Attention and Working Memory Deficits in OCD

Checking Behaviour

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The evidence for memory impairments in obsessive-compulsive disorder (OCD) is mixed (Hermans et al., 2008). For example, findings are inconsistent, whether OCD have poorer memory capacity compared to neruo-typical controls, or whether verbal memory is less affected than visuospatial memory (Muller and Roberts, 2005b). Some evidence (Greisberg and McKay, 2003) pointed to a more subtle interaction with executive dysfunction leading to impaired memory performance.

In a review of 58 experiments Harkin and Kessler (2011) argued that rather than classifying memory deficits in OCD by modality, for example verbal vs visuospatial, it is more instructive to classify the experiments by their task demand in terms of Executive function (E), Binding complexity (B) and memory Load (L). Using the EBL classification system in combination with the Baddeley model of working memory (Baddeley 2000) with an episodic buffer, performance in working memory tasks could be better explained in terms of task demands of executive function. For example, working memory (WM) performance of subclinical OCD checkers can be impaired if presented with irrelevant but misleading information during the retention period.

The aim of this thesis was firstly, using magnetoencephalography (MEG) and a paradigm designed to provoke executive dysfunction in OCD participants, to measure the neural correlates of deficient working memory processing. Secondly, to use MEG to investigate the neural correlates of attentional bias and executive dysfunction in OCD checking behaviour when engaged in an endogenous attention (Stroop) task. Lastly, using transcranial magnetic stimulation (TMS) to target task relevant brain areas in attempt to affect beneficially the task performance of OCD checker participants engaged in an exogenous attention (Inhibition of Return) task, an endogenous attention (Stroop) task and in the working memory task.

Using ecologically valid stimuli that resonate with the checkers' OCD related concerns, the neuroimaging data revealed different patterns of activity, comparing subclinical OCD checkers with neuro-typical controls. These patterns are consistent with the stimuli provoking deficient executive function in the subclinical checkers. The brain activity recorded was consistent with repeated memory checking and poor suppression of irrelevant stimuli. Efforts to remediate executive dysfunction with TMS were only partially successful.

In accord with the EBL classification system, the ecologically valid threat stimuli in combination with the WM and Stroop tasks were successful in exploiting executive dysfunction in subclinical checkers in domains of working memory and endogenous attention. Neural correlates of the impaired processing were measured successfully using MEG.

Key Words: Obsessive-compulsive disorder, magnetoencephalography, transcranial Magnetic Stimulation, working memory, attention.

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3-D	Three Dimensional
ACC	Anterior Cingulate Cortex
AMT	Active Motor Threshold
ANOVA	Analysis of Variance
APA	American Psychiatric Association
BDD	Body Dysmorphic Disorder
BG	Basal Ganglia
BOLD	Blood oxygen level dependent
Calc	Calcarine
CBT	Cognitive Behavioural Therapy
CdN	Caudate Nucleus
CNTRL	Control
cm	Centimetre
CS	Central Sulcus
CTOA	Cue-Target Onset Asynchrony
dACC	dorsal Anterior Cingulate Cortex
DICS	Dynamic Imaging of Coherent Sources
dlPFC	dorsolateral Prefrontal Cortex
dpTMS	Double Pulse Transcranial Magnetic Stimulation
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
EB	Episodic Buffer
EBL	Executive Function – Binding Complexity - Load
EEG	Electroencephalography
EMG	Electromyograph
FDI	First Dorsal Interosseous
FDR	False Discovery Rate
FEF	Frontal Eye Fields

fMRI	Functional Magnetic Resonance Imaging
Hipp	Hippocampus
Hz	Hertz
ICA	Independent Component Analysis
Inf FG	Inferior Frontal Gyrus
Ins	Insular
IOR	Inhibition of Return
IPL	Inferior Parietal Lobe
IPS	Intra Parietal Sulcus
IR	Infrared
K	Kelvin
LCMV	Linearly Constrained Minimum Variance
LG	Lateral Geniculate
LTM	Long Term Memory
M1	Primary Motor Cortex
MEG	Magnetoencephalography
MEP	Motor Evoked Potential
mFC	Medial Frontal Cortex
MNI	Montreal Neurological Institute
mOFC	Medial Orbital Frontal Gyrus
MRI	Magnetic Resonance Imaging
ms	Millisecond
MTG	Medial Temporal Gyrus
MTL	Medial Temporal Lobe
OCD	Obsessive-Compulsive Disorder
OFC	Orbital Frontal gyrus
PCC	Posterior Cingulate Cortex
pHipp	Parahippocampus
Put	Putamen
rTMS	Repetitive Transcranial Magnetic Stimulation

SMA	Supplementary Motor Area
SMG	Supramarginal Gyrus
SPL	Superior Parietal Lobe
SSRI	Selective Serotonin Reuptake Inhibitor
SSS	Signal space separation
STG	Superior Temporal Gyrus
T	Tesla
tACS	Transcranial Alternating Current Stimulation
TES	Transcranial Electric Stimulation
TBS	Theta Burst Stimulation
Thal	Thalamus
TM	Trademark
TMS	Transcranial magnetic stimulation
tSSS	Temporal signal space separation
VOCI	Vancouver Obsessive Compulsive Inventory
WM	Working Memory
Y-BOCS	Yale-Brown Obsessive Compulsive Scale

1 Introduction

The evidence for memory impairments in OCD is mixed (Hermans et al., 2008). For example, findings are inconsistent, whether OCD have poorer memory capacity compared to neruo-typical controls, or whether verbal memory is less affected than visuospatial memory (Muller and Roberts, 2005a). Some evidence (Greisberg and McKay, 2003) pointed to a more subtle interaction with executive dysfunction leading to impaired memory performance.

In a review of 58 experiments Harkin and Kessler (2011) argue that rather than classifying memory deficits in OCD by modality, for example verbal vs visuospatial, it is more instructive to classify the experiments by their task demand in terms of Executive function (E), Binding complexity (B) and memory Load (L). Using the EBL classification system in combination with the Baddeley model of working memory (Baddeley, 2000) with episodic buffer, the performance of OCD subjects in working memory tasks could be better explained in terms of task demands and executive impairment. For example, working memory (WM) performance of subclinical OCD checkers can be impaired if presented with irrelevant but misleading information during the retention period.

The first aim of this thesis was to identify the neural correlates of executive dysfunction, in the context of the EBL classification, in checking behaviour that would lead to poorer performance in WM. This was undertaken using MEG measurements and ecologically valid stimuli (Harkin et al., 2011) designed to evoke working memory deficits through executive dysfunction in OCD participants. The second aim of this thesis was to use MEG measurements to investigate the neural correlates of attentional bias and executive dysfunction in OCD when engaged in an endogenous attention (Stroop) task. The third aim of this thesis was to use transcranial magnetic stimulation (TMS) to target task relevant brain areas and affect beneficially the task performance of OCD checker participants engaged in an exogenous attention (Inhibition of Return) task, an endogenous attention (Stroop) task and in the working memory task.

1.1 OCD Introduction

Obsessive-compulsive disorder (OCD) is a condition that affects approximately 1-3% of the population, (Stein et al., 1997). The condition is defined by obsessions and compulsions. Obsessions manifesting as repeated, intrusive, unwanted, distressing thoughts, urges or mental images. These obsessions can be perceived by the sufferer as meaningless, irrelevant, and inappropriate. Compulsions being defined in DSM-V (APA, 2013) as acts the person feels compelled to undertake, often in a maladaptive effort to reduce the distress invoked by the

obsessions (Muller and Roberts, 2005b), but the obsessions persist despite the compulsive actions undertaken in attempt to suppress or dispel the obsession.

OCD is not a single condition but heterogeneous, divided into broad categories, defined by their dominant trait. 'Washing', a contamination obsession with compulsions concerning cleaning, 'Checking', a fear of harm obsession with security checking compulsions, 'Ordering and Counting' a symmetry obsession with compulsions concerning ordering or counting, and compulsions 'Aggressive, Sexual or Religious Obsessions', an obsession with taboo or unacceptable thoughts. 'Hoarding' behaviour identified in previous editions of the DSM as a subtype in OCD, under DSM-V (APA, 2013) is no longer defined as a core dimension of OCD but considered to be a disorder related to OCD.

OCD patients may have obsessions in more than one dimension. The rates of occurrence have been estimated as contamination thoughts (55%), inappropriate aggressive (50%), sexual thoughts or images (32%), symmetry and or exactness (36%) (Abramowitz et al., 2003); (Rasmussen and Tsuang, 1986). The prevalence rate of common compulsions has been estimated as checking (80%), cleaning and washing (46%), and counting and ordering (21%) (Abramowitz et al., 2003) (Rasmussen and Tsuang, 1986).

Within the general population the most common compulsions found are 'Checking' and 'Washing' (Ball et al., 1996). The most common subtype, characterized by checking compulsions, occurs in over 50% of OCD patients (Henderson Jr and Pollard, 1988, Rasmussen and Eisen, 1992, Stein et al., 1997), with an additional 15% of the general population demonstrating sub-clinical checking compulsions (Stein et al., 1997).

OCD patients find the obsessions distressing which leads to compulsive behaviours in attempt to negate the disturbing thoughts. The compulsions provide a short-term reduction in anxiety for the sufferer, but in this way, by avoiding addressing the obsession and stopping a natural release from the anxiety, the short-term relief negatively reinforces the compulsive behaviour (Rachman and de Silva, 1978). Additionally, the compulsion induced actions serve maintain the obsessional thoughts and increase the likelihood of their reoccurrence and strengthen the maladaptive process of compulsive actions (Abramowitz et al., 2003).

Estimates for the 12 month population prevalence of OCD range between 1-2% (Heyman et al., 2001, Torres et al., 2006, Henderson Jr and Pollard, 1988) with the lifetime occurrence estimated at 1-3% of the population. Approximately 80% of the general population experience intrusive thoughts that in content are indistinguishable from clinical obsessions (Rachman and de Silva, 1978); (Salkovskis and Harrison, 1984). However, for the OCD clinical population such thoughts

are more frequent, intense and longer lasting. Compared to unipolar mood and anxiety disorders, people with OCD are less likely to be married, more likely to be unemployed (Torres et al., 2006) and to report impaired social and occupational functioning.

OCD may be present at a clinical or sub-clinical level of severity. Within the clinical population, diagnosis of the condition is often in conjunction with other conditions, including, but not limited to, depression, Tourretes syndrome, anxiety disorder and learning disorders. Evidence for a further sub-division with OCD classification (Taylor, 2012) of 'early onset', childhood and early adolescent, and 'late onset', late adolescent and early adulthood has been suggested.

Although the exact aetiology of OCD is remains unresolved, a consistent picture is emerging. Evidence points to a strong genetic link, with OCD tending to run in families. Secondary to the genetic factor, OCD may also in part be acquired behaviour being passed on from one generation to the next. The onset of OCD symptoms and behaviour show in two distinct groups, childhood onset and teenage onset. In terms of brain structures, evidence from converging sources indicate OCD to be associated with fronto-striatal abnormalities with particular involvement of the limbic system. (Henderson Jr and Pollard, 1988, Rasmussen and Eisen, 1992, Stein et al., 1997)

1.2 OCD and Neurobiology

Excessive doubting and repetitive actions are common symptoms of OCD and are suggestive of specific brain areas and circuits, the fronto orbital cortex, dorsolateral prefrontal cortex and anterior cingulate cortex, each connected with basal ganglia. These brain structures that have been found to be associated in response inhibition, action planning, organisation strategies and monitoring outcomes of previous actions (Rauch et al., 1998). The direct pathway projects form orbitofrontal cortex to ventromedial caudate and on to globus pallidus and substantia nigra, then via thalamus and back to the orbitofrontal cortex. In the indirect pathway information from ventromedial caudate passes via the basal ganglia before going to thalamus and return path to the cortex (Fornaro et al., 2009) The orbitofrontal – striatal circuit is involved in emotional regulation, reward processing and inhibitory control (Milad and Rauch, 2012a)

Dorsolateral prefrontal – striatal circuit mediates processing of information in temporary states relevant to working memory and executive functioning (Goldman-Rakic, 1992) As such the dorsolateral network is likely to be important in investigating memory deficits under executive dysfunction in working memory tasks.

Anterior cingulate – striatal circuit mediates performance and response competition, error detection and response selection. It is also implicated in working memory processes (Milad et

al., 2007) The importance of dACC in OCD pathogenesis is demonstrated by greatly reduced symptom severity in OCD patients following anterior cingulotomy (Darin D. Dougherty et al., 2002). Analysis of cortical activity during Stroop task (Schlösser et al., 2008)identified enhanced connectivity between dACC and dorsolateral prefrontal cortex, implicating its role in deficient error processing in OCD subjects and a structure to be investigated.

1.3 OCD and Genetics

Family studies have shown (Nicolini et al, 2009) that OCD traits are passed on through the generations but the degree to which this is due to genetic traits or learned OCD behaviour in the family environment remains unclear. The rate of OCD in first degree relatives is 12%, whereas in relatives of neuro-typical controls the rate is 2% ((Pauls et al., 1995); (Alsobrook II et al., 1999). First degree relatives also show higher rates of generalised anxiety disorder and agoraphobia, (Nestadt et al., 2000b) suggesting these conditions are strongly related to an OCD phenotype. Higher rates of tics have been identified ((Nestadt et al., 2000); (Hanna et al., 2005) in relatives of probands with OCD, and conversely higher rates of OCD in relatives of probands with tics. Evidence points to a genetic influence in OCD, whether in pure form or with co-morbidities (Nicolini et al., 2009).

Twin study data analysed through structured equation modelling (Van Grootheest et al., 2005) found for children, genetic influences account for 45-65% of heritable OCD symptoms, while for adult studies the role of genetics is assessed to be 27-47%. The remaining 53-73% variance is composed of environmental factors that affect OCD symptomology.

1.4 OCD and Attention

Attentional Bias

Although OCD is not classified as an anxiety disorder in DSM-V (American Psychiatric Association, 2013), OCD sufferers often experience anxiety and attentional biases (Muller & Roberts, 2005). In OCD the attentional biases are towards threatening stimuli that are emotionally salient to their individual OCD dimension, for example contamination or harm (Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & Van, 2007; MacLeod, Mathews, & Tata, 1986). In attending to threat stimuli people with OCD are prevented from appropriately orienting to the task relevant information and stimuli in their environment (Muller & Roberts, 2005; Radomsky & Rachman, 2004). The threat stimuli become overrepresented, while the task relevant non-threatening stimuli are underrepresented within the encoding of the person's environment.

OCD has been studied using a modified Stroop paradigm, namely an emotional Stroop task. In this threat related and neutral words are presented in different colours and subjects are asked to name the colour but not pay attention to the word. When the semantic meaning of the word captures the subject's attention, there is a delay in naming the colour, producing the Stroop effect (Muller & Roberts, 2005). Although some studies have shown OCD participants attentional bias towards threat related words (Foa et al., 1993) (Lavy et al., 1994) other studies have failed to replicate the finding (Moritz et al., 2008) finding no attentional bias on the emotional Stroop task with OCD checkers and OCD washers compared with healthy controls. From this failure to demonstrate attentional bias and colour naming delay, it was proposed that threat related words by themselves may not be sufficiently evocative to produce an attentional bias and that threat imagery might provide a more potent and effective stimulus for this purpose.

An fMRI neuroimaging study employing OCD participants and an emotional Stroop task (Van den Heuvel et al., 2005) did not find evidence of attentional bias in the behavioural data but analysis of the brain activity revealed increased activity in anterior cingulate cortex and limbic regions. This suggests that although the attentional bias effect in OCD may not always be overtly demonstrated by a task in behavioural data, OCD subjects are processing the threat stimuli differently from neurotypical subjects.

Attention Inhibition

It is a symptom of OCD (Muller and Roberts, 2005b) that individuals with OCD often have great difficulty inhibiting negative thoughts associated with their obsessions. The inability to inhibit an irrelevant information stream, cognitive inhibition, will compromise processing of task relevant information. An OCD subjects' difficulties in inhibiting irrelevant information is increased when that information is emotionally salient, relevant to the OCD symptoms (McNally et al., 2001). Task performance may be compromised by the cognitive interference of task-irrelevant but emotionally salient information competing with the processing of task-relevant information (Tipper and Cranston, 1985).

Attention inhibition has been investigated using a negative priming paradigm (Tipper, 1985) in which the previous distractor item becomes the target item. Neuro-typical participants are quicker to respond when the target item was not previously presented. When the distractor is represented as the target, delayed response is thought to occur because the inhibition process has to be overcome before the target stimulus can be processed. Paradoxically, (Enright and Beech, 1990) OCD participants were quicker to respond than neuro-typical subjects, displaying less negative priming. In a subsequent study (Enright and Beech, 1993) an effect of negative priming was observed for OCD checkers but not for other OCD subtypes.

OCD subjects have been shown to have attentional biases toward threatening information and stimuli (Bar-Haim et al., 2007). They may also show hypervigilance toward stimuli that are

emotionally salient to their obsession, combined with deficient attentional inhibition to suppress irrelevant stimuli, OCD subjects will be compromised in their ability to efficiently attend to and process information relevant to their goals (Muller and Roberts, 2005a, Radomsky and Rachman, 2004).

1.5 OCD checking and Memory

The literature exploring the relationship between memory deficits and OCD is inconsistent for review see (Hezel and McNally, 2016, Muller and Roberts, 2005a) with the body of evidence suggesting memory impairments are not simply a result of a general mnestic deficit or domain specific (verbal or visuospatial memory) deficit. Studies have even shown people with OCD to perform better than controls, however OCD was associated with decreased memory confidence (Radomsky et al., 2006) particularly in context of threat related content. Deficits in executive functions and failure to implement effective problem-solving strategies by OCD participants across multiple studies revealed a pattern consistent with frontostriatal executive dysfunction (Greisberg and McKay, 2003).

However, (Deckersbach et al., 2000) in a study investigating deficits in verbal and non-verbal memory recall, poorer performance by OCD participants was attributed to the employment of suboptimal memorizing strategies. Similarly, (Savage et al., 1999) OCD subjects in a drawing task, performed poorly because they fixated on irrelevant details of the diagram which impaired their memory recall when later required to draw the complex figure from memory.

In an experiment involving the checking ‘on/off’ status of a gas stove (relevant stimuli) and light switches (irrelevant stimuli), it has been shown (van den Hout and Kindt, 2003a) the act of repeated checking results in the recollection of the memory of the checking act to become less vivid and less detailed. In both OCD and healthy participants, the subject’s confidence in the memory was reduced. Possibly the lack of confidence in the recalled memory is a motivation in OCD checking (Radomsky and Rachman, 2004). Although confidence in the memory was affected, accuracy of memory recall was not.

It has been observed (Radomsky and Rachman, 2004) that managerial workers who require good memory skills for their work but suffer with OCD checking, do not report general problems with memory recall when the memory task is not relevant to their checking behaviour. The task may be accomplished well even when the memory task is difficult. However, when checking behaviours are engaged by a task relevant to their checking dimension, anxiety increases and attention is focussed toward the perceived threat and to monitoring their emotional reaction to that threat. With attention uninhibited and diverted from the current task, the details of the checking event are poorly memorized, leading later to the retrieval of a poor memory the event.

Memory impairments in OCD may be related to deficits in executive functions and employment of poor organisational strategies, such that memory impairments are secondary to executive dysfunction rather than deficits of the memory system (Harkin & Kessler, 2009). Within the framework of Baddeley's extended model (Baddeley 2000) of working memory that includes an episodic buffer, Harkin & Kessler (2009) proposed that executive dysfunction mediated by unsuppressed stimuli or thoughts, impaired faithful operation of memory bindings within the working memory system. See figure 1-1, and below an explanation of the EBL (Harkin and Kessler, 2011) classification system and its relevance to working memory deficits.

1.6 EBL classification system

A review of the literature (Greisberg and McKay, 2003) examining the neuropsychological features of obsessive-compulsive disorder identified that a deficit in organizational strategies in general, suggesting problems in executive functioning could be sufficient to induce memory impairments in OCD subjects. In this analysis, memory impairments are secondary to executive dysfunction and it is the task requirements and executive deficits that differentiate the performance of OCD subjects from controls (Olley et al., 2007).

Baddeley's extended model (Baddeley, 2000) of working memory (WM) that includes an episodic buffer, offers a framework within which can be proposed a mechanism by which memory impairments can arise from executive dysfunction (Harkin and Kessler, 2011). Baddeley's extended model of WM comprises a central executive, three sub-systems, the visuospatial sketch pad, phonological loop and episodic buffer. The episodic buffer is a temporary store that can interface with long term memory (LTM) representations, flexibly manipulate and modifying information to facilitate problem solving. The central executive can control the content of the episodic buffer (EB) by selectively attending to particular information sources, whether it be other elements of working memory, information retrieved from long term memory or perceptual information.

Baddeley's model of working memory is conceived of as a limited capacity temporary store in which information in the episodic buffer can be integrated, manipulated and modified in pursuit of goal driven tasks such as reasoning, comprehension and learning. See Figure 1-1. The Central Executive can influence the contents of the EB by attending to a particular source of information, which may be from WM, LTM or perceptual. The EB provides a mechanism not only that can represent the environment but also create new cognitive representations necessary in problem solving.

Information presented in visual scenes usually comprises a complex mixture of features, for example colour, shape, size, orientation and location. The complex nature of the features of 'real world' objects is at odds with the limited capacity of WM for maintaining individual object features such as colours or orientations, or integrated objects with colours and orientations (Luck and

Vogel, 1997). Real world objects have nested properties, their features relate to the object, the object to its location and many other contextual associations. Successful memory performance requires accurate encoding, maintenance and retrieval of such multimodal bindings which is facilitated by the episodic buffer (Baddeley, 2000) that can flexibly manipulate information in the temporary store and access long term memory representations. In this framework (Harkin et al., 2011) of WM, executive dysfunction in checkers fails to inhibit intrusive stimuli, diverting attentional resources to the intrusive stimuli at the cost of attending to and preserving the fidelity of the current items in WM, thus interfering with fragile multimodal bindings in the EB, adversely affecting information content in WM.

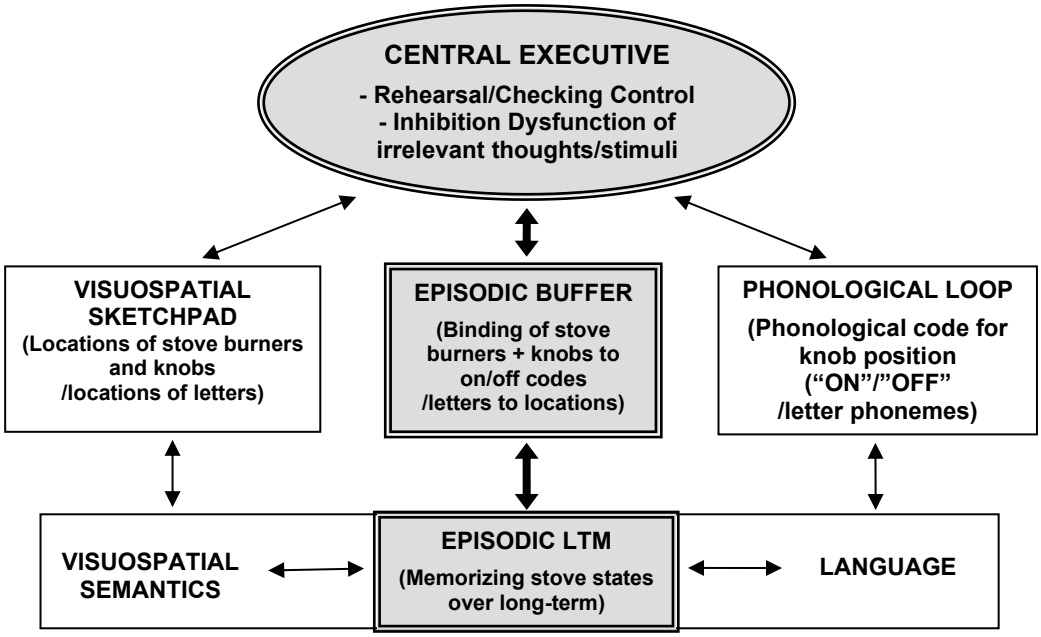

Figure 1-1. Representation of the main components of Baddeley (2000) model of WM, incorporating the episodic buffer. The grey parts of the WM framework highlight the components proposed (Harkin and Kessler, 2011) to be involved in compulsive checking. A specific central executive dysfunction (inhibition of irrelevant thoughts/stimuli) interferes with binding of the episodic buffer disrupting memory performance over the short-term and potentially the long term. Component boxes are annotated to indicate the multimodal bindings arising in chapter 3, WM MEG study.

The EBL (Executive Function Efficiency (E), Binding Complexity (B) and Memory Load (L)) classification system (Harkin and Kessler, 2011) seeks to predict and classify WM deficits in compulsive checking on the dimensions of Executive Function Efficiency, Binding Complexity and Memory Load. In this system memory impairments observed in OCD checking can be explained by executive dysfunction.

Successful executive functioning comprises (Wolters and Raffone, 2008) of three functions, attentional control, maintenance and integration. Attentional control provides top-down selection

of task relevant representations and inhibition of task irrelevant stimuli. The maintenance operation holds task relevant representations in an active state. Integration is the flexible manipulation and binding of information for the task goals. In the context of the studies reported in this thesis, OCD memory impairments may occur when experiment manipulations provoke checking behaviour impairments in executive functioning. For example, when the encoding set resonates with checking symptomology leading to a division of attention between the threat stimuli and encoding, (Coles and Heimberg, 2002) degrading the quality of multimodal bindings and memory performance.

In the studies reported here, it is on the dimension of Executive Function Efficiency (High-Checkers vs Low-checkers) that the experiments were investigated and the role of attentional control, endogenous (top-down) and exogenous (bottom-up), implicated by the EBL model as important in checking behaviour. The parameters of Binding Complexity and Memory Load were not varied in each individual experiments.

Exogenous attention is a reflexive mechanism for detecting quickly salient events and stimuli that appear outside the current focus of attention, so that processing resources can be reoriented to the new stimulus (Carretié, 2014). In contrast endogenous attention is effortful, goal driven direction of processing resources.

Attentional control refers to an individual's ability to regulate (Cisler and Koster, 2010) their attentional allocation, for example, the suppression of exogenous emotional distractions by purposeful 'top-down' regulation. Such effortful inhibitory control (Posner and Rothbart, 2000) engages executive function to override the automatic response.

OCD and subclinical checkers have an attentional bias towards stimuli salient to the dimension of their OCD symptoms (Moritz et al., 2009, Amir et al., 2009, Bradley et al., 2016, Hezel and McNally, 2016) and engage increased levels 'top-down' processing (Ciesielski et al., 2011) in order to maintain normal performance. Signatures of increased 'top-down' processing in checker participants might therefore be found in components of the endogenous attention network (Hopfinger et al., 2000, Sanchez et al., 2016, Chica et al., 2013), such as medial frontal cortex including ACC, frontal eye fields (FEF), supplementary motor area (SMA), dorsolateral prefrontal cortex (dlPFC), medial temporal lobe (MTL) and inferior parietal lobe (IPL).

Figure 1-2 illustrates how brain regions may interact under conditions of deficient executive functioning supports OCD checking behaviour with increased theta processing between PFC and MTL and under conditions of attention bias towards task irrelevant stimuli increased theta processing supports activation of attention networks in parietal cortex and fails to suppress processing of irrelevant visual stimuli by the occipital cortex.

1.7 Aims

Reiterating the aims presented at the beginning of this chapter, the first aim of this thesis was to identify the neural correlates of executive dysfunction, in the context of the EBL classification, in checking behaviour that would lead to poorer performance in WM. This was undertaken using MEG measurements and ecologically valid stimuli (Harkin et al., 2011) designed to evoke working memory deficits through executive dysfunction in OCD participants.

The second aim of this thesis was to use MEG measurements to investigate the neural correlates of attentional bias and executive dysfunction in OCD when engaged in an endogenous attention (Stroop) task.

The third aim of this thesis was to use transcranial magnetic stimulation (TMS) to target task relevant brain areas and affect beneficially the task performance of OCD checker participants engaged in an exogenous attention (Inhibition of Return) task, an endogenous attention (Stroop) task and in the working memory task.

1.8 Chapter outline

Chapter 2 presents the methods that are referred to in the experiment chapters and are methods that were used in this thesis. Chapter 3 addresses the first aim, to investigate the neural correlates of executive dysfunction in the working memory task. Chapter 4 the working memory task is revisited using repetitive transcranial magnetic stimulation (rTMS) in attempt to modify task performance observed in the MEG working memory experiment.

Chapters 5 and 6 explore the role of attention in OCD checking behaviour. Chapter 5 explores endogenous attention processes by means of the Stroop task. In this chapter the neural correlates measured by MEG are reported and also a separate experiment in which double pulse TMS was applied during a Stroop task in attempt to modify participant performance. Chapter 6 focusses on exogenous attention, in which the effects of rTMS on performance in an inhibition of return paradigm was explored.

The findings of the working memory and attention tasks are brought and discussed in chapter 7.

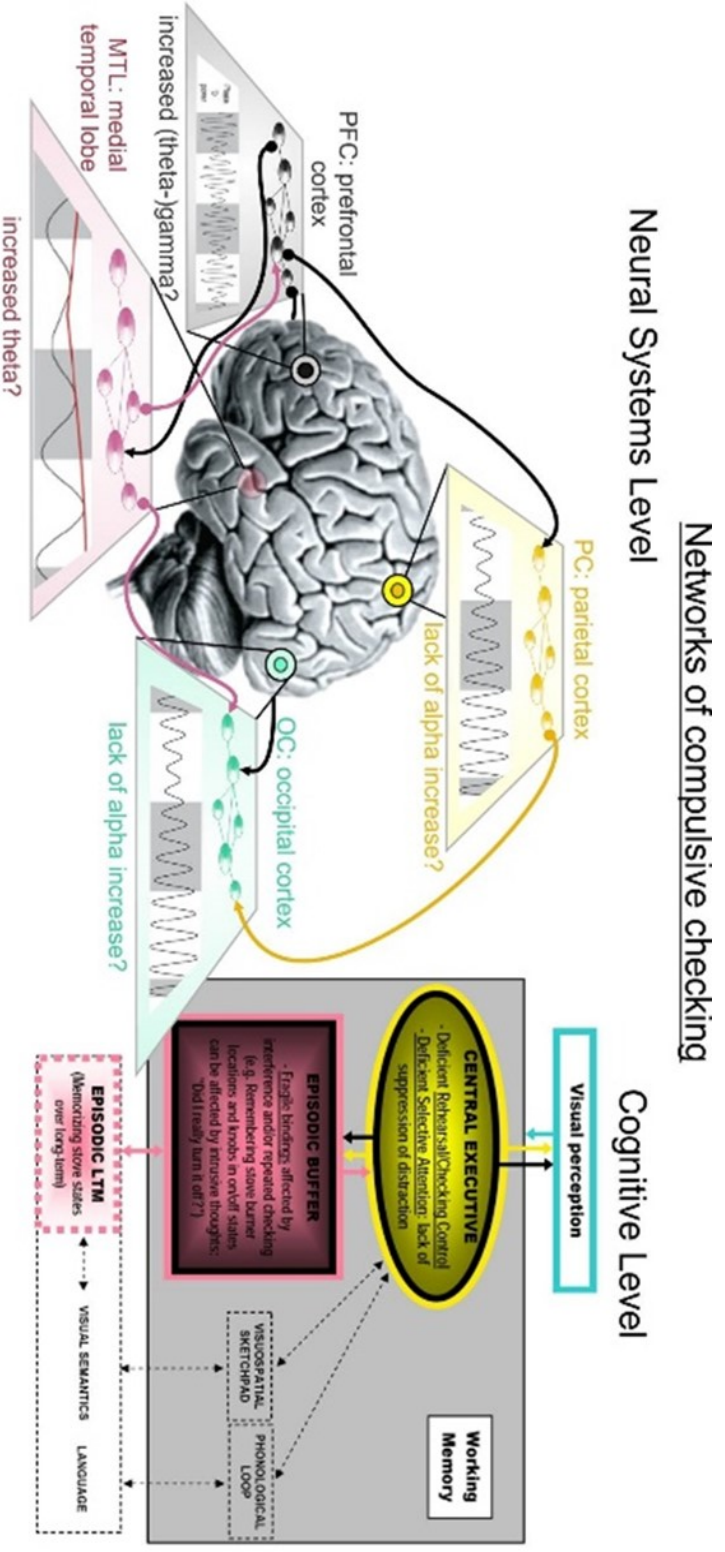

Figure 1-2 Obsessive-compulsive checking behaviours mediated by executive dysfunction. Checking / rehearsal behaviour resulting from executive dysfunction leading to increased theta processing in PFC and MTL as a signature of repeated activation of WM bindings. Unsuppressed attentional bias towards salient but irrelevant stimuli arising from executive dysfunction is mediated by increased theta processing in PFC, activation of parietal attention networks and deficient suppression of processing in visual cortex.

2 General Methods

2.1 Vancouver Obsessive Compulsive Inventory (VOCI)

Introduction

The majority of participants in the studies reported here were recruited from the undergraduate student population at Aston University. The students selected to take part were unmedicated and not clinically diagnosed with OCD. Part of the selection is their suitability for Transcranial Magnetic Stimulation for which psychotropic medication, such as might be prescribed for anxiety, is contraindicated under the Aston University research guidance for TMS.

In addition to being contraindicated for Transcranial Magnetic Stimulation psychotropic medication is a potential confound to the study because of the interaction it is designed to have on the limbic system, the natural functioning of which is the focus of the studies.

This presents a difficulty in recruiting suitable participants for the investigations. Those with a clinical diagnosis of OCD are likely to be medicated and therefore unsuitable to take part in the studies. It is reported that 2-3% (Stein et al., 1997) of the population has clinical severity OCD and a further 15% possess sub-clinical level OCD symptoms. It is from the sub-clinical, unmedicated population that participants were recruited. Subclinical OCD groups (Mataix-Cols et al., 2003, Mataix-Cols et al., 1999) are appropriate in researching cognitive behaviour of OCD, and have the advantage of reduced incidence of comorbidities and medication compared to clinical OCD groups.

Self-Report and Administered Questionnaires

Performance of subclinical OCD checking participants was contrasted against low-checking controls. A number of clinical and research tools exist to guide the recruitment of participants to ‘checker’ and ‘low-checker’ cohorts. These assessment tools are in the form of questionnaires, structured and semi-structured interviews. They can be categorised as either ‘administered’ or ‘self-report’ instruments. Each has their advantages and limitations.

Researcher or clinician administered questionnaires and interviews have the advantage that the interviewer can assist responders where poor language skills or reading ability might be problematic. Potentially, an interviewer with experience of the field is able to explore the responder’s symptoms more carefully and arrive a more accurate assessment than might otherwise be achieved. However, a number of disadvantages may arise with administered assessments (Grabill et al., 2008). They require a significant investment of time by both the clinician or researcher and participant. The accuracy of the data gathered relies heavily on the training and ability of the person administering the assessment. This could lead to bias greater variability in psychometric properties of the test (Shaffer et al., 2004) when compared to self-report assessments.

Self-report instruments by their nature are more easily administered (Grabill et al., 2008) but can suffer from a number of disadvantages. Without a researcher on hand to guide the responder, not all participants may interpret the scale responses in the same way. Different levels of language and reading skills among participants may skew results and OCD symptoms or characteristics not explicitly addressed by the questionnaire will be under reported.

However, these advantages and limitations apply to reporting instruments in general and not to the particular circumstances of the current study. Participants were in the majority drawn from a university student population and as such possessed a good level of language and reading ability. The focus of the selection process was to identify high and low responders on the checking subscale, rather than acquiring an accurate and complete measurement of an individual participant's overall OCD status. Additionally, student participants may not be prepared to invest the time and effort to complete a structured or semi-structured interview as well as the TMS or MEG tasks. With these caveats, a self-report questionnaire that captures the essential checking subscale information, is straight forward and quick for participants to complete would be the most desirable.

VOCI Self-Report Questionnaire

The Vancouver Obsessive Compulsive Inventory (VOCI), is a self-report, 55 element questionnaire that assesses severity of behavioural OCD symptoms on the dimensions of 'contamination', 'checking', 'obsessions', 'hoarding', 'needing to get things just right' and 'indecisiveness'. Participants rate their response to each question on a five point Likert scale. 0 corresponding to 'not at all', 1 'a little', 2 'some', 3 'much', or 4 'very much'.

For this study a reduced version of the VOCI questionnaire, comprising 36 questions that are the 'checking', 'obsessions', 'needing to get things just right' and 'indecisiveness' dimensions was used to select suitable participants. From the 36 questions, just the scores for the six checking dimension questions were used to group participants. Participants with checking dimension scores of 1 to 3 were assigned to the 'low-checker' cohort, participants scoring 10 or above, were assigned to the 'checker' cohort. Participants with intermediate scores were declined from the study.

The VOCI (Thordarson et al., 2004) was developed from the Maudsley Obsessional Compulsive Inventory (MOCI) a self-report instrument for measuring observable compulsive behaviour such as checking and washing. The VOCI was designed to be an improvement on the MOCI in that the questions were expressed in simpler, more easily understood language, to be a better assessment of obsessive-compulsive behaviour in obsessions, hoarding and covert rituals. The scoring scale was changed from dichotomous 'true' or 'false' reporting to a Likert scale that would have value in measuring OCD symptom changes, for example, following treatment.

The VOCI instrument demonstrated high internal consistency (Thordarson et al., 2004), and in particular with the checking subscale with OCD patients ($a = 0.96$) and student non-clinical controls ($a = 0.92$).

Test-retest reliability (Thordarson et al., 2004) with OCD patients was high (r = 0.96), with a mean retest delay of 47 days. A lower test-retest reliability (r = 0.56) was observed with student participants, mean retest delay 11 days. The lower reliability score was attributed to 'range restriction', the reported mean item scores being 0 or 1.

Convergent reliability (Thordarson et al., 2004) was demonstrated against other contemporary OCD assessment methods, Padua Inventory-Washington State University Revision (PI-WSUR) (r = 0.85), MOCI (r = 0.74), Yale-Brown Obsessive-Compulsive Scale self-rating severity scale (YBOCS-SR) (r = 0.67) and Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) (r = 0.14). In this test low correlation values of the Y-BOCS reported not only with VOCI but other OCD assessment tools. This was attributed (Grabill et al., 2008) to a possible procedural error, perhaps a lack of training in the clinicians delivering the test.

Testing the VOCI checking subscale (Thordarson et al., 2004) with OCD patients with a known diagnosis, OCD checkers (n=47) reported a mean checking subscale score of 15.6, (SD=7.91). OCD patients without a checking diagnosis (n=40) reported a mean score on the checking subscale of 8.35, (SD=7.90)

The VOCI has been criticised (Grabill et al., 2008) for there being limited evidence of discriminant validity. More recently a new self-report assessment instrument, the Vancouver Obsessional-Compulsive Inventory-Revised (VOCI-R), a combination of the VOCI and Symmetry Ordering and Arranging Questionnaire (SOAQ) (Radomsky and Rachman, 2004) has been proposed(Gonner et al., 2010). The checking subscale elements of the VOCI-R are taken unchanged for the VOCI. Discriminant validity tests of the VOCI-R on the checking subscale (Gonner et al., 2010) showed low correlations with Penn State Worry Questionnaire (r = 0.29), Beck Depression Inventory (r=0.09) and Beck Anxiety Inventory (r=0.19), indicating good discriminant validity. By extension, because the checking subscale elements of the VOCI-R are taken unchanged from the VOCI, the discriminant validity results hold for the VOCI checking subscale also.

Conclusion

Whilst some general criticisms remain of the VOCI (Grabill et al., 2008) in not addressing ordering and arranging symptoms, doubts and mental neutralizing, and its unknown sensitivity to treatment effects, across a number of reported evaluations of its efficacy, the checking subscale is the best performing part of the VOCI and has been demonstrated to have very good internal consistency, convergent and discriminant validity. For the purposes of this study it is a suitable self-report instrument for use in selecting student participants for sub-clinical 'checker' and control 'low-checker' cohorts.

2.2 Magnetoencephalography

Introduction

Magnetoencephalography (MEG) is a technique by which the magnetic fields generated by the electro-chemical activity of neurons is measured using superconducting quantum interference devices (SQUID). The magnetic fields detected by MEG (Hämäläinen et al., 1993) are generated by intracellular currents in the dendrites of pyramidal cells. These magnetic fields are of the order 10-12T to 10-15T (Vrba and Robinson, 2001).

In comparison to fMRI, MEG offers high temporal resolution, typically 1kHz but up to 12kHz with the latest scanner (Hall et al., 2014) technology, whereas for fMRI ~5s is not uncommon and ~1s may soon be typical (Garcés et al., 2017) with sub-millimetre spatial resolution. MEG spatial resolution and localisation accuracy depends on a number of factors, including, MEG-MRI coregistration accuracy, the model of the magnetic field measurements and how they project onto the brain. A spatial resolution of 6mm might be achieved and location accuracy may be less accurate (Hillebrand and Barnes, 2003).

In comparison to fMRI (Uğurbil et al., 2013) for which currently a spatial resolution down to 2mm and temporal resolution near to 1Hz can be achieved with suitable 3T scanners. MEG has an advantage over EEG in that the magnetic fields detected in MEG are not subject to dispersion effects and inhomogeneities in the conduction path from neuron to sensor, to which the electric potentials detected by EEG are susceptible. This, together with MEG systems generally comprising a larger number of sensors, MEG techniques enable better localisation of cortical sources compared to EEG techniques. Unlike EEG in which the signal is referenced to a baseline potential, the magnetic signal detected by MEG is reference free.

Oscillatory neuronal activity is in the range 0.5-1000Hz, but due to decreasing signal to noise at higher frequencies, the useful frequency range (Lopes da Silva, 2013) measured by MEG techniques is approximately 0.5-90Hz. This frequency range comprises frequency bands, delta(1-4Hz), theta(4-8Hz), alpha(8-13Hz), beta(13-30Hz) and gamma(>30Hz). MEG data can be used to gain insight into brain function and behaviour through the study, for example, of oscillatory power changes in these frequency bands, in specific regions of the brain, in response to a task or stimulus.

The dendritic current flows approximately perpendicularly to the cortex. Depending on the gyral and sulcal folds of the cortex, the current flow ranges from being tangential to radial with respect to the skull surface. If modelled as a sphere, only tangential currents would produce a magnetic field outside the sphere that is a field detectable by the MEG sensors, (Hämäläinen et al., 1993).

The magnetic field generated from a single neuron is too weak to be detected by MEG. Only the combined magnetic fields from an assembly of aligned and simultaneously activated neurons are sufficiently strong to be detectable (Nunez and Silberstein, 2000). Such an assembly of neurons occupies a volume of about 10 cubic millimetres.

Measurement of Magnetic Fields

The detection of the oscillatory neuromagnetic field and the generation of a time-varying voltage representation of that magnetic field is achieved using SQUIDs in combination with inductively coupled pickup coils and amplifiers. A SQUID is a superconducting ring approximately 3mm in size with one or more insulating breaks, named Josephson Junctions, in the ring. Under superconducting conditions, achieved by immersing the SQUIDS in liquid Helium at a temperature of 4.2ºK, electrons can pass through the insulating junctions by means of quantum mechanical tunnelling. A magnetic field passing through the superconducting ring will modulate the current flowing through the SQUID, from which a voltage signal can be generated and the magnetic field can be measured.

To increase the sensitivity of the SQUID to the magnetic field a larger pickup coil is used to receive a larger proportion of the magnetic field and couple it to the SQUID sensor. The time-varying voltage induced by the magnetic field is inductively coupled to an amplifier and passed to measurement electronics outside of the liquid Helium environment. The pickup coil may be arranged in different ways to make it more or less sensitive to fields from different directions and orientations. Dependent on their configuration (Hari and Kaukoranta, 1985), the pickup coils are referred to as either magnetometers for single coil or gradiometers which use combinations of oppositely wound coils. The Elekta Neuromag TRIUX MEG system (Elekta Neuromag, Oy) employs a combination of magnetometers (102 off) and planar gradiometers (204 off) comprising 306 channel sensors in total. The sensitivity of SQUIDs to magnetic fields requires that MEG systems are housed within magnetic shielded rooms to isolate the sensors from environmental noise.

Although the two sensor types have different qualities, for example, magnetometers are better suited to detecting deeper cortical sources, while gradiometers are less noisy (Garcés et al., 2017). After denoising the MEG data using Signal Space Separation techniques, the two types of sensor yield equivalent source localisations.

Maxfilter Pre-processing (data cleaning)

The sensitivity of the SQUID sensors to the low strength neuromagnetic fields means they are also sensitive to other magnetic field sources which are noise to the MEG signals. Before

conducting an MEG measurement participants were screened to ensure they remove any metal items that can affect the recording.

The two main sources of noise artefact were then environmental (for example, 50Hz mains line and nearby moving vehicles) and biological (for example, eye blinks and eye movement, jaw and neck muscle activity, cardiac signals).

The Elekta MEG system requires that signal data are pre-processed using the Maxfilter software program. Within Maxfilter, there is implemented two methods of removing environmental and biological noise artefacts, Signal Space Separation method (SSS) and a temporal extension of the method (tSSS). Using these methods (Taulu et al., 2005) signals that originate from outside the sensor array (environmental noise) are separated out from those that are received from within the sensor array, which include both neurological signals as well as biological noise artefacts. The biological artefacts can be removed using tSSS with exploits temporal correlations (Taulu and Simola, 2006) to distinguish between signals inside the sensor array and those generated near the sensor helmet.

Data Cleaning Pipeline

The data were processed in a Matlab software environment using the Fieldtrip (Oostenveld et al., 2011) signal processing and analysis toolbox. For ease of data processing, speed and data size, the data were down sampled to 300Hz. Data were low pass filtered with the filter stop at 70Hz and line noise filtered at 50Hz and its harmonics. Channels that were ‘dead’ or intermittently noisy were removed from all data sets for that experiment.

The next stage in data cleaning was to look at the signal power in the trials, as measured by signal variance. It was assumed that trials or channels with high signal variance were strongly contaminated by noise artefact. The data can be cleaned by either removing channels or trials. Where possible only individual noisy trials were removed rather than channels. Removing channels unnecessarily would be too invasive to the data.

The final stage of artefact removal was to isolate unwanted signals of biological origin, such as cardiac signals, eye blinks and jaw clenching. This was achieved with Independent Component Analysis (ICA) using the Fieldtrip toolbox (Oostenveld et al., 2011).

Following ICA decomposition the sensor channels were ‘repaired’ by interpolating signal data from the missing channels nearest neighbours. Under ideal circumstances the data now ‘clean’, with all physiological noise and non-physiological noise removed, the data are ready for beamformer analysis.

Beamformer analysis

The MEG signals received by the sensors near the surface of the scalp tend to be dominated by the signals from cortical sources closest to the sensor. Using beamformer techniques that were initially developed for use in radar type applications (Van Veen et al., 1997) it is possible to recast the measured MEG signals to estimate the location within the brain and the strength of the cortical sources that give rise to the signals measured near the scalp.

Broadly, source estimation involves two steps, generating a 'forward model' and an 'inverse solution'. The forward model is a prediction of the signals received at the sensors for any given distribution of current sources within the brain. In the analysis conducted in this study, forward models were constructed for each participant based on individual head models derived from their MRI. The accuracy of the forward model relies on the accuracy of the volume conduction head model. Here a 'single shell' head model (Nolte, 2003), that employs the Boundary Element Method (BEM) to produce a semi-realistic head model was used. This provides superior performance compared to the simpler isotropic sphere head model. The forward model is produced by dividing the numerical model of the brain volume into a regular three-dimensional grid. The forward model describes the signal received by each MEG sensor from a unit current source located within the grid. This is repeated for a current source at each grid location so that a complete description of the signal received by each MEG sensor from a unit current source at each location within the brain is obtained.

The inverse problem concerns estimating the distribution of currents inside the head that gave rise to the MEG data. The inverse problem is ill-posed, meaning that there is no unique distribution of cortical sources that can satisfy the solution (Larson et al., 2014). For example, the magnetic field from current sources aligned radially from the origin are not detectable by sensors outside the head. Different source localisation solutions can be obtained by adding such 'silent' current sources without affecting the 'goodness of fit'. A practical solution to the inverse problem is obtained by bounding the solution. For the Dynamic Imaging of Coherent Sources (DICS) and Linearly Constrained Minimum Variance (LCMV) beamformer the source localisation estimates are obtained by minimising the source power at a given grid location subject to two constraints. The 'unit-gain' constraint requires that the inverse filter recovers the source amplitude with unit gain. Secondly it is assumed that sources are uncorrelated. In practice however,(Gross et al., 2001, Van Veen et al., 1997) discrete sources with correlations of up to 0.5 can be resolved sufficiently well.

2.3 Transcranial Magnetic Stimulation

Introduction

Transcranial magnetic stimulation (TMS) is a technique that employs pulses of magnetic energy to generate electric currents within the brain by the process of electromagnetic induction. In this way neurons within a specific brain region and period of processing can be stimulated and the effects of such stimulation on task performance used to investigate brain function. In the research described later, two types of TMS pattern were used, dual pulse (dpTMS) and repetitive pulse (rTMS). The dpTMS was employed to stimulate a particular brain region at a specific time after presentation of a picture stimulus when task relevant information would be processed. In a separate experiment an rTMS technique was used to entrain particular rhythms (6Hz Theta, or 10Hz Alpha) within specific brain regions prior to presentation of a picture stimulus with the aim of amplifying a 'deficient cortical oscillation' to improve task performance in a lower performing cohort.

This section describes briefly the equipment used to generate and deliver the TMS pulses to the participant and an over view of the mechanism by which neuron activity can be modulated by magnetic stimulation.

Equipment

TMS is a non-invasive brain stimulation technique in which, by means of electromagnetic induction, electric currents are generated within the cortex, sufficient to activate neurons into firing. To do this a TMS system is designed to produce large, transient, focussed, magnetic fields.

The basic elements of a TMS system comprise a large capacitor, typically charged to several kilovolts, resistor and a Thyristor electrical switch. Used together these generate a current of several kiloamperes which discharges through coiled wires to produce a brief (150us) magnetic field. Modern TMS systems produce peak field intensities of between 1.5T and 2.5T at the coil (Thielscher and Kammer, 2002), sufficient to induce electric fields of 150V/m within the cortex and generate action potentials.

A transient field is required because electromagnetic induction requires a changing magnetic field. The magnetic pulses are generated by passing a large transient current through coil loops. The coils are contained within a handheld wand. The Figure 8 type coil used here, the coils are arranged side by side, to provide some focussing to the magnetic field produced. The peak magnetic field generated with the Figure 8 coil is approximately twice what might be generated with the coils arranged as a single solenoid. The peak magnetic field of the Figure 8 coil attenuates more quickly away from the peak than would a solenoid coil arrangement. Thus the Figure 8 coil type arrangement is less likely to stimulate neurons away from the targeted area than might a solenoid type coil.

Although some TMS systems provide some control over the current discharge allowing the 'shape of the magnetic pulse' (temporal profile of the magnetic pulse) to be determined by the user, TMS may be categorised as either mono-phasic or bi-phasic. Describing the magnitude and polarity profile of the magnetic pulse produced, a mono-phasic system produces a half-sinusoid shaped pulse whereas a biphasic system produces a sinusoid shaped profile.

The two key differences between these systems are firstly, that the pulse repetition rate of bi-phasic systems can be 100Hz and higher, whereas mono-phasic systems have slower pulse repetition rates, typically less than 1Hz. Secondly, the direction of the induced current is in the opposite direction, i.e., using the same coil connected to a mono-phasic system, the direction of the induced current is reversed with the bi-phasic system. A bi-phasic TMS system was used in the conduct of the TMS experiments reported here.

TMS Coils

A variety of TMS coil types have been designed to optimise, depending on the cortical target of interest, the delivery of the magnetic pulse to the cortex. In this research a 70mm Alpha Figure 8 and a 110mm double cone were used. The Figure 8 coil comprises two coils, oppositely wound and placed side by side (Jalinous, 1991) so that the magnetic field reaches peak intensity in a small volume between the coils. The induced current is tangential to the coils, which at the site of peak field between the coils, is in line with the handle of the coil. It is important that during an experiment the coil is pointed consistently so the direction of induced current and hence the stimulation conditions are consistent across all trials.

Figure 2-1. Figure 8 (left) and Double-cone (right) TMS coils. The circular parts of the coil contain windings that generate focus the magnetic field. The magnetic field generated by the figure 8 coil reaches maximum intensity approximately 2cm below the centre point of the coil, where the two circular windings meet. The point of maximum magnetic intensity with the double-cone coil occurs between the two coil windings, approximately 5cm from the handle.

The properties of the magnetic field generated by a Figure 8 coil, being relatively focal (Cohen et al., 1991) and high intensity, means it is well suited to stimulating superficial cortical targets. A Figure 8 coil, depending on the stimulation intensity, is thought to be effective in stimulating the cortex between 1.5 and 3.0cm below the scalp (Thielscher and Kammer, 2002).

The double-cone coil is designed for stimulating deeper cortical targets such as ACC. The shape of the double-cone coil produces a less focal field compared with the Figure 8 coil, but one that

is more homogenous at target and may therefore be better suited to targeting deeper structures. The peak field region of the double-cone coil lies in the volume between the two arms of the coil. Being less focal, the double-cone coil has the disadvantage, compared the Figure 8 coil, of requiring a higher stimulator input to produce a comparable peak magnetic field intensity. Participants often find the higher stimulator outputs used with the double-cone coil cause uncomfortable stimulation of peripheral nerves in the face and scalp, particularly the trigeminal nerve. As a result, the double-cone coil is usually less well tolerated by participants than a Figure 8 coil.

Neuronavigation

In conducting the TMS experiments reported, a BrainSight (TM) frameless stereotactic neuronavigation was used to track and record the location of each active and sham TMS pulse applied. The BrainSight neuronavigation system uses an infra-red optical-tracking system employing a camera to measure in 3D space the locations of infra-red (IR) retroreflective markers attached to the TMS coil and on a headband worn by the subject.

At the start of a TMS experiment, the participant's head and structural MRI scan are coregistered in a common reference space by using a computer tracking pointer to locate on the participant's scalp anatomical landmarks (tip of nose, nasion, tragus of the ears and the external angles of the eyes) that are easily visible on both the participant's structural MRI and their scalp surface anatomy. The coregistration, if done correctly, links the structural MRI, head surface anatomy and the three-dimensional (3-D) scalp representation generated by the neuronavigation software.

In this way, with IR location markers attached to the TMS coil and worn by the participant, both the position and orientation of the coil can be tracked relative to the participant's head. The navigation software can then be used to guide the experimenter to place the coil on the participant's head at the required location and with the correct coil orientation to give the correct cortical stimulation. As well as coil location and angle, the navigation software records positioning errors in both location and angle, to submillimetre and sub-degree level. Firstly, this enables the trial-to-trial coil position repeatability to be high and also the ability to identify and discard trials where the coil was misplaced and off target. Using the neuronavigation system in combination with an individual's structural head MRI, it was found that previously located stimulation sites on the scalp could be required to 1mm accuracy for repeat TMS sessions weeks later. Stimulation of the motor cortex, for example the first dorsal interosseous muscle (FDI), suggested the TMS coil must be placed with a position circle error of less than 3mm diameter so that the FDI muscle is activated well and at a low stimulation intensity and no other muscle activations are observed.

Successful magnetic stimulation of motor cortex or visual cortex will produce a tangible response in the form of muscle twitch or phosphenes that provide immediate positive feedback to the experimenter that the correct cortical target has been located. Unfortunately, stimulation of other parts of the brain not directly connected to motor and visual cortex will not induce effects such as muscle twitch or phosphenes that are immediately detectable by the experimenter or subject.

Areas that do not provide such positive feedback are termed ‘silent brain areas’ and include, for example ACC and dlPFC, which are relevant to the TMS studies presented. To target these areas accurately the target brain structure was identified on each individual’s structural MRI and the neuronavigation software relied upon to guide the TMS coil to the correct location on the subject’s scalp. With correct set up of the TMS and navigation equipment it was anticipated that targets in motor and non-motor areas were located equally well. The magnetic field generated through the TMS coil is focussed at one point, at the centre of the figure of eight coil. The magnetic field decreases rapidly in intensity away from this focus point. Practical measurements targeting different parts of the motor cortex suggest the figure of eight TMS coil was focal to the same degree as the positioning accuracy of the neuronavigation software, with a circle of error of less than 3mm diameter.

In the TMS studies reported here, the preference was to use individual participant MRIs with the neuronavigation system. This approach had the advantage (Lefaucheur et al., 2014) of enabling the cortical region of interest to be localised accurately, based on brain anatomy rather than surface features of the scalp, thereby providing as accurate as possible target stimulation. The main disadvantage of this approach is the extra time and resources required to generate and process the individual MRI scans.

Mechanism of neuron stimulation

Behavioural studies employing TMS often target ‘silent areas’ of the brain, that is to say areas that do not produce outputs (e.g., a finger movement) that are easily measured at the time of the stimulation. It was assumed in this work that the mechanisms by which TMS stimulates motor pathways is functionally similar to how TMS stimulates neurons in ’silent’ regions of the cortex.

Studies comparing motor-neuron stimulation with transcranial electric stimulation (TES) and TMS indicate that neuron stimulation occurs via the axons rather than the neuron cell bodies. TES and TMS are non-invasive stimulation techniques. TES employs either direct or alternating currents which are applied through electrode pads attached to the scalp. The low intensity current used in TES (typically <2mA) (Wassermann et al., 2008) stimulate brain cells that lie along the conduction path between the applied electrode pads. So long as the scalp area between electrode pads is dry and free of electrically conductive media such as perspiration or saline, the electrical circuit along which the TES currents pass is formed between the pads and through the cortex. If properly prepared and dried, the path between electrode pads across the scalp surface will be electrically high resistance and will not form an electrical circuit. Studies in which primary motor cortex is stimulated with TES and TMS, involving recordings of patients with implanted spinal electrodes have shown the characteristics of TMS induced corticospinal descending activity.

TES generated descending corticospinal volleys recorded at the level of the cervical spinal cord show a series of early and late descending volleys, distinguished by their onset latency. The first volley results from direct excitation of the corticospinal neuron at its axon hillock and has the shortest latency and has been named the direct-wave or D-wave. Later waves follow at intervals of 1.2–2.0 ms and result from indirect trans-synaptic corticospinal excitation via different sets of intracortical neurons that project onto the pyramidal neurons (Groppa et al., 2012). These later volleys are named indirect-waves or I-waves.

Similarly, TMS generates descending corticospinal volleys. Comparing latencies of TMS and TES induced volleys shows the motor cortex tends to activate I-waves rather than the D-wave. TMS will generate D-waves but generally only at stimulation intensities much higher than threshold. It is not currently known if the exact same mechanism observed in the primary motor cortex in which TMS indirectly stimulates neurons through trans-synaptic inputs, holds true for all other areas of the cortex, (Rossi et al., 2009).

Detailed modelling studies, mostly of motor cortex stimulation, have taken into account tissue inhomogeneities in the cortex as well as boundaries between cerebrospinal fluid (CSF/grey and grey/white matter), and have shown that induced electric fields are generally strongest in the crown of the gyrus (Opitz et al., 2013). When this type of calculation is combined with models of typical varieties of cortical and subcortical neurons, it seems likely that TMS of the motor cortex will activate cortical interneurons in the gyral crown or lip of the sulcus, as well as pyramidal neurons in the lip of the sulcus or slightly deeper (Opitz et al., 2013, Salvador et al., 2011).

These last two points means that in general TMS is likely to be most effective within the gyrus, where neurons follow the bend of the gyrus and when the TMS coil is positioned to direct the stimulating current along the length of the axon. This implies that the TMS coil should be positioned in a direction tangential to the fold of the gyrus for optimal stimulation. This approach was taken when stimulating ‘silent’ regions of the cortex with the Figure 8 coil. The coil position was guided using the participant’s structural MRI and a frameless stereo tactic neuro-navigation system to locate the gyrus of interest and positioning the TMS coil over the region of interest, flat onto the surface of the scalp and tangentially to the gyrus of interest. In this way the cortical interneurons in the gyral crown or lip of the sulcus are within the influence of the peak magnetic field.

Determination of Motor Threshold and Experiment Stimulation Intensity

The strength of the induced electric field is a function of stimulator intensity and distance from coil to the cortical target. The probability that a neuron will be stimulated by the induced electric field depends on, in part, the strength of the induced field and the cortical excitability. Due to differences in participants’, their head shape, brain size and arousal state, it is not appropriate to use a fixed stimulator output. It is necessary to tailor the TMS intensity to the current state of the

participant's physiology. Commonly, to do this a measurement of the individual participant's TMS motor threshold is made and the experiment TMS intensity is referenced to that threshold.

In the TMS experiments reported here the motor threshold measurement was based on TMS induced muscle contractions in the first dorsal interosseous (FDI) muscle. The muscle contractions were detected using an EMG bipolar surface electrode. Although muscle contractions may be detected by observing the resulting finger movement, the electrode measurement is able to detect muscle activity that may not result in a finger movement, and thus provides a more reliable measurement. It has been estimated that motor thresholds based on observations of muscle twitch are approximately 10% (0–30%) higher than motor thresholds based on EMG recordings (Westin et al., 2014). The voltage measured across the muscle by the surface electrode in response to a TMS stimulation is called a motor evoked potential (MEP).

In measuring the motor threshold, firstly the region of the motor cortex that maps to the FDI is localised by finding the position on the scalp where the TMS coil can produce muscle contractions in the FDI. This is termed finding the 'hot spot'. Once the 'hot spot' is found the stimulator intensity is reduced to a level where no FDI muscle contraction will be produced and then incrementally increased in steps of 3% of maximum stimulator output (MSO). The stimulation level is increased until 50% of the stimulations produce an electrode output, an MEP, of at least 50uV. The 50% threshold was commonly applied to 10 trials, but more recently (Julkunen et al., 2012) suggest that this provides a poor estimate of the motor threshold and that 20 trials are required to produce reproducible results. The change in procedure for estimating motor threshold, from 10 to 20 trials, is not thought to have made a difference as the 3% step sizes employed here are a finer resolution than those of 5%, suggested by the standard protocol reported by (Julkunen et al., 2012). When conducting 20 trial estimates of motor threshold, the estimate at 10 trials was within 1% of the 20-trial estimate.

In the TMS experiments the pattern of stimulation pulses can be applied in many ways. Depending on the pulse pattern, the aim is to produce either a disruptive or a beneficial facilitatory effect on cortical processing. In the TMS experiment reported, a double pulse stimulation and repetitive pulse trains were employed.

Double Pulse TMS (dpTMS)

TMS employed as a single pulse or at interpulse intervals greater than a second, is used as an inhibitory stimulus that disrupts ongoing cortical processes. Whether this is by a 'virtual lesion' or by a neuronal 'noise' mechanism, is as yet unclear (Siebner et al., 2009). The 'virtual lesion' may occur because of the cortical silent period (CSP) observed to occur following the initial MEPs, a time period in which the previously stimulated neurons do not fire. The CSP is a GABAergic inhibition (Rossi et al., 2009) and typically lasts from between 20ms to 70ms, but may increase to well beyond 100ms at higher stimulation intensities. The neuronal 'noise' mechanism is

hypothesised to result from TMS stimulated neurons firing out of sequence relative to the ongoing cortical processing. The outputs of these mistimed stimulated action potentials are thought to act as 'noise' on the cortical information flow. By applying TMS pulses in low repetition rate groups, typically pairs, cortical processing in a particular region may be disrupted over a period of several hundred milliseconds.

Repetitive Pulse TMS (rTMS)

Whereas single pulse TMS is primarily has an inhibitory effect on the cortex (Rossi et al., 2009), repetitive TMS is generally facilitory. Multiple neural mechanisms are involved in the means by which magnetic stimulation may produce inhibitory or facilitative effects depending on stimulation intensity, pulse timing and frequency (Gentner et al., 2008) (Iezzi et al., 2008). These include temporary synaptic changes similar to long- term depression (LTD) and long-term potentiation (LTP), changes in network excitability and feedback loops.

Studies including TMS and transcranial alternating current stimulation (tACS), (Thut et al., 2011b) have found that rhythmic stimulation entrain neuron populations, when the stimulation is tuned to the natural frequency of the target neurons, and change behaviour. For example, alpha frequency stimulation of visual areas (Romei et al., 2010) can selectively enhance visual detection of targets in the visual field ipsilateral to the stimulated hemisphere, while impairing detecting of contralateral targets. . TMS applied in short trains of 5 pulses at alpha frequency (Thut et al., 2011a) have been shown to briefly promote the ongoing alpha cortical oscillations, with the number of neurons recruited to oscillate at the driving frequency increasing with each pulse of the stimulation. After the driving stimulation ceases the phase of the entrained alpha rhythm begins to drift away from that of the driving pulse train, however the effect lasts for a few cycles. Behavioural effects with entrainment are strongest when the entrainment frequency exactly matches the intrinsic oscillation frequency of the neuron population being targeted (Thut et al., 2011a). Stimulating neuron populations with frequencies different from their intrinsic oscillation frequency produces little or no effect on the natural oscillation frequency of the targeted neuron population. In this sense 'off frequency' stimulation can be considered similar to a sham condition in that the natural oscillation frequency is unchanged. The intrinsic oscillation does not shift in frequency toward the frequency of the applied stimulation (Romei et al., 2010, Hanslmayr et al., 2014), and is like a sham condition in terms of effects on behaviour.

2.4 Discussion

The focality of TMS is sometimes questioned, the TMS coil is generally large (>70mm) compared to the cortical region being targeted and may have a wider influence on the cortex than anticipated. Although the magnetic field generated by the coil extends beyond the dimensions of the coil, only the central part of the field pattern is sufficiently intense to stimulate the cortex. Limiting the stimulation intensity to that of the motor threshold means that only cortical structures down to the depth of the FDI region of the motor cortex may be stimulated, and only if the coil is

aligned appropriately to the folds of the cortex. When locating the motor 'hot spot', in order to elicit an MEP, the coil must be placed to within a couple of millimetres of the centre of the 'hot spot'. Taken together this suggests that TMS is quite focal does not produce widespread stimulation of neurons. As such it is a suitable technique to modulate specific superficial cortical targets in the investigation of human behaviour.

Computer modelling studies (Opitz et al., 2013) and TMS literature suggest that the mechanisms by which TMS produces action potentials in neurons within the motor cortex hold true for other areas of the human cortex. However, as the thickness of the skull is not uniform over the whole head, the distance from scalp to brain surface may not be the same. Although the difference in distance may only be a few millimetres, it can have a significant effect on the induced electric field at the neuron. Modelling and empirical measurements show that optimal stimulation occurs when the coil is positioned so the induced electric field is tangential to the fold of the sulcus and directed along the length of the neuron. Using individual MRIs and neuronavigation software the TMS experiments were set up so that the TMS coil was positioned in this way, with the best probability of stimulating the target neurons.

3 An MEG Investigation of Working Memory in a Dual Task paradigm

3.1 Introduction

Reviews of the OCD literature concerning investigations of deficits and biases in memory and attention, for example, Muller and Roberts (2005b), Cuttler and Graf (2009), has shown results as seemingly inconsistent in memory for verbal information, with more consistent evidence for impairments in non-verbal memory recall. In their review, Cuttler and Graf (2009), find similar patterns of deficits of memory performance both OCD checkers and low-checkers indicating that deficits in memory are not unique to checkers and therefore unlikely to contribute to the compulsion to check. Repeated checking (Boschen and Vuksanovic, 2007, Radomsky et al., 2014, van den Hout and Kindt, 2003b) has been shown to erode memory vividness, confidence and detail significantly reduced, though not accuracy of recall. Extending their previous research to include clinical OCD subjects as well student controls, Radomsky et al. (2014), found checking accuracy decreased, but there were no differences in memory accuracy between the two groups and noted that decreases in memory recall accuracy appear to be a product of, rather than a cause of checking behaviour and that non-verbal memory impairments in OCD are secondary to executive deficits (Greisberg and McKay, 2003, Olley et al., 2007). In addition to memory deficits OCD checking is associated with attentional biases and problems with inhibition (Muller and Roberts, 2005b).

In a review of 46 OCD memory studies, Harkin and Kessler (2011), explain previously inconsistent and domain specific (verbal vs non-verbal) experimental findings in the literature in terms of interference with the episodic buffer in the (Baddeley, 2000) model of working memory. The episodic buffer proposed as a component of working memory that integrates visual, spatial, verbal and temporal information and acts as an interface mechanism to the long term memory store

Impairment in the operation of the episodic buffer (Harkin and Kessler, 2009) that serves to interfere with the stored multimodal representations, would disrupt the process of encoding, maintenance, and retrieval necessary for accurate memory function. In the EBL model, a modification to the Baddeley (2000) model of working memory, Harkin and Kessler (2011) proposed three dimensions on which OCD symptomology may lead to deficits in working memory performance. The three dimensions of the EBL model being executive function efficiency (E), binding complexity (B) and memory load (L). The EBL model explains the inconsistent results of OCD memory studies reported in the literature that tests by classifying which of the EBL dimensions the studies tested. Studies in which the employed stimuli were relevant to OCD symptomology and in which the task demands in terms of binding complexity and memory load avoided floor or ceiling effects, differences in performance between OCD and neuro-typical groups may be detected. However, studies that manipulated only the dimensions of binding complexity or memory load may show decreased test performance as the tests became harder but fail to differentiate between OCD and neuro-typical subjects. In the EBL model of working

memory and OCD, it is executive dysfunction provoked by OCD symptomology in response to OCD salient stimuli that leads to poorer performance in memory studies. In terms of the EBL model, the executive function efficiency (E) was manipulated in the experimental, but the dimensions of binding complexity (B) and memory load (L) were held constant. In this way the MEG study examined the effect of executive dysfunction on neuro-oscillatory activity in OCD subjects and compared the observations with that of neuro-typical subjects.

This MEG study uses the second of two working memory tasks (Harkin et al., 2011) which have previously shown performance differences in recall accuracy comparing checker with low-checker participant groups. Where previously behavioural differences in terms of memory recall accuracy were explored, here the cortical oscillatory signatures of these behavioural performance differences were explored.

This working memory task was designed to engage the episodic buffer by using sufficiently complex stimuli that require multimodal bindings to remember specific object features and spatial locations and to manipulate episodic buffer functioning during the working memory retention interval on half the trials with misleading information. The paradigm uses ecologically valid stimuli, pictures of kitchen electrical appliances, designed to resonate with and tap into attentional biases within the checking group. The expectation was that checkers bias towards checking behaviour relevant stimuli leads to impaired ability to suppress misleading information and will induce a stronger effect of executive dysfunction compared with low-checkers.

If the paradigm successfully engages OCD behaviours in the checker group the MEG neuro-oscillatory differences with low-checkers should be observable and predictable. Converging evidence from neuroanatomical models and neuroimaging studies for example,(Ahmari and Dougherty, 2015, Huey et al., 2008, Mataix-Cols et al., 2003, van den Heuvel et al., 2009) point to the likely functional differences. Dysfunctional cortico-striato-thalamo-cortical (CSTC) circuits have been found to underpin OCD symptomology. CSTC circuits have been implicated in higher order cognitive functions such as inhibition of compulsive behaviour, action selection and attentional allocation. Structural and functional imaging studies (Ahmari and Dougherty, 2015) have shown hyperactivity and structural differences in ACC, PFC, basal ganglia, OFC and thalamus comparing OCD patients with healthy controls. Limbic structures involved in reward and emotion such as amygdala, cingulate cortex and memory structures such as hippocampus are commonly implicated (Huey et al., 2008) in OCD. Increased recruitment of frontoparietal network during a working memory task (de Vries et al., 2014) has been reported as a possible compensatory mechanism for deficits in executive functioning in OCD patients. Hyperactivity of bilateral frontoparietal network, left dorsal frontal areas and left precuneus were associated with better task performance. Task related increases in functional connectivity between frontal areas and bilateral amygdala was also reported. In addition to OCD specific circuits, OCD patients have also shown in Working memory tasks (Nakao et al., 2009) (Menzies et al., 2008) greater activation compared to controls in the right dorsolateral prefrontal cortex (DLPFC), left superior temporal gyrus (STG), left insula, cuneus and right orbitofrontal cortex.

Hypothesis 1. If checking is reflected in the excessively repeated re-activation of episodic WM content, then enhanced activity and connectivity involving PFC and the MTL alongside ACC and the limbic system should be observed in theta oscillations for high checkers compared to low checkers and even more so when distractors are introduced (Figure 3-1). Increased theta activity could reflect an inappropriate attempt to integrate and check the distractor information which would then interfere with WM performance. Harkin and Kessler (2009).

Hypothesis 2. If checking is related to a lack of suppression of distracting information, we should observe a lack of related brain signatures (i.e., alpha-power increase and/or beta-desynchronization; see Figure 1-2) in relation to the distractor in an selective attention paradigm as well as in a WM paradigm when a distracting cue is presented during maintenance. In the latter case we also expect a systematic relationship between lack of suppression signatures and increased theta activity that could reflect increased checking (Figure 1-2).

3.2 Method

Participants

The participant population recruited principally on their VOCI checking sub-scale score were assigned to one of two groups, checkers (n=14) and low-checkers (n=14). The checking cohort had VOCI scores ranging from 12 to 30, and the low-checker scores ranged from 0 to 3. Participants were medication free at the time of testing.

Participants were recruited through Glasgow University and were paid a fee for participating.

Working Memory paradigm

The working memory paradigm designed to resonate with and provoke OCD checking behaviour, uses pictures of electrical appliances arranged within a kitchen scene.

The stimulus was a picture of four electrical appliances located on a black and white kitchen worktop that forms a grid of six possible locations. The appliances were indicated to be powered ‘ON’ or ‘OFF’ by the presence of a bright or dull red power indicator light on the appliance image. The kitchen scene was presented for 5000ms during which time participants were required to commit to memory the appliance type, its location and power state. A patterned mask screen was then presented for 1500ms.

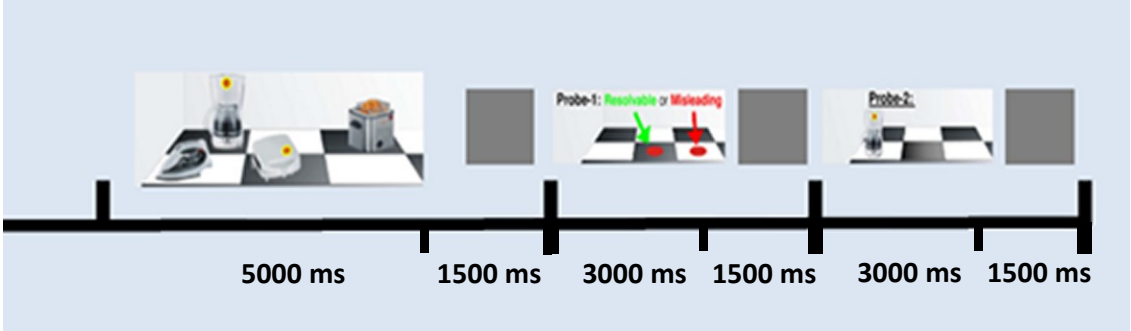

Figure 3-1. *The Working Memory task was to remember the electrical items presented in the first screen, their location on the grid, and if they were switched 'on' or 'off'. Mask screens, shown here as grey squares, were presented before each probe question. Performance in Probe-2, recalling if the displayed item was in the correct location, was influenced by Probe-1, which asks if the item in the location indicated was switched 'on' or 'off'. For half the trials an appliance had been shown at the indicated grid square (resolvable trials), but for half the trials there was no appliance in the location indicated (unresolvable trials), and the available options of 'yes' or 'no' were not adequate to address the question. The performance of Checkers on Probe-2 was worse on unresolvable trials compared to resolvable trials. The nature of Probe-1 affected Probe-2 working memory accuracy.*

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Following an initial presentation of the four kitchen appliances, the experiment requires the participant to respond to two probes. Firstly, with the grid now empty of electrical appliances, one square highlighted. Participants were required, via button response pad, to say if the appliance that was in that square was 'ON' or 'OFF'. For half the trials the highlighted square was previously occupied by an appliance and the question can be answered (resolvable trials), but for half the trials the indicated square was previously empty (unresolvable trials). In these trials the probe was misleading (unresolvable trials). On unresolvable trials the mismatch between the memory of the initial kitchen scene and the kitchen scene implied by probe-1, combined with the limited choice of only 'ON' or 'OFF' responses in unresolvable trials, promoted additional memory checking to confirm the trial was unresolvable. Probe-1 was presented for 3000ms and followed by a mask screen for 1500ms.

Finally, probe-2, the working memory task, presented an electrical appliance in one of the grid locations for 3000ms and the participant was asked if the item was in the same location as when it was shown initially as part of a group of four appliances. Probe-2 was always resolvable with responses given via the button response pad. Probe-1 makes the working memory task a dual task paradigm increasing work load, which in combination with resolvable and unresolvable conditions manipulated performance on Probe 2, the working memory probe.

A behavioural pilot (Harkin et al., 2011) showed that performance in probe-2, the working memory task, was affected by probe-1. The unresolvable question in probe-1 led to more errors in the working memory question, with checkers more susceptible to the effects of probe-1 than low-checkers.

It appeared that differences in memory and attention processing arising during the time period in which participants mentally process probe-1 which adversely affected their working memory performance as measured by accuracy on probe-2. The detrimental effect of probe-1 was

greatest with the checkers. The time period of probe-1 responses was selected to investigate the differences in oscillatory activity that led to deficient working memory performance in checking behaviour.

MEG data collection and pre-processing

The MEG data sets recorded at Glasgow University by Dr Hongfang Wang, using a 4D-Neuroimaging Magnes 3600 WH MEG system, a magnetometer detection array comprising 248 channels.

Data were recorded with a sampling rate of 1000Hz. Recording sessions were split into three blocks, each of 96 trials and approximately 20 minutes duration. Although this was primarily due to a limitation of the MEG system, short breaks between recording sessions enabled the participants to take short rest breaks.

The data were processed in a Matlab software environment using the Fieldtrip (Oostenveld et al., 2011) signal processing and analysis toolbox. For ease of data processing the data were down sampled to 300Hz. Data were low pass filtered with the filter stop at 70Hz and line noise filtered at 50Hz and its harmonics. The three data blocks, comprising an individual's MEG recording, were combined into one record. Eight of the channels were 'dead' or intermittently noisy. The eight channels were removed from all data sets.

The next stage in data cleaning was to look at the signal power in the trials, as measured by signal variance. It was assumed that trials or channels with high signal variance were strongly contaminated by noise artefact. The data can be cleaned by either removing channels or trials. It was decided to remove individual trials rather than channels, thinking it would overall be less invasive to the data.

The final stage of artefact removal was to isolate unwanted signals of biological origin, such as cardiac signals, eye blinks and jaw clenching. This was achieved with Independent Component Analysis (ICA) using the Fieldtrip toolbox (Oostenveld et al., 2011). Up to five ICA components were deleted from each data set.

Following ICA decomposition, the sensor channels were 'repaired' by interpolating signal data from the missing channels nearest neighbours. Under ideal circumstances the data now clean, comprising 248 sensor channels with all physiological noise and non-physiological noise removed.

The final stage of pre-processing was completed by splitting the data for each participant at trial level into resolvable and unresolvable blocks, indexed by the condition on Probe 1. These were then grouped by cohort, checker and low-checker, according to the participant's VOCI score.

3.3 Results

Behavioural Data

The validity of the WM paradigm in provoking deficient executive functioning during episodic working memory task was confirmed by the behavioural data that show at the group level performance differences between 'checkers' and 'low-checkers' in Probe-2 accuracy, dependent on Probe1, whether 'resolvable' or 'unresolvable'. Overall 'checkers' performed less well than 'low-checkers', but also significantly worse on 'unresolvable' compared with 'resolvable' trials.

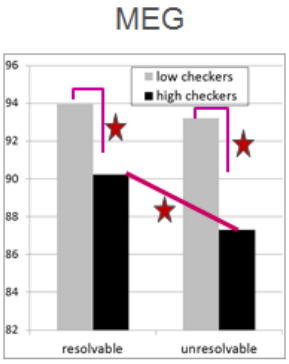

***Figure 3-2**. Group x Trial Type. Probe-2 accuracy for group (low vs low-checker) with each trial type (resolvable and unresolvable). Behavioural accuracy data shows Checkers performance was generally worse in this working memory task compared with Low-Checkers. Checkers' performance was affected by the distractor, probe 1, being worse on unresolvable trials compared with resolvable trials. *Denotes significance at p<0.05 level.*

Analysis methods

The MEG data associated with the response to Probe 1 was analysed in both sensor level and source space. A 3000ms period starting from the onset of Probe 1 and encompassing the key pad response was taken as the active period. The baseline period was taken from a 3000ms period before the onset of the corresponding trial. The mask period prior to Probe 1 was not suitable as this period was likely contaminated by the participants' anticipation of an 'unresolvable' question, an effect likely to be greater for the checking cohort, (Min et al., 2011).

Data Driven analysis

At the participant level, the MEG data were sorted into two groups, Unresolvable and Resolvable, based on the Probe 1 condition. The time domain MEG data were then 'cleaned', as outlined in Chapter 2, MEG Methods, with signal artefacts removed using a combination of filtering, ICA and excluding noisy MEG channels.

The behavioural data showed that the deleterious effect on working memory occurs during probe-1 and as such the MEG data analysis was limited to the first 2 seconds of probe-1 response time window in which participants made their responses. The time 2 second period analysed was long enough to capture the brain activity in the time period in which participants processed probe-1, but excluded brain activity that was unrelated to probe-1 that occurs after participants have made their key pad responses. A 2 second window before the start of each trial was chosen as

the baseline. This time window occurs in the short interval between trials and was thought to be least contaminated by trial conditions or mental processing associated with anticipating for example the onset of Probe 1.

Using the multi-taper method of spectral decomposition, time-frequency representations of resolvable and unresolvable conditions were produced for each magnetometer sensor and averaged across each participant separately. Baseline correction was performed by subtracting the time-frequency baseline data from each condition. An average of each dataset, by cohort, checker or low-checker, and by condition, resolvable or unresolvable was obtained. The topology of these time-frequency data varied with the location of the magnetometer sensor by the raw data was recorded. For the purposes of conducting further analysis, such as source level analysis, with the data it is desirable to define frequency bands upon which statistical tests may be performed.

Studies have shown (for example, (Klimesch, 1999) (Hanslmayr et al., 2012), (Jensen and Tesche, 2002)) that power changes in brain activity associated with cognitive processing and task performance occur in particular frequency bands and that these frequency bands are representative across healthy individuals. The frequency bands investigated here were, 4-7Hz (theta), 8-12Hz (alpha), 12-15Hz (low beta) and 18-22Hz (high beta). Although the exact frequency range of each band can vary very slightly from individual to individual, the frequency band naming, for example, theta, alpha, beta, still applies.

Inspecting the topology of the time-frequency data, the frequency windows in which significant power changes occurred were identified. An average of several sensors in the region of the medial frontal cortex were selected (see Figure 3-3) to inform the process of defining the frequency windows relevant to the working memory task and to be used in statistical testing.

The choice of medial frontal cortex as the ‘seed’ location in defining the frequency bands was guided by the strong likelihood it was likely to be involved in and differentially active (Anderson et al., 2010, Cavanagh and Frank, 2014, Euston et al., 2012) in a working memory task, processing Probe 1 resolvable and unresolvable stimuli and also because along with the limbic system, hippocampus and amygdala, forms part of the so called “affective” neuro-circuit (Anderson et al., 2010, Cavanagh and Frank, 2014, Euston et al., 2012, Krack et al., 2010, Milad and Rauch, 2012b) implicated in OCD behaviour.

Within the ‘checker’ time-frequency plots (A and B in Figure 3-3) focussed on sensors around medial frontal cortex, significant changes in oscillatory power as Probe 1 was processed, were observed in frequency windows, 4-7Hz (theta), 7-11Hz (alpha), 11-15Hz (low beta), 18-22Hz (high beta). The frequency bands identified in the time-frequency plots were a close match but not an exact match with the text book definition of theta, alpha, and beta frequency bands listed above. This variance may be explained by considering the natural variation in the frequency bands across individuals and by the limitations of the signal processing and statistical analysis to resolve the precise edges of each frequency band. Comparing oscillatory activity between resolvable and unresolvable conditions (C and D in Figure 3-3) the pattern of frequency bands

was clearer still. Sensor level cluster analysis was then conducted using the four frequency bands identified.

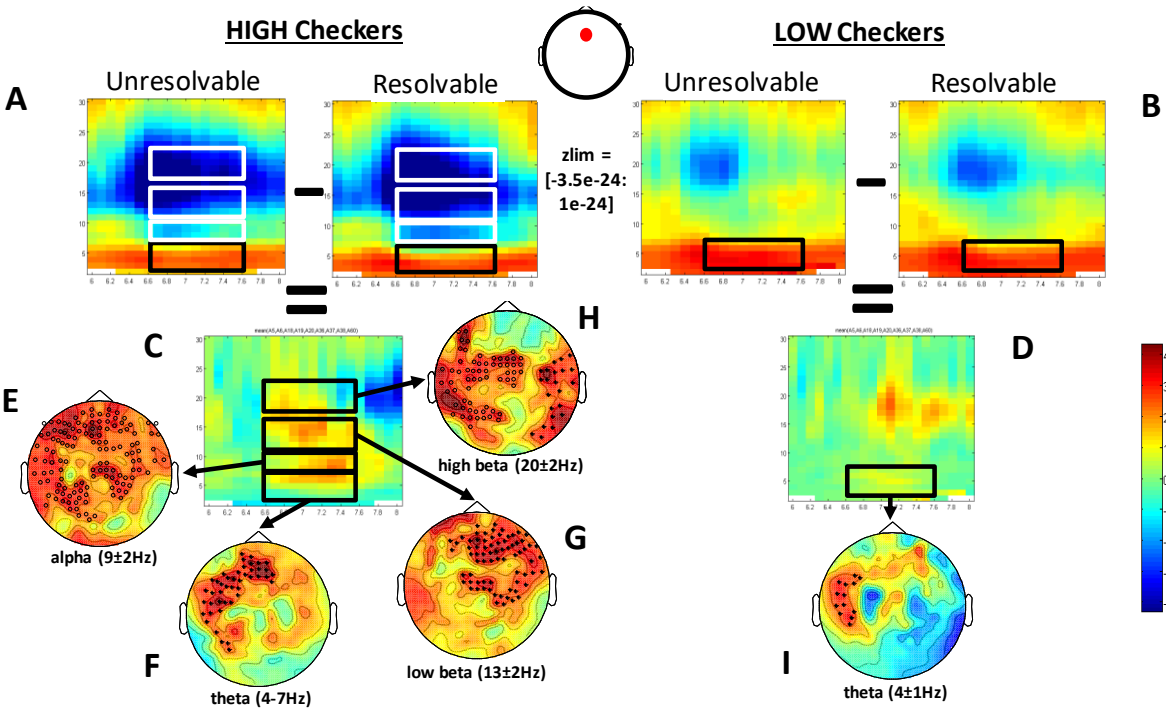

Figure 3-3. *Comparing time-frequency data for resolvable and unresolvable (A and B) conditions reveals different patterns of oscillatory power comparing checkers and low-checkers (C and D). These differences in oscillatory power were tested for statistical significance using cluster plot analysis. For checkers significant increases in cortical power were observed in theta, alpha and beta bands (E, F, G and H). Low-checkers however only displayed significant differences between resolvable and unresolvable conditions in Theta power (I). The colour scale represents brain activity, colours yellow and red indicate areas of increased brain activity, whereas colours blue indicate areas of reduced activity. In plots E, F, G, H and I, data points represented by 'o' and 'x' signify areas where activity was significantly increased, at p<0.01 and p<0.05, respectively.*

Sensor Level Analysis - Cluster Based Permutation tests

The cleaned time series data were separated into 'resolvable' and 'unresolvable' blocks, and by individual participant, were processed using a multi-taper approach (Oostenveld et al., 2011) to produce time frequency representations of the active and baseline periods, over a frequency band of 2Hz to 30Hz. The data were then baselined by subtracting the baseline time-frequency data from the active time-frequency data. The data for each participant and each condition were then averaged across trials. These averaged, baselined time-frequency sensor level data were then analysed using cluster-based permutation analysis. The cluster analysis localises in a spatio-spectral-temporal dimension, regions of statistically significant oscillatory activity.

Cluster based sensor level analysis was conducted of the two second time period in which participants processed their answer following the onset of probe-1. Initially the analysis was conducted by dividing the two second time window into 100ms blocks and investigating the time course of significant clusters. By this way it was found that across the participant groups, the time period 0.6s to 1.6s within the 2 second window of Probe 1 response period, was when significant activation occurred. The cluster plots (see Figure 3-3, E,F,G,H, L) show the significant ($p<0.05$) regions of cortical power difference, averaged over the time period 0.6s to 1.6s and averaged over the frequency band indicated. Individual plots compare power differences between Unresolvable trials and Resolvable trial conditions within each cohort.

The 'checkers' show significant oscillatory power differences in the four selected frequency bands comparing resolvable and unresolvable conditions. The 'non-checkers', however, only show significant Theta band processing.

The aim of this MEG study was to identify group differences in cortical activity during the time period participants were processing their response to Probe-1, with the aim to understand better the behavioural data which showed performance differences in the Probe-2 working memory task, which for checkers was influenced by Probe-1 being a resolvable or unresolvable trial.

Source location was conducted in theta band only as the other frequency bands investigated did not significant power differences across conditions and cohorts.

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Source Level Analysis

Using the same trial level time-frequency representations that led to the sensor level cluster analysis, cortical source reconstruction for each individual, 'resolvable' and 'unresolvable' condition, was conducted using Dynamical Imaging of Cortical sources (DICS) a frequency domain beamformer method, (Oostenveld et al., 2011). Although sensor level analysis as shown in Figure 3-3 can reveal areas of relatively high or low brain activity and is an important step in analysing brain activity, the data and images produced are referenced to the MEG sensors and not directly the subjects' brain. Using senor level analysis alone it is difficult to identify in which brain region the significant activity was detected, especially if the source was not cortical but a deeper brain structure. A better estimate of where in the brain significant activity occurred can be obtained using source level analysis techniques, in which data produced are referenced to the brain rather than the MEG sensors. Source level analysis has the advantage of enabling activity in deeper brain areas to be resolved where they might otherwise be opaque to sensor level analysis techniques.

The active period being 3000ms starting at Probe 1 onset with the passive period taken from the 3000ms period prior to trial onset.

The forward model was constructed for each individual using their MRI structural head scan. To facilitate group analysis, each individual's data was normalised by transforming to a common template using the Montreal Neurological Institute (MNI) coordinate system.

The source level data for each condition and individual was averaged across trials using a 'common filter' beamformer approach. The 'common filters' approach is considered a more robust method as source localisations generated with separate filters can be biased by differences in the spatial filter parameters between conditions. With an aim similar to that applied to the sensor level analysis presented in Figure 3-3 above, but to identify the brain structures in which differences in cortical activity occur during the Probe 1 time period, source level analysis was conducted using cluster based statistical techniques. The analysis comprised two stages. Firstly, separate analysis within each group (checker and low-checker) to identify significant differences in cortical activity between trail conditions (unresolvable trials and resolvable trials). These data are shown in Figure 3-4. These separate group data where then combined and used to identify significant differences between the participant cohorts (checker and low-checker). These data are shown in Figure 3-5.

Source level power differences ($p < 0.05$) between Probe1 conditions (unresolvable vs resolvable) by group are shown in Figure 3-4. The areas of stronger theta activity in unresolvable trials highlighted in the 'checker' group (red) are consistent with the limbic system processing implicated in OCD behaviour (Anderson et al., 2010, Etkin et al., 2011, Hannula and Ranganath, 2008, Krack et al., 2010), particularly ACC, left Amygdala, MTL and Basal Ganglia. The 'low-checker' group also shows widespread activation in ACC, but in a markedly different area compared to the 'checker' group. They also show reduced theta activity in right dlPFC for 'unresolvable' compared to 'resolvable' trials (blue).

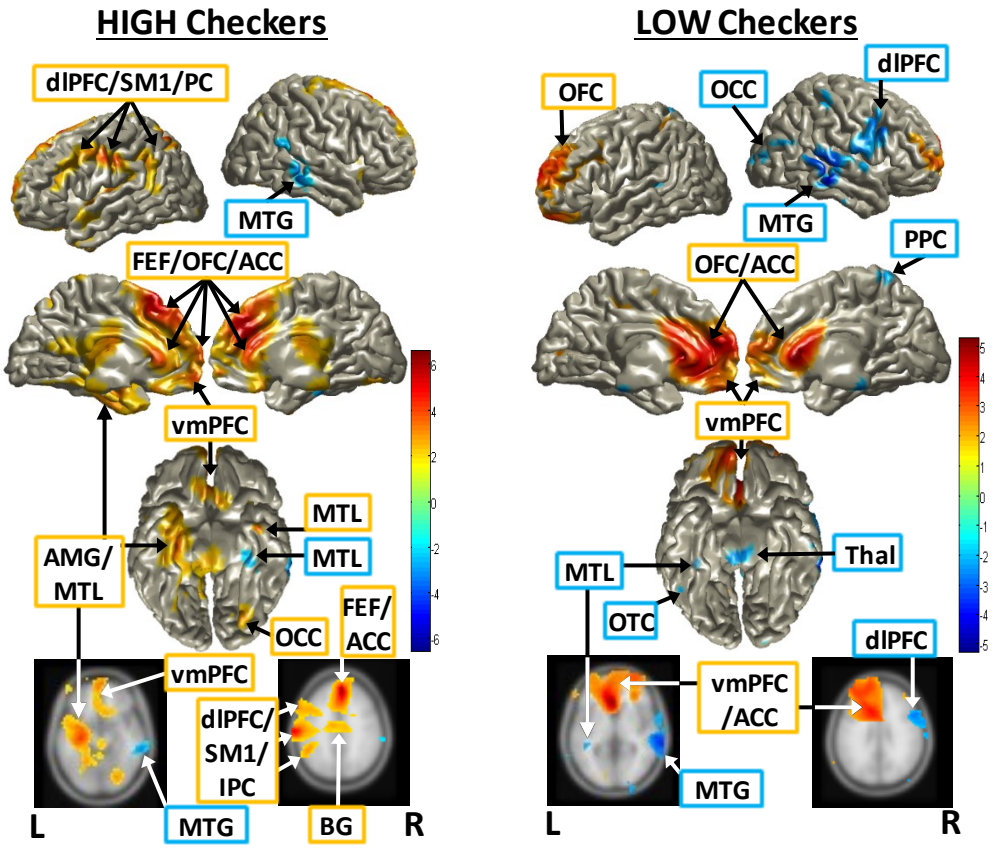


Figure 3-4. *Source localisations show the differences in theta band cortical power, comparing 'unresolvable' vs 'resolvable' conditions in 'checkers' and 'low-checkers'. Both groups display significant activation in medial frontal cortex, though in different regions which may reflect different processing mechanisms. Left Amygdala was preferentially active with the 'checker' cohort and may reflect a resonance with the electrical appliance stimuli and their checking behaviour. The 'low-checker' group shows reduced activity in right dlPFC which may reflect that for this group the 'unresolvable' probe was easily dismissed and so requiring less memory processing. AMG=amygdala; ACC=anterior cingulate cortex; MTL=medial temporal lobe (hippocampus, parahippocampus); MTG=middle temporal gyrus; IPC=inferior parietal cortex; PPC=posterior parietal cortex; OCC=occipital cortex; SM1=primary sensorimotor cortex; dlPFC=dorso-lateral prefrontal cortex; vmPFC=ventro-medial prefrontal cortex; FEF=frontal eye fields; OFC=orbitofrontal cortex; Thal=thalamus. The colour scale represents z-score statistical values. Colours yellow and red indicate areas of significantly increased brain activity, whereas colours blue indicate areas of significantly reduced activity.*

Using the within groups differences (unresolvable vs resolvable) data shown in Figure 3-4, a 'differences of differences' comparison between the two groups (checkers vs low-checkers) can be made. Figure 3-5 shows this comparison. Compared to 'low-checkers', group level activation in rostral ACC was decreased for 'checkers' when trying to answer the 'unresolvable' probe1. The decrease in rostral ACC power at group level may at first appear paradoxical, to indicate less rostral ACC processing for the checkers. The apparent decrease occurs because the checkers needed to apply comparatively similar levels of processing to both trial types (resolvable vs unresolvable) whereas the low-checkers were able to apply more efficient theta processing to the task, applying their processing resources to the resolvable trials and much less to the unresolvable trials. This resulted in more rostral ACC processing to the unresolvable trials and less for the trials that could not be resolved.

The net result shows in the group differences as a decrease in power for high checkers compared to low checkers. Taken in context of the within groups contrasts where high checkers activate dorsal ACC associated with top-down control and fear processing (Etkin et al., 2011), whereas activity for low checkers was located more strongly in rostral ACC, associated with error monitoring (Mohanty et al., 2007).

Conversely, a relatively increased level of theta activity in unresolvable trials was seen in Amygdala, medial temporal lobe, and Thalamus for the 'checker' group, brain structures that form part of the limbic system which was implicated in OCD behaviour.

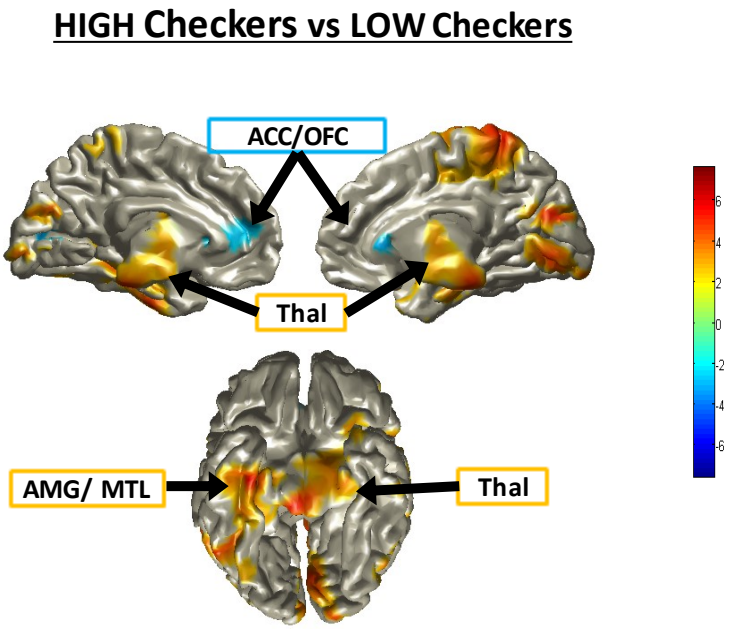


Figure 3-5. *Checker vs Low-Checker. Taking the difference between the theta band source level data, checker (unresolvable vs resolvable condition) and the low-checker (unresolvable vs resolvable condition), using cluster based analysis the significant differences ($p<0.05$) in oscillatory power between the two groups during Probe1 condition was revealed. AMG=amygdala; ACC=anterior cingulate cortex; MTL=medial temporal lobe (hippocampus, parahippocampus); OFC=orbitofrontal cortex; Thal=thalamus. The colour scale represents z-score statistical values. Colours yellow and red indicate areas of significantly increased brain activity, whereas colours blue indicate areas of significantly reduced activity.*

Following on from the sensor level cluster analysis performed with the 'checker' data in alpha and beta band frequencies in which significant areas of oscillatory power were found, source localisations, again comparing 'unresolvable' vs 'resolvable' conditions, were conducted for the 'checker' group. Across alpha and beta bands (Jensen and Tesche, 2002, Klimesch et al., 1997, Klimesch et al., 1994) ACC and OFC implicated in OCD shows increased activity during the 'unresolvable' probe. These data show that in Alpha band, structures of the limbic system Thalamus, ACC and OFC were preferentially activated. However, the medial temporal lobe which was evident in the theta band source data (see Figure 3-5), in alpha and beta band analysis

it was not. This consistent with medial temporal lobe activity being driven in theta. Other structures that ae commonly identified in dysfunctional OCD neural circuits, are vmPFC in alpha band, and SMA in both alpha and low beta band data. The increased activity (red) in 'unresolvable' compared to 'resolvable' probes was consistent with the literature (Nakao et al., 2005) reporting these regions to be hyperactive in OCD.

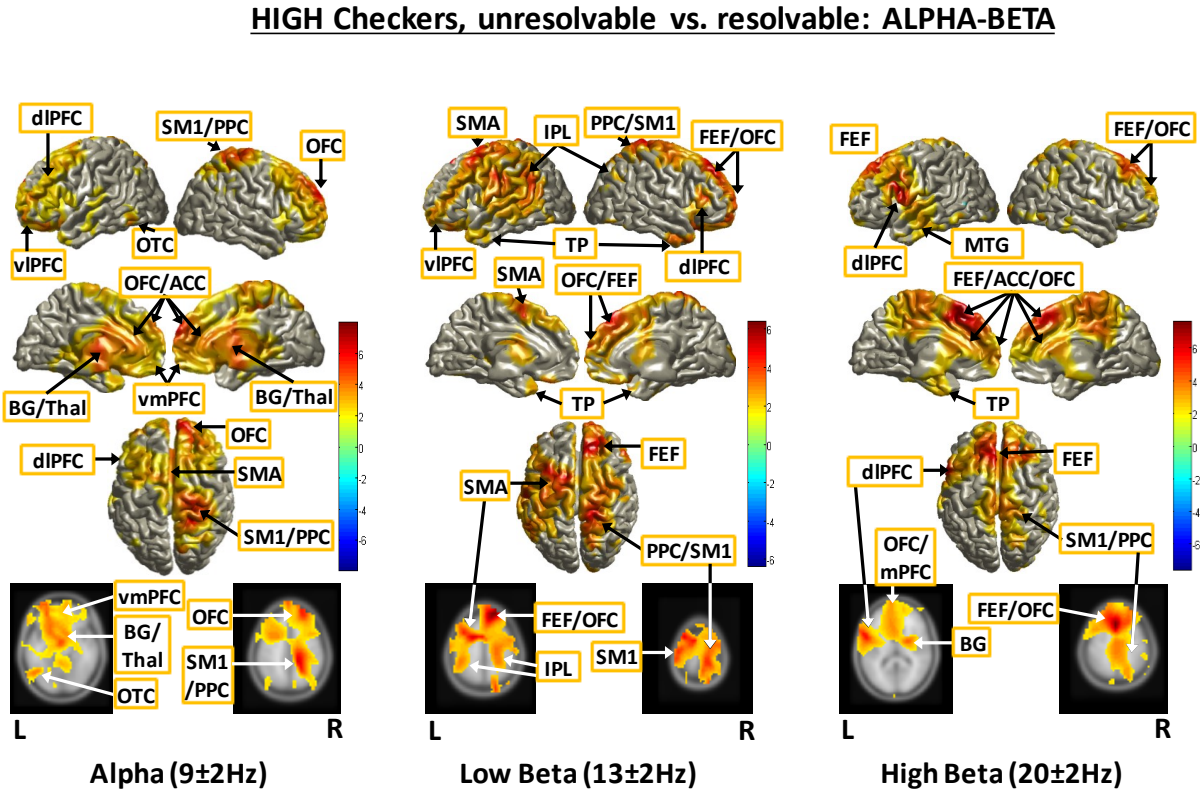


Figure 3-6. *ACC and OFC show increased activation across the frequency bands with additional activation of Thalamus / Basal Ganglia in Alpha band. AMG=amygdala; ACC=anterior cingulate cortex; MTL=medial temporal lobe (hippocampus, parahippocampus); MTG=middle temporal gyrus; TP=temporal pole; IPL=inferior parietal lobule; SM1=primary sensorimotor cortex; PPC=posterior parietal cortex; dlPFC=dorso-lateral prefrontal cortex; mPFC=medial prefrontal cortex; vmPFC=ventro-medial prefrontal cortex; vlPFC=ventro-lateral prefrontal cortex; FEF=frontal eye fields; OFC=orbitofrontal cortex; Thal=thalamus; BG=basal ganglia; OTC=occipito-temporal cortex. The colour scale represents z-score statistical values. Colours yellow and red indicate areas of significantly increased brain activity, whereas colours blue indicate areas of significantly reduced activity.*

3.4 Discussion

The aim of this working memory MEG study was to identify functional cortical networks driving deficient memory performance in OCD checking behaviour, to find their location within the brain and their oscillatory characteristics. The aim was then to select suitable cortical targets for further investigation with TMS.

The working memory paradigm, by employing ecologically valid visual stimuli, was successful in provoking deficient executive functioning leading to impaired working memory performance especially in unresolvable trials in the 'checker' group compared to the 'low-checker' group. This result was evident in both the group level behavioural data and the group level differences found in the MEG source level data. Results that were consistent with the OCD research literature.

Although decreased oscillatory power (increased processing) was found in alpha and beta bands for the 'checker' group in 'unresolvable' compared to 'resolvable' trials, only in theta band (see figure 3-4) did both groups ('checker' and 'low-checker') show significant differences between 'unresolvable' and 'resolvable' conditions. We therefore focussed primarily on theta band source analysis and group comparisons.

Contrasting the source level theta power by groups ('low-checker' vs 'checker'), see figure 3-5, the significant differences in activity were decreased theta processing for 'checkers' in rostral ACC, while increased theta activity for 'checkers' was observed in thalamus, amygdala, MTL and OFC. The blue colouring in region of rostral ACC for the 'difference of differences' plot indicates the difference in theta power between unresolvable and resolvable conditions was on average smaller for the checkers than the low-checker cohort. This suggests checkers engaged a higher baseline level of theta processing across the task in order to maintain task performance. In this sense, the 'difference of differences' decreased theta rostral ACC processing for the 'checkers' might indicate deficient decision uncertainty conflict processing (Mohanty et al., 2007, Rushworth et al., 2007, Ridderinkhof et al., 2004a) and resolution that might lead to increased memory checking with 'unresolvable' Probe1, interfering with fragile bindings and hence leading to poorer working memory performance.

At the group level, the data appears to show that the 'checkers' display a less focal, more distributed activation across ACC compared with 'low-checkers'. Again pointing to less efficient ACC processing of the 'unresolvable' condition within the 'checker' group.

Increased theta power in thalamus, MTL and OFC in 'unresolvable' trials may reflect hyperactivity in these areas consistent with dysregulation (Mataix-Cols et al., 2003, Nakao et al., 2005, Sakai et al., 2011) hypotheses and brain structure changes observed OCD.

Source level analysis, comparing 'unresolvable' vs 'resolvable' trials, theta power in the dlPFC, which was involved with working memory and executive function (Cavanagh and Frank, 2014, Curtis and D'Esposito, 2003, Sauseng et al., 2005), was modulated by task condition, only in the 'low-checker' group. This lack of response in 'checker' right dlPFC activity may reflect memory processing not being adapted to the different demands of 'unresolvable' vs 'resolvable' conditions and was suboptimal in the 'checking' group.

The areas of cortical activation, especially those highlighted in theta band analysis were consistent with established models of dysfunctional neurocircuits in OCD.

The pattern of beta band activity revealed in figure 3-6, FEF, PPC, IPL, SMA, dlPFC and OFC, is consistent with engagement of attention networks. The contrast being unresolvable vs

resolvable, the beta frequency activity suggests checkers are more effortful in their attempt to provide an answer for the unresolvable probe. The relatively increased alpha band activity during unresolvable trials might be explained if the left dlPFC's role in target-directed attention, memory management and decision making is an inhibitory one. The increased alpha power would therefore imply the dlPFC inhibitory function is not engaged and deficient attentional processes mediated by beta oscillations are allowed to be enabled rather than suppressed. However the widespread nature of the alpha band activity may also be interpreted as checkers needed to employ increased top-down control (alpha inhibition) during the unresolvable probe condition in attempt to suppress checking behaviour and maintain task performance.

From the analysis of these MEG data, oscillatory activity in the ACC and right dlPFC seem to be related to deficient 'checking' performance and were anatomically superficial targets that might be suitable for manipulation by TMS (in contrast MTL and amygdala).

Following the hypothesis outlined in the introduction that OCD behaviour was a result of dysregulated neural circuits, the role of ACC and right dlPFC will be investigated using rTMS to modulate temporarily the ongoing rhythmic activity of the selected cortical targets. The oscillatory manipulation and induced change in checking behaviour task performance will inform about the function of these structures in OCD checking.

4 Investigation of Working Memory in a dual task paradigm with TMS

4.1 Introduction

In Chapter 3 the results of a MEG working memory task were presented. The paradigm replicated a WM behavioural task developed (Harkin et al., 2011) to explore how executive dysfunction in OCD checkers may lead to impairments in working memory (Harkin and Kessler, 2011, Harkin et al., 2011, Greisberg and McKay, 2003). Checkers' performance in the WM task was hampered by an intermediate probe. Failing to inhibit attention toward this irrelevant but salient stimulus, processing the probe interferes with attention resources allocated to bindings, and thus detrimentally affects the encoding, maintenance and/or retrieval of the multimodal memory bindings necessary to successfully complete the WM task. In this explanation of Checker's memory impairments, deficits in working memory performance are secondary to executive dysfunction (Olley et al., 2007, Omori et al., 2007).

In the key elements, Checkers performing worse than Low-checkers, with performance on unresolvable trials worse than for resolvable trials, the results of the MEG study matched well with those previously reported (Harkin et al., 2011). The cortical areas highlighted in the MEG study are associated with attentional processing and control (Hopfinger et al., 2000, Cohen, 2014, Vanderhasselt et al., 2009, Mansouri et al., 2009, Schlosser et al., 2010), supporting the conclusions drawn previously from the behavioural study (Harkin et al., 2011), that memory impairments in OCD checkers is secondary to executive dysfunction.

Figure 4-1 below, summary results presented in Chapter 3, a MEG WM study, show the oscillatory activity in theta band during the time that the intermediate, probe-1, was being processed. It was during this time that a lack of attentional inhibition causes interference with working memory processes for the Checkers, particularly on unresolvable trials.

The source localisation data for the high checkers shows MTL engagement, perhaps indicating memory processing as the checkers recheck their memory for the initial kitchen scene against the intermediate probe. Amygdala activation supports the interpretation that the probe was emotionally relevant to the OCD symptoms and may require greater executive control in order to suppress this stimulus. Activity in medial frontal cortex (mFC), comprising dorsal ACC, rostral ACC, pre-SMA and medial frontal gyrus, could reflect decision uncertainty conflict processing (Rushworth et al., 2007, Ridderinkhof et al., 2004a), in attempting to resolve the mismatch between the encoded memory set of the initial kitchen scene presented and probe-1 on unresolvable trials where the choice of response options point to solutions that were not part of the initial kitchen scene. In unresolvable trials none of the response options were valid.

In contrast to the high checkers, the low checkers show decreased activation of right dlPFC comparing unresolvable trials vs resolvable trials. This may reflect the Low checkers being better able to suppress or simply dismiss the unresolvable probe. Activity in the right dlPFC, important in executive functioning and working memory the decreased activation in theta band

(unresolvable vs resolvable trials) may be a signature of efficient executive control in which low checkers were able to quickly address the unresolvable trials so that the limited attention resources were applied to the fragile memory bindings needed to successfully process the WM task.

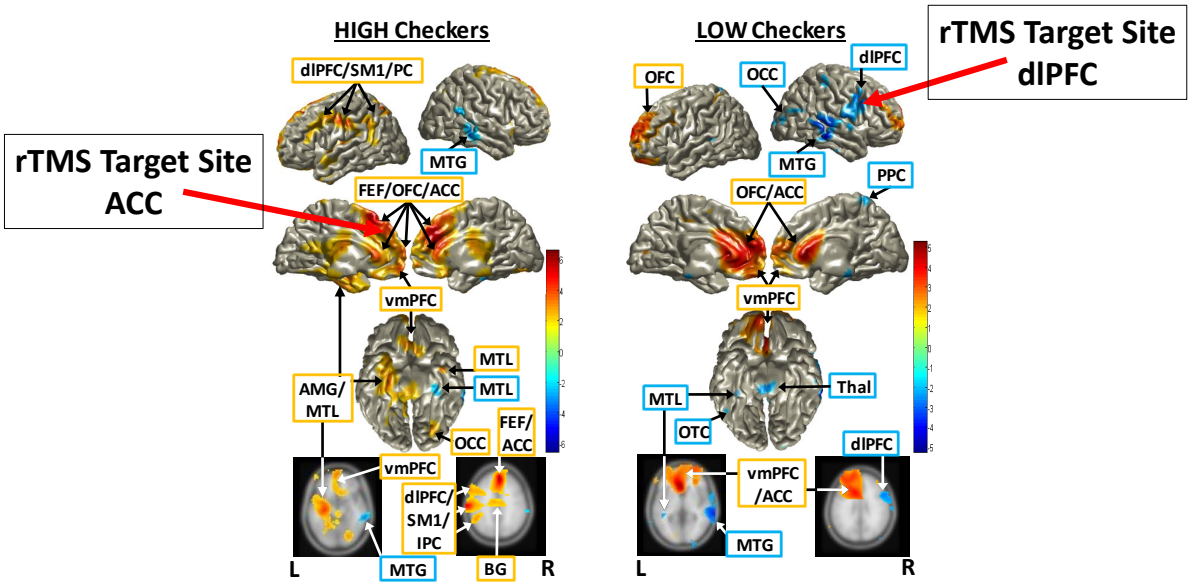


Figure 4-1. The brain areas chosen for targeting with rTMS in this experiment were selected based on the results highlighted in the theta frequency band MEG data presented in Chapter 4. These data show for high checkers increased cortical activation in dorsal ACC and with low checkers a decrease in activation of right dlPFC. The colour scale represents z-score statistical values. Colours yellow and red indicate areas of significantly increased brain activity, whereas colours blue indicate areas of significantly reduced activity.

The ACC and dlPFC show differences in activation between high and low checkers. High checkers show more dorsal activation of ACC structures, whereas for low checkers the ACC activation was located more rostral. The low checker MEG data shows decreased activation of right dlPFC, comparing unresolvable vs resolvable trials. The high checker data shows no significant difference in right dlPFC activity, unresolvable vs resolvable trials.

For this reason, the difference in theta band power between high and low checkers in dACC and right dlPFC, and that these cortical areas form part of an attention network crucial to participabts' performance in this working memory as highlighted above, these two brain regions were selected for further investigation with repetitive TMS.

Targeting dACC and right dlPFC (indicated by red arrows in Figure 4-1) using repetitive TMS (rTMS), this study aimed to entrain the ongoing oscillations at these sites (Thut and Pascual-Leone, 2010, Thut et al., 2011a, Thut et al., 2011b) to either alpha (10Hz) or theta (6Hz) frequency during time when the intermediate probe was processed to understand better the role of theta band processing.

Oscillatory activity in neural population will become (Thut et al., 2011a, Hanslmayr et al., 2014) entrained by rTMS if the stimulation frequency matches closely that of the natural ongoing

frequency of the neural population or if the neural population can support such frequencies under natural conditions. The entrainment effect has been reported to last for only a brief time, up to 2s, after the stimulation pulses cease. After which time the oscillations transition to the natural ongoing frequency and amplitude of the neural population. Similarly, arrhythmic stimulation (Zmeykina et al., 2021) has been found to suppress the ongoing oscillatory activity.

Targeted rTMS entrainment has been shown to have beneficial effects on WM performance (Bagherzadeh et al., 2016, Hanslmayr et al., 2019, Hanslmayr et al., 2014, Brunoni and Vanderhasselt, 2014).

rTMS entrainment has been shown to enhance cognitive performance in patient groups where pre-test performance was deficient but not in healthy controls whose pre-test task performance was nominal (Brunoni and Vanderhasselt, 2014).

In addition to a task dependent deterioration in WM memory performance, unresolvable vs resolvable trials, the MEG working memory data in Chapter 4 identified group level differences in oscillatory power in right dlPFC (Low checker decrease) and dorsal ACC (High checker increase).

Hypothesis 1. Entrainment of right DLPFC theta band oscillations.

Attentional control mediated by theta band oscillations was deficient in low-checkers particularly when processing probe-1 in unresolvable trials led to worse performance in the MW task. Reinforcing theta band oscillations by rTMS will improve attentional control and hence performance in the WM task compared to the sham rTMS condition and alpha rTMS. The WM performance in healthy controls (Low checkers) was not deficient, therefore sham, theta or alpha frequency rTMS will have no significant effect on their task performance.

Hypothesis 2. Entrainment of dorsal ACC theta band oscillations.

Compared to the Low checkers, checkers engage increased theta processing in dorsal ACC when processing probe-1, unresolvable trials vs resolvable trials, and this was associated with poorer task performance. Entraining theta band oscillations in dorsal ACC during probe-1 processing will stimulate dorsal ACC and worsen the performance of low-checkers. The performance of checkers, who naturally engage increased theta processing, will not be affected by theta entrainment. Sham and alpha frequency stimulation rTMS will not affect ongoing theta processing and will have no significant effect on either checkers or low-checkers.

4.2 Method

Participants

Participants were recruited from the student and staff population at Aston University. The participant group comprising mainly of psychology undergraduate students.

Participants were primarily recruited on their VOCI checking sub-scale score were assigned to one of two groups, checkers (n=16, mean age 21.3 years) or low-checkers (n=19, mean age 22.2 years). The checker cohort had VOCI scores ranging from 7 to 18, and the low-checker scores ranged from 0 to 3. Participants with VOCI scores of 4, 5 or 6 were excluded. Participants were medication free at the time of testing. MRI and TMS safety questionnaires were used to screen out those that may not undertake the experiment safely.

Working Memory Task

The working memory task (Harkin et al., 2011) was the same as that used in the MEG experiment reported in Chapter 4. Comprising ecologically valid pictures of electrical appliances arranged within a kitchen scene it was designed to resonate with and provoke OCD checking behaviour, exploiting inefficient executive functioning in the checkers group with the aim of inducing more response errors and longer reaction times compared to the control group.

The stimulus comprised a picture of four electrical appliances located on a black and white kitchen worktop that forms a grid of six possible locations. The appliances were indicated to be powered 'ON' or 'OFF' by the presence of a bright or dull red power indicator light on the appliance image. The kitchen scene was presented for 5000ms during which time participants were required to commit to memory the appliance type, its location and power state. A patterned mask screen was then presented for 1500ms. Timed to finish as probe-1 screen was displayed, on 'TMS active' trials, 15 TMS pulses were delivered at either 6Hz or 10Hz.

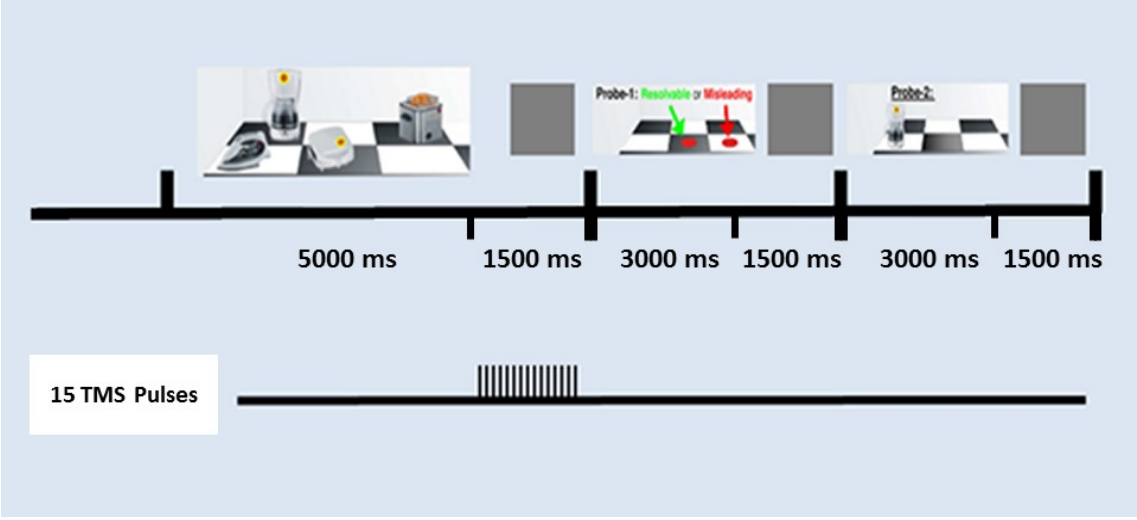


Figure 4-2. Working memory paradigm stimulus. Participants attempt to commit to memory details of the initial kitchen scene, the type of electrical appliance, its grid square location and power state. The probe-1 question interfered with the fragile memory bindings adversely affecting performance on probe-2, especially for unresolvable trials.

Probe-1 showed an empty kitchen scene with one square highlighted. Participants were required to answer 'YES' or 'NO' via a button response pad, to indicate if the appliance that was in the

highlighted square was ‘ON’ or ‘OFF’. For half the probes the highlighted square was previously unoccupied and the probe question was therefore ‘unresolvable’.

A trial completed with probe-2, the working memory task, in which a picture of an electrical appliance was shown in one of the grid locations and the participant was asked if the item was in the same location as when it was shown initially as part of a group of four appliances. The probe-2 question was always resolvable and could be answered correctly with either a ‘YES’ or ‘NO’ response via the button response pad as appropriate.

TMS protocol

An rTMS protocol was used to modulate oscillatory activity at the target cortical sites. A series of 15 TMS entrainment pulses was applied, see Figure 4-2. At the same time as the rTMS was applied, a train of audible clicks designed to mask the sound of the rTMS pulses was played through earphones worn by the participant. The rTMS stimulation was produced by triggering a sequence of single TMS pulses rapidly. The different rTMS frequencies were produced by adjusting the inter-pulse timing used, 167ms generating a 6Hz pulse train, and 100ms generating a 10Hz TMS pulse train. The audible ‘clicks’ were presented at a frequency of 30Hz. The frequency of 30Hz was chosen as it was a multiple of both 6Hz and 10Hz.

In ‘TMS sham’ trials the audible clicks were played to the participant but the rTMS pulses were not generated. In both types of trial, ‘active’ or ‘sham’, the TMS coil was positioned on the participants’ scalp over the stimulation sites, dACC and right dlPFC. The trials were presented in 20 blocks, each block comprised 16 trials. A single rTMS frequency was used for all trials within a block. The rTMS frequency, 6Hz or 10Hz, was alternated between blocks. Half the participants were assigned to start on 6Hz rTMS and half on 10Hz. Within each block of 16 trials, half of the trials were ‘active’ rTMS, in which both TMS pulses and audible clicks were applied, and half the trials were ‘sham’ condition, in which no TMS pulses were applied and only audible clicks delivered to the participant. The order in which ‘sham’ and ‘active’ rTMS trials were delivered within a block was randomised.

A Magstim Super Rapid2 (Magstim Company) type TMS stimulator with ‘figure of eight’ alpha coils was used to generate and deliver the magnetic pulses. The heating effect of rTMS on the coils required the use of two alpha coils. Swapping coils on each block ensured that the internal windings of the coils would not be damaged by overheating in the course of an experiment block. It was sufficient to alternate coils with each experiment block, allowing the just used coil time to cool.

A TMS neuronavigation system (Brainsight) was used to guide the TMS coils to the correct position on the participants’ scalp. Before a participant attended for the rTMS experiment, they underwent an MRI scan to record their T1 structural MRI for use in the neuronavigation system. Using SPM8, the MRIs were warped to the Montreal Neurological Institute (MNI) coordinate system and loaded into Brainsight. The MNI coordinates of the cortical targets was obtained from the MEG WM data and the applied to the transformed MRI image data, was used to locate

the TMS stimulation targets in left hemisphere over the dACC and right hemisphere dorsolateral prefrontal cortex. Using the individual T1 structural MRI the TMS targets were setup in the neuronavigation software so that the TMS coil would be oriented such that the peak magnetic field was perpendicular to the cortical gyrus so that the volume of interest was maximally stimulated.

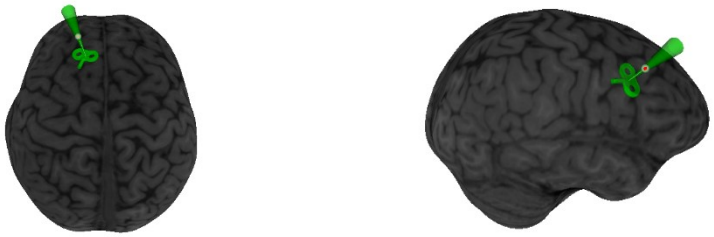


Figure 4-3. Example of TMS targets set up in Brainsight neuronavigation software, showing left hemisphere mFC and right hemisphere dlPFC targets

The accuracy of the Brainsight neuronavigation system relies on the successful co-registration of the participant with their MNI transformed MRI image during the setup of the experiment. The co-registration step was checked and redone if found to be inaccurate.

The MNI coordinates for dACC and right dlPFC targets were derived from the WM MEG dataset.

	X	Y	Z
Left Hemisphere dACC	-10	23	43
Right Hemisphere dlPFC	50	12	36

Table 4-1. MNI target coordinates used to locate brain regions targeted with TMS.

The TMS intensity used in the experiment was set relative to each subject's active motor threshold (AMT) as established by the lowest intensity single pulse stimulation (Rossi et al., 2009, Rossini et al., 2015) required to produce a voltage potential of 50μV or greater, recorded by an EMG sensor placed on the subject's right hand first dorsal interosseous (FDI) muscle, in 5 out of 10 stimulations. The stimulation intensity was set at 90% AMT for the right dlPFC and at 110% AMT for dACC. The different stimulation intensities used for dACC and right dlPFC reflect their different depths within the brain (i.e., their distances from the scalp) and the need to compensate for the decrease in magnetic field strength with distance from the TMS coil.

Adjusting the stimulator output for each target in this way, the aim was to generate the same magnetic field strength at both targets so that the strength of the rTMS effect would be equal for both dACC and right dlPFC.

4.3 Results

Probe-2 Response Accuracy

Response Accuracy under rTMS sham condition

The probe-2 accuracy data for rTMS sham condition trials, i.e. when rTMS was inactive, is presented below, figure 4-4. The rTMS sham condition data show a similar pattern (Harkin et al., 2011) in the accuracy scores as reported in the literature and seen previously with the MEG working memory experiment reported in Chapter 3. The Checkers performance was poorer than the Low-checkers on both trial types, and their performance on unresolvable trials (83%) worse than for resolvable trials (85%). The data presented in Figure 4-4 did not reach statistical significance, interaction Probe1 x Group $F(1,33) = 1.11$, $p = 0.30$, partial eta squared = 0.033. In the absence of active rTMS stimulation, the working memory experiment appears to have worked as intended. For Checker participants the presentation of probe-1 during the retention period, interfered with later memory recall for probe-2, with unresolvable trials causing the greatest interference with working memory performance.

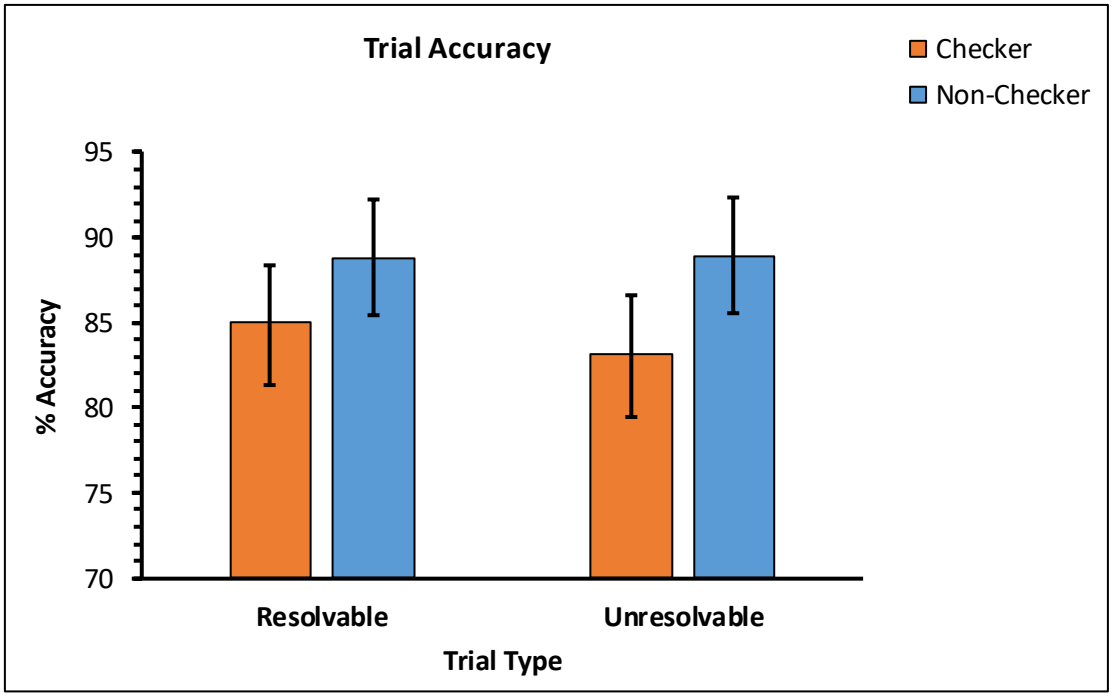


Figure 4-4. Probe-2 accuracy, comparing trial type (resolvable vs unresolvable) by group (Checker vs Low-checker) for rTMS sham trials in which rTMS was not active. The mean accuracy scores shown were derived from the combined data of dACC and right-dlPFC datasets. Error bars indicate 95% confidence interval.

Design

The data were separated into two sets according to the TMS target site, one dataset containing only trials that targeted dACC, the other, trials targeting right dlPFC.

The data were analysed using a repeated measures ANOVA, with Group (Checker vs Low-checker) the between-subject factor, and Frequency (Alpha vs Theta), Probe-1 (Resolvable vs Unresolvable) and TMS (Sham vs Active) being the within-subject factors. The data were analysed on Probe-2 response accuracy and response latency. An alpha level of 0.05 was used in the statistical tests.

ACC dataset: Accuracy

A repeated measures ANOVA was conducted to investigate the effects of rTMS, stimulation frequency and trial type on the accuracy of probe-2 responses. The results reported with Greenhouse-Geisser correction found no significant main effects.

The non-significant main effects found are, rTMS $F(1,33) = 0.44$, $p = 0.51$, partial eta squared = 0.01. Main effect of Stimulation frequency $F(1,33)= 0.01$, $p = 0.94$, partial eta squared < 0.001 and the main effect of Trial type, $F(1,33) = 3.68$, $p = 0.06$, partial eta squared = 0.10. The main effect of Group (Checker vs Low-checker) was not significant, $F(1,33) = 1.22$, $p = 0.28$, partial eta squared = 0.04. No other interactions were significant.

DLPFC dataset: Accuracy

A repeated measures ANOVA was conducted to investigate the effects of rTMS, stimulation Frequency and Trial type on the accuracy of probe-2 responses. The results reported with Greenhouse-Geisser correction found no significant main effects.

The non-significant main effects found are, rTMS $F(1,33) = 2.63$, $p = 0.11$, partial eta squared = 0.07. The main effect of Stimulation frequency $F(1,33) = 3.17$, $p = 0.08$, partial eta squared = 0.09, and Trial type $F(1,33) = 0.37$, $p = 0.55$, partial eta squared = 0.01. The main effect of Group was not significant, $F(1,33) = 2.38$, $p = 0.13$, partial eta squared = 0.07. No other interactions were significant.

The Frequency x rTMS x Group interaction approached significance, $F(1,33) = 2.97$, $p = 0.09$, partial eta squared = 0.08, but further analysis by individual Group were not significant.

Probe-2 Response Latency

Response Latency under rTMS sham condition

The response latency data under rTMS sham condition data show a similar pattern to that reported in the literature (Harkin et al., 2011) with response times on Unresolvable trials (1174.0 ms) being longer than for Resolvable trials (1143.1 ms), however the effect of Trial type under rTMS sham conditions did not reach significance, $F(1,33) = 2.44$, $p = 0.13$, partial eta squared = 0.07.

ACC dataset: Response Latency

A repeated measures ANOVA was conducted to investigate the effects of rTMS, stimulation Frequency and Trial type on the latency of probe-2 responses. The results reported with Greenhouse-Geisser correction found one significant interaction between Trial type x rTMS x Group, $F(1,33) = 7.91$, $p = 0.008$, partial eta squared = 0.19.

The non-significant main effects found are, rTMS $F(1,33) = 1.30$, $p = 0.26$, partial eta squared = 0.04. The main effect of Stimulation frequency $F(1,33) = 0.87$, $p = 0.36$, partial eta squared = 0.03, and Trial type $F(1,33) = 1.87$, $p = 0.18$, partial eta squared = 0.05. The main effect of Group was not significant, $F(1,33) = 0.03$, $p = 0.96$, partial eta squared = 0.00. No other interactions were significant.

Further analysis of the interaction between Trial type x rTMS x Group revealed for the Checker participants, a detrimental effect of rTMS in slowing response times in unresolvable trials, Trial type x rTMS $F(1,15) = 7.24$, $p = 0.017$, partial eta squared = 0.33. For Low-checkers there was no influence on response latency, Trial type x rTMS $F(1,18) = 1.44$, $p = 0.25$, partial eta squared = 0.07

DLPFC dataset: Response Latency

A repeated measures ANOVA was conducted to investigate the effects of rTMS, stimulation Frequency and Trial type on the latency of probe-2 responses. The results reported with Greenhouse-Geisser correction found a significant main effect of Trial type $F(1,33) = 8.04$, $p = 0.008$, partial eta squared = 0.20.

No other significant main effects were found, rTMS $F(1,33) = 2.01$, $p = 0.17$, partial eta squared = 0.06. Stimulation frequency, $F(1,33) = 0.71$, $p = 0.41$, partial eta squared = 0.02. No significant interactions were found.

The Trial type x rTMS x Group interaction approached significance, $F(1,33) = 3.94$, $p = 0.056$, partial eta squared = 0.11, but further analysis by Group differences were not significant.

4.4 Discussion

Analysis of sham trials showed the working memory task worked as expected, with Checkers performing worse than Low-Checkers on accuracy, and Checker performance on 'unresolvable' trials worse than on 'resolvable' trails. The group differences did not reach significance.

The lack of significant TMS main or interaction effects shows the rTMS aspect of the experiment in attempting to modify participant performance was not successful.

The importance of theta oscillations and their role the ACC and dlPFC in attentional control and conflict processing reported in the literature and theta entrainment by transcranial stimulation has been demonstrated and shown to temporarily modify performance in cognitive tasks. In this context, the lack a significant interaction of TMS on working memory performance in this task was likely to be due to the rTMS parameters used in the experiment rather than rTMS being an unsuitable technique for the task.

If accepting that the experimental approach was sound, the interaction results may provide an answer to the outcome. The interaction Frequency x rTMS x Group for dlPFC stimulation approached significance in both response accuracy and latency measures, and taken together with the significant interaction Trial type x rTMS x Group with ACC stimulation, this could indicate the rTMS intensities (90% AMT for dlPFC and 110% AMT for ACC) were just below threshold to give a consistent and robust entrainment effect.

The significant rTMS interaction found in the analysis of the latency data following stimulation of the ACC might support the sub-threshold rTMS interpretation of these data. The response times for Checkers increased on unresolvable trials following active rTMS. In this explanation the sub-threshold rTMS failed to entrain the cortical oscillations robustly (hence no effect of Frequency) but was of sufficient intensity to interfere with the ongoing oscillations and be detrimental to ACC processing. This cortical 'noise' interference preferentially affected the Checkers shown in the MEG working memory study to employ dorsal ACC, whereas low-checkers displayed stronger activation in rostral ACC, too deep within the brain to be influenced by rTMS in this experiment.

Due the lack of significant results, in particular no significant interactions involving rTMS frequency, it is not possible to comment on the hypothesis tested, the influence of alpha and theta entrainment on processing 'resolvable' vs 'unresolvable' trials. Further, it was possible, as explained above, that the rTMS was acting as 'noise interference' rather than entraining specific frequencies.

4.5 Limitations

The absence of a significant interaction of Group x Trial type in sham the condition suggests the participant numbers should be increased and / or recruitment of checking participants with higher scores on the VOCI checking subscale. The absence of a significant group difference under sham conditions may make an effect of rTMS more difficult to detect.

Participant were not controlled for anxiety or depression, which both conditions can produce cognitive impairments that affect performance in this experiment.

In targeting dACC with TMS, the magnetic field passes through and may stimulate the more superficial areas of the cortex that were in its path, such as medial frontal gyrus, before reaching the dACC. Any effects of TMS would therefore not be isolated purely to dACC processing in theta band. Likewise, alpha band rTMS stimulation may affect neural circuits associated with alpha power which may have complex interaction with theta oscillatory processes and cognitive behaviour.

5 Investigating Endogenous Attention via the Stroop Task

5.1 Introduction

Stroop Colour-Word Task

The Stroop interference effect (Stroop, 1935) in the form of its classic colour-word naming task requires the subject, reading from a list of stimuli, to name aloud the colour of each the list items. The list items may be classed as 'congruent', 'incongruent' or 'neutral'. A 'congruent' stimulus would present different colour words printed in the ink colour of the word (e.g., the word 'blue' written in blue ink) and an 'incongruent' stimulus is where the colour words and ink colour are mismatched (e.g., the word 'blue' written in yellow ink). A 'neutral' stimulus is where no word with a recognised meaning is presented but instead a series of letter characters are presented (e.g., 'XXXX' written in blue ink).

The Stroop effect is demonstrated when participants reading from lists of stimuli name aloud the colour of the ink. Naming aloud as quickly as possible, response times and error rates are higher when a participant reads from a list of 'incongruent' colour stimuli, compared to lists of 'congruent' or 'neutral' lists. Participants usually read the congruent words more easily, being faster and making fewer errors compared with reading the incongruent words. When the colour indicated by the word is different from the colour of the ink in which the word is printed, different mental representations of the printed word are activated. One representation set containing the semantic meaning of the word and another set, the colour representation of the ink colour. These different mental representations are activated and compete to be the response produced. This response competition in incongruent trials usually results in slower response times and higher error rates compared to congruent trials. The Stroop interference effect, longer response times and higher error rates in incongruent trials, is robust (MacLeod, 1991) and in the colour-word form of the task is resistant to practice effects. An alternative explanation for the interference mechanism, 'Automaticity', (MacLeod, 1991) suggests that processing information in one dimension requires more attention that processing in the other dimension. Word reading being a more highly practiced and developed skill than colour naming, is undertaken preferentially and requires fewer attention resources. MacLeod and MacDonald (2000) further proposed that the conflict would exist on congruent as well as incongruent trials. This view is supported (Goldfarb and Henik, 2007) by measurements of response time comparing congruent word trials with non-words.

Emotional Stroop Task

The classic Stroop task has been adapted to investigate the effect of emotions on Stroop interference, of which the Emotional Stroop and Pictorial Stroop tasks are two examples. The emotional Stroop has been used to investigate attentional biases and inhibition in disorders such as addiction, anxiety disorder, panic disorder, depression, and schizophrenia, as well as OCD. In the emotional Stroop task participants read from lists of neutral words and negative emotional,

symptom salient words, saying the colour in which the words were printed. The interference mechanism differs from the classic Stroop in that the conflict lies between the word meaning and its emotional relevance of the participant, rather than the incongruence of the colour and the word as a result of activation of fear responses or mood congruent semantic networks. If the emotionally relevant semantic content cannot be inhibited and attention is selectively paid to the task irrelevant emotional words, then greater impairment of colour-naming performance should be observed on these words, (Yiend, 2010), compared with colour naming of matched neutral words.

Pictorial Stroop Task

Following a failure to find an effect of attentional bias in OCD participants towards OCD relevant words in a Stroop task, Moritz et al. (2008), the research question was reinvestigated in a modified paradigm using pictures, Moritz et al. (2009). With the visual stimuli OCD patients showed a slower response to targets preceded by an OCD relevant cue. This result suggests that pictorial stimuli may have greater valence with OCD participants, eliciting attentional biases where inconsistent results have previously been obtained with word stimuli alone.

Another variation of the Stroop task is the pictorial Stroop in which words are embedded within pictures, (MacLeod, 1991). Like colour naming, picture naming is slower than reading the word out loud. In this TMS study a pictorial Stroop paradigm is used in which pictures of electrical appliances relevant to OCD checking behaviours were used. Pictures showed the power state of the electrical appliance with either a bright red indicator light (switched 'ON') or a dull red indicator light (switched 'OFF'). Pictures with indicator lights 'ON' (emotional) were expected to resonate with and promote checking behaviours while pictures with the indicator light 'OFF' (neutral) would not activate checking. Within the picture the spatial location of the word is varied from picture to picture, as this location uncertainty (MacLeod, 1991) and consequent visual search is necessary in order to maintain the interference effect. The Stroop interference is further maintained by mixing 'emotional' and 'neutral' trials, which is thought to split attention over the two dimensions, word, and picture.

Converging evidence from neuroimaging and lesion studies (Carter and Van Veen, 2007) highlight the role of dorsal ACC in error detection and dlPFC in cognitive control during Stroop tasks. In OCD an increased distractibility for irrelevant information (Van den Heuvel et al., 2005) is associated with upregulation of ACC and top-down control via a frontal network, including dlPFC. The role of ACC and dlPFC of particular importance in OCD (Ciesielski et al., 2011) as part of a prefrontal and dACC network mediating top-down cognitive, with dACC and lateral prefrontal networks hypothesised to implement an adaptive compensatory mechanism.

The role of the ACC was investigated using a dual pulse TMS protocol designed to interfere with processing within the ACC.

5.2 Behavioural Pilot

5.2.1 Introduction

The use of emotional words in OCD Stroop research has had mixed results (Summerfeldt and Endler, 1998), with consistent findings reported only with 'contamination' stimuli relevant to OCD 'washing' subtype. It has been suggested that word stimuli (Moritz et al., 2008) are not sufficiently salient to provoke OCD behaviours in experiment test situations and that better success may be achieved with picture stimuli. A set of electrical kitchen appliance picture stimuli have been developed (Harkin et al., 2011) that have elicited differences in performance behaviour comparing subclinical checkers with low-checkers in an inhibition of return task. The efficacy of these picture stimuli for use in a Stroop task were tested and compared against classic colour-word and emotional Stroop paradigms.

5.2.2 Method

Participants

Participants were recruited from the student population at Aston University using the Aston University Psychology Research Participation scheme. The participant group comprising of psychology undergraduate students.

A total of 30 participants were recruited, 23 females and 7 males (mean age of 20.1). Participants were primarily recruited on their VOCI checking sub-scale score were assigned to one of two groups, checkers (n=15) and low-checkers (n=15). Based on previous research by Harkin & Kessler, 2009; 2011) participants with scores of 3 or lower were assigned to the low-checker group. Participants with scores of 7 or higher were assigned to the checker group. Participants with intermediate VOCI scores of 4, 5 or 6 were excluded from the study. In the study, the checking cohort had VOCI scores ranging from 7 to 18, and the low-checker scores ranged from 0 to 3. Participants were medication free at the time of testing.

Stimuli

The word Stroop task consisted of emotional words ('Control', 'Check', 'Accident', 'Fire', 'Doubt', 'Fail', 'Fatal', 'Uncertain') relevant to a checking specific subtype (Rao et al, 2010) and neutral words ('Emblem', 'Stands', 'Pencil', 'Clause', 'Buttons', 'Granite', 'Overall', 'Folders'). Colour words, ('Red', 'Lime', 'Blue', 'Yellow', 'Black', 'White', 'Orange', 'Purple'), were presented in congruent or incongruent colours while neutral and emotional words were presented in any colour (emotional words were expected to interfere with colour naming due to emotional content rather than due to semantic contradiction). The stimuli for the pictorial Stroop task involved pictures of home appliances such as mixers, headphones, speakers, stoves and microwaves. Each picture of the different home appliances was manipulated to include either the word ON or OFF as well as one ON or OFF button underneath. The pictures of home appliances represent ecologically valid stimuli that resonate with the some of the checking related statements in the VOCI questionnaire, for example, if checking and rechecking switches, appliances, faucets and doors was a problem (Radomsky and Rachman, 2004). The use of these images in OCD checking

behaviour studies has been shown to be effective, (Harkin et al., 2012), when used in an inhibition of return paradigm, subclinical OCD showed deficient disengagement of attention (Harkin et al., 2012) form the kitchen appliance pictures.

Experiment 1. Stroop Colour-Word Task

The word Stroop task consisted of 68 randomly presented trials, 8 trials for each of 8 conditions (congruency: congruent vs incongruent, dimension: word vs colour, word type: neutral vs emotional), plus 4 practice trials. The stimulus words comprised a set of eight 'neutral', 'colour' and 'emotional' words. The experiment was presented as a computer based task as shown in figure 5-1 below. Each trial begins with an instruction, displayed for 2000ms, to either 'read the word' or 'name the colour'. After presentation of a fixation cross for 1000ms a word was displayed. The participant then speaks their response which was recorded by microphone and then presses the keyboard spacebar to stop the recording and proceed to the next trial. The response reaction times for each trial was measured by analysing the recordings to find the speech onset time. This was done using WavePad Music Editor software.

***Figure 5-1**. Stroop Colour-Word task in which the participant was asked to either name the word or colour in which the word was written. After speaking their responses which were recorded by microphone, participants pressed a computer keyboard spacebar to move on to the next trial.*

Experiment 2. Stroop Picture-Word Task

The Pictorial Stroop experiment consisted of 132 randomly presented trials, 8 trials for each of 16 conditions (state: on vs off, word: on vs off, appliance: threat vs neutral, dimension: state vs word). The first 4 trials were practice trials. It was presented as a computer-based task in which a series of pictures of small kitchen electrical appliances were displayed on an LCD computer monitor screen, see figure 5-2 below. The kitchen appliance images each showed a red power light. In half the images the power light was dull red indicating the device was powered 'off' and in half the images the power light was bright red indicating it was switched 'on'. Similarly,

embedded in each image was either the word ‘on’ or the word ‘off’. A complete set of images for each appliance therefore comprised four pictures, for the four combination pairs of lights and words. The pictures of home appliances belonged to either a threat group (microwave, stove, water kettle, iron, mixer etc.) or a neutral group (speakers, computer mouse, electronic toothbrush, remote controller etc.). A self-regulated break was administered halfway through the pictorial Stroop task (64 trials in each block). The break lasted until the participants were ready to complete the rest of the task by pressing the computer keyboard spacebar.

***Figure 5-2**. Stroop Picture-Word task in which the participant was asked to either name the word in the picture or name the power state of the appliance, as indicated by the power light. Valid responses were either ‘On’ or ‘Off’. After speaking their responses which were recorded by microphone, participants pressed a computer keyboard spacebar to move on to the next trial.*

In each trial, participants were tasked either ‘Name the State’ or ‘Name the Word’, meaning the power state of the appliance, whether ‘ON’ or ‘OFF’, or the word superimposed on the image, again being ‘ON’ or ‘OFF’. Following a fixation cross of 1000ms duration, the image was displayed. The participants’ response was spoken into a microphone and the participant stopped the recording for each trial by pressing the keyboard spacebar. The response reaction times for each trial was measured by analysing the recordings to find the speech onset time. This was done using WavePad Music Editor software.

5.2.3 Results

Colour-Word Stroop

On average the checker group were slower to respond in all condition combinations of the Colour-Word Stroop task. A three-way mixed ANOVA exploring the effect of target dimension (colour or word), congruence (congruent or incongruent) and group (low-checker or checker) was conducted. A main effect of group $F(1,28) = 24.3$, $P < .000$, partial eta squared = 0.47, shows the overall average difference in response times between the two groups across conditions was statistically significant.

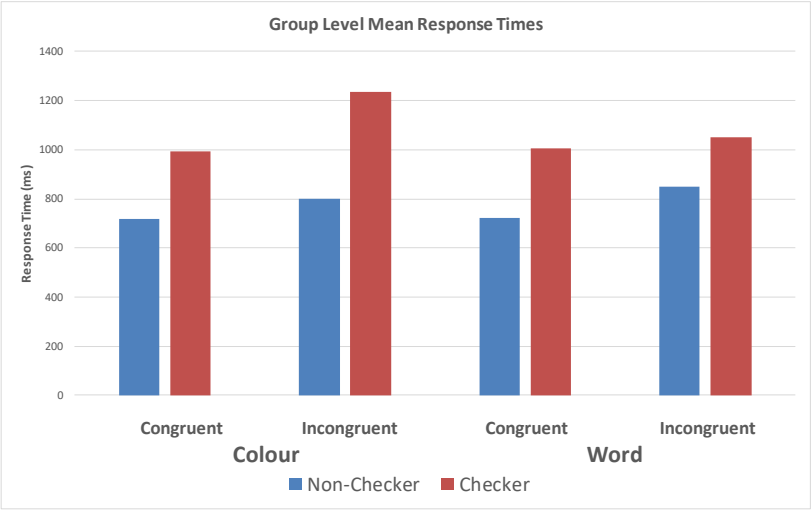


Figure 5-3. *The mean response time data in the colour-word Stroop task shows that the subclinical OCD checker group were as a group, slower than the low-checkers in their voice responses.*

The main effect for congruence reached significance, $F(1,28)=16.8$, $P < .000$, partial eta squared = 0.38, showing that for both groups response times were slower on incongruent trials compared with congruent trials. An interaction effect between dimension (colour/word), congruence (congruent/incongruent) and group (low-checker/checker) reached significance $F(1,28)=4.3$, $P < .047$, partial eta squared = 0.13.

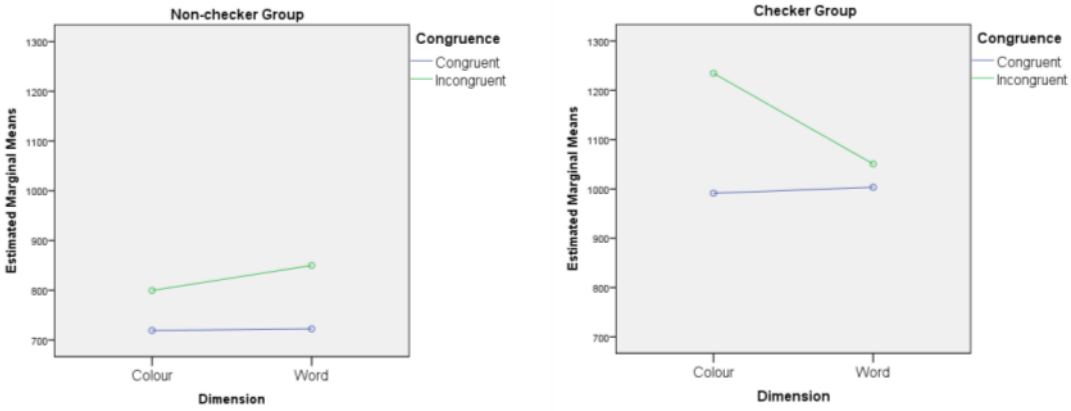


***Figure 5-4**. An interaction effect between dimension (colour/word), congruence (congruent/incongruent) and group (low-checker/checker) was found.*

Average response time difference between incongruent and congruent conditions for the low-checker group was 80ms and 127ms for colour and word conditions respectively. For the checker group the differences were 240ms and 47ms. Using Bonferroni corrected paired samples t-tests only the checker responses on the colour naming dimension showed significant response time differences, $t(14) = 3.02$, at a significance level of $p<0.05$.

Emotional-Word Stroop

A two-way between groups analysis of variance was conducted in which a main effect of group, reached significance ($F(1,28)=10.16$, $p = 0.004$, partial eta squared = 0.27). The checker group were significantly slower in response time compared to low-checkers in the emotional Stroop task.

However the interaction between emotional word (emotional/neutral) and group (low-checker/checker) did not reach significance ($F(1,28)=1.39$, $p = 0.25$, partial eta squared = 0.15). Although not reaching significance in this experiment ($F(1,28)=3.6$, $p = 0.068$, partial eta squared = 0.11) checkers appear to be responding more quickly to emotional words than neutral words.

***Figure 5-5**. Subclinical checkers performed more slowly on the emotional word Stroop task compared to low-checkers. However, statistical tests did not find the response times to be significantly slower.*

The main effect of group was significant (F(1,28)=6.77, p = 0.015, partial eta squared = 0.20) with checkers having slower response times, taking approximately 120ms longer to respond than the low-checkers. There was no interaction between emotional word and colour naming and group, (F(1,28)=0.05, p = 0.82, partial eta squared = 0.002).

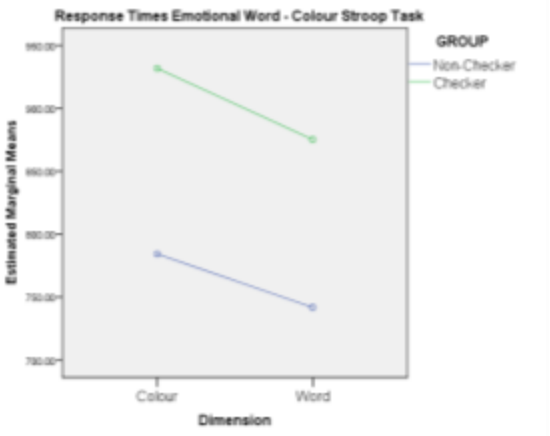


***Figure 5-6**. Although the checker group were slower in responding, main effect of group, there was no statistically significant difference in response times as an effect of colour or word.*

Picture-Word Stroop

A five-way mixed ANOVA was conducted, the within factors were Dimension (word/power state), Congruence (congruent/incongruent), Target (ON/OFF), and Appliance type (neutral/threatening) and a between group factor, group (low-checker vs checkers). Here congruence was when the word, 'ON' or 'OFF', matched the power state of the light indicated in the picture. The dimension refers to whether the trial task was to name the word or the power

state indicated on the appliance. Congruence refers to whether the word ('ON' or 'OFF') matched the power state of the appliance, as indicated by its power light. Target referred to the dimension of the naming item (either the word or the image), whether it was 'ON' or 'OFF'. Appliance type, whether a neutral or threatening image for OCD checking behaviour.

The main effect of group reached significance again ($F(1,28) = 45.12$, $p < 0.001$, partial eta squared = 0.62), indicating that high checkers responded generally more slowly on the pictorial Stroop paradigm in comparison to the low checkers. The main effect of dimension reached significance ($F(1,28) = 24.74$, $p < 0.001$, partial eta squared = 0.47), indicating all participants were slower when asked to name the power state of the appliance ("on" or "off") in comparison to reading the word ("on" or "off"). A main effect of congruence ($F(1,28) = 62.59$, $p < 0.001$, partial eta squared = 0.69), indicates that all participants were slower on incongruent compared to congruent trials.

The interaction effect between congruence (congruent versus incongruent) and group (high checkers versus low checkers) reached significance ($F(1,28) = 7.14$, $p = 0.012$, partial eta squared = 0.20) this shows that checkers experience stronger Stroop interference compared to low-checkers in the pictorial Stroop paradigm.

Figure 5-7 shows the Stroop interference effect as measured by reaction time differences, incongruent minus congruent trials, was twice the magnitude for checkers compared to low-checkers, with reaction time differences of ~80 milliseconds compared to ~40 milliseconds.

The difference in magnitude of the Stroop inference effect was not due to a speed-accuracy trade off. It was possible that checkers were slower, taking longer but being more accurate. Figure 5-8 shows that in fact the checkers were less accurate, though the interaction between group and accuracy did not reach significance ($F(1,28) = 4.00$, $p = 0.054$, partial eta squared = 0.13). Overall for the pictorial Stroop task, incongruent trials were slower and less accurate than congruent trials and this effect was more pronounced for checkers.

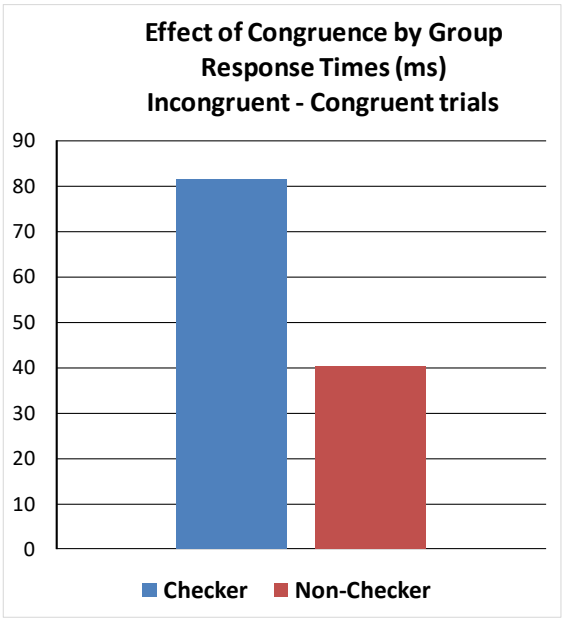


***Figure 5-7**. Stroop interference measured in milliseconds on the basis of congruence by group.*

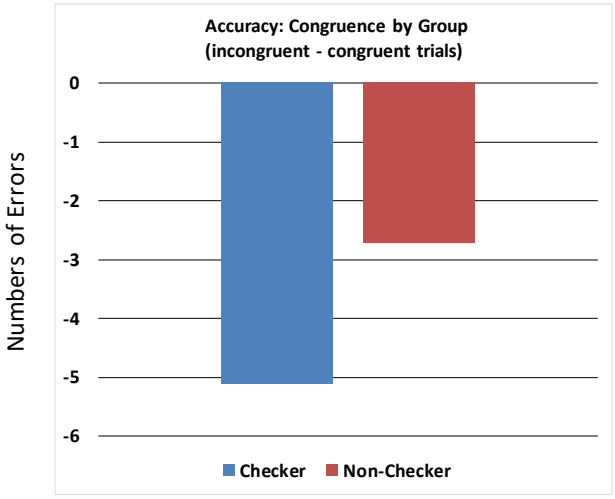


***Figure 5-8.** Accuracy of high checkers versus low checkers, revealing no speed for accuracy trade-off.*

Main effects were obtained for Dimension (power state/word) $F(1,28) = 24.74$, $p < 0.001$, partial eta squared = 0.47, Congruence (congruent/incongruent) $F(1,28) = 62.59$, $p < 0.001$, partial eta squared = 0.70, Target (ON/OFF) $F(1,28) = 10.51$, $p = 0.003$, partial eta squared = 0.27, and Group (low-checker/checker) $F(1,28) = 45.12$, $p < 0.001$, partial eta squared = 0.62. Participants on average, independent of group, responded quicker when the stimulus was congruent, word reading or the correct response was “ON”.

A 4-way interaction effect between Dimension (power state/word), target (ON/OFF), appliance (neutral/threat), and group (low-checker/checker) reached significance ($F(1,28) = 6.0$, $p = 0.021$, partial eta squared = 0.18). Figure 5-9 shows that both checkers and low-checkers were slower

responding to picture stimuli of threatening appliances when asked to name the word, irrespective of the correct answer being “ON” or “OFF”.

The response times were longer for both checkers and low-checkers when the picture was a threatening appliance, except for one experiment condition. For checkers, responding to name the power state of a threatening appliance that was switched “ON”, in only this case was the pattern reversed and responses were quicker compared to neutral pictures.

Figure 5-9. *Investigating a 4-way interaction between Dimension*Target*Appliance*Group, the average response times were slower for threatening images except in one case where checkers respond to a threatening image that was shown switched “On”.*

5.2.4 Discussion

Reviews of studies (Bar-Haim et al., 2007, Summerfeldt and Endler, 1998) using a Stroop task with OCD checking participants have found the results to be mixed. Whereas the emotional Stroop effect has been shown to be robust with conditions such as depression and anxiety, results for OCD were equivocal. The Stroop studies reviewed were not the classic colour-word Stroop paradigm, but emotional Stroop tasks, in the majority employing ‘threat words’ thought to be salient to the participants’ concerns. It was suggested that it is the heterogeneous and individual nature of OCD checking symptomology that is the underlying cause for inconsistent

emotional Stroop results. The emotional content employed in the task was insufficiently emotional to the participants, each with their different symptom concerns. However, pictorial stimuli rather than word-based stimuli (Moritz et al., 2008, Moritz et al., 2009) have been found to resonate with OCD patients and are more effective in evoking OCD checking behaviours.

The purpose of the Stroop behavioural pilot was to compare the ability of a Classic Stroop, an Emotional Stroop and Pictorial Stroop paradigm to evoke behavioural differences, as measured by response times, and assess their suitability for use in an MEG and a TMS experiment, to investigate the functional differences between checkers and low-checkers.

The Emotional word Stroop stimuli (Rao et al., 2010) and the Pictorial kitchen appliance stimuli (Harkin et al., 2011) were adapted from previously conducted studies reported in the literature.

In the three Stroop current experiments, a main effect of Group and Congruence was observed. However, it should be noted that congruence in colour-word and picture-word paradigms will refer to different aspects of the stimuli. Generally, checkers took longer to respond than low-checkers and congruent trials were answered more quickly than incongruent trials. This is consistent with findings reported for depression and anxiety participants performing the Stroop task.

In the colour-word Stroop experiment, the interference effect in this sample group (n=15) was found to be significant for the checker group for colour, incongruent versus congruent trials. The classic Stroop task is robust (MacLeod, 1991) in producing interference effects and a significant effect might be expected.

The emotional Stroop paradigm produced a significant main effect of Group, low-checkers being on average faster in reaction time. However, there was no interaction effect observed between word type (emotional vs. neutral), naming dimension (colour vs. word) and group. For this cohort there was no evidence of a Stroop interference effect for emotional words on colour naming, or comparing reaction times in naming neutral compared with emotional words. This result was consistent with previous research (Moritz et al., 2008) which suggests emotional words were not sufficiently salient to evoke OCD behaviours and induce Stroop interference.

The pictorial Stroop task employed ecologically valid imagery of kitchen electrical appliances adapted from previously reported research, (Harkin et al., 2012, Harkin et al., 2011), in which they were used successfully in a working memory task and an inhibition of return paradigm to elicit behavioural differences between OCD checkers and low-checkers. The use of these stimuli was currently untested in a Stroop paradigm.

In the pictorial Stroop task main effects of Dimension (power state / word), Target (ON / OFF), Appliance (neutral / threat) and Group were observed. Participants responded quicker to naming the word, when the answer was “ON” and on average, when the appliance was ‘neutral’. Checkers were generally slower in their reaction times. This general pattern of slower reaction times for trials involving ‘threat’ compared to ‘neutral’ picture stimuli was reversed for the checker group when asked to name the power state when the power light was shown “ON”. In this one condition the pattern of reaction times was reversed, with faster responses when the stimulus

was ‘threatening’. It could be argued that as the checker response times to ‘threat’ stimuli were similar in the name the ‘word’ and name the ‘state’ conditions that the effect was a longer response time to the neutral stimulus. This interpretation does not fit with the general pattern observed here and in Stroop interference generally that word reading was quicker than colour naming, or as in this task ‘state’ naming. The correct interpretation appears to be that in naming the ‘state’ in ‘ON’ conditions, a ‘facilitation’ effect occurs and reaction times for checkers was quickened. This result suggests the checkers have an attentional bias towards the particularly threatening stimulus, a ‘threat’ stimulus in an active state, which enables them to respond more quickly to naming the ‘state’ in this specific experiment condition. The attentional bias was indicative of a deficient inhibition of return response, the checkers attention lingers on the threatening light of the threatening appliance.

In these experiments differences in the level of Stroop interference, as an effect of Group, was observed in both the classic and pictorial Stroop tasks but not the emotional Stroop task. It could be argued that with larger group sizes a significant effect may have been found in the emotional Stroop task, but as the group sizes will be similar for the MEG and TMS experiments, the interference effect needs to be sufficient large to be seen with this number of participants. On this basis the emotional Stroop task would not be appropriate for the MEG and TMS experiments.

Although the classic Stroop did produce an interference effect by Group, the pictorial stimuli were likely to be evoking a different interference mechanism (MacLeod, 1991), one that is more specific to the OCD checking symptomology. The pictorial stimuli, shown to produce different behavioural responses in OCD checkers and low-checkers in working memory and inhibition of return paradigms, appear also to be effective in the Stroop task and can be used to investigate functional differences in endogenous attention in OCD checking behaviour.

5.3 MEG Pictorial-Stroop Task

5.3.1 Introduction

In Chapter 1, the role of compromised working memory in OCD checking was explored in the context of the EBL classification system proposed by Harkin et al. (2011) and executive dysfunction interference with the episodic buffer. In the working memory MEG study, Chapter 3, the addition of an intermediate working memory probe which caused OCD checking participants’ memory recall accuracy performance to be affected more than control participants, in particular for the misleading/unresolvable trials. The unresolvable probe does not match with the encoded memory set for the trial presented. Low checkers appear to be able to suppress this distraction, whereas high checkers, were either more distracted by the misleading probe because it does not match with the encoded set or were unable to suppress the urge to recheck their memory to resolve the mismatch. For the high checkers, the deficit executive control leading to a process of failing to inhibit the distractor or rechecking memory set, impairs attention dependent bindings

within the episodic buffer, resulting in a memory impairment on unresolvable trials and poorer performance in the working memory task.

High checkers showed deficient vmPFC and latPFC theta activity, but increased theta band power in FEF, amygdala, medial temporal lobe and thalamus during misleading/unresolvable trials, possibly explained by attention resources directed towards task irrelevant imagery that was emotionally salient to OCD checkers.

In this MEG Stroop study the role of endogenous attention will be investigated, which in the context of executive dysfunction and control of attention resources, and in light of the results of the behavioural pilot (Chapter 5) was expected to be poorer for OCD checkers.

Converging evidence from neuroimaging and lesion studies for example, (Carter and Van Veen, 2007, Ciesielski et al., 2011, Van den Heuvel et al., 2005) highlight the role of dorsal ACC in error detection and dlPFC in cognitive control during Stroop tasks. Furthermore, abnormally increased activation of the ACC with high conflict Stroop paradigms has been found in OCD subjects (e.g. Ciesielski et al. (2011)) and proposed as a mechanism by which OCD subjects maintain normal response time performance in the Stroop task.

In addition to its role in error detection and resolving information stream conflict, the ACC is part of the so called 'limbic' circuit involved in attention mechanisms that serve to regulate both cognitive and emotional processing. In this respect the ACC may play a larger role for Checkers in ecologically valid Stroop tasks designed to provoke OCD related fears and behaviours. This larger role may be evidenced by differences in cortical oscillatory power.

The focus of the analysis was in theta band which has been shown to index for cognitive processing (e.g. (Nigbur et al., 2011),(Cohen and Donner, 2013). In addition the power in alpha and beta bands was also presented.

For participants to accurately and speedily process the Stroop task, participants will exercise components of the executive (Alvarez and Emory, 2006), in particular directed attention, inhibition, monitoring and working memory. These cognitive functions are associated with activation of frontal lobe areas, with dlPFC, vlPFC and anterior cingulate typically reported (e.g. Macdonald et al, 2000; Pardo et al, 1990, Cohen et al, 1997; Tsuchida and Fellows, 2009). Regions of IPL with network connections to frontal lobes form a fronto-parietal network involved in directing attention and memory (Baddeley, 1998; Diwadkar, Carpenter and Just, 2000; Petrides and Pandya, 2002; Sauseng et al, 2002). The mid-DLPFC region and posterior lateral frontal regions, including the premotor rostral area, are connected with posterior parietal areas (Petrides and Pandya, 2002). The thalamus a central hub for limbic circuit and projections to the frontal cortex (Krack et al., 2010) are likely brain areas to be involved in Stroop task. The frontal cortex is strongly linked with the limbic region of the medial temporal lobe. This network important for memory and the regulation of emotional responses.

Taken together, based on the literature, areas expected to be preferentially activated during the Stroop task include structures of the frontal cortex associated with executive function and limbic

system, in particular ACC, dlPFC, amygdala, thalamus and globus pallidum. In addition fronto-parietal networks involved in spatial attention were likely to be represented in the MEG data. In OCD (Cavedini et al., 2006) dysfunction in neural circuit involving OFC, cingulate gyrus, caudate nucleus, putamen, globus pallidus and thalamus has been found to generate a higher baseline level of activity.

Hypothesis

It was expected that areas typically involved in attention tasks and in the Stroop task (Pardo et al., 1990), for example, ACC, dlPFC, FEF and SMA were engaged differently by the checker cohort. Reported in OCD participants, abnormally increased (Ciesielski et al., 2011) activity within the anterior network for top-down inhibitory control in OCD may be a compensatory mechanism necessary in maintaining a normal level of functioning. Poorer inhibitory control over top-down selective attention may mean the checker cohort were more strongly drawn to imagery salient to their symptomology, dwelling longer and taking longer to make their response - and especially so when information is incongruent (Stroop interference). It was expected that the attention of low checkers would not be especially drawn to the imagery of electrical appliances. For low checkers, electrical appliances and their power state would be a neutral stimulus in terms of Stroop Interference.

Pictorial Stroop Task

Employing the same pictorial Stroop stimuli as was used in the Stroop behavioural pilot, reported in Chapter 5, this MEG sort to investigate the oscillatory signatures and in particular the differences in brain activity between Checkers and Low-checkers when processing imagery salient to the Checkers' checking behaviour.

In this study, participants were presented with images of electrical appliances (Harkin & Kessler, 2009) found to resonate with OCD checking behaviours and elicit a Stroop effect (see Chapter 5 Stroop Behavioural Pilot). The images show the appliances in either an 'ON' or 'OFF' state. Imposed on the images was a word, either 'ON' or 'OFF'. Depending on the trial instruction, participants indicated either the state of the appliance or the word by means of pressing one of two buttons on a response pad. In this respect the paradigm used in the MEG recordings differed from the pilot study where the responses were spoken rather than indicated via a manual press of a button.

5.3.2 Method

Participants

Applicants to the study were from the student and staff population at Aston University. An MRI safety questionnaire and VOCI questionnaire were used to select those applicants suitable to take part in the study. Based on their VOCI checking subscale score, participants eligible to take

part, were assigned to one of two groups, checkers or low-checkers. The checking cohort (n=13) comprised those participants that achieved VOCI scores 7 or above, and the low-checker cohort (n=11) comprised those with scores ranging from 0 to 3. Applicants to the study who scored 4, 5 or 6 on the VOCI checking subscale were declined from the study. Participants were medication free at the time of testing.

Pictorial Stroop Task

The Stroop task consisted of two conditions, a congruent and an incongruent condition. The stimuli were pictures of small kitchen electrical appliances along with the word, either 'ON' or 'OFF'. The power light in the picture of the electrical appliance was either dull red (indicating its state was powered 'OFF') or bright red (indicating its state was powered 'ON').

Participants were asked to either 'Name the State' or 'Name the Word'. Participants answered the question, indicating 'ON' or 'OFF', by pressing one of two keys on a response button pad using their index or middle finger. Participants were instructed to make their responses as fast as possible whilst still being accurate.

The Stroop task was presented in six blocks of 64 trials each, resulting in 384 individual trials. Within each block trials were counterbalanced to provide equal numbers of congruent and incongruent trials, equal numbers of 'ON' and 'OFF' correct responses and equal numbers of 'Word' or 'State' probes. The order in which the stimuli-probe combinations were presented was randomised.

The Stroop task employed here used a manual button press response instead of the 'classic' vocalised response. The manual response design enables easier and more consistent measurement of response time performance in comparison to identification of the initiation of a vocalised answer and minimizes movement and muscle-related artefacts associated with speaking whilst seated inside the MEG scanner.

The trial sequence started with the probe question being presented for 2000ms, followed by a blank screen of 2000ms duration and then the stimulus picture. The stimulus picture was displayed for a maximum of 4000ms or until the participant made a response via the button pad, whichever event was sooner. Each trial concluded with the presentation of a fixation cross for 2000ms. After making their button pad response participants were informed via a sound signal played through earphones whether their response had been correct or not. The researcher was able to monitor the audio feedback and advise participants showing a high error rate to slow down slightly to be more accurate.

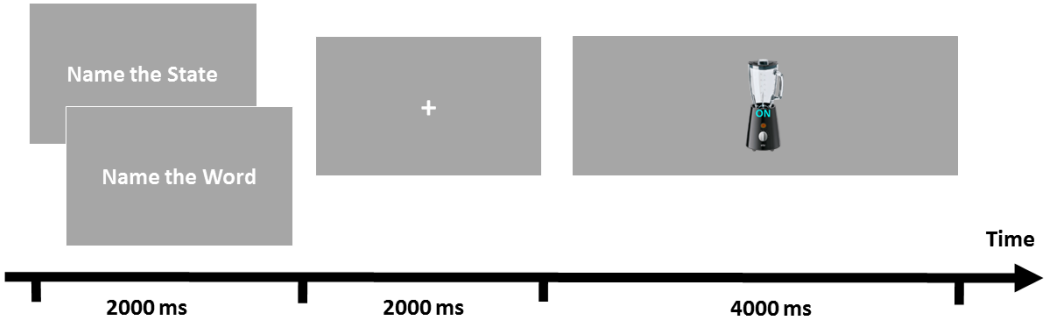


Figure 5-10. *Stroop Picture-Word task in which the participant was asked to either name the word in the picture or name the power state of the appliance, as indicated by the power light. Valid responses were either 'On' or 'Off'. Responses were made using a button pad.*

The Stroop task was implemented in ePrime running on a PC connected to a video projector. The Stroop stimuli were projected onto a transparent screen within the MEG magnetically shielded room. Before starting data measurements, all participants were instructed in how to complete the Stroop task, how audio feedback indicates correct and incorrect responses and briefly practiced using the response button pad. The screen position was adjusted so the stimulus images were sharp and clear. Participants who needed vision corrected to normal either wore their own contact lenses or were temporarily provided with non-metallic MEG compatible spectacles with a suitable lens prescription.

MEG

The MEG data where recorded at the Aston Brain Centre with an Elekta Neuromag306 Triux MEG system, comprising 102 magnetometers and 204 planar gradiometer sensors.

The data for each participant where acquired in six blocks, each of approximately 8 minutes in duration. In the preprocessing steps, motion compensation was applied to the data, and the head position for each individual, re-referenced to first block. In the analysis presented, only the planar gradiometer data were used.

5.3.3 Results

Behavioural Data

Figure 5-11 below shows the mean response reaction times, by cohort and experiment condition, congruent vs incongruent.

As indicated in the bar charts, a significant difference in reaction times was found when comparing congruent and incongruent trials, with incongruent trials on average being more difficult to process and generating slower response times. This confirms the paradigm was

generating a Stroop effect. However, unlike the pilot study, no group effect was found, there was no significant difference between the groups in their reaction times.

There was a necessary difference introduced in how participant responses were recorded when moving from the pilot study to the MEG study. In the pilot study participants spoke their responses whereas in the MEG study, participants being seated in the MEG scanner were required to remain silent and be as still as possible. They therefore used a button response pad to indicate their responses. The button pad response was used in the MEG study to minimise head movements and to avoid jaw movements completely. The activation of jaw muscles associated with speech and neck muscles associated with head movements would have introduced noise artifacts that were much larger than the brain signals being investigated, and degraded the MEG data recorded.

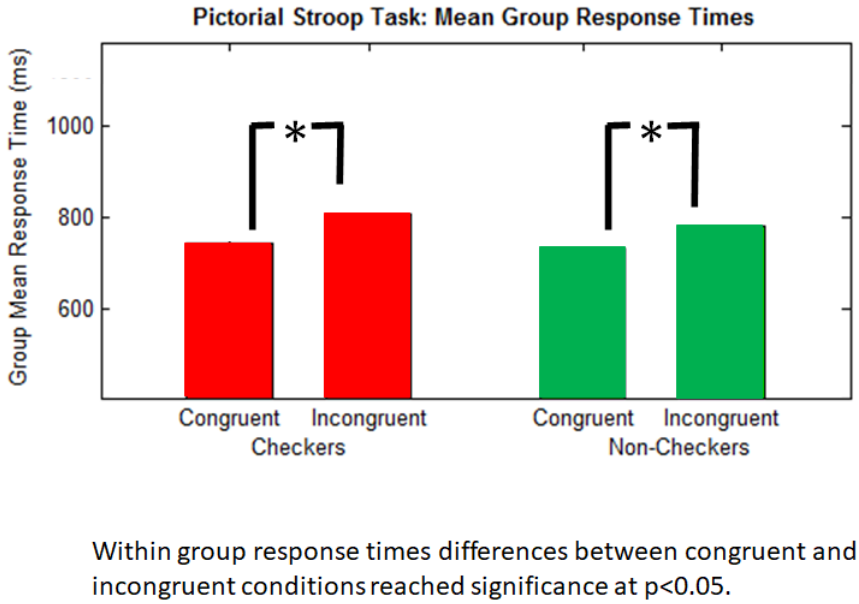


Figure 5-11 There was a significant within group difference in the response times between the two conditions, congruent and incongruent. This indicates the task was working as a Stroop task. However, there isn't a significant difference between groups. On this basis the checkers were performing as well as the low-checkers, not showing any particular deficit in performance. The error bars indicate the 95% confidence interval. * Denotes significance at p < 0.05 level.

Analysis methods

Sensor Level Analysis - Cluster Based Permutation tests

The data were processed in a Matlab software environment using the Fieldtrip (Oostenveld et al., 2011) signal processing and analysis toolbox. For ease of data processing the data were down sampled from 1000Hz to 300Hz. Data were low pass filtered with the filter stop at 70Hz and line noise filtered at 50Hz.

The cleaned time series data, were organised into ‘congruent’ and ‘incongruent’ blocks, and by individual participant. The aim was to analyse data during the decision making period, just prior to the participant noting their answer via a keypad. Because the response time was quite variable between and within participants, the data were referenced to the button press. In this way data segments -0.6s to -0.1s before the button response were selected for analysis. The actual data segment selected was longer as it included ‘padding data’ needed for the time-frequency anaylsis. A period of 0.5s duration recorded when the mask was displayed was used a baseline reference period. The resulting data were processed using a multi-taper approach (Oostenveld et al., 2011) to produce time frequency representations of the active and baseline periods, over a frequency band of 2Hz to 30Hz. Using Fieldtrip software functions the data were then baselined by subtracting the average baseline time-frequency data from the active time-frequency data. The data for each participant and each condition were then averaged across trials. These averaged, baselined time-frequency sensor level data were then analysed using false discovery rate (Benjamini and Hochberg, 1995) statistical analysis. The spatial-temporal nature of MEG data, sampling brain activity simultaneously across many time-points and sensor locations, leads to a multiple comparisons problem when conducting statistical comparisons between conditions and participants. Standard statistical procedures such as Bonferroni correction often used to control for type 1 errors (false positives) in pair-wise comparisons would be too strict a criterion if applied to the multiple comparisons required with MEG data. The false discovery rate method instead of setting a threshold to avoid any false positives, controls for a low proportion of false positives. In a multiple comparisons analysis the false discovery rate method avoids type 2 errors (false negatives) with the moderate penalty of allowing a small proportion of type 1 errors (false positives), whereas a Bonferroni correction would prevent type 1 errors at the severe penalty of accepting a high proportion of type 2 errors.

Sensor level analysis was conducted of the time period of interest, -0.6s to 0.1s referenced to the button response, designed to capture attention and executive processing in the period when the participant reaches their decision on whether the trial was ‘congruent’ or ‘incongruent’. The cluster plots (see figure 5-16) show the cortical regions where power differences between trial conditions reached statistical significance ($p<0.05$). In the plots shown the data were averaged over the time period -0.6s to 0.1s and averaged over the frequency band indicated. Individual plots compare power differences between incongruent trials and congruent trial conditions within each cohort.

The ‘checkers’ show significant oscillatory power differences in the theta and beta frequency bands comparing incongruent and congruent trials. While the ‘low-checkers’ engage frontal cortices equally in both conditions, the ‘checkers’ employ significantly higher theta band processing during the ‘incongruent’ trials compared to ‘congruent’ trials. The beta oscillatory power for ‘checkers’ shows the difference in cortical activity between conditions to be more widely distributed. The ‘checkers’, in processing the ‘incongruent’ stimuli engage medial frontal cortex more strongly compared to ‘congruent’ trials, perhaps indicating they need greater effort in cognitive control / executive function to resolve the ‘incongruent’ trials. The data show ‘low-

checkers' generating similar levels of theta power for both trial conditions when deciding on their response to the Stroop task. This suggests 'low-checkers' apply relatively equal levels of theta processing to both conditions, in contrast to the 'checker' cohort who engage greater theta processing in medial frontal cortex to the 'incongruent' condition. In pattern of alpha band power appears to be quite similar comparing 'checker' and 'low-checker' topographical plots, making it difficult to identify a pattern of differences in cortical activity that might be relevant to the experiment and participant performance. In beta band the difference in the distribution of activity comparing trial conditions and cohorts, suggests a more widespread difference in cortical activity for 'checker' participants. The data may suggest that 'checkers' engage fronto-parietal networks differently, depending on the trial condition. The 'low-checker' beta band data does not show this differential engagement.

The aim of this MEG study was to identify cortical structures relevant to deficient cognitive control / executive functioning arising from OCD checking behaviour as indexed by significant differences in cortical power comparing 'checkers' and 'low-checkers'. Source location was conducted in theta (4-6Hz), alpha (10-12Hz) and beta (17-21Hz) bands as these three frequency bands showed significant power differences across conditions and cohorts.

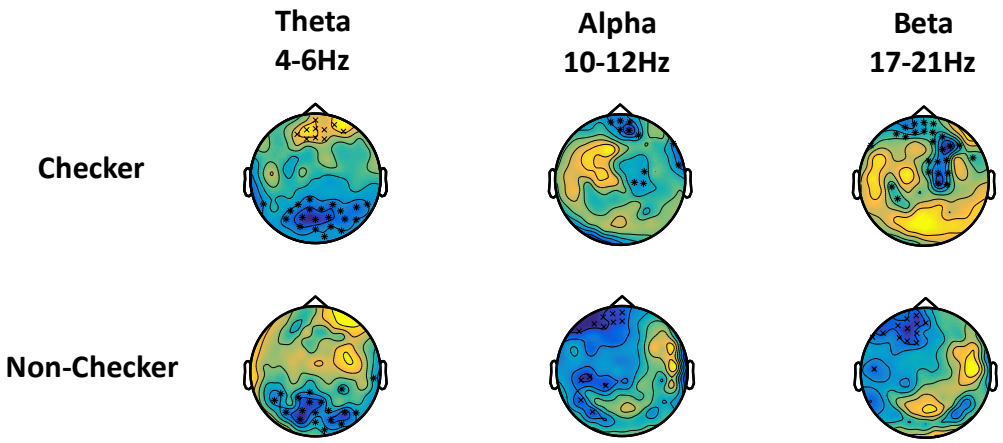


Figure 5-12. *The group averaged differences in cortical oscillatory power, incongruent vs congruent conditions, were statistically analysed using a false discovery rate (FDR) statistical test. The data shown were response locked and show averaged cortical activity during the time 0.5 to 0.1 seconds before participants noted their answer via a button box keypad. In theta band the main contrast difference in the cortical activity comparing cohorts as demonstrated by the cluster plots, checkers show significant power differences over medial frontal cortex, comparing incongruent vs congruent conditions. Checkers display higher theta power during the incongruent trials. Low-checkers show no significant difference (incongruent vs congruent) in theta power over medial frontal cortex. In the beta band checkers show decreased parietal activation compared to low-checkers comparing incongruent vs congruent conditions. The pattern of clusters was similar for checkers and low-checkers in alpha and beta frequency bands. The data are colour coded, with yellow colour indicating areas of increased activity, while blue indicates areas of reduced activity. Data indicated by an Asterix symbol indicate data significance at p<0.05, while a cross symbol indicates data reached significance level of p<0.01.*

Source Level Analysis

Using the same trial level time-frequency representations that led to the sensor level cluster analysis, cortical source reconstruction for each individual, 'congruent' and 'incongruent' condition, was conducted using Dynamical Imaging of Cortical sources (DICS) a frequency domain beamformer method, (Oostenveld et al., 2011).

The active period being -500ms to -100ms before the participant indicated their response by pressing a key on the button pad. The 400ms passive period was taken from the interval in which the fixation cross appeared before onset of the picture stimulus.

The forward model was constructed for each individual using their MRI structural head scan. To facilitate group analysis, each individual's data was normalised by transforming to a common template using the Montreal Neurological Institute (MNI) coordinate system.

The source level data for each condition and individual was averaged across trials using a 'common filter' beamformer approach. The 'common filters' approach is considered a more robust method as source localisations generated with separate filters may be biased by differences in the filter parameters rather than the MEG data. The data were plotted by frequency band, theta (4-6Hz), alpha (10-12Hz) and beta (15-19Hz)

The following figures show the results that reached significance ($p<0.05$), firstly by group differences and then by within-group differences (incongruent-congruent) to show the factors driving the differences between-groups (Checker – Low-checker).

Theta Band (4-6Hz)

In theta band there was greater activation identified in supplementary motor area and frontal eye fields for the Checker cohort. Posterior cingulate cortex and mid-cingulate cortex / posterior portion of ACC. The Checkers also show increased activity of right orbital frontal cortex compared to the Low-checkers as well as increased activity of the Calcerine/Cuneus areas. The Checkers show a relative decrease in activation of the superior parietal lobe and superior temporal gyrus. Significant differences in activation were seen in basal ganglia, in region of Insula, Putamen and Pallidum.

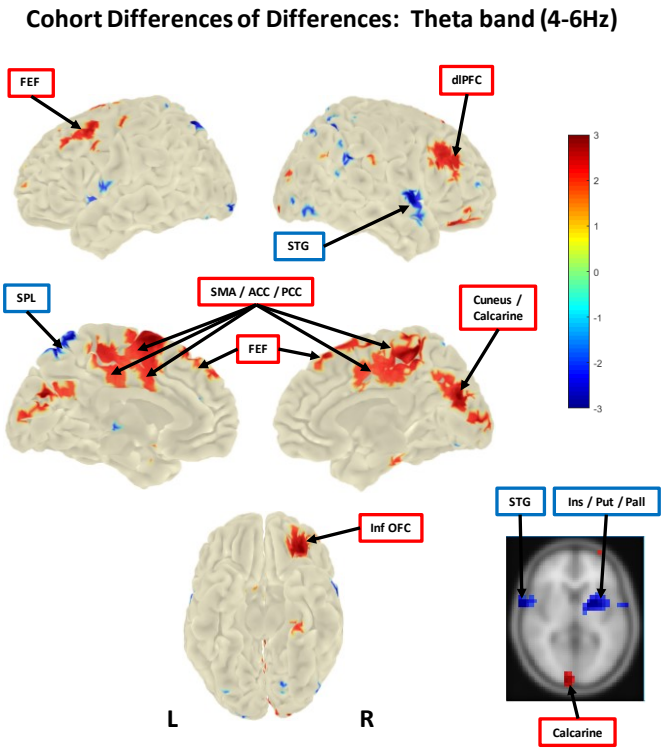


Figure 5-13. Theta band group differences (Checker vs Low-checker, Unresolvable vs Resolvable) show preferential activation of brain regions associated with endogenous attention (inferior parietal lobe, superior temporal sulcus, ACC) and target processing (visual cortex, superior parietal lobe, dorsolateral prefrontal cortex, ACC). ACC=anterior cingulate cortex; dlPFC=dorso-lateral prefrontal cortex; FEF=frontal eye fields; Inf OFC=Inferior orbital frontal cortex; Ins=Insular; Pall=Globus pallidus; PCC=posterior cingulate cortex; Put=Putamen; SPL=Superiour parietal lobe; SMA=Supplementary motor area; SPL=Superiour parietal lobe; STG=Superior temporal gyrus. The colour scale represents z-score statistical values. Colours yellow and red indicate areas of significantly increased brain activity, whereas colours blue indicate areas of significantly reduced activity.

Although the group differences show many areas of increased activation, this is a relative measure and as seen below in figure 5-19, may be the result of a reduction in activation in specific brain regions of the Low-checkers, showing in the group differences as a relative increase.

The activity of the ACC highlighted in figure 5-18, thought to be important in resolving Stroop stimuli (Pardo et al., 1990, Galer et al., 2015), and to play a prominent role in OCD checking behaviour (Ciesielski et al., 2011), was here, the result of a power decrease in the Low-checker cohort (incongruent vs congruent) that appears as an increase in power at the group level (Checker vs Low-checker). No significant difference in ACC activation was found in the Checker cohort, comparing between congruent and incongruent conditions. Similarly the increased activation of dlPFC and Cuneus seen in the group differences above, was the result of a decrease in the Low-checker data.

The Checkers reveal increased activation of SMA and FEF, whereas the Low-checkers show no differences in this region associated with visual search related eye movements. Checkers also

show decreased activity in superior temporal gyrus. An increase in activation of superior parietal lobe was identified in Low-checkers, but no differences were found in the Checker cohort data.

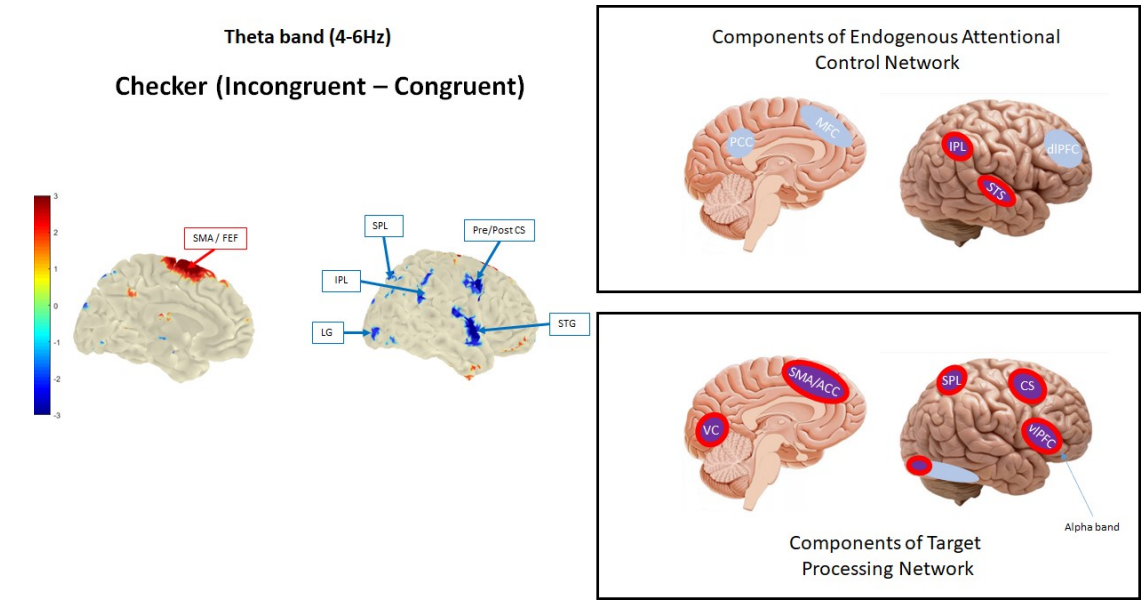


Figure 5-14. At the group level the significant checker power in SMA/FEF, SPL and visual cortex are signatures consistent with brain regions associated with target processing networks. ACC=anterior cingulate cortex; CS=Central sulcus; dlPFC=dorsolateral prefrontal cortex; FEF=frontal eye fields; IPL=Inferior parietal lobe; LG=Lateral geniculate nuclei; PCC=posterior cingulate cortex; SMA=Supplementary motor area; SPL=Superior parietal lobe; STG=Superior temporal gyrus. The colour scale represents z-score statistical values. Colours yellow and red indicate areas of significantly increased brain activity, whereas colours blue indicate areas of significantly reduced activity.

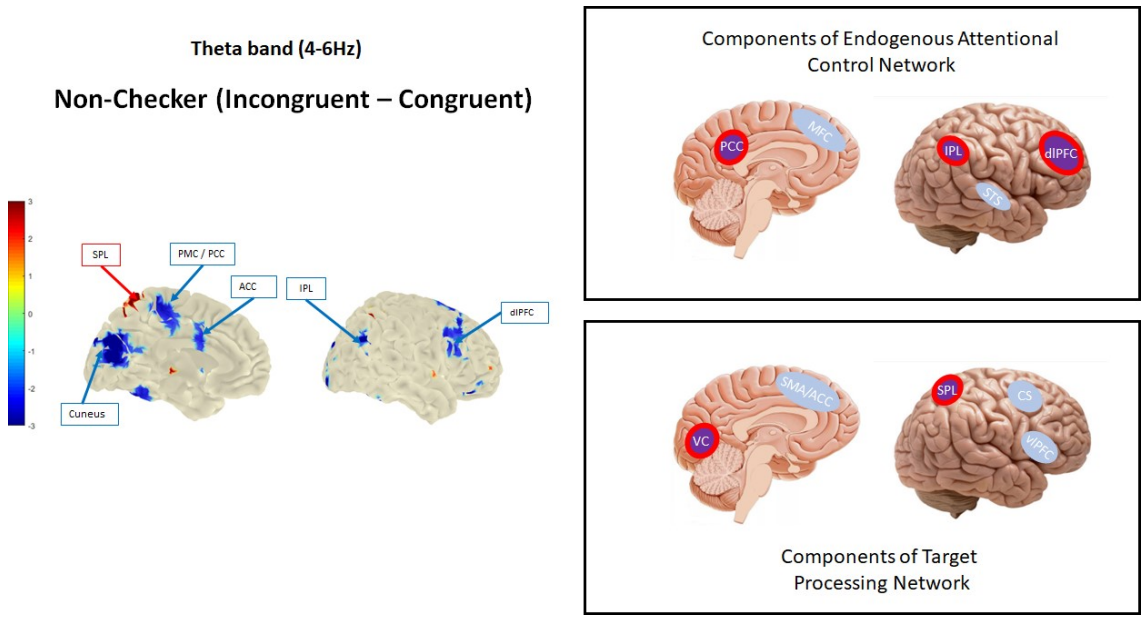


Figure 5-15 At the group level the significant low-checker power differences located in PCC, ACC, dlPFC, SPL and visual cortex are consistent with brain regions associated with endogenous

attentional control networks. ACC=anterior cingulate cortex; CS=Central sulcus; dlPFC=dorsolateral prefrontal cortex; FEF=frontal eye fields; IPL=Inferior parietal lobe; LG=Lateral geniculate nuclei; PCC=posterior cingulate cortex; SMA=Supplementary motor area; SPL=Superior parietal lobe; STG=Superior temporal gyrus. The colour scale represents z-score statistical values. Colours yellow and red indicate areas of significantly increased brain activity, whereas colours blue indicate areas of significantly reduced activity.

The data presented in figures 5-14 and 5-15, shows patterns of theta band activity differences between incongruent and congruent conditions for checkers and low-checkers and is compared with brain regions implicated in networks (Hopfinger et al., 2000) (Corbetta and Shulman, 2002) for top-down attentional control and target processing. While the data revealed that both checkers and low-checkers display significant activity in brain areas associated with nodes of both top-down attentional control and target processing networks, the pattern of activity in checkers shows more elements of the target processing network, while the brain activity of the low-checkers appears to match better with the network for top-down attentional control.

Alpha Band (10-12Hz)

In alpha the group differences show involvement of parietal lobe, with increased power within inferior parietal lobe and decreased power within superior parietal lobe. Increased alpha power was shown in posterior portion of right orbital frontal cortex and decreased power in medial orbital cortex.

In deeper brain structures associated with limbic circuit, increased alpha power was seen in the region of right basal ganglia, putamen, caudate nucleus and thalamus, and in the area of the left Hippocampus.

A broad area of increased power was seen in the region of lingual gyrus and calcerine.

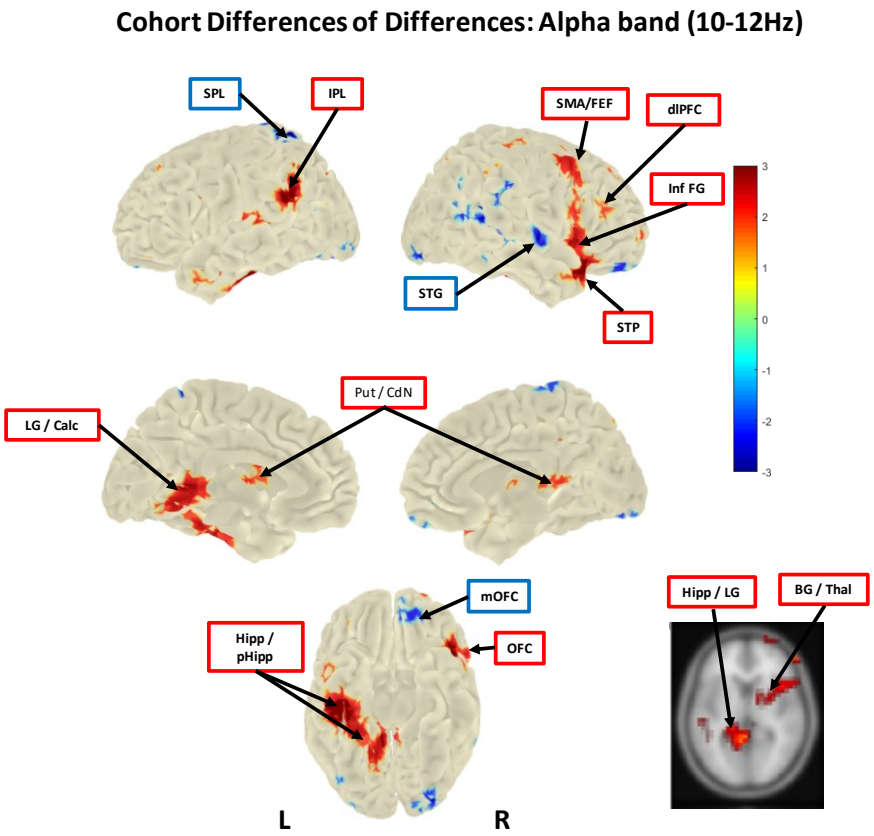


Figure 5-16. The pattern of activity in hippocampus, basal ganglia and thalamus could reflect a heightened emotional response in checkers to the visual stimuli with low-checkers remaining neutral in their response. Calc=Calcerine; CdN=Caudate nucleus; dlPFC=dorsolateral prefrontal cortex; FEF=frontal eye fields; Hipp=Hippocampus; Inf FGL=Inferior frontal gyrus; LG=Lateral geniculate nuclei; mOFC=Medial orbital frontal cortex; OFC=Orbital frontal cortex; PCC=posterior cingulate cortex; pHipp=Parahippocampus; Put=Putamen; SMA=Supplementary motor area; SPL=Superior parietal lobe; STG=Superior temporal gyrus; STG=Superior temporal pole; Thal=thalamus. The colour scale represents z-score statistical values. Colours yellow and red indicate areas of significantly increased brain activity, whereas colours blue indicate areas of significantly reduced activity.

At the group level, the areas of significant power difference were different between the two cohorts. For Checkers increased power was found in motor cortex, inferior frontal gyrus, calcarine and region of thalamus/basal ganglia. Decreased power in area of superior temporal lobe and orbital frontal cortex.

Low-checkers showed decreased power in right supplementary motor area and frontal eye fields, right inferior frontal gyrus and right temporal pole. Increased alpha power was recorded in superior parietal lobe.

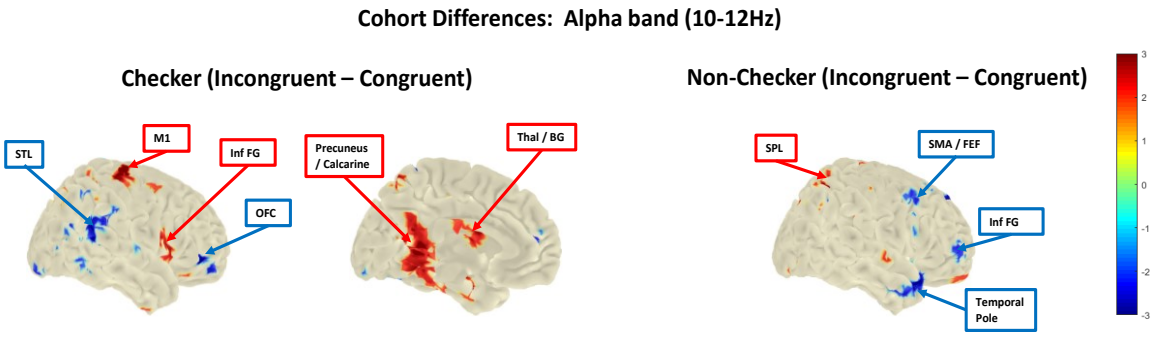


Figure 5-17. Power differences in basal ganglia, thalamus and orbitofrontal cortex suggests checkers are engaging limbic circuit consistent with OCD checking behaviour. BG=basal ganglia; FEF=frontal eye fields; Inf FG=Inferior frontal gyrus; M1=Primary motor cortex; OFC=Inferior orbital frontal cortex; SMA=Supplementary motor area; SPL=Superior parietal lobe; STL=Superior temporal lobe; Thal=thalamus. The colour scale represents z-score statistical values. Colours yellow and red indicate areas of significantly increased brain activity, whereas colours blue indicate areas of significantly reduced activity.

Beta Band (15-19Hz)

In the lower beta frequency band, comparing between cohorts results relatively higher beta power was seen for the Low-checker group, in right superior temporal gyrus, left dlPFC and medially in area of frontal eye fields and supplementary motor area. Decreased power was seen in superior parietal lobe and left medial temporal gyrus. In deeper brain areas, significantly decreased power was found in right caudate nucleus, insula and medial temporal gyrus.

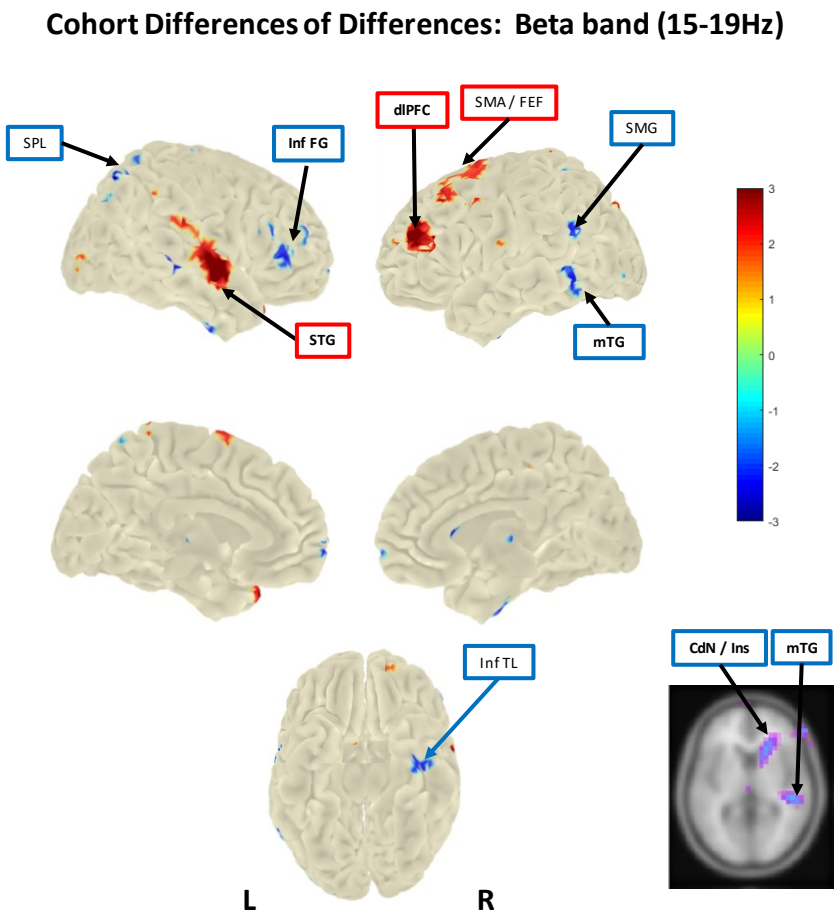


Figure 5-18. The power difference data in beta band are sufficient clear to identify specific networks of activity, but are consistent with activation of attentional control and target processing networks. CdN=Caudate nucleus; dlPFC=dorsolateral prefrontal cortex; FEF=frontal eye fields; Inf FG=Inferior frontal gyrus; Inf TL=Inferior temporal lobe; Ins=Insular; MTG=Medial temporal gyrus; SMA=Supplementary motor area; SMG=Supramarginal gyrus; SPL=Superior parietal lobe; STG=Superior temporal gyrus. The colour scale represents z-score statistical values. Colours yellow and red indicate areas of significantly increased brain activity, whereas colours blue indicate areas of significantly reduced activity.

Looking at the results at the cohort level it can be inferred that the increased power observed at the right superior temporal gyrus in the group differences was driven by a power increase observed in the Checker cohort, whereas the power increase in the group differences in left dlPFC was dominated by a power decrease over the left dlPFC in the Low-checker results.

At the group level, the Checkers show decreased power at the region of the right dlPFC / inferior frontal gyrus, but the result was not strong enough to show through into the differences between groups.

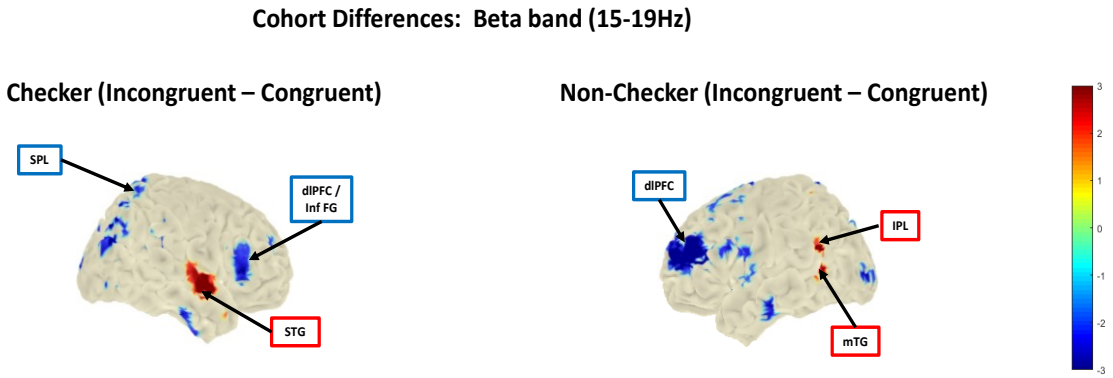


Figure 5-19. The cohort differences do not identify many brain regions from which to identify the network processing. However, preferential activation of dlPFC and STS is associated with attentional control networks and consistent with the expected behaviour in this task. dlPFC=dorsolateral prefrontal cortex; Inf FG=Inferior frontal gyrus; IPL=Inferior parietal lobe; mTG=Medial temporal gyrus; SPL=Superior parietal lobe; STG=Superior temporal gyrus. The colour scale represents z-score statistical values. Colours yellow and red indicate areas of significantly increased brain activity, whereas colours blue indicate areas of significantly reduced activity.

5.3.4 Discussion

At n=14, and n=16, the sizes of the two groups recruited into this study was relatively small for a MEG study. Increasing the participant numbers, by a relatively small number, for example, to n=20 in each group, would be expected to have a noticeable and beneficial impact on the robustness of the results obtained. In this context of relatively low participant numbers, the emphasis that can be placed on the beamformer localisation and identification of deeper brain sources such as hippocampus and basal ganglia must be weighed carefully. However, the localisation of significant power in these deeper areas was consistent with the results reported in Chapter 3, Working Memory MEG study.

Possibly the most notable result in these MEG data was the absence of a strong power signature associated with processing in ACC as might be expected in a Stroop task. Although the Stroop task is often associated with ACC activation, increases in cortical power have not always been found. There are a few possible reasons that might explain why no significant activity in ACC was found in this study in the frequency bands investigated. The trials were counterbalanced so that state and word trials were interleaved meaning ACC was involved in both congruent and incongruent trials. Recording brain signals in the MEG scanner requires the participant to be very still and relaxed. The Stroop effect relies in part on the immediacy of the participant's response, not thinking about the conflict but providing the answer quickly. This active participation is more difficult to accomplish in the MEG scanner, without adversely affecting the data collection. Compounding the problem, sitting still in the MEG scanner is quite tiring and the paradigm was quite long and repetitive. Together these experimental issues may have slowed

the participants and reduced the vividness of the ACC response. However, these MEG results were not entirely surprising when considered alongside those obtained in the Stroop – TMS study, reported in Chapter 7.

Although the anticipated activation of ACC was not observed, power changes in areas that might be signatures of attention networks were seen. Elements of frontoparietal networks (Meyer et al., 2018, Hopfinger et al., 2000), for example FEF, SMA, SPL, dlPFC, which have been identified as involved in directed attention processes were also found within the MEG data. This can be interpreted as showing the two cohorts were treating the kitchen appliance imagery differently. It was expected that the OCD checkers would find the imagery more relevant and be compelled to apply more attention resources to these stimuli. The theta band activity shown in figures 5-14 and 5-15 could be interpreted to show this. While the patterns of brain activity appear to show both checkers and low-checkers engaging elements of top-down attentional control and target processing networks, the checkers' brain activity show more strongly the nodes of the target processing network being engaged. This suggests the features of the stimuli that are salient to OCD checker symptomology caused the checkers to engage the target processing network more strongly.

Across the frequency bands investigated (theta, alpha and low beta), elements of the limbic system displayed significantly different levels of activity across conditions and cohorts. This result supports the hypothesis (Krack et al., 2010) that a cortical loop involving ACC, frontal cortices and basal ganglia, stimulated by OCD salient images is important in OCD behavioural responses. The emotional response in the OCD cohort may be 'threat', which could drive the need to deploy more attention resources to monitor the image they find threatening.

Low-checkers show congruence effect in theta processing in dlPFC, whereas Checkers did not. For the low-checkers, the reduced dlPFC theta power incongruent vs congruent is counter intuitive if increased theta power is expected on incongruent trials, here more theta processing was applied to the congruent condition, when activation of fewer attention resources might be expected. The absence of such a congruence effect in the Checker data may suggest executive control was not as well applied, resulting congruent and incongruent trials being given the same level of attention resources, indicating a lack of inhibition, leading to inefficient processing and poorer behavioural performance.

5.4 TMS and Pictorial Stroop Task

5.4.1 Introduction

The Stroop task measures the ability with which one is able to attend to one dimension while suppressing the irrelevant dimension. The ACC is a component of attention control networks (Ridderinkhof et al., 2004b, Hopfinger et al., 2000) crucial to the efficient and successful processing of Stroop stimuli. OCD subjects tend to have difficulty inhibiting stimuli (Van den Heuvel et al., 2005) that are salient to their obsession. The ACC is thought to play an important

role in mitigating the processing conflict (Botvinick et al., 2004, Cohen, 2014) brought on by the Stroop effect. Deficient ACC processing and structural brain differences in OCD (Ciesielski et al., 2011, Piras et al., 2015) are linked with OCD symptomology.

In this context, this study made a further attempt at stimulating ACC with TMS in effort to better understand the role of ACC in attention control and checking behaviour. The TMS protocol used in this study differed significantly from that used in the rTMS WM study reported in chapter 4. In this study a double-cone TMS coil was used to stimulate mFC / ACC with a double pulse. The double-cone coil is of a different shape to the figure eight alpha coil used in the rTMS WM study, and was designed specifically to stimulate deeper areas within the brain, such as the ACC. The double pulse has a disrupting effect on the cortical processing in the area stimulated by a process of inhibiting cortical excitability (Rossi et al., 2009, Groppa et al., 2012) for a few 100 ms following each pulse. The pulses were timed to occur when participants were processing the Stroop stimuli. For OCD participants who may over engage conflict processing associated with ACC, the TMS may have a beneficial effect on their response times.

5.4.2 Method: Experiment 3. Pictorial Stroop with dual pulse TMS

Participants

Participants were recruited from the student and staff population at Aston University. The participant group comprising mainly of psychology undergraduate students.

Participants were primarily recruited on their VOCI checking sub-scale score were assigned to one of two groups, checkers (n=16) and low-checkers (n=22). The checking cohort had VOCI scores ranging from 7 to 18, and the low-checker scores ranged from 0 to 3. Participants with VOCI scores of 4, 5 or 6 were excluded. Participants were medication free at the time of testing. As well as the VOCI questionnaire participants completed a TMS safety questionnaire to screen out those that may not receive TMS safely.

Pictorial Stroop Task

The Pictorial Stroop experiment, programmed using E-Prime, was presented as a computer based task in which a series of instructions and pictures of small kitchen electrical appliances were displayed on an LCD computer monitor screen. The kitchen appliance imagery was taken from the same image set used in the MEG working memory task in which it was found the ACC cortical power differed between checking and low-checking participant groups.

Participants were tasked either ‘Name the State’ or ‘Name the Word’, meaning the power state of the appliance, whether ‘ON’ or ‘OFF’, or the word superimposed on the image, again being ‘ON’ or ‘OFF’.

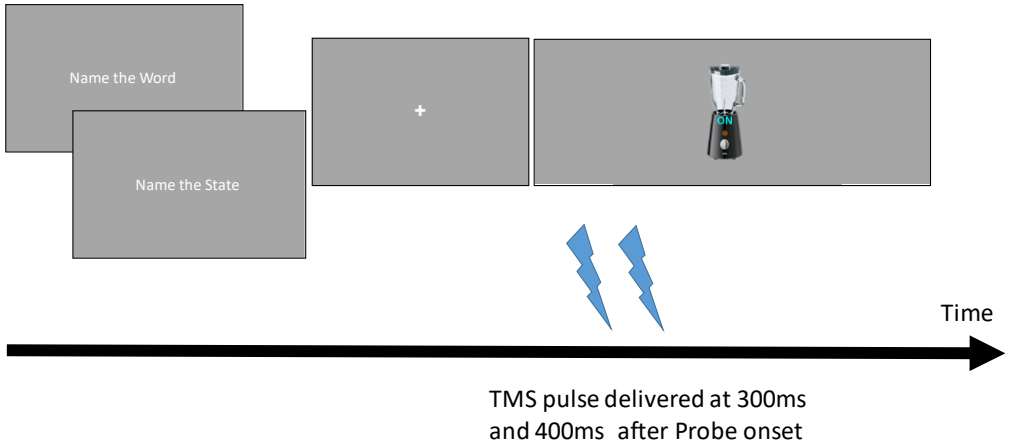


Figure 5-20. The timeline of each trail, showing timing of TMS pulses.

The power light in the picture of the electrical appliance was either dull red (indicating its state was powered 'OFF') or bright red (indicating its state was powered 'ON'). This was the state referred to by the instruction 'Name the State'. Within the same picture there was printed a word, either 'ON' or 'OFF'. This was the word referred to by the instruction 'Name the Word'.

Following the displayed instruction to either 'Name the State' or 'Name the Word' and the presentation of the picture, participants responded by speaking their answer, either 'ON' or 'OFF', into a microphone. The answer was recorded in a '.wav' file onto computer. The recording was initiated by the E-Prime computer program when the picture of the electrical appliance appeared. A double pulse TMS stimulation was applied at 300ms and 400ms after the appearance of the electrical appliance. The stimulation sites were the anterior cingulate cortex (ACC) and a control site (CTRL), for which the scalp stimulation site (Hayward et al., 2004) was found by locating a position 4cm posterior to motor cortex.

The response timeout was 4000ms. To speed the study for the participant and help maintain participant engagement, once the response had been spoken, the experimenter stopped the recording by means of a wireless Bluetooth control device. This allowed the experiment to progress to the next trial.

The primary metric for the experiment was reaction time on correct response trials. Participants were instructed to be accurate in their responses but also to be as fast as possible. To aid measurement of reaction times, participants were asked to make their responses crisp and definitive so there was no doubt about the onset of the response or whether the response was intended to be 'ON' or 'OFF'. Feedback on the accuracy of each trial was provided in the form of a sound signal played through earphones. The experimenter also provided feedback and encouragement.

TMS protocol

The ACC is a relatively deep structure to target with TMS. The method employed here was adapted from a previous study (Hayward et al., 2004) in which the ACC was stimulated at 90%

of the active motor threshold (AMT) during a number Stroop task. A dual pulse TMS protocol was used, in which a TMS pulse was delivered at 300ms and another TMS pulse at 400ms after Stroop probe onset. Single pulses and rTMS at frequencies of 1Hz or lower, have an inhibitory effect on cortical processing (Rossi et al., 2009) and was in this study designed to interrupt ACC processing for approximately 200ms after the first pulse was delivered. Whereas in the rTMS WM study the stimulation would only have effect (Hanslmayr et al., 2014, Thut et al., 2011b) if the stimulation frequency matched that of the underlying neuronal population.

The TMS stimuli were delivered using a Magstim Super Rapid2 biphasic pulse generator combined with a double cone coil. This type of TMS coil with the coil arms shaped to cup around the head was designed specifically for stimulating deeper structures by producing a broader Magnetic field that penetrates deeper into the head. Because the ACC is located deeper within the brain than the hand motor area, it would be inappropriate to use a finger MEP derived threshold to set the intensity for stimulating the ACC. For this experiment a visible TMS induced toe movement was used to set the stimulation threshold. The toe motor area maps onto a part of the cortex that is at a similar depth as the ACC and thus provides a guide to the TMS intensity required to stimulate the ACC.

The location of the stimulation sites for ACC and CTRL were determined for each participant using the international 10-20 measurement system commonly used when applying EEG electrodes to the scalp, and following the method described by (Hayward et al., 2004). The ACC stimulation site was at a point 1.5cm anterior to the 1/3 distance nasion to inion. The PAC stimulation site was located 4cm posterior to the motor cortex. As the stimulation sites were located using the international 10-20 measurement system rather than the Brainsight neuronavigation system, it was not necessary to obtain MRI head scans for each participant. The Brainsight neuronavigation system was used however, to record the ACC and CTRL locations at the beginning of an experiment so that the neuronavigation system could be used to guide the coil back to the exact same locations when changing between stimulation site when starting the next measurement block.

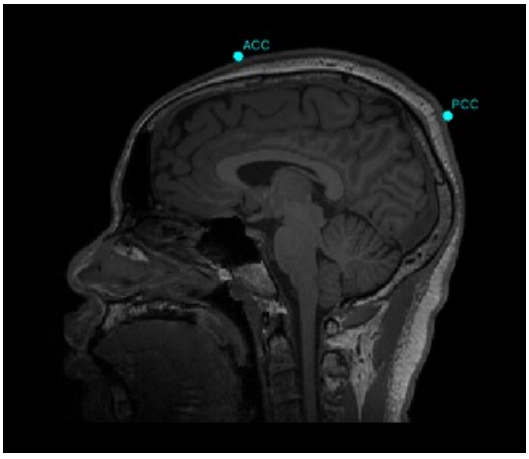


***Figure 5-21**. Brainsight neuronavigation system derived image showing location of ACC and control site target.*

Determination of stimulation intensity

The location of the motor cortex was found by holding the double cone coil approximately 1cm to one side of the midline sagittal plane so that the central part of the magnetic field covered the foot area of the motor cortex of one hemisphere rather than cerebral spinal fluid in the inter-hemisphere space between the two hemispheres of the brain. Starting posterior to the motor cortex and at a low stimulation intensity, working forwards in small increments of a few millimetres to a point anterior of the motor cortex, a stimulation was delivered at each step increment. Guided by what the participant reported feeling, for example nothing or a sensation in the leg or foot, the location of the foot motor area was determined.

During this procedure the participant had removed their shoes and socks so that the slightest TMS induced movements could be observed. The participant was seated in a chair with their legs relaxed and flexed at the knee, with their feet resting on a platform, so that their feet were raised 15cm off the ground. Their feet were resting on the backs of their heels so that their toes were relaxed and pointing upwards. In this arrangement, with feet and legs relaxed, a resting motor threshold would be obtained.

Using this procedure, once the foot area of the motor cortex was located, before each stimulation the participant was instructed to 'tense their toes' so that a TMS movement would be a measure of the active motor threshold. On the instruction 'tense toes' participants would curl their toes upwards by approximately 5mm and with feet still, hold that position for a couple of seconds after the TMS pulse had been delivered. After the TMS pulse, participants relaxed their toes. The intensity of the stimulation was increased until a visible movement of the toe or foot was obtained. The coil position was optimised by finding the position where the lowest stimulation intensity would produce a toe movement. The active motor threshold being the lowest TMS stimulator level at which a visible toe movement was observed. The stimulation intensity used in the experiment was set at 90% of the active motor threshold (AMT).

For a small number of participants, a visible movement of the foot or toe was not detected and a stimulation threshold could not be determined. These participants were declined from the study and took no further part in the Stroop task.

TMS Experiment procedure

After locating the foot area of the motor cortex and establishing the AMT, using a tape measure a point 4cm posterior to the motor cortex was located for the CTRL and the coil position at that point saved in Brainsight neuronavigation system. Similarly, the coil location at the ACC point was saved.

During the experiment the double cone coil was held in position using a lockable the arm attached to the framework on which the participant chin rest was fixed. Normally a figure of eight coil was held in position by the experimenter so that its position can be adjusted to compensate for any movements of the participant's head. The double cone coil, positioned over the central vertex of

the head with the handle pointed upwards was too heavy and too high to be continuously held in position by the experimenter. Resting on top of the head, along the central vertex, the double cone coil tended not to exert pressure to cause the participant's head to move away from the initial position. In that sense the double cone coil had a neutral effect on the participant's head position. The Brainsight tracking system monitors the position of the coil and the participant's head in three-dimensional space, reporting distance moved from the starting position. Using this facility, it was possible to monitor the position of the coil on the participant's head to ensure the coil remained in position to stimulate the required area. A position error of up to 5mm was accepted.

Analysis Methods
Response Time Measurement

The participants' verbal responses were recorded and stored as .wav files. The response time and response ('ON' or 'OFF') data were recovered manually by listening to each recorded response. To aid this process and to reduce transcription errors, an analysis tool was written using Matlab. As well as replaying the .wav file, the analysis tool showed the time domain and time-frequency spectrogram representation of the verbal response. Zooming in on the audio file, the tool enabled short sections of the response to be played, enabling the onset of speech to be identified. The start of speech was located on the time domain representation and the corresponding time automatically measured. The participant's response, 'ON' or 'OFF' was noted by selecting the appropriate check box on the analysis tool. For trials where no response was given or the response unclear, the trial was marked for rejection. The response times, responses and trial numbers were saved as text files to be combined with the experiment data recorded by E-Prime.

5.4.3 Results

Pre-processing of the raw data revealed that four low-checker participants were unusually quick in their responses, with most responses occurring before the time of the TMS stimulations. These data were excluded from the analysis as these responses would be independent of the TMS condition. Outlier data were pruned from the datasets by excluded responses times that were longer than two standard deviations of the population mean, i.e. response times longer than 1250ms.

With the remaining datasets low-checker (n=18) and checker (n=16) a four-way mixed ANOVA was conducted. The within subjects factors were stimulation site (ACC and CNTRL), stimulation (TMS and sham), congruency (congruent and incongruent) and group (checker and low-checker). A significant interaction was observed between TMS condition and Stimulation site, incongruent versus congruent stimuli, ($F(1,32) = 4.86$, $p=0.035$). A Stroop effect, reaction times being longer for incongruent than for congruent stimuli was seen when TMS sham and active

was applied over the control site, and for sham TMS over ACC, but the Stroop effect was diminished with TMS applied over ACC.

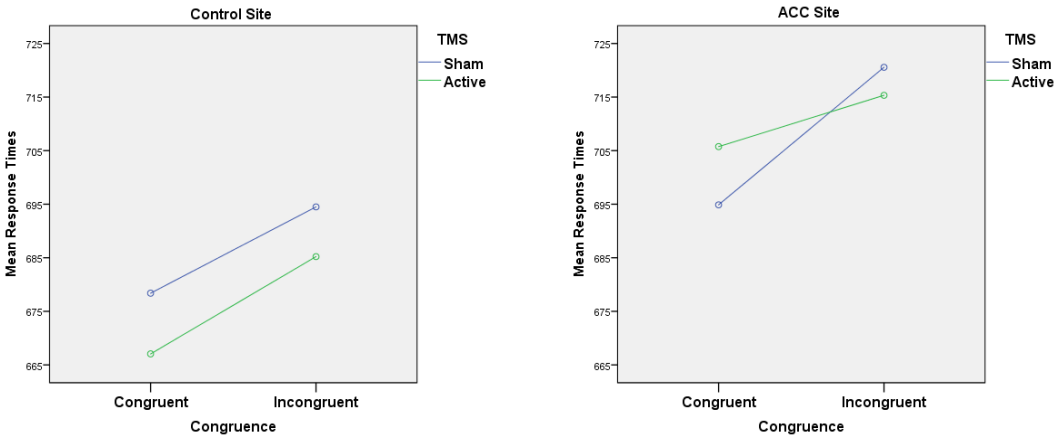


Figure 5-22. A significant Interaction TMS and congruency was found, indicating an effect of stimulating the ACC on task performance.

An interaction between TMS x Group x Congruency, ($F(1,32) = 4.48$, $p = 0.042$) was found. Taking response times across the two stimulation sites, checker participant response times were unaffected by TMS, showing a Stroop effect difference between congruent and incongruent conditions. Low-checkers showed similar response times to checkers on congruent conditions but a beneficial effect of TMS on incongruent conditions with faster response times compared to sham TMS.

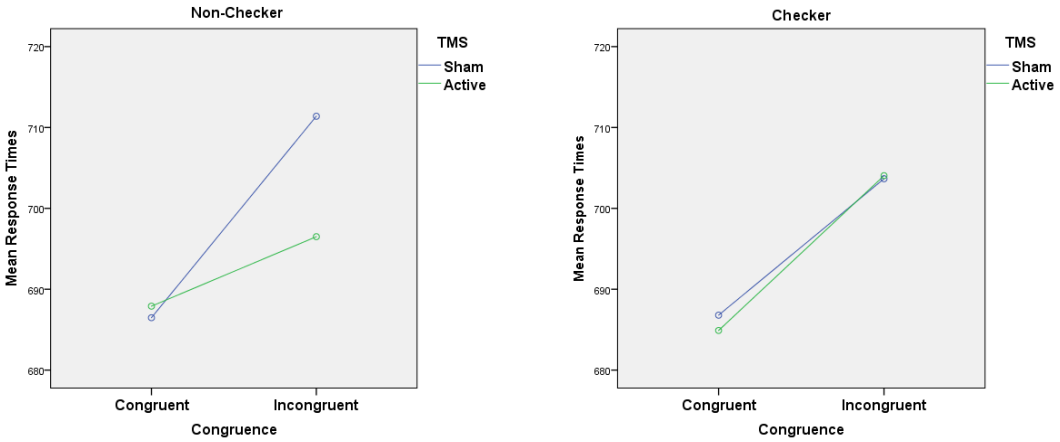


Figure 5-23. An interaction between Group and TMS revealed that active TMS had a facilatory effect for low-checkers only, improving their response time on incongruent trials.

5.4.4 Discussion

The results in figure 5-23 show stimulating with dual pulse TMS diminishes the Stroop effect by reducing response times to incongruent condition stimuli for low-checkers. This accords with the literature which highlights the role of ACC involvement in selective attention and processing

conflicting information streams, such as is required when completing a Stroop task. This effect of stimulation site did not reveal an interaction with the cohort groups. However, there was no effect of TMS stimulation on response times for checkers.

It is interesting that low-checkers show an effect of TMS whereas the non-checkers do not. If the experiment apparatus performed equally across the groups, the different TMS outcomes on incongruent trials could suggest that low-checkers are processing the incongruent trials in a different way, perhaps recruiting additional brain structures to the task that were not influenced by the TMS.

The small influence of TMS on ACC processing and reactions times was not the anticipated result, expecting checkers to have a greater involvement of ACC and hence a greater effect on reaction times due to TMS induced inhibition. However, the results obtained in the MEG experiment reported in Chapter 5 may offer some insight. The MEG data suggest the ACC may be activated to differing degrees comparing checker and low-checker cohorts. The MEG data did not reveal significant activity within the ACC or CTRL sites in this Stroop task for the checker cohort when comparing congruent and incongruent conditions. Significant activity was recorded in the area of mid cingulate cortex and posterior ACC for the low-checkers. The ACC and CTRL being the chosen sites for the TMS study, may explain why in figure 5-13 above, an effect of TMS was observed in low-checkers rather than checkers. This result may indicate that parts of the network involved in Stroop processing, other than ACC and CTRL have a more dominant effect in Stroop processing and reaction times for the Checker cohort.

An interaction between TMS*cohort*congruence was found, but contrary to the starting hypothesis, the checker cohort, expected to engage the ACC more actively in this task, gained no benefit from TMS. The low-checker cohort however, did show a beneficial effect of TMS in that their response times for incongruent conditions were faster with active TMS compared to sham. A TMS-ACC effected reduction in response times for incongruent trials was also found by Hayward et al., 2003.

In the role of the ACC acting in the direction of attention to relevant information in the processing of conflicting information streams, a disruption of this process by TMS might be expected to lead to longer response times. Disrupting ACC processing may lead to attentional processing resources not being engaged, thereby reducing response times

Group differences in TMS response times may arise from trait behavioural differences between the groups. The low-checkers generally responding more quickly than checkers, will on average be processing the Stroop stimuli earlier in time. It was possible the TMS pulses were occurring at the wrong time, too late, to show an effect on ACC processing with the checker group. Single pulse TMS has a transient inhibitory effect lasting approximately between 30ms and 100ms after the pulse was delivered. The duration of inhibition depends on a number of factors, pulse

intensity being one. With TMS pulses delivered at 300ms and 400ms after stimulus presentation, and considering the moderately low TMS intensity employed, the window in which TMS was likely to be effective in inhibiting cortical processing may reasonably range from approximately 300ms to 450ms. The problem of ensuring TMS coincides with the processing of interest can be resolved by increasing pulse intensity and the number of pulses delivered to broaden the temporal window of influence. Unfortunately, this will increase the amount of peripheral nerve activation, which was uncomfortable for the participant and a common side effect when using the double-cone coil. As well as being poorly tolerated, painful TMS may have add adverse and difficult to predict behavioural effects to the experiment, masking any direct effects the TMS may have on cortical processing.

The choice of control site, 4cm posterior to motor cortex, was in part guided by (Hayward et al., 2003) a previous TMS-Stroop experiment, but also practical considerations of where else the coil may be positioned to avoid stimulating areas involved in processing the task. The wide angled double-cone coil is quite broad in its focus compared to a Figure8 coil and it may not be possible to position the double-cone coil in a true control site so that it has no influence on the experiment. figure 5-13, the interaction between TMS and Site, shows that unlike stimulation of ACC, the Control site does not change the direction of response times, incongruent were always slower than congruent responses, but that responses under active TMS were faster than sham. This indicates the Control site was involved in processing the Stroop stimuli and does not provide an optimal control against which to compare ACC. Located 4cm posterior to motor cortex, the double-cone coil was likely to influence parietal cortex and deeper within the brain, the posterior cingulate cortex. Both structures are implicated in processing of pictorial stimuli, but their effect on Stroop processing at the time of TMS pulses requires further investigation to resolve.

6 Investigating Exogenous Attention via Inhibition of Return task and rTMS

6.1 Introduction

Part of the symptomology of obsessive-compulsive disorder (OCD) is that sufferers experience uncontrolled intrusive thoughts which are thought to result from deficient inhibitory processes (Lehnen and Pietrowsky, 2015). A number of experiment paradigms have been developed to explore response inhibition, of which one is 'Inhibition of Return' (IOR), (Posner et al., 2007).

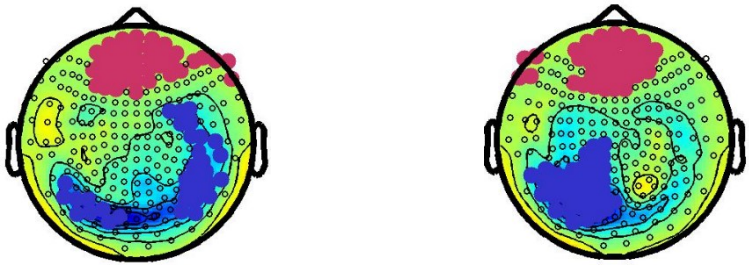
Typically, an IOR paradigm consists of presenting two stimuli in opposite peripheral visual fields, with a 'cue' briefly highlighting one of the peripheral locations. Following a short interval (typically between 400 and 1000ms) a 'target' stimulus is presented at one of the peripheral locations. When the 'cue' is not predictive of the 'target' location (an irrelevant cue) the IOR effect may be exhibited via exogenous attention processes and is commonly measured in the response time taken to indication at which peripheral location the 'target' appeared. When the cue-target onset asynchrony (CTOA) is less than 200-300ms, responses to valid cued targets is faster than for invalid cued targets. Under IOR conditions, typically when CTOA is greater than 300ms, (Losier and Klein, 2001), response times for trials in which 'target' and 'cue' are collocated (valid trials) is slower compared to trials in which 'target' and 'cue' appear in different peripheral locations (invalid trials). IOR is an inhibitory process by which attention is biased away from previously attended locations and objects, towards novel locations and objects. Impaired IOR may result when a subject perseverates on previously attended locations or objects. Perseveration is a feature of OCD behaviour.

Results of IOR experiments conducted with OCD participants has been mixed, for example Nelson et al. (1993) found no IOR effect for right visual targets and decreased IOR for left visual targets. Lehnen and Pietrowsky (2015) found IOR not to be generally diminished in OCD patients but dependent on the visual hemi-field of the stimulus. Moritz and von Muhlenen (2005) found OCD patients to show a similar pattern of IOR as healthy controls. Similarly Abramovitch et al. (2015), using a go/no go response inhibition paradigm found no statistical difference between sub-clinical obsessive compulsive participants and the matched controls but did report reduced response inhibition in OCD subjects. Harkin and Kessler (2012) report decreased IOR with OCD participants when using a paradigm with OCD symptom salient stimuli but suggest this was not a general deficit in IOR but rather a 'disengage deficit' when attention captured by the salient stimuli. The emotional relevance of a stimulus (Brosch et al., 2011) is an important feature influencing unconscious attention mechanisms that may be modulated by internal states or traits. The amygdala, involved in processing emotional information is thought to modulate the processing of incoming sensory stimuli through feedback to visual cortex and biasing signals to fronto-parietal attention regions (Pourtois et al., 2005).

Anxious individuals show vigilance (Muller and Roberts, 2005b) for threatening stimuli, directing attention towards the threat location and responding faster to targets presented there, whereas

control subjects tend to direct attention away from the threat information. Similar behaviour has been found in OCD subjects (Amir et al., 2009) showing attentional bias towards OCD threatening word stimuli compared to neutral words. The attentional bias was found to correlate with OCD symptom severity. Employing an eye tracking experiment, (Bradley et al., 2016), found that OCD subjects did not attend to OCD relevant stimuli any faster than control subjects, but once attention was captured by the threat stimuli, OCD subjects paid more attention to the OCD salient stimuli. Rather than a vigilance bias, (Bradley et al., 2016), found OCD subjects exhibited an attention maintenance or delayed disengagement bias that correlated with OCD symptom severity. In this experiment, ecologically valid stimuli comprising pictures of kitchen electrical appliances, relevant to OCD checking behaviour were used (Harkin et al., 2012). The irrelevant cue was a power light on the appliance picture briefly flashing red. The IOR paradigm elicited the classic IOR response in control subjects, but reduced IOR in OCD participants. The result suggests the OCD participants attention was captured by the power light briefly switching on and they were slower than control subjects to disengage attention away from the threat stimuli of a powered electrical appliance.

The rTMS experiment reported here relies on results from a previous IOR study (Wang et al., in prep) that used MEG to investigate the exogenous attention in OCD checkers. The paradigm used in this rTMS study reported here is identical to that of the MEG study, apart from the element of rTMS stimulation. The details of the paradigm are reported in the method section, 6.2, in the section titled “Inhibition of Return (IOR) and rTMS Paradigm”. The initial topographical cluster results of the MEG study, figure 6-1, show the loci of the alpha band power desynchronizations (highlighted in dark blue), within the regions identified blue in figure 6-1 below. The cluster with largest magnitude on each hemisphere was taken as the target location for the rTMS stimulation in the IOR rTMS experiment reported here.



11Hz Cue Left 11Hz Cue Right

Figure 6-1. *Z-score power. Checker vs Low-Checker. An alpha band power desynchronization (shown in blue) occurred in the contralateral posterior parietal area when participants reflexively attended the cue. The group statistics show that on average, alpha power in this region was lower for Checker participants than for Low-Checker subjects, i.e., less inhibition, more attention processing in contralateral parietal areas. Increased alpha power over mFC indicates more inhibition, i.e., less cognitive processing. Source analysis identified the centre of the desynchronizations to be located in Brodmann Area BA7, specifically, Left and Right Intraparietal Sulcus (IPS). The data that reached statistical significance (p<0.05) are colour coded either red or blue. Red colouring indicates areas of significantly increased activity, while blue indicates areas of significantly reduced activity.*

The areas of statistically significant cortical activity shown in figure 6-1 match well with fronto-parietal attention networks identified in the literature as mediating IOR. Consistently (Meyer et al., 2018, Peelen et al., 2004) a fronto-parietal network consisting of premotor cortex, posterior parietal cortex, medial frontal cortex and right inferior frontal cortex, (Corbetta and Shulman, 2002) the right temporoparietal junction, intraparietal sulcus involved in object-centered attention (Yantis and Serences, 2003) and frontal eye fields.

The aim of this study was to stimulate the left or right intraparietal sulcus (target identified from MEG data) to briefly entrain neural oscillations to either 10Hz alpha or 6Hz theta rhythms and probe the effect on IOR performance. Enhancement of ongoing cortical oscillations has been demonstrated (Thut et al., 2011b) with pulse trains comprising as few as five pulses. Alpha band oscillations (Jensen and Mazaheri, 2010, Klimesch, 2012) reflect an inhibitory control mechanism with increased alpha power controlling cognitive processing and decreased alpha power indicating a release of functional inhibition. As discussed in the main introduction, a lack of inhibitory control to rumination on specific thoughts and to manage distraction by symptom salient stimuli thought to underlie OCD.

With alpha oscillations thought (Klimesch, 2012) to be fundamental to the efficient directing of attention to relevant stimuli through a process of input suppression and selection, modulating alpha band power via TMS at appropriately selected cortical targets (Klimesch et al., 2003, Romei et al., 2010, Sauseng et al., 2009) may be able to induce changes in task performance in the IOR task.

In spatial cueing and hemifield tasks (Klimesch, 2012), alpha power increases over the ipsilateral (cortical inhibition) than the contralateral hemisphere where stimulus processing occurs.

The alpha band topoplots in figure 6-1 above, show group differences in alpha activity comparing Checker against Low-Checker. The topoplots show the Checker participants displaying greater alpha power in frontal medial and lateral cortices and a larger desynchronization of alpha power over contralateral parietal cortex. Together these can be interpreted as the Checker cohort displaying less cognitive control (higher alpha power in medial frontal and lateral cortices) to ignore the irrelevant cue and greater allocation of attention resources (lower alpha power in contralateral parietal cortex) to attend to the ecologically valid stimulus.

The MEG IOR data (Wang et al., in prep) showed at the group level, checker participants compared to low-checkers, exhibit lower alpha band power contra-laterally in IPS during the time period when cue stimuli are processed. This suggests that checker participants allocate more attentional resources, less inhibition, to the irrelevant cue. This disengage deficit was reflected in the weaker effect of IOR observed in checker data compared to low-checkers.

Hypothesis

Stimulating IPS with a short train of 10Hz rTMS was expected to increase local cortical alpha power beneath the TMS coil. For checker participants with cue stimuli presented in the contralateral hemifield, this would reduce the magnitude of the cortical alpha power decrease, serving to inhibit OCD symptom related attention to, and processing of, the irrelevant cue, normalising their IOR response. Referenced to the side on which rTMS was applied, processing of cue stimuli presented in the ipsilateral hemifield will be largely unaffected as the cortical alpha power beneath the coil will already be in a relatively high alpha power state, inhibiting the contralateral hemifield. In summary, ipsilateral rTMS stimulation was likely to have little effect on IOR response, whereas, contralateral rTMS stimulation was designed to normalise the IOR response. For low-checker participants contralateral rTMS stimulation will not enhance further that ongoing oscillation and will have little effect on inhibition in that hemifield. Ipsilateral rTMS stimulation may enhance slightly the low amplitude alpha oscillation, (Thut et al., 2011b) potentially affecting slightly the IOR effect, but the effect is likely to be slight rather than preventing targets (Romei et al., 2010) from being detected in the ipsilateral hemifield.

6.2 Method

Participants

Participants were recruited on their VOCI checking sub-scale score and assigned to one of two groups, checkers (n=16) and low-checkers (n=16). The checking cohort had VOCI scores ranging from 7 to 18, and the low-checker scores ranged from 0 to 3. Participants with scores of 4, 5, or 6 were declined from the study. Participants were medication free at the time of testing. To ensure the correct cortical structures were stimulated with the rTMS, Brainsight neuronavigation system was used. For this, participants were required to have an MRI head scan, from which a head model was constructed in software. The head model was used by Brainsight software to aid the experimenter in positioning the TMS coil at the correct location on the scalp. Only participants who passed the MRI and TMS screening questionnaires and had suitable VOCI scores were accepted into the study.

Participants were recruited from the student and staff population at Aston University. The participant group comprising mainly of psychology undergraduate students.

Inhibition of Return (IOR) and rTMS Paradigm

An element of the EBL (Executive-Functioning Efficiency, Binding Complexity, Memory Load) model of executive dysfunction (Harkin and Kessler, 2011) is that encoding and binding of information into working memory is impaired by attention being inappropriately directed to irrelevant stimuli.

It was shown in the dual task working memory experiment that an intermediate probe employing pictures of electrical kitchen appliances had a more disruptive effect on the working memory task for checkers than low-checkers. The EBL model suggests this is in part due to checkers attention being biased towards to the irrelevant stimuli at the expense of fulfilling the working memory task.

Based on the results of the MEG working memory task (see Chapter 3) it was anticipated that the images of electrical kitchen appliances have a greater distracting effect for checkers than low-checkers. An MEG attention task, conducted with checker and low-checker participants showed differences in alpha band cortical activity within the superior parietal lobe. The IOR experiment in combination with rTMS was designed to investigate the greater attention bias shown to the picture stimuli by checkers compared with low-checkers. Using trains of seven TMS pulses at 6Hz (Theta band) and 10Hz (Alpha Band) directed over left and right superior parietal lobes the aim was to entrain cortical oscillations (Thut et al., 2011a) with the superior parietal lobe that enhance or disrupt the alpha generator, thereby to enhance or disrupt the attention bias effect. The expectation was for 10Hz entrainment to maintain or enhance the ongoing alpha rhythm in the area stimulated, whereas 6Hz entrainment would disrupt and diminish the ongoing alpha oscillation.

The IOR rTMS computer based task, a Psychophysics Toolbox program written in a Matlab environment, used pictorial stimuli based on those employed in the MEG working memory task. Initially, a black and white 'checker board' kitchen scene was presented with the middle left and right squares occupied by electrical appliances. The power lights for both appliances were coloured dull red, indicating the appliances were powered 'OFF'.

After 1000ms a green fixation cross was displayed centrally on the screen and a bell sound played through ear phones to the participant. After a jittered 'wait' period of either 600, 800 or 1000ms, the rTMS pulses commenced.

The seven rTMS pulses were produced at either 6Hz (Theta band) or 10Hz (Alpha band) frequencies. During the period of the pulses being administered to the superior parietal cortex, the light on one of the appliances was made bright red, to indicate it has been powered 'ON'. After 300ms the light returns to dull red, indicating it has been powered 'OFF' again. The light becoming dull red again was made to coincide with the last pulse of the rTMS pulse train. With 6Hz rTMS stimulation the pulse train lasts 1000ms, and at 10Hz the pulse train was 700ms in duration. To protect the participants' hearing from the loud click of the TMS coil, participants wore earphones during the experiment. It has been shown that auditory stimuli can produce entrainment. To avoid an acoustic entrainment effect resulting from the 6Hz or 10Hz click sound produced by the TMS coil, a 30Hz clicking sound was played to the participant through the earphones during the period that TMS was active. The frequency of 30Hz was chosen as the pulses of both 10Hz and 6Hz rTMS would coincide temporally with the 30Hz click train. The auditory click train was compiled from a recording of a single TMS pulse and designed to match the frequency characteristics of the TMS coil.

After the last rTMS pulse and the power light had flashed 'OFF', there was a wait period of 750ms. A blue box then highlights one of the electrical appliance images for 100ms. Using a computer mouse with two buttons (left and right), the participant indicated as quickly as possible, which side of the screen the blue box appeared, either left or right. The response period timeout duration was 2000ms. A short rest period of 4000ms followed, during which an image of eyes blinking indicated the participants may blink or rest their eyes before the next trial started.

During the experiment participants were sat comfortably in a chair with their chin resting on a chin rest. The computer monitor was positioned centrally in front of them at a distance of 45cm.

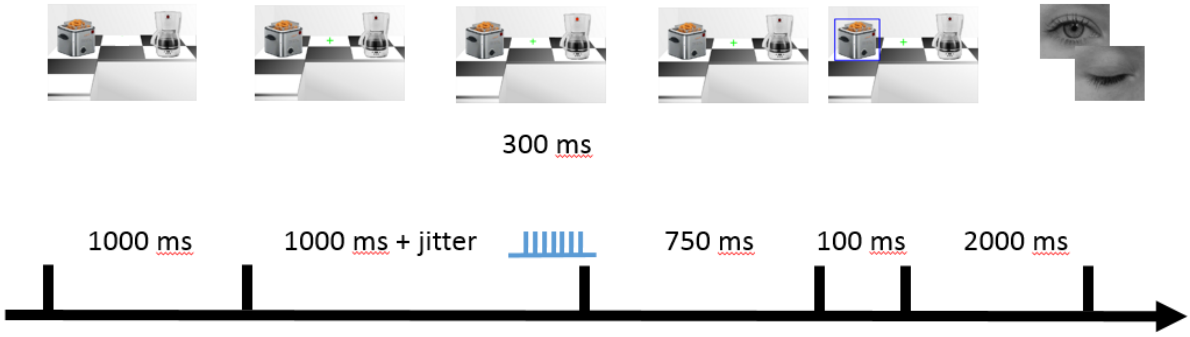


***Figure 6-2**. The timeline of an individual trial, the blue 'picket fence' indicates the point at which the TMS pulses were applied.*

TMS protocol

Prior to the participants' arrival, using SPM8, the MNI transform matrix was obtained for each individual's T1 weight MRI image. The MRI images were loaded into Brainsight and the MNI transformed MRI image data used to locate TMS stimulation targets in the right hemisphere motor cortex, left and right superior parietal lobes.

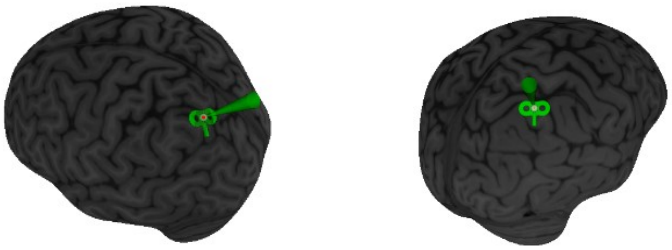


***Figure 6-3**. Example of TMS targets set up in Brainsight neuronavigation software, showing left and right Superior Parietal Lobe targets*

The accuracy of the Brainsight neuronavigation system relies on the successful co-registration of the participant with their MNI transformed MRI image during the setup of the experiment. The co-registration step was checked and redone if found to be inaccurate.

The Intraparietal sulcus targets (Brodmann Area BA7) were established using MNI coordinates derived from another MEG IOR attentional study (Wang et al., in press).

	X	Y	Z
Left Intraparietal Lobe	-30	-70	52
Right Intraparietal Lobe	50	-54	60

***Table 6-1**. **MNI target coordinates used to locate brain regions targeted with TMS**.*

On the day of the experiment, before starting the experiment, to ensure they were fit to take part, participants completed a TMS safety screening questionnaire and study consent form.

TMS was applied using a Magstim Super Rapid2 biphasic pulse generator. The TMS coils used were 70mm figure of eight coils. Stimulation intensity was set at 90% of the individual's resting motor threshold. The resting motor threshold was established by measuring the TMS induced contraction of the first dorsal interosseous muscle of the left hand. Threshold being the TMS intensity, as a percentage of maximum stimulator output, required to produce a 50uV peak to peak MEP with a probability of 50% over 10 measurements (Rossi et al., 2009).

Before starting the experiment, the stimulation targets setup in Brainsight for the superior parietal lobes were checked and adjusted so that the TMS figure of eight coil rested normal to the scalp and was oriented anterior-posterior current flow at an angle of 30 degrees to the sagittal plane.

6.3 Results

Analysing the IOR response times, there was a significant main effect of Validity $F(1,34) = 16.46$, $p<0.01$, indicating an IOR effect was observed. There was also a significant interaction between Validity and Checker, $F(1,34)=4.20$, $p<0.05$, indicating there was a difference in how the IOR effect manifest in each group, Checker and Low-Checker. Analysing the data separately, by Checker and Low-Checker cohort, an effect of Validity was seen for the Low-Checker cohort, $F(1,18)=28.456$, $p<0.01$, but Validity did not reach significance for the Checker cohort. There was a main effect of Target for the Low-Checkers, $F(1,18)=6.893$, $p<0.05$.

With only a main effect of Validity, it is difficult to give a general interpretation of the pattern of IOR response times shown in Figures 6-4 and 6-5 below.

Although a difference in IOR effect was observed, as might be expected if the Checker participants' attention was drawn to the irrelevant cue on invalid trials, the direction of the IOR was in the opposite direction to that expected. As can be seen in Figure 6-4 below, showing response time differences (Invalid - Valid), the differences tend to be positive valued, indicating participant's attention was not inhibited at the 'Valid' cue location, leading to negative difference values, as would be expected in a standard IOR experiment.

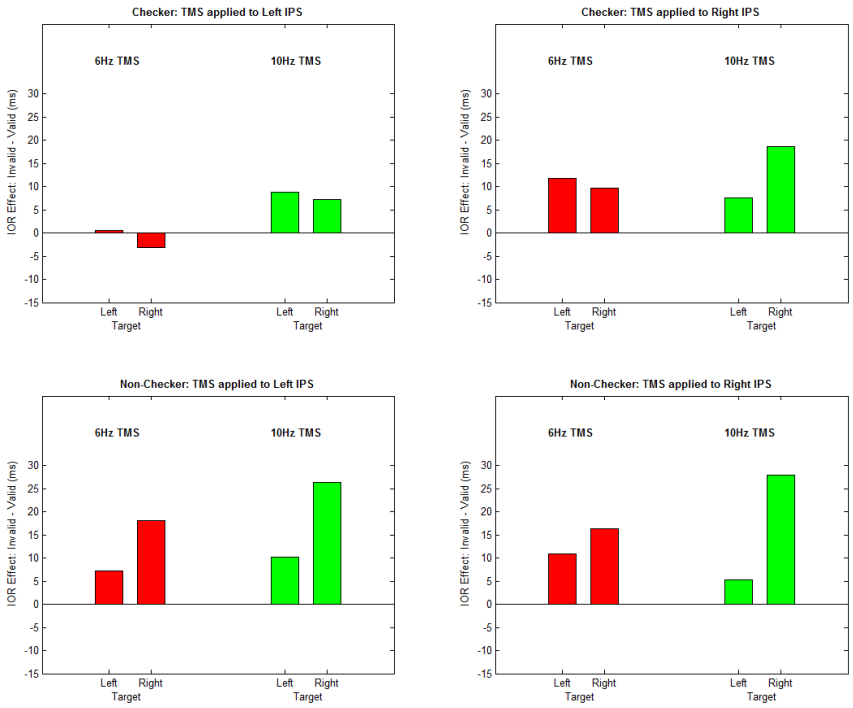


Figure 6-4. A possible effect on response times was observed, the effect was in the opposite direction to that expected of the classical IOR effect. The results did not reach significance ($p<0.05$).

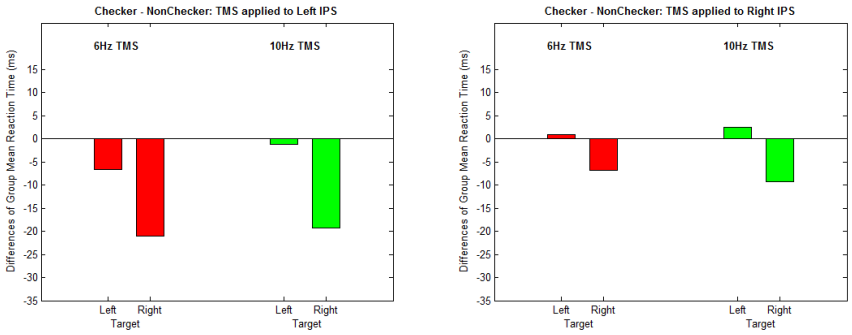


Figure 6-5. Group differences did not reveal a significant differences in the way checkers and low-checkers completed the IOR study.

6.4 Discussion

It was anticipated that the response time data would show a difference in IOR effect comparing the two stimulation frequencies and by cohort. A baseline stimulation protocol of 6Hz rTMS was used, because based on prior MEG measurements, theta power was not found to be significant in IOR processing in left and right IPS. A previous behavioural study (Harkin et al., 2011) had shown 'checker' participants to display a disengagement deficit when presented with electrical appliance stimuli. MEG data suggested that increasing alpha power in IPS using 10Hz rTMS might inhibit attention to irrelevant but symptom salient cues, thereby moderating IOR processing to possibly normalise the IOR response in the 'checker' cohort.

Following the IOR rTMS experiment, a repeated measures analysis of variance (ANOVA) of the response time data revealed a main effect of Validity, and an interaction between Validity and Cohort. This indicates the electrical appliance pictures were important to how the participants performed, and that the stimuli were successful in evoking differences in the way checkers and low-checkers were processing the cue stimuli.

However, the response time data overall tend to show a 'benefit' (quicker response times) for the cue being presented at the same location as the target, rather than a 'cost' (slower response times) as would be expected in a standard IOR effect. Although an effect of Validity and Validity x Cohort was found as would be expected in an IOR experiment, the positive valued response profile obtained was in the opposite direction of that anticipated. The 'valid' cues were not being preferentially inhibited at long CTOA as expected in standard IOR conditions.

The statistical analysis did not show a main effect of stimulation Frequency, stimulation Site or Target location. The statistical data therefore does not support the hypothesis that modulating IPS at alpha frequency with 10Hz rTMS will preferentially affect IOR processing compared with 6Hz stimulation. It was anticipated that an effect of stimulation Site would be observed in

response times for stimuli presented to the contralateral side. Not finding an effect of Frequency or Site raises the question of whether theta band was a good baseline against which to compare alpha band stimulation as both frequencies may have had an impact on the cue stimuli processing within IPS.

The design of the rTMS protocol was guided by allied MEG data (Wang et al.,) and experimental considerations. The MEG data appeared to show that theta band oscillations were not prominent during the IOR task at left and right IPS, the cortical sites targeted with rTMS. On this basis it was anticipated that theta (6Hz) stimulation would not have a significant influencing effect on the IOR experiment and could act as an appropriate baseline against which alpha (10Hz) rTMS could be compared.

It is usual in TMS experiments that the baseline condition, a 'sham' or 'no pulse' condition, be used against which to interpret the results of the active stimulation condition. In this experiment all conditions were active TMS with TMS coil positioned to optimally stimulate the underlying cortex. The decision to employ 6Hz rTMS and not use a standard 'sham' condition was based on a number of experiment considerations. Two commonly used 'sham' techniques are to either transmit no pulses while holding the TMS coil in position on the participant's head, or to rotate the coil through 90º so the pulses are ineffective in stimulating the underlying cortex. Both these techniques were rejected as they may allow the 10Hz entrainment to build in strength, potentiating the cortex to 10Hz oscillations over the course of the experiment as more blocks of 10Hz rTMS were delivered. A specific aim of the experiment design was to limit 10Hz entrainment to the time period in which cue was presented and that the 10Hz entrainment not contaminate the time when the target was displayed. The 'no pulse' condition may enable an ongoing 10Hz oscillation to become entrained as it would not impose a different rhythm that would counteract any echo after effects of the alpha rTMS. 'No pulse' has the added disadvantage that the sensation on the scalp was very different from the active condition and as such may not be an adequate control condition. In contrast, alternating 10Hz and 6Hz entrainment rhythms at the block level it was expected this would prevent an ongoing 10Hz entrainment process from developing. In addition to a 'no pulse' TMS condition not feeling the same to the participant, it does not replicate the attentional bias that can be induced by the scalp sensations in active TMS conditions. TMS applied laterally has been shown to bias attention toward stimuli presented ipsilateral to the TMS stimulation site. In respect of scalp sensation and potential biases in attention, 6Hz and 10Hz rTMS stimulation would be similar in effect. More complex control conditions can be employed, such as stimulating at a number of intensities. If the effect of TMS varies with intensity, showing no effect subthreshold and increasing effect as intensity was increased in regular steps to and above threshold, this was very strong positive evidence for an effect of TMS. Such an approach greatly increases the number of trials required and duration of the experiment. If used in this experiment it could, over time, potentiate the cortex to 10Hz oscillations and would therefore be unsuitable. Trying meet the competing requirements for a 'not too long' experiment, having sufficient trials per condition, a baseline condition that replicates the sensations and potential attentional bias of the active TMS condition, and did not entrain the

cortex to a specific oscillation over time, an rTMS baseline stimulation appears the best option in meeting these different needs. Possibly choosing a frequency different from the individual's ongoing theta frequency may be effective.

In this experiment, in separate blocks, both left and right IPS were stimulated. The MEG data suggested both sites to be implicated in IOR processing. The complexity of the results may have been easier to interpret if a neutral cortical site, one not expected to be involved in IOR processing was used for a control stimulation site. Analogous to a 'sham' TMS condition, comparing the behavioural response of a control site with IPS stimulation would help to disentangle the effect of TMS induced scalp sensations from the effect TMS may be having on cortical processing. This approach was problematic with this paradigm as IOR processing involves many cortical regions, in particular fronto-parietal networks and occipital visual processing. It was difficult therefore to identify with confidence a suitable silent cortical target that would not be involved in IOR processing.

The data did not reveal a simple pattern of effect and may indicate the stimulation was having a more complex interaction with IPS processing than anticipated. The positive valued response time differences (Invalid-Valid) were what might be expected to be produced by patients with right hemisphere parietal lesions (Losier and Klein, 2001, Vivas et al., 2006). This may indicate that the rTMS was acting to disrupt the ongoing cortical oscillations rather than promoting rhythms at the stimulation frequency. Inhibitory TMS, 1Hz rTMS applied for 10 minutes over parietal cortex (Hilgetag et al., 2001) can induce extinction effects in the contralateral hemifield while also enhancing attention to ipsilateral targets. Taken together, it was possible the 6Hz and 10Hz rTMS induced transient lesions leading to neglect and extinction effects if the rTMS was acting to interrupt cortical processing rather than to facilitate. The resulting interaction with IOR processing would be complex and difficult to disentangle within the current dataset.

The variance in response times in the current dataset was relatively high and the IOR validity effect (Invalid-Valid response times) observed was relatively modest compared to the underlying response time data. Compared to the current experiment (n=38), a substantially larger sample size (n=98) was recruited for the behavioural experiment (Harkin and Kessler, 2012) which found similar sized Validity measurements and on which this experiment was based. The MEG experiment (Wang et al, in prep) on which this IOR rTMS experiment was based, also struggled to show robust data when moving from sensor based topological cluster plots to source space analysis. The rTMS IOR effect was potentially small and may involve a more complex interaction with TMS than was observed in the purely behavioural experiment. A much larger sample size may help to clarify the direction of effects within the current dataset. A source of variability in the data that might arise was if the rTMS entrainment was not equally effective amongst all participants. When applying alpha rTMS it is recommended (Thut et al., 2011b) to tune the rhythm to the individual's alpha frequency. In this study, all participants received 10Hz stimulation. The strength of entrainment (Thut et al., 2011b, Hanslmayr et al., 2014, Notbohm et al., 2016) is related to how closely the entrainment frequency matches the individual's ongoing

oscillation frequency. This may have resulted in 10Hz stimulation being less effective for some participants, and greater variability in the data.

In fiigure 6-5 the group differences (Checker – Low checker) in IOR validity data was presented. If both groups were responding in the same way to TMS and the IOR paradigm, it might be expected the group differences would tend towards zero. Although the underlying data did not reach statistical significance, as described above, the pattern of Validity effects shown in Figure 6-5, suggests checkers and low-checkers were processing the left hemifield targets in a similar fashion as the differences between the two groups was low. The response time differences for right hemifield targets was much larger, suggesting there was a difference between checkers and low-checkers in how these targets were processed independent of 6Hz or 10Hz rTMS but affected by differential salience of the kitchen appliance stimuli. Reports of hemifield biases in OCD IOR have been reported in the literature (Bourgeois et al., 2012, Bourgeois et al., 2013, Chica et al., 2011, Hilgetag et al., 2001), but the literature is inconsistent, with some reporting left hemifield biases, others right side biases and others finding no bias.

Statistical analysis of the response time data shows a difference in how Checkers and Low-Checkers respond to the electrical appliance stimuli. However, the generally positive values of the Validity data were consistent with IOR performance in patients with parietal lobe lesions. The rTMS intervention appears to have influenced task performance, but the precise nature of that effect may be complex, involving neglect and extinction phenomena, which with the current dataset, was difficult to resolve. The data may become clearer if the experiment were run with a larger group size, incorporating a ‘sham’ condition, and targeting only one active hemisphere.

7 Discussion

Obsessive-compulsive disorder (OCD) is a condition that affects approximately 1-3% of the population. The condition is defined by obsessions and compulsions. Obsessions manifesting as repeated, intrusive, unwanted, distressing thoughts, urges or mental images. These obsessions can be perceived by the sufferer as meaningless, irrelevant, and inappropriate.

OCD checking is defined by sufferers propensity for repeated checking, for example that electrical switches are turned 'off' or doors locked. The act of checking does not salve the need to check again. It is paradoxical that the act of repeated checking can reduce one's confidence in the result of the checking procedure, which in turn serves to continue the checking behaviour. OCD sufferers also display attentional biases for the things that give them concern, for example a red light indicating that electrical switches have not been turned off.

Analysis of the neuropsychological features of obsessive-compulsive disorder (Greisberg and McKay, 2003) identified that failing to implement efficient organizational strategies to solve working memory tasks, suggesting problems in executive functioning could be sufficient to induce memory impairments in OCD subjects. Rather than a problem of core memory capacity, it was executive dysfunction that differentiated OCD subjects from controls. Building on this idea of executive deficits, (Harkin and Kessler, 2011), proposed a classification system to identify a mechanism by which intact memory function in OCD can become poor in certain tasks and situations. The EBL (Executive Function Efficiency (E), Binding Complexity (B) and Memory Load (L)) classification system (Harkin and Kessler, 2011) seeks to predict and classify WM deficits in compulsive checking on the dimensions of Executive Function Efficiency, Binding Complexity and Memory Load.

When a task does not involve content related to their OCD condition and a working memory is demanding only on the axes of Binding Complexity and Memory Load, OCD people may preform the task just as well as a neuro-typical control. It is when the OCD symptom related stimuli invade the OCD sufferers information stream that executive resources needed for efficient performance become diverted from the goal seeking task and task performance is adversely affected. Temporary and fragile bindings within the working memory episodic buffer (Baddeley 2000) necessary to successfully progress through one's environment may not be maintained for accurate encoding and retrieval. An inability to suppress irrelevant information will allow that information to compete and interfere with the efficient working of the episodic buffer. This may lead to checking and rehearsal strategies in order to maintain the fidelity of the memory bindings needed to task goals.

An outcome of the EBL classification system in combination with the Baddeley model of working memory including the episodic buffer, is that predictions can be made as to the neural activity that must support executive dysfunction, poor working memory performance and attentional biases. The fronto-striatal network important in neuroanatomical models of OCD, the PFC and

OFC supporting executive functioning, MTL and hippocampus in memory function (OCD checking behaviours) with occipital and frontoparietal networks supporting attention processes (OCD stimulus bias).

The aims of this thesis were firstly to identify the neural correlates of executive dysfunction, in the context of the EBL classification, in checking behaviour that would lead to poorer performance in WM. This was undertaken using MEG measurements and ecologically valid stimuli (Harkin et al., 2011) designed to evoke working memory deficits through executive dysfunction in OCD participants.

The second aim of this thesis was to use MEG measurements to investigate the neural correlates of attentional bias and executive dysfunction in OCD when engaged in an endogenous attention (Stroop) task.

The third aim of this thesis was to use transcranial magnetic stimulation (TMS) to target task relevant brain areas and affect beneficially the task performance of OCD checker participants engaged in an exogenous attention (Inhibition of Return) task, an endogenous attention (Stroop) task and in the working memory task.

Chapter 3 presented the dual task working memory paradigm in which OCD subjects were unable to suppress an irrelevant stimulus leading to impaired encoding and retrieval of task relevant information. The pattern of neural activity in OCD checker participants matched well with prediction. Failing to suppress the distracting irrelevant information brain activity associated with attention network was detected as well increased brain activity in PFC, MTL and ACC regions supporting memory processes and increased demands on executive functioning in attempt to maintain task performance.

Chapter 4 expanded the working memory experiment with the inclusion of rTMS in attempt to inhibit deficit executive processes during the retention period of the working memory task. Using theta frequency to entrain dlPFC and improve attentional control to task relevant stimuli, and theta entrainment of ACC so that low-checkers may engage the same deficient ACC processing as the checkers. Unfortunately, the attempt at rTMS entrainment failed to yield any significant performance changes to either checkers or low-checkers.

Chapter 5. Neural correlates of endogenous attention in OCD checking behaviour were investigated with the use of the Stroop task. Different versions of the Stroop task were employed, the classic colour-word task, and emotional Stroop paradigm using OCD symptom related words and a pictorial Stroop task using the ecological valid kitchen appliance images employed in the working memory experiments. The classic Strop task produced a robust effect with the checker cohort. The emotional Stroop task produced no Stroop interference for emotional words on colour naming or in reaction times naming neutral words vs emotional words. The lack of a Stroop effect though disappointing was not entirely unexpected as previous researchers in this field, for example Moritz et al., 2008 have postulated that words are not enough. A more reliable Stroop effect is obtained with OCD participants when using picture stimuli associated with the

dimension of their disorder. With the pictorial Stroop task, the OCD cohort were generally slower in their reaction times except when asked to name the power state when the image showed the light to be 'ON', OCD participants were faster in their response times. The result was interpreted as an attentional bias to 'ON' states which produced a 'facilitation' effect leading to faster response times.

The pictorial Stroop task was repeated in a MEG scanner so that the neural activity could be recorded. The classic ACC signature of Stroop interference was not demonstrated in the experiment, although signatures of attention networks and target processing networks were revealed in the data for both low-checkers and checkers. However, the attention control network was better defined in the low-checker cohort, whereas the checker data showed a preference for the target processing network. This may point to how the two cohorts were processing the task, the low-checkers engaging stronger attention control while the checkers were processing the features of the picture stimuli.

The pictorial Stroop paradigm using images of kitchen appliances was adapted to include dual pulse TMS. The TMS was applied during the period when the Stroop stimuli would be process, before the response initiation. Targeting the ACC, it was hoped the TMS pulses would disruption ACC processing and facilitate the participants response. Only the low-checkers showed an effect of TMS, and only on the incongruent condition. This could mean the experiment worked as intended, on the high conflict condition in which the ACC is most strongly engaged, the TMS disrupted the ACC processing in a faciliatory manner, leading to a faster response time. If as has been seen in the neuroimaging data, there are subtle differences between checkers and low-checkers in which brain areas are most strongly engaged in the tasks and in this task, checkers are engaging not only the ACC to process the conflict, the TMS didn't target the other unknown structure and response times were not affected.

Chapter 6. An attempt to use rTMS with an exogenous IOR experiment was unsuccessful.

The kitchen appliance images were effective in provoking OCD behaviours of memory checking and attention bias in the checker cohort. The MEG studies were successful in acquiring images and were supportive of the predictions about the patterns off neural activity expected. Moderately larger cohort sizes, 5 or 10 participants per cohort, would have made a good difference and the effects observed would be more robust.

The application of TMS was not as fruitful as initially hoped. The entrainment protocols were more difficult to make effective than anticipated. The dual pulse TMS may have been effective and with larger group sizes the result may have been more categorical.

Overall, the data obtained, particularly in MEG, support the EBL model explanation for executive dysfunction leading to working memory deficits.

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