-set representations remains ill defined in their work. Information about combining external cues and new goals, verbalisation of internal goals and activations of new potential actions in the premotor regions could all be combined in the left IFJ.

This account of left IFJ function suggests an important role in task switching and perhaps in particularly in task set preparation. During task-set preparation multiple mental processes related to the task-set need to be managed and sustained over time, if the IFJ does play such a central role coordinating various processes that would be important before the initiation of action, its activation might be stronger and more prolonged when the task context has changed but no specific action is required yet.

Right Inferior frontal cortex

The right inferior frontal cortex has often been associated with inhibition (Aron et al. 2004). Recent studies have been able to show functional differences between regions within the right inferior frontal cortex (Aron, 2007; Chikazoe et al., 2009).

The right IFG region is thought to be important for response/behavioural inhibition (Aron et al., 2004, Aron 2007). Nee et al. (2007) found this region to be consistently reported by imaging studies which used a variety of paradigms of interference control. Aron et al. (2003) found that patients with damage to the right inferior frontal gyrus had longer stopping times on a stop-signal task. These results were confirmed by TMS studies of this region (Aron, 2007; Chambers et al., 2006). Verbruggen, Aron, Stevens and Chambers (2010) used continuous theta burst stimulation (cTBS) to interfere with normal processing in the right IFJ as well as right IFG during a novel stop-signal task which people either made a simple response to a stimulus, withheld a response or performed a dual task.

Stimulation of the right IFG interfered with performance in both the dual task context and the stop signal trials. The interference in the dual task condition was not dependent on SOA. This suggests the IFG's importance for control of action might not be restricted to an inhibitory role. Verbruggen et al. (2010) suggest the right IFG has a more general role in updating action plans. Right IFJ cTBS stimulation caused impairment on the stop signal trials as well the dual task trials. Crucially, the effect of TMS on the dual task trials interacted with that of stimulus onset asynchrony (SOA). Based on the "locus of slack" interpretation of that interaction (Pashler, 1994), Verbruggen et al. argued that the interaction with SOA showed that TMS was interfering with the perceptual phase of the reaction time. This suggests that the role of the right IFJ may be associated with a perceptual one and particularly involved in detecting changes in task relevant stimulus properties, required in both stop-signal trials and dual task contexts. Verbruggen et al. argue that this is a function not specifically related to inhibition; stopping in the stop-signal condition could simply be another action plan. Following this argument, it is possible that the reports of right IFJ activations in switch-repeat contrasts and preparation studies reflects a process of detecting visual changes that signal a change of task context (like a visual task cue or a visual change in stimulus signalling a new task). The necessity to detect the need for a new task could be equally important in paradigms which allow task-set preparation as well as for tasks in which cue and stimulus appear simultaneously.

The results of these studies however are, limited to inhibiting or selection of a particular action plan (in the paradigms discussed above, the participants already know the specific action that needs to be performed). Whether inhibition happens at set level, is still an open question and this uncertainty is furthered strengthened by the fact that the involvement of the right IFG in switching is not reported in all switching studies or studies of preparation.

Considering its proposed role in response inhibition, it is conceivable that the right IFG plays a role in proactively overcoming response conflict which is sometimes seen in task switching paradigms in the form of a preparatory benefit for response incongruent trials (as discussed earlier). This has however, to my knowledge, not been studied yet.

Premotor cortex

A number of task switching studies reporting switch minus repeat contrasts as well as task switching studies that attempted to isolate cue- related activations from stimulus related activations, implicate the premotor cortex to be important for task-set reconfiguration (Liston, Matalon, Hare, Davidson, & Casey, 2006; Ruge, Braver, & Meiran, 2009).

The premotor cortex is thought to play an important role, preceding specific categories of complex hand movement like grasping, for example when a cue is presented to prepare a particular movement. It is thought to form an important bridge in the transformation between visual perception and motor responses in accordance with a learned stimulus-response rule (Luppino & Rizzolatti, 2000; Mars, Piekema, Coles, Hulstijn, & Toni, 2007). Neurons in the premotor cortex of monkeys code for specific hand action. Some neurons are specifically active when fixating on the object of actions, some discharge when the action is performed and others in both situations. The premotor cortex has been found to be active when specific actions need to be prepared or when actions need to be changed in the context of an already prepared action (Mars et al. 2007). Mars et al. (2007) used a paradigm in which participants were trained to respond to 1 of 4 stimuli using one of 2 fingers, with two stimuli mapped to each finger. On 70% of the trials one of the stimuli would be presented and after a delay a tone would indicate the need to respond. On 13% of trials a second stimulus was presented during the delay that required a different finger movement. On 2% of the trials a third stimulus indicated a 2nd switch. The remaining trials were neutral trials on which a question mark was presented, and then the stimulus indicating the finger movement was presented after a delay together with the tone. The fMRI data showed that the left dorsal premotor cortex was important for preparation of action, irrespectively of the presence of an earlier action plan. The right precentral gyrus in the premotor cortex was found to be important when the prepared action was changed during the stimulus-tone delay. Bucd et al. (2010) used paired-pulse TMS to show that the ventral premotor cortex had a excitatory effect on the primary motor cortex when participant initiated a goal directed grasping movement, the influence became inhibitory however when the goal suddenly changed. This suggests that premotor areas are important in the concrete execution of a particular movement based on an internal goal (as is needed

to make a button press in accordance with the current task after stimulus onset) or stopping of a wrong movement.

The importance of the premotor area in the control of action and action preparation however has been mostly found in preparation of a particular movement or alterations between them. During preparation of task-set there is no specific action yet available to prepare. In switch minus repeat contrasts, actions need to be performed on the basis of learned stimulus-response rules in both switch as well as repeat trials. And on repeat trials, the actual action can be different from the task before, so action changes are no more characteristic of switch than of repeat trials. Task-switching studies do often show an interaction between task-switching and response repetition, where task switching is harder when the response remains the same (i.e. switch costs are higher), however this is mainly due to the elimination of response priming on switch trials and not an actual increase in reaction time on switch trials where the response remains the same (Rogers & Monsell, 1995). Activation of this region is not often reported in task-switching studies and its involvement could be the result of specific experimental conditions.

Medial frontal cortex

The literature above shows that medial frontal areas are often found to be activated in imaging studies of task-switching and pro-active task-set control. In this section I discuss some of the potential contributions of two different medial frontal regions, namely the ACC and pre-SMA/SMA. Many similar functions have been attributed to these regions and it is still up for debate what the precise differences between these regions are. It is possible that these differences are a matter of degree and that the functional emphasise changes gradually throughout the medial frontal cortex (Nachev, et al., 2008).

Anterior Cingulate Cortex

Whether or not the ACC is more active on task switch than on repeat trials is not very clear. ACC activations have been found by some task-switching studies running switch minus repeat contrasts (see above). But for example, Dreher et al. (2003) used fMRI to study neural activations in a comparison between switching between tasks and doing them

simultaneously. They found that the ACC was activated only in the dual task condition (as compared to a baseline composed of the mean of two single task conditions).

The ACC seems particularly active when errors are made, monitoring reinforcement history and updating action values accordingly. It is also thought to play an important role in monitoring response conflict (Ridderinkhof, van den Wildenberg, Segalowitz, & Carter, 2004; Rushworth, 2008). For example, Yeung, Botvinick, & Cohen (2004) showed that a connectionist model that used monitoring of response conflict to detect possible errors, could correctly simulate the timing and sensitivity to task parameters of the error-related negativity (ERN) component of ERP observed in association with incorrect responses. The ERN is detected primarily in electrodes over the medial frontal cortex and Yeung at al suggest that it reflects ACC activity. However, it is hard to determine what the exact origin of ERP signals are and others have suggested that monitoring response conflict activates a more superior region towards pre-SMA, whereas monitoring of errors and negative feedback activates a more anterior region (i.e. ACC) (Ridderinkhof et al., 2004).

The outcome monitoring processes ascribed to the ACC are often related to situations of an exploratory nature in which action is guided by monitoring errors and adapting behaviour accordingly and less in situations where a cue guides a specific action (Rushworth, 2008). In a task-switching paradigm, the cue does not indicate a specific action and monitoring of action outcome is likely to be important to perform successfully in a task-switching paradigm (e.g. maximise correct responses), as task switches potentially result in errors on incongruent stimuli if components of task-set is not suitably adjusted.

Supplementary Motor Cortex

The pre-SMA and SMA are part of the Supplementary Motor Cortex (SMC) which also contains the Supplementary Eye Field. Patients with SMC damage show a diversity of symptoms like motor neglect, utilisation behaviour and Alien Limb syndrome (Nachev, 2008) The pre-SMA has been found to be important in cognitive control in several task switching studies (Dreher & Grafman, 2003; Nachev, et al., 2008; Rushworth, Hadland, Paus, & Sipila, 2002; Yeung, et al., 2006) -- as I elaborated above.

Studies of pre-SMA function suggest this region could be very important in the preparation of motor functions (Picard & Strick, 1996), in implementing stimulus-action

rules at a higher motor level (Brass & Von Cramon, 2002) and when different actions compete and may need to be inhibited (Nachev et al., 2008, Mars et al. 2007). Its close proximity with the SMA (which is in turn connects to the primary motor cortex) and strong connections to the DLPFC and inhibitory connections to sub-cortical structures like the Sub-Thalamic Nucleus (STN), have led people to hypothesise that it has a function in translating voluntary internal representations into concrete actions as well as mediating response conflict at the motor level (Nachev, 2008). It is also thought to play a role in forming S-R associations, for example when learning complex sequences of hand movements (Hikosaka et al., 1996; Nachev, et al., 2008). Yeung et al. (2006) suggest that the pre-SMA is involved in managing between task-set interference. Overcoming task-set inertia is a process that might underlie the RISC effect.

This suggests a potential role during task-set reconfiguration by altering the stimulus-response mapping in accordance with the new task by selecting new mappings and/or inhibition of irrelevant mappings, which facilitates the selection of the correct response. As mentioned in the previous section on the ACC, both ACC as well as the more dorsal medial regions are often thought to be involved in monitoring action outcomes and situations of response conflict. Increasingly, a potential divide is thought to exist between the ACC and pre-SMA in which the ACC is more involved in monitoring action outcome and the pre-SMA is more active during situations of response conflict (Rushworth, 2008). Taylor, Nobre, & Rushworth (2007) applied TMS during a flanker task and examined the lateralised readiness potential (LRP), which typically indicates levels of activations in the lateral motor cortex when participants make left and right responses. Stimulation of pre-SMA caused an increase in this LRP signature of the inappropriate response activation by the flanker. This suggests that the pre-SMA exerts a top-down modulation of the motor cortex by increasing activations related to the correct response in situations which afford response conflict.

Besides neuroimaging studies, other sources of evidence have also suggested that the pre-SMA is important for switching. Isoda & Hikosaka (2007) recorded the activity of cells in the pre-SMA of monkeys in a task-switching paradigm. They found that particular neurons code for different possible actions and the number of neurons coding for a particular action depended on the task context. However, the study of task-switching in

monkeys requires extensive training (often consisting of thousands of trials) which raises the question of whether they really switch between task-sets or depend on associative learning of all the relationships between the cue, stimulus and response.

Rushworth et al. (2002) used fMRI-guided TMS to study the function of the pre-SMA in two special intermittent-instruction paradigms in which subjects switched, either between alternative S-R mappings for the same task or between attending to colour or shape. In their response reversal experiment, a series of stimuli (red triangles or rectangles) were presented. The subject pressed the left button for a triangle and the right button for the rectangle or vice versa, depending on a cue. Switch or stay cues would appear every 9 to 11 trials; after a switch cue, the response mapping was reversed. In their attention switching experiment, subjects had to attend to either the colour or the shape of one of two stimuli, a triangle and square, one of them red and the other one green, to identify the target stimulus and discriminate a character superimposed on it. Every 9-11 trials a cue indicated to either continue to attend to the same dimension or switch to the other dimension to identify the relevant stimulus; the discrimination task remained the same. TMS over the pre-SMA during the cue and the first trial of a block specifically increased RTs on switch trials during the response switching task, but not during the visual switching task (see the TMS section of this chapter for a more extensive discussion).

A substantial amount of evidence therefore exists that the pre-SMA is important during task-switching, potentially through altering stimulus to motor mappings or overcoming task-set or response inhibition or a mix of these functions. In Chapter 4 I will present 2 TMS studies I have run to study the role of medial frontal cortex in preparatory task-set reconfiguration.

The Parietal Cortex

In my review of imaging studies of task-switching above, I showed that switch-repeat contrasts frequently yield activations in the parietal lobe. These parietal activations are mostly located in areas BA7 and BA40. Reported activations include bilateral parts of the IPS, postcentral gyrus, angular gyrus (ANG) and supramarginal gyrus (SMG). More medial activations are also found in the cuneus and precuneus. Almost all of the switch-repeat contrasts as well as the preparation contrasts in these studies yield parietal activations, but

the precise locations of these activations in the parietal lobes are highly variable over studies. Activations are reported in both hemispheres, but switch-minus repeat parietal activations are more frequent in the left hemisphere. The preparation-related activations appear more bilateral.

The question of what kind of role these regions of parietal cortex might play in task set control is still open. One problem is that many control paradigms have difficulty making a distinction between the control functions of the frontal and parietal lobe. There are probably intimate functional relationships between the frontal and parietal lobe in exerting cognitive control, and without precise chronometric evidence it is difficult to isolate behaviours related to processes located in specific parts of the network (Bunge, Hazeltine, Scanlon, Rosen, & Gabrieli, 2002). I will discuss two potential roles the parietal cortex might play in task-set control. The first is control of visual attention and second is its role in altering established links between sensory input and motor output.

Attentional processes have been consistently linked to the parietal lobes. Wager et al. (2004) performed a meta-analysis on 30 fMRI attention switching studies (I will discuss this paper in more detail in the meta-analysis section of this Chapter) and found the parietal cortex to be important for attention switching, regardless of the type of switching paradigm used. The authors also argue that parietal lobe activations are consistently observed in situations in which stimulus-response relationships change.

Even though the role of visual attention in task-set control has been, with a few honourable exceptions (Meiran, et al., 2000; Meiran, et al., 2008; Rushworth, Passingham, & Nobre, 2005), neglected to date, it is possible that it plays an important role. One aspect that supports this notion is that regions that have been associated with task-set control have also been associated with performance in visual search paradigms (Walsh & Cowey, 1998), especially in situations where a change is needed in what is attended to. For example, Schenkluhn, Ruff, Heinen and Chambers (2008) applied TMS to three locations along the right IPS. They had participants do a visual search task where a cue helped them to find a target. The cue indicated either the colour of the target or its location within a circle of distracters. They applied stimulation between the cue and the stimulus. TMS over the SMG reduced the benefit of a location cue specifically, whereas TMS over the anterior IPS reduced the cuing benefit for both location and colour. These results provide evidence that

regions in the parietal lobe are involved in changing different aspects of the attentional stream.

One of the parietal cortex's attentional roles is in altering attended location (Rushworth & Taylor, 2006; Wager, et al., 2004). However, it is unlikely that parietal involvement in task-set reconfiguration is limited to reorientation of attention in space, because task switching paradigms that activate parietal cortex not all confounded the attended location with task. A significant number of task-switching paradigms use a stimulus that is comprised of a letter and a digit. This could mean that the participant needs to alter the location that is attended to when switching from the "odd/even" condition to the "consonant/vowel" condition. However, most paradigms counterbalance the location of the letter and digit so that it is not predictable. In the Meiran task (Meiran, 1996) participants change between determining whether a target has appeared on the left or the right side of a 2 by 2 matrix or whether it appeared on the upper or lower part of the matrix. Since the target can appear in any box in each trial type, participants cannot predict its location. They may need to alter spatial aspects of their visual attention (is the target on the left or the right or on the top or bottom part), but altering attended location is not confounded with switching. In the often used, "higher/lower, odd/even" digit task pair and the "colour/shape" task pairs, the visual information is always in the same place (although it could be argued that shape discrimination requires attention to the edge of the shape while colour discrimination does not. Hence shifting spatial attention, as a parietal function, is unlikely to be the origin of all parietal activations in the imaging literature on task switching, though it may contribute when there is an association between location and task.

A different possibility is that on switch trials, parts of the parietal cortex are involved in altering the bias of the perceptual stream to process the new relevant stimulus attribute (e.g. focusing on colour instead of shape) (Le et al., 1998). Since most task-switching paradigms use bivalent stimuli and each stimulus affords a particular response in both tasks, it is important to attend to the right visual feature. When switching between judging the colour or judging the shape of a stimulus for example, one has to switch to a different perceptual dimension when switching tasks. The often used "higher/lower, odd/even" digit tasks however do not require one to alter their attention to a different perceptual dimension

and imaging studies using these tasks also report parietal activations (Dreher & Grafman, 2003).

Chiu and Yantis (2009) let people switch between perceptual locations as well as between category rules. A conjunction analysis showed that a region in the medial superior parietal cortex was activated by switch cues in both switch tasks.

The nature of the task-set reconfiguration processes in the parietal lobe could also reflect a function more related to motor control. The involvement of the parietal lobe in re-orienting covert spatial attention as well as coding visual space has been shown repeatedly (Rushworth & Taylor, 2006). Especially the right parietal lobe seems to plays a central role in determining the focus of attention as well as initiating saccades (Rushworth & Taylor, 2006). Many experiments, attempting to separate attentional focus and oculomotor control have substantiated the idea that both processes are, even though separate, highly related as well as greatly overlapping in neural-correlates (Colby & Goldberg, 1999; Rushworth, Johansen-Berg, Gobel, & Devlin, 2003). A similar relationship has been shown to exist between covert attention and other response modalities, like limb movements (Rushworth, et al., 2003). For example, Milner and Goodale (1992) showed that patients with parietal lesions had trouble controlling their hands in order to grab an object.

Rushworth, Ellison and Walsh (2001) applied TMS to stimulate 2 regions in the left and right parietal cortex during the response time of a visual orientation task and a motor reorientation task. In the visual reorientation task a cue indicated where a target would appear, and participants had to press one of 4 buttons depending on the location of the target. On some trials however the cued location was wrong and participants needed to change their attentional focus. In the motor reorientation task participants rested two fingers on two of four buttons. A cue indicated one of two possible hand reconfigurations which needed to be performed on stimulus arrival; the middle and index finger pressed down on two out of four buttons; one stimulus required participants to move their index finger to a different button and another stimulus required them to move their middle finger. On a number of trials, the cue was incorrect and the participants had to adapt their prepared change in configuration to the other option. Stimulation of the right angular gyrus (ANG) 20 ms after stimulus presentation slowed participants down on the invalidly cued trials of

the visual reorientation task. Stimulating the left supramarginal gyrus (SMG) specifically slowed participant's responses on the invalidly cued trials of the motor reorientation task.

Ellison, Rushworth and Walsh (2003) conducted four experiments to challenge the often held notion that the right posterior parietal cortex (rPPC) plays an essential role in binding features in a visual search task (Treisman & Gelade, 1980) They argued that the rPPC plays a role in any difficult visual search task and that it is particularly important for visuo-motor transformations. On each trial the participants saw a search array and had to judge whether the target was absent or present. 500 ms of rTMS was applied over the rPPC on search array presentation. In Experiment 1 the difficulty in visual search was manipulated. Participants were presented with a set of hard as well as a set of easier feature search tasks and conjunction search tasks. TMS over rPPC had an negative effect on the easy and the hard conjunction tasks but not on the feature tasks. In Experiment 2, TMS increased reaction time on a conjunction search task in which the location of the target was unpredictable, but not on conjunction tasks in which the target was always presented in the centre of the screen. TMS had no effect on any of the feature tasks. In Experiment 3 the effect of TMS on a conjunction task did not change when the number of distractors was manipulated. In Experiment 4 the authors first replicated the effect of rPPC stimulation during a basic conjunction search task. After practicing the task for 2500 trials however, the effect disappeared. The authors then altered the response finger mapping and the rPPC rTMS effect returned. These results confirmed the notion that the rPPC is involved in conjunction search tasks, but, since the effect disappeared when the stimulus was presented in the middle of the screen, it seems unlikely that binding features is the explanation of the rPCC's involvement (Ellison et al., 2003). The fourth experiment shows that the effect of the TMS can be manipulated by making changes to the response mappings only. Ellison, Rushworth and Walsh argue that the that rPPC function is best viewed as being part of the action selection process.

A question that follows from the idea that parietal processes during TSR are related to selection of the appropriate actions is; are these processes also involved when the actual movement is not yet known? In a cued task switching paradigm, the cue will limit the number of possible motor responses, but it will not predict the actual movement that needs to be made. So are these processes primarily involved in preparing a specific movement or

are they also involved in more abstract action selection processes? Several findings suggest that this could be the case.

Chao and Martin (2000) showed people images of tools, the presentation of which was correlated with activation in the left posterior parietal cortex. Seeing a tool on a picture without any notion of actually executing a movement, could be interpreted as preparatory activity related to potential movement, rather than a real one. This could be a specific hand movement, like grasping the handle, but could also reflect a range of potential actions, limited by the tool's affordances.

Rushworth, Paus and Sipila (2001) used event related fMRI in the two special switching paradigms used by Rushworth et al. (2002) as reviewed above, to induce reversals of S-R mappings, or shifts in attention between colour and shape. The results show differences in the parietal regions activated by response reversals and shifts in the relevant dimension. Response mapping reversals correlated with activations in the posterior lateral IPS, the medial and anterior IPS, posterior superior lobule and the SMG. Visual dimension switching induced activations in the parieto-occipital region, posterior superior parietal lobule and IPS. The greater activation on response mapping reversal trials suggests that parietal regions are involved in altering stimulus-response mappings.

In summary, it appears that parietal regions differ in whether they are primarily involved in the control of visual attention or whether they are more closely related to the preparation of action. The more posterior regions of the parietal cortex seem to be more associated with visuo-spatial attention, whereas the more anterior regions seem to be more related to visuo-motor transformations (Rushworth et al., 2001, Chambers et al., 2004).

Results from patient studies, imaging and TMS also suggest that parietal region's functions may differ between hemispheres. Overall, the evidence seems to suggest that the left posterior parietal cortex seems to be more dominant in premotor attention while the right side seems to be involved in orienting covert attention (Rushworth et al., 2001). The fact that lesions in the left parietal cortex rarely lead to hemi-spatial neglect and that right sided lesions seldom lead to ataxia, seems to support this notion. So even though many functions related to motor function, as in the primary motor cortex, are contralateral to the effector, these early intentional motor functions are lateralised more to the left (Culham & Valyear, 2006). For example, Rushworth (2001), mentioned above, found parietal

premotor attention processes related to movements in the left hand to be almost solely found in the lateral hemisphere. However, these hemispheric differences are relative. The dominance of the right hemisphere does not mean that the left parietal lobe is not involved in control of covert attention or the right side is totally unrelated to motor control (Culham & Valyear, 2006, Rushworth 2003). Moreover, while patient studies and many TMS studies very consistently support this lateralisation (Rushworth & Taylor, 2006, Culham & Valyear, 2006), the fMRI literature often shows bilateral activations, with respect to the motor functions of parietal lobe (Culham & Valyear, 2006)

When circumstances change, parietal lobe processes deal with changes in the location and content bias of the attentional stream and are involved with changes in eye movements and motor planning accordingly (Andersen & Buneo, 2002). The parietal cortex could therefore form a bridge between perception and action during task switching and possibly alter this bridge when there is a need for behavioural change.

A meta-analysis to be reported in Chapter 3 will shed more light on which parietal regions are consistently involved in either switch minus repeat contrasts and studies reporting activations related to task-set preparation. In Chapter 5 I will present three TMS studies I have run to study the role of the IPS in task-set reconfiguration.

1.12 Relations between the parietal and frontal cortex in TSR.

The foregoing suggests that many regions implicated in task switching are also important in the early stages of action selection, especially regions in the supplementary motor regions, inferior frontal regions and parietal cortex. A possible interpretation of this within the context of task switching it that the pre-motor/supplementary motor regions on the one hand and parietal regions on the other hand play an analogous role in determining action and action sets, in that they both prepare action. The first one forms a premotor bridge between the internal world of working memory and the motor cortex (Nachev, et al., 2008) and the latter forms a premotor bridge between the outside world of perception and the motor cortex. The interaction between both systems is a complex and carefully managed process, the outcome of which determines what we do. The internal expressions of goals and rules could be present in the left IFJ, steering internal motor selection.

Ideas about pre-frontal cortex being the source of top-down biasing of attention implemented by more posterior processes have been around for quite some time (Desimone and Duncan, 1995). It is likely that such biasing happens in task-set control (Miller and Cohen, 2001), but is by no means proven. One way of testing this is to see whether the frontal cortex is activated earlier than the parietal regions.

Brass, Ullsperger, Knoesche, von Cramon, & Phillips (2005) recorded ERPs during a task switching paradigm in which they used one or two cues per trial and two cues per task. This way they could isolate cue switches from task switches by analysing trials with 2 different cues following each other, both indicating the same task (cue switches, but task does not.) and isolate task switches from cue switches by analysing trials in which the cue switched and the task switched with trials in which the cue switched but the task did not switch. They tested the idea that the prefrontal cortex should be activated earlier within the process of task-set reconfiguration than the parietal cortex, which followed from the notion that the frontal cortex imposes a biasing influence on the parietal cortex during task-set reconfiguration. And indeed, dipoles placed in the IFJ bilaterally and the right IPS (based on imaging data from Brass & Von Cramon, 2004) showed earlier activations of the frontal regions during task-set preparation than the parietal.

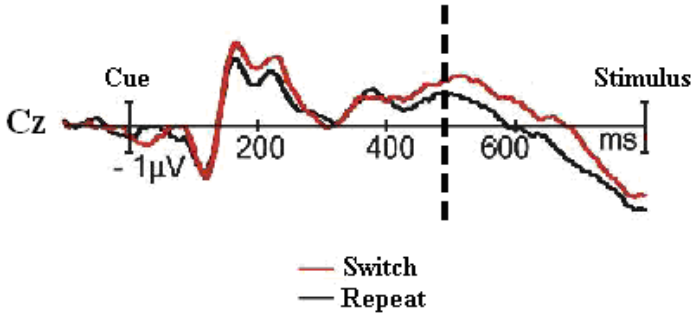
TMS provides a tool for interfering with particular parts of a network. Its chronometric precision offers the potential for establishing the order in which two components of the control network are activated during, for example, task-set preparation. However, it is first necessary to establish temporal windows within which application of TMS to candidate regions is effective. A starting point in the search for such windows is ERP data.

1.13 EEG research on TSR

As discussed above, the limited temporal resolution of fMRI makes it difficult to isolate preparatory activity in the scanner. In the experiments to be reported, I used TMS to study whether certain brain regions are essential for aspects of task-set preparation. To apply TMS, one must have a hypothesis, not only about where to stimulate, but also when. In this section I discuss several experiments which have used EEG/ERP to study task-set

preparation during the cue-stimulus interval, and which provide data about when preparatory activity effectively related to task-set control may be occurring. Several ERP studies have found pre-stimulus components related to switching in both predictable switching and cueing experiments (Karayanidis, Coltheart, Michie, & Murphy, 2003; Rushworth, et al., 2005; Tieges, Snel, Kok, Plat, & Ridderinkhof, 2007) mostly starting at around 400 ms after the cue.

Figure 1.3 ERP data from Lavric et al. 2008.



Lavric, Mizon and Monsell, (2008) used a task-cueing paradigm to study whether these components were related to preparing for an upcoming switch. The stimulus was one of four shapes displayed in one of four colours. The participants were asked to identify (with one of four key presses) either the shape or the colour of the stimulus. On each trial a cue indicated the task. The cue stimulus interval (CSI) was either 200 ms or 800 ms depending on the block. In the long CSI condition, an extended positivity developed over the posterior scalp (accompanied by a negativity over the anterior scalp) from about 400 ms after the cue to the end of the CSI (and a little beyond) on switch trials relative to repeat trials (see Figure 1.3). This positivity was linked to successful preparation in two ways: its amplitude correlated over subjects with the RISC effect, and it was substantial for the fastest RT tercile of the switch and repeat trials – for which the participant was presumably well-prepared — but minimal for the slowest RT tercile, for which the participant was presumably less well prepared. This relatively late component, peaking 300 ms before stimulus onset (between 500 ms and 600 ms post cue onset) (see Figure 1.3), and then sustained up to stimulus onset, was interpreted by Lavric et al. as a signature of pre-stimulus TSR. On short CSI trials, a similar but briefer positivity was found (superimposed

on the general negativity seen post-stimulus on switch trials) 300 ms after the stimulus was presented (i.e. 500 ms after the cue), Lavric et al. (2008) interpreted this as TSR triggered by the cue but occurring after stimulus onset (because there was no time to accomplish it before). A similar positivity could also be discerned on long-CSI trials from the slowest RT tercile. Lavric et al. (2008) interpreted this as TSR needing to be performed after the stimulus because it had not been adequately accomplished before. (Other correlates of task-switching are seen in the pre-stimulus ERPs, but they are not relevant to our present purposes — see Lavric et al., 2008, for review.)

Some of the TMS studies to be reported in later chapters used exactly the same task pair as Lavric et al.'s (2008) ERP study, so its timing data is the most directly relevant. But it is worth pointing out that a number of studies have found an ERP correlate of preparation for a switch with similar timing using other task pairs. Rushworth et al. (2002) used a paradigm similar to the visual attention switching paradigm (VS task) used in the TMS study reported earlier. Every 8-17 trials a cue indicated to either switch task-set or stay in the current one. They measured cue-related ERPs during 1400 ms following cue presentation. Their results show a negative right frontal component and a positive left lateral posterior component between 360 ms and 440 ms post cue-onset. A second large positive component in posterior and central regions ranged from 520 ms to 1080 ms. Finally a negative frontal switch related modulation was found between 720 ms and 1400 ms.

In their study mentioned earlier Brass et al. (2005) found a switch related preparation component 470 ms after cue presentation, contrasting trials in which the cue meaning switched with trials in which the cue switched, but not its task meaning. Nicholson, Karayanidis, Davies and Michie (2006) found a similar task switch related component during the cue-stimulus interval emerging 400 ms after cue-onset.

The ERP data clearly suggests that preparatory processes start to take place about 400 ms after the cue onset and it seems clear that a TMS intervention should be applied within a period starting 400 ms after until cue presentation. The time before the start of the preparatory process is presumably needed for processing and interpreting the cue.

1.14 Transcranial Magnetic Stimulation studies of TSR

Little work has been reported so far using TMS to study task-set control. Earlier, I described several experiments which used TMS to study cognitive functions related to task-set control, such as control of individual actions (Mars et al., 2007) and studies of response conflict (Chambers et al., 2007; Taylor, et al., 2007; Verbruggen, et al., 2010).

The only task-switching study of which I am aware is the series of experiments reported by Rushworth et al. (2002) and already introduced above. These used fMRI-guided TMS to study the function of medial PFC in two special intermittent-instruction paradigms in which participants switched, either between alternative S-R mappings for a two choice classification of a single stimulus, or between attending to colour or shape to locate the target object (among two) for the same discrimination task. In their fMRI study, they found that response-reversals activated (inter alia) pre-SMA. In their TMS experiments, they targeted a short train of pulses on the same pre-SMA locus (using the individual's switch>stay activation peak) either between the cue and the first item of a run or after the presentation of the first item of a run. Stimulation during the cue interval substantially lengthened RT on switch but not repeat trials, while post-stimulus stimulation did not selectively impair performance on switch trials. The fMRI experiment also found that a medial region, on the SMA/pre-SMA border, was activated by attention shifts between colour and shape, but targeting TMS on this region during the cue interval did not significantly impair preparation. Stimulation of a control site had no effect on either task.

One potential reason for the low number of TMS studies of task-switching is the unclear picture from the literature to date of the location of brain regions involved in task-set control: there are a number of somewhat ill-defined candidate regions. Since TMS affects a relatively limited region of the cortex, it is important to have strong and relatively precise *a priori* hypotheses about which regions are most likely to be important. For this reason, I turned to quantitative meta-analytic techniques that attempt to extract from the existing neuro-imaging literature a consistent picture of which brain regions are most consistently reported as activated by task-switching and/or by preparation for a task. In the following two chapters, I review the meta-analyses of Wager et al. (2004) and Derfuss et al. (2005), and then report my own meta-analysis using the kernel-density analysis technique of Wager, Lindquist and Kaplan (2007)

In Chapters 4 to 6, I then present the results of a number of studies attempting to interfere with task-set preparation using TMS. TMS methodology is first introduced in Chapter 2. In an ideal world, the TMS studies would all have followed and been guided by the meta-analyses. In practice, however, the meta-analytic work has evolved over a couple of years from a rather basic approach of plotting the activation peaks reported in available studies on glass brains to the quantitative analysis reported in Chapter 3. More imaging studies have also become available in that time. Hence the candidate areas for the TMS studies in Chapter 4 and 5 were chosen initially on the basis of the relatively primitive glass brain approach, and the published evidence available at the time.

Chapter 2: Methods

In the research reported in this thesis I employed three neuroscientific methods; TMS, quantitative meta-analysis of published neuroimaging data and fMRI. In the first half of the following chapter I will discuss Transcranial Magnetic Stimulation and in the second half I will outline the workings of Multilevel Kernel Based Density Analysis (MKDA) which I used to run a meta-analysis on published imaging data. In Chapter 6 I will outline how I used fMRI to identify participant-specific activations in the left IFJ.

2.1 Transcranial Magnetic Stimulation

TMS is a technique that uses electromagnetic induction to generate random action potentials in cortical tissue (Barker & Jalinous, 1985). Application of this stimulation to particular brain regions can be used to interfere with ongoing cognitive processes. TMS provides a non-invasive method that can, in principle, prove that processing in a particular brain region is used in successfully performing a cognitive ability (O'Shea & Walsh, 2007). The logic is similar to making use of cases of brain damage, but the effects of TMS are very brief, reversible, and subject to experimental control. And unlike for example standard uses of fMRI and EEG, TMS can be used to make causal inferences about the region's involvement in a particular cognitive process. Under particular conditions, TMS can also be applied to facilitate cognitive function (Silvanto & Muggleton, 2008).

In this chapter I will focus on the use of TMS in the study of cognition and in particular the study of task-set control. TMS is also increasingly applied in for example clinical diagnostics, rehabilitation and treatment, but a discussion of these topics is beyond the scope of the current thesis. In cognitive neuroscience, TMS can be used both to study the function of a particular brain region and as a chronometric tool to study the timing of particular cognitive processes. In the next section I will outline the basic workings of TMS and how it has been used in cognitive experiments looking at task-set control. At the end of this chapter I will explain how I have used TMS in the experiments outlined in this thesis.

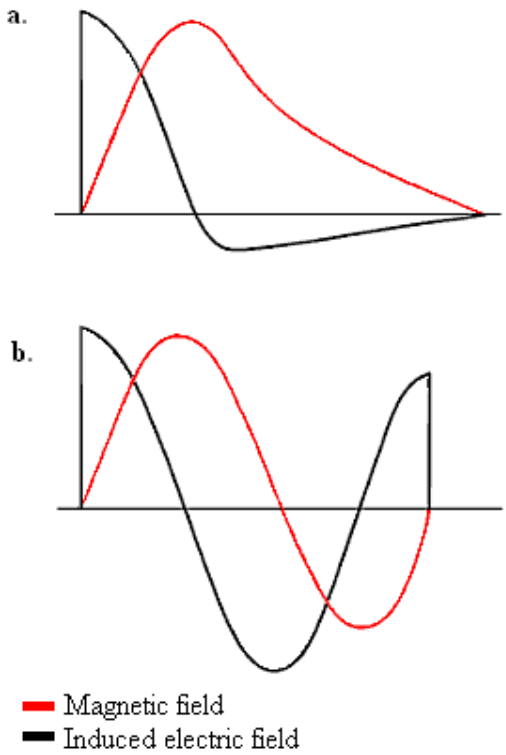


Figure 2.1a Waveform created by a monophasic stimulator where red reflects the time course of the magnetic field and black reflects the induced electric field. b. Waveform created by a biphasic stimulator

2.1.1 Monophasic and biphasic TMS.

TMS works on the basis of Faraday's law of magnetic induction. This law states that a change in an electromagnetic field induces a current in a nearby conductor. Similarly, in TMS a brief electromagnetic field is used to induce currents in nearby neural tissue.

A TMS stimulator basically consists of a capacitor which stores large amounts of electrical charge, an induction coil (usually consisting of copper wire) and a switch. When the switch is closed, the energy is released in the form of a strong current which travels through the coil. This creates a magnetic field surrounding the coil. The change in the magnetic field induces an electric current in any nearby conductors, which in the case of TMS is the cortical surface of the human brain (Walsh & Pascual-Leone, 2003).

Original TMS studies used monophasic coils (monophasic means the pulse only has a polarity in one direction) which induced a current according to the waveform depicted in Fig 2.1a (Barker, 1999). The current in the coil builds up at a fast rate until it reaches a peak after which it dissipates and the capacitor needs to recharge. The induced electrical field peaks during the build-up of the current in the coil. The need to recharge the capacitor from zero meant that the pulses could only be delivered at a relatively slow rate and therefore early stimulators could only reach up to 0.25 Hz. Various applications of TMS however, require a far higher frequency. For example, in the experiments outlined in this thesis I applied small trains of pulses (3 pulses at 20Hz) to create a stronger and longer lasting

interference than would be achieved by applying a single pulse. These pulses should, in order to have the desired disruptive effect, be applied in a very short space of time. A monophasic stimulator is not capable of reaching these frequencies.

The biphasic TMS pulse makes it possible to stimulate at much higher frequencies. These higher frequencies are achieved because 50-80% of the energy released during the discharge is reverted back into the capacitor. This way, less recharging time is required (Walsh & Pasqual-Leone, 2003). A schematic of the biphasic waveform is depicted in Fig 2.1b (Barker, 1999). The term "biphasic" refers to the two opposite polarities present in the wave form. After the initial discharge, the current is sent back into the coil in the opposite direction, creating an additional rapid change in magnetic field strength. This induces a second peak current in the nearby conductor (a peak of the opposite polarity to the first one).

Biphasic and monophasic pulses are applied in similar ways, but their effects do seem to show some differences. For example, Sommer, Jansen, Drager, Steinstrater, Breitenstein, Deppe, et al. (2006) found a lower average motor threshold with biphasic than with monophasic stimulators. I have only used a biphasic stimulator in my research and in the following section I will limit the discussion accordingly.

2.1.2 Effect of the induced current on the axons.

TMS works by inducing a current along the neurons in the cortex which then induce action potentials. Because the axons in which the current is induced behave essentially like ‘leaky’ capacitors, it is important that the rise in the magnetic field happens quickly (Walsh & Pascual-Leone, 2003). In order for the inducted current to become strong enough to induce an action potential along the axon, the field must build up fast enough before the current can ‘leak’ away. The strength of the neural activation is directly related to the rate of change in the electric field (Walsh & Pascual-Leone, 2003). In order to induce an action potential the induced electric field must differ across the cell membrane of the axon that is stimulated. The relationship between the change in induced field and direction of the axon partly determines the strength of the current induced. No current will be induced if the direction of the electric field is the same as the direction of the axons (Walsh & Pascual-

Leone, 2003). This relationship is however not a straightforward one, making it hard to precisely predict the influence of stimulation on a particular place in the cortex. Not being able to model this precisely however does not necessarily pose a problem for the use of TMS in studying cortical function. Stimulation affects thousands of neurons at a time. We do not need a precise characterisation of that effect, but it is essential that TMS depolarises enough neurons in that region to have a distorting effect on the ongoing 'normal' neural activity – i.e. by inducing chaotic activity.

2.1.3 Effect of coil direction

Studies looking at the effects of coil direction have found differences for both monophasic as well as biphasic stimulators. For example phosphene threshold (the lowest level of stimulator output at which a visual phosphene can be created by stimulating over V1) depends on the direction of the coil (Kammer, Beck, Erb, & Grodd, 2001). Different cell types and direction of connections throughout the cortex means that the effect of coil direction differs between cortical regions. This complex relationship between brain and coil direction means that it is important to keep a constant coil direction throughout an experiment and that the coil direction used during an experiment is reported by the experimenters.

2.1.4 Virtual lesioning

TMS is most often used to disrupt ongoing normal brain processes. Even though the influence on a particular brain area depends on factors such as cell type, cell orientation and coil orientation, the crucial factor is the ability to generate enough action potentials to have a disruptive influence on the processes at work in the targeted region. Whatever the precise influence on different neurons, stimulation is unlikely to induce any coherent neural activation. For example, if one stimulates the motor cortex, the behavioural response is always random contractions in musculature mapped to that area of motor cortex. It is not possible to induce an effective and coherent motor movement, hence the induced activation can be considered neural noise (O'Shea & Walsh, 2007). When the motor cortex is

stimulated during a coherent hand action (e.g. opening a door), the hand will move in a random fashion, effectively reducing the speed and accuracy of the hand action (so that opening the door takes longer). This same idea is applied to cognitive functions. If TMS is applied during a working memory task and the region stimulated is employed during this task, this will affect the successful execution of this working memory task in a negative way, irrespectively of the precise influence of the stimulation. We refer to this disruption of cognitive processes as *virtual lesioning* (O'Shea & Walsh, 2007).

There is increasing evidence that situations do exist in which TMS can be used to enhance performance during paradigms (Silvanto & Muggleton, 2008). The crucial factor seems to be the moment at which the stimulation is applied. A single pulse which is applied just before the onset of the cognitive process of interest (rather than during) can sometimes improve task performance. Silvanto and Muggleton (2008) suggest that before the onset of the cognitive process, the neurons in a particular region are in their resting state. When a single TMS pulse is applied, the activation level of all the neurons is raised, potentially facilitating subsequent processing.

Virtual lesioning can be done in both online and offline designs. In an online design, a virtual lesion is briefly induced at some point during an experimental trial by applying a single pulse or train of pulses (often 3 to 5 pulses at 10 to 25 Hz). The neural interference caused by the TMS will last from the start of stimulation up to a few tens of milliseconds after the stimulation has stopped. If processes in the targeted cortical region make an essential contribution at a particular moment during the trial, applying TMS at that moment should negatively affect participants' performance. This way we can show the necessity of the cortical region at that specific moment in performing the paradigm normally (Walsh and Pascual-Leone, 2003). However, on-line TMS is accompanied by noise and other side effects (discussed below) that may distract the participant or have alerting/arousing effects, and this needs to be controlled for.

In an offline design, stimulation is applied before a series of trials in such a way that the stimulated region will be affected for several minutes after the stimulation has finished. This way there is no need for TMS during the testing phase, and it is less of a problem to control for the side-effects of TMS. Nor do the researchers need to have an hypothesis

about the timing of the critical processes, because the effect of stimulation lasts throughout the series of trials. But, by the same token, offline designs are not capable of studying the temporal dynamics of the processes at interest. One way of applying offline TMS is by stimulating at 1Hz for about 20min (Munchau, Bloem, Irlbacher, Trimble, & Rothwell, 2002). Recent offline designs, however, often use continuous Theta burst stimulation (cTBS; 50 Hz trains every 200 ms for about 20 to 30 s). This is a special kind of stimulation that will have an effect on the stimulated area for about 20 minutes up to an hour (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005).

Thus, online TMS allows us to study chronometric properties of cognitive processes. Offline designs are very useful when the goal of the experiment is to test the involvement of a brain region in a cognitive ability without being interested at which moment these processes happen or when a temporal hypothesis is not available. They also involve more complex safety issues, and the duration of the experiment is limited by the persistence of the disruption (Rossi, Pessoa Desimone & Ungerleider, 2009; Rossi, Hallett, Rossini, Pascual-Leone, & Safety, 2009)

2.1.5 Spatial resolution

The type of coil used has a considerable influence on the spatial resolution of stimulation. In the experiments outlined in this thesis, I used a standard "figure of eight" coil. I will therefore focus my discussion on this coil type.

One could look at spatial resolution in two ways: in relation to what happens to the neurons in the brain and in relation to whether the activations lead to behavioural consequences. Even though the actual influence of TMS on a particular brain region is difficult to model there are several sources of evidence that show TMS to have a good effective spatial resolution. Siebner et al. (1998) for example, combined TMS and fMRI to determine the TMS induced activations during stimulation of the motor cortex (to elicit a specific finger movement) and compared this to the BOLD signal associated with a voluntary movement of the finger. Both activations in the motor cortex were in the same location and showed a clear similarity in shape and size (Siebner et al., 1998).

Using TMS to stimulate particular muscles in the hand further shows its spatial specificity. Stimulation sites in the motor cortex between 0.5cm and 1cm apart cause different muscles to twitch (O'Shea & Walsh, 2007). This does not mean that cells associated with other fingers are unaffected by the stimulation, but a lack of behavioural results suggests this effect is sub threshold and the effective stimulation is limited to one finger. When studying cognitive functions by interfering with ongoing processes, this *effective* spatial resolution is arguably the most important.

Further confirmation of the spatial resolution of TMS comes from various cognitive experiments which compared the effect of stimulation on behaviour between cortical regions that were very close together in space. Studies done by Rushworth et al. (2002), Schenkluhn et al. (2008) and Verbruggen et al. (2010) as discussed before compared regions that were around 10-20mm apart and showed that stimulation resulted in distinctly different behavioural effects.

Besides the effect on the cortical region directly underneath the coil, TMS can also have indirect effects. In some cases it has been shown that when TMS is applied to a particular part of the brain, it affects regions that are interconnected with the stimulated region. Studies combining TMS with functional imaging for example, showed induced activations in the target site, but also in regions connected to the target region (Bohning et al., 1997; Paus, 1999; Paus et al., 1997; Robertson, Theoret, & Pascual-Leone, 2003). It is also possible to induce indirect neuro-chemical interactions; Strafella, Paus, Barrett and Dagher (2001) showed that rTMS over the left DLPFC facilitated dopamine release in the ipsilateral caudate nucleus (Strafella & Paus, 2000).

These indirect effects of stimulation keep open the possibility that any behavioural effects of the stimulation are due to the effects of the indirect spread of interference to interconnected regions. However the effect of interference is strongest at the target site. When the result of stimulation is also in accordance with fMRI evidence of localisation, for example, the most likely conclusion about the interference effect would be that it originates in the directly targeted cortical region. It is nonetheless important to keep in mind that indirect effects could play a role.

2.1.6 Temporal resolution

One of the great promises of TMS is that it can study the chronometry of the processes in a particular brain region during a cognitive task or determine the sequence in which cortical regions contribute to a particular cognitive function. Unlike other techniques it can interfere with processing at a specific moment. The length of a single TMS pulse is about 1 ms. The actual effective length of the influence essentially depends on the recovery time of the affected neurons (Walsh & Pascual-Leone, 2003). Assessing the actual length of this recovery is difficult because there are many factors involved which differ from site to site (e.g. type of neurons, angle of stimulation in relation to the neurons etc). In practice however, experiments have managed to show behavioural differences between the effects of single pulses, applied at different moments as close as 10 ms apart (Corthout, Uttl, Walsh, Hallett, & Cowey, 1999; Pitcher, Garrido, Walsh, & Duchaine, 2008).

The high temporal resolution makes it possible to assess the contribution of a particular brain region at different moments in time. Pitcher et al. (2008) stimulated the right occipital face area (rOFA) and the face area of the right somatosensory cortex (rSC). Participants had to discriminate between facial expressions and stimulations of both areas led to behavioural impairment on this task as opposed to a face identification task as well as stimulation of a control site. Pitcher et al. subsequently tested the time-course of the TMS effect on both areas. TMS (double pulse, 40ms apart) was delivered with the first pulse at 20 ms, 60 ms, 100 ms, 130 ms, 170 ms, 210 ms and 250 ms after stimulus onset. The stimulation had a negative effect on accuracy when applied to the rOFA at 60ms and to the rOFA at 100 ms and 130 ms. The effect was not present at the other timings.

The downside of the high temporal resolution is that it is often important to have a fairly precise hypothesis, a priori, about when a particular cortical region might be active (or when a particular process occurs) during performance of the task of interest. Parallel electrophysiological experiments can be helpful in localising the processes of interest in time, and to some extent in space.

2.1.7 Experimental control and the accessory sensations generated by TMS

TMS causes a number of sensations unrelated to the effect of stimulation on neural activity. On-line experimental designs must control for the potential interference with performance due to these accessory sensations. When the current passes through the coil, a clear click can be heard and there is some sensation in the scalp directly underneath the coil. If the stimulation site is near any of the neck or facial muscles it can induce muscle twitches in those surrounding muscles, resulting in for example, twitches in the eye region or jaw. These muscle twitches can be distracting and uncomfortable, especially when repeated many times during an experiment. Some participants tolerate these side-effects phlegmatically; others can be made quite anxious by them, with the potential for effects of emotional arousal as well as from attention to the accessory sensations per se.

The effects on behaviour are not necessarily disruptive; they also have the potential (probably when not too uncomfortable) to increase the alertness or motivation of the participant in what may otherwise be a boring experiment and improve performance. This may have knock-on effects on performance in no-TMS blocks if these are included. That is, the contrast between the accessory stimulation in the TMS blocks and that in the no-TMS blocks may cause subjects to relax and 'take a break' in the no-TMS blocks so that they are undermotivated in those blocks, relative to a standard behavioural experiment with no TMS. This can be particularly important when task performance requires deliberate effort, such as active preparation for a change of task.

In pilot work on dLPFC stimulation I included no-TMS blocks, but found that it was hard to get the RISC effects in these blocks that were obtained with the same paradigm in participants who were not exposed to TMS blocks; the explanation seems to be that in contrast with the TMS blocks in which there is some arousal from, and need to attend away from, the sensory consequences of TMS, participants "take a break" in the no TMS blocks and make less effort.

Both negative and positive consequences of the side effects of TMS require specific experimental control, especially when using online TMS. A standard way of controlling for these effects is to include blocks of trials in which a control site is stimulated instead of the target site. The control site should be chosen so that the brain region stimulated is highly unlikely to be involved in the processing required for the task, and so that stimulation of it

should generate the same quality and severity of accessory sensation as the target site. It can however often be difficult to find a control site which feels the same, but of which one can be confident is not involved in the processes being studied. In task-set preparation, for example, many frontal regions have been reported to be involved, but because of the unique sensations associated with frontal TMS, a good control site should be located there as well.

Another way of reducing the side effects of stimulation is to use an offline design. This way, any annoying feelings are limited to the time before doing the actual experimental blocks of trials. But being stimulated in a TMS lab is a unique experience and it may be desirable to also stimulate a control site even in offline studies.

Many researchers have used a "sham TMS" condition to control for the sensations caused by TMS. Well known examples are stimulation over the same area, but with a lower output or turning the coil on its side. Both techniques however feel distinctly different and when asked, participants can easily identify the sham condition (Rossi, Ferro, Cincotta, Ulivelli, Bartalini, et al. 2007). Some sham approaches also have a cortical influence which should be taken into account when applying them in a scientific design (Lisanby, Gutman, Luber, Schroeder, & Sackeim, 2001).

Unfortunately, most forms of experimental control, except for using lower stimulator output, require a blocked design, unless two simulators and two coils are used, which fire in alternation. This however can be impractical, because of the costs involved and both sites need to be far enough apart to accommodate both coils. A potential alternative to a blocked contrast of experimental and sham stimulation is a coil which can be switched, from trial to trial, unpredictably between standard and sham stimulation. The latter can be achieved by having two coils wound together, that can be pulsed in phase, or antiphased, the latter cancelling out most of the field, but leaving the click and some surface stimulation. An example is given by Sommer, Jansen, Drager, Steinstrater et al. (2006). An advantage is that the participant does not know in advance whether the stimulation will be Type A or Type B, and cannot adjust accordingly, as in a block design. However, this solution requires a custom coil and switching circuitry that would be prohibitively expensive for our lab.

2.1.8 Ways of targeting the desired brain region.

The high spatial resolution of TMS warrants a precise and consistent method of targeting the brain region. As a way of describing the locus of stimulation consistently across participants, early studies used standard EEG electrode locations on the 10/20 system. But consistency of scalp location in any system is no guarantee of consistency of brain location, as the relationship between cortical morphology and scalp location shows considerable interpersonal variation. Over time more sophisticated ways of targeting TMS have been developed. Each comes with its own advantages and disadvantages as well as possible inferences.

Using structural MRI images, it is possible to identify a particular morphological structure (in relation to standard sulci and gyri) in each individual participant and use this to target the same structure. This allows for a very strong anatomical inference to be made. For example, as discussed earlier, Schenlung et al. (2008) targeted 3 different places along the right IPS, by locating them on the structural scan of each participant. They showed that stimulating these targets, located in close vicinity of each other, had differential effects on performance of a visual search task.

The imaging literature can provide such a hypothesis about where to apply stimulation. Imaging studies report average peak activations in the form of coordinates in, for example, the MNI atlas. It is possible to match a participant's brainscan to this atlas and target a specific location using such a set of coordinates. However, from average activations in the imaging literature it can be difficult to assess which precise cortical region is the source of the activations reported, and there is considerable lack of consistency across reports. These difficulties will be reviewed in more detail in the second part of the chapter, in which I describe attempts to deal with the inconsistencies across studies using meta-analysis. When an experiment targeted on the basis of the imaging literature is successful, it opens up the possibility to conduct further structurally guided experiments to determine more precisely which particular structure(s), located in the vicinity of the original target coordinate, is the locus of this activation. However, using any average coordinate, whether from a single study or a meta-analytic coordinate, necessarily ignores differences in brain anatomy and spatial patterns of cortical activations that exist

between people; the mapping between functions and morphology varies over individuals (Walsh & Pascual-Leone, 2003).

The "gold standard" method for targeting TMS would appear to be to use fMRI to identify the locus of task-related cortical activations in individual participants, and apply TMS in the same participants on the basis of that localisation. fMRI-guided TMS is more time consuming than the first two targeting approaches, but potentially requires fewer participants. Sack, Kadosh, Schuhmann, Moerel and Walsh (2009) compared four different ways of targeting TMS. They repeated an experiment in which they had shown parietal TMS to influence size congruency judgements. Four groups of 4 to 5 participants each did the same experiment using different targeting strategies. Targeting was based on EEG electrode positions, anatomical targeting, a mean Talairach coordinate, or guided by individual fMRI localisations. Power analyses based on each group's results revealed differences in the number of participants needed. Using fMRI-guided targeting, a significant effect was found with 5 participants. Structural targeting would require (for the same level of significance) 9 participants, Talairach coordinate would need 13 and using EEG locations would require 47 participants to get a reliable effect (Sack, et al., 2009). It must be noted that 5 participants is a somewhat small number for a power analyses, but the study does indicate differences in sensitivity between the various targeting methods.

However, the gold-standard is expensive (much longer scanner sessions are needed), and has other disadvantages. Localising task-relevant activations securely from BOLD contrasts in individual participants is not easy (the difficulty might also depend on the cognitive function under investigation). And performing the same task in an fMRI study as in a later TMS study means that the participant is always more practiced in the latter. Both protocols tend to involve some discomfort and anxiety, but there is no guarantee that the effects on performance are equivalent. Some might find the scanner relatively relaxing, others claustrophobic; the scanner involves high levels of repetitive noise, while TMS involves only very brief clicks, which do not sound particularly loud, though they do induce high peak pressures.

2.1.9 How will I use TMS.

In Chapter 1, I gave an overview of the limited TMS research done in studying task-set control and related subjects. One of the possible reasons why TMS has not been widely used to study task-set control could be the lack of precise hypotheses about areas involved in cognitive control (Nee, Wager, & Jonides, 2007; Wager & Smith, 2003). Also, as mentioned before, many regions of interest with respect to task-set control are located in the prefrontal cortex, where controlling for the effects of accessory sensations, especially in online designs, can be problematic.

As discussed in Chapter 1, the three most commonly applied approaches of TMS in the study of task-set control and related investigations, are now cTBS, online virtual lesioning (sometimes in combination with ERP recordings) and using motor evoked potentials (MEP) and ERPs as a dependent measure (Candidi, Vicario, Abreu, & Aglioti, 2010; Rushworth, et al., 2002; Taylor, et al., 2007; Verbruggen, et al., 2010). The focus of the research reported in this thesis was on studying preparation effects by using online TMS. In a similar way to Rushworth et al. (2002) I apply TMS to interfere with preparation effects in task switching paradigms. One merit of the focus on stimulation during the preparation interval in a task-switching experiment is that we can be reasonably sure that we are not interfering with stimulus processing and response selection and task execution directly.

The ability of TMS to interfere with cortical processes, allows us to use TMS, not just to localise processes to a particular cortical region; it can also be a powerful tool to differentiate between various cognitive theories (Other commonly used neuroscience techniques like fMRI and EEG are correlational in nature, which makes it by definition difficult to test a cognitive theory. TMS however can be used to study cognition in a similar way to the study of patients.

The goals of the project reported in this thesis were twofold:

(1) To identify cortical regions consistently involved in task-set control in the fMRI literature, and determine whether TMS applied to them at times suggested by ERP experiments interferes with the behavioural manifestations of task-set preparation. The aim is to prove that activity in particular cortical regions at particular points in time is necessary for task-set preparation.

(2) Finding more than one such region, and distinguishing among the behavioural consequences of stimulating such regions, would exploit TMS to study the functional components of task-set control as well as the chronometry of the underlying processes.

2.2 Meta-analysis

2.2.1 Introduction

In the last fifteen years, the number of cognitive neuroscience papers using fMRI has steadily increased. The variability in results between imaging studies, however, can make it difficult to assess which regions of the brain are consistently involved in a particular cognitive process or skill and under which circumstances this changes. The variability between the results of imaging experiments, quantifying seemingly similar concepts, is likely to become greater as the cognitive functions studied become more complex. Not only do the regions studied probably show a more complex functional localisation (for example

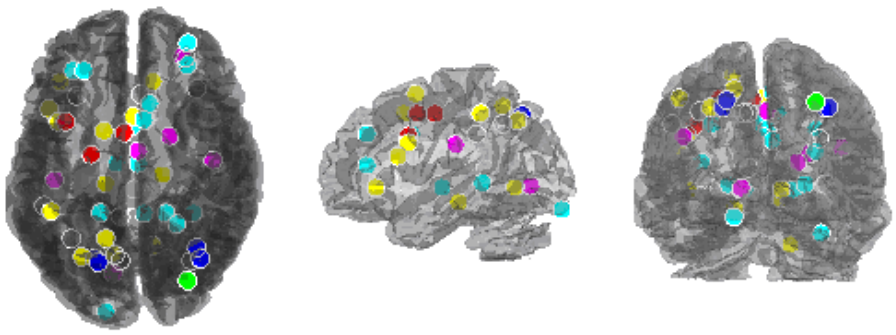


Figure 2.2 Switch minus repeat contrast results from the first 8 studies depicted in Figure 1.1 displayed in different colours.

functional localisation in the primary motor cortex is probably more straightforward than in the prefrontal cortex), but paradigms of, for example, cognitive control probably reflect an assembly of different cortical functions whose organisation can change due to seemingly small alterations in experimental setup. The complex dynamics, both in place and time are difficult to detect using the BOLD signal. In Chapter 1 (See Figure 1.1) I showed the distribution of peaks reported by a number of task-switching studies contrasting switch trials and repeat trials. Even though these are very similar studies, they show a high variability in reported activations. Fig 2.2 illustrates this variability by showing the distribution of eight studies taken from Figure 1.1 and depicting each study's peak activations in a different colour.

Chapter 2: Methods

Besides the complexity of the processes that underlie many cognitive abilities, there are other possible reasons for a high variability in results. Many imaging studies do not correct for family-wise error (FWE). Essentially most fMRI Experiments do not test enough participants to account for the vast number of multiple comparisons (Yarkoni, Poldrack, Van Essen, & Wager, 2010). This means that classic methods of FWE correction, like a Bonferroni correction (which however do not take into account the fact that adjacent voxels are not independent), would possibly hide many effects and even though more sophisticated FWE correction methods have been developed, many studies report results at, for example, $p<0.001$ uncorrected. This means that the fMRI results have a high Type 1 error rate, the results of which could explain some of the inter-study variability. Wager, Lindquist and Kaplan (2007) estimate that at least 10 to 20% of peaks reported in the literature are Type 1 errors. The variability in results also increases due to differences in experimental setup and scanner equipment as well as different paradigms used.

One way of addressing this problem is to do a quantitative meta-analysis to determine which regions of the brain are consistently (FWE corrected) correlated with a particular paradigm or a particular contrast from a particular paradigm. Meta-analysis can also play an important role in confirming or disconfirming common assumptions made about the contribution of certain regions. When analysed in a quantitative way, these assumptions often do not hold up (Yarkoni et al. 2010).

Meta-analysis of imaging data can be used to determine consistent activations among different types of paradigms that are thought to have common underlying processes (Wager, et al., 2007). It can be very useful to test for commonalities in different contrasts that are thought to measure similar processes and to determine consistent differences which can increase our understanding of potential functional differences between contrasts. It can also be a very powerful approach to identify consistent activations related to a cognitive concept when the literature offers few direct replications.

Quantitative meta-analysis can also be used to analyse consistency among studies reporting the same contrast (the variability in Figure 1.1 illustrates the need for such an analysis). Because the data are derived from similar contrasts, the results of this analysis will also be easier to interpret than when the data comes from more variant sources. In order to do such an analysis however, there need to be enough imaging studies that have

run this contrast. Unfortunately, direct replications of experiments are rare in the imaging literature (Yarkoni, et al., 2010)

Nee et al. (2007) employed both strategies using a Multi-Level Kernel Density Analysis (see below) to study consistent activations across a range of conflict tasks (Flanker, Simon, Go/No-Go, Stimulus-response compatibility task, Stroop and Stop-Signal). In their analysis they tested for consistency among all task types. This revealed consistent activations in the ACC, DLPFC, IFG, posterior parietal cortex and anterior insula, suggesting that these regions are important during conflict situations in general. In order to answer the question whether there are consistent differences between the paradigms, the authors ran specific analyses on the various tasks. In the Stroop paradigm they further specified specific contrasts, running two separate analyses on contrasts between incongruent and congruent trials as well as contrasts between incongruent and neutral trials. This allowed them to further break down the set of regions, identified in the first analysis. They showed that parts of the network contributed differently to different task types. For example, the contrasts between incongruent and congruent trials in the Stroop paradigm showed greater consistent activations in the ACC whereas the incongruent versus neutral contrast showed greater consistent activations in the left DLPFC and the left posterior parietal lobe. If the available literature allows for such a contrast specific analyses, it becomes possible to identify which contrasts are related to specific parts of the network and make the neural differences between seemingly similar paradigms visible.

Besides overcoming methodological shortcomings and variance in results, integrating results from multiple imaging studies can serve other important goals. It can be an excellent way of forming new hypotheses and identifying a region of interest (ROI) in imaging studies as well as suggesting TMS studies (Yarkoni et al. 2010).

Several methods to conduct such a meta-analysis have been developed. I will discuss in detail two techniques that have been the most influential in the study of cognitive control in recent years, namely the Activation Likelihood Estimate (ALE) method, and (Multi-level) Kernel Density Analysis (MKDA). I will also briefly mention some other ways of identifying consistent activations.

2.2.2 Early ways of addressing consistency in imaging data

The complex nature of neuro-anatomy often makes interpreting imaging data a difficult exercise. Getting to grips with patterns and consistencies among a set of imaging studies can be especially difficult. This, and the great variability in results, has inspired ways to describe neural substrates of cognitive tasks using meta-analysis (Hunton, Miezin, Buckner, vanMier, Raichle, & Petersen, 1996; Turkeltaub, Eden, Jones, & Zeffiro, 2002). Initially, this was done by combining activated regions from different studies into a table in order to identify possible patterns (Buckner & Petersen, 1996; Turkeltaub, Eden, Jones, & Zeffiro, 2002). Farah and Aguirre (1999) plotted the reported peaks of PET and fMRI studies of visual recognition in a brain image using the Talairach coordinate system (Talairach and Tournoux, 1967). They used these images to guide their review of the functional anatomy. This allowed for a review which was not based on the various anatomical labels used in the included studies. This is an important step forward, because of variability in the way anatomical labels are applied. This variability can bias subjective assessment towards labels that have been used in the past. For example, it is often unclear whether an activation in located in the cingulate cortex or the supplementary motor cortex. If previous research indicated the importance of the cingulate cortex, authors can be inclined to choose the cingulate label for this activation. It is therefore important to remove these labels when applying a meta-analytical approach.

2.2.3 Activation Likelihood Estimate

Turkeltaub et al. (2002) introduced the first quantitative statistical approach to test which regions are consistently activated in a number of imaging studies, called Activation Likelihood Estimate (ALE). ALE starts by selecting the studies that will be included in the analysis. The coordinates of the peaks reported by these studies are entered into a database. Activations that are reported in the Talairach coordinate system are all transformed to the MNI brain atlas. The peaks reported in the literature are a reflection of a cluster of activated voxels. In order to model the spatial extent of the activations, each of the activations is transformed into a 3 dimensional Gaussian distribution (Eickhoff et al., 2009). This results

in a probability map in which each voxel is assigned a probability that at least one activation falls in that location (Turkeltaub et al. 2002).

To determine what this probability would be assuming no consistency, a thousand probability maps are produced in the same way as the initial probability map, but based on a set of randomly distributed peaks (the same number of peaks in the observed map). This map is used as the null hypothesis to compare with the observed probability map. In the ALE analysis the results are False Discovery Rate (FDR) corrected, which allows a maximum of 5% of the resulting peaks to be a Type 1 Error.

Derrfuss et al. (2005) as mentioned in Chapter 1, used the ALE method to study the consistent contribution of the left IFJ in paradigms which required participants to activate task-set representations.

2.2.4 Multilevel Kernel Density Analysis

Kernel Density Analysis is a method first developed by Wager et al. (2003). The original KDA works in a similar way to ALE. The reported peaks are transformed in 10mm spheres (instead of a Gaussian distribution). This smoothing procedure produces a histogram which reflects the estimated number of peaks located within 10mm of each voxel. The analysis compares the observed activation map with the result of a series of Monte Carlo simulations which assume a random distribution. Unlike the ALE the results of the original KDA are fully corrected for family-wise error (FWE).

Neither procedure, however, allows for the fact that the reported peaks are not independent. The reported peaks come from contrasts run in individual studies. If there is a difference in the number of peaks reported in the included studies, ALE and KDA will allocate a bigger weighting to the studies that report more peaks, biasing the overall results. To overcome this problem Wager et al. (2007) developed Multilevel Kernel based Density Analysis (MKDA).

The multilevel aspect is achieved by making a smoothed activation map, per reported contrast, before making an overall observed activation map. Reported peaks are gathered in a database (MNI coordinates) and the contrast of origin is coded in an extra variable. For each contrast, the peaks are replaced by a spherical kernel with a radius of

10mm (Eickhoff et al., 2009). The spheres will overlap at points but each voxel that is located within a least one sphere is allocated a value of 1 (all voxels will end up having a value of 0 or 1). The result is a smoothed histogram of 0s and 1s, reflecting reported peaks, for each contrast. These activation maps are then added together to produce an overall observed activation map. The value in each voxel of this map reflects the number of contrast maps that show activation in or near this voxel. The weight of each contrast in the overall map is adapted to the sample size. It is also possible to add an additional weighting based on the analysis used (fixed or random).

In this procedure the individual peaks are nested in the contrast in which they were published. Since peaks from the same contrast, that are located in close proximity, are regarded as one (as the maximum activation of each voxel is set to 1), the excessive contribution of studies reporting more voxels is reduced.

In order to determine which voxels are more activated than expected by chance the observed map is compared to an activation map based on at least 5000 Monte Carlo simulations. These simulations place the observed number of activations coordinated from the activation map at random locations. Each simulation computes the number of activations per voxel and computes the maximum proportion across the brain. After completing the simulations, the frequency with which a maximum probability of activations of a certain size is seen in the brain, under the null hypothesis, can be calculated. This way a threshold is created which restricts the chance of a false positive, anywhere in the brain to 5% (Wager et al. 2007)

In order to compute a difference between 2 sets of contrasts (for example, if you want to compare contrasts that look at switching with preparation with contrasts looking at switching without preparation), the difference between the levels of activation in each voxel is calculated and the Monte Carlo simulations are run using these differences.

It is also possible to test whether a particular set of studies consistently activates a larger region (in terms of number of activated voxels) than would be expected by chance. Voxels are entered into a cluster based on a statistical inclusion criterion (e.g. $p<0.001$ uncorrected). The Monte Carlo simulations are used to determine the minimal amount of voxels a cluster must have to differ significantly from chance (FWE corrected) based on

this threshold. The more lenient the inclusion criterion, the more extensive the cluster must be to differ reliably from chance.

2.2.5 Limitations of meta-analysis of imaging data

The great variation in results coming from imaging studies warrants the use of objective quantitative analysis techniques to test which regions are consistently activated under similar conditions. Currently, the MKDA meta-analysis technique provides the best quantitative way to make this assessment. However there are some important limitations to be considered. First of all, the way contrasts are included remains a matter of concern. As in other forms of meta-analysis, study inclusion is a potential source of bias. It is therefore important to identify clear criteria for inclusion. These criteria should be formulated on the basis of the actual contrasts run. The imaging contrasts should either be the same (e.g. only include contrasts between switch and repeat trials in task-switching experiments) or they should aim to operationalize a similar cognitive concept (e.g. include contrasts between incongruent and congruent trials from studies using a Stroop task as well as studies using Flanker tasks).

As pointed out before, the choice of selection criteria also influences the inferences that can be made. Choosing a criterion on the basis of a particular contrast rather than a particular cognitive concept can lead to different conclusions. This is made more concrete in Chapter 3, where I employ both approaches.

Unfortunately, publications of imaging studies do not report the actual spatial extent of the activations. (In recent years, cluster sizes are more often reported but they do not show the distribution of the cluster). This means that, in a quantitative meta-analysis, the extent of the activations needs to be modelled (e.g. the 10mm kernel in the KDA). Unfortunately, important information about the distribution of the BOLD signal in the included contrasts is lost this way.

It is also important to point out that the results of a meta-analysis reflect only a part of the truth. Not all of the non-consistent activations stem from Type 1 errors. Meta-analysis does not capture the complex dynamics that are present in the brain when participants perform the various paradigms in the scanner. The meta-analytic results are the

regions we can be confident are activated across similar contrasts and are not related to specific experimental circumstances.

Chapter 3: Meta Analysis

The use of TMS requires very specific hypotheses about which locations in the brain potentially host the cognitive function of interest. In the last decade, an extensive literature has documented the neural correlates of task-set control as examined by means of fMRI. This has revealed a large number of brain regions including a number of frontal and parietal regions thought to be involved in task-set control. In this chapter, I report the results from meta-analyses I have conducted to provide hypotheses about where TMS stimulation might interfere with task-set control. This Chapter is written in the format of an article to be submitted to the journal NeuroImage.

3.1 Introduction

The term "task-switching" has been used in a variety of ways in the imaging literature. We start by defining what we mean by a task switching procedure in this meta-analysis. We understand an experiment to be a task switching procedure when there are at least two tasks "in play" and the task can change from one trial to another. On any given trial the participant is required to perform one of them when the stimulus occurs. Each task typically requires a perceptual or semantic judgements (e.g., identify the colour or shape of a stimulus, classify a letter as consonant or a vowel, etc.). Each judgement outcome is associated with a (typically manual) response from a small set of responses (e.g., pressing of a button or moving a joystick in a particular direction). The task is usually specified by some sort of task cue preceding or accompanying the stimulus (or even, in a few studies, following the stimulus). The task performed can be the same as on the previous trials ('task-repeat' trial) or different ('task-switch' trial). Typically the stimulus presented on each trial affords both tasks (a "bivalent" stimulus when there are two tasks), though it is certainly possible to include univalent stimuli that afford only one task either because no response is specified for that stimulus for the other task, or because the stimulus does not possess the relevant attribute for the other task.

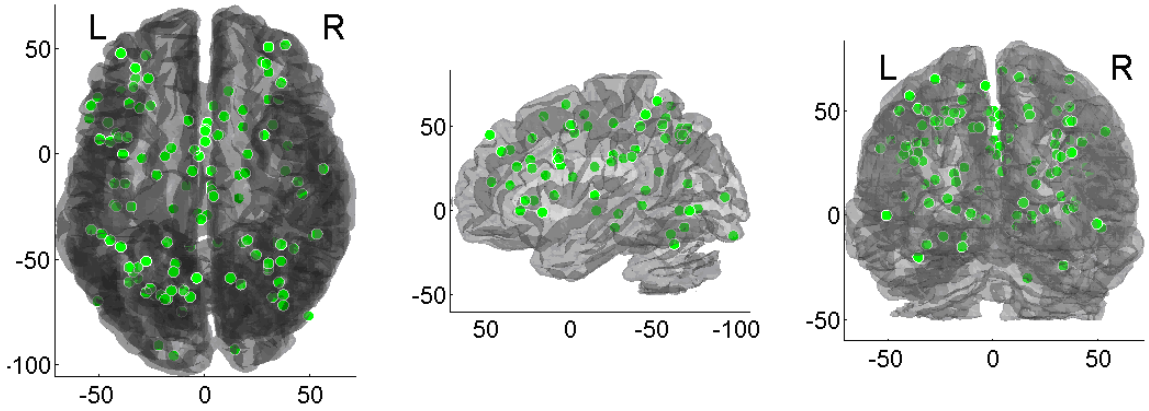


Figure 3.1a Peak activations reported in 18 switch minus repeat contrasts that did not attempt to isolate preparatory activations (cue and stimulus appear together or their related activations are not isolated in the BOLD signal).

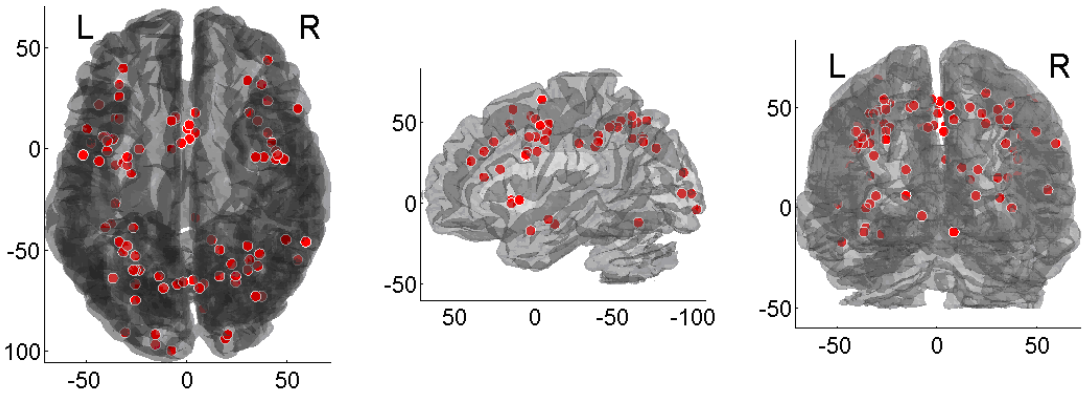


Figure 3.1b Peak activations reported in 10 studies that have adapted the task-switching paradigm in an attempt to isolate preparatory activations (see Table 3.1) to isolate cue related activations from stimulus related activations.

On average, participants usually take longer to respond and make more errors on a switch trial than on a repeat trial. This difference is called the switch cost (Rogers & Monsell, 1995). Often, a cue is used to indicate which task is to be performed on the following trial. When the cue stimulus interval (CSI) is made longer, thus increasing the time available for preparation, other things being equal, the switch cost decreases. This suggests people can prepare for an upcoming new task, without having yet seen the stimulus that is, they can do at least some part of the operations required to successfully change their "task-set" ahead of stimulus onset. Preparation however does not completely

abolish the switch cost. These *residual costs* reflect those parts of the switching process that require stimulus information, or reflect forms of carry-over of the prior state that are immune to voluntary preparation (Monsell 2003). Although preparation does not entirely abolish switch costs, the reduction in switch costs with enough time to prepare, in a task switching paradigm, provides a measure of top down task-set control (Monsell & Mizon, 2006).

Note that this situation differs from, for example, a rule-set switching paradigm (which has sometimes been referred to as a task-switching paradigm in the imaging literature) in which participants switch between stimulus-response mappings, while the task (e.g. perceptual or semantic judgement) remains the same.

Using fMRI in combination with a task-switching paradigm, it is in principle possible to map brain areas involved in the various aspects of switching tasks. A number of task-switching studies have investigated which brain regions are more active on switch trials than on repeat trials. Peak activations from a set of 18 studies are shown on a "glass brain" in Fig 3.1a. In recent years an increasing number of studies have also tried to map the brain regions involved in anticipatory task-set control, by attempting to isolate brain activity during the preparation interval. This is however, far from straightforward. In behavioural data, the benefit of advanced preparation for reducing the switch cost seems to reach its asymptote as the CSI reaches around 0.5 sec -1.0 sec. Hence the optimal preparation interval is generally of the order of one second. Using BOLD-fMRI, it is very hard to resolve activations associated with pre-stimulus preparation and post-stimulus processing when they occur so close in time. The various ways in which researchers have addressed this problem will be described below.

Switch-specific activations (i.e. greater activation on task-switch than on task-repeat trials, other things being equal) have frequently been reported in the pre-supplementary motor cortex (pre-SMA), anterior cingulate cortex (ACC), right inferior frontal gyrus (rIFG), bilateral inferior frontal junction (IFJ), bilateral middle frontal gyrus, cuneus, pre-cuneus, and a range of regions in the bilateral inferior and superior parietal lobule (see Table 3.2 for which studies reported switch minus repeat contrasts). The actual locations of activations found in the various studies show a large amount of variability (as illustrated by Figure 3.1 and below). Some of the possible reasons for this are differences

between paradigms, inflation of type I error rate in statistical tests[3] and the complex dynamics of the underlying neurophysiological processes. The large number of different activations, reported between imaging studies, and variations in the exact locations referred to by particular labels, have made it difficult to assess which of these regions are consistently activated.

Studies looking at task-set preparation (via measures of cue-triggered activity on a switch trial) and articles reporting the difference between task switch and repeat trials (not looking at preparation) have reported a similar set of regions. A closer look at the exact locations however suggests that there might be differences in which brain regions are more consistently activated during switching and preparing for switching. Here we present the results from two quantitative meta-analyses, using the Multilevel Kernel Density Analysis procedure (Wager, Jonides, & Reading, 2004; Wager, et al., 2007). Unlike earlier meta-analyses of task switching (Derrfuss, Brass, Neumann, & von Cramon, 2005; Wager, et al., 2004) we only include studies reporting true task switch-repeat contrasts[4], taking advantage of the extensive use of similar switch-repeat contrasts in the imaging literature subsequent to these reviews and ensuring a high level of consistency of paradigms included in the analysis. The second analysis examines which areas are consistently involved in task-set preparation.

There are two ways to conduct a meta-analysis of neuro-imaging data (Wager et al., 2007). If enough studies are available, one can test which brain areas are consistently activated by the same contrast, in our case a switch versus repeat contrast in a task switching paradigm. A second way is to test which areas are consistently activated by different paradigms that are hypothesised to measure a similar psychological construct. Here we use the first approach to test for consistent switch related activations. We use the second approach to look for consistencies between different studies looking at preparatory task-set control. However consistency in paradigm design among studies included in the second approach is higher than earlier meta-analysis (i.e. all studies are cued task-switching

[3] Wager et al. (2007) estimate the average Type I error rate to be as high as 10-20% of reported activations.
[4] Besides task-switching studies as we define them, Derfuss et al. also included response rule reversal paradigms and Wisconsin Card Sorting Tests. Wager et al. also included various forms of attention switching studies such as paradigms requiring participant to switch between attending to different locations, between different stimulus attributes or between different objects as well as response rule reversal paradigms.

paradigms, but they differ in the ways they have been adapted to accommodate the slowness of BOLD signal, see below).

The need to study which areas are consistently activated between studies is apparent. Figure 1a shows the activations from 18 studies reporting a switch minus repeat contrast, illustrating the high variability in imaging data (even though the paradigms included are relatively consistent). Even if the same brain regions are reported in several studies, the exact location within those regions differs. Many task-switching studies for example report posterior parietal activations, but the actual distribution of the activations in this region is more variable than one might assume on the basis of the labels used in the literature. Quantitative meta-analysis provides us with the means to identify which precise locations in various structures are consistently activated.

3.1.1 Meta-analysis of switch minus repeat contrasts.

In the first meta-analysis we ask which brain regions are consistently involved on switch-repeat contrasts. This may be seen as an update of Wager et al. (2004). Wager et al. (2004) reported a meta-analysis of fMRI studies whose paradigms required attention switching (the authors included different type of attention shifting, namely shifting spatial location, stimulus attribute, task, response rule or object). Their kernel density analysis (pooling over different forms of attention switching) showed consistent activations in the intra-parietal sulcus bilaterally (IPS), the medial frontal cortex (MFC), left occipital lobe and the right premotor cortex. Notably, they did not find frontal activations other than in the MFC. Derrfuss et al. (2005) did a meta-analysis looking at the involvement of the frontal lobe in retrieving task representations, including only frontal activations. They included task switching studies, response rule reversal studies and studies using computer analogues of the Wisconsin card-sorting test (WCST), which they argued all required retrieval of task representations. They found frontal activations in the IFJ and IFG bilaterally, ACC/pre-SMA, superior frontal gyrus and the right insula. The authors suggest that the discrepancy between their results and those of Wager et al. is due to differences in the contrasts selected for inclusion. They argued that Wager et al.'s analyses were less sensitive to the requirement to update task representations (Wager did include rule reversal and task-switching, but no WCST). Both Wager et el. and Derrfuss et al. included a number of

contrasts that arguably captured rather different phenomena. For example, in a WCST, the task changes without informing the participant. He or she will keep applying the old task, until a numbers of errors will lead the participant to conclude that the task has changed. This error monitoring/decision making process in order to determine whether or not to change task, is qualitatively different (and probably requires additional cognitive processes) from a cued-task switching paradigm, in which the current task is cued on every trial. Even though the selected contrasts may have considerable functional overlap, the use of different paradigms can make it difficult to interpret the results. After all, it is not entirely clear what these common processes are and the contradictions between the findings of the two meta-analyses show that apparently small differences in contrast selection can lead to different results.

The studies included in this part of our analysis share similarities with those included in Wager et al. and Derrfuss et al., but the overall consistency of the paradigms included is much higher, in part because a number of suitable task-switching studies have been published in the interim. Thus, unlike earlier meta-analyses, which pooled over a variety of control paradigms, the contrasts included in our analysis are switch-repeat contrasts from task-switching paradigms, as defined before.

Given the large number of studies now available, we also tested whether there are consistent differences in the locations of the switch-repeat differences in brain activity for different categories of tasks between which participants switched.

3.1.2 Meta-analyses of preparatory activations.

In the second meta-analysis we address the question of which areas are consistently involved in *preparation* for a task switch. We do this by employing two strategies. In the first strategy we focused on 2 subgroups of the 18 switch-repeat contrasts (used in the analysis described above) which did not aim to study cue-related activations. The first subgroup consists of switch-repeat contrasts in which there was an interval of more than 250 ms between stimulus and cue (many imaging studies use a non-zero CSI even though they did not aim to study cue-related preparatory activations). The second subgroup is switch-repeat contrasts in which the cue and stimulus were simultaneous or the CSI was less than 250 ms. By comparing these two groups we aim to test whether including a

substantial CSI (and thus the potential to prepare) results in consistent differences compared to including a short or no CSI. CSIs of only 100 or 200 ms are assumed to be insufficient to interpret the cue and start preparation before the stimulus. Task-set reconfiguration accounts tend to assume that the same task-set reconfiguration process is performed before the stimulus when the CSI is long, but afterwards when it is short or zero (Lavric, et al., 2008; Monsell & Mizon, 2006). This might lead one to expect that any task-set reconfiguration related brain activation revealed by the switch-repeat contrast would be similar in the two sets of studies, given the poor temporal resolution of fMRI. Alternatively, advance task-set preparation might result in unique activations.

The second strategy we used was to examine consistency among contrasts intended to measure task-cue related activity for task-switch versus non-switch trials. The difficulty in using fMRI to distinguish between events taking place close in time has led authors to come up with different designs that in theory make it possible to distinguish cue-related activity from stimulus-related activity. Some have increased the preparation time to several seconds (e.g. 12 sec, Kimberg, Aguirre, & D'Esposito 2000; 6 sec, Sohn & Anderson 2000) to remove the superimposition of the BOLD signals for pre-stimulus preparation and post-stimulus processing. They have observed extra cue-related activation when the cue signals a change of task. But as well as the long waits being boring and demotivating for the participant (an important factor where we are trying to study a voluntary process), this approach might create a situation in which participants postpone preparatory activity until late in the interval and must engage in extra working memory maintenance activity to maintain the identity of the cue until they reconfigure task set, or the task-set itself once achieved. Some authors have contrasted a condition where the cue indicated the upcoming task with one where there was a cue which was not informative with regard to the task to be executed (another task cue would be presented on all trials concurrent with the stimulus). The contrast of informative cue trial minus non-informative cue trial may be expected to reveal the areas involved in task-set preparation (Luks, et al., 2002). Others have introduced an unpredictable proportion of trials on which the cue is not followed by a stimulus, intended to capture cue-triggered preparation without stimulus-related activity (Brass and von Cramon 2002). However, the absence of a stimulus following the cue, on a number of trials, could reduce the incentive for participants to prepare for a task switch. And indeed,

several such studies have failed to find any difference in activation between cues which signal a switch of task, and those that signal a repeat (See Table 3.2).

The different approaches used to isolate cue related activity have given us some insight into the neural correlates of cue related activity, but like the switch minus repeat contrasts discussed earlier, the published results have shown considerable variability (see Figure 3.1b). My analysis asks the question of which areas, if any, show consistent activations across these studies of task-set preparation. In this second strategy, there is more heterogeneity in the contrasts I include (though all the studies used some variant of a cued task switching paradigm) and it will test different types of contrasts that aimed to measure the same construct. The hope is that consistent activations should be the ones not dependent on the particular way the paradigms were adapted to isolate preparatory activation.

A lack of reliably different activations between switch and repeat trials, found by a number of studies attempting to isolate preparatory activations, can make it difficult to interpret these data, because these imaging results could represent both task-set preparation and generic preparation. Even when there is no task-switching, the opportunity to prepare for an upcoming stimulus and response leads to faster responses than when there is no preparation, and there is a substantial literature on warning-signal effects (Posner,1978; Niemi & Näätanen, 1981; Nobre, Correa and Coull, 2007). In this meta-analysis I find areas that are more activated when preparing for a new task-set as well as areas that are involved in preparing both trial types.

The meta-analysis method we used in these meta-analyses (Multilevel Kernel Density Analysis, MKDA), developed by Tor Wager et al. (2007), unlike the methods used by earlier meta-analyses of task-switching imaging data, controls for the fact that peaks coming from the same study (i.e. from a contrast reported by a particular paper) are not independent. If one assumes, similar to earlier meta-analysis, that each reported peak is an independent measurement (as if all peaks come from one big study), studies that report more peaks than others would be given a greater weight in the outcome of the meta analysis.

In order to run the meta-analyses introduced above, I constructed a database of 27 task switching studies (some reporting more than one contrast of interest). These studies report 18 switch-repeat contrasts (not investigating task-set preparation) and 15 contrasts examining task-set preparation (albeit using different contrasts types to accomplish this).

Chapter 3: Meta Analysis

3.2 Methods

Table 3.1 Selected contrasts from studies that adapted the task switching paradigm to isolate preparatory activations (isolate the BOLD signal related to the cue from that of the stimulus).

Study	Contrast (as named in the publications)	Behavioural evidence for switch specific preparation
Brass & Von Cramon (2002)	Cue only vs non event	No
Brass et al. (2004)	Meaning switch minus cue switch	Yes
Chiu (2009)	Cue evoked rule switch vs rule hold	Yes
Gruber (2006)	Cue vs target	Yes
Luks (2001)	Informative cues vs neutral cues	Yes
Ruge et al. (2005)	Task transition by preparation interval	Yes
Slagter (2006)	Cue only Switch> repeat by MR frame (mixed)	No
Shi (2009)	Cue only switch minus repeat	No
Jamadar (2010)	Informative cues vs neutral cues	Yes
Ruge (2009)	Contrasting advanced target and advanced cues	No
Sohn (2000)	Scans during foreknowledge period (foreknowledge vs no foreknowledge)	No
Forstmann (2005)	Switch cue vs task cue	Yes
Sakai & Passingham (2003)	Inst delay spat>verbal	No
Madden (2010)	Cue only switch minus repeat old and young	No
Bunge (2003)	Cue activity switch minus repeat $p<0.005$	Yes

3.2.1 Selection of fMRI studies

As mentioned above, we selected two groups of studies. The first reported a switch minus repeat contrast, not attempting to isolate preparatory activations. The second reported a contrast in which the authors adapted the paradigm to isolate preparatory activations. Some studies reported both types of contrast.

The contrasts included in this meta-analysis are shown in Table 3.2. Studies were included in the switch minus repeat analysis (not isolating preparation), if they reported a switch minus repeat contrast which was not adapted to distinguish between cue and stimulus related activity. I will refer to this group as the standard Sw>Rep group (studies using a "standard" switch minus repeat contrast that is not adjusted to isolate preparatory activations). So for example, if a study looked at neural correlates of task switching (switch minus repeat) in a patient population and reported the switch-repeat contrast of healthy controls separately, without attempting to isolate preparation related activation, the control data was included in our standard Sw>Rep group. We report analyses sub-dividing this group as a function of whether there was a long (>250 ms) preparation interval or not A contrast was included in the preparation database, when an fMRI task switching paradigm was used to study task-set preparation , i.e. the task switching paradigm was adapted to be able to study preparatory activity as distinct from post-stimulus activity. We refer to this group as the Prep group. We report analyses of activation contrasts (a) attempting to capture any additional activation during preparation for a task switch versus a task repeat -- essentially the switch-repeat x preparation interaction, and (b) activation contrasts intended to capture preparatory versus post-stimulus processing ignoring the difference between switch and repeat trials.

To be included, studies had to report activation peaks in either MNI or Talairach (Talairach and Tournoux, 1967) coordinates (on rare occasions papers have stated only the anatomical labels). Only studies using event-related fMRI designs were included (hence all were post-1999). We did not include contrasts between mixed and single task blocks because this contrast measures not just the neuro-correlates of the transient switch cost, but also those of the mixing cost. Reaction times even of task-repeat trials in a mixed block are typically longer than in a single task block (Fagot, 1994; Braver, Reynolds et al. 2003; Monsell 2003). All studies included treated participants as random effects. fMRI analysis software treats group analysis as a random effect analysis by default (so that the findings

are generalisable beyond the participants of the study). If the authors did not report whether they used a fixed or random effect analysis, we assumed it to be a random effect analysis. Studies that have used PET (of which there are a small number) were not included to avoid the variability due to the differences between PET and fMRI. Only results from whole brain analyses were included; results from region of interest analyses were not included.

Table 3.2 Contrasts included in the meta-analyses

Meta Analysis	Sw-Rep	Sw-Rep CSI	Sw-Rep noCSI	Prep X Switch	Prep Pooled
Badre 2006	X		X		
BrassVonCramon 2002					X
Brass 2004	X	X		X	
Braver 2003	X	X			
Bunge 2003				X	
Chiu 2009	X	X		X	
Erickson 2005	X		X		
Forstmann 2005					X
Gruber 2006					X
Gu 2008	X	X			
Hyafil 2009	X		X		
Jamadar 2010a	X	X			X
Jamadar 2010b	X	X			
Kimberg 2000	X		X		
Liston 2006	X		X		
Luks 2002	X	X			X
Madden 2010				X	
Rubia 2006	X		X		
Ruge 2005				X	
Ruge 2009	X				X
Sakai 2003					X
Slagter 2006				X	
Shi 2010				X	
Smith 2004	X		X		
Sohn 2000	X		X		X
Sylvester 2003	X		X		
Yeung 2006	X				
Nr of Contrasts	18	7	9	7	8

33 contrasts were included in the various analyses. Column 2 shows the studies reporting switch>repeat contrasts. Column 3 and 4 show which one of these had a CSI longer than 250ms and which did not. Column 5 and 6 show which studies reported contrasts which isolated preparatory activations. Column 5 shows the studies reporting reliable preparatory activations which were bigger on switch trials than on repeat trials. Column 6 shows studies which found preparatory activations, but did not find them to be switch specific and consequently reported these activations pooled over switch and repeat trials. Studies contributing to both columns 2 and 5 or 6, reported both a switch>repeat contrast as well as a preparation contrast.

3.2.2 Multi-level Kernel Density Analysis (MKDA)

MKDA is a quantitative meta-analysis technique to analyse 3 dimensional imaging data (for a review see Wager et al., 2007). It aims to identify consistencies within the reported peak activations of a number of imaging studies. As mentioned before the unique feature of MKDA is that it takes into account that reported peaks are not independent, but are nested in contrasts which are reported in studies. This means that the analysis takes into account that some studies report more peaks then others. Also, unlike, for example, the Activation Likelihood Estimate (ALE)(Turkeltaub, et al., 2002) method and a number of imaging papers, the MKDA method compensates for the family-wise error that arises in the meta-analysis.

First, all included peaks are converted into MNI space. The voxels reported as peak activations are replaced by a 10mm sphere of voxels (Eickhoff, et al., 2009; Wager, et al., 2007). Each voxel that is located within at least one sphere is given a value of 1; the remaining voxels are given a value of 0. An activation map, consisting of 0s and 1s is created for each of the included contrasts included. This procedure ensures that activations from the same study, located in close proximity, are not duplicated.

To adjust for differences in the sample size between studies, each reported contrast is weighted by the square root of the sample size used and these maps are then combined into an overall activation map. Each voxel in this map is given a value which represents the number of contrasts that report activations in (or within kernel distance of) that voxel.

To determine which activations in the observed map are greater than would be expected by chance, a Monte Carlo simulation was run. On each iteration, an equal number of peak activations, as found in the observed map, were placed at random distributed locations. For each of the meta-analyses, we ran a Monte Carlo simulation consisting of 15000 iterations. The observed map was then compared with the random activation map to determine which areas show a greater density of reported activations then would be expected based on the random map and we determine the associated probability, thus controlling Type 1 error. A similar analysis can also be used to compare two different conditions. The Monte-Carlo simulation then produces a sampling distribution reflecting the differences in activation between the conditions that would be expected by chance.

The analyses also provided an extent-based measure which identified clusters with a size bigger than expected by chance. This is accomplished by including voxels at an uncorrected level of $p<0.001$ and determining the minimum cluster size at which the likelihood of one such cluster (consisting of this number of adjacent voxels) appearing is less than 5%.

3.2.3 Specific analyses

In order to test which areas were consistently involved in switch-repeat contrasts we ran an overall meta-analysis on the database, consisting of the standard Sw>Rep group. In order to test what areas are involved in cue related activity specifically, we ran the following analyses:

- (1) We ran separate analyses on the standard Sw>Rep group contrasts which had a CSI of more than 250 ms and contrasts that had a CSI of less than 250ms (the difference between these groups should be interpreted with caution, because the possibility remains that differences in consistently activated regions are not due to the ability to prepare, but due to differences in timing of processes during the CSI between regions which could influence their detectability with fMRI). We also specifically tested which areas were more activated in task switching studies with a cue stimulus interval then without (CSI>noCSI).
- (2) We ran a meta-analysis on the Prep contrasts that isolated task-cue related activity and reported differences between switch and repeat trials.
- (3) We ran a meta-analysis on the Prep contrasts that isolated task-cue related activity that did not find greater activations on switch trials than on repeat trials.

In additional analyses to test whether switch-related brain regions might depend on the type of tasks being switched between, we grouped the standard SW>REP group contrasts that used similar tasks. There were three obvious groups among the 18:

- Contrasts from studies using the letter/digit task from Rogers and Monsell (1995): two characters are displayed — a letter and a digit; the task is to classify the letter as consonant versus vowel, or the digit as odd versus even (5 contrasts)

- Contrasts from studies using tasks which requiring attention to one of two dimensions of a visual stimulus, for example judging shape versus colour (5 contrasts)
- Contrasts from studies in which the stimulus was a digit, and the task was to classify the digit as odd/even or high/low (8 contrasts)

3.3 Results

3.3.1 Switch-Repeat

The results of standard Sw>Rep group analysis are shown in Table 3.3 and Figure 3.2. Reliable consistent activations were found in the left IFJ and pre-SMA. The left superior parietal lobe showed considerable significant results at cluster level, but only 2 voxels in this region survived when individually corrected.

Table 3.3 Results of the standard Sw>Rep group

Anatomical Area	MNI x	y	z	Hem	voxels
IFJ	-44	8	34	L	81
MFG/IFG	-50	14	30	L	1
ACC/Pre-SMA	2	12	46	M	35
SPC	-28	-64	46	L	2
Pre-SMA	-2	10	56	L	30

IFG=inferior frontal junction, IFG=inferior frontal gyrus,
MFG=medial frontal gyrus, SPC=superior parietal cortex,
SMA=supplementary motor area, ACC=anterior cingulate cortex,

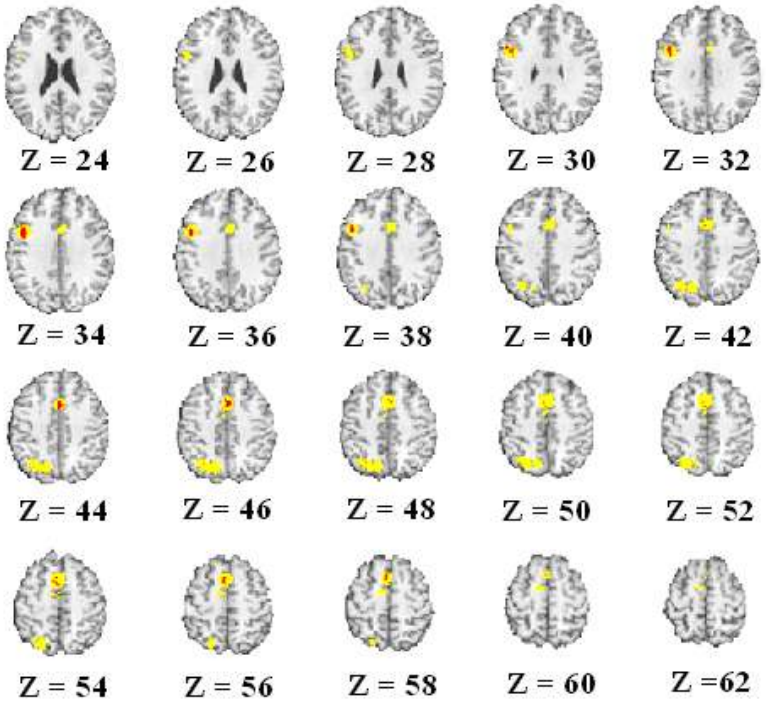


Figure 3.2a Results of the standard Sw>Rep group.
Red = more active than expected by chance ($p<0.05$, FWE cor.)
Yellow = activation extends further than expected by chance

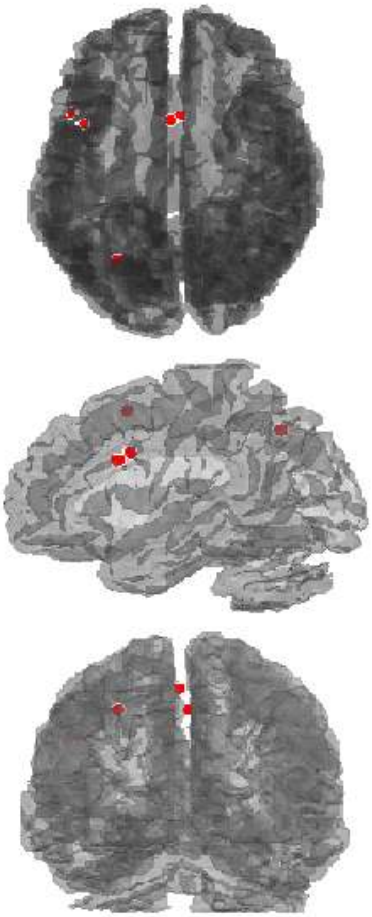


Figure 3.2b Results of the standard Sw>Rep group displayed in transparent brains

We then split up these contrasts into studies with a cue-stimulus interval of more than 250 ms (allowing for preparation) and less then 250 ms. The results of the analyses of both data sets are displayed in Table 3.4 and Figures 3.3-3.5. Studies with a long CSI show consistent activations in the left IFJ. Studies that did not allow for preparation show reliable activations in the ACC. Also a direct contrast between both groups (long CSI> noCSI and noCSI> CSI) shows these differences to be reliable

We also ran separate analyses on the standard S>R group contrasts for three subgroups of studies defined by task. None of these analyses showed reliably greater switch related activity than expected by chance.

Table 3.4 Results of the standard Sw>Rep group, CSI bigger (CSI) or smaller than 250 ms (no CSI).

Anatomical Area	MNI x	y	z	Hem	voxels
CSI					
IFJ	-44	6	36	L	103
	-44	8	34	L	61
	-44	6	38	L	42
noCSI					
ACC/Pre-SMA	2	16	46	M	16

IFJ=Inferior Frontal Junction, ACC=Anterior Cingulate Cortex, pre-SMA=pre- Supplementary Motor Area

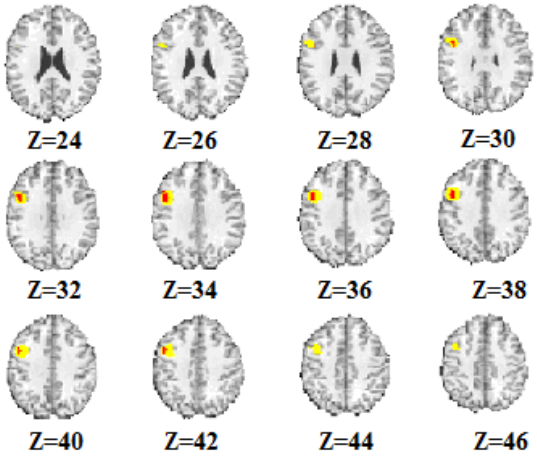


Figure 3.3 Results meta-analysis of the standard Sw>Rep group with a CSI longer than 250 ms

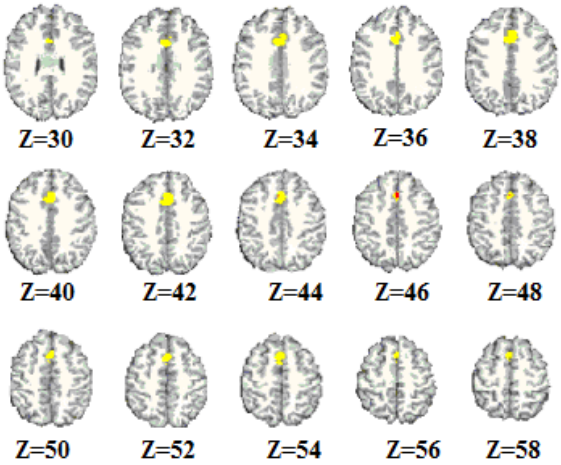
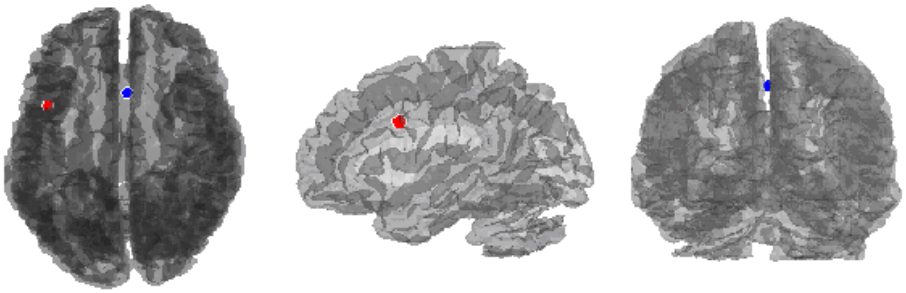


Figure 3.4 Results meta-analysis of the standard Sw>Rep group with a CSI shorter than 250 ms

Figure 3.5 Results of the standard Sw>Rep group displayed in transparent brains.
Red = CSI > 250 ms
Blue = CSI < 250 ms



3.3.2 Preparation

Table 3.5 shows the results from the analysis of studies that attempted to isolate preparatory activations. We analysed contrasts (reported by these studies) showing a reliable switch by preparation interaction and contrasts that found preparatory activations but did not report a reliable preparation by switch interaction (see Table 3.1 and 3.2). The results of the latter

therefore reflect preparatory activations, pooled over switch and repeat trials (thus being likely to reflect preparatory activity not specific to switch trials). Results of both analyses are also shown in Table 3.5, Fig. 3.6, 3.7 and 3.8.

Analysis of the switch related preparatory activity shows the left superior parietal lobule to be consistently more activated during the preparatory interval on switch than on repeat trials. Analysis of the generic preparatory activity shows consistent activations in the IFJ (mainly left, 1 voxel activated in the right IFJ), right SPL, precuneus, pre-SMA and a small activation in the right precentral sulcus.

Table 3.5 Results from the meta-analysis of studies isolating preparatory activations.

Anatomical Area	MNI x	y	z	Hem	voxels
Switch>Repeat					
SPC	-32	-54	46	L	46
Pooled contrasts					
IFJ	44	4	34	R	1
IFJ	-42	2	38	L	53
SPC	34	-54	46	R	107
Precuneus	12	-72	48	R	60
Pre-SMA	-2	8	56	M	34
Precentral Sulcus	38	-4	54	R	3

IFJ=Inferior Frontal Junction, IFG=Inferior Frontal Gyrus, SPL=Superior Parietal Lobule, sLOC=Lateral Occipital Cortex Superior Division, pre-SMA=pre-Supplementary Motor Area

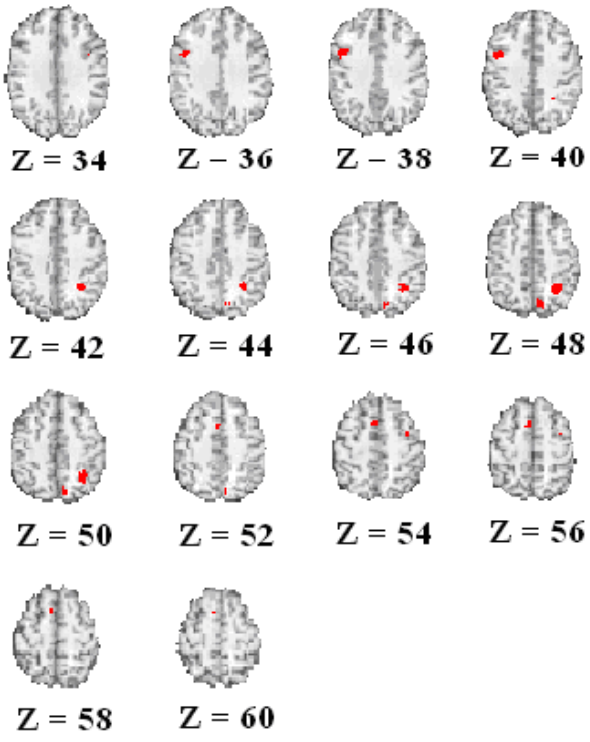


Figure 3.7 Results from the meta-analysis of studies isolating preparatory activations pooled over switch and repeat.

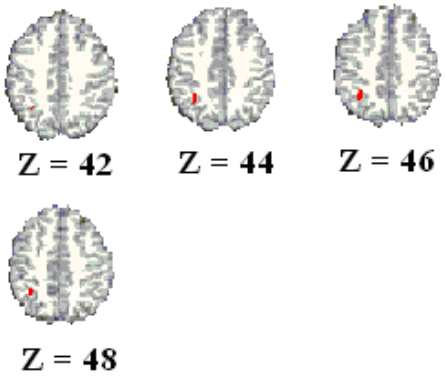


Figure 3.6 Results from the meta-analysis of studies isolating preparatory activations reporting a reliable Switch>Repeat contrast.

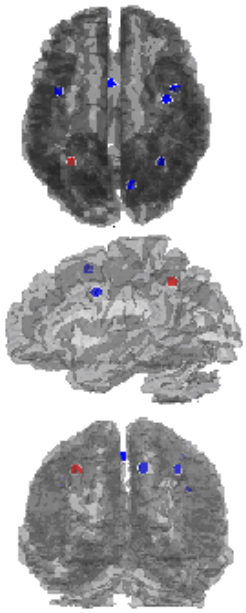


Figure 3.8 Results from the meta-analysis of studies isolating preparatory activations displayed in a transparent brain.
Red = switch specific
Blue = pooled over switch and repeat

3.4 Discussion

3.4.1 The frontal-parietal network

The regions identified as important to task-set control are all part of a complex of frontal and parietal regions that have been identified as involved in a variety of cognitive control paradigms (these include regions in the dorsal and ventral lateral prefrontal cortex (e.g. bilateral IFJ, IFG and middle frontal gyrus) MFC (e.g. preSMA/ACC), SPL and precuneus). The results of our analysis allow us to identify which parts of this network are consistently involved in task switching and/or task-set preparation and which are not.

3.4.2 Standard Sw>Rep group.

When we select switch minus repeat contrasts the results of our MKDA show two consistently activated regions; the MFC and the left IFJ. The analysis did not show more consistent activation in the parietal cortex than can be expected by chance (except for 1 voxel in the left superior parietal lobule), though the majority of studies included did report parietal activations. However, if we apply an extent-based criterion (coupled with uncorrected voxel-wise thresholding) instead, we do see reliable left superior parietal lobule activations. This suggests that the parietal cortex is involved in switching, but the exact location of these activations seem highly variable between studies.

In analyses of three sub-groups of the Sw>Rep group, we attempted to test whether the tasks used to switch between influenced which brain regions are more active during switch trials then during repeat trials and found no consistent results. It is however possible that, because the number of studies in these groups is relatively small and inconsistencies large, we cannot identify such regions at this time.

3.4.3 Switch related preparation

In order to work out which areas are involved in switch related preparation, we employed two strategies. The first was to compare standard Sw>Rep group contrasts between studies with a preparation interval and with studies without (see Table 3.4).We divided the standard Sw>Rep group paradigms into a group in which there was a CSI longer than 250 ms and a group in which the CSI was smaller than 250 ms. In the first group, the

participants would have had the ability to prepare for the upcoming switch, even though studying cue related activity was not the purpose of the studies. When we looked at the activations of both groups, the difference is very distinct. The left IFJ was consistently activated in the group that had the opportunity to prepare, whereas the medial frontal cortex activation was only seen in the group that did not (Table 3.4). This difference survived a direct contrast run between the two groups, showing that it holds up to strict statistical scrutiny. As pointed out before, this contrast needs to be interpreted with caution, because the observed difference could, besides a role in task-set preparation, also reflect a difference in timing of the processes in the left IFJ and the dMFC during the CSI, consequently affecting their detectability.

The second strategy was to analyse the studies looking at cue related activity and reporting the preparation by switch interaction (or some equivalent) (see Table 3.5). Consistent switch related preparatory activations are found in the left superior parietal lobule. The same region showed a greater extent of activations for the standard Sw>Rep group, but there were no greater consistent activations in any particular voxel in this region.

Unlike the CSI>noCSI analysis describe above, our analysis of preparatory contrasts, only showed consistent activations in the left IFJ in the analysis which pooled over switch and repeat trials (see below). These two pieces of evidence put together appear to be in conflict. On the one hand left IFJ was more activated on switch than on repeat trials only in studies with a long CSI. On the other hand, studies specifically intended to isolate cue-related from stimulus-related activity found no consistent switch-specific preparatory activations in the left IFJ.

3.4.4 Non switch-specific preparation

Our analysis of preparation studies which attempted to isolate preparatory activations (for example, by contrasting informative cues with neutral cues) but did not find a reliable difference between preparation on switch trials versus preparation on repeat trials (these studies therefore reported preparatory contrasts pooled over switch minus repeat trials) revealed activations in the right IPL, precuneus, left IFJ and pre-SMA. This analysis shows their involvement in preparation but does not tell us whether processes in these regions relate specifically to task-set control.

3.4.5 Left inferior frontal junction

Our results only partly confirm earlier reports that the left IFJ is an important player in task-set control. The left IFJ is located at the crossing of the inferior precentral sulcus and the inferior frontal sulcus, which places it on the intersection of important language areas, working memory related areas as well as the premotor cortex (Brass et al., 2005). We show that the left IFJ is specifically involved in switch minus repeat contrasts when preparation is possible. Our analysis shows no consistent left IFJ activations when switching without preparation suggesting a specific role in preparatory processes. But the lack of consistent left IFJ activations in studies isolating cue-related activations on switch trials means that whether processes in this region are switch specific, remains an open question.

The left IFJ is often thought be important for updating working memory (Wager & Smith, 2003) which has often been thought to play a vital role in task-set reconfiguration; the activation/suppression task-goals of retrieval of S-R rules could be viewed as a form of procedural working memory (Kieras and Meyer, 2000). Consequently, one potential role of the left IFJ could be one of managing task-rules and/or goals.

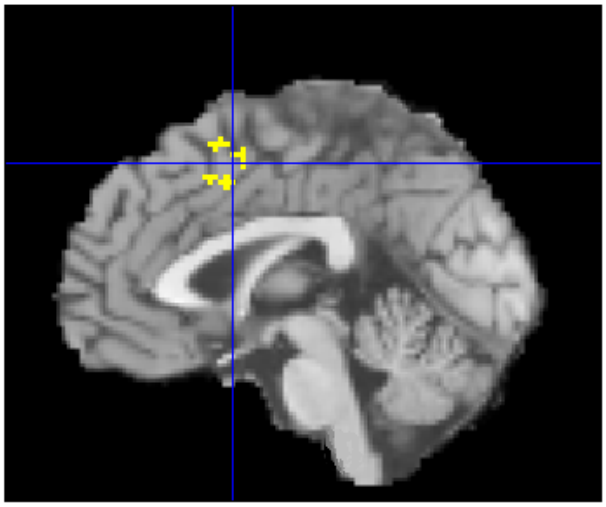
Brass, Derrfuss, Forstmann and von Cramon (2005) suggest that the IFJ integrates signals coming from the premotor, verbal processes and working memory domains when task-set representations are updated. What the precise nature of these task-set representations is, remains somewhat unclear.

Our results do seem to shed some doubt the idea that the updating of task representations is the left IFJ's primary function during task-set control as this would be a requirement regardless of whether participants had time to prepare or not. The fact that left IFJ is consistently activated when there is a longer cue-stimulus interval suggests a somewhat different, related argument: the left IFJ could be particularly active when either the same or a changed task representation need to be maintained over time, but with stronger activation when the task changes. Such a (merely quantitative) amplification of the left IFJ activation by switching might require more statistical power to pick up using the BOLD signal than is available in these studies. Perhaps the active maintenance of the task rules in the left IFJ feeds "lower" more motor and visual attention related preparatory activations which would start adapting to the new task state. This would also be in line with the idea that the left frontal cortex is an important source of higher cognitive control (Miller and Cohen 2001).

3.4.6 Medial frontal cortex

Our analysis suggests that the MFC is important for switching without preparation. It also shows it is involved in preparation, but no consistent differences between switch-related and repeat-related preparation in the MFC were detected by the analysis. Both the ACC and the pre-SMA have both been implicated in task-set control. The location of the consistent activations found by these meta-analyses, seem to be concentrated in the more dorsal pre-SMA (see Figure 3.9) but some border the ACC.

Figure 3.9 Standard Sw>Rep results in the MFC



The pre-SMA has been associated with several processes that could be important for task switching and task-set preparation. The pre-SMA's proximity to the SMA (which in turn connects to the primary motor cortex) as well as strong connections to the DLPFC and inhibitory connections to the Sub-Thalamic Nucleus, has led to the idea that it is important in translating voluntary internal representations into concrete actions as well as mediating response conflicts at motor level (Nachev et al., 2008)

The pre-SMA is thought to be involved in preparing motor activity (Picard and Strick 1996) and more specifically in implementing stimulus-response rules at a higher motor level (Brass and Von Cramon 2002). Nachev et al. (2008) hypothesise that the reason the pre-SMA is active during multiple forms of control is that pre-SMA processes are related to the complexity of the current condition-action associations. They suggest that when a new task context requires a new set of stimulus-action associations, this region would be more active.

Alternatively these medial regions potentially play a role in preventing people from making a wrong response during task switching. Taylor, Nobre and Rushworth (2007) used

TMS and EEG to interrupt normal processing in the left pre-SMA during a flanker task. This interruption caused the motor cortex on the incorrect side to become more active (as measured by the lateralised readiness potential) and increase error rates on incongruent trials requiring a right response, showing that the pre-SMA exerts context specific influence over the motor cortex in situations which induce response conflict. On the basis of the findings of Taylor et al. (2007) one could hypothesise that the pre-SMA maintains the right stimulus-response set (which would reduce response conflict).

Our results support the idea that MFC is important for switching, but there is no evidence that it is specifically important for top-down control of task-set reconfiguration. ERP and TMS data however, do suggest that switch related preparatory activations exist in the medial frontal cortex (Lavric, et al., 2008; Rushworth, et al., 2002). The ERP data show this activation to be very brief. Perhaps this makes it difficult to reliably detect the switch related activations using fMRI. Perhaps the pre-SMA becomes active in the cue-stimulus interval (in both switch and repeat trials) to maintain or reactivate a response and maintain an alert state of the motoric systems in anticipation of action.

3.4.7 Parietal Cortex

Our results show consistent activation in both the left (switch by CSI interaction) and the right (CSI pooled over switch and repeat trials) IPS. The parietal lobe is thought to play an important role in the transition between visual perception and motor action (Rushworth and Taylor 2006). Regions surrounding the IPS have been associated with two processes that could be important for task-set reconfiguration. Updating visual attention and movement adjustment could both potentially benefit the correct execution of a new task. Even though both left and right IPS regions seem to be important for both processes, the right hemisphere seems to be more dominant in redirecting visual attention, whereas the left seems to be more dominant in adjusting motor output (Rushworth, Ellison, et al., 2001).

Within the parietal cortex, our analysis shows no consistent locus of activation in the standard Sw>Rep group. Activations in the parietal cortex are frequently found in switch minus repeat trial contrasts, but they appear to be highly variable in terms of location. One idea would be that the location in the parietal cortex depends on the tasks used to switch between. This would suggest that when we select switch minus repeat

contrasts which used similar tasks, activations in the parietal cortex would become more consistent. Our task-based analyses however do not show any consistent activations, which means that this remains an open question.

The left IPS region is consistently involved in preparing on switch trials and is therefore likely to play an important role in task-set reconfiguration. Meiran et al. (2008) suggests an important role for attentional adjustment towards to correct stimulus feature in task-set reconfiguration, (Meiran, et al., 2008), but it has not been extensively investigated. A potential role for the left IPS in task-set reconfiguration could be to pre-emptively bias visual attention towards the stimulus attribute that is required by the current task set. However, as mentioned before, the visual attentional processes seem to be more lateralised to the right hemisphere.

Another possibility is that the left IPS plays a role in altering stimulus-response relationships. Tunik et al. (2005) applied TMS to this region and found that it disrupted people's ability to adjust grasping movement when the goal changed. Rushworth, Ellison and Walsh (2001) applied TMS to stimulate two regions in the left and right parietal cortex during the response time of a visual orientation task and a motor reorientation task. Stimulation of the right angular gyrus slowed participants when they had to reorient visual attention. Stimulating the left supramarginal gyrus specifically slowed participant's responses when they had to reconfigure a prepared hand configuration.

Consistent right IPS activations are found in our overall preparation analysis and not in the switch minus repeat trials, so on the basis of our results we cannot say anything about whether this preparatory region is switch related or not. Schenkluhn et al. (2008) used TMS to stimulate the same right IPS region we found (as well as two other locations). TMS was applied before stimulus onset in a visual search task where a cue helped participants to find a target, by either revealing its colour or its location. TMS over the location found in our results reduced the cuing benefit for both location and colour (TMS over the supramarginal gyrus reduced the benefit of a location cue specifically). This shows that the right IPS region might also be important for biasing visual attentional processes during the cue-stimulus interval. A more motoric function however, remains possible. For example, Ellison, Rushworth and Walsh (2003) found that stimulating the right IPS with TMS makes it harder to ignore distractors, but this effect goes away when the visual search task is practiced extensively. When they reversed the response rules for target present and target

absent, the negative influence of TMS stimulation of the IPS on visual search was reinstated. This suggests that the IPS could be important when remapping the relationship between visual stimuli and manual responses. Whether the left IPS's role in task-set reconfiguration is one of visuo-motor transformations or one of biasing visual attention remains open.

Our results show consistent preparatory activations in the precuneus, but these activations are not bigger on switch trials then on repeat trials. Chiu and Yantis (2009) found the precuneus to be commonly activated during shifting spatial attention and switching stimulus-response rules. Further study of the nature of precuneus processes during task-set reconfiguration should shed further light on this.

3.4.8 The right frontal cortex

One interesting conclusion we can take from these results is that, both in switching and preparation for switching we find no consistent right frontal cortex activations. When preparation is pooled over switch and repeat trials we find small activations in the right IFJ and precentral culcus. The right frontal cortex, especially right IFJ and right IFG are often linked to processes of response inhibition, a mental operation which is often considered to be a vital part of cognitive control (Aron 2007). Our data however provide no evidence that, at least the inhibitory processes potentially located in the right IFJ and right IFG are a major component of task-set reconfigurations. The pre-SMA has also been implicated in inhibition, but the results have been inconsistent and some TMS studies for example, have failed to confirm this (Verbruggen, et al., 2010).

3.4.9 The same, just earlier?

It has been an open question whether there are qualitative differences between the processes required to change task with and without preparation. This is difficult to determine using behavioural data. ERP data suggest that the switch-related preparatory posterior positivity found during the CSI, "moves" to the post-stimulus phase in the paradigm, when the CSI is too short to prepare (Karayanidis, et al., 2003; Lavric, et al., 2008), i.e. that the same reconfiguration process occurs before or after the stimulus, depending on the time available to prepare. The results of my meta-analysis, however,

suggest a somewhat different possibility. Differences in activations between task switching studies with and without the ability to prepare suggest that, in neural terms at least, qualitatively different processes may be at work during preparation for a task switch than when switching without preparation.

Using correlational methods limits what we can conclude. One possibility would be that for example the left IFJ is active during switching without preparation, but for a shorter duration, making it more difficult to detect. Hence similar processes would be at work, but for different amounts of time. It is perhaps reasonable to say that the results from the meta-analysis are a clear indication that differences exist, but it is premature to say anything specific about the nature of these differences.

3.4.10 Earlier meta analyses

The results from our meta-analysis seem to disagree with the findings from Wager et al.'s (2004). Wager et al.'s analysis was based on a smaller set of task-switching studies and did not focus on preparatory processes. When we compare our results of the switch minus repeat contrasts several differences emerge. Unlike Wager et al. we do find reliable activations in the left IFJ. They found strong activations in the bilateral anterior insula, which we do not. Also, the results of our standard Sw>Rep group analysis concerning parietal cortex seems to suggest a large spatial variability and unlike Wager et al. we do not find large consistent activations in the right parietal cortex nor do we see many right frontal activations. Our results suggest that the left hemispheric activations in the parietal cortex found by Wager et al. are especially important for altering task-set.

Our results only partially substantiate the findings of Derrfuss et al. Our finding that switching studies with a long-CSI are associated with more activations in the left IFJ seems to support their claim that the left IFJ is essential for task-set control. Our analysis of studies isolating preparation relation activation suggest that the left IFJ is involved in preparatory processes, but we find no evidence that this is specific to task-set reconfiguration.

These differences could be caused by the heterogeneity of paradigms in earlier meta-analyses and show it is important to study consistent differences between contrasts that are thought to reflect similar processes.

3.4.11 Conclusion

Our meta-analyses have been able to identify regions which we can be confident are consistently activated during task-switching experiments. We identified regions implicated in pro-active task-set control, regions important for switching without preparation and a number of regions of which further study should determine whether they contribute to pro-active task-set control or play a more generic preparatory role.

It is of course important to keep in mind that during the execution of a task-switching paradigm, large parts of the brain are involved because they host task-specific mental operations, and activation of these may contribute to switch costs -- e.g. via task-set inertia (Yeung, et al., 2006). These task-specific activations, which for the most part, get filtered out in our analysis, potentially play an important role in the dynamics of specific control situations.

Our results, combined with a growing knowledge of the functionality of regions identified here as being involved in task-set reconfiguration, increasingly support the idea that task-set reconfiguration is a distributed process comprising several sub-processes. Further research focusing on the precise nature of the switch-related preparatory activity in these regions as well as the temporal dynamics of these processes, will further increase our understanding of which processes contribute to task-set reconfiguration and how their contributions and the dynamics of their interaction depend on the task conditions.

Chapter 4: The role of dorsal medial frontal cortex

4.1 General introduction

In this chapter, I will describe two experiments aimed initially at investigating whether the pre-SMA (a region in the dorso-medial frontal cortex) is necessary for task-set control, but — as it turned out — also implicating SMA. The experiments also investigate the more specific issue of whether the dMFC plays an important role in pro-active control of response conflict during task-switching.

As described in both Chapter 1 and 3, published imaging studies investigating neural correlates of task-switching as well as patient studies have often found that the dorsal medial frontal cortex is active when participants perform paradigms requiring task-set control (Shallice, et al., 2008; Brass & von Cramon, 2004; Chiu & Yantis, 2009; Forstmann, Brass, Koch, & von Cramon, 2005; Liston, et al., 2006; Luks, et al., 2002; Madden, et al., 2010; Smith, Taylor, Brammer, & Rubia, 2004; Sohn & Anderson, 2001; Sohn & Carlson, 2000).

The results from my meta-analysis, discussed in Chapter 3, showed consistent MFC activations for switching and in particular for switching without preparation (see Chapter 3, Table 3.4). Studies specifically isolating preparatory activations also found consistent medial frontal activations, but in those studies there was little evidence to support the idea that this was specific for switch trials (see Chapter 3, Table 3.5).

In Chapter 1 and 3 I reviewed existing literature on the potential contribution of the medial frontal cortex during task-switching. Several functions have been suggested for the medial frontal cortex which could contribute to the RISC effect, including higher motor function, possibly the inhibition of irrelevant responses (Nachev, et al., 2008; Taylor, et al., 2007; Yeung, et al., 2006) or the reconfiguration of stimulus-response mappings in accordance with internal goals (Nachev, et al., 2008; Rushworth, et al., 2002).

Besides the study done by Rushworth et al. (2002) which studied the role of the dMFC in response-set shifting, no TMS experiments so far have studied whether the dMFC is necessary for task-set preparation per se. In Experiment 1 I tested whether two locations in the medial frontal cortex were important for task-set preparation, namely the pre-SMA and the SMA. On the basis of Rushworth et al.'s (2002) finding that the pre-SMA is

essential during pro-active control of switching between response sets, I hypothesised that the pre-SMA could be important during the cue-stimulus interval of a task-switching paradigm as well. That they found no such effect when stimulating the SMA suggested that this region in the dMFC might not be involved in preparation of S-R rules per se, but it could be involved in other aspects of task-set.

In Chapter 1, I described how response-incongruent stimuli in task-switching experiments take longer to respond to than congruent stimuli and how these incongruence costs, signifying conflict between the appropriate response and that afforded by the other task, often (but not always) reduce when given time to prepare. This effect allows one to test whether anterior and/or posterior regions of the dMFC are also involved in pro-active overcoming of response interference, by seeing whether stimulation during the CSI disrupts the reduction in the congruence effect achieved by preparation.

4.2 Experiment 1

In the first Experiment I stimulated during the cue-stimulus interval of a cued task-switching paradigm to study whether stimulating the pre-SMA or SMA (the latter initially chosen as a control site, following Rushworth et al., 2002) would negatively affect the ability to prepare for a switch trial. The timing of stimulation was based on Lavric et al.'s (2008) electrophysiological study of task-set preparation using the same tasks and similar stimuli. Participants were verbally cued to identify the shape or colour of a coloured shape as one of four values, with the same set of four responses used for both tasks.

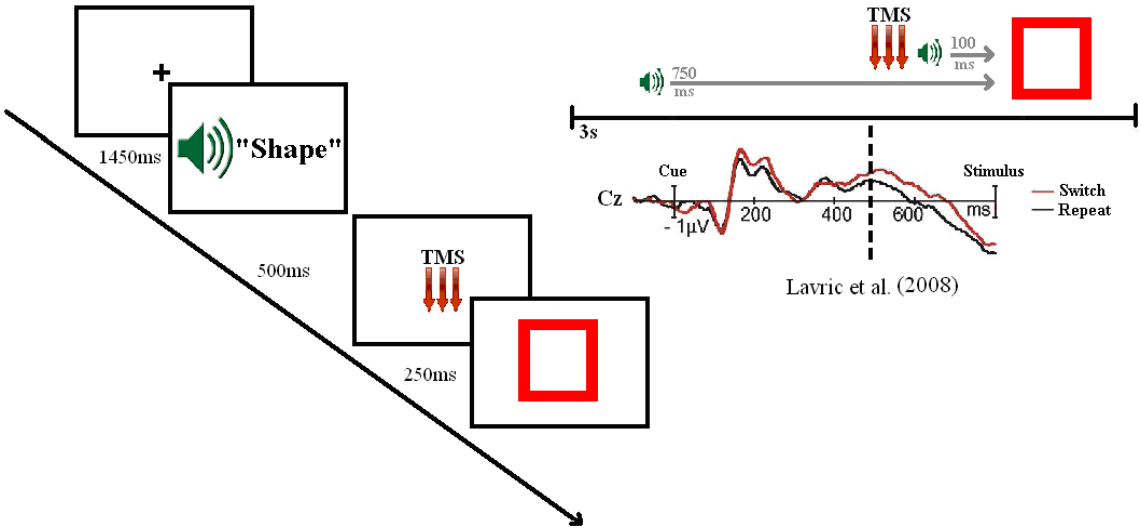
4.2.1 Participants

16 healthy participants, for whom structural MR scans had been obtained, took part in Experiment 1 (mean age 22, 9 male). All participants passed the safety screening and gave informed consent as approved by the ethics committee of the Exeter University School of Psychology. One participant was excluded and replaced because of experienced discomfort.

4.2.2 Procedure

Participants were tested sitting with their face in a chin and head rest, eyes 75 cm from the screen of a LaCie Electron Blue 19" CRT refreshing at 100 Hz, their left and right middle and index fingers resting on the “z”, "x", "n" and “m” keys of a standard PC keyboard.

Figure 4.1 Paradigm used in Experiment 1.



Left: an example of a trial in the long CSI condition. The fixation cross remained on the screen until stimulus onset. The auditory cue was presented 750ms before stimulus onset. Right: TMS time: The 100ms TMS train (3 pulses at 20Hz) starts 250ms before stimulus onset in bothCSI conditions. Consequently, in the short CSI condition the TMS starts 150ms before cue onset.

I used a task-cueing paradigm in which the stimulus was a coloured shape, and the tasks were to identify either its colour (as "red", "green", "blue" or "yellow") or its shape (as "circle", "triangle", "square" or "pentagon") with a key press (see Figure 4.1). The

stimulus came from a set of 16 comprising each combination of 4 shapes and 4 colours. The four colours and four shapes were mapped onto the same four response keys. At the beginning of each trial, there was a fixation cross, lasting either 1450 ms (before a long CSI trial) or 1950 ms (before a short CSI trial). This was followed by an auditory cue word ("colour", "paint", "shape", or "form") which indicated the current task (e.g., which stimulus attribute to respond to). The cue words were recorded in a male voice (native English speaker) with a duration of 250 ms and presented on stereo speakers either side of the monitor. I used two cues per task to avoid immediate repetition of cues and any confound between cue repetition and task-repetition. Cue repetition has been shown to lead to facilitation of performance over and above any effect of task repetition (Logan & Bundesen, 2003); the avoidance of cue repetition is an efficient way of dealing with this problem (Monsell & Mizon, 2006).

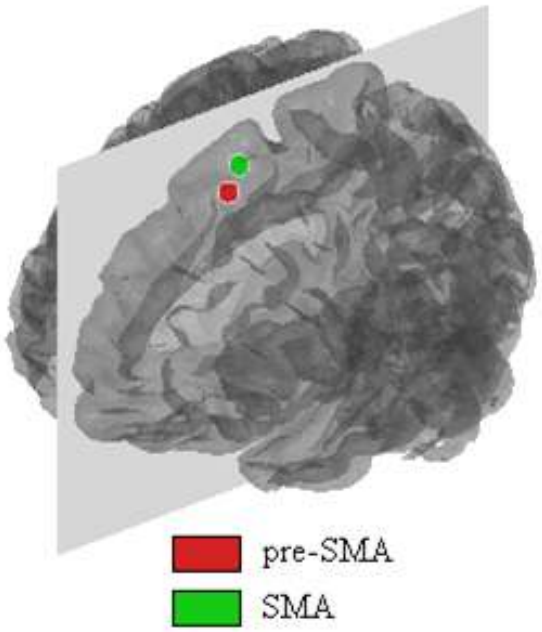
After a CSI of either 100 ms or 750 ms (following cue onset), a stimulus was presented (in the centre of the screen) until one of the four keys was pressed. If the wrong response was given, an image indicating the correct response appeared for 2s. Otherwise, the interval from response to the next stimulus was 2.3 seconds. All stimuli presented afforded both tasks: each stimulus was presented equally often so that a quarter of the stimuli were mapped to the same response for both tasks (congruent) and three quarters to different responses depending on the task (incongruent).

The experiment was run in two sessions on separate days. The sessions were identical except that before the start of session 1, TMS screening and calibration was done and participants received 5 training blocks. The first two blocks were single task blocks of 32 trials (CSI 500 ms) to practice the response mappings for each task and familiarise the participants with the cues. The next two blocks mixed the two tasks as in the experimental blocks (one short CSI and one long CSI). And the final practice block was a mixed task block with a long CSI and TMS (3 pulses at 20Hz) was applied during the CSI to habituate participants to the stimulation.

4.2.3 Design

CSI and TMS condition were manipulated between blocks, with 24 experimental blocks (12 per session) each of 48 trials (following a start-up trial), 4 blocks for each combination of TMS condition (pre-SMA, SMA and a flipped coil condition) and CSI (short/long). The order of blocks was counterbalanced as follows: In each half session of six blocks, CSI changed every block and TMS condition changed every 2 blocks. The sequence reversed in the second half of the session. Both TMS and CSI condition sequences were counterbalanced between participants, so that each sequence appeared equally often in each part of the paradigm. New pseudo-random trial sequences were generated for each participant so that each pair of blocks of the same kind contained 1/3 task-switch trials and 2/3 task repeat trials each, 1/4 congruent trials and ¾ incongruent trials (as a consequence of the nature of the stimuli) as well as an equal number of combinations of task, and response, and so that stimuli occurred equally often in each combination. Immediate stimulus repetitions were allowed.

Figure 4.2 TMS targets in Experiments 1 and 2.

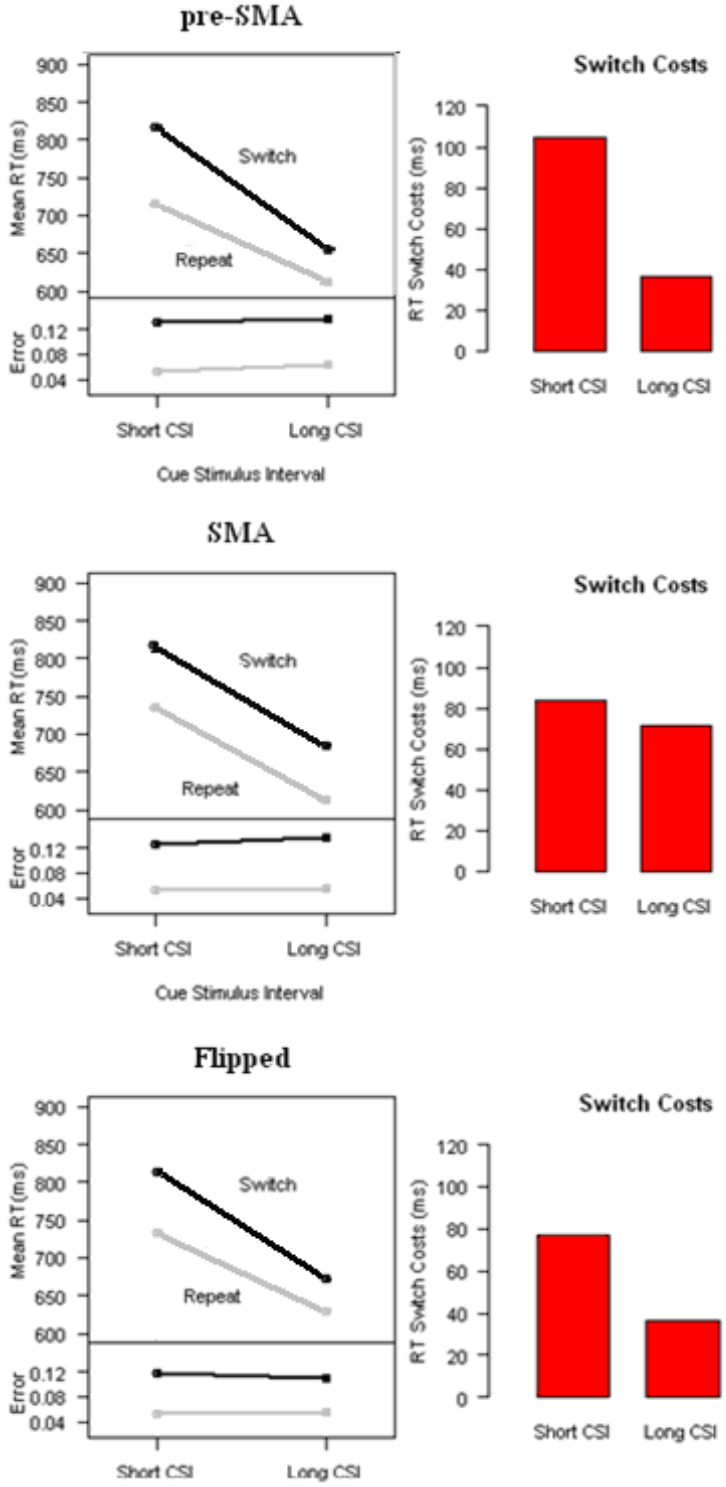


4.2.4 TMS

A Magstim Rapid 2 Stimulator (Magstim, Whitland, Wales, UK) and a Magstim 70mm figure-of-8 coil was used to apply stimulation in a train of 3 pulses at 20Hz at 110% of visible motor threshold, as determined at the beginning of the session (an average intensity of 54% of maximum output). The stimulation was applied 250 -150 ms before stimulus onset, and hence 500-600 ms after cue onset in the long CSI condition, and immediately prior to cue onset in the short-CSI condition (see Figure 4.1).

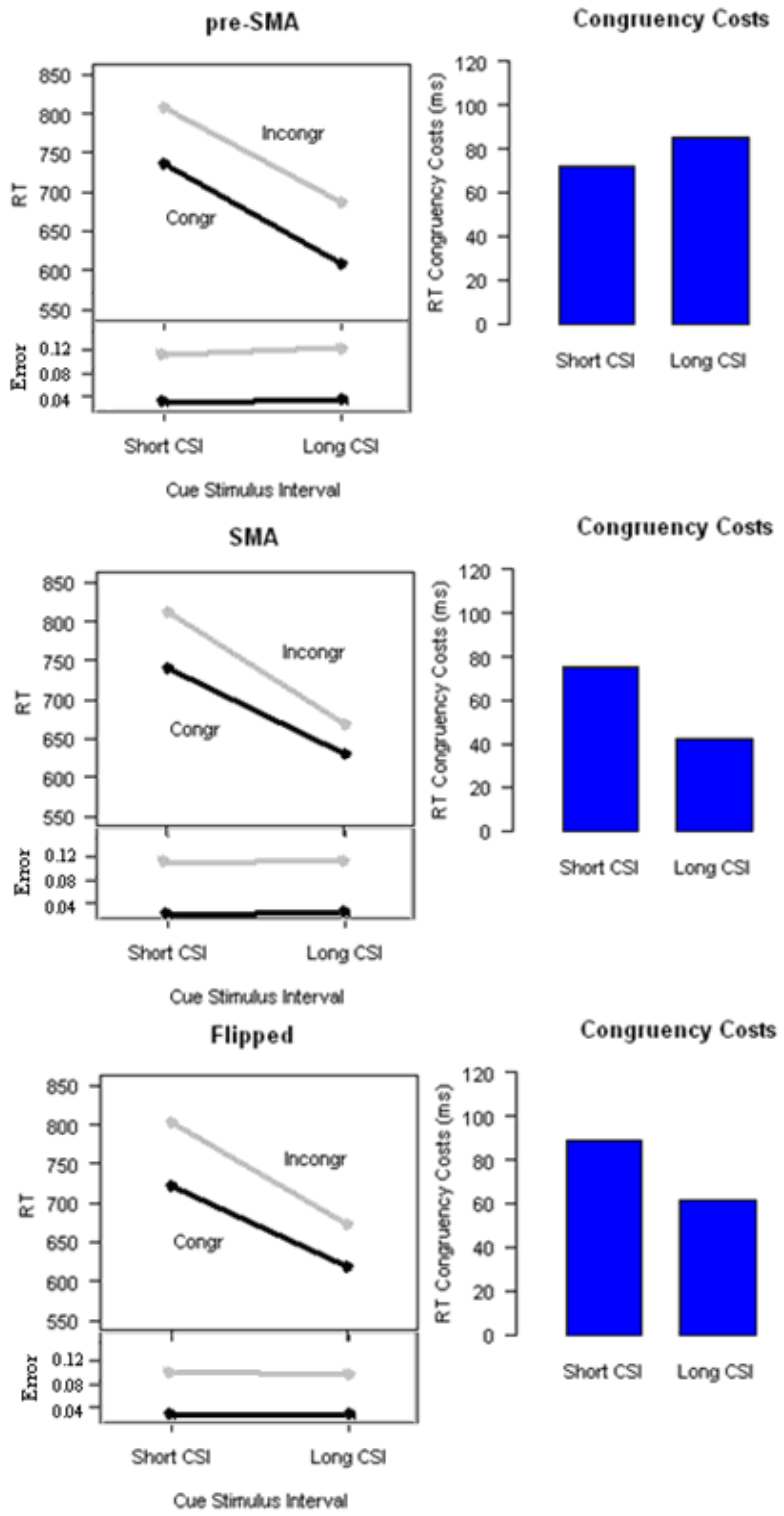
In one third of the blocks I stimulated over left pre-SMA (MNI -10, 9, 53) and in one third the left SMA (MNI -8, 3, 60) — see Figure 4.2. The SMA site was selected because I thought it was unlikely to be involved in task-set control and it matched the pre-SMA site well in terms of the intensity of scalp sensations and auditory click burst resulting from the TMS pulse train. In the other third of the blocks, the coil was turned upside down and placed in between the SMA and pre-SMA targets. When the coil is upside down the effective field induced under the scalp is reduced, resulting for example in higher motor thresholds. In this condition the effective stimulation is lower than in the other conditions and potentially below the threshold in that region. This could potentially act as a useful control, since appropriate control sites can be difficult to select when studying cognitive control in frontal regions using TMS. Over the target sites and in the flipped condition, the coil was positioned with the handle to the rear, using the BrainSight stereotaxic targeting system, relative to an MR image acquired for each participant using a 1.5 Tesla Philips Gyroscan Intera.

Figure 4.3 Switch related results of Experiment 1



Left: Mean RTs and error rates for switch and repeat trials as a function of CSI.
Right: Switch costs

Figure 4.4 Congruence results of Experiment 1.



Left: Mean RTs and error rates for congruent and incongruent trials as a function of CSI.
Right: Incongruency costs

4.2.5 Results

Excluding trials following errors, and the first trial of each block, I computed mean correct RT and error rate for each combination of TMS condition, task switch/repeat, congruence and task, averaged over response, and submitted them to ANOVA.

Figure 4.3 shows the mean reaction times and error rates for switch and repeat trials (left panels) and switch costs (right panels) as a function of CSI for the three TMS conditions. Because some participants could tell the difference between the flipped condition and the real TMS conditions, its appropriateness as a control condition may be compromised. For this reason I will focus on comparing the results between the two "real" TMS conditions. There were reliable main effects of CSI, switch and congruence for reaction times [5](the main effects of switch and congruence were also reliable for error rates). Contrary to our expectation (based on Rushworth et al., 2002), when the pre-SMA was stimulated, a substantial reduction in switch cost with increasing CSI was seen (from 109 ms to 34 ms), $F(1, 15)=6.37$, $p=0.023$. (The flipped-coil condition also showed a substantial reduction in switch cost for RT — from 75 to 36 ms — and it was reliable, $F(1, 15)=5.55$, $p=0.033$.) But when SMA was stimulated, this reduction was almost eliminated (the switch cost reduced only from 85 to 73 ms with increasing CSI). The location (SMA, pre-SMA) by switch by CSI interaction was reliable for RT, $F(1, 15) =4.64$, $p=0.048$. For error rates, the interaction was not reliable, $F(1, 15)=2.92$, $p=0.108$, but it was consistent with the RT interaction. The location by CSI by switch interaction including all three TMS conditions was not reliable for reaction times $F(1, 15) =2.46$, $p=0.107$ nor for error rates, $F(1, 15)=.50$, $p=0.611$, because of a larger variability in flipped coil condition. Error rates showed no RISC effect in any location ($F<2$ for all TMS conditions).The impact of TMS applied to the SMA on RT was, moreover, primarily seen on the long-CSI switch trials (32 ms slower than in the pre-SMA condition). RTs on repeat trials in the long CSI condition were slightly faster (by 7 ms).

Figure 4.4 shows mean reaction times for congruent and incongruent trials and incongruence costs as a function of CSI for the three TMS conditions. When the SMA was

[5] The main effects of CSI, switch and congruence were reliable for reaction times in all my experiments (and most were reliable for error rates as well). I will mention these effects briefly in each results section, the Degrees of Freedom, F-values and p-values can be found in the ANOVA source tables in the Appendix. An overview of the appendices is given on page 225.

stimulated preparation reduced incongruence costs from 72 ms to 39 ms, $F(1, 15)=8.67$, $p=0.010$. (And the flipped condition incongruence cost also reduced from 85 ms to 61 ms $F(1, 15)=3.94$, $p=0.066$). But when the pre-SMA was stimulated, this reduction was fully abolished (the incongruence cost actually increasing from 75 ms to 82 ms), The location (SMA/pre-SMA) by CSI by congruency interaction was reliable $F(1, 15)=8.36$, $p=0.011$. There was no detectable equivalent interaction in the error rates, $F(1, 15)=0.17$, $p=0.683$. The location by CSI by congruency interaction for all three locations was also reliable for RT, $F(1, 15)=5.14$, $p=0.012$, but not for the error rates $F(1, 15)=.29$, $p=0.769$. The error rates showed no reduction in congruence effect for all three locations ($F<2$ for all three locations). The negative effect of TMS over the pre-SMA on RT was, in part due to slower long-CSI incongruent trials (11 ms slower than in the SMA condition) and in part due to faster RTs on repeat trials in the long CSI condition (by 35 ms).

There was a reliable effect of task on RT, $F(1, 15)=21.24$, $p<0.001$ and error rates $F(1, 15)=6.84$, $p=0.019$, with the colour task being harder than the shape task. Task showed reliable interactions with both switch $F(1, 15)=7.77$, $p=0.014$, not reliable in the error rates $F(1, 15)=1.30$, $p=0.271$ and congruence $F(1, 15)=7.40$, $p=0.016$, also significant in the error rates $F(1, 15)=7.14$, $p=0.017$. The switch cost (shape task=51 ms, colour task=86 ms) and the congruence effect (shape task=54 ms, colour task=87 ms) were both bigger in the harder task. The effects in the error rates were in the same direction (switch costs: shape task=0.041, colour task=0.055, congruence effect: shape task=0.064, colour task=0.12). These effects were present in all three TMS conditions ($F<1$ for reaction times in the location by task, location by switch by task and location by congruency by task interactions. None of these interactions was reliable for error rates, see (Appendix A)

4.2.6 Discussion

Based on previous research, I expected TMS during preparation to disrupt task-set preparation when it was applied to pre-SMA, but not when it was applied to SMA. What I observed was both different from, and more complex than, this prediction. A “normal” reduction in switch costs was seen with stimulation of pre-SMA (and in the flipped coil condition) but it was essentially abolished by stimulation of SMA. However, a different

index of task-set preparation, the reduction in the incongruence cost with preparation, showed the opposite pattern: the "normal" (or at least common) reduction was seen when SMA was stimulated (and in the flipped-coil condition), but abolished by stimulation of pre-SMA. This constitutes a *prima facie* double dissociation of cortical regions responsible for (a) some component of proactive reconfiguration of task-set that reduces switch costs and (b) proactive suppression of response-level interference from the irrelevant task-set that reduces the congruence effect.

Because the remapping of S-R rules is thought to be an important part of reconfiguring task set (see Section 1.5), the finding that pre-SMA stimulation during the preparation interval did not impair performance on switch trials, would seem to be at odds with the results of Rushworth et al.'s (2002). They found that preparation for a reversal of S-R rules was substantially impaired by TMS to the pre-SMA. Reversing a 2-choice S-R mapping (while participant continue to perform the same perceptual discrimination), as in Rushworth et al.'s experiment, is certainly different from switching between both perceptual dimensions and two 4-choice S-R mappings, as in the present study. The latter would seem more complex but both would appear to share the requirement to remap stimuli to responses.

One of the more interesting implications of the results of this study is that the reduction in switch costs with preparation, and the reduction in congruence effects with preparation, might, at least in this situation, depend on separate processes. One might assume that a better establishment of the changed task-set would mean that the stimulus-response mappings belonging to the current task context are stronger and the irrelevant S-R mapping has less impact on response selection when the stimulus occurs. However, the literature suggests that a reduction in congruence effects sometimes does (Goschke, 2000) and sometimes does not (Meiran, et al., 2000; Rogers & Monsell, 1995) accompany a reduction in congruence effects, so this dissociation is not without precedent.

One possible implication of the discrepancy between my results and those of Rushworth et al. (2002) would be that switching response sets is not an essential part of task-set reconfiguration. However there are several other possibilities. For example, the temporal and spatial properties of the preparatory processes related to response set switching paradigms could be dissimilar to processes related to switching response set

during task- switching (e.g. the fact that each set of S-R mappings is linked to a different perceptual discrimination could result in a different organisation of brain processes). Other differences between the paradigms could also be important. For example, Rushworth et al. (2002) used a paradigm in which participants switched between two sets of two responses whereas our paradigm utilised four responses.

The fact that stimulation of the pre-SMA reduced the preparation benefit for trials which are high in response conflict suggests a potential role in the regulation of this response conflict. This would be in conjunction with the findings of Taylor et al. (2007). However, Taylor et al., similarly to other studies in response conflict, stimulated during stimulus presentation. The results from Experiment 1 suggest that this overcoming of conflict in the pre-SMA could potentially be performed pro-actively. Conflict resolving functions during the CSI cannot, however, rely on repressing a particular response, because until the stimulus arrives, it is unclear which response to suppress. A preparatory form of response inhibition therefore, would require the inhibition of a set of stimulus-response relationships instead.

Perhaps the role of the pre-SMA during preparation is one of top-down control in anticipation of conflict (e.g. by increasing the activation of the correct stimulus-response mappings and/or inhibition the irrelevant mappings). This could fit our results as well as the findings of Rushworth et al. (2002). The requirement to switch response rules within one task, created associations between each stimuli and both possible responses. During stimulus presentation the incorrect response is retrieved and the execution of this response needs to be prevented. This might be extra difficult on switch trials in which the incorrect mapping is most active. A cue indicating that one needs to switch response mappings can be indicative for upcoming response conflict and might trigger a monitoring system. In my experiment, three out of four trials are incongruent and therefore cause response conflict. Consequently, the task cue could be a relatively good indicator for such conflict and provide information as to which response mappings are going to be irrelevant. Such a role would also fit the pro-active nature of these processes; after potential conflict is detected, the necessary processes related to proactive control of conflict could be made active in anticipation. Following this logic, the information content of the cue should be a requirement for this system to impose control. Otherwise, preparation for incongruency

should depend on the response stimulus interval instead of CSI (because just the arrival of a new trial would act as an indicator of potential conflict and the more time between trials, the more time to deal with it). Since the alternative mappings are the most active on switch trials, analogue to the response set-switching task, more conflict control might be required on switch trials.

Figure 4.5 Reaction times for the CSI by congruence interaction for switch and repeat trials when stimulating pre-SMA and SMA.

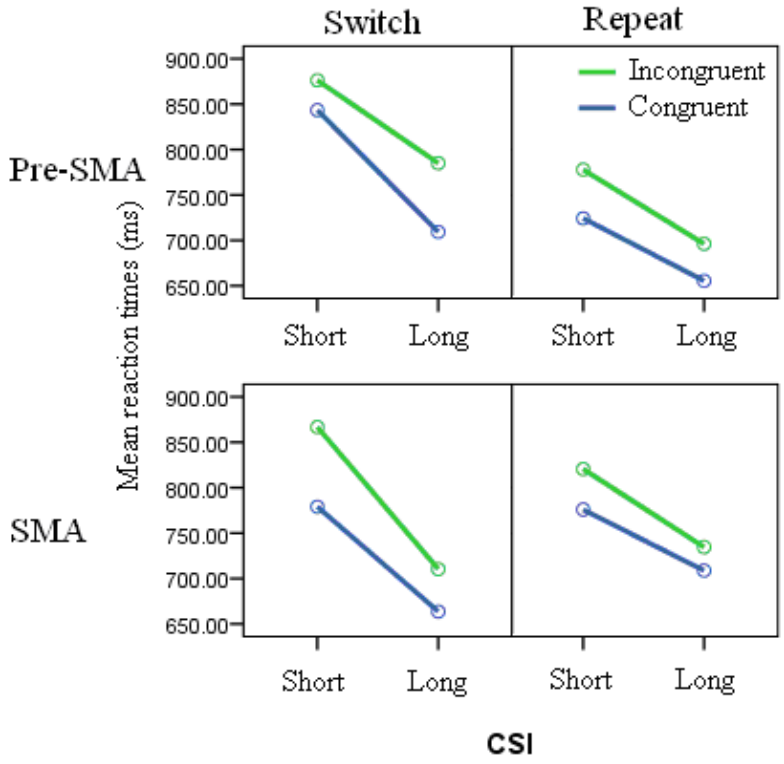


Table 4.1 Error rates for the CSI by congruence interaction for switch and repeat trials when stimulating pre-SMA and SMA.

Pre-SMA		Short CSI	Long CSI
Switch	Incongruent	0.172	0.169
	Congruent	0.015	0.041
Repeat	Incongruent	0.060	0.081
	Congruent	0.025	0.022
SMA			
Switch	Incongruent	0.158	0.164
	Congruent	0.023	0.040
Repeat	Incongruent	0.067	0.073
	Congruent	0.017	0.018

If such a proactive control system is more important on switch trials then this would suggest that the stimulation effect on the reduction in incongruency by preparation is driven

by the incongruent switch trials. The location (SMA/pre-SMA) by CSI by switch by congruency interaction was not significant $F(1, 15)=2.479$, $p=0.136$, nor for error rates, $F(1, 15)=.952$, $p=0.345$. But the mean reaction times do suggest such an effect (see Figure 4.5 and Table 4.1). The CSI by incongruency interaction is reversed on switch trials when stimulating pre-SMA. The error rates show a small reduction in congruency effect in 3 out of four conditions except repeat trials in the pre-SMA condition In this last condition there is a small increase in incongruency cost with increasing CSI. This contradicts the reaction time data, but error rates on repeat trials are very low (See Table 4.1) and therefore potentially a more volatile measure.

Our finding that stimulation of the more posterior region of the dMFC, the SMA, reduces the preparatory benefit for switch trials and therefore attenuating the RISC effect, is surprising and raises the question what task-parameter might be being modulated in that region and why it apparently does not have a role in overcoming conflict between the current and previously activated task-sets.

One possible task-set parameter is the modulation of higher order motor actions; a set of potential movements. The SMA is thought to be important in control of motor actions that are internally initiated; it has been shown to be active just before a hand movement and it is thought to be important for learning action sequences (Siebner et al., 1998, Nachev et al., 2008). It seems therefore plausible that the SMA plays a role in preparing the possible responses in response to an internally driven top-down signal to alter task-set. Since, in my experiments, the possible movements are the same in both tasks, the TMS effect in Experiment 1 suggests that these possible movements are prepared in relation to a particular stimulus. However, if this is the case, it remains unclear why TMS over the SMA did not affect the preparatory benefit for incongruent trials, since a successful preparation the right stimulus-response mappings is likely to reduce response conflict on stimulus onset.

4.3 Experiment 2

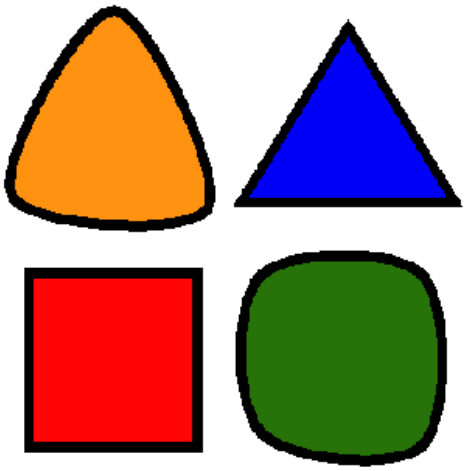
In Experiment 2 I aimed to replicate the results obtained in Experiment 1, using a somewhat different paradigm, adapted to improve the power of the experiment for studying

effects of congruence, and to be more like many of the binary classification experiments in the literature. Although Experiment 1 obtained response congruence effects, its main purpose was to study the RISC effect. To maximise this effect (following Monsell and Mizon, 2006) I chose a switch probability of 33%. In addition, the use of an identification task with four alternatives (e.g. four colours and four shapes) meant that congruent stimuli only appeared in 25% of trials. Hence there were relatively few trials in the switch-congruent cells. In Experiment 2 I used binary colour and shape classification tasks, and, to equate the amount of data per cell, used an equal number of congruent and incongruent trials and changed the probability of a task-switch to 0.5. While these changes risked reducing the measured RISC effect, and possibly reduced the motivation for anticipatory defence against conflict (as the proportion of congruent stimuli was now 50%), this is in fact more typical of task-cuing experiments in the literature. An additional advantage is the similarity to Rushworth et al. (2002) in terms of the number of responses, though the present study still differs in the requirement to switch perceptual dimensions.

4.3.1 Participants

16 healthy participants took part in Experiment 2 (mean age 23, 7 were male). All participants passed the safety screening and gave informed consent in accordance with the ethics committee of the Exeter University School of Psychology. Four participants were excluded and replaced because of technical problems during testing (e.g. discomfort and head movements).

Figure 4.6 Examples of the stimuli used in Experiment 2



4.3.2 Procedure

The experiment was conducted using the same laboratory setup as was used in Experiment 1.The stimulus was a coloured shape, and the tasks were to classify either its colour (as "warm"/"cold") or its shape (as having or not having curved edges) with a left or right key press (using the either the left or the right index finger). The stimulus (see Figure 4.6 for

examples) came from a set of 36 — the possible combinations of 6 shapes (3 with curved edges and 3 with straight edges) and 6 colours (3 warm colours — red, yellow and orange, and 3 cold colours — dark blue, azure and light green)[6].

At the beginning of each trial, there was a fixation cross, lasting either 1450 ms (before a long CSI trial) or 1950 ms (before a short CSI trial). This was followed by an auditory cue word ("colour", "paint", "shape", or "form") which indicated the current task (e.g., which stimulus attribute to respond to). After a CSI of either 100 ms or 750 ms, a stimulus was presented (in the centre of the screen) until a response was made with left or right hand. If the wrong response was given, an image depicting a keyboard and an arrow pointing at the right response appeared for 2 s. Otherwise, the interval from response to the next stimulus was 2.3 seconds. All stimuli presented afforded both tasks: half of the stimuli were mapped to the same response for both tasks (congruent) and half to different responses depending on the task (incongruent).

4.3.3 Design

There were two CSIs, three TMS conditions (pre-SMA, SMA and flipped-coil), just as in Experiment 1, and their combinations were tested in 24 blocks spread over two sessions. In each half session of six blocks, CSI changed every block and TMS condition changed every 2 blocks. The sequence reversed in the second half-session. Both TMS, response mappings (see below) and CSI condition sequences were counterbalanced between participants, so that each sequence appeared equally often in each part of the paradigm

Each block contained 36 trials (following the warm up trial) at the beginning. New pseudo-random trial sequences were generated for each participant so that each pair of blocks of the same kind contained half task-switch trials and half task repeat trials each and an equal number of combinations of task, congruence, and response, and so that stimuli occurred equally often in each combination. The response mappings were counterbalanced between participants so that each stimulus served equally often as congruent and incongruent: in half of the participants the right button was mapped on warm colours and

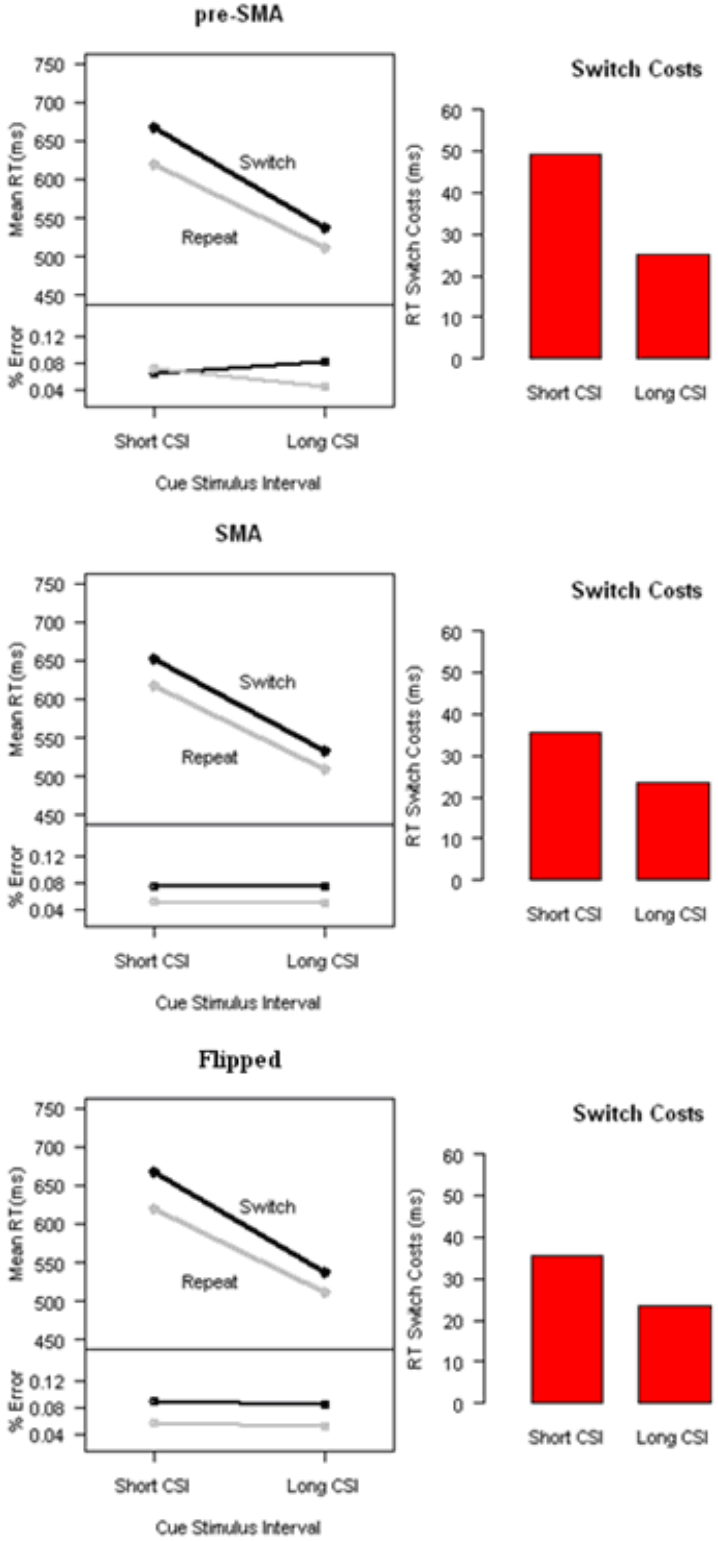
[6] This pair of tasks, with auditory cues, has been used in an unpublished experiment in our lab (Monsell and Mizon) and was found to yield substantial switch costs that reduced to an asymptote with 600 ms of preparation.

the left button on cold colours: in the other half of the participants this mapping was reversed.

4.3.4 TMS

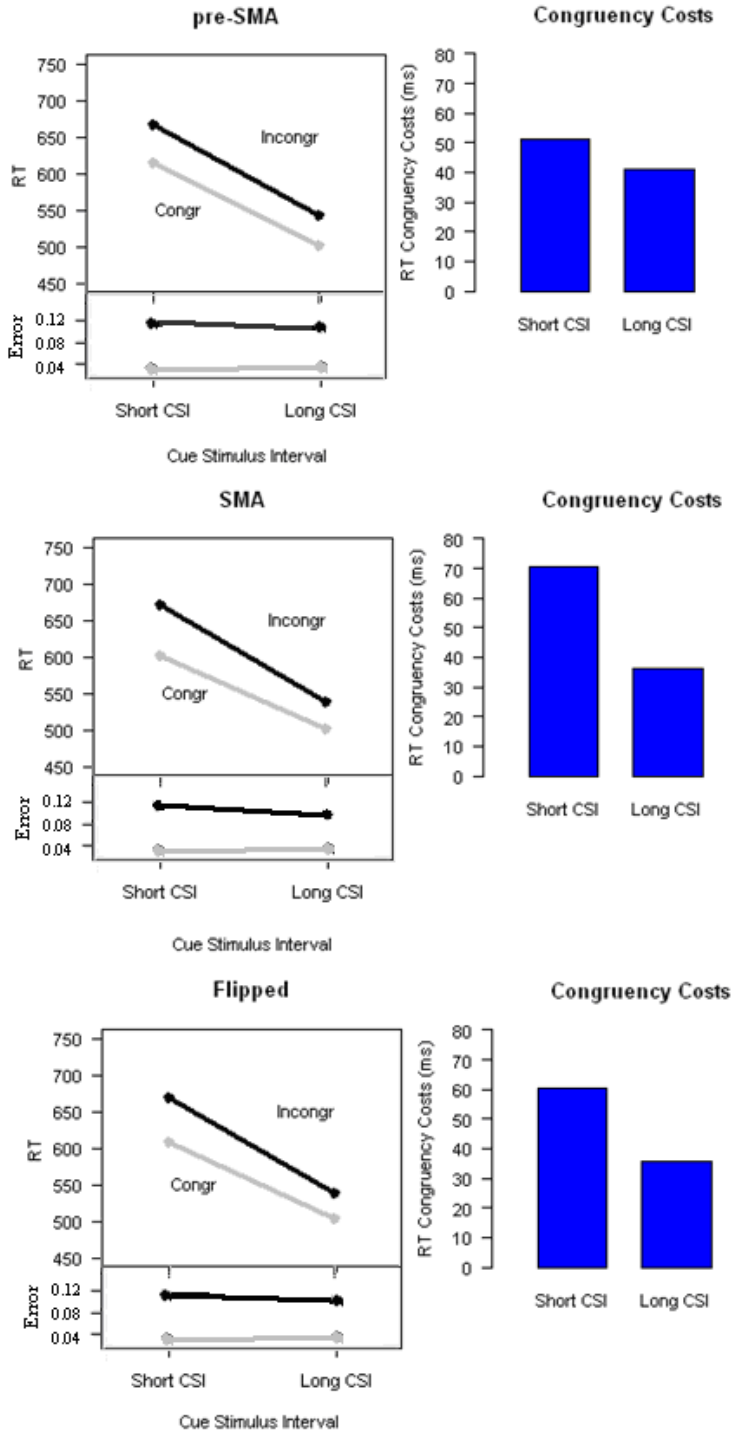
The stimulation protocol, stimulation conditions, and coil direction used in Experiment 2 were identical to those used in Experiment 1.

Figure 4.7 Switch related results for Experiment 2.



Left: Mean RTs and error rates for switch and repeat trials as a function of CSI.
Right: Switch costs

Figure 4.8 Congruence results for Experiment 2.



Left: Mean RTs and error rates for congruent and incongruent trials as a function of CSI.
Right: Incongruency costs

4.3.5 Results

Excluding trials following errors, and the first trial of each block, I computed mean correct RT and error rate for each combination of TMS condition, switch/repeat, congruence and task, averaged over response, and submitted them to ANOVA. Figure 4.7 shows the mean reaction times and error rates for switch and repeat trials (left panels) and switch costs (right panels) as a function of CSI for the three TMS conditions. As for Experiment 1, I will focus on comparing the results between both real TMS conditions. There were reliable main effects of CSI, switch and congruence for reaction times (the main effects of switch and congruence were also reliable for error rates). When the pre-SMA was stimulated, a substantial reduction in switch cost with increasing CSI was seen (from 50 ms to 25 ms). This reduction was smaller (from 37 to 25 ms) when SMA was stimulated. When stimulated using a flipped coil the switch costs reduced from 35 ms to 24 ms. The difference between the RISC effect for pre-SMA and SMA conditions was due to the short CSI condition rather than the long CSI condition, and the three-way interaction — TMS location (pre-SMA/SMA) by switch by CSI — was not reliable. $F(1, 15)=.19$, $p=0.667$. A reversed RISC effect was found in error rates in the pre-SMA condition, though this also was not reliable, $F(1, 15)=2.92$, $p=0.108$. The location by CSI by switch interaction for all three TMS conditions was not reliable for the reaction times $F(1, 15)=.15$, $p=0.865$ nor for error rates $F(1, 15)=2.61$, $p=0.109$.

Figure 4.8 shows the mean reaction times for congruent and incongruent trials and incongruency costs as a function of CSI for the three TMS conditions. When the SMA was stimulated the usual reduction in the congruence effect was observed (from 70 ms to 35 ms). When the pre-SMA was stimulated however, this reduction was attenuated (from 51 to 41). This however is due to mixture of a reduced incongruence cost at the short CSI condition and a higher incongruence cost at the long CSI (Reaction times on incongruent trials during the long CSI condition when stimulating pre-SMA were 7 ms slower than when stimulating SMA). Incongruence costs reduced from 60 ms to 35 ms when stimulating with a flipped coil. But the location (pre-SMA/SMA) by congruency by CSI interaction was reliable neither for RTs, $F(1, 15)= .30$, $p=0.590$., nor for error rates $F(1, 15)=.17$, $p=0.680$. The interaction between location, CSI and congruence for all three TMS

conditions was not reliable for reaction times F(1, 15)=.90, p=.417 nor for error rates F(1, 15)=.17, p=0.831.

There was no reliable effect of task F(1, 15)=2.11, p=.167. Task did interact with congruency F(1, 15)=5.44, p=0.034. As in Experiment 1, the congruence effect was larger in the colour task than in the shape task. This was not reliable in the error rates F(1, 15)=3.02, p=0.103, but the direction was the same.

4.3.6 Discussion

The results of Experiment 2 did not replicate the results found in Experiment 1. However there were signs of similar effects. In Experiment 2, the RISC effect was smaller in the SMA condition than in the pre-SMA condition and the reduction in the incongruency effect was smaller in the pre-SMA condition than in the SMA condition. When comparing SMA to pre-SMA, however the data suggest that, to some extent, this pattern could be the consequence of larger switch costs in the short CSI condition for the pre-SMA condition and a larger incongruency effect in the short CSI condition when stimulating the SMA. Since stimulation is applied before the cue in the short CSI condition, these patterns possibly did not reflecting an effect on task-specific preparation. However, there is at least a hint of the double dissociation found in Experiment 1.

When comparing the results of Experiment 1 and 2, the main question is evidently why the results found in Experiment 2, were different from those in Experiment 1? The obvious possibility is that the changes made to the paradigm in Experiment 2 either abolished the effects of the TMS upon the RISC effect and the reduction in incongruency effect, or at least weakened them to the point of non-significance. The following changes might be critical:

- A change in the probability of a task switch (.5 rather than .33);
- A change in the probability of an incongruent stimulus (.5 rather than .25);
- Two rather than four response alternatives;
- The use of classification tasks rather than identification tasks.

4.3.6.1 Probability of a switch trial

To balance the number of incongruent and congruent trials in all conditions, I changed the switch-repeat distribution to 50% switch trials and 50% repeat trials. Monsell and Mizon (2006) showed that reducing the p(switch) from 50% to 25% increased the size and consistency of the RISC effect (see also Schneider and Logan, 2007). That is, fewer switch trials increased the measured benefit of preparation, Monsell and Mizon argued that, when the chance of a switch is higher, participants might already start preparing for a new task before the cue is presented, consequently reducing the effect of a long CSI as compared to a short CSI. This suggests that changing the probability changes people's behaviour and potentially affects control processes in the dMFC

4.3.6.2 Probability of an incongruent trial

The reduction in incongruency effect is not so well understood, but it is conceivable that, as processing of the irrelevant dimension results in response facilitation for congruent stimuli, that the benefit of preparation targeted at reducing such conflict depends on the number of congruent stimuli. In Experiment 1 25% of the stimuli were congruent, compared to 50% in Experiment 2, which may reduce the benefit of conflict reducing preparation. However, it must be acknowledged that the size of the congruence effect and its reduction with preparation were similar in size to Experiment 1, so the effect of anticipation of conflict would have to be subtle to explain the difference.

4.3.6.3 Number of stimulus-response mappings

In my meta-analysis I did not find reliable medial frontal activations related to preparation for a switch trial specifically. The vast majority of imaging studies included in the meta-analysis used binary classifications (e.g. only 2 buttons) and a 50% switch rate, similar to Experiment 2. The lack of switch specific preparatory dMFC engagement in the results of the meta-analysis therefore supports the idea that these aspects might hold the cause of the different results between Experiment 1 and 2. Nachev et al. (2008) reviewed the existing evidence on medial frontal cortex functionality and came to the conclusion that it seemed to

involve situations of more complex condition-action association. Changing the response complexity of the paradigm (from 2 sets of 4 possible responses to 2 sets of 2 possible responses) might have resulted in a reduction of medial frontal involvement or a different distribution in both time and place of these processes. However, Rushworth et al. (2002), had participants reverse 2 stimulus-response mappings and found an effect on switch trials when stimulating the pre-SMA, but not when stimulating the SMA. Changing our paradigm to tasks with 2 mappings, instead of 4, did not result in a similar finding for the pre-SMA (the effect on switching during stimulation of the SMA lost reliability). As pointed out before, it is a possibility that reversing a 2-choice S-R mapping (while continuing to perform the same perceptual discrimination), employs different neural processes than switching between different dimensions (in which responses change their meaning to values on the other dimension).

4.6.3.5 Use of a classification task

A possible explanation for the difference in results between Experiment 1 and 2 is that the effects I found in Experiment 1 depended on the type of task used to switch between. In my meta-analysis, I found dMFC to be important for switching, but I did not find any evidence for the existence of task-related switch minus repeat activations (see Chapter 3, Table 3.3). Additionally, Yeung et al. (2006) showed that the dMFC is important for switching, independent of task. These results suggest that the difference in results between Experiment 1 and 2 is not the consequence of the use of different tasks, but it remains a possibility.

4.7 General Discussion

Experiment 1 demonstrated an interesting dissociation of proactive control of switch costs and S-R interference, with SMA stimulation substantially attenuating the RISC effect, and pre-SMA stimulation eliminating the reduction in congruence effects with preparation. As already noted, this dissociation is not unprecedented in the literature as a whole, in that congruence effects sometimes do and sometimes do not reduce along with switch costs when participants are able and motivated to prepare for a task change.

Unfortunately, Experiment 2, in which a number of changes were made to the paradigm, did not strongly support this outcome, though with the eye of faith an attenuated if unreliable version of the dissociation can still be seen. I have considered above some of the reasons why the changes made could have had this effect. Further experiments will be required to establish which differences are critical. But unfortunately the time and resources available do not allow such experiments to be completed within my PhD project.

One issue I have not yet discussed is the flipped coil condition used in these experiments -- in which I applied the TMS coil upside down. In preliminary tests I found this to result in a motor threshold 10% – 20% higher. Consistent with this weakened effect, overall the results found in this condition demonstrated effective preparation with respect to both switch costs and congruence effects, approximating the results in the TMS conditions in which TMS had no impact. In Experiment 1, the switch cost reduction in this condition was similar to the reduction found when stimulating pre-SMA and the incongruence cost reduction was similar to the reduction found with SMA stimulation.

The difficulty is that, as indicated by some of the participants, this condition may be experienced as involving lower intensity stimulation, so that some participants relaxed in the flipped-coil blocks, making the results more variable (see Chapter 2, Paragraph 2.1.7).

Chapter 5: TMS over the right intraparietal sulcus attenuates preparatory task-set control

This chapter is based on a paper to be submitted to the Journal of Cognitive Neuroscience by November 2011, but I have inserted into this chapter a description of a pilot experiment that will not be included in the paper.

5.1 Introduction

In daily life we often need to shift between various tasks. In order to successfully switch from one task to another, one needs to activate the appropriate set of mental operations needed to correctly execute the new task (Monsell, 2003). The ability to do so is thought to be essential for accomplishing flexible goal-directed behaviour.

One of the principal ways of studying the ability to switch between tasks is the task-cueing paradigm (Monsell & Mizon, 2006). In this paradigm each stimulus is preceded by a task-cue indicating which task needs to be performed. The task can either be the same as on the last trial ('task-repeat trial') or different ('task-switch trial'). Participants typically take longer to respond (and make more errors) on switch than on repeat trials: there are "switch costs". When the interval between the task cue and the stimulus is increased, all other things being equal, not only is RT reduced, indicative of preparation, but switch costs are also reduced (Meiran, 1996; Monsell & Mizon, 2006; Rogers & Monsell, 1995) This suggests that participants can use the interval to prepare for the change of task. However, there is typically a "residual" switch cost no matter how much time and motivation is given for preparation. The reduction in switch costs ("RISC") effect may be seen as a measure of endogenous task-set control, the residual cost as indicative of the limits of that preparation (Monsell & Mizon, 2006; Rogers & Monsell, 1995)

The precise nature of the underlying processes responsible for the RISC effect has been the object of considerable debate in recent years (Allport, et al., 1994; Logan & Bundesen, 2003; Monsell & Mizon, 2006; Yeung & Monsell, 2003a). The most commonly held view is that the switch cost and the preparation effect result from a mixture of task-set

reconfiguration processes and the overhead of overcoming interference from the previously activated task-set (Kiesel et al., 2010; Monsell, 2003; Vandierendonck, et al., 2010).

Task-set reconfiguration, a process triggered when a new task-goal is activated in working memory (Rubinstein et al., 2001), may involve adjustment of a number of different parameters (Logan & Gordon, 2001; Vandierendonck, et al., 2010); the settings, tunings, or linkages of the various component processes required to accomplish one task rather than another. A number of these parameters have been considered as candidates for what can be configured in advance of the stimulus (Kiesel, et al., 2010; Vandierendonck, et al., 2010). For example, Meiran Kessler and Adi-Japha (2008) suggested that preparation can bias attentional settings toward processing a newly relevant stimulus dimension — e.g. when switching from classifying shape to classifying colour. Mayr and Kliegl (2000, 2003) proposed activation or alteration of S-R rules as a critical component of task-set preparation.

The second potential source of switch costs is interference from the previous task set(s). That is, regardless of preparatory efforts, either the previous task-set persists -- " task-set inertia" (Allport, et al., 1994; Yeung & Monsell, 2003a), or the previous task-set is reactivated by the stimulus (Waszak, Hommel & Allport, 2003). Either way, the result is inappropriate attention or response activation via inappropriate S-R rules, and consequently, decision time is increased by the resulting interference. It requires at least one completion of the new task all the way to response to overcome this inertia (Meiran, 2000; Schuch and Koch, 2003). Task-set reconfiguration and interference due to persistence or reactivation of a task-set are neither mutually exclusive nor independent, as successful reconfiguration mitigates the effects of interference (Monsell, 2003; Vandierendonck, et al., 2010). Indeed, one tempting account of the empirical function relating switch cost to CSI is that the RISC component indexes the rate of task-set reconfiguration, and the asymptotic component the limit on its ability to overcome interference.

A number of studies have used fMRI to study what happens in the brain during preparation. However, the low temporal resolution of the BOLD signal makes it difficult to distinguish between activation resulting from neural activity related to the cue (e.g., preparatory activity) and activity related to the stimulus. In order to make this distinction,

the paradigm has been adapted to accommodate the low temporal resolution in different ways. Several studies have simply increased the cue-stimulus interval to prevent preparation activity from overlapping with stimulus related activations (e.g. 12 sec, Kimberg & D'Esposito, 2000; 6 sec, Sohn & Anderson, 2000). Such long preparation intervals, however, make the paradigm very slow and potentially boring (reducing the motivation to prepare) and increase the likelihood that participants postpone preparing for the next trial until towards the end of the interval, or prepare and then need to engage in additional maintenance activities.

Other studies have isolated cue related activity by introducing "cue only" trials (Brass & von Cramon, 2002; Madden, et al., 2010; Shi, et al., 2010). In these experiments on some trials, the task cue was not followed by a stimulus. The BOLD signal collected on those trials, following cue presentation, can only be made up by preparatory activity. The absence of a stimulus following a proportion of cues, however, may critically reduce the motivation to prepare in advance of the stimulus. Also, the omission of an expected stimulus could in itself result in a consistent BOLD response.

Luks et al. (2002) manipulated the information content of the cue. Informative cues (cues which indicated which task needed to be done at stimulus arrival) potentially hold more preparatory activity than non-informative cues, which do not indicate any task information (on each trial an additional informative task-cue is presented with the stimulus) and a contrast between them could reveal neural activations related to preparatory task-set reconfiguration.

The results of these imaging studies show activation in a set of frontal and parietal regions. These areas include: medial frontal cortex, the inferior frontal junction (IFJ) bilaterally, inferior frontal gyrus bilaterally and superior parietal lobule bilaterally (Brass & von Cramon, 2002, 2004; Chiu & Yantis, 2009; Forstmann, Brass, Koch, & von Cramon, 2005; Gruber, et al., 2006; Jamadar, et al., 2010; Luks, et al., 2002; Madden, et al., 2010; Ruge et al., 2005; Ruge, et al., 2009; Sakai & Passingham, 2003; Shi, et al., 2010; Slagter et al., 2006; Sohn & Anderson, 2001; Sohn & Carlson, 2000). However, a number of these imaging studies, that attempted to isolate preparatory activations, have not found reliable differences between preparing on a switch trial and a repeat trial (Brass & von Cramon, 2002; Forstmann, et al., 2005; Gruber, et al., 2006; Jamadar, et al., 2010; Luks, et al., 2002;

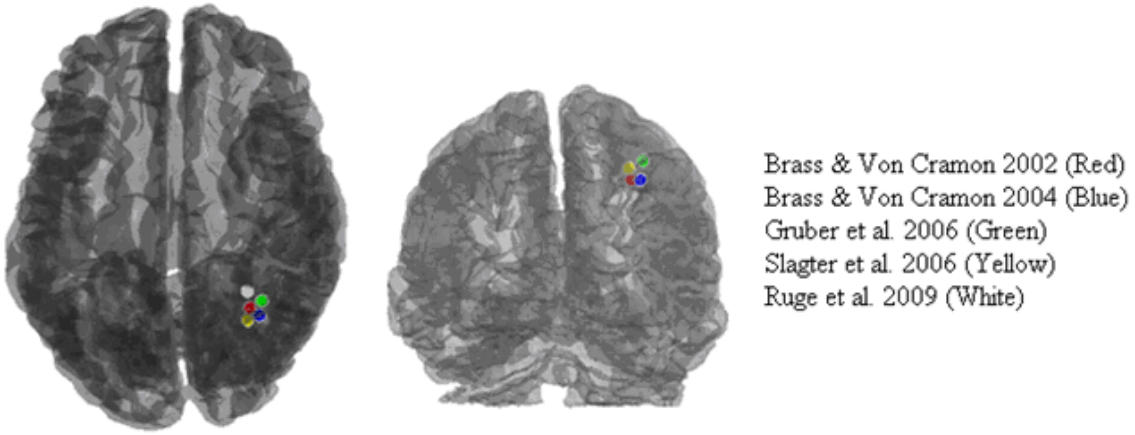
Sakai & Passingham, 2003; Sohn & Carlson, 2000). There are however reasons why advance preparation for a task switch may not reveal itself in these studies. Inasmuch as it is an optional and effortful process, it may be discouraged by the unusual circumstance of being in the scanner. And both the behavioural switch cost and its reduction with switch costs are amplified when the probability of a task switch is below 0.5 (Monsell and Mizon, 2006), possible because participants tend to prepare for a switch before the task cue when the probability is 0.5, as in these imaging studies.

Given the combination of such methodological issues and the absence of switch related preparatory activations in several studies, it remains difficult to draw hard conclusions about the involvement of these areas in preparation for a task switch. For example, a number of imaging studies have run switch minus repeat contrasts using task-switching paradigms without isolating cue-related activations and they report a similar set of regions (Erickson et al., 2005; Sylvester et al., 2003). It is of course likely that the same areas are involved in task-set preparation as well as in task switching without preparation (the same processes need to be reconfigured in both situations; it is just the timing that changes). It is, however, also possible that this overlap could also be due to the difficulties of studying preparation separately from stimulus related activations using fMRI.

In the current study we were interested in the involvement of the right IPS during the preparation interval. A detailed analysis of the imaging literature suggests that activations in the right IPS are often reported in studies looking at task-set preparation. Five out of ten studies looking at task set preparation (see Figure 1), report cue related right IPS activations. Two of these report larger preparatory activations on switch trials then on

repeat trials (Brass & von Cramon, 2004; Slagter, et al., 2006).

Figure 5.1 Right intraparietal sulcus location reported to be activated during the preparation interval.



Reports of right IPS activations are less frequent in studies reporting contrasts looking at task transition without preparation. Of eight studies which reported an event related switch-repeat contrast, in which participants did not get time to prepare, only two reported activations near the right IPS (Erickson, et al., 2005; Kimberg, et al., 2000). This would suggest that the right IPS could be specifically involved in preparatory processes and that preparing for a task-switch could involve qualitatively different processes from switching without the ability to prepare.

However, given the various ways in which researchers have had to adapt the paradigm to isolate cue related activations, the possibility exists that the more frequent reporting of right IPS activations in those studies is related to these adaptations. This idea is consistent with the fact that a good number of the studies reporting a switch versus repeat contrast without isolating cue-related activations, employed a paradigm with a substantial cue stimulus interval (e.g. more than 250 ms) in which case, participant did have the ability to prepare. Hence is conceivable that switch-specific preparatory processes form a part of the source of the extra BOLD signal on switch as compared to repeat trials, and if the right IPS is important for switch related preparation, one could expect a greater occurrence of right IPS activations in these studies. However, of five such studies, only one reported right IPS switch minus repeat activations (Jamadar, et al., 2010).

Chapter 5: TMS over the right IPS attenuates preparatory task-set control

Another standard limitation of the fMRI studies is that they cannot tell us whether the brain activations observed are essential to preparation, or merely epiphenomenal. In the current study, we used Transcranial Magnetic Stimulation (TMS) to test whether the right IPS plays an important role in preparing for a task switch. In Experiment 4 we applied TMS during the preparation interval to study the involvement of the right IPS in preparatory task-set control. In Experiment 5 we stimulated after stimulus onset to study its contribution to reconfiguration without preparation.

Because of its high temporal resolution, TMS is particularly well suited to distinguish between brain processes that happen close in time. TMS uses electromagnetic induction to stimulate a small region of the cortex. This stimulation causes the axons of the neurons in the targeted region to depolarise and fire in a random fashion, effectively slowing down the normal brain processes (O'Shea & Walsh, 2007). This technique has been successfully used to study preparatory processes. For example, Rushworth et al. (2002), using the "intermittent instruction" variant of the task-cueing paradigm. The cue indicated that the participant either should or should not reverse the response assignments for the next few trials in a two-choice RT task — i.e. prepare to change or maintain the S-R mapping, all other things being equal. A short train of TMS pulses applied to the pre-Supplementary Motor Area (pre-SMA) during the cue-stimulus interval selectively impaired performance on the first stimulus after the S-R mappings changed, indicating that pre-SMA was necessary for successfully accomplishing this preparation (Rushworth, et al., 2002).

Here we apply a similar logic to examine the role of IPS in preparation for switches between classification tasks requiring attention to different perceptual dimensions. We stimulated on every trial of a standard task-cueing experiment. The timing of the stimulation was based on ERP data reported by Lavric, Mizon and Monsell (2008). They cued identification of the colour or form of a coloured shape presented after a 200 or 800 ms CSI. During the 800 ms interval, they found an extra positivity on switch trials, developing over the posterior scalp (as well as a negativity over the anterior scalp) from 400 ms after cue presentation, reaching a maximum some 500 ms after cue onset and remaining substantial until the stimulus onset. The amplitude of this preparation-for-a-switch component correlated over subjects with the behavioural RISC effect. A partitioning of switch and repeat trials into fast versus slow RT trials, showed that this ERP component

was specific for trials with faster responses — presumably those on which participants were well-prepared. With a 200 ms CSI, a similar component could be seen after the stimulus, superimposed on the general extra negativity seen post-stimulus on task switch trials, and again reaching a maximum at about 500 ms after cue onset.

In the present experiments participants classified objects by colour or shape, with a 100 ms or 750 ms CSI following an auditory verbal task cue. (A prior experiment with these cues and task pair in our lab had established a reduction in switch costs asymptotic at a CSI shorter than 750 ms). We used a short 20 Hz train of 3 pulses (i.e. a 100 ms train) to disrupt processing in either the right IPS or a control site on every trial. In the first experiment (Experiment 4) the pulse train began 300 ms before stimulus onset. Using a 750 ms CSI, this is 500 ms after the cue, at about the time the preparation-related ERP component in the Lavric et al. study reached its peak. With a 100 ms CSI, the pulse train preceded the task cue. Hence if right IPS is important to task-set reconfiguration, we would expect TMS to disrupt preparation more on switch trials than on repeat trials at the 750 ms interval, but to have no such selective effect at the 100 ms CSI. We expected to observe a RISC effect when stimulating a control site and an attenuation of this RISC effect when stimulating the right IPS.

Having found evidence for this pattern, in a second experiment (Experiment 5) we asked whether the role of right IPS is limited to advance preparation, or whether it also plays a role when reconfiguration is required without the opportunity to prepare.

5.2 Experiment 3 Pilot study (thesis only)

Before I conducted the two experiments to be reported in this paper I ran a pilot study in which I stimulated both the left and right IPS. The imaging literature suggests a potential important role for both in pro-active task-set control (see Chapters 1 and 3). Because it formed the basis for the two main experiments, I will briefly present the results before continuing with the main experiments. In this experiment, just as in Experiment 1, reported in Chapter 4, participants identified the colour or shape of a stimulus as one of four values with the same set of four keys, and the task was cued with one of four verbal cues (two per task).

5.2.1 Participants

13 healthy participants took part (mean age 21, 5 male). All passed a safety screening protocol for TMS and gave informed consent in accordance with the ethics committee of the Exeter University School of Psychology.

5.2.2 Procedure & Design

The experiment was conducted over two sessions. Its procedure and design were identical to the procedure and design used in Experiment 1 in which I stimulated the dMFC (see Chapter 4). As in the earlier study there were 3 TMS conditions. I stimulated the left (MNI -33, -51, 51) and right IPS (MNI 33, -51, 51) and a control region (0, -25, 60). The TMS protocol was also the same as the first experiment described in chapter 4 and stimulation was applied with the handle to the rear.

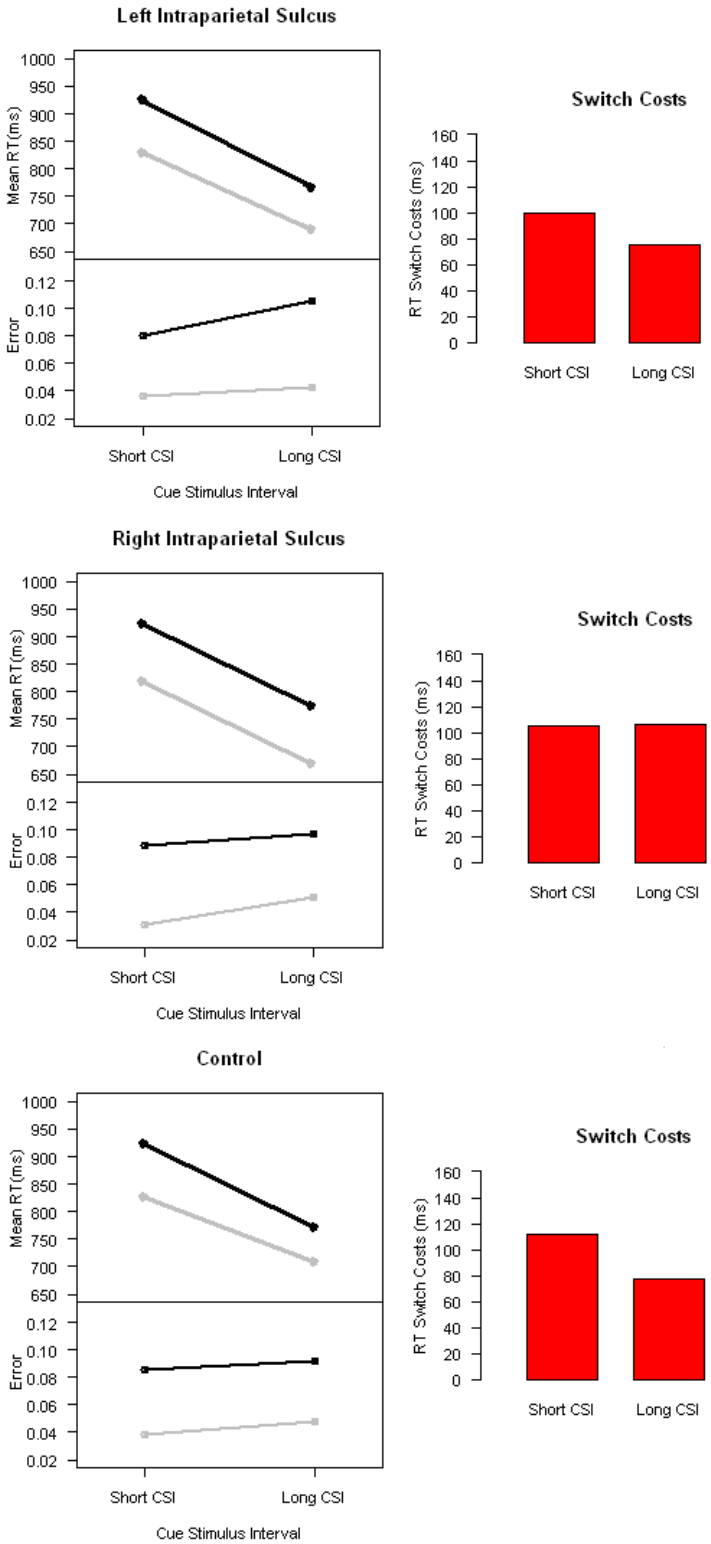
5.2.3 Results

Excluding trials following errors, and the first trial of each block, I computed mean correct RT and error rate for each combination of TMS site, switch/repeat, task, congruence, (averaged over response) and submitted them to ANOVA. Figure 5.2 (below) shows the mean reaction times and error rates (left panels) as well as switch costs (right panels) as a function of CSI for the three TMS target sites. As expected, there were reliable main effects of CSI, switch and congruency for reaction times and these were also reliable in the error rates (see appendix E). There was a main effect of Task $F(1, 12)=31.75$, $p<0.001$ which was not reliable in the error rates $F(1, 12)=1.62$, $p=0.228$. Additionally there was a reliable interaction between congruency and task, where the difference between congruent and incongruent trials was less for the shape task $F(1,12)=8.34$, $p=0.014$ (not present in the error data, $F(1, 12)=2.66$, $p=0.129$). The difference in task difficulty reduced with CSI, $F(1, 12)=7.06$, $p=0.021$, not reliable in the error rates, $F(1, 12)=0.06$, $p=0.812$ and on switch trials, the difference in congruency between tasks was larger $F(1, 12)=6.96$, $p=0.022$ (not

reliable in error data). As expected, there was a reduction in switch costs when stimulating the control site (from 112 to 79 ms) and there was a similar reduction in switch costs observed in the left IPS condition (from 101ms to 72 ms). However, no reduction in switch costs was observed when stimulating the right IPS (104 ms to 109 ms). The location by CSI by switch interaction was however not reliable, $F(1, 12)=.954$, $p=0.399$, (also not reliable in the error rates, $F(1, 12)=1.43$, $p=0.259$. A direct comparison of the location by CSI by switch interaction between the left IPS and the control site showed this not to be reliable $F(1, 12)=0.26$, $p=0.875$, nor was a direct comparison between the right IPS and the control site $F(1, 12)=1.482$, $p=0.247$ or between left and right IPS $F(1, 12)=1.05$, $p=0.327$.

There was no reliable interaction between location, CSI and congruence for reaction times $F(1, 12)=.63$, $p=0.509$, nor for error rates $F(1, 12)=0.82$, $p=0.422$. There was no reliable reduction in incongruency in any location ($F<1$ for the CSI by congruency interaction in each location).

Figure 5.2 Switch related results of Experiment 3.



Left: Mean RTs and error rates for switch and repeat trials as a function of CSI.
Right: Switch costs

5.2.4 Discussion

Stimulation of the right IPS and the left IPS resulted in attenuation of the RISC effect seen in the control condition. Whereas the attenuation was only partial for stimulation of the left IPS, it was complete for stimulation of the right IPS However, the location by CSI by switch interaction was not reliable (nor was a direct comparison between the right IPS and the control site). The reason for this may be that, even though there was a reduction in switch costs when the control site was stimulated, it was smaller than we would normally expect. The location chosen as a control site was relatively close to the SMA (which could present a larger problem than I initially expected). When stimulating the SMA in Experiment 1 (using the same paradigm as in this pilot) an attenuation of the RISC effect was observed. It is therefore possible that in some participants, due to individual structural variation and coil positioning errors, stimulation of the control site affected processes near the SMA. In Experiment 4, I sought to replicate the finding that stimulation of the right IPS negatively affects our ability to prepare for a task switch. To prevent accidental stimulation of medial frontal regions I stimulated a control site approximately 0.5 cm more posterior to the control site used in this pilot experiment and positioned the coil with the handle to the side

5.3 Experiment 4

We used a task-cueing paradigm in which the stimulus was a coloured shape, and the tasks were to classify either its colour (as "warm"/"cold") or its shape (as having or not having curved edges) with a left or right key press (using the either the left or the right index finger).

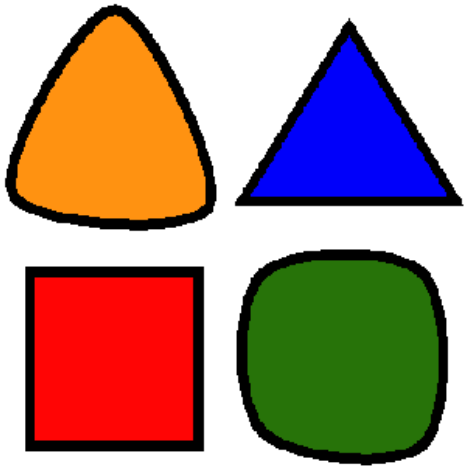
5.3.1 Participants

16 healthy participants took part (mean age 23, 9 male). All passed a safety screening protocol for TMS and gave informed consent in accordance with the ethics committee of the Exeter University School of Psychology. Two participants were excluded and replaced because of technical problems during testing (e.g. head movements or discomfort).

5.3.2 Procedure

Participants were tested sitting with their head in a chin and head rest, eyes 75 cm from the screen of a LaCie Electron Blue 19" CRT refreshing at 100 Hz, their left and right index fingers resting on the "v" and "m" keys of a standard PC keyboard.

Figure 5.3 Examples of stimuli used.



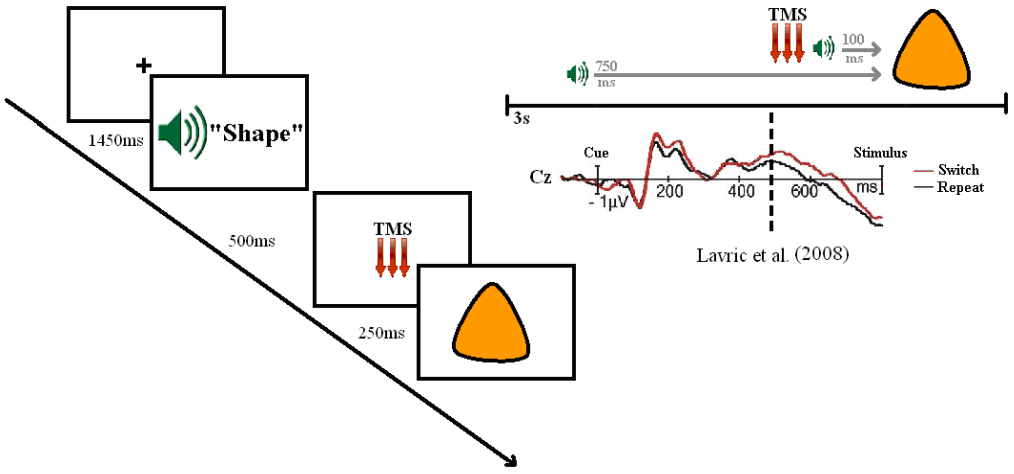
The stimulus (see Figure 5.3 for examples) came from a set of 32 comprising half the possible combinations of 8 shapes (4 with curved edges and 4 with straight edges) and 8 colours (4 "warm" colours — yellow, pink, red and orange, and 4 "cold" colours — light blue, dark blue, light green and dark green). At the beginning of each trial there was a fixation cross, lasting either 1450 ms (before a long CSI trial) or 1950 ms (before a short CSI trial). This was followed by an auditory cue word ("colour", "paint", "shape", or "form") which indicated the current task (e.g. the stimulus attribute to which to respond). The cue words were recorded with duration 250 ms and presented on stereo speakers either side of the monitor. We used two cues per task, in order to avoid immediate repetition of cues and any confound between cue repetition and task-repetition. (Cue repetition has been shown to lead to facilitation of performance over and above any effect of task repetition, Logan and Bundesen, 2003; the avoidance of cue repetition is an efficient way of dealing with this problem (Monsell & Mizon, 2006).

After a CSI of either 100 ms or 750 ms, a stimulus was presented (in the centre of a LaCie Electron Blue 19" CRT refreshing at 100 Hz) until a left or right response was made. If the wrong response was given, an image depicting a keyboard and an arrow pointing at the correct response appeared for 2s. Otherwise, the interval from response to the next stimulus was 2.3 seconds. All stimuli presented afforded both tasks: half of the stimuli

were mapped to the same response for both tasks (congruent) and half to different responses depending on the task (incongruent). The response mappings were counterbalanced between participants so that each stimulus served equally often as congruent and incongruent.

Before the start of the experiment, participants received a brief training session. The training consisted of 5 blocks. The first two blocks were single task blocks (with a CSI of 500 ms). In one block participants did the colour task for 32 trials and in the other the shape task for 32 trials. These were followed by two blocks in which the tasks were mixed as in the experimental blocks (one with the long CSI condition and one with the short CSI condition). The final block was designed to habituate the participant to the feeling of TMS. It was mixed task block with a long interval and TMS was applied (3 pulses at 20Hz) during the CSI.

Figure 5.4 Paradigm used in Experiment 4.



Left: an example of a trial in the long CSI condition. The fixation cross remained on the screen until stimulus onset. The auditory cue was presented 750ms before stimulus onset. Right: TMS time: The 100ms TMS train (3 pulses at 20Hz) starts 250ns before stimulus onset in both CSI conditions. Consequently, in the short CSI condition the TMS starts 150ms before cue onset.

5.3.3 Design

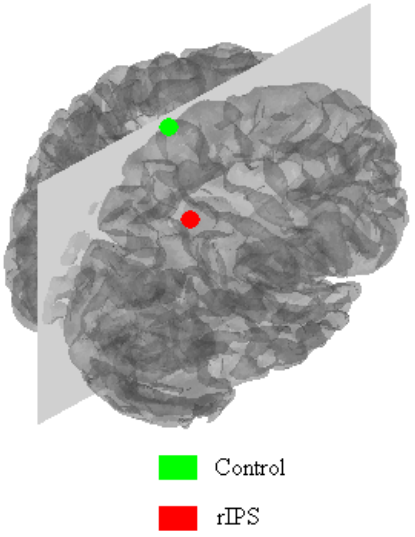
CSI and TMS site were manipulated between blocks, with 8 experimental blocks of 48 trials (following a start-up trial), 2 blocks for each combination of TMS site and CSI. CSI

changed every block and TMS condition changed every 2 blocks. Both TMS and CSI condition sequences were counterbalanced between participants, so that each block type appeared equally often in each part of the session New pseudo-random trial sequences were generated for each participant so that each block contained 1/3 task-switch trials and 2/3 task repeat trials, each including an equal number of trials for each combination of task, congruence, and response, and with stimuli occurring equally often in each combination of task, congruence, and response. Immediate stimulus repetitions were allowed.

5.3.4 TMS

A Magstim Rapid 2 Stimulator (Magstim, Whitland, Wales, UK) and a Magstim 70mm figure-of-8 coil was used to apply stimulation in a train of 3 pulses at 20Hz at 110% of visible motor threshold, as determined at the beginning of the session (an average intensity of 54% of maximum output). The stimulation was applied 250 -150 ms before stimulus onset, and hence 500-600 ms after cue onset in the long CSI condition, and immediately prior to cue onset in the short-CSI condition (see Figure 5.4).

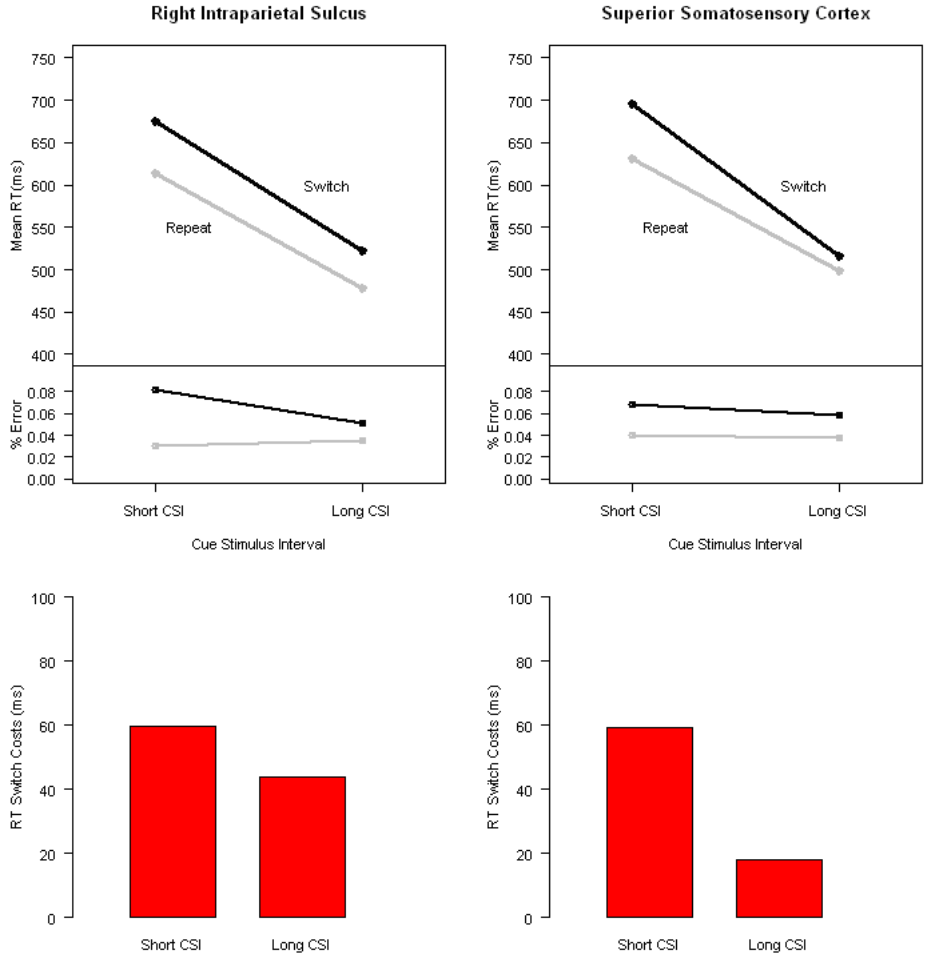
Figure 5.5 TMS targets in Experiments 4 and 5.



In half the blocks we stimulated over right IPS (MNI 33, -51, 51), in the other half a control site over medial superior somatosensory cortex (MNI 0, -30, 60) — see Figure 5.5. The control site was selected because it was unlikely to be involved in task-set control and matched the right IPS site well in terms of the intensity of scalp sensations and auditory click burst resulting from the TMS pulse train. The coil was positioned over the r-IPS site, with the handle to the rear, and over the control site with the handle to the right, using the BrainSight stereotaxic targeting system, relative to an MR image acquired for each participant, using a 1.5 Tesla Philips Gyroscan Intera. The TMS site changed every two

blocks (see above).

Figure 5.6 Switch related results of Experiment 4.



The top graphs show the mean RTs and error rates in each CSI condition for both locations. The bottom bar charts show the switch costs per CSI and location.

5.3.5 Results

Excluding trials following errors, and the first trial of each block, we computed mean correct RT and error rate for each combination of TMS site, switch/repeat, task, congruence (averaged over response) and submitted them to ANOVA. Figure 5.6 shows the mean

reaction times and error rates (top panels) as well as switch costs (bottom panels) as a function of CSI for the two TMS target sites. As expected there were reliable main effects of CSI (only in RTs), switch (RT and error rates), congruency (RT and error rates) and a reliable interaction between CSI and switch, overall switch costs were lower in the long CSI (reliable in the reaction times and nearly significant in error rates) (See appendix G & H). When the control site was stimulated, a substantial reduction in switch cost with increasing CSI was seen, as expected, from 58 ms to 18 ms. This reduction was substantially attenuated (from 59 to 43 ms only) when right IPS was stimulated, and the location by CSI by switch interaction was reliable, $F(1, 15)=7.06$, $p=0.029$. This interaction was not reliable in the error rates, $F(1, 15)=1.43$, $p=0.249$.

The negative effect of right IPS TMS on RT was, moreover, specific to the long-CSI switch trials: RTs on repeat trials for both CSIs and switch trials for the short CSI were slightly faster (by about 20 ms in each case), though not reliably so ($F<2$ in each case); only on the long CSI-switch trials was the RT longer.

There was no reliable location by CSI by congruency interaction in the reaction times, $F (1, 15)=.43$, $p=0.524$ nor in the error rates $F(1, 15)=.00$, $p=0.992$.

Finally there was a (just) reliable location by switch by congruency by task interaction $F(1, 15)=4.80$, $p=0.045$. This interaction was not reliable in the error rates, $F(1, 15)=.01$, $p=0.942$. Even though not reliable, in terms of reaction times, the colour task was harder than the shape task, the switch costs were somewhat smaller for the colour task (shape task=50 ms, colour task=39 ms) and the congruence effect was somewhat bigger for the colour task (shape task=41 ms, colour task=45 ms). When stimulating the control site, the switch costs in the colour task were lower on congruent trials than in the shape task. On incongruent trials the switch costs in the colour task trials, were equal to the switch costs in the shape task. When stimulating the right IPS this effect was reversed. The switch costs in the shape task were smaller on congruent trials than the switch costs in the colour task, whereas in incongruent trials the switch costs for the colour task were smaller than on the shape task. Effects in the error rates did not show the same effect: in both TMS conditions, the switch costs were higher on for the colour as for the shape in both congruent as well as incongruent trials.

5.3.6 Discussion

Stimulation over right-IPS during preparation for the stimulus reliably attenuated (by about half) the standard reduction in the RT cost of a task switch with preparation observed in the control condition. (The error rates showed a slightly stronger RISC effect in the right IPS condition, but this interaction for error rates was nowhere near reliable.) This strongly suggests that right IPS plays a role in some aspect of task-set reconfiguration that can be carried out under endogenous control in anticipation of the stimulus. In Experiment 5, we asked (as outlined in more detail in the introduction) what role it might play in post-stimulus processing, with and without an opportunity for preparation.

5.4 Experiment 5

The second experiment asked whether the right IPS is important for task-set reconfiguration after stimulus onset (with or without the ability to prepare), or specifically during anticipatory preparation for a task switch. To test this, we stimulated during the latent interval (i.e. between stimulus and response), instead of during preparation. We stimulated the right IPS 300-400 ms after stimulus onset on trials with a short CSI and a long CSI. This is the point at which Lavric et al. observed a switch related positivity on short CSI trials. If the right IPS contribution to task transition is specific to preparation, there should be no difference in switch costs between stimulating the right IPS and a control region on either long CSI or short CSI trials. If right IPS processes are active during the CSI during long CSI trials, but pushed forward in time to follow the stimulus onset when there is no opportunity to prepare, then the switch costs in the short CSI condition, should be specifically increased. If switch costs were increased on both short and long CSI trials in comparison to a control site, that would suggest that right IPS activity is important for task-switching regardless of the opportunity to prepare.

5.4.1 Participants

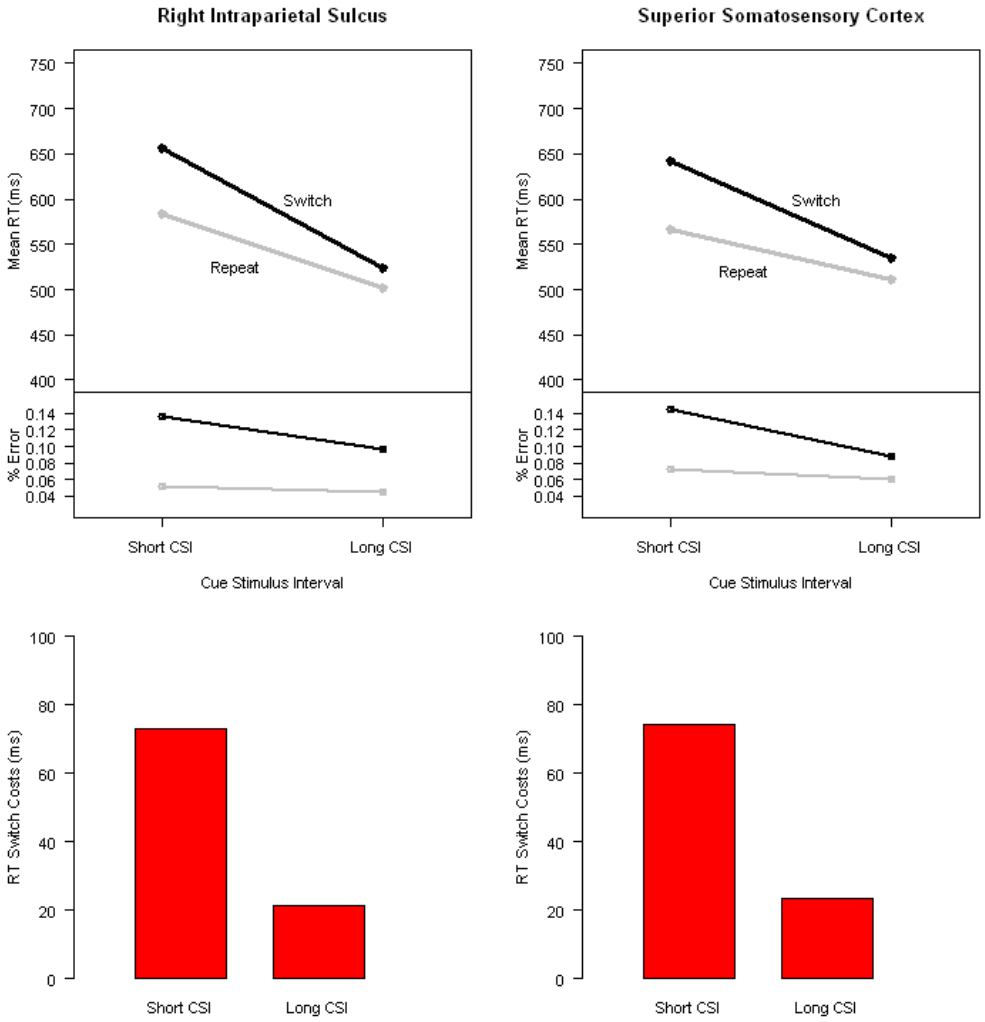
10 healthy participants (mean age 22, 4 male) passed safety screening and took part with informed consent. Except for the onset of the TMS pulse train, the experiment was identical

to Experiment 1. We stimulated at 110% of visible motor threshold (average 53%) between 300 ms and 400 ms post stimulus onset (3 pulses at 20Hz).

5.4.2 Procedure & Design

Experiment 5 was in every respect the same as Experiment 4 except for the moment of stimulation. In both short- and long-CSI blocks, we targeted the pulse train at the point in time (starting 300 ms after stimulus onset) when Lavric et al. (2008) found that the ERP positivity associated with a task switch could be seen overriding the general post-switch task-switch negativity on trials with a 200 ms CSI.

Figure 5.7 Switch related results of Experiment 5.



The top graphs show the mean RTs and error rates in each CSI condition for both locations. The bottom bar charts show the switch costs per CSI and location.

5.4.3 Results

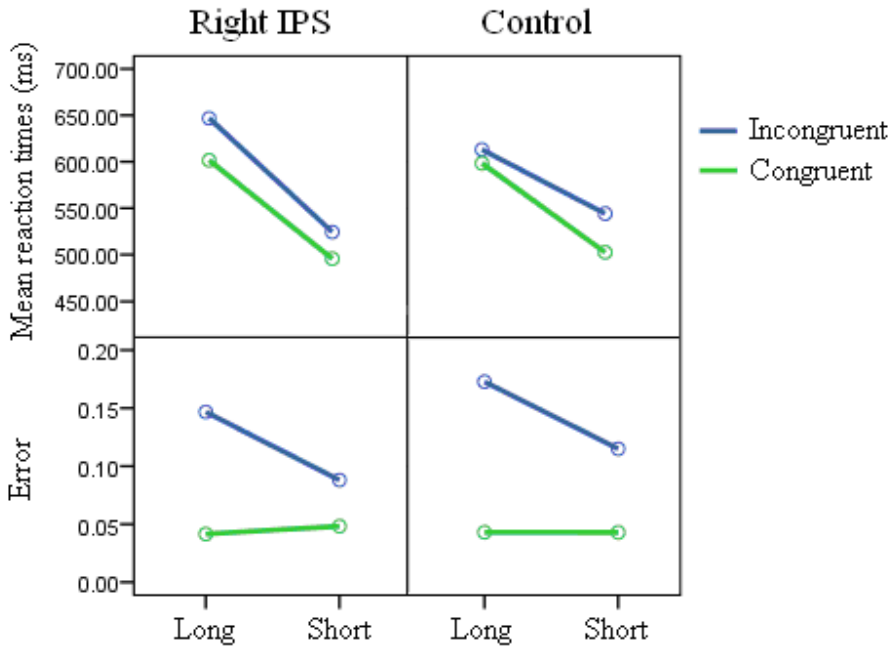
Data exclusions were as for Experiment 4. Figure 5.7 shows the mean reaction times for switch and repeat trials as well as switch costs as a function of CSI for the right IPS and control TMS target sites. The top graphs show the mean reaction times and error rates for both locations as a function of CSI. The bottom bar charts show the switch costs per CSI

and location. As expected, there were reliable main effects of switch/repeat, CSI, congruency and task. These main effects were, except for the main effect of task, also reliable in the error data (see appendix I and J). As before, there was a reliable CSI by switch interaction, $F(1, 9)=14.19$, $p=0.004$, indicative of successful preparation on a task switch trial. This interaction was also significant in the error data, $F(1,9)=8.78$, $p=0.016$.

The switch cost reduced with preparation from 73 ms to 23 ms when TMS was applied over the control site. But with TMS over right IPS, the switch cost also reduced from 72 to 21, and there was no sign of a location by switch interaction, $F(1,9)=0.07$, $p=0.795$, this interaction was also not reliable for the error data, $F(1,9)=59$, $p=0.460$, or a location by CSI by switch interaction, $F(1,9)=0.13$, $p=0.728$. This interaction was also not reliable for the error data, $F(1, 9)=0.003$, $p=0.959$.

The RTs showed an unexpected but statistically reliable location by CSI by congruency interaction, $F(1,9)=6.32$, $p=0.033$ (see Figure 5.8). This interaction was not reliable for the error rates, When stimulating the right IPS a reduction in the incongruency effect was observed (from 45 ms to 29 ms), when stimulating the control site however, this effect was reversed (from 15 ms in the short CSI to 42 ms in the long CSI). The increase was not reliable by itself $F(1,9)=1.75$, $p=0.219$. There is no support for the three way interaction in the error data, $F(1,9)=0.05$, $p=0.82$, for which stimulation in either location was accompanied a marked reduction in the congruence effect with increasing CSI.

Figure 5.8 Congruence results Experiment 5.



5.4.4 Discussion

In Experiment 4 we stimulated the right IPS during the cue stimulus interval. The attenuation of the reduction in switch costs with increasing CSI indicated that the TMS significantly reduced the ability of participants to prepare for an upcoming task switch. Stimulation at the same time relative to the stimulus, but before the cue on trials with a short CSI, did not affect performance. This shows that the processes present in the right IPS form an essential part of our ability to proactively alter task related processes in accordance with an internal goal and consequently reduce the switch costs.

In Experiment 5 we stimulated the right IPS after stimulus onset. If the task-set control processes in the right IPS, suggested by Experiment 4, were purely preparatory in nature (as the imaging literature may be taken to suggest), stimulation after the stimulus on trials when there was no time to prepare should now have no effect on performance. If processes in the right IPS were important for a task-set reconfiguration process needed on

all trials, but which could be done in advance of the stimulus, we would now expect an effect on the switch costs in the short CSI condition, when there was no time to prepare, but not in the long-CSI condition. Finally, if right IPS involvement were critical for post stimulus-switch-related processing after stimulus onset regardless of the opportunity to prepare, we would have expected an effect on switch costs on both long- and short-CSI trials. Experiment 5 provided no evidence of a disruptive effect of post-stimulus TMS on performance or switch costs at either CSI.

Post-stimulus stimulation of the control region in Experiment 5 did have an unexpected effect. For RTs only, the reduction in congruence effect with preparation often observed, and observed here in the rIPS condition, was abolished. However, the error rates show a large reduction in congruence effect with preparation in both conditions. It is unclear whether the RT effect was spurious, or related somehow to the fact that medial parietal regions have been associated with control of response conflict (Nee, Wager, & Jonides, 2007).

Taken together, the results of both experiments suggest that the role of the right IPS in task-set control is limited to advance preparation for a change of task, or perhaps to maintenance of just-changed task-parameters. Of course null effects of TMS are notoriously hard to interpret. Perhaps the stimulation was simply not effective in suppressing processing in the underlying brain region, or perhaps it was applied at the wrong time. We can be reasonably confident that neither of these explanations is likely to be true for Experiment 5. The ERP data which correctly predicted the time course of the processes during preparation, also gave us a clear indication about the timing of the relevant post-stimulus processing. And we stimulated with the same pulse train, location and intensity as in Experiment 4, which did have a disruptive effect on ongoing processes. Unless post-stimulus reconfiguration is more resilient to TMS interference, ineffective stimulation seems an unlikely source of the null effect. Hence it most likely that right IPS is not involved in (or has a less important role in) post-stimulus reconfiguration, or that its role pre-stimulus is more to do with maintenance of changed task-set parameters until the stimulus than with reconfiguration per se.

The former may seem a surprising conclusion, especially given the widespread assumption, as in Lavric et al.'s (2008) interpretation of their data, that post-stimulus task-

set reconfiguration is essentially the same as pre-stimulus reconfiguration, but delayed. But it can be seen as consistent with our review of the imaging data. Right IPS activations were consistently reported in studies focusing on cue-related preparatory activations but not consistently reported in switch minus repeat contrasts which did not specifically target cue related processes. Moreover our results suggest that it is unlikely that this difference between the two kinds of imaging studies is due to the adaptations of the paradigm to accommodate the low temporal resolution of the BOLD signal, since our findings show right IPS involvement, without adapting the paradigm.

Earlier we considered processes that might be responsible for the reduction in switch costs with preparation. Could the right IPS play a role in inhibiting the irrelevant task-set? A meta-analysis by Nee et al. (2007) examined which cortical regions were consistently involved in a range of interference control paradigms (Stroop, go/no-go, flanker and stimulus –response compatibility).They found no evidence of right IPS activations related to most of the contrasts tested, though activations located close to the IPS but more inferior were found for congruent minus neutral contrasts in the Stroop paradigm (Nee, et al., 2007). Obviously these paradigms measure various forms of interference (e.g. response interference) and not necessarily task-set interference. Imaging studies looking specifically at overcoming task-set interference are rare. In an fMRI study done by McDonald et al. (2000) participants had to switch between the classic Stroop tasks (reading the colour name and naming the colour in which a colour word is printed). On each trial, participants were cued to do one of the two tasks. Preparatory activations were examined by using a long cue-stimulus interval (to separate cue and target related activations). Cue-related activations were bigger in the left dorso-lateral prefrontal cortex when naming colour than when reading words, suggesting a role in overcoming the interference of a well practised task, but no parietal activations were reported (MacDonald, et al., 2000).

Typically the RISC effect does not completely abolish the switch costs, but the benefit of preparation reaches an asymptote, with optimal preparation being reached after a CSI of between 500 ms and 1000 ms. These residual switch costs are often attributed to interference from the previous task-set carrying over from the earlier trial or being reactivated by the stimulus. If the latter is true than our results showed no indication that

stimulation of the right IPS results in difficulty in overcoming this interference, since post-stimulus application of TMS on trials with a long CSI, did not increase the size of the residual switch costs. Mars et al. (2007) studied the neural correlates of preparing a motor response in the context of an earlier performed motor action using fMRI[7]. Mars et al. showed that the right posterior IPS (close to our target site, see Figure 5.9) is important in programming a motor movement, regardless of whether an earlier plan was present. This suggests that these activations are not specific to overcoming interference from the existing motor plan.

If a process in the right IPS contributes to the process of task-set reconfiguration (in some way other than suppressing interference) the question arises which task-parameter does it reconfigure? As suggested by Meiran (2000) and others, in many task-switching experiments it is likely that an important component of task-set is changing which stimulus attribute one is attending to (e.g. colour or shape). Several models of what a task-set could consist of also suggest that the stimulus-response mappings (e.g. which stimulus affords which action) need to be changed in accordance with the new task-set (Vandierendonck, et al., 2010). The parietal lobe is thought to play an important role in the transition between visual perception and motor action (Rushworth & Taylor, 2006). Regions surrounding the IPS have been credited with updating visual attention as well as altering stimulus-response relationships. Both processes could potentially benefit the correct execution of a new task.

Research suggests that both left and right IPS may contribute to both processes, but the right hemisphere seems to be more important in redirecting visual attention, whereas the left seems to be more important in adjusting motor output. Rushworth, Ellison et al. (2001), for example, used TMS to show the importance of two regions near the IPS for each of these two processes (Rushworth, Ellison, et al., 2001). In the visual reorientation task, participants were cued to respond to a particular location on the screen. On some trials the location cue was invalid and participants had to quickly reorient their attention to the new location on stimulus arrival. In the motor task participants held two fingers over two buttons, a cue indicated which finger to move on stimulus onset. Again on some trials, the cue was invalid and participants needed to change the prepared response. TMS over the left

[7] Interference accounts of the residual cost attribute it to executing S-R rules in the context of continued activation (or re-activation) of earlier S-R rules.

anterior supramarginal gyrus particularly interfered with the ability to change a prepared movement and stimulation of the right angular gyrus (see Figure 5.9) interfered with reorientation of visual attention. Tunik et al. (2005) had participants grab a small bar with their thumb and index finger and showed that stimulation of the left IPS impaired the ability to readjust a hand movement, when the bar turned and required a different hand movement

There is a great deal of evidence that the parietal cortex is vital for reorienting visual attention in space (Rushworth & Taylor, 2006). As our stimuli were all presented centrally, spatial reorientation is unlikely to play a major role, though it is possible that there is some reorientation of attention to the object's periphery for the shape task, and to the centre for the colour task. However, there is increasing evidence that different regions along the IPS perform different tasks in managing visual attention (Kanwisher & Wojciulik, 2000). Le, Pardo and Hu (1998) had participants alternate between judging shape and judging colour (using red and green circles and squares). When comparing switching blocks with blocks in which participants focused only on one dimension, they found the right IPS to be more active. This suggests that the right IPS is important when shifting attention between dimensions. Rushworth, Paus et al. (2001) used an intermittent cueing paradigm (a cue to switch or stay every 9-11 trials) in which participants switched between attending to the colour of the stimulus and attending to the shape. An occasional probe task was used to check whether people attended to the right location. Switching between dimensions correlated with activations in both the left and right IPS (see Figure 5.9). However, the peak location in the right hemisphere was in a location slightly different from the target site used in the current study (Rushworth, Paus, et al., 2001).

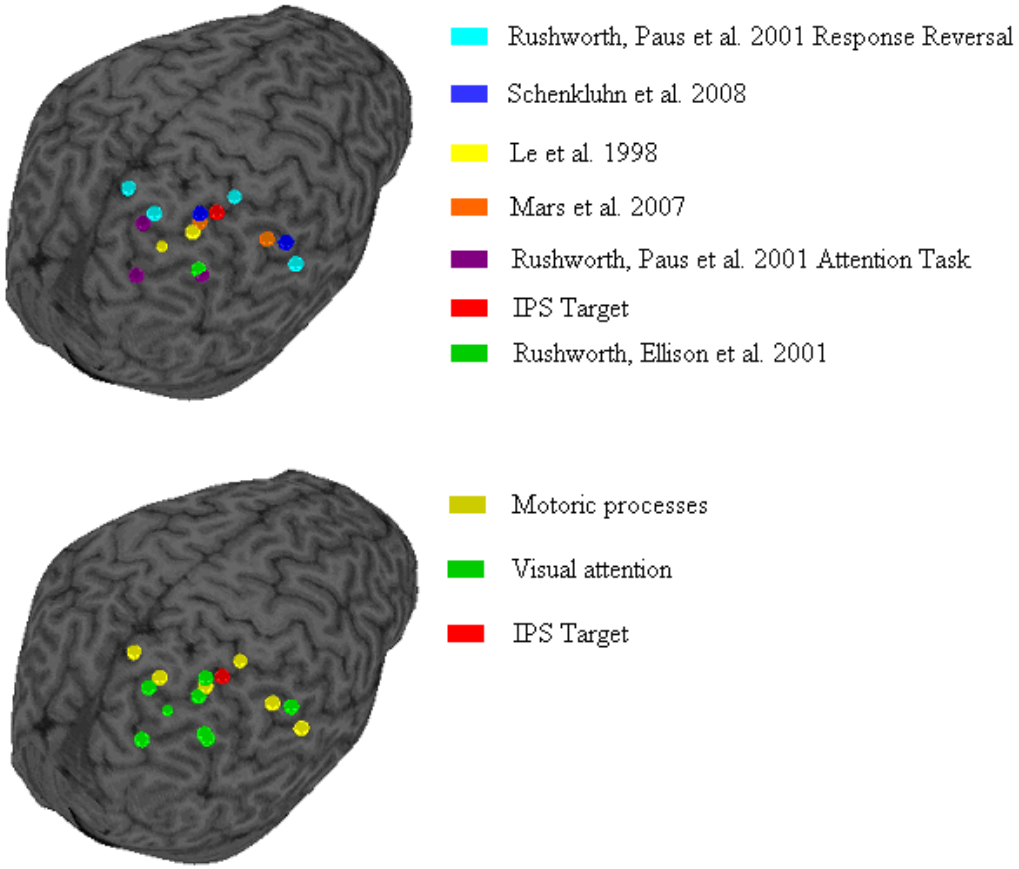
Schenkluhn Ruff, Heinen and Chambers (2008) applied TMS during cue presentation in a visual search task. Participants were required to find a stimulus among a set of distractors. A cue was presented 600 ms before the onset of the array. This cue indicated either the location of the search target or the colour of the search target. They found that stimulating different points along the right IPS (see Figure 5.9) attenuated the advantage of being cued to focus on the correct stimulus feature, being cued for the correct stimulus location, or both.

These results support the idea that the IPS is involved in changing the attended location, dimension or feature in advance of the stimulus. But a role in the management of stimulus-response mappings remains a possibility. Rushworth, Paus et al. (2001) used a paradigm in which participants switched between two sets of response mappings. Bilateral parietal activations (see Figure 5.9) were found on switch trials. The results discussed earlier by Mars et al. (2007) also show that the right IPS is important in programming actions (Mars, et al., 2007).

The right IPS location stimulated in the present study seems similar to that associated by Le et al. (1998) and Schenkluhn (2008) (see Figure 5.9) with the pro-active biasing of visual attention towards a different dimension (e.g. colour or shape). Also, most studies show a more important role for the left hemisphere in the updating of stimulus-response relationships (Kanwisher & Wojciulik, 2000; Rushworth & Taylor, 2006), and many task-switching studies report left IPS activations. Hence it is possible that right IPS is primarily responsible for attention-shifting while left IPS is primarily responsible for S-R remapping. However, the response reversal activations found by Rushworth, Paus et al. (2001) and the activations found by Mars et al. (2007) were in right IPS close to our stimulation site (see Figure 5.9), so a role for right IPS in S-R remapping or response

preparation cannot be ruled out.

Figure 5.9 Reported locations in fMRI and TMS studies looking at motoric processes and visual attention processes in the right parietal cortex as well as the location targeted in this study.



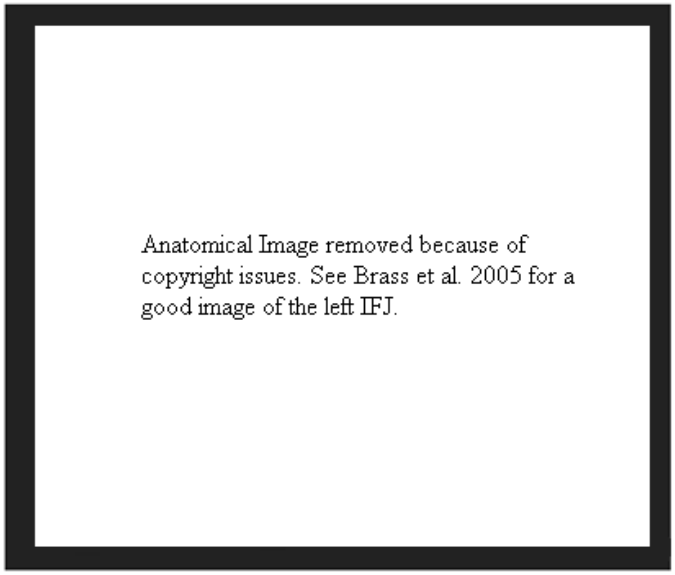
Our study illustrates how preparatory processes can be studied using TMS, and opens up the possibility of studying the precise time course of these processes and comparing the time course across regions. Reconfiguration of the various parameters of a task-set may be hierarchically organised: formation of a new goal, then re-biasing of attention, then activation of S-R rules; alternatively, multiple parameters may be altered in parallel. Present evidence is inconclusive (Vandierendonck, et al., 2010) and TMS studies could help provide an answer to this question.

Obviously it is possible that the right IPS influence found in Experiment 4 is specific to the particular pairs of tasks. Hence another target for future research would be to determine whether similar results could be obtained for other task pairs used in research on task-switching, which for example, do not require a switch between perceptual dimensions, such as the “higher/lower” “odd/even” digit task pair.

Chapter 6: Stimulation of the left inferior frontal junction during the CSI using TMS

In Chapter 1 I discussed the potential role of the left inferior frontal junction (IFJ) in task-set control. In a number of imaging experiments studying task-set control, activations have been reported in the left lateral dorsal and ventral PFC. These activations seem to be particularly abundant in the posterior part of the middle frontal gyrus, inferior frontal sulcus and inferior frontal gyrus. (See also the meta-analyses in Chapter 3). Brass, Derrfuss, Forstmann and von Cramon (2005) suggest that a region located near the junction of the inferior frontal sulcus and the inferior precentral sulcus (see figure 6.1), which they refer to as the inferior frontal junction, is particularly important in task-set control. The IFJ is located at the conjunction of a number of regions potentially harbouring functions important for implementing a new task (e.g. language, working memory and premotor areas). Brass et al. argue that it updates task representations in accordance with the new task, but this concept remains ill-defined.

Figure 6.1 Inferior frontal junction (adapted from Brass et al., 2005)



Imaging studies suggest the left IFJ is involved in task switching. Several task-switching studies attempting to isolate preparatory activations have revealed activations in the region of the left IFJ (Brass & von Cramon, 2004; Forstmann, et al., 2005; Gruber, et al., 2006). Task switching studies reporting switch minus repeat contrasts also often show these activations (Brass & von Cramon, 2004; Ruge, et al., 2005). In their meta-analysis Derfuss et al. (2005) showed that the left IFJ was consistently activated in a variety of

paradigms related to task-set control (e.g. task-switching, response reversal, WCST). The results from my meta-analysis (see Chapter 3) showed the left IFJ to be consistently involved in switch minus repeat contrasts and in the experiments isolating preparatory activations, but preparatory activations were only found when the results were pooled over switch and repeat trials.

The imaging data therefore suggests some role during task-switching but it remains unclear whether it plays a role in pro-active task-set reconfiguration. To investigate this, I stimulated the left IFJ during the CSI of a task-cueing paradigm. However, because of the diversity of results in the left inferior frontal cortex in the imaging literature, it was unclear where to apply stimulation. In a pilot study (N=4), using an MNI target based on the report by Brass et al. (2005), I found no indication of an effect. I therefore decided to use fMRI in the same paradigm to locate brain activations in this region for each participant separately. I then used TMS to stimulate the region that was more activated on switch trials than on repeat trials and was closest to the coordinates identified by Brass et al. (2005) and by my meta-analysis (which were approximately in the same location). Using fMRI to target TMS in the same individuals and in the same task is sometimes regarded as the "gold standard" — potentially superior to using a coordinate averaged from other participants in the same or a closely related fMRI experiment, or derived from a meta-analysis. However, as we shall see, in some situations the superiority may be illusory, so this study is also of some methodological interest.

In the experiment, the application of TMS during the preparation interval served as the test of whether any left IFJ activation found is involved in task-set preparation. In the fMRI phase, I did not attempt to adapt the paradigm to isolate the brain activation associated with pre-stimulus preparation from that associated with post-stimulus processing. As we have seen, this is difficult to do, and the several means used to do it (such as including cues not followed by stimuli) are problematic: they may even discourage the task-set preparation I wished to investigate. I simply ran the same long- and short-CSI conditions in the fMRI experiment as in the TMS study to follow. Whether or not these activations were actually important for preparation would be revealed by stimulating them during the CSI.

Chapter 6: Stimulation of the left IFJ during the CSI using TMS

Using online TMS on frontal regions does pose practical problems, because of their proximity to facial muscles. The muscle twitches induced can be experienced by participants as mild and tolerable, or as quite uncomfortable, so a non-trivial proportion of participants (22%) did not complete the experiment because of such discomfort. For the same reason, it is important to use a control site whose muscle and skin sensation effects are similar -- i.e. another frontal site. Considering the widespread activations found in the frontal cortex related to cognitive control, choosing such a site is not uncomplicated. Both dorsal and ventral lateral prefrontal cortices (bilaterally) have been widely associated with control of task-set and conflict. Only the anterior part of the dMFC (just anterior to the pre-SMA) seems to be relatively clear of such activations. For example, Wager et al. (2004) do not find consistent activations related to switching paradigms in the more anterior dMFC region nor does the meta-analysis I presented in Chapter 3. Importantly, earlier stimulation, using the same paradigm, of the somewhat more posterior pre-SMA did not have an impact on the RISC effect (see Experiment 1 in Chapter 4). Additionally, stimulation of this site causes comparable discomfort to stimulating left IFJ. However, in their meta-analysis, Nee et al. (2007) did find consistent activations related to the Stroop task (incongruent minus congruent contrasts) close to this region (somewhat more posterior and ventral) and the stimulation study mentioned above did find an effect on incongruent trials for the pre-SMA. The choice of this site means that one can be reasonably confident that stimulation does not impact on the RISC effect (based on earlier stimulation results), but I cannot exclude the possibility that it will have an effect on the preparation benefit for incongruent trials (CSI by congruence effect interaction). Unfortunately, our current understanding of frontal regions which are "uncomfortable" enough to compare to left IFJ stimulation, is not detailed enough to find a site of which we can be confident that it does not interfere with either index of task-set preparation.

The results of the imaging data and meta-analysis suggest two possible roles of IFJ during preparation. The switch minus repeat contrasts (with a CSI>250 ms) suggest a specificity for a change of tasks, in which case, stimulation of the left IFJ during a long CSI could result in a smaller RISC effect. However, most imaging studies using techniques for isolating preparatory activations have not found switch minus repeat differences. If any preparatory processes are not switch specific, stimulation should result in longer reaction

times on both switch and repeat trials in the long CSI -- i.e. reduce the overall benefit of preparation.

6.1 Methods

6.1.1 Participants

All participants passed the safety screening and gave informed consent in accordance with the criteria of the ethics committee of the Exeter University School of Psychology. 23 healthy participants took part in the fMRI phase. 16 (of the 23) healthy participants completed the TMS phase (mean age 23, 5 were male). The other seven did not complete the TMS phase due to personal reasons or technical problems during testing (discomfort: N=5, exclusion criteria acquired between fMRI and TMS phase: N=2).

6.1.2 Procedure

The paradigm used in this experiment was identical to the one used in the first experiment in which I studied the dMFC (Experiment 1, Chapter 4) as well as the paradigm used in the preliminary IPS pilot experiment (Experiment 3, Chapter 5): participants identified with one of four responses the colour or shape of one of 16 stimuli (4 colours and 4 shapes). As in those studies (and the ERP study of Lavric et al., 2008), switch probability was 33%, and 25% of the stimuli were congruent. Because of the loud noise in the scanner, I used visual instead of auditory cues (as did Lavric et al, 2008; see Figure 6.2). For each task, one cue was a word and the other an image indicating the task. The cue, presented in the middle of the screen, appeared at the same time as the onset of the auditory cue in the earlier experiments and remained on the screen until a response was made. The stimulus then appeared surrounding the cue. After a short CSI of either 100 ms or a long CSI of 750 ms, the stimulus was presented until one of the four keys was pressed. If an error was made, an

Figure 6.2 Visual cues used in the fMRI and TMS experiments

image indicating the correct response appeared for 2s. Otherwise, the interval from response to the next stimulus was 2.3 seconds.

6.1.3 Design of the fMRI phase

CSI (long and short) was manipulated between blocks, with 12 experimental blocks of 48 trials (following a start-up trial). The order of blocks was counterbalanced as follows. In each session CSI changed every block except between blocks 6 and 7, so that the order of blocks reversed in the second part of the session. 12 participants started with a short CSI block, 11 with a long CSI block. Of these 23 participants 16 then took part in the TMS phase, 8 of which started with a short CSI block in the fMRI phase and 8 started with a long CSI block. New pseudo-random trial sequences were generated for each participant so that each pair of blocks of the same kind contained 1/3 task-switch trials and 2/3 task repeat trials each and, similar to Experiment 1, the nature of the stimuli meant that 1/4 of the trials was a congruent trial and 3/4 was an incongruent trial. Each pair of blocks of the same kind also contained an equal number of combinations of task and response, and stimuli occurred equally often in each combination. Resting breaks of 30s were included between each block and the next. The self paced nature of the paradigm in combination with a jitter interval (random length between 0 and 1s) at the start of the experiment ensured that events and image acquisition were not linked in time. A bonus system was used according to which participants received a small monetary reward when they responded fast (to increase the motivation to prepare) and accurately. A score was presented at the end of each block: the faster the responses and the lower the error rate, the higher the score. A higher score resulted in a higher monetary reward (£0.50-£2) on top of a standard hourly rate.

6.1.4 Design of the TMS phase

CSI (long and short) and TMS (left IFJ and control) target site were manipulated between blocks, with 8 experimental blocks of 48 trials (following a start-up trial), 2 blocks for each combination of TMS target site and CSI condition. The order of blocks was counterbalanced as follows: In each session CSI changed every block and TMS condition every 2 blocks. Both TMS and CSI condition sequences were counterbalanced between

participants. New pseudo-random trial sequences were generated for each participant so that each pair of blocks of the same kind contained 1/3 task-switch trials and 2/3 task repeat trials each; as in the fMRI phase, the nature of the stimuli meant that 1 in 4 of the trials was a congruent trial and 3 in 4 were incongruent. Each pair of blocks of the same kind also contained an equal number of combinations of task and response, and stimuli occurred equally often in each combination. A bonus system was in place which was identical the one used during the fMRI phase.

6.1.5 fMRI data acquisition

Images were collected using a 1.5-T Phillips Gyroscan magnet and a 8-channel SENSE Head Coil. A T2-weighted echo planar sequence was used (TR=3000 ms, TE=50 ms, flip angle=90°, 35 transverse slices, 2.5 x 2.5 x 2.5 mm in-plane resolution, ascending acquisition). A total of 800 volumes were acquired per participant. Standard structural MRI was performed after functional scanning using a 3-D T1-weighted pulse sequence (TR=25 ms, Te=4.1 ms, flip angle=30°, 160 axial slices, 0.9 x 0.9 x 0.8 mm).

6.1.6 fMRI guided targeting

The TMS target near the left IFJ was determined for each participant separately by analysing their fMRI data and identifying the nearest switch related activation (in the switch > repeat contrast) to the left IFJ (as defined by Brass et al., 2005)

6.1.7 TMS

Both TMS equipment and TMS protocol were the same as in the other TMS experiments. Stimulation was applied in a train of 3 pulses at 20Hz. For 10 subjects it was applied at 110% of visible motor threshold, as determined at the beginning of the session. In 6 participants stimulator output was somewhat reduced (2-5%) to decrease eye and facial twitching caused by frontal TMS stimulation (an average intensity of 52% of maximum output). The stimulation was applied 250 -150 ms before stimulus onset, and hence 500-600 ms after cue onset in the long CSI condition, and immediately prior to cue onset in the

short CSI condition. In half of the blocks I stimulated over left IFJ and in half of the blocks over a control site (anterior dMFC MNI 0, 30, 60).

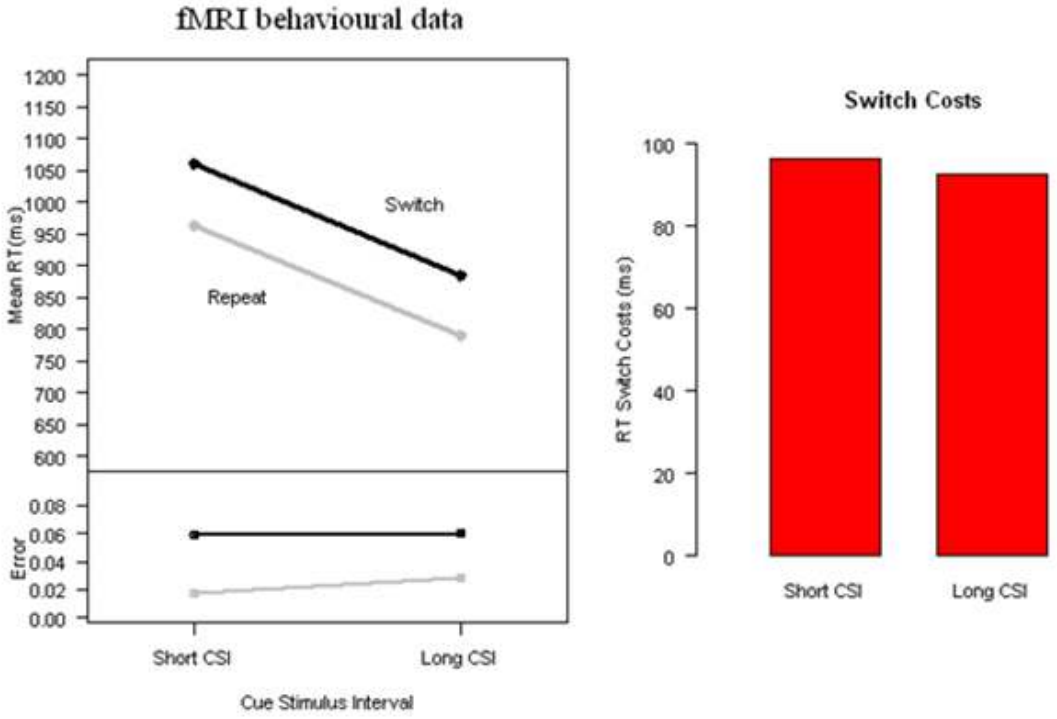
6.2 Results

6.2.1 fMRI behavioural results

Excluding trials following errors, and the first trial of each block, we computed mean correct RT and error rate for each combination of CSI, switch/repeat, congruence and task, averaged over response, and submitted them to ANOVA.

Figure 6.3 shows the mean reaction times and error rates for switch and repeat trials (left panels) and switch costs (right panels) as a function of CSI. Contrary to our expectation, there was no substantial reduction in switch cost with increasing CSI. The switch by CSI interaction was not reliable, $F(1, 22) = 0.05$, $p = .827$. For error rates, there was a very modest and non-reliable reduction, $F(1, 22) = 1.45$, $p = .241$.

Figure 6.3 Behavioral results from the fMRI experiment



Left panel shows mean reaction times and error rates as a function of CSI and switch/repeat.
Right panel shows switch costs as a function of CSI.

6.2.2 fMRI data analysis and results.

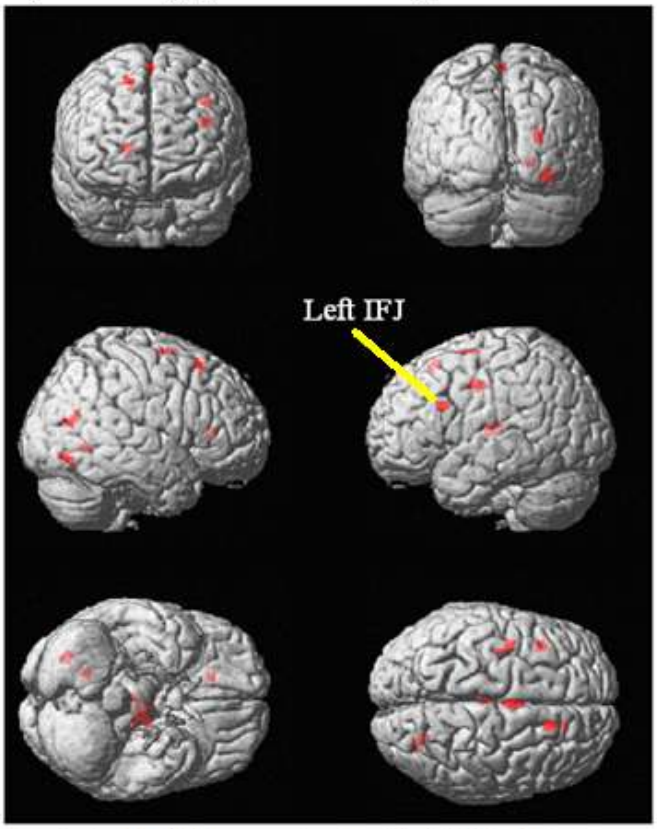
I pre-processed the imaging data using SPM8 (Welcome Trust Centre for Neuroimaging). Differences in image acquisition time were corrected, by re-referencing all slices to the middle one (slice 17). The images were corrected for motion artefacts. The realigned images were spatially normalized to the MNI-305 template (Montreal Neurological Institute). Following normalisation the images were spatially smoothed with a Gaussian kernel of 8mm FWHM. To determine the activations elicited by the manipulations of interest the standard General Linear Model approach was employed: first the predicted activation time-course ('regressor') was estimated for each experimental condition by convolving the timing of the cue onset on each trial in the respective condition with the canonical haemodynamic response function (HRF) and its time and dispersion derivatives (the derivatives were modelled for reducing the error term by capturing temporal delays

and variability). Subsequently, the regressors were correlated with the fMRI signal within the General Linear Model framework separately for each voxel in the brain volume. Prior to the regressions, a high pass filter (1/128 Hz) was applied to remove low frequency drift. There was a separate regressor for the error trials and trials after error (cue-locked). To partial out the residual effects of head movement, motion parameters extracted during motion correction were also entered in the model as nuisance regressors. A regression coefficient (beta), estimated for each condition (e.g. switch)/voxel/participant, represented the degree to which the activity of the given voxel was modulated by the respective condition. To contrast repeat activations with switch activations, differences between betas were computed for every voxel and participant to create contrast images. The results of the participant-level contrasts were used to identify the TMS target in each participant. Starting with strict correction for multiple comparisons (FWE correction), the statistical threshold was reduced gradually until an activation near the left IFJ was found (within 10mm of the dimensions of the left IFJ as defined by Brass et al. (2005).

The contrast images of all participants were then entered into the group-level, random-effects, analysis. The contrast of interest was switch trials minus repeat trials; if the left IFJ is more important during the CSI of a switch trial than of a repeat trial, a cue-locked switch>repeat contrast should reveal activations near the IFJ. The TMS experiment would reveal whether or not these activations reflect preparatory processes. The contrast images were subjected to a one sample t-test ($p<0.001$, cluster size>10, uncorrected). Results are reported in MNI space (see Table 6.1 and Figure 6.4*)*. MNI coordinates were converted, only for labelling purposes, to Talairach space (Talairach and Tournox, 1988) and entered into the Talairach Daemon (Lancaster et al., 2000) to determine anatomical labels

Switch specific activations were found near the left IFJ in the inferior frontal gyrus and near the right inferior frontal gyrus, but the latter was deeper in the brain (see Figure 6.3 and Table 6.1). Further frontal activations were found along the superior frontal gyrus, including on the border of the SMA and pre-SMA and in the precentral gyrus in the premotor areas. Switch related activations were also found in the posterior cingulate, occipital lobe and the thalamus.

Figure 6.3 Imaging results of fMRI experiment.



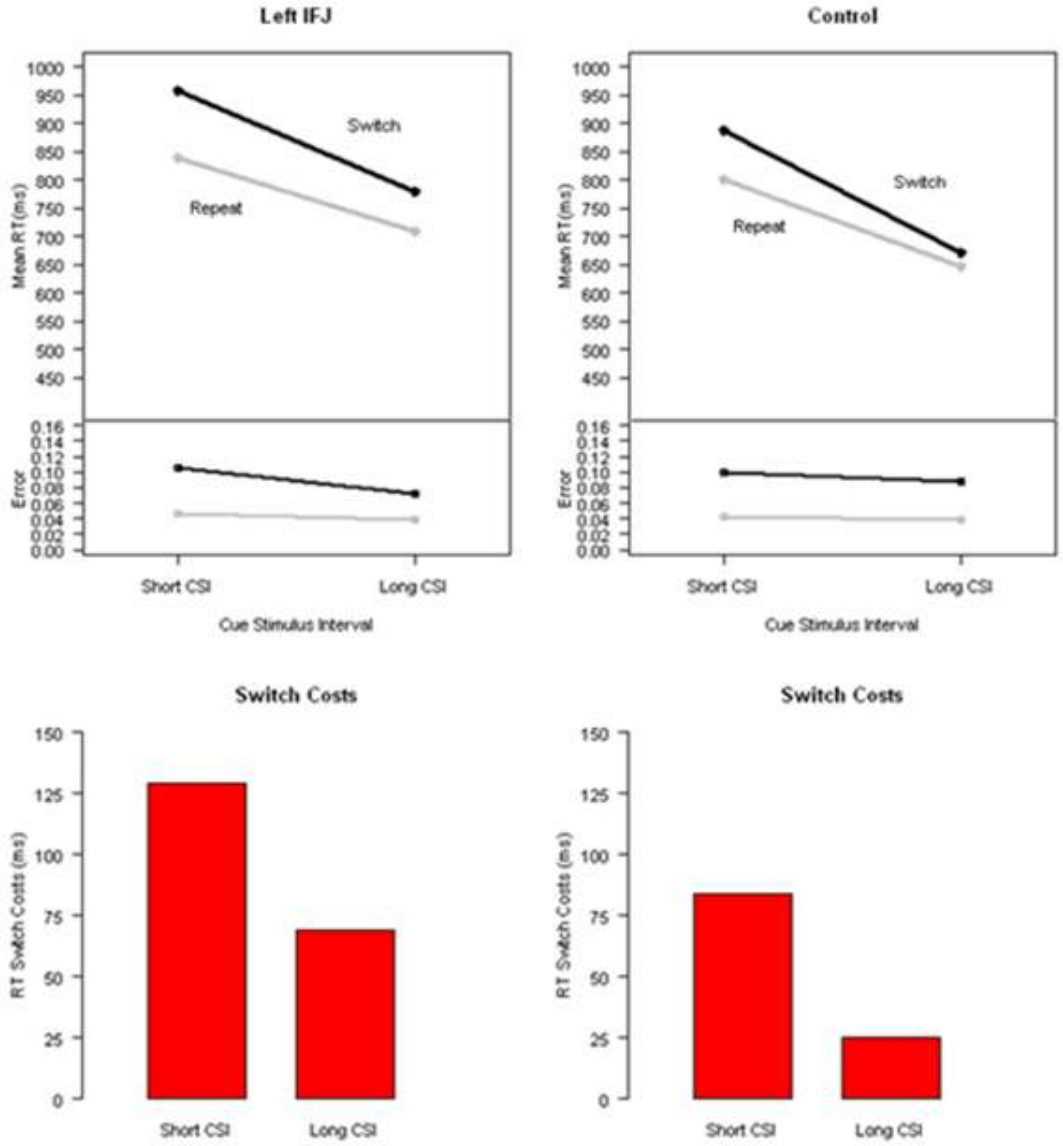
Cue-locked switch > repeat contrast (p<0.001, cluster> 10 uncorrected)

Table 6.1 fMRI results.

Region	Hem	MNI			T	Z	Size
Frontal							
Inferior Frontal Gyrus	L	-40	14	26	4.56	3.79	20
Inferior Frontal Gyrus (act white matter)	R	18	34	10	4.35	3.66	14
Superior Frontal Gyrus	R	16	26	54	4.26	3.60	13
Superior Frontal Gyrus (SMA/preSMA)	M	2	0	64	3.99	3.43	17
Precentral Gyrus	L	-40	-6	40	4.22	3.57	18
Parietal							
Posterior Cingulate	R	26	-68	16	5.35	4.24	28
Occipital							
Lingual Gyrus	R	20	-58	-2	4.34	3.65	17
Middle Occipital Gyrus	R	30	-74	-10	4.21	3.57	25
Sub Cortical							
Thalamus	L	-10	-22	12	4.11	3.51	85

Switch>Repeat, p<0.001, cl>10 (uncorrected)

Figure 6.5 Results from the TMS experiment.



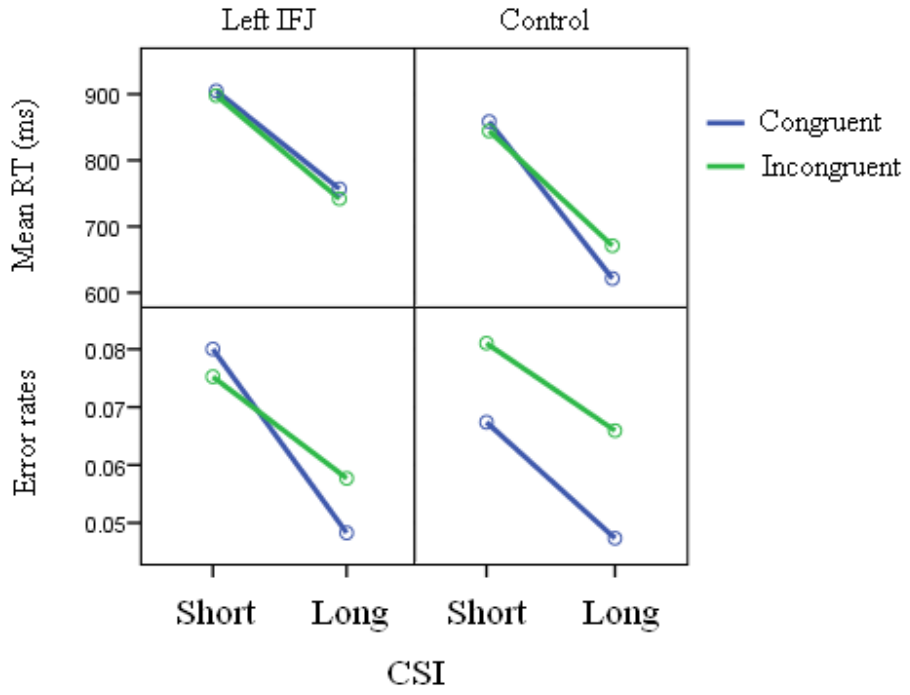
Top panels show mean reaction times and error rates as a function of CSI and switch/repeat for both TMS locations.
Bottom panels show switch costs as a function of CSI for both TMS locations

6.2.3 TMS results

Excluding trials following errors, and the first trial of each block, mean correct RT and error rate were computed for each combination of TMS condition, CSI, switch/repeat, congruence and task, averaged over response, and submitted them to ANOVA. I excluded one participant because this person had a very negative RISC effect (-2.5 times standard deviation) in the left IFJ condition. Consequently, this participant created an overly amplified impression of the predicted elimination of the RISC effect in the RTs resulting from TMS over the left IFJ in the mean reaction times. That is, an apparently strong effect in the mean data, in the direction I was looking for, was due largely to this participant alone. Removing this participant's data changed no results from significant to insignificant or vice versa.

Figure 6.5 shows the mean reaction times and error rates (after this exclusion) for switch and repeat trials (left panels) and switch costs (right panels) as a function of CSI for the two TMS target sites. There were significant main effects of switch/repeat and CSI (see appendix K and L for a complete overview of the ANOVA results. Contrary to our expectation, when the left IFJ was stimulated, a substantial reduction in switch cost with increasing CSI was seen (from 127 ms to 72 ms). A reduction was also observed (from 82 to 24 ms) when control site was stimulated. This RISC effect was smaller in the left IFJ condition, both absolutely and proportionally, but the location by switch by CSI interaction was not reliable, $F(1, 14) = .15$, $p=0.707$. In contrast, the error rates suggest a greater RISC effect in the left IFJ condition but this interaction was also not reliable, $F(1, 14)=1.00$, $p=0.328$.

Figure 6.6 Mean reaction times and error rates for the location by CSI by congruence interaction



There was a reliable main effect of location on RT $F(1,14)=10.74$ $p=0.005$, with higher mean reaction times for the left IFJ condition. This main effect was not reliable for the error rates $F(1, 14)=.12$, $p=.738$. There was also a significant location by switch interaction $F(1, 14)=10.01$, $p=0.0007$, which also was not reliable for the error rates $F(1, 14)=.29$, $p=0.600$. Average switch costs in both CSI conditions were higher in the left IFJ condition than in the control condition. Moreover, the increase in switch costs was specifically due to an increase in reaction times on switch trials; the main effect of location for switch trials only was highly reliable $F(1, 14)=20.67$, $p<0.0001$ whereas the main effect of location for just repeat trials did not reach the conventional level of significance $F(1, 14)=3.73$, $p=0.074$.

Congruence effects are displayed in Figure 6.6. There was no reliable main effect of congruence for RT, $F(1, 14)=.09$, $p=.771$, or for error rate, $F(1, 14)=.26$, $p=0.617$. The location by CSI by congruency interaction was not reliable for RTs, $F(1, 14)=2.01$, $p=.173$, or for error rates, $F(1, 14)=0.161$, $p=.695$, though there is a rather surprising suggestion of the congruence effect increasing when a long CSI allows preparation.

There was a reliable effect of task F(1, 14)=14.56, p=.002, with colour task being harder than the shape task. This was also the case in the error rates F(1, 14)=5.87, p=0.03. There was a reliable interaction between task and CSI F(1, 14)=15.26, p=.002 which was also signtificant in the error rates F(1, 14)=8.94, p=.01. Task showed a reliable interaction with location F(1, 14)=5.00, p=.042 (see Figure 6.7), the interaction in the error rates was in the opposite direction but was not reliable F(1,14)=1.71, p=.212. Stimulation of the left IFJ increased the reaction times on both tasks, but reliably more so in the colour task. The difference in task difficulty was reduced by preparation, but this effect did not differ between locations for reaction times F(1, 14)=.01, p=.927 (see Figure 6.8) error rates F(1, 14)=2.02, p=0.117. And finally the location by congruency by task three way interaction was significant F(1, 14)=5.21, p=.039 (see Figure 6.9), but not for the error rates F(1, 14)=.972, p=.341. When stimulating IFJ, the difference in task difficulty was smaller for

Figure 6.7 Mean reaction times and error rates for the location by task interaction

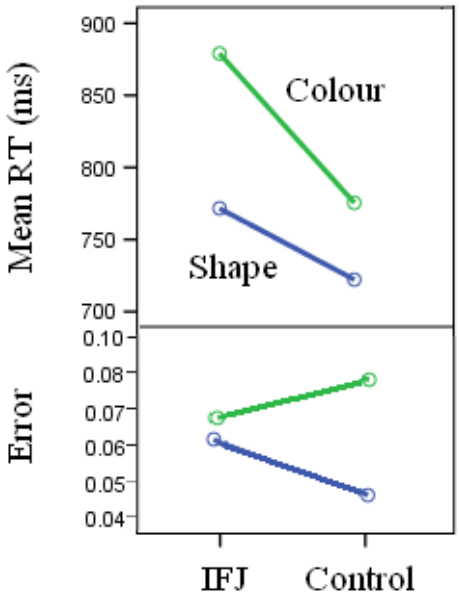
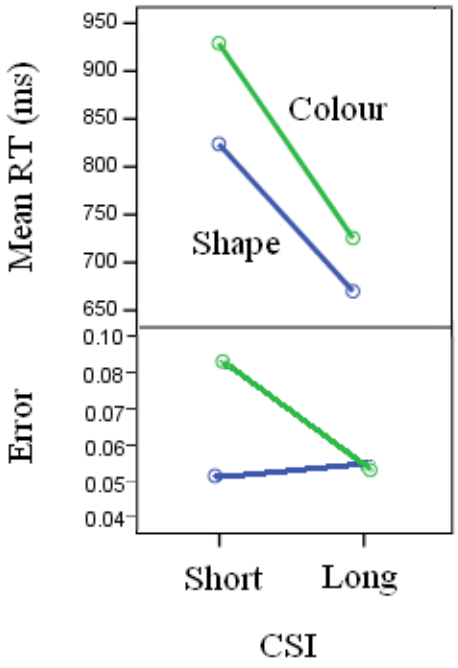
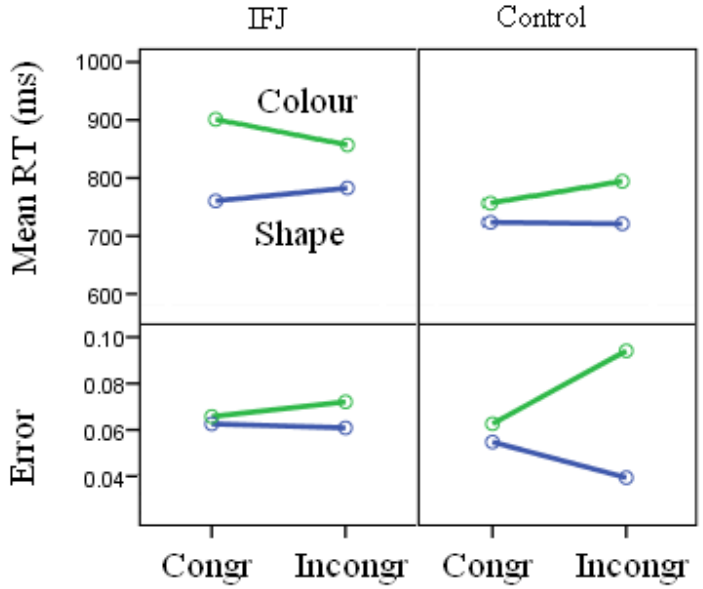


Figure 6.8 Mean reaction times and error rates for the CSI by task interaction



congruent trials, but when the control site was stimulated this effect was reversed. This seems to be mainly caused by reduced incongruent reaction times for the colour task, when stimulating the control site.

Figure 6.9 Mean reaction times and error rates for the location by task interaction



6.2.4 Localisation of the TMS site.

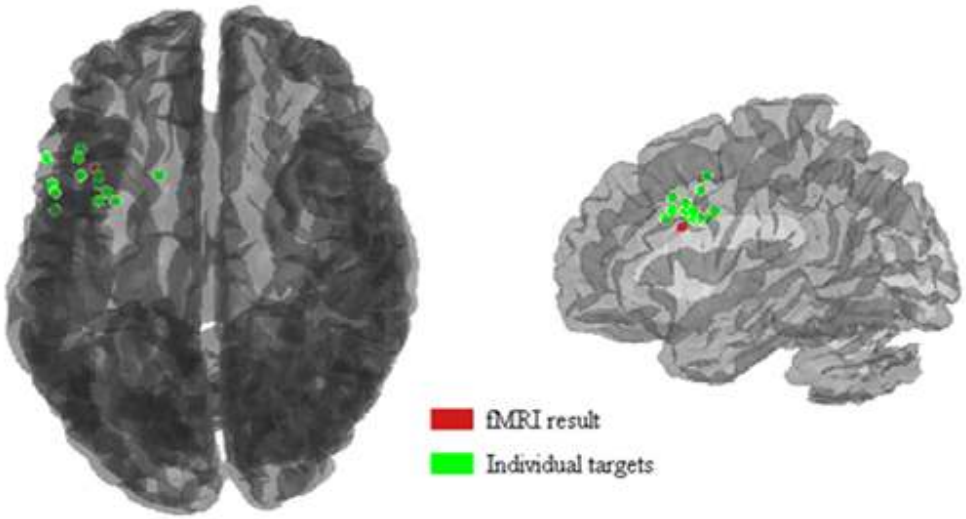
As noted above, although targeting the TMS location using each participant's own fMRI activation contrast may seem optimal, the noise in estimating individual peak fMRI activations, and in their relation to the region actually responsible, may subvert this optimality. As Figure 6.10 shows, there was substantial variation in the locus of the participants' peak left inferior frontal activations relative to the fMRI group mean results for the switch > repeat contrast. In as much as individual localisations are noisy and imperfect it may be that the average activation location over participants would have been a better guide.

With this in mind, in Figure 6.11[8] I show the relation between, on the one hand the Euclidian distance between the individual's peak activation and that obtained from the

[8] Figure 6.10 shows that the fMRI average is not in the middle of the targeted coordinates as one might expect. This is partly because more participants were included in the fMRI study then in the TMS study. Also the peaks targeted in the TMS study reflect a cluster of voxels of varying size, spread in terms of location and

group data and, on the other, the participant's RISC effect contrast. The latter was determined by subtracting the switch cost in the long CSI from that in the short CSI (i.e the higher this number, the greater the RISC effect). A remarkably strong positive correlation was obtained, $r(13)=0.67$, $p=0.006$. When the TMS was applied to the mean switch > repeat activation, the RISC effect was reduced. To exclude the possibility that this correlation is not due to the effect of stimulation but the consequence of some relationship between the effectiveness of preparation and the individual's peak activation for the switch/repeat effect I also ran a correlation between the distance between the individual's peak activation in the IFJ and that obtained from the group data with the RISC effect in the control condition, which was not reliable, $r(13)=0.37$, $p=0.163$ (see Figure 6.12).

Figure 6.10 Mean fMRI result near the left IFJ and individual targeted coordinates



statistical strength. All this information is included in the fMRI group analysis and the peak of the group therefore does not have to be in the middle of the individually targeted peaks.

Figure 6.11 Correlation between the RISC effect in the left IFJ condition and the distance between the targeted coordinates and the result of the fMRI study in this region

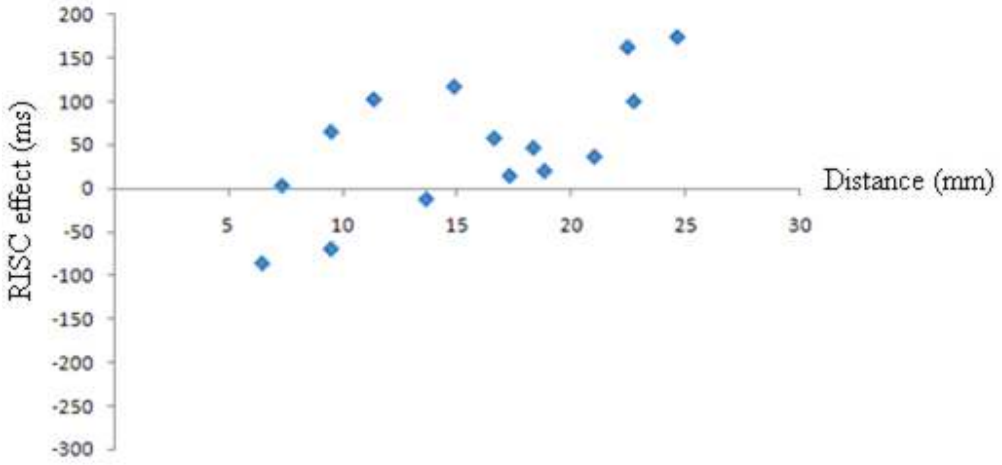
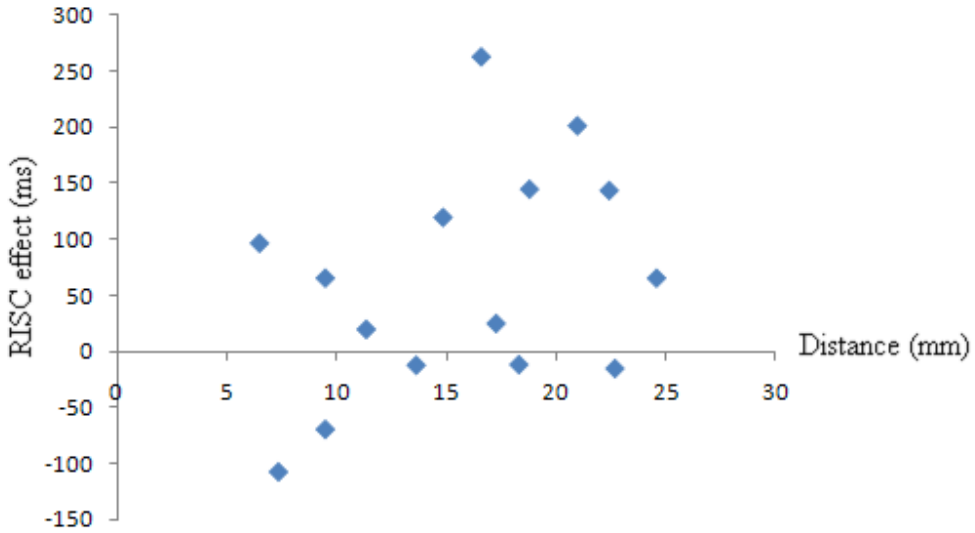


Figure 6.12 Correlation between the RISC effect in the control condition and the distance between the targeted coordinates and the result of the fMRI study in this region



Similarly, I determined the correlation between the RISC effect in the study and the Euclidian distance from the IFJ location found in my meta-analysis in Chapter 3 (see figures 6.10, 6.11 & 6.12). There was a small positive correlation with the result from 18 switch minus repeat contrasts and the RISC effect in the IFJ condition, r(13)=0.30 (see Figure 6.13 and Chapter 3, Table 3.3) and there was no noteworthy correlation between the

Chapter 6: Stimulation of the left IFJ during the CSI using TMS

Euclidean distance from the meta-analyses results in the left IFJ based on 15 studies that attempted to isolate preparatory activations by using a paradigm adapted to the low temporal resolution of the BOLD signal and the RISC effect in the IFJ condition, r=0.12(see Figure 6.14 and Chapter 3, Table 3.5).

Figure 6.13 Correlation between the RISC effect during the left IFJ stimulation and the distance between the targeted coordinates and the result of the meta-analysis of the switch minus repeat contrasts

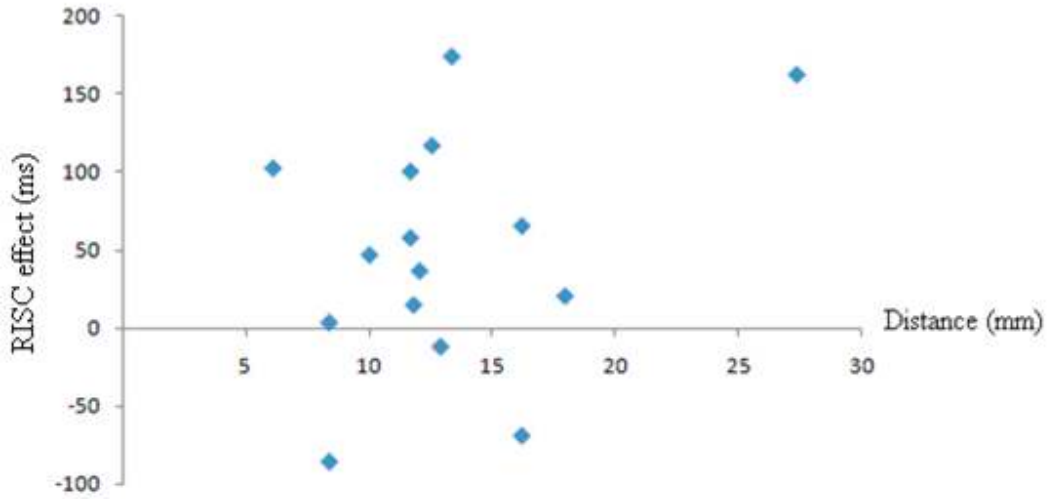
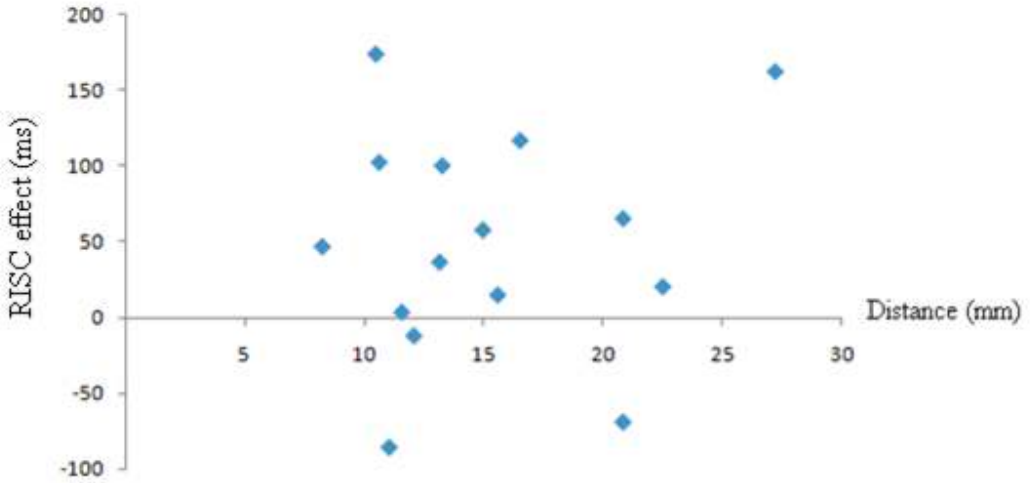
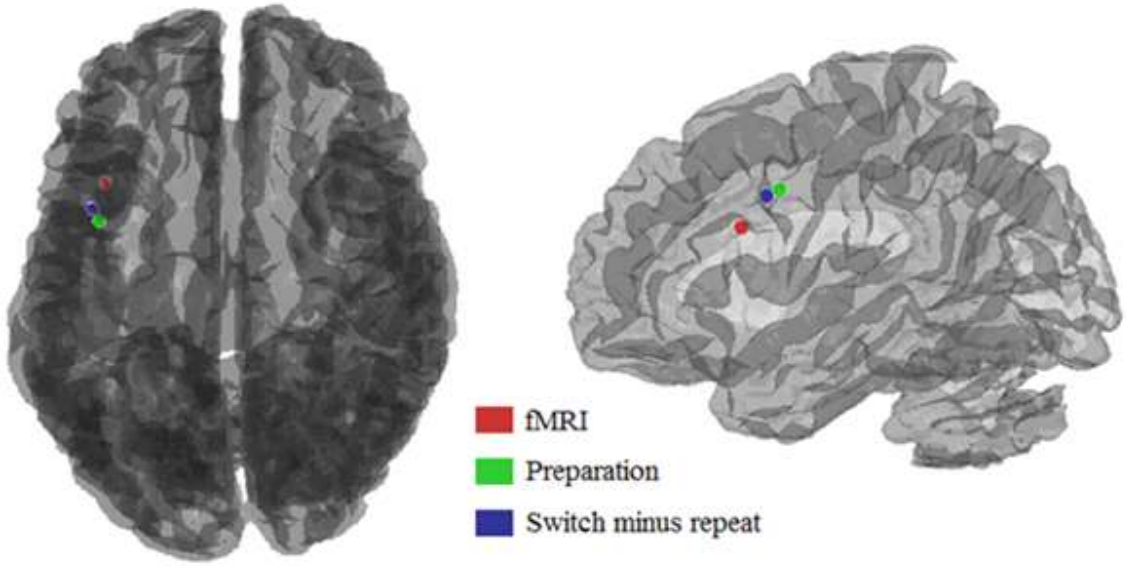


Figure 6.14 Correlation between the RISC effect during the left IFJ stimulation and the distance between the targeted coordinates and the result of the meta-analysis of studies attempting to isolate preparatory activation, pooled over switch and repeat trials



In order to shed some light on whether there was a relationship between the quality (e.g. the extent to which the signal in each person reflected a genuine measure of switch related preparatory activations) and the ability to reduce the RISC with TMS over the target I also examined correlations (a) between the RISC effect and the strength of the fMRI signal in each person and (b) between the RISC effect in the TMS phase (stimulating left IFJ) and the RISC effect in the fMRI phase. Both correlations were negligible.

Figure 6.15 fMRI and meta-analyses results near the IFJ



6.3 Discussion

TMS, guided by individual switch>repeat activations found near the left IFJ using fMRI, resulted in an increase of average RT in both the long CSI and short CSI as compared with a control site and increased the switch costs as compared to the control site. Moreover these effects were largely due to an increase in reaction times on switch trials. These results show that the IFJ is specifically important for task-set reconfiguration and the fact that stimulation was applied during the CSI suggests that the IFJ might house processes for the pre-stimulus phase of a switch trial. It must however be noted that stimulation just before cue onset affected the switch costs on short CSI trials as well, which leaves open the possibility that the effect of the TMS endured after the stimulation ended and effected non preparatory switch related processes.

Even though the overall location by CSI by switch interaction was not reliable, the reduction in switch costs was relatively bigger in the control site (-72%) than in the IFJ condition (-48%) (the error rates however show the opposite pattern). Because I stimulated in different places in each person, the possibility exists that the overall results and a lack of a reliable location by RISC interaction was due to variability in the appropriateness of the

TMS location in the IFJ region. If this regions hosts switch related preparatory activations then the switch>repeat contrast from the group analysis could reveal peaks in this region (since the BOLD signal related to the CSI is imbedded in this contrast). And indeed, there was a strong positive relationship between the RISC effect and the Euclidean distance between the target in each person and the centre of switch-related activations near the left IFJ in the group fMRI result (switch> repeat). The closer a participant's targeted location was to the switch-related activation peak from the average fMRI data, the smaller the RISC effect was when stimulated[9]. This result suggests that, in spite of the absence of a reliable effect in the average behavioural data, the left inferior PFC might play an important role in proactive task-set control. The combination between the fMRI group results and the results from the TMS experiment indicate that the source of these proactive task-set control processes is located about 1 cm along the inferior frontal sulcus anterior to the peak activation found in the meta-analyses and to the IFJ as defined by Brass et al. (2005) (see Figure 6.15).

TMS over the left IFJ also had a particular negative impact on the mean reaction times in the colour task (which is also the more difficult task as measured by response latency and error rate) as opposed to the shape task, suggesting a possible role in the colour task or a higher involvement in more difficult tasks.

This study found no reliable difference between IFJ and control site in the effect of stimulation on the reduction in the congruence effect with increasing CSI: indeed there was little sign of any congruence effect at the short CSI to reduce by preparation.

6.3.1 Discomfort due to stimulation

Since an effect of TMS over IFJ on performance was present in both short CSI (when stimulation is before the cue) and long CSI conditions, it is important to take into account the possibility that stimulation of the left IFJ simply caused more discomfort than the control site, interfering with overall performance. Seven people did report a difference in feelings between both locations; six reported that they felt the left IFJ more than the control site and one person the other way around. However, only one of those described these

[9] As pointed out before, the absence of a similar correlation between the RISC in the control condition and the distance between the targeted coordinate and the group S>R results ensures this is due to stimulation in the left IFJ site and not due to a relationship between the location of the individuals activation and the success of preparation.

feelings as causing discomfort. And there was no correlation between overall reaction time in the left IFJ condition, r(13)=0.08 or size of RT switch cost, r(13)=-0.27 with the level of difference in sensations between the TMS sites as indicated by the participants (participant comments were rated on a scale from 1 to 3). Also, as described in the method section of this chapter, any potential participant with clear muscle twitching resulting from stimulation of either site was not included in the study. Because the stimulation targets in the left IFJ condition were close together, the correlation shown in Figure 6.11 cannot be explained on the basis on effects of discomfort. Also, error rates were not higher in the IFJ condition, which one might expect when discomfort is particularly high in that condition compared to the control site.

6.3.2 Concurrence with the imaging literature

The imaging literature on task-set preparation contains several reports of a lack of differences between switch and repeat trials (see review in Chapter 1 and 3). The results of the present study however suggest that the region surrounding IFJ hosts processes active during the pre-stimulus phase particularly important to switch trials, and that a specific region (approximately 10mm anterior of the centre of the IFJ), activated in the switch minus repeat contrast, could be particularly important during preparation for a task switch.

The difference between the location of control processes along the inferior frontal sulcus in my meta-analyses as well as in the imaging literature and the location identified in this study, could potentially be explained by the existence of variations between paradigms. For example, many experiments included in my meta-analyses as well as those included in Brass (2005) use different tasks to switch between, often using the letter/digit task pair (odd/even, consonant/vowel) introduced by Rogers and Monsell (1995). Such differences in the tasks used could be one of the sources of the great variability of active frontal regions reported in imaging studies of task-set control.

6.3.3 fMRI behavioural results

Like a number of fMRI studies of task-set preparation, the behavioural results of the fMRI experiment showed no reliable RISC effect (though the subsequent TMS experiment did).

It is not entirely clear why this is the case. One possible cause could be a combination of the scanner environment and the nature of the RISC effect. If the reconfiguration account of the RISC effect is correct, getting the effect requires participants to engage in an optional and probably effortful process. Their willingness to do so may be vulnerable to the context in which they must perform, and their motivational state. It is possible that, even though there was a bonus for rapid and accurate performance, the loud noises, darkness, feeling of enclosure, and lying down in the scanner distract from or reduce motivation for engaging in advance preparation.

The lack of a RISC effect means the imaging results from the switch minus repeat contrast cannot be interpreted as containing preparatory activations. However, the fact that theTMS was applied during the CSI and, the relationship between the left IFJ activation and the effect of stimulation on the RISC effect are suggestive of the presence of preparatory processes in this region. Perhaps the combination of the TMS results and the fMRI results suggest the possibility that this region is important during preparing for switching as well as switching without preparation.

6.3.4 Is TMS guided by individual fMRI activations the gold standard?

The results of the TMS study showed that the fMRI guided approach did not work quite as intended. The average switch>repeat peak activation from the group fMRI analysis was a better predictor of the effective TMS site for disrupting task-set preparation than the individual peak activation. By lowering the threshold until a potential target was found, I increased the Type 1 error rate in some participants, which consequently increased the chance of targeting a false positive. This however does not seem to explain why the individual targets were not always a good guide since there was no relationship between the statistical threshold at which the target was acquired in each person and that person's RISC effect.

Sack et al. (2009) showed that fMRI guided experiments required the smallest number of participants to show a reliable effect when compared to other ways of targeting (see Chapter 2). However these studies were done using perhaps more consistent and predictable imaging results (as compared to the difficulties in measuring preparatory BOLD

signal in task-switching) and in the parietal not the frontal cortex, where functional localisation is possibly more diffuse than in some other regions of the brain.

It is likely that many different processes happen during the switch trials of a task-cuing paradigm and between-participant variability in frontal activations during switching is likely to be high. The fMRI-guided approach might therefore become less efficient in paradigms with larger complexity and variability of the underlying processes. The reason why the fMRI-guided approach did not precisely identify a locus of proactive task-set control in some of our participants might be that other switch-related processes were also active in that region. The fact that stimulation affected the switch costs in both long and short CSI conditions points in this direction.

6.3.5 Task specific effects

Stimulation of the left IFJ also had more impact on reaction times on the colour task specifically. This suggests that the region surrounding the left IFJ is either specifically important for the colour task or that, since the colour task is the harder one, it becomes more important when a more difficult task is executed. There is evidence that the inferior frontal sulcus contains task-specific processes, but these are especially related to language (e.g. Yeung et al., 2006).

6.3.6 The possible role of the left IFJ in task-set reconfiguration.

These results show that, in line with my meta-analysis as well as earlier work by, among others, Brass et al. (2005), the inferior frontal region near the IFJ is important for task-set reconfiguration. Additionally, the correlation between the RISC effect and the distance from the individual targets in TMS study and switch specific fMRI group result as well as the fact that the TMS was applied during the CSI suggest the presence of processes in this region that are specifically important in the pre-stimulus phase of a switch trial. The results from this study also suggest that the locus of control lies somewhat more anterior along the inferior frontal sulcus than the IFJ. As pointed out before, the actual location of the control region might depend on the type of tasks used to switch between.

In Chapter 1, I mentioned the idea that this region, considering its vicinity to important language, working memory and premotor areas, could combine information from these areas and be involved in retrieving and maintaining task rules in verbal working memory and perhaps provide other motor and visual attention regions with signals to start preparing for a changed task.

After a cue is presented on a switch trial, this region could retrieve the new task rules (and possibly suppress the old ones), which would be in accordance with the idea that this region is important for updating working memory(Wager & Smith, 2003). On a repeat trial the task rules still need to be maintained/refreshed in verbal working memory, which would explain why it is difficult to distinguish switch specific preparatory activations using fMRI. Also, the TMS results show that, even though the reaction times on repeat trials were not reliably affected by IFJ stimulation as opposed to the control site ($p=0.074$), they were higher in the IFJ condition.

Besides retrieving the task-rules, other possibility remain; perhaps verbal processes are used to generate the task ‘goal’ or to generate a verbal label for the perceptual dimension to attend to (e,g, ‘attend to colour’).

Chapter 6: Stimulation of the left IFJ during the CSI using TMS

Chapter 7: General Discussion

7.1 Summary of results & conclusion

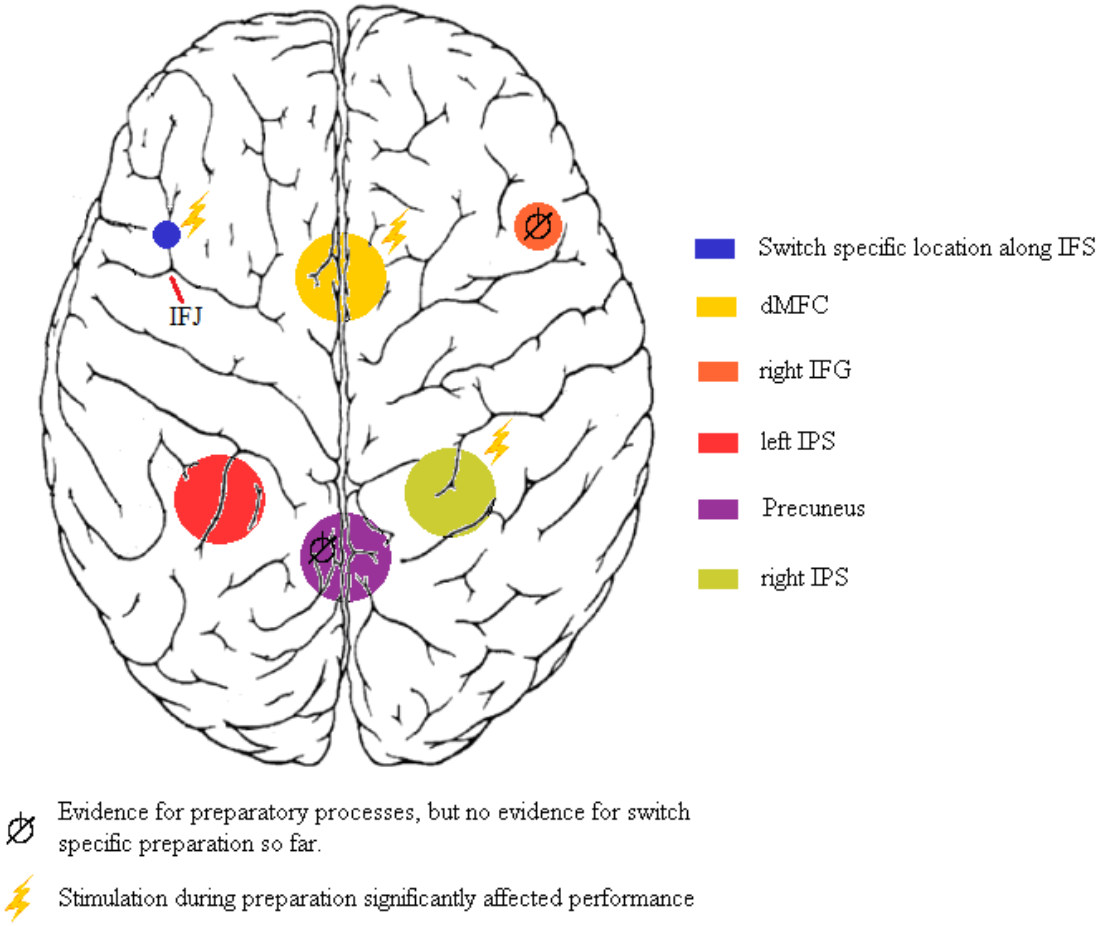
Since the introduction of fMRI a number of imaging studies have been done using task-switching paradigms to try to identify which brain regions show more activation on task-switch trials than on task-repeat trials. An increasing number of studies has also tried to identify which regions are important for specific aspects of task-set control. In Chapter 1, I presented peak activations from these studies together to show how inconsistent the activations obtained are. One of the goals of my thesis project was to identify, with a novel meta-analysis of available imaging studies, brain regions consistently related to switching between tasks and in particular to preparatory task-set reconfiguration. The second goal of this project was to use TMS to study whether certain regions are necessary for aspects of task-set control, especially task-set preparation. As described in Chapter 2, TMS has two advantages over fMRI for studying preparatory phenomena: it has high temporal resolution, and it also allows us to determine whether a region contributes causally to task-set control, rather than being merely epiphenomenally activated. But TMS studies cannot randomly sample the surface of the scalp and potential times for stimulation; they must rely on fMRI studies to suggest candidate regions and ERP studies to suggest the timing of control-related processes. Thus the two goals were closely related. Ideally, the imaging meta-analysis would precede the TMS studies to guide the selection of regions to stimulate, but it must be acknowledged that, given the pragmatics of a PhD project, the two strands of the thesis were developed more in parallel. And of course a number of imaging studies have been published since I began the project, so the database for the meta-analysis has evolved.

In my meta-analysis I studied which regions were consistently activated in the whole set of task-switch minus task-repeat contrasts available in the literature, as well as in a sub-group of studies intended to explore preparatory task-set control more specifically. Switch minus repeat contrasts showed consistent activations in dorsal MFC and the left IFJ. An extent based criterion revealed a consistent contribution of the left superior parietal cortex, but these activations seemed to be quite variable with respect to their precise location. Splitting up the switch minus repeat contrasts into a group with CSIs longer than 250ms (providing an opportunity for pre-stimulus preparation) and a group with a CSI

shorter than 250ms (little or no opportunity) gave the unexpected result that the left IFJ was consistently involved in studies with a long CSI and the dMFC in studies with the short CSI.

I also analysed the results from studies that adapted a task-switching paradigm to isolate the BOLD signal, specifically related to preparatory activations. The studies were split up in two groups: a group that found reliable differences between preparatory activations on switch trials as opposed to repeat trials and a second group that did not find such differences and therefore reported the preparatory activations pooled over switch and repeat trials. The results of these analyses found consistent preparation related activations that were reliably bigger on switch trials then on repeat trials, in the left IPS. Additionally, the analyses showed consistent preparation related activations, pooled over switch and repeat trials, in the right IPS, the dMFC, precuneus and the left IFJ as well as one voxel in the right IFG and three voxels in the right precentral gyrus. The approximate locations of all but the last of these regions are shown in Figure 7.1.

Figure 7.1 Cortical regions found to be important for preparation in this thesis.



In a series of task-cuing studies, I applied a short train of TMS pulses to a number of these regions. In all the studies the cue specified one of two tasks requiring attention to the colour or shape of a visual object. The stimuli could be congruent (same response in both tasks) or incongruent (response depended on the task). In all but Experiment 5, the TMS was applied either during a long CSI, at a time indicated by ERP evidence to be critical for task-set preparation, or at the same time before the stimulus but also before the task cue in a short-CSI condition. In the task-cueing paradigm, effective task-set preparation can be indexed by a *reduction in the switch cost* (RISC) with increasing CSI, and/or by a reduction in the congruence effect with increasing CSI. The question, then, was whether TMS during preparation would attenuate these effects relative to their magnitude when a control site was stimulated.

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Experiment 1 stimulated the pre-SMA and the SMA; the tasks were to identify either the colour or shape of the stimulus as one of four alternatives; switch tasks were in a minority, and 75% of the stimuli were incongruent, Stimulation of the SMA resulted in an attenuation of the RISC effect whereas stimulation of the pre-SMA resulted in an attenuation of the reduction in the congruence effect. In Experiment 2, I tried to replicate these findings using binary shape and colour classification tasks, and with the proportion of congruent and incongruent trials, and of switch and repeat trials, equated. The results of this study showed signs of the same effects, but these were unfortunately not reliable.

In Experiment 3, the initial pilot experiment on the contribution of parietal regions in pro-active control of task-set, I stimulated the left and the right IPS as well as a control site, during preparation, using the same tasks as in Experiment 1. There was a RISC effect when left IPS or the control site was stimulated, but stimulation of the right IPS abolished the RISC effect. However, the location by CSI by switch interaction was not reliable. I hypothesised that this was due, at least in part, to the location of the control site being too close to the SMA and the direction the coil was positioned in the control condition. In Experiment 4, focusing on the right IPS, I therefore moved the control site to a more posterior location and changed the coil direction. When the control site was stimulated, there was evidence of task-set preparation, as indexed by a significant RISC effect, but stimulation of the right IPS had a negative effect on people's ability to prepare for a switch trial, as indicated by a substantial attenuation of that RISC effect. These results are a clear indication that the right IPS hosts processes important for preparatory task-set reconfiguration.

The meta-analysis of imaging data had suggested that this region was more activated on task-switch than on task-repeat trials, but only when there was time available for preparation, suggesting that its role in task-set reconfiguration might be limited to advance preparation. In Experiment 5, I tested this by stimulating after stimulus onset. This had no effect on performance or switch costs, supporting the somewhat surprising suggestion from the imaging meta-analyses that some brain regions associated with anticipatory preparation for a task-switch are not involved (or are much less involved) when the task-switches are required without preparation.

My final experiment (Experiment 6) targeted the region in left inferior frontal cortex known as the inferior frontal junction. I stimulated during the CSI of a task-cuing study using the same paradigm as in Experiments 1 and 3. In this study, I used fMRI in the same paradigm to identify the individual switch-specific activation in the left inferior frontal cortex of my participants which I then used to target the TMS in the same individual. The results of the experiment showed that stimulation of the region surrounding the left inferior frontal junction increased the switch costs in both short and long CSI conditions. Furthermore the closer stimulation was applied to the average point of peak activation along the left inferior frontal sulcus obtained for the whole group of participants (switch>repeat trials), the more it reduced the ability to prepare. This result suggests that this particular region along the left IFS, might be specifically important for preparing for a switch trial.

In summary, these experiments have identified the following regions as playing a role in task-set preparation: medial frontal cortex (Experiment 1, though Experiment 2 provided only weak evidence); right intra-parietal sulcus (Experiments 3 and 4), and left inferior frontal junction (Experiment 6). In addition to these localisations, the experiments provide evidence at least suggestive of two intriguing functional dissociations.

First, I exploited two potential behavioural indices of effective preparation for a change of task: the RISC effect and the reduction in the congruence effect with increasing CSI. In the behavioural literature, the RISC effect is quite often not accompanied by a reduction in the congruence effect (Monsell and Mizon, 2006). As far as I am aware, no systematic analysis has been done testing whether the converse is ever the case; it seems probable that researchers may not have examined their data for a reduction in the congruence effect in the absence of a RISC. Hence, one might have speculated that advance task-set preparation has two degrees or levels of efficacy: the first level activates the new task-set sufficiently to get the appropriate task done when the stimulus occurs -- perhaps by reorienting attention to the relevant dimension. The second achieves more in the way of suppression of the irrelevant S-R rules, but perhaps requires more control effort, so it is not always seen[10]. However, the results of Experiment 1 provide evidence for

[10] Note that this is different from the two-stage accounts of task-set reconfiguration proposed to explain the residual cost. See review in Chapter 1.

something more radical: a double dissociation between the RISC and the reduction in the congruence effect. TMS to the pre-SMA eliminated the latter effect leaving the RISC; TMS to SMA had the opposite effect. This suggests that suppressing the impact of the irrelevant S-R rules and reconfiguring other aspects of task-set, such as the dimension to which attention is biased, may be effected by different parts of the control network, and independently rather than as steps of increasing difficulty.

The second functional dissociation suggested by the results is between brain regions that are active during preparation for a change of task, and brain regions activated post-stimulus by the need to change tasks when no preparation was possible. It is a common assumption of task-set reconfiguration theories that, given the opportunity to prepare, the participant can accomplish the same reconfiguration process before the stimulus that they would otherwise need to perform after the stimulus (Roger and Monsell, 1995; Karayanidis, Coltheart, Michie, & Murphy, 2003; Monsell & Mizon, 2006; Lavric, et al., 2008); i.e. the same process simply moves forward in time from after, to before the stimulus. And in electrophysiological studies, it has been claimed that the late posterior positivity signature of task-set reconfiguration seen on long RSI/CSI trials behaves as this would predict, being detectable after the stimulus on short CSI trials (Karyanidis et al, 2003; Nicholson et al., 2005; Lavric et al, 2008). My findings suggest a different picture. The effects of TMS applied to right IPS in Experiments 4 and 5 suggest that this region is specifically important for preparation, but not for switching without preparation. Of course it is possible that the post-stimulus TMS, though targeted in time on the basis of the ERP data, missed the critical activity. However, the meta-analysis also suggested a dissociation: medial frontal cortex is more involved when switching with a small or no CSI and the left IFJ when switching with a long CSI (although, as indicated in Chapter 3, this contrast needs to be interpreted with caution). Additionally the right IPS is consistently found by studies isolating preparatory activations but not by studies that contrast switch trials with repeat trials without looking at preparation. Hence there may be qualitative differences between preparing for a switch and switching without preparation.

7.2 Methodological issues

The variability of localisations across fMRI studies is a problem for using fMRI studies to select precise regions to target with TMS. The use of meta-analytic techniques to identify consistent regions of activation across such studies is surely an improvement on impressionistic sampling of the literature, though it does depend on assumptions about the appropriate groupings of studies for the meta-analysis. Then one must translate from these average peak activations to the appropriate locus over an individual scalp. The next step in sophistication is to target TMS activation on the basis of a prior fMRI study using the same paradigm though this too requires translation from average data to individual coil placement. A further increment still would seem to be to use the same participants in the fMRI and the TMS study, and target the TMS for individuals on the basis of their own peak activations. This strategy has been successful in some TMS studies in other domains. This was the strategy I attempted to apply in Experiment 6, and the results suggest that this may be a step too far for task-switching.

First, a full FWE correction often did not reveal individual switch versus repeat differences. Second, as discussed in Chapter 3, switch minus repeat contrasts often show great variability in terms of imaging results. In these circumstances, individual peak activations are likely to be a very noisy guide to the optimum coordinates for TMS. In fact my data suggested they were inferior to the average peak activation for the whole group of participants. The overall RISC effect did not show a reliable attenuation from individually targeted TMS of IFJ. But the closer an individual's targeted area was to the group peak activation, the more TMS during preparation attenuated the RISC.

Hence one might argue that using fMRI in the same paradigm with another group of participants and taking their average peak activation as the target is no worse, and may be better, because it does not require the TMS session to follow an fMRI session (though switch costs are quite robust to practice, Rogers and Monsell. 1995).

Moreover, apart from the cost in time and resources, there is at least some evidence that task-set preparation -- a voluntary process -- is vulnerable to the distractions and anxiety of being tested in the scanner: no RISC effect has been detected in some fMRI studies (Sohn et al.,2000; Sakai & Passingham, 2003), as well as no difference in cue-

related activations on switch and repeat trials. In my own fMRI experiment, the RISC effect was very weak in the scanner, but robust in the TMS control condition.

In my experiments meta-analysis of imaging data has turned out to be an adequate guide to localise regions apparently associated with preparation for a task switch, and it is certainly less labour intensive and expensive. This does not mean there is no place for the fMRI-guided approach when, for example, one is studying a region that is not very consistently associated with the function of interest (but still appears interesting). Or when one has reasons to believe the paradigm used differs in some key respect from the majority of the studies used by the imaging literature.

7.3 Task related processes

The task-switching literature is remarkable for the wide range of pairs of tasks used, and it seems likely that some of the differences between pairs of tasks might have important consequences for the brain regions and processes involved. For example, my studies focus on switches between tasks requiring attention to different perceptual dimensions (colour and shape). Other studies have required switches between semantic attributes (e,g, the magnitude and parity of digits). In as much as I could examine this issue in my meta-analysis, I found no differences in consistent activations between the different types of task pair. This could however be merely a consequence of the relatively low number of contrasts in each group.

Another feature of my experiments is that the two tasks of the pair are quite similar to each other, differing only in the perceptual dimension relevant and the meaning of the responses. I might have seen more task-specific effects if I used tasks requiring processing in very different domains. For example , Yeung et al. (2006) used a word task and a face task and showed several regions to be specifically related to switching to one of the tasks. For example the left IFG was specifically active when switching to the word task and the right IFS was specifically related to switching to the face task (see Chapter 1).

Throughout my thesis I used two types of task to switch between; classification tasks (Experiments 2, 4 & 5) and identification tasks (Experiment 1, 3 & 6). Differences in the effect of TMS between these two types shows a mixed picture; the results in Chapter 4 on the role of the dMFC show a difference in the effect of TMS on the RISC and reduction

in the congruence effect with increasing CSI in these two types of task. In Chapter 5 however, similar results of stimulation of the right IPS were obtained for both types of task (attenuation of the RISC effect), although stimulation of the right IPS during the classification tasks did leave a small RISC effect, whereas stimulation during the identification tasks fully abolished the RISC effect.

7.4 Future research

7.4.1 Other brain regions

Other than the regions I have already tried, the meta-analyses suggest three cortical regions which are candidates for a role in proactive task-set control using TMS (see Figure 7.1). The first would be the left IPS. In my pilot experiment (Experiment 3), I found that preparation while stimulating the left IPS reduced the switch cost from 101 ms to 72 ms. This did not significantly differ from preparation while stimulating in the right IPS in which no RISC effect was observed. This reduction seems to be smaller than that found in other experiments, such as when stimulating the pre-SMA using the same paradigm in Experiment 1, which led to a reduction in switch cost from 109 ms to 34 ms. The possibility remains that, even though a RISC effect was observed, it might still be affected by stimulation. The left IPS is also the only region that turned out to be reliably more activated during preparation on switch trials then on repeat trials in studies of task set preparation. Additionally, source localisation of the switch-related preparatory component in the ERP data (as done by Lavric et al. 2008) suggests that left parietal activations are related to proactive task set control. It would therefore be a logical step to stimulate the left IPS and compare the RISC effect to stimulation of a control site, similar to the first right IPS study I did after the pilot (Experiment 4).

Another region that would be interesting to stimulate is the right inferior frontal gyrus. This region has been associated with resolving response conflict (Aron, 2007) and damage to it increases switch costs and congruence effects in a switching paradigm (Aron et al, 2004). My meta-analysis shows some indication that this region may be involved during the CSI. It would be interesting to test whether it has switch specific proactive properties during task switching. If stimulation of the IFG during the CSI affects the RISC

effect, then this would provide support for the idea that inhibitory processes play a role during task-set preparation.

Finally it would be interesting to stimulate the precuneus. This region is consistently found by studies of proactive control, however so far, except results from source localisation in ERP studies (Rushworth et al., 2002, Lavric et al, 2008), there is no evidence that this is task-switch specific. It would be very interesting to further explore this region's contribution during task switching.

7.4.2 Relationship between the RISC effect and reduction in the congruence effect with increasing CSI

The double dissociation I found in Experiment 1 on the dMFC, suggests that the RISC and the reduction in the congruence effect might depend on separate underlying processes associated with slightly different regions of dMFC. To further study the relationship between these effects, a better understanding is needed of the conditions under which preparation leads to a reduction in response conflict. For example, it is conceivable that, like to RISC, the consistency of the reduction in the congruence effect might depend on switch frequency and incongruency/congruency ratio. Perhaps participants are less inclined to prepare for potential response conflict, if the number of congruent trials is high. Additionally, it might be possible to replicate the double dissociation by stimulating different regions. For example, because of its proposed role in response inhibition, stimulation of the right IFG might attenuate the preparation benefit for response incongruent trials specifically and a within subject comparison with stimulation of the left IFS could conceivably reproduce this double dissociation.

7.4.3 Chronometric properties

Because of the temporal precision of the stimulation, and its short-lived effect, TMS is particularly suitable to study the timing of cognitive functions associated with particular brain regions. I exploited this relatively crudely in my experiments on the right IPS, stimulating before and after stimulus onset. It would be interesting to study differences between preparatory and post-stimulus switch-related contributions of other regions as well. For example, if it is true that components of task-set reconfiguration move forward in

time into the preparation interval (on most trials) when the interval is long enough, then in a brain region responsible for such a component, the effect of stimulating after the stimulus should depend on CSI. If the CSI is short, post stimulus onset stimulation should increase the switch costs, whereas, the same stimulation on long CSI trials should not have this effect.

Another possibility would be to study the chronometric properties of the preparatory processes in each of the regions involved more precisely. In Experiments 1,2,3,4 and 6 I applied the TMS during the same 100 ms interval 500 ms after the cue, it is however possible to stimulate at different moments during the CSI, perhaps using a shorter TMS burst, for example lasting 50 ms. If we were to find differences in when the particular regions are vulnerable to stimulation, then this could be useful in formulating potential hypotheses about the relationships between these regions. For example, it is often presumed that the source of proactive control is in the frontal cortex and that this somehow biases ongoing processes in the parietal cortex. If this is true then one could hypothesise that frontal contributions start before parietal contributions do. It could also contribute to our knowledge of whether task-set is as a hierarchically organised structure or whether different task-parameters are adjusted in parallel (Vandierendonck, et al., 2010).

This kind of research is however not easy to accomplish. The behavioural phenomena of interest in task switching paradigms are often complex interactions and, in order to get enough experimental power, an experiment probing several test moments greatly increases the number of trials. Also, there is likely to be great variability in what actually happens during the CSI on different trials. For example, there is evidence that an individual's average performance on prepared switch trials is a mixture of slow and fast trials, possibly reflecting successful and unsuccessfully prepared trials (De Jong, 2000). This variability can make it difficult to successfully find consistencies in the chronometric properties of the processes under study.

7.4.4 Functional contributions of brain regions to task-set preparation.

What we know about the regions involved in pro-active control suggests a number of hypotheses about what might be happening during task-set preparation. Throughout the thesis I have touched on some of these possible hypotheses. Having determined that it is

possible to disrupt preparation by applying TMS to region R, the logical next step is to use TMS to start testing hypotheses about the functional role of region R to task-set preparation. I will briefly discuss some of the possible next experiments for the three regions I stimulated.

Right IPS. In Chapter 5 I propose that right IPS might be involved in altering the attentional bias to attend to a different perceptual feature (e.g. changing from attending to colour to attending to shape). In the imaging literature this region has however also been implicated in preparation when switching between tasks that do not require a switch in perceptual dimension. For example, some experiments used the Rogers and Monsell (1995) task pairs, presenting a letter-number pair and asking participants to classify the digit as odd/even task or the letter as consonant/vowel task (Brass & von Cramon, 2004; Ruge, et al., 2009); although some attentional selection is required here, it is not obviously selection of different perceptual dimensions. Perceptual selection is even less obviously required when participants are presented with just a single digit to classify by either parity or magnitude. If stimulation of the right IPS during the CSI of such an experiment had an effect similar to that in Experiment 4, we could be confident that biasing perceptual attention is not the only process happening in that region, or broaden our concept of attention to accommodate selection of semantic attributes.

dMFC. A potential next step in studying the role of the dMFC during task-set preparation following from my work would be stimulate the pre-SMA and SMA during the CSI of a task switching experiment, while manipulating the number of stimulus-response mappings used per task. One of the possible reasons for the difference in results between Experiment 1 and 2 is the use of a paradigm employing 4 stimulus-response mappings per task in Experiment 1 and two stimulus-response mappings per task in Experiment 2. As described before, it is thought that the dMFC might play an important role in the management of stimulus-response rules (see Chapter 3 & 4). The proposed manipulation could provide us with a way of testing whether the contribution of the pre-SMA and SMA to proactive task-set control differs depending on the number of stimulus-response mappings used. It might be interesting to test whether this manipulation should be implemented block wise

(change the number of stimulus-response mappings between blocks) or whether stimulation of the dMFC has a differential effect on proactive control when varying the number of stimulus-response mappings per task on a trial to trial basis. The first scenario is more similar to Experiment 1 and 2 in which the number of mappings differed between experiments. The second scenario could potentially provide compelling evidence that the contribution of the dMFC depends on the number of stimulus-response mappings to be prepared on the present trial. However, if stimulus-response complexity is an important factor for dMFC involvement, such a mixed block might be complex enough in itself, resulting in an effect of stimulation on trials with a binary task as well.

Left inferior-frontal junction. The results of the fMRI-guided study of the region surrounding the left IFJ (Experiment 6) suggested that the source of switch specific preparatory activations was about 1 cm more anterior along the IFS than the junction with the precentral sulcus. This suggests that perhaps it is not (only) the IFJ that is important for task-set control, as suggested by Brass et al. (2005), but processes located further along the left IFS. I would be interesting to test this idea by comparing the effects of stimulation at different locations along the IFS.

One potential reason for the difference in location between my study and the IFJ could be the fact that the paradigm used differed in some respect from most of the paradigms used in the imaging literature (which mostly use binary classification tasks). Comparing the results from applying stimulation at different places along the IFS on the RISC effect in my paradigm with applying the same stimulation during a paradigm in which participants switch between binary classification tasks could reveal effects of paradigm differences on the location of the source of switch related preparatory processes along the IFS.

The results from the meta-analyses suggest that the IFJ region is not strongly associated with switch-specific processes when the paradigm does not allow time to prepare. A logical next step would be to stimulate the switch > repeat peak from the fMRI data after stimulus onset, similar to the IPS post-stimulus study (Experiment 5). This experiment could also provide further evidence for the existence of qualitative differences between preparing for a switch trial and switching without the ability to prepare.

Its location near Broca's area points to a potential role in verbal processing during preparation. One possibility is that it is important for verbal rehearsal of the task rules in advance of the stimulus. Another possibility is that verbalisation plays a role in retrieving goal or task-rules into procedural working memory during preparation. A potential way of testing whether its contribution is of a verbal nature is to do a within subject comparison between the effects on the RISC effect of articulatory suppression (Miyake et al., 2004) and TMS to left IFS, during the CSI. If both cause a similar effect, than this adds to the idea that this region's contribution involves verbal processes.

7.5 Conclusion

It was the intention of the work laid out in this thesis to further our understanding of the neural basis of proactive task-set control through the use of meta-analysis and the application of TMS to show the essential contributions of various brain regions to our ability to exert top-down control during task-switching. I think my experimental work and quantitative analysis of the imaging literature have successfully achieved such advancement. It is my hope that, by showing that this type of cognitive control can be manipulated in this way, my findings will open up new possibilities to further explore the specific functional contributions of the various brain regions involved in proactive task-set control and the organisation between them.

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Appendix

Overview appendices

	ANOVA tables
Appendix A	Reaction times Experiment 1
Appendix B	Error rates Experiment 1
Appendix C	Reaction times Experiment 2
Appendix D	Error rates Experiment 2
Appendix E	Reaction times Experiment 3
Appendix F	Error rates Experiment 3
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Appendix H	Error rates Experiment 4
Appendix I	Reaction times Experiment 5
Appendix J	Error rates Experiment 5
Appendix K	Reaction times Experiment 6
Appendix L	Error rates Experiment 6

Appendix A ANOVA table reaction times Experiment 1 (all 3 TMS conditions)

	Type III Sum of Squares	df	Mean Square	F	Sig.
Loc	4058.553	2.000	2029.277	.215	.808
Error(Loc)	282996.887	30.000	9433.230		
CSI	3364057.948	1.000	3364057.948	98.971	.000
Error(CSI)	509855.122	15.000	33990.341		
Switch	904418.077	1.000	904418.077	116.194	.000
Error(Switch)	116755.705	15.000	7783.714		
Congruency	955040.232	1.000	955040.232	91.151	.000
Error(Congruency)	157163.432	15.000	10477.562		
Task	585633.141	1.000	585633.141	21.239	.000
Error(Task)	413594.823	15.000	27572.988		
Loc * CSI	10994.639	2.000	5497.319	1.120	.340
Error(Loc*CSI)	147288.712	30.000	4909.624		
Loc * Switch	18356.295	1.617	11351.289	2.296	.130
Error(Loc*Switch)	119899.887	24.257	4942.967		
CSI * Switch	86629.343	1.000	86629.343	16.304	.001
Error(CSI*Switch)	79700.836	15.000	5313.389		
Loc * CSI * Switch	30587.084	1.851	16521.583	2.465	.107

Appendix

Error(Loc*CSI*Switch)	186138.404	27.770	6702.831		
Loc * Congruency	7574.563	1.581	4790.358	.797	.435
Error(Loc*Congruency)	142575.357	23.718	6011.234		
CSI * Congruency	6582.127	1.000	6582.127	1.652	.218
Error(CSI*Congruency)	59776.454	15.000	3985.097		
Loc * CSI * Congruency	33763.756	2.000	16881.878	5.136	.012
Error(Loc*CSI*Congruency)	98602.367	30.000	3286.746		
Switch * Congruency	17693.771	1.000	17693.771	5.564	.032
Error(Switch*Congruency)	47697.306	15.000	3179.820		
Loc * Switch * Congruency	1844.831	1.603	1150.997	.265	.721
Error(Loc*Switch*Congruency)	104574.971	24.042	4349.648		
CSI * Switch * Congruency	8291.752	1.000	8291.752	1.152	.300
Error(CSI*Switch*Congruency)	107955.753	15.000	7197.050		
Loc * CSI * Switch * Congruency	22213.814	1.780	12478.115	1.683	.207
Error(Loc*CSI*Switch*Congruency)	197986.948	26.703	7414.317		
Loc * Task	442.157	2.000	221.079	.047	.954
Error(Loc*Task)	141061.291	30.000	4702.043		
CSI * Task	39851.078	1.000	39851.078	7.770	.014
Error(CSI*Task)	76932.348	15.000	5128.823		
Loc * CSI * Task	1110.141	2.000	555.070	.120	.888
Error(Loc*CSI*Task)	139268.018	30.000	4642.267		
Switch * Task	56924.395	1.000	56924.395	11.457	.004
Error(Switch*Task)	74526.954	15.000	4968.464		
Loc * Switch * Task	2514.440	1.972	1274.789	.342	.710
Error(Loc*Switch*Task)	110287.412	29.587	3727.620		
CSI * Switch * Task	4625.308	1.000	4625.308	.737	.404
Error(CSI*Switch*Task)	94197.412	15.000	6279.827		
Loc * CSI * Switch * Task	1376.574	1.687	816.209	.147	.829
Error(Loc*CSI*Switch*Task)	140586.523	25.298	5557.173		
Congruency * Task	53450.700	1.000	53450.700	7.396	.016
Error(Congruency*Task)	108409.391	15.000	7227.293		
Loc * Congruency * Task	891.090	2.000	445.545	.070	.932
Error(Loc*Congruency*Task)	190659.947	30.000	6355.332		
CSI * Congruency * Task	148.506	1.000	148.506	.049	.828
Error(CSI*Congruency*Task)	45672.082	15.000	3044.805		

Appendix

Loc * CSI * Congruency * Task	11149.224	1.664	6702.051	2.479	.112
Error(Loc*CSI*Congruency*Task)	67457.263	24.953	2703.339		
Switch * Congruency * Task	21305.678	1.000	21305.678	3.581	.078
Error(Switch*Congruency*Task)	89250.769	15.000	5950.051		
Loc * Switch * Congruency * Task	4476.238	1.954	2290.514	.578	.563
Error(Loc*Switch*Congruency*Task)	116074.359	29.314	3959.722		
CSI * Switch * Congruency * Task	5179.187	1.000	5179.187	.761	.397
Error(CSI*Switch*Congruency*Task)	102130.581	15.000	6808.705		
Loc * CSI * Switch * Congruency * Task	6631.826	1.649	4020.953	.594	.529
Error(Loc*CSI*Switch*Congruency*Task)	167583.934	24.740	6773.871		

Appendix B ANOVA table error rates Experiment 1 (all 3 TMS conditions)

	Type III Sum of Squares	df	Mean Square	F	Sig.
Loc	.014	1.766	.008	1.434	.255
Error(Loc)	.146	26.485	.005		
CSI	.004	1.000	.004	1.954	.182
Error(CSI)	.034	15.000	.002		
Switch	.445	1.000	.445	47.542	.000
Error(Switch)	.140	15.000	.009		
Congruency	1.590	1.000	1.590	20.579	.000
Error(Congruency)	1.159	15.000	.077		
Task	.193	1.000	.193	6.842	.019
Error(Task)	.422	15.000	.028		
Loc * CSI	.007	1.804	.004	1.355	.273
Error(Loc*CSI)	.079	27.061	.003		
Loc * Switch	.007	2.000	.004	2.220	.126
Error(Loc*Switch)	.049	30.000	.002		
CSI * Switch	.000	1.000	.000	.005	.943
Error(CSI*Switch)	.050	15.000	.003		
Loc * CSI * Switch	.002	1.992	.001	.500	.611
Error(Loc*CSI*Switch)	.069	29.884	.002		
Loc * Congruency	.002	1.546	.001	.276	.704
Error(Loc*Congruency)	.112	23.186	.005		
CSI * Congruency	.000	1.000	.000	.013	.909

Appendix

Error(CSI*Congruency)	.011	15.000	.001		
Loc * CSI * Congruency	.001	1.955	.000	.258	.769
Error(Loc*CSI*Congruency)	.044	29.322	.001		
Switch * Congruency	.317	1.000	.317	23.506	.000
Error(Switch*Congruency)	.202	15.000	.013		
Loc * Switch * Congruency	.005	1.424	.004	.716	.455
Error(Loc*Switch*Congruency)	.107	21.354	.005		
CSI * Switch * Congruency	.007	1.000	.007	8.908	.009
Error(CSI*Switch*Congruency)	.011	15.000	.001		
Loc * CSI * Switch * Congruency	.005	1.757	.003	1.103	.340
Error(Loc*CSI*Switch*Congruency)	.067	26.355	.003		
Loc * Task	.009	1.873	.005	1.382	.267
Error(Loc*Task)	.103	28.091	.004		
CSI * Task	.006	1.000	.006	3.127	.097
Error(CSI*Task)	.029	15.000	.002		
Loc * CSI * Task	.001	1.779	.000	.135	.851
Error(Loc*CSI*Task)	.085	26.686	.003		
Switch * Task	.008	1.000	.008	1.304	.271
Error(Switch*Task)	.094	15.000	.006		
Loc * Switch * Task	.001	1.995	.000	.146	.865
Error(Loc*Switch*Task)	.074	29.924	.002		
CSI * Switch * Task	.000	1.000	.000	.064	.804
Error(CSI*Switch*Task)	.018	15.000	.001		
Loc * CSI * Switch * Task	.004	2.000	.002	.770	.472
Error(Loc*CSI*Switch*Task)	.081	30.000	.003		
Congruency * Task	.140	1.000	.140	7.144	.017
Error(Congruency*Task)	.294	15.000	.020		
Loc * Congruency * Task	.001	1.897	.000	.108	.888
Error(Loc*Congruency*Task)	.080	28.454	.003		
CSI * Congruency * Task	.002	1.000	.002	.295	.595
Error(CSI*Congruency*Task)	.122	15.000	.008		
Loc * CSI * Congruency * Task	.001	1.768	.001	.278	.733
Error(Loc*CSI*Congruency*Task)	.067	26.520	.003		
Switch * Congruency * Task	.023	1.000	.023	4.363	.054
Error(Switch*Congruency*Task)	.078	15.000	.005		

Appendix

Loc * Switch * Congruency * Task	.012	1.398	.009	2.142	.153
Error(Loc*Switch*Congruency*Task)	.085	20.977	.004		
CSI * Switch * Congruency * Task	.004	1.000	.004	.559	.466
Error(CSI*Switch*Congruency*Task)	.102	15.000	.007		
Loc * CSI * Switch * Congruency * Task	.006	2.000	.003	.888	.422
Error(Loc*CSI*Switch*Congruency*Task)	.106	30.000	.004		

Appendix C ANOVA reaction times Experiment 2 (all 3 TMS conditions)

	Type III Sum of Squares	df	Mean Square	F	Sig.
Loc	310.592	2.000	155.296	.007	.993
Error(Loc)	669881.763	30.000	22329.392		
CSI	2715346.173	1.000	2715346.173	196.119	.000
Error(CSI)	207680.660	15.000	13845.377		
Switch	160283.088	1.000	160283.088	26.831	.000
Error(Switch)	89608.443	15.000	5973.896		
Congruency	525409.578	1.000	525409.578	62.645	.000
Error(Congruency)	125806.481	15.000	8387.099		
Task	145454.383	1.000	145454.383	2.113	.167
Error(Task)	1032635.458	15.000	68842.364		
Loc * CSI	213.603	1.849	115.522	.013	.983
Error(Loc*CSI)	247738.215	27.735	8932.183		
Loc * Switch	6092.738	1.816	3354.180	1.822	.183
Error(Loc*Switch)	50148.336	27.247	1840.514		
CSI * Switch	21666.818	1.000	21666.818	10.348	.006
Error(CSI*Switch)	31407.562	15.000	2093.837		
Loc * CSI * Switch	1557.925	2.000	778.963	.146	.865
Error(Loc*CSI*Switch)	160446.739	30.000	5348.225		
Loc * Congruency	1973.912	1.463	1349.622	.337	.650
Error(Loc*Congruency)	87815.142	21.939	4002.786		
CSI * Congruency	27156.728	1.000	27156.728	7.049	.018
Error(CSI*Congruency)	57790.335	15.000	3852.689		
Loc * CSI * Congruency	5000.937	2.000	2500.469	.900	.417
Error(Loc*CSI*Congruency)	83364.855	30.000	2778.828		
Switch * Congruency	3526.019	1.000	3526.019	1.201	.290
Error(Switch*Congruency)	44023.251	15.000	2934.883		

Appendix

Loc * Switch * Congruency	4010.116	2.000	2005.221	.532	.593
Error(Loc*Switch*Congruency)	113082.518	29.998	3769.724		
CSI * Switch * Congruency	6073.907	1.000	6073.907	2.846	.112
Error(CSI*Switch*Congruency)	32013.403	15.000	2134.227		
Loc * CSI * Switch * Congruency	733.178	2.000	366.589	.110	.896
Error(Loc*CSI*Switch*Congruency)	99855.700	30.000	3328.523		
Loc * Task	16053.065	1.898	8456.712	2.231	.128
Error(Loc*Task)	107921.261	28.474	3790.175		
CSI * Task	19057.197	1.000	19057.197	8.537	.011
Error(CSI*Task)	33484.817	15.000	2232.321		
Loc * CSI * Task	2160.361	1.493	1447.390	.249	.717
Error(Loc*CSI*Task)	130178.710	22.389	5814.440		
Switch * Task	17.886	1.000	17.886	.003	.957
Error(Switch*Task)	90965.052	15.000	6064.337		
Loc * Switch * Task	1082.758	2.000	541.379	.213	.810
Error(Loc*Switch*Task)	76410.789	30.000	2547.026		
CSI * Switch * Task	6033.246	1.000	6033.246	2.484	.136
Error(CSI*Switch*Task)	36436.270	15.000	2429.085		
Loc * CSI * Switch * Task	51.979	2.000	25.990	.010	.990
Error(Loc*CSI*Switch*Task)	75332.555	30.000	2511.085		
Congruency * Task	42421.041	1.000	42421.041	5.445	.034
Error(Congruency*Task)	116867.559	15.000	7791.171		
Loc * Congruency * Task	3894.009	2.000	1947.005	.748	.482
Error(Loc*Congruency*Task)	78053.389	30.000	2601.780		
CSI * Congruency * Task	1301.816	1.000	1301.816	.841	.374
Error(CSI*Congruency*Task)	23207.845	15.000	1547.190		
Loc * CSI * Congruency * Task	373.139	2.000	186.569	.095	.910
Error(Loc*CSI*Congruency*Task)	58961.970	30.000	1965.399		
Switch * Congruency * Task	3354.662	1.000	3354.662	.985	.337
Error(Switch*Congruency*Task)	51099.116	15.000	3406.608		
Loc * Switch * Congruency * Task	4671.223	2.000	2335.612	1.665	.206
Error(Loc*Switch*Congruency*Task)	42092.577	30.000	1403.086		
CSI * Switch * Congruency * Task	11.748	1.000	11.748	.008	.930
Error(CSI*Switch*Congruency*Task)	22278.405	15.000	1485.227		
Loc * CSI * Switch * Congruency * Task	347.545	2.000	173.772	.083	.920

Appendix

Error(Loc*CSI*Switch*Congruency*Task)	62683.977	30.000	2089.466

Appendix D ANOVA table error rates Experiment 2 (all 3 TMS conditions)

	Type III Sum of Squares	df	Mean Square	F	Sig.
Loc	.011	1.979	.006	.648	.529
Error(Loc)	.253	29.684	.009		
CSI	.001	1.000	.001	.448	.513
Error(CSI)	.047	15.000	.003		
Switch	.079	1.000	.079	7.893	.013
Error(Switch)	.150	15.000	.010		
Congruency	1.213	1.000	1.213	48.874	.000
Error(Congruency)	.372	15.000	.025		
Task	.176	1.000	.176	3.190	.094
Error(Task)	.827	15.000	.055		
Loc * CSI	.000	2.000	.000	.011	.989
Error(Loc*CSI)	.072	30.000	.002		
Loc * Switch	.012	2.000	.006	1.181	.321
Error(Loc*Switch)	.147	30.000	.005		
CSI * Switch	.016	1.000	.016	2.395	.143
Error(CSI*Switch)	.097	15.000	.006		
Loc * CSI * Switch	.018	1.473	.012	2.606	.109
Error(Loc*CSI*Switch)	.101	22.090	.005		
Loc * Congruency	.008	2.000	.004	1.410	.260
Error(Loc*Congruency)	.085	30.000	.003		
CSI * Congruency	.018	1.000	.018	5.181	.038
Error(CSI*Congruency)	.053	15.000	.004		
Loc * CSI * Congruency	.002	1.899	.001	.173	.831
Error(Loc*CSI*Congruency)	.140	28.487	.005		
Switch * Congruency	.028	1.000	.028	5.696	.031
Error(Switch*Congruency)	.074	15.000	.005		
Loc * Switch * Congruency	.022	1.913	.011	4.054	.030
Error(Loc*Switch*Congruency)	.081	28.699	.003		
CSI * Switch * Congruency	.003	1.000	.003	.578	.459
Error(CSI*Switch*Congruency)	.066	15.000	.004		
Loc * CSI * Switch * Congruency	.021	1.851	.012	3.053	.067

Appendix

Error(Loc*CSI*Switch*Congruency)	.105	27.764	.004		
Loc * Task	.009	1.670	.005	.884	.408
Error(Loc*Task)	.148	25.048	.006		
CSI * Task	.006	1.000	.006	1.788	.201
Error(CSI*Task)	.049	15.000	.003		
Loc * CSI * Task	.004	2.000	.002	.537	.590
Error(Loc*CSI*Task)	.107	30.000	.004		
Switch * Task	.010	1.000	.010	1.941	.184
Error(Switch*Task)	.080	15.000	.005		
Loc * Switch * Task	.007	2.000	.004	.893	.420
Error(Loc*Switch*Task)	.121	30.000	.004		
CSI * Switch * Task	.001	1.000	.001	.103	.752
Error(CSI*Switch*Task)	.079	15.000	.005		
Loc * CSI * Switch * Task	.009	2.000	.004	.916	.411
Error(Loc*CSI*Switch*Task)	.139	30.000	.005		
Congruency * Task	.093	1.000	.093	3.018	.103
Error(Congruency*Task)	.460	15.000	.031		
Loc * Congruency * Task	.023	2.000	.012	4.255	.024
Error(Loc*Congruency*Task)	.081	30.000	.003		
CSI * Congruency * Task	.007	1.000	.007	3.261	.091
Error(CSI*Congruency*Task)	.034	15.000	.002		
Loc * CSI * Congruency * Task	.007	2.000	.004	.804	.457
Error(Loc*CSI*Congruency*Task)	.136	30.000	.005		
Switch * Congruency * Task	.016	1.000	.016	4.507	.051
Error(Switch*Congruency*Task)	.053	15.000	.004		
Loc * Switch * Congruency * Task	.004	1.761	.002	.441	.623
Error(Loc*Switch*Congruency*Task)	.126	26.414	.005		
CSI * Switch * Congruency * Task	.000	1.000	.000	.009	.926
Error(CSI*Switch*Congruency*Task)	.067	15.000	.004		
Loc * CSI * Switch * Congruency * Task	.011	2.000	.006	1.293	.289
Error(Loc*CSI*Switch*Congruency*Task)	.129	30.000	.004		

Appendix

Appendix E ANOVA table reaction times Experiment 3

	Type III Sum of Squares	df	Mean Square	F	Sig.
Loc	20773.705	2.000	10386.853	1.053	.365
Error(Loc)	236837.200	24.000	9868.217		
CSI	3204956.047	1.000	3204956.047	63.517	.000
Error(CSI)	605496.753	12.000	50458.063		
Switch	1440710.048	1.000	1440710.048	79.217	.000
Error(Switch)	218243.899	12.000	18186.992		
Congruency	848300.697	1.000	848300.697	35.772	.000
Error(Congruency)	284569.241	12.000	23714.103		
Task	696759.305	1.000	696759.305	31.754	.000
Error(Task)	263308.481	12.000	21942.373		
Loc * CSI	20405.065	2.000	10202.532	1.567	.229
Error(Loc*CSI)	156300.412	24.000	6512.517		
Loc * Switch	10328.423	1.576	6553.929	.624	.510
Error(Loc*Switch)	198731.729	18.911	10508.813		
CSI * Switch	13517.507	1.000	13517.507	3.807	.075
Error(CSI*Switch)	42610.174	12.000	3550.848		
Loc * CSI * Switch	11257.423	2.000	5628.711	.954	.399
Error(Loc*CSI*Switch)	141532.939	24.000	5897.206		
Loc * Congruency	5646.798	1.729	3265.041	.481	.598
Error(Loc*Congruency)	140751.061	20.754	6781.985		
CSI * Congruency	7625.084	1.000	7625.084	1.864	.197
Error(CSI*Congruency)	49088.722	12.000	4090.727		
Loc * CSI * Congruency	6518.168	1.621	4020.108	.635	.509
Error(Loc*CSI*Congruency)	123227.169	19.457	6333.408		
Switch * Congruency	4388.272	1.000	4388.272	.976	.343
Error(Switch*Congruency)	53952.294	12.000	4496.024		
Loc * Switch * Congruency	1174.016	2.000	587.008	.078	.925
Error(Loc*Switch*Congruency)	180222.637	24.000	7509.277		
CSI * Switch * Congruency	4549.375	1.000	4549.375	1.359	.266
Error(CSI*Switch*Congruency)	40160.265	12.000	3346.689		
Loc * CSI * Switch * Congruency	6619.219	2.000	3309.610	.522	.600
Error(Loc*CSI*Switch*Congruency)	152196.961	24.000	6341.540		
Loc * Task	4227.733	2.000	2113.866	.240	.789

Appendix

Error(Loc*Task)	211522.527	24.000	8813.439		
CSI * Task	37266.971	1.000	37266.971	7.057	.021
Error(CSI*Task)	63369.000	12.000	5280.750		
Loc * CSI * Task	13673.768	1.701	8040.105	1.260	.299
Error(Loc*CSI*Task)	130214.834	20.408	6380.471		
Switch * Task	287.290	1.000	287.290	.038	.850
Error(Switch*Task)	91738.147	12.000	7644.846		
Loc * Switch * Task	3265.035	2.000	1632.517	.355	.705
Error(Loc*Switch*Task)	110326.535	24.000	4596.939		
CSI * Switch * Task	3320.135	1.000	3320.135	.811	.386
Error(CSI*Switch*Task)	49121.825	12.000	4093.485		
Loc * CSI * Switch * Task	5777.469	1.713	3372.213	.515	.577
Error(Loc*CSI*Switch*Task)	134571.281	20.559	6545.586		
Congruency * Task	101520.838	1.000	101520.838	8.345	.014
Error(Congruency*Task)	145982.030	12.000	12165.169		
Loc * Congruency * Task	7634.680	1.671	4567.981	.790	.446
Error(Loc*Congruency*Task)	115960.833	20.056	5781.806		
CSI * Congruency * Task	.245	1.000	.245	.000	.993
Error(CSI*Congruency*Task)	38120.924	12.000	3176.744		
Loc * CSI * Congruency * Task	3106.602	1.393	2229.912	.334	.644
Error(Loc*CSI*Congruency*Task)	111666.070	16.718	6679.471		
Switch * Congruency * Task	18409.065	1.000	18409.065	6.962	.022
Error(Switch*Congruency*Task)	31731.617	12.000	2644.301		
Loc * Switch * Congruency * Task	2159.648	2.000	1079.824	.237	.791
Error(Loc*Switch*Congruency*Task)	109537.124	24.000	4564.047		
CSI * Switch * Congruency * Task	1727.286	1.000	1727.286	.779	.395
Error(CSI*Switch*Congruency*Task)	26596.604	12.000	2216.384		
Loc * CSI * Switch * Congruency * Task	13076.369	1.897	6893.794	1.092	.349
Error(Loc*CSI*Switch*Congruency*Task)	143642.727	22.762	6310.642		

Appendix

Appendix F ANOVA table error rates Experiment 3

	Type III Sum of Squares	df	Mean Square	F	Sig.
Loc	.002	2.000	.001	.207	.815
Error(Loc)	.113	24.000	.005		
CSI	.027	1.000	.027	6.995	.021
Error(CSI)	.046	12.000	.004		
Switch	.194	1.000	.194	25.577	.000
Error(Switch)	.091	12.000	.008		
Congruency	.485	1.000	.485	56.102	.000
Error(Congruency)	.104	12.000	.009		
Task	.027	1.000	.027	1.617	.228
Error(Task)	.200	12.000	.017		
Loc * CSI	.001	2.000	.000	.179	.838
Error(Loc*CSI)	.051	24.000	.002		
Loc * Switch	.002	1.615	.001	.298	.699
Error(Loc*Switch)	.071	19.378	.004		
CSI * Switch	.000	1.000	.000	.002	.963
Error(CSI*Switch)	.085	12.000	.007		
Loc * CSI * Switch	.004	1.996	.002	1.428	.259
Error(Loc*CSI*Switch)	.034	23.953	.001		
Loc * Congruency	.003	2.000	.001	.581	.567
Error(Loc*Congruency)	.059	24.000	.002		
CSI * Congruency	.000	1.000	.000	.085	.775
Error(CSI*Congruency)	.021	12.000	.002		
Loc * CSI * Congruency	.003	1.480	.002	.822	.422
Error(Loc*CSI*Congruency)	.050	17.764	.003		
Switch * Congruency	.099	1.000	.099	29.689	.000
Error(Switch*Congruency)	.040	12.000	.003		
Loc * Switch * Congruency	.000	2.000	.000	.097	.908
Error(Loc*Switch*Congruency)	.041	24.000	.002		
CSI * Switch * Congruency	.000	1.000	.000	.029	.867
Error(CSI*Switch*Congruency)	.011	12.000	.001		
Loc * CSI * Switch * Congruency	.000	2.000	.000	.086	.918
Error(Loc*CSI*Switch*Congruency)	.035	24.000	.001		
Loc * Task	.007	2.000	.004	1.117	.344

Appendix

Error(Loc*Task)	.080	24.000	.003		
CSI * Task	.000	1.000	.000	.059	.812
Error(CSI*Task)	.051	12.000	.004		
Loc * CSI * Task	.013	2.000	.006	2.160	.137
Error(Loc*CSI*Task)	.070	24.000	.003		
Switch * Task	.000	1.000	.000	.040	.845
Error(Switch*Task)	.034	12.000	.003		
Loc * Switch * Task	.003	2.000	.001	.507	.608
Error(Loc*Switch*Task)	.070	24.000	.003		
CSI * Switch * Task	.000	1.000	.000	.181	.678
Error(CSI*Switch*Task)	.026	12.000	.002		
Loc * CSI * Switch * Task	.015	2.000	.007	3.143	.061
Error(Loc*CSI*Switch*Task)	.057	24.000	.002		
Congruency * Task	.044	1.000	.044	2.658	.129
Error(Congruency*Task)	.199	12.000	.017		
Loc * Congruency * Task	.002	2.000	.001	.239	.789
Error(Loc*Congruency*Task)	.110	24.000	.005		
CSI * Congruency * Task	.004	1.000	.004	1.330	.271
Error(CSI*Congruency*Task)	.038	12.000	.003		
Loc * CSI * Congruency * Task	.000	2.000	.000	.033	.967
Error(Loc*CSI*Congruency*Task)	.058	24.000	.002		
Switch * Congruency * Task	.000	1.000	.000	.003	.961
Error(Switch*Congruency*Task)	.063	12.000	.005		
Loc * Switch * Congruency * Task	.011	2.000	.005	2.016	.155
Error(Loc*Switch*Congruency*Task)	.063	24.000	.003		
CSI * Switch * Congruency * Task	.001	1.000	.001	.317	.583
Error(CSI*Switch*Congruency*Task)	.022	12.000	.002		
Loc * CSI * Switch * Congruency * Task	.012	2.000	.006	4.028	.031
Error(Loc*CSI*Switch*Congruency*Task)	.035	24.000	.001		

Appendix

Appendix G ANOVA table reaction times Experiment 4

	Type III Sum of Squares	df	Mean Square	F	Sig.
Loc	12773.114	1.000	12773.114	.574	.460
Error(Loc)	333683.316	15.000	22245.554		
CSI	2960594.590	1.000	2960594.590	101.885	.000
Error(CSI)	435871.074	15.000	29058.072		
Switch	261629.818	1.000	261629.818	22.155	.000
Error(Switch)	177135.457	15.000	11809.030		
Congruency	233978.875	1.000	233978.875	36.311	.000
Error(Congruency)	96657.005	15.000	6443.800		
Task	2974.663	1.000	2974.663	.282	.603
Error(Task)	158350.780	15.000	10556.719		
Loc * CSI	286.816	1.000	286.816	.041	.843
Error(Loc*CSI)	105972.077	15.000	7064.805		
Loc * Switch	5083.786	1.000	5083.786	1.255	.280
Error(Loc*Switch)	60754.959	15.000	4050.331		
CSI * Switch	24114.962	1.000	24114.962	10.446	.006
Error(CSI*Switch)	34629.317	15.000	2308.621		
Loc * CSI * Switch	5324.540	1.000	5324.540	5.818	.029
Error(Loc*CSI*Switch)	13727.851	15.000	915.190		
Loc * Congruency	936.498	1.000	936.498	.353	.561
Error(Loc*Congruency)	39807.233	15.000	2653.816		
CSI * Congruency	5233.732	1.000	5233.732	1.102	.311
Error(CSI*Congruency)	71267.917	15.000	4751.194		
Loc * CSI * Congruency	1005.845	1.000	1005.845	.426	.524
Error(Loc*CSI*Congruency)	35392.337	15.000	2359.489		
Switch * Congruency	7032.461	1.000	7032.461	3.427	.084
Error(Switch*Congruency)	30778.324	15.000	2051.888		
Loc * Switch * Congruency	313.767	1.000	313.767	.112	.743
Error(Loc*Switch*Congruency)	42037.926	15.000	2802.528		
CSI * Switch * Congruency	186.016	1.000	186.016	.062	.806
Error(CSI*Switch*Congruency)	44732.553	15.000	2982.170		
Loc * CSI * Switch * Congruency	248.352	1.000	248.352	.181	.677
Error(Loc*CSI*Switch*Congruency)	20578.165	15.000	1371.878		
Loc * Task	96.110	1.000	96.110	.059	.812

Appendix

Error(Loc*Task)	24578.666	15.000	1638.578		
CSI * Task	12.534	1.000	12.534	.003	.958
Error(CSI*Task)	65583.027	15.000	4372.202		
Loc * CSI * Task	1585.373	1.000	1585.373	.519	.482
Error(Loc*CSI*Task)	45790.733	15.000	3052.716		
Switch * Task	3019.179	1.000	3019.179	1.165	.297
Error(Switch*Task)	38871.988	15.000	2591.466		
Loc * Switch * Task	4521.827	1.000	4521.827	1.731	.208
Error(Loc*Switch*Task)	39191.140	15.000	2612.743		
CSI * Switch * Task	4899.077	1.000	4899.077	1.803	.199
Error(CSI*Switch*Task)	40747.722	15.000	2716.515		
Loc * CSI * Switch * Task	1126.967	1.000	1126.967	.475	.501
Error(Loc*CSI*Switch*Task)	35578.976	15.000	2371.932		
Congruency * Task	1068.635	1.000	1068.635	.385	.544
Error(Congruency*Task)	41601.616	15.000	2773.441		
Loc * Congruency * Task	1725.524	1.000	1725.524	1.077	.316
Error(Loc*Congruency*Task)	24027.139	15.000	1601.809		
CSI * Congruency * Task	996.225	1.000	996.225	.266	.614
Error(CSI*Congruency*Task)	56233.072	15.000	3748.871		
Loc * CSI * Congruency * Task	525.467	1.000	525.467	.269	.611
Error(Loc*CSI*Congruency*Task)	29283.485	15.000	1952.232		
Switch * Congruency * Task	1117.256	1.000	1117.256	.334	.572
Error(Switch*Congruency*Task)	50221.578	15.000	3348.105		
Loc * Switch * Congruency * Task	16700.266	1.000	16700.266	4.801	.045
Error(Loc*Switch*Congruency*Task)	52176.321	15.000	3478.421		
CSI * Switch * Congruency * Task	6519.178	1.000	6519.178	1.999	.178
Error(CSI*Switch*Congruency*Task)	48922.891	15.000	3261.526		
Loc * CSI * Switch * Congruency * Task	2.957	1.000	2.957	.001	.975
Error(Loc*CSI*Switch*Congruency*Task)	43532.838	15.000	2902.189		

Appendix H ANOVA table error rates Experiment 4

	Type III Sum of Squares	df	Mean Square	F	Sig.
Loc	.000	1.000	.000	.012	.915
Error(Loc)	.040	15.000	.003		
CSI	.013	1.000	.013	1.699	.212

Appendix

Error(CSI)	.116	15.000	.008		
Switch	.122	1.000	.122	15.210	.001
Error(Switch)	.120	15.000	.008		
Congruency	.367	1.000	.367	27.526	.000
Error(Congruency)	.200	15.000	.013		
Task	.002	1.000	.002	.292	.597
Error(Task)	.104	15.000	.007		
Loc * CSI	.001	1.000	.001	.476	.501
Error(Loc*CSI)	.040	15.000	.003		
Loc * Switch	.004	1.000	.004	1.648	.219
Error(Loc*Switch)	.035	15.000	.002		
CSI * Switch	.017	1.000	.017	3.634	.076
Error(CSI*Switch)	.071	15.000	.005		
Loc * CSI * Switch	.006	1.000	.006	1.439	.249
Error(Loc*CSI*Switch)	.061	15.000	.004		
Loc * Congruency	.000	1.000	.000	.062	.807
Error(Loc*Congruency)	.075	15.000	.005		
CSI * Congruency	.033	1.000	.033	3.439	.083
Error(CSI*Congruency)	.145	15.000	.010		
Loc * CSI * Congruency	.000	1.000	.000	.000	.992
Error(Loc*CSI*Congruency)	.179	15.000	.012		
Switch * Congruency	.060	1.000	.060	13.860	.002
Error(Switch*Congruency)	.064	15.000	.004		
Loc * Switch * Congruency	.001	1.000	.001	.353	.561
Error(Loc*Switch*Congruency)	.054	15.000	.004		
CSI * Switch * Congruency	.008	1.000	.008	1.865	.192
Error(CSI*Switch*Congruency)	.065	15.000	.004		
Loc * CSI * Switch * Congruency	.004	1.000	.004	.861	.368
Error(Loc*CSI*Switch*Congruency)	.070	15.000	.005		
Loc * Task	.003	1.000	.003	1.098	.311
Error(Loc*Task)	.045	15.000	.003		
CSI * Task	.000	1.000	.000	.028	.869
Error(CSI*Task)	.109	15.000	.007		
Loc * CSI * Task	.001	1.000	.001	.466	.505
Error(Loc*CSI*Task)	.017	15.000	.001		

Appendix

Switch * Task	.004	1.000	.004	.489	.495
Error(Switch*Task)	.127	15.000	.008		
Loc * Switch * Task	.011	1.000	.011	2.714	.120
Error(Loc*Switch*Task)	.061	15.000	.004		
CSI * Switch * Task	.026	1.000	.026	3.879	.068
Error(CSI*Switch*Task)	.099	15.000	.007		
Loc * CSI * Switch * Task	.002	1.000	.002	.969	.340
Error(Loc*CSI*Switch*Task)	.026	15.000	.002		
Congruency * Task	.000	1.000	.000	.004	.952
Error(Congruency*Task)	.067	15.000	.004		
Loc * Congruency * Task	.002	1.000	.002	.522	.481
Error(Loc*Congruency*Task)	.060	15.000	.004		
CSI * Congruency * Task	.000	1.000	.000	.021	.886
Error(CSI*Congruency*Task)	.044	15.000	.003		
Loc * CSI * Congruency * Task	.000	1.000	.000	.008	.931
Error(Loc*CSI*Congruency*Task)	.042	15.000	.003		
Switch * Congruency * Task	.000	1.000	.000	.022	.885
Error(Switch*Congruency*Task)	.100	15.000	.007		
Loc * Switch * Congruency * Task	.000	1.000	.000	.005	.942
Error(Loc*Switch*Congruency*Task)	.049	15.000	.003		
CSI * Switch * Congruency * Task	.011	1.000	.011	3.043	.102
Error(CSI*Switch*Congruency*Task)	.055	15.000	.004		
Loc * CSI * Switch * Congruency * Task	.000	1.000	.000	.080	.781
Error(Loc*CSI*Switch*Congruency*Task)	.046	15.000	.003		

Appendix I ANOVA table reaction times Experiment 5

	Type III Sum of Squares	df	Mean Square	F	Sig.
Loc	538.987	1.000	538.987	.072	.794
Error(Loc)	67137.537	9.000	7459.726		
CSI	773131.892	1.000	773131.892	23.735	.001
Error(CSI)	293156.584	9.000	32572.954		
Switch	144865.070	1.000	144865.070	14.096	.005
Error(Switch)	92491.418	9.000	10276.824		
Congruency	85184.642	1.000	85184.642	40.576	.000
Error(Congruency)	18894.275	9.000	2099.364		

Appendix

Task	286652.025	1.000	286652.025	8.856	.016
Error(Task)	291316.460	9.000	32368.496		
Loc * CSI	20224.074	1.000	20224.074	1.922	.199
Error(Loc*CSI)	94678.893	9.000	10519.877		
Loc * Switch	169.178	1.000	169.178	.072	.795
Error(Loc*Switch)	21150.954	9.000	2350.106		
CSI * Switch	49843.800	1.000	49843.800	14.188	.004
Error(CSI*Switch)	31617.641	9.000	3513.071		
Loc * CSI * Switch	649.197	1.000	649.197	.129	.728
Error(Loc*CSI*Switch)	45223.868	9.000	5024.874		
Loc * Congruency	1539.510	1.000	1539.510	.403	.541
Error(Loc*Congruency)	34383.303	9.000	3820.367		
CSI * Congruency	538.267	1.000	538.267	.102	.757
Error(CSI*Congruency)	47545.899	9.000	5282.878		
Loc * CSI * Congruency	9432.247	1.000	9432.247	6.324	.033
Error(Loc*CSI*Congruency)	13424.240	9.000	1491.582		
Switch * Congruency	172.677	1.000	172.677	.077	.788
Error(Switch*Congruency)	20211.032	9.000	2245.670		
Loc * Switch * Congruency	12742.658	1.000	12742.658	4.719	.058
Error(Loc*Switch*Congruency)	24300.344	9.000	2700.038		
CSI * Switch * Congruency	10814.672	1.000	10814.672	3.121	.111
Error(CSI*Switch*Congruency)	31188.841	9.000	3465.427		
Loc * CSI * Switch * Congruency	1226.859	1.000	1226.859	.864	.377
Error(Loc*CSI*Switch*Congruency)	12773.500	9.000	1419.278		
Loc * Task	27.074	1.000	27.074	.010	.924
Error(Loc*Task)	25604.817	9.000	2844.980		
CSI * Task	2966.284	1.000	2966.284	.571	.469
Error(CSI*Task)	46787.201	9.000	5198.578		
Loc * CSI * Task	1011.055	1.000	1011.055	.498	.498
Error(Loc*CSI*Task)	18278.791	9.000	2030.977		
Switch * Task	16895.869	1.000	16895.869	3.769	.084
Error(Switch*Task)	40345.887	9.000	4482.876		
Loc * Switch * Task	450.272	1.000	450.272	.365	.561
Error(Loc*Switch*Task)	11098.627	9.000	1233.181		
CSI * Switch * Task	946.568	1.000	946.568	.383	.551

Appendix

Error(CSI*Switch*Task)	22260.144	9.000	2473.349		
Loc * CSI * Switch * Task	1115.027	1.000	1115.027	1.890	.202
Error(Loc*CSI*Switch*Task)	5310.675	9.000	590.075		
Congruency * Task	38344.772	1.000	38344.772	7.541	.023
Error(Congruency*Task)	45765.467	9.000	5085.052		
Loc * Congruency * Task	3224.248	1.000	3224.248	1.444	.260
Error(Loc*Congruency*Task)	20090.884	9.000	2232.320		
CSI * Congruency * Task	5473.249	1.000	5473.249	1.115	.318
Error(CSI*Congruency*Task)	44160.035	9.000	4906.671		
Loc * CSI * Congruency * Task	842.616	1.000	842.616	.142	.715
Error(Loc*CSI*Congruency*Task)	53292.148	9.000	5921.350		
Switch * Congruency * Task	407.065	1.000	407.065	.081	.783
Error(Switch*Congruency*Task)	45365.970	9.000	5040.663		
Loc * Switch * Congruency * Task	.769	1.000	.769	.001	.977
Error(Loc*Switch*Congruency*Task)	8157.530	9.000	906.392		
CSI * Switch * Congruency * Task	1438.897	1.000	1438.897	.379	.553
Error(CSI*Switch*Congruency*Task)	34153.438	9.000	3794.826		
Loc * CSI * Switch * Congruency * Task	6237.842	1.000	6237.842	1.789	.214
Error(Loc*CSI*Switch*Congruency*Task)	31377.842	9.000	3486.427		

Appendix J ANOVA table error rates Experiment 5

	Type III Sum of Squares	df	Mean Square	F	Sig.
Loc	.012	1.000	.012	1.232	.296
Error(Loc)	.088	9.000	.010		
CSI	.060	1.000	.060	11.418	.008
Error(CSI)	.048	9.000	.005		
Switch	.240	1.000	.240	11.100	.009
Error(Switch)	.194	9.000	.022		
Congruency	.602	1.000	.602	8.765	.016
Error(Congruency)	.618	9.000	.069		
Task	.171	1.000	.171	3.521	.093
Error(Task)	.437	9.000	.049		
Loc * CSI	.000	1.000	.000	.041	.844
Error(Loc*CSI)	.038	9.000	.004		
Loc * Switch	.002	1.000	.002	.595	.460

Appendix

Error(Loc*Switch)	.026	9.000	.003		
CSI * Switch	.026	1.000	.026	8.783	.016
Error(CSI*Switch)	.027	9.000	.003		
Loc * CSI * Switch	.000	1.000	.000	.003	.959
Error(Loc*CSI*Switch)	.052	9.000	.006		
Loc * Congruency	.016	1.000	.016	2.202	.172
Error(Loc*Congruency)	.066	9.000	.007		
CSI * Congruency	.076	1.000	.076	3.579	.091
Error(CSI*Congruency)	.191	9.000	.021		
Loc * CSI * Congruency	.000	1.000	.000	.055	.820
Error(Loc*CSI*Congruency)	.046	9.000	.005		
Switch * Congruency	.075	1.000	.075	6.229	.034
Error(Switch*Congruency)	.108	9.000	.012		
Loc * Switch * Congruency	.007	1.000	.007	.621	.451
Error(Loc*Switch*Congruency)	.104	9.000	.012		
CSI * Switch * Congruency	.040	1.000	.040	9.080	.015
Error(CSI*Switch*Congruency)	.039	9.000	.004		
Loc * CSI * Switch * Congruency	.006	1.000	.006	.418	.534
Error(Loc*CSI*Switch*Congruency)	.125	9.000	.014		
Loc * Task	.004	1.000	.004	.556	.475
Error(Loc*Task)	.064	9.000	.007		
CSI * Task	.048	1.000	.048	3.690	.087
Error(CSI*Task)	.118	9.000	.013		
Loc * CSI * Task	.006	1.000	.006	1.201	.302
Error(Loc*CSI*Task)	.043	9.000	.005		
Switch * Task	.019	1.000	.019	1.140	.313
Error(Switch*Task)	.147	9.000	.016		
Loc * Switch * Task	.023	1.000	.023	4.446	.064
Error(Loc*Switch*Task)	.048	9.000	.005		
CSI * Switch * Task	.012	1.000	.012	1.310	.282
Error(CSI*Switch*Task)	.080	9.000	.009		
Loc * CSI * Switch * Task	.000	1.000	.000	.000	.983
Error(Loc*CSI*Switch*Task)	.079	9.000	.009		
Congruency * Task	.054	1.000	.054	2.322	.162
Error(Congruency*Task)	.209	9.000	.023		

Appendix

Loc * Congruency * Task	.002	1.000	.002	.633	.447
Error(Loc*Congruency*Task)	.025	9.000	.003		
CSI * Congruency * Task	.018	1.000	.018	1.675	.228
Error(CSI*Congruency*Task)	.097	9.000	.011		
Loc * CSI * Congruency * Task	.001	1.000	.001	.035	.856
Error(Loc*CSI*Congruency*Task)	.192	9.000	.021		
Switch * Congruency * Task	.000	1.000	.000	.055	.821
Error(Switch*Congruency*Task)	.053	9.000	.006		
Loc * Switch * Congruency * Task	.001	1.000	.001	.068	.800
Error(Loc*Switch*Congruency*Task)	.078	9.000	.009		
CSI * Switch * Congruency * Task	.003	1.000	.003	1.386	.269
Error(CSI*Switch*Congruency*Task)	.022	9.000	.002		
Loc * CSI * Switch * Congruency * Task	.000	1.000	.000	.011	.918
Error(Loc*CSI*Switch*Congruency*Task)	.152	9.000	.017		

Appendix K ANOVA table reaction times Experiment 6

	Type III Sum of Squares	df	Mean Square	F	Sig.
Loc	702611.367	1.000	702611.367	10.744	.005
Error(Loc)	915534.480	14.000	65395.320		
CSI	3832025.828	1.000	3832025.828	34.175	.000
Error(CSI)	1569807.582	14.000	112129.113		
Switch	654755.809	1.000	654755.809	26.606	.000
Error(Switch)	344533.074	14.000	24609.505		
Congruency	1330.496	1.000	1330.496	.088	.771
Error(Congruency)	212093.231	14.000	15149.516		
Task	775109.876	1.000	775109.876	14.565	.002
Error(Task)	745035.218	14.000	53216.801		
Loc * CSI	84861.940	1.000	84861.940	3.020	.104
Error(Loc*CSI)	393401.512	14.000	28100.108		
Loc * Switch	74091.026	1.000	74091.026	10.009	.007
Error(Loc*Switch)	103633.625	14.000	7402.402		
CSI * Switch	88965.973	1.000	88965.973	5.746	.031
Error(CSI*Switch)	216749.275	14.000	15482.091		
Loc * CSI * Switch	2138.044	1.000	2138.044	.147	.707
Error(Loc*CSI*Switch)	203104.256	14.000	14507.447		

Appendix

Loc * Congruency	24509.348	1.000	24509.348	1.825	.198
Error(Loc*Congruency)	187996.260	14.000	13428.304		
CSI * Congruency	23476.194	1.000	23476.194	1.118	.308
Error(CSI*Congruency)	293871.146	14.000	20990.796		
Loc * CSI * Congruency	38805.809	1.000	38805.809	2.066	.173
Error(Loc*CSI*Congruency)	262915.100	14.000	18779.650		
Switch * Congruency	7726.257	1.000	7726.257	.595	.453
Error(Switch*Congruency)	181647.459	14.000	12974.818		
Loc * Switch * Congruency	10886.455	1.000	10886.455	.562	.466
Error(Loc*Switch*Congruency)	271396.340	14.000	19385.453		
CSI * Switch * Congruency	15467.542	1.000	15467.542	1.166	.299
Error(CSI*Switch*Congruency)	185748.305	14.000	13267.736		
Loc * CSI * Switch * Congruency	3543.597	1.000	3543.597	.442	.517
Error(Loc*CSI*Switch*Congruency)	112246.750	14.000	8017.625		
Loc * Task	88020.054	1.000	88020.054	5.004	.042
Error(Loc*Task)	246240.430	14.000	17588.602		
CSI * Task	73996.383	1.000	73996.383	15.263	.002
Error(CSI*Task)	67874.676	14.000	4848.191		
Loc * CSI * Task	198.449	1.000	198.449	.009	.927
Error(Loc*CSI*Task)	319249.580	14.000	22803.541		
Switch * Task	66114.718	1.000	66114.718	2.407	.143
Error(Switch*Task)	384588.116	14.000	27470.580		
Loc * Switch * Task	7101.604	1.000	7101.604	.358	.559
Error(Loc*Switch*Task)	277695.684	14.000	19835.406		
CSI * Switch * Task	61421.512	1.000	61421.512	1.905	.189
Error(CSI*Switch*Task)	451472.409	14.000	32248.029		
Loc * CSI * Switch * Task	7845.437	1.000	7845.437	1.327	.269
Error(Loc*CSI*Switch*Task)	82789.695	14.000	5913.550		
Congruency * Task	5124.682	1.000	5124.682	.438	.519
Error(Congruency*Task)	163893.550	14.000	11706.682		
Loc * Congruency * Task	85776.537	1.000	85776.537	5.206	.039
Error(Loc*Congruency*Task)	230666.999	14.000	16476.214		
CSI * Congruency * Task	24598.495	1.000	24598.495	2.448	.140
Error(CSI*Congruency*Task)	140673.880	14.000	10048.134		
Loc * CSI * Congruency * Task	32335.203	1.000	32335.203	1.379	.260

Appendix

Error(Loc*CSI*Congruency*Task)	328212.812	14.000	23443.772		
Switch * Congruency * Task	54441.797	1.000	54441.797	2.216	.159
Error(Switch*Congruency*Task)	343940.297	14.000	24567.164		
Loc * Switch * Congruency * Task	12510.089	1.000	12510.089	.407	.534
Error(Loc*Switch*Congruency*Task)	429812.746	14.000	30700.910		
CSI * Switch * Congruency * Task	44924.476	1.000	44924.476	1.221	.288
Error(CSI*Switch*Congruency*Task)	514966.185	14.000	36783.299		
Loc * CSI * Switch * Congruency * Task	10210.358	1.000	10210.358	.861	.369
Error(Loc*CSI*Switch*Congruency*Task)	165978.629	14.000	11855.616		

Appendix L ANOVA table error rates Experiment 6

	Type III Sum of Squares	df	Mean Square	F	Sig.
Loc	.001	1.000	.001	.117	.738
Error(Loc)	.097	14.000	.007		
CSI	.034	1.000	.034	3.463	.084
Error(CSI)	.136	14.000	.010		
Switch	.384	1.000	.384	19.645	.001
Error(Switch)	.274	14.000	.020		
Congruency	.003	1.000	.003	.262	.617
Error(Congruency)	.173	14.000	.012		
Task	.044	1.000	.044	5.874	.030
Error(Task)	.106	14.000	.008		
Loc * CSI	.008	1.000	.008	.856	.370
Error(Loc*CSI)	.123	14.000	.009		
Loc * Switch	.001	1.000	.001	.288	.600
Error(Loc*Switch)	.038	14.000	.003		
CSI * Switch	.017	1.000	.017	2.289	.153
Error(CSI*Switch)	.102	14.000	.007		
Loc * CSI * Switch	.006	1.000	.006	1.029	.328
Error(Loc*CSI*Switch)	.082	14.000	.006		
Loc * Congruency	.001	1.000	.001	.142	.712
Error(Loc*Congruency)	.097	14.000	.007		

Appendix

CSI * Congruency	.002	1.000	.002	.426	.525
Error(CSI*Congruency)	.069	14.000	.005		
Loc * CSI * Congruency	.001	1.000	.001	.161	.695
Error(Loc*CSI*Congruency)	.090	14.000	.006		
Switch * Congruency	.029	1.000	.029	2.233	.157
Error(Switch*Congruency)	.183	14.000	.013		
Loc * Switch * Congruency	.005	1.000	.005	.722	.410
Error(Loc*Switch*Congruency)	.096	14.000	.007		
CSI * Switch * Congruency	.011	1.000	.011	2.242	.156
Error(CSI*Switch*Congruency)	.069	14.000	.005		
Loc * CSI * Switch * Congruency	.003	1.000	.003	.399	.538
Error(Loc*CSI*Switch*Congruency)	.099	14.000	.007		
Loc * Task	.017	1.000	.017	1.707	.212
Error(Loc*Task)	.143	14.000	.010		
CSI * Task	.054	1.000	.054	8.942	.010
Error(CSI*Task)	.084	14.000	.006		
Loc * CSI * Task	.018	1.000	.018	2.024	.177
Error(Loc*CSI*Task)	.124	14.000	.009		
Switch * Task	.002	1.000	.002	.321	.580
Error(Switch*Task)	.085	14.000	.006		
Loc * Switch * Task	.001	1.000	.001	.085	.775
Error(Loc*Switch*Task)	.141	14.000	.010		
CSI * Switch * Task	.028	1.000	.028	8.661	.011
Error(CSI*Switch*Task)	.045	14.000	.003		
Loc * CSI * Switch * Task	.002	1.000	.002	.152	.703
Error(Loc*CSI*Switch*Task)	.196	14.000	.014		
Congruency * Task	.023	1.000	.023	2.809	.116
Error(Congruency*Task)	.113	14.000	.008		
Loc * Congruency * Task	.011	1.000	.011	.972	.341
Error(Loc*Congruency*Task)	.163	14.000	.012		
CSI * Congruency * Task	.014	1.000	.014	1.444	.249
Error(CSI*Congruency*Task)	.138	14.000	.010		
Loc * CSI * Congruency * Task	.006	1.000	.006	.439	.518
Error(Loc*CSI*Congruency*Task)	.190	14.000	.014		
Switch * Congruency * Task	.010	1.000	.010	1.212	.289

Appendix

Error(Switch*Congruency*Task)	.112	14.000	.008		
Loc * Switch * Congruency * Task	.008	1.000	.008	.714	.412
Error(Loc*Switch*Congruency*Task)	.164	14.000	.012		
CSI * Switch * Congruency * Task	.016	1.000	.016	1.282	.277
Error(CSI*Switch*Congruency*Task)	.177	14.000	.013		
Loc * CSI * Switch * Congruency * Task	.013	1.000	.013	.826	.379
Error(Loc*CSI*Switch*Congruency*Task)	.221	14.000	.016		