Clarifying the neural basis of obsessive compulsive disorder : a combined structural and functional magnetic resonance imaging study

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**CLARIFYING THE NEURAL BASIS OF OBSESSIVE COMPULSIVE DISORDER:
A COMBINED STRUCTURAL AND FUNCTIONAL MAGNETIC RESONANCE
IMAGING STUDY**

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School of Social Sciences

A thesis submitted to the Nanyang Technological University in partial fulfilment of the
requirements for the degree of
Doctor of Philosophy

2019

Statement of Originality

I certify that all work submitted for this thesis is my original work. I declare that no other person's work has been used without due acknowledgement. Except where it is clearly stated that I have used some of this material elsewhere, this work has not been presented by me for assessment in any other institution or University. I certify that the data collected for this project are authentic and the investigations were conducted in accordance with the ethics policies and integrity standards of Nanyang Technological University and that the research data are presented honestly and without prejudice.

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Authorship Attribution Statement

This thesis contains material from 1 paper published in the following peer-reviewed journal(s) where I was the first and/or corresponding author.

Study 1 in the thesis is published in full as “G.K. Eng, K. Sim, & S.H.A. Chen. (2015). Meta-analytic investigations of structural grey matter, executive domain-related functional activations, and white matter diffusivity in obsessive compulsive disorder: an integrative review. *Neuroscience and Biobehavioral Reviews*, 52, 233-257.”

The contributions of the co-authors are as follows:

- Prof Chen provided the initial project direction and overall project supervision.
- All authors co-designed the study.
- I performed the analysis, interpreted the results and prepared the manuscript drafts.
- Prof Chen and A/Prof Sim revised the manuscript drafts and provided guidance in the interpretation of the findings.

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Abstract

Obsessive-compulsive disorder (OCD) is a debilitating disorder with limited treatment efficacies. This could partly be attributed to inadequate knowledge of the neurobiological basis of the disorder. Even though OCD has a prevalence rate of 3% in Singapore, research in OCD is relatively lacking compared to other psychiatric conditions. Existing neuroimaging literature in OCD have commonly reported abnormalities within the fronto-striatal regions, and some studies also indicated the involvement of the cerebellum in the disorder. However, exact contributions of the cerebellum in OCD pathophysiology have been unexplored.

This thesis aims to clarify the neural basis and examine aberrant neural activity involved in OCD pathophysiology. Four studies are presented in this thesis. Study 1 presents a meta-analysis to synthesize existing findings of differences in structural grey matter and executive-function task-related activations between OCD samples and controls. Results indicated group differences in frontal-thalamic and cerebellar grey matter, and task-related activations in the cingulate, parietal and caudate regions. These findings suggest probable involvement of regions beyond the cortico-striatal-thalamo-cortical (CSTC) circuitry in OCD pathophysiology. Findings from Study 1 set the stage for subsequent neural investigations.

Studies 2 to 4 embark on empirical investigations of the neural correlates of OCD. 21 patients with OCD and 17 age- and gender- matched controls participated in a systematic investigation of neural alterations in OCD using non-invasive neuroimaging of function and structure. Structural alterations in grey matter via voxelwise morphometry approaches (VBM) are evaluated in Study 2. Compared to controls, patients with OCD demonstrated increased grey matter volume (GMV) in the postcentral gyrus, reduced GMV in the insula, and both increased and reduced GMV in the cerebellar lobules. Study 3 investigates task-related functional activations during verbal and visual working memory and response

inhibition tasks. Compared to controls, OCD samples generally showed decreased neural activations during working memory. Patients with OCD performed poorer than controls in the high-load condition of the visual working memory task, and had reduced activations in the fusiform gyrus and cerebellar regions during visual working memory. Even though there were no significant group differences in terms of behavioural performances in the verbal working memory task, OCD samples demonstrated reduced cerebellar activity during the task. For the response inhibition task, compared to controls, patients with OCD showed increased activations in the frontal regions that indicated probable involvement of compensatory mechanisms. Interestingly, altered cerebellar activations were implicated in all three tasks. Next, Study 4 evaluates resting-state intrinsic activity in key resting-state networks of executive control network, default mode network, salience network and sensorimotor networks (Study 4a) and in functional connectivity with the cerebellum (Study 4b). Results showed aberrant intrinsic activity in the four resting-state networks in OCD samples; altered functional connectivity with the cerebellum involved regions within the CSTC such as the anterior cingulate, anterior-medial orbitofrontal area and thalamus. Other regions that showed altered functional connectivity with the cerebellum included the insula, middle-posterior cingulate and postcentral gyrus. In general, OCD samples showed reduced functional connectivity between the cerebellum and cortical and sub-cortical regions.

Findings from the current thesis are consistent with past studies and extend the involvement of the CSTC in OCD pathophysiology to other brain regions. In addition, the current thesis postulates an involvement of the insula and the salience-processing network, and dysfunctional sensory gating processes that could contribute to the clinical manifestations in OCD. It is noteworthy that alterations involving the cerebellum appear to be consistently

implicated across all analyses. These findings provide strong support for the involvement of the cerebellum in OCD pathophysiology. Implications of these findings are discussed.

CHAPTER 1: INTRODUCTION

Obsessive-compulsive disorder (OCD) is a heterogeneous and debilitating condition with an often chronic prognosis. It is diagnosed in 2-3% of the global population (Kessler, Petukhova, Sampson, Zaslavsky, & Wittchen, 2012; Ruscio, Stein, Chiu, & Kessler, 2010; Subramaniam, Abidin, Vaingankar, & Chong, 2012), and has been identified by the World Health Organization as the top 20 causes of years of life lived with disability for 15- to 44-year olds (World Health Organization, 2001). OCD is characterized by the presence of obsessions and/or compulsions. Obsessions are recurrent and persistent thoughts, urges or images that cause marked distress, while compulsions refer to repetitive and time-consuming behaviours or mental rituals that individuals feel compelled to perform to reduce the anxiety caused by the obsessions. These obsessions and compulsions are time consuming (> 1 hour a day) and significantly interfere with one's daily functioning or social relationships (American Psychiatric Association, 2013). Previously classified as an anxiety disorder in the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (American Psychiatric Association, 2000), OCD is currently listed in a new section in DSM-5 under Obsessive-Compulsive and Related Disorders. Disorders in this category included OCD, body dysmorphic disorder, trichotillomania, hoarding disorder and excoriation. Common key features among the symptomatology of these disorders are the nature of obsessive preoccupation and repetitive behaviours (American Psychiatric Association, 2013).

Treatment options for patients with OCD include pharmacotherapy, psychotherapy, and deep brain stimulation (DBS). However, there are limitations in each intervention option. Pharmacotherapy using selective serotonin reuptake inhibitors (SSRIs) are the first line of treatment for OCD (Graybiel & Rauch, 2000). Even though approximately 40-60% of patients fail to respond to SSRI treatment (Davidson & Bjorgvinsson, 2003; Kaplan & Hollander, 2003), SSRIs are still preferred over other medications due to more benign side

effects (McKay et al., 2015; Schruers, Koning, Luermans, Haack, & Griez, 2005). For psychotherapy, exposure and response prevention (ERP) are considered first-line treatment (Janardhan, Sundar, Narayanaswamy, & Math, 2017; Pittenger, Kelmendi, Bloch, Krystal, & Coric, 2005). Even though ERP has proven effective with about 50% efficacy in the treatment of OCD (Skapinakis et al., 2016), most patients experienced substantial discomfort as they are typically refrained from performing compulsions to reduce/neutralize emotional reactions that are elicited when confronted with the feared stimulus in therapy. Therefore, patients' refusal to engage in the treatment, drop-out, and lack of qualified therapists are key challenges to ERP (Schruers et al., 2005). Lastly, an effective but invasive treatment option for OCD is DBS. DBS is a focal neuro-modulatory approach that involves implanting electrodes in specific brain regions to alter regional neuronal activity using electrical pulses. Studies that treated patients with OCD using DBS had mostly applied high frequency stimulation ranging between 100 to 300 Hz on the striatal area (anterior limb of the internal capsule, ventral capsule, ventral striatum, nucleus accumbens, ventral caudate), subthalamic nuclei or inferior thalamic peduncle (Alonso et al., 2015). The electrodes are connected via wires to a battery-operated neurostimulator that is implanted in the chest. Even though a recent meta-analysis reported a global responder rate of 60% in DBS (Alonso et al., 2015), its utility in OCD is limited to patients who are treatment refractory. The most commonly reported side effects of DBS were hypomania, increased anxiety, and surgical side effects such as infection and hemorrhage risks (Alonso et al., 2015; Alonso et al., 2013). Moreover, since the neurostimulator is battery-operated, patients undergo repeated surgeries to replace the battery.

In view of substantial limitations in existing therapeutic options and chronic course of the disorder, more effective non-invasive therapeutic options, such as repetitive transcranial

magnetic stimulation (rTMS) and transcranial direct-current stimulation (tDCS) are needed. TMS and tDCS use rapidly changing magnetic field, and weak electrical currents, respectively, to modulate activity in the underlying cortical tissue (Dayan, Censor, Buch, Sandrini, & Cohen, 2013). Even though some may question traditional non-invasive stimulation techniques as less focal compared to DBS (Hartwigsen, 2015), the focality of non-invasive techniques can be improved using frameless stereotaxy neuro-navigation and appropriate use of deep-stimulation coils for TMS and simulations of current flow predictions for tDCS (Gough, Nobre, & Devlin, 2005; Hartwigsen, 2015). In terms of the duration of therapeutic effects, existing studies have showed support for long-term benefits of non-invasive brain stimulation on behavioural and clinical outcomes in psychiatric disorders such as depression (Janicak et al., 2010), although more research is required to evaluate that in patients with OCD.

The supplementary motor area (SMA) and the orbitofrontal cortex (OFC) have been considered appropriate targets for low frequency rTMS in OCD (Berlim, Neufeld, & Van den Eynde, 2013). However, consensus on the success of rTMS on these targets have been mixed. Some studies observed improvements in symptoms in OCD patients following rTMS treatment (Berlim et al., 2013; Mantovani et al., 2013; Russo et al., 2014), but others failed to observe superior effects over sham conditions (Pelissolo et al., 2016; Trevizol et al., 2016). The lack of consistent findings did not allow recommendations to be made according to evidence-based guidelines for a rTMS protocol for therapeutic use in OCD (Lefaucheur et al., 2014). Existing explorations of non-invasive treatment using tDCS in OCD also reported limited success (Rehn, Eslick, & Brakoulias, 2018). Modest symptom reductions of about 26% was observed with cathode stimulation over the left orbitofrontal cortex and anodal stimulation over the right cerebellum (Bation, Poulet, Haesebaert, Saoud, & Brunelin, 2016).

Separately, a montage involving the pre-supplementary motor area (pre-SMA) cathodal stimulation and extra-cephalic anodal stimulation were also reported suitable for OCD (Bation et al., 2016; Senço et al., 2015). However, the montage was applied on a small sample, and therefore has limited generalizability (Narayanaswamy et al., 2015). Considering the increase in studies that postulate the involvement of other regions in OCD, limited success of these non-invasive techniques could be attributed to lack of clear understanding of the neurobiology of OCD that is required for the development of more effective targets or montages for therapeutic neuromodulation.

Previous studies frequently recruited patient samples with diverse comorbid conditions. As patients with comorbid conditions may demonstrate different neurobiology and neuropsychological profiles (Bottas, Cooke, & Richter, 2005; Cardoner et al., 2007), the inclusion of these samples increase the complexity in interpreting observed findings and attributing observed abnormalities to the disorder *per se*. By setting more stringent recruitment criteria for patients without comorbid conditions, and utilizing a combination of neuroimaging analytic investigations, this thesis employs a systematic approach to understand the psychopathology of OCD that sets the basis for follow-up studies to explore non-invasive therapeutic approaches in OCD.

The thesis adopts a multimodal approach using structural and functional neuroimaging techniques to help map out the cortical structures and functional networks underlying OCD. Chapter 2 reviews literature on existing neuroimaging and neuropsychology findings in OCD to provide rationale for the investigation framework for the thesis. Chapter 3 presents a meta-analysis to quantitatively consolidate existing neuroimaging findings. This is followed with an overview of the empirical study and a presentation of behavioural and clinical findings in our sample of OCD patients and controls

(Chapter 4). Structural grey matter alterations using voxel-based morphometry (Chapter 5), and group differences in functional activations during working memory and response inhibition tasks (Chapter 6), and intrinsic activity during resting-state scanning (Chapter 7) are also evaluated and reported. The thesis concludes with an overall discussion to integrate all findings (Chapter 8). The research framework for this thesis is presented in Figure 1-1.

Figure 1-1. Research framework on the four studies conducted in this dissertation.

CHAPTER 2¹: LITERATURE REVIEW

¹ Publication: A part of this literature review has been published in a journal article as it appears in “G.K. Eng, K. Sim, & S.H.A. Chen. (2015). Meta-analytic investigations of structural grey matter, executive domain-related functional activations, and white matter diffusivity in obsessive compulsive disorder: an integrative review. *Neuroscience and Biobehavioral Reviews*, 52, 233-257.”

Chapter Overview

This chapter presents a literature review of existing neuroimaging and neuropsychological research conducted in patients with OCD. This begins with an introduction of the leading neural model in OCD and the main structures within the model, followed with a discussion of complementary and alternative models that have been proposed to explain the OCD phenomenology. Next, a literature review is presented to discuss neuropsychological performances and corresponding neuroimaging findings in OCD. This is important, considering an abundance of research have postulated selective cognitive impairments in patients with OCD, albeit with some inconsistencies. This chapter closes with a discussion on the motivation for our research investigations and reiteration of the research framework.

Standard Model of CSTC Circuitry in OCD

The cortico-striato-thalamo-cortical (CSTC) circuitry, also known as the fronto-striato-thalamo-cortical circuitry, has been an influential model for OCD pathophysiology for the past two decades (Cavedini, Gorini, & Bellodi, 2006; Christian et al., 2008; Milad & Rauch, 2012). Early single photon emission computed tomography (SPECT) and positron emission tomography (PET) studies reported increased cerebral perfusion and glucose metabolic rates in the orbital frontal regions, and less consistently, in the striatum regions in OCD patients at resting state (Baxter et al., 1987; Harris, Hoehn-Saric, Lewis, Pearlson, & Streeter, 1994; Swedo et al., 1989). Symptom provocation paradigms also observed increased regional cerebral blood flow in the orbitofrontal cortex, anterior cingulate and caudate nucleus in patients with OCD compared to controls (Rauch et al., 1994); and increased blood flow in these regions were significantly correlated with symptom severity (McGuire et al., 1994). These findings, taken together, postulate the involvement of the CSTC circuitry in OCD, involving regions such as the orbitofrontal cortex, striatum, thalamus and the anterior

cingulate regions. Since then, the model has been influential in guiding follow-up investigations in OCD samples. A simplified illustration of the CSTC circuitry is shown in Figure 2-1.

The Orbitofrontal Cortex (OFC)

The OFC is involved in motivational aspects of behaviours (Kringelbach, 2005; Rolls, 2004), behavioural planning (Elliott, Rees, & Dolan, 1999), decision-making and inhibitory control during the suppression of a response that was previously rewarding but now inappropriate (Elliott, Dolan, & Frith, 2000; Rolls, 2004). These reports indicated the role of the OFC in coding reward-related information, such as reward/outcome value, reward probabilities and expectancies (Gottfried, O'Doherty, & Dolan, 2003; Y. Li, Vanni-Mercier, Isnard, Mauguière, & Dreher, 2016), and in representing associations between reward-related information to outcomes (Schoenbaum & Roesch, 2005).

The OFC can be broadly parcellated into medial (mOFC) and lateral (lOFC) subdivisions with differentiating roles and connectivity patterns (Elliott et al., 2000; Kahnt, Chang, Park, Heinzle, & Haynes, 2012; Kringelbach & Rolls, 2004; Zald et al., 2014). The mOFC is particularly involved in monitoring and decoding representations of reward-value information (Kringelbach & Rolls, 2003; Pauls, Abramovitch, Rauch, & Geller, 2014), and has extensive innervations with the ventral striatum, anterior insula, angular gyrus, anterior and posterior cingulate, retrosplenial and entorhinal cortices (Beckmann, Johansen-Berg, & Rushworth, 2009; Laird et al., 2009; Zald et al., 2014). The lOFC has strong connections with the amygdala, thalamus, insula, temporal pole, intraparietal sulcus, and dorsolateral prefrontal cortex (Kahnt et al., 2012; Zald et al., 2014). Unlike the mOFC that is generally involved in monitoring reward values, the lOFC is more emotionally-laden and is involved in processing emotion-relevant information (Elliott et al., 2000), evaluating reward loss that could motivate behavioural changes, overriding behavioural options based on previous reward values of

options and outcomes, and is also implicated in response inhibition (Elliott et al., 2000; Kringelbach & Rolls, 2003). However, specific involvement of the mOFC and IOFC in OCD pathophysiology have been mixed, with most studies not making distinctions between the subdivisions (McGovern & Sheth, 2017; Saxena & Rauch, 2000).

The Basal Ganglia

Central to the CSTC circuitry is the basal ganglia. The main input nucleus of the basal ganglia is the striatum which consists of the caudate nucleus and putamen, and the main output nuclei of the basal ganglia are the globus pallidus internal segment and substantia nigra pars reticulata (Tepper, Abercrombie, & Bolam, 2007). The striatum receives excitatory inputs from many cortical regions and thalamic nuclei that are modulated by neurotransmitters such as gamma-aminobutyric acid (GABA), dopamine, substance P, glutamate, and enkephalin (Graybiel & Rauch, 2000; Tepper et al., 2007; Utter & Basso, 2008). These innervations project to the output nuclei in two main pathways. In the direct pathway, innervations project directly to the output nuclei of the basal ganglia before reaching the thalamus and other cortical regions. In contrast, innervations of the indirect pathway first project to the globus pallidus (external segment) and subthalamic nuclei, thereafter reaching the output nuclei, thalamus and other cortical regions (Tepper et al., 2007; Utter & Basso, 2008). The direct pathway has been classically viewed as excitatory that facilitates actions, and the indirect pathway as inhibitory (Deniau & Chevalier, 1985; Gerfen et al., 1990). Existing studies postulated that abnormalities in the CSTC circuitry observed in OCD were mediated by imbalances between the direct and indirect pathways of the basal ganglia, and hence patients experienced difficulties inhibiting their obsessions and compulsions (Saxena, Bota, & Brody, 2001; Saxena, Brody, Schwartz, & Baxter, 1998). Excess activity in the CSTC circuitry have also been thought to reduce the threshold for recurrent obsessions and repetitive and ritualistic compulsive behaviours, thereby maintaining

the cycle of obsessions and compulsions (McGovern & Sheth, 2017; Saxena & Rauch, 2000).

Imbalances between direct-indirect pathways of the basal ganglia have cascading implications. Even though the basal ganglia innervates the thalamus, superior colliculus and the pedunculopontine nucleus, these innervations project to cortical wide regions via the thalamus through a series of organized and parallel circuits, and innervate regions such as the dorsolateral prefrontal cortex (DLPFC), anterior cingulate (ACC), and IOFC (Alexander & Crutcher, 1990; Di Martino et al., 2008), therefore affecting the CSTC circuitry and beyond.

Figure 2-1. A simplified illustration of the CSTC circuitry.

(A) Regions within the cortico-striato-thalamo-cortical circuitry: Orbitofrontal cortex (Blue); Anterior Cingulate Cortex (Red); Thalamus (Purple); Striatum (Green) – Putamen, Caudate Nucleus. (B) A simplified illustration of innervations within the CSTC circuitry. Red solid arrows indicate excitatory glutamatergic innervations, and dashed arrows indicate inhibitory GABAergic innervations. In brief, in the direct pathway, glutamatergic signals from the frontal areas (mainly the OFC and ACC) leads to excitation of the striatum, which increase inhibitory signals of the SNr and GPi, and the thalamus, where excitatory glutamatergic outputs are sent to the OFC and ACC. In the indirect pathway, glutamatergic signals from the OFC and ACC inhibits the GPe, which inhibits the SNr and GPi, and the STN. The direct pathway has been considered as excitatory, and the indirect pathway as inhibitory. Output nuclei of the basal ganglia are also projected to the superior colliculus, reticular formation, lateral habenula, and the pedunculopontine nucleus (Tepper et al., 2007).

OFC = orbitofrontal cortex; ACC = anterior cingulate cortex; GPe = globus pallidus external segment; STN = subthalamic nuclei; SNr = substantia nigra pars reticulata; GPi = globus pallidus internal segment.

The CSTC Circuitry – In Need of a Revision?

Even though the CSTC model of OCD has gained dominance in the recent years, emerging neuroimaging findings on the pathophysiology of OCD have indicated its inadequacy in explaining the phenomenology of the disorder. Increasing reports have urged for the consideration of several hypotheses, networks and regions to complement the CSTC model towards a better understanding of OCD pathophysiology. These include the dorsolateral prefrontal cortex (DLPFC)-dorsal caudate circuitry, affective dysfunction network, dorsal anterior cingulate cortex (dACC) as a hub for cognitive control, and other structures such as the cerebellum and parietal cortex. These proposals provide additional factors of consideration in understanding the OCD phenomenology.

Dorsolateral Prefrontal Cortex (DLPFC) – Dorsolateral Caudate Circuit

The DLPFC-dorsolateral caudate circuit is also known as the executive network and is involved in executive functions such as cognitive flexibility and inhibition (Grahn, Parkinson, & Owen, 2008). The CSTC model has been thought to provide an explanation to why patients with OCD engage in recurrent obsessions and compulsions, and the executive network complements that by providing a cognitive view on why individuals with OCD experience difficulties switching to new and more adaptive behaviours even when they are aware that their obsessions and compulsions are excessive and dysfunctional (Saxena & Rauch, 2000).

Cognitive Control and dACC

Cognitive control has been considered as one of the core dysfunctions in OCD. Cognitive control refers to the ability to attend to relevant information while ignoring irrelevant ones, adjust behaviours according to shifting goals, and override automatic responses for more adaptive behaviours (McGovern & Sheth, 2017). Seen as a hub of cognitive control, the dACC is involved in several cognitive processes such as performance

monitoring, action selection and goal-directed behaviours, and is found to be activated during threat assessment and generalization of fear in patients with OCD (Saxena & Rauch, 2000; van den Heuvel et al., 2010). The dACC has extensive connectivity with other regions, such as the DLPFC, subcortical and limbic structures including the lateral basal nucleus of amygdala (Barbas & De Olmos, 1990; Morecraft et al., 2007), and motor regions such as primary, premotor and supplementary motor regions (Paus et al., 1996). Considering its wide range of connectivity and functions, the dACC has been proposed as a focus of dysfunction in OCD pathophysiology (McGovern & Sheth, 2017; Milad et al., 2007; Milad & Rauch, 2012).

Affective Dysfunctions and Networks

Relatively less understood is the involvement of affective dysfunction in OCD. Affective dysregulation is operationalized as heightened anxiety levels, dysregulated emotional states, with deficits in processing rewards and emotional stimuli. According to this view, individuals with OCD experience difficulties inhibiting thoughts and feelings that are often accompanied by anxiety, and engage in compulsions to neutralize the anxiety and distress (Milad & Rauch, 2012). Dysfunctional fear mechanisms and fear extinction processes were also postulated to drive and maintain compulsions (Milad et al., 2007; Schienle, Schafer, Stark, Walter, & Vaitl, 2005), though no studies have yet examined fear extinction and fear retention in OCD.

Wood & Ahmari (2015) proposed the involvement of a dysfunctional corticolimbic-ventral striatal network in pathologic compulsive behaviours and affective dysregulations that consists of the IOFC, mOFC, amygdala, ventral tegmental area and the ventral striatum (Wood & Ahmari, 2015). Dysfunctions in the ventral striatum were suggested to contribute to compulsive behaviours through ineffective evaluation and representation of actions and outcomes in a dysfunctional reward-learning and habit-like manner (Gillan et al., 2014; Gruner, Anticevic, Lee, & Pittenger, 2016; Wood & Ahmari, 2015). The role of the amygdala

in OCD pathophysiology is less clear. Some studies reported amygdala hyperactivity in OCD patients when viewing symptom-provoking and non-specific emotional stimuli (Cardoner et al., 2011; Mataix-Cols & van den Heuvel, 2006; Simon, Kaufmann, Musch, Kischkel, & Kathmann, 2010), but one study had reported amygdala hypoactivity during non-specific stimuli (Cannistraro et al., 2004). Even though it may be potentially important to understand affective dysfunctions in OCD, these constructs are better investigated using emotional/negative and symptom/anxiety-provoking stimuli, and are out of scope of the current study.

Other Structures: Cerebellum

Existing literature have often reported abnormal activity in structures that were not within the standard model. In this section, we explore two structures: the cerebellum (Roth et al., 2007; Woolley et al., 2008), and the parietal cortex (Huyser, Veltman, Wolters, de Haan, & Boer, 2010; Page et al., 2009).

Traditionally thought to be involved in movement-related functions, the cerebellum is also involved in higher cognition (Chen & Desmond, 2005; Lee et al., 2005; Rapoport, van Reekum, & Mayberg, 2000; Yeganeh-Doost, Gruber, Falkai, & Schmitt, 2011). A meta-analysis that evaluated the functional topography of the cerebellum reported that motor/sensorimotor tasks activated the anterior cerebellum lobules, and higher-order cognition such as working memory, and executive functions (such as set-shifting and inhibition) activated the posterior cerebellum (Stoodley & Schmahmann, 2009). These findings are consistent with the anterior sensorimotor vs. posterior cognitive dichotomy of the cerebellum. According to this proposal, the cerebellum can be divided into two zones based on its functional connectivity profiles: a sensorimotor zone and a supramodal zone (O'reilly, Beckmann, Tomassini, Ramnani, & Johansen-Berg, 2009). The sensorimotor zone is functionally connected to the sensory, motor and visual regions, and comprises the anterior

lobes including lobules I-V and a secondary representation in lobule VIII. The supramodal zone includes Crus I, Crus II, and lobule VIIa of the posterior cerebellum, and has strong connectivity with prefrontal and inferior parietal regions (O'reilly et al., 2009; Stoodley & Schmahmann, 2010). Lobule IX is also considered as part of the posterior cerebellum, with key roles in visual guidance of movement (Glickstein et al., 1994), and involvement in the default mode network (Habas et al., 2009).

Considering the involvement of the cerebellum in higher-order cognition such as inhibition and set-shifting functions, neural alterations involving the cerebellum are to be expected in OCD as these functions have been thought as core deficits in OCD pathophysiology. Indeed, existing studies have reported increased (Koprivova et al., 2009; Pujol et al., 2004) and decreased cerebellar grey matter volumes (Kim et al., 2001), and altered cerebellar activations during cognitive control tasks such as switching and interference (Henseler et al., 2008; Nabeyama et al., 2008; Nakao, Nakagawa, Yoshiura, et al., 2009; Page et al., 2009; Woolley et al., 2008). However, altered cerebro-cerebellar involvement in executive functions have not been well studied in OCD, which the current thesis attempts to address. Moreover, past findings of cerebellar anomalies were reported amongst others and no analyses were specifically planned to evaluate neural alterations in the cerebellum.

In terms of connectivity, the cerebellum has reciprocal connections with several frontal regions that occur via the cerebello-thalamo-cortical and cortico-ponto-cerebellar loops (Ito, 2008; Kelly & Strick, 2003; Middleton & Strick, 2000a; Schmahmann & Pandya, 1989), and have projections with the fronto-striatal regions, thalamus, and the ACC (Krienen & Buckner, 2009; Middleton & Strick, 2000a, 2000b; Schmahmann & Sherman, 1997), which are also key regions of the CSTC. Few studies have evaluated cerebellar connectivity in OCD, and existing reports demonstrated altered cerebro-cerebellar connectivity in OCD

samples within the cerebellum (Zhang et al., 2011) and increased connectivity between the medial occipital/cerebellum and fronto-parietal regions (Stern, Fitzgerald, Welsh, Abelson, & Taylor, 2012) in patients with OCD compared to controls. However, relationships between cerebellar connectivity and clinical indices were not observed/reported. Interestingly, a separate study had reported increased connectivity between the cerebellum and caudate/putamen, and between the cerebellum and dorsolateral prefrontal cortex in patients with OCD following 4 weeks of cognitive-behavioural therapy (Moody et al., 2017). Considering all of the above, the cerebellum appears to be involved in OCD pathophysiology. However, its involvement in OCD pathophysiology has not been systematically evaluated nor explored. Limited understanding of cerebellar involvement in the pathophysiology of OCD could also be attributed to the scanning practice of many studies excluding the cerebellum during image acquisition. Considering the far-reaching innervations of the cerebellum to other cortical and sub-cortical regions, further research is necessary to investigate the role of cerebellar abnormalities in OCD.

Other Structures: Parietal Cortex

The parietal cortex works in tandem with other regions such as the DLPFC, inferior frontal cortex, and the OFC (Horn, Dolan, Elliott, Deakin, & Woodruff, 2003) and is involved in several cognitive processes, such as attentional set-shifting, planning, response inhibition, visuospatial processing and visual memory (Hampshire & Owen, 2006; Nagahama et al., 1996). In view of its functions, it has been suggested that the parietal regions, in particular the supramarginal and angular gyri, operate as part of a posterior attention system that is important in disengaging spatial attention (Posner & Petersen, 1990) and cognitive control.

Consistent with this argument, evidence from cognitive studies reported abnormalities in OCD samples in parietal regions such as the supramarginal gyrus and angular gyri during

tasks of executive functioning, for example, attentional set-shifting, planning, and response inhibition (de Wit, de Vries, et al., 2012; Morein-Zamir et al., 2016; Page et al., 2009; Roth et al., 2007; van den Heuvel et al., 2005). Meta-analyses also reported reduced grey and white matter volumes in several parietal regions, such as the precuneus, supramarginal gyrus, postcentral gyrus, and the angular gyrus in OCD patients compared to controls (Menzies, Williams, et al., 2008; Radua & Mataix-Cols, 2009a; Rotge et al., 2010).

Interestingly, parietal abnormalities have been reported as possible endophenotypic markers for OCD (Menzies et al., 2007; Menzies, Williams, et al., 2008). Compared to non-proband controls, patients with OCD and their unaffected first-degree relatives showed reduced fractional anisotropy (Menzies, Williams, et al., 2008) and increased grey matter density in the parieto-cingulo-striatal system that was associated with reduced inhibitory control in a stop-signal task (Menzies et al., 2007). A separate study also reported reduced activity in OCD patients and their relatives in the left supramarginal gyrus (BA40), bilateral IOFC and lateral prefrontal cortex during reversal learning (Chamberlain et al., 2008). These findings suggest potential predisposing genes for OCD and locus of dysfunction in OCD (Menzies, Chamberlain, et al., 2008).

Summary

We presented the CSTC circuitry and emerging hypotheses, networks and regions that complement the CSTC circuitry in understanding OCD pathophysiology. The CSTC circuitry mainly consists of the OFC, ACC, thalamus and basal ganglia regions. Other networks and regions that have been postulated in OCD pathophysiology include the DLPFC-caudate network that attempted to explain for difficulties experienced by OCD patients in switching to new and more adaptive behaviours; the dACC as a hub for cognitive control; and lastly, affective networks that consist of the IOFC, mOFC, amygdala and ventral striatum regions that were postulated to maintain compulsive behaviours via dysfunctional reward-learning

mechanisms. Existing studies have also commonly reported abnormalities in the cerebellum and parietal cortex in OCD samples, and we consider their involvement in the pathophysiology of OCD. The review of networks/regions implicated in OCD pathophysiology appeared to involve the OFC, dorsolateral, anterior cingulate, striatum, cerebellar and parietal regions.

Working Memory and Executive Function Task Difficulties in OCD

OCD has been associated with neuropsychological deficits (Cottraux & Gerard, 1998; Purcell, Maruff, Kyrios, & Pantelis, 1998b). This is reasonable considering the structural and functional alterations in OCD involving the CSTC, cerebellum and parietal cortex and the functions sub served by these regions. Existing reports on evidence for deficits in neuropsychological domains are abundant but inconsistent, and reviews postulated that failures to control for co-morbid conditions potentially contributed to inconsistent findings (Chamberlain, Blackwell, Fineberg, Robbins, & Sahakian, 2005; Kuelz, Hohagen, & Voderholzer, 2004). In this section, we discuss task domains that are frequently implicated in OCD: Verbal and visuospatial working memory (de Vries et al., 2013; Henseler et al., 2008) and executive functioning domains, specifically response inhibition (Chamberlain, Fineberg, Blackwell, et al., 2007; Kang et al., 2013; Maltby, Tolin, Worhunsky, O'Keefe, & Kiehl, 2005; Menzies et al., 2007), interference (Huysen, Veltman, Wolters, de Haan, & Boer, 2011; Schlosser et al., 2010) and set-shifting (Britton et al., 2010; Gu et al., 2008; Han et al., 2011; Remijnse et al., 2006).

Verbal and Visuospatial Working Memory

Existing literature on verbal and visuospatial working memory performances in OCD patients have been mixed. Some studies reported deficits in verbal working memory in patients with OCD (Deckersbach, Otto, Savage, Baer, & Jenike, 2000; Savage et al., 2000), but not others (Boone, Ananth, Philpott, Kaur, & Djenderedjian, 1991; Christensen, Kim,

Dysken, & Hoover, 1992; Kuelz et al., 2004; Zielinski, Taylor, & Juzwin, 1991), and this was similar for visuospatial working memory, for example (Deckersbach et al., 2000; Savage et al., 2000) VS (Ciesielski et al., 2007; Henseler et al., 2008).

Inefficient Organizational Strategies. The seemingly inconsistent findings have been hypothesized to attribute to an underlying executive function impairment that mediates the ability to utilize efficient strategies (Savage et al., 1999). Patients with OCD did not appear to demonstrate significant differences relative to controls in tasks that assess attention span and require sustained attention, for example digit forward and backward spans and verbal list learning tests (Boone et al., 1991; Christensen et al., 1992; Kuelz et al., 2004; Zielinski et al., 1991). On the other hand, poorer performances were observed in OCD samples in tasks such as the California Verbal Learning Test (CVLT) (Deckersbach et al., 2000; Savage et al., 2000), where aurally presented stimuli could be semantically clustered for enhanced encoding and retrieval. Patients also showed poorer scores than controls in visuospatial and nonverbal working memory tasks, such as the Rey Osterrieth Complex Figure test (Deckersbach et al., 2000; Martinot et al., 1990), CANTAB spatial recognition memory task (Nielen & Den Boer, 2003; Purcell et al., 1998b) and visual n-back tasks (van der Wee et al., 2003). Instead of processing visual information as integrating wholes, OCD samples may tend to place their focus on irrelevant details and process information as fragmented units, hence affecting encoding and retrieval (Kuelz et al., 2004; Olley, Malhi, & Sachdev, 2007).

Verbal Mediation. Taking into consideration that deficit performances were more consistently observed in nonverbal tasks, some suggested that OCD samples tended to demonstrate deficits in tasks that limit verbal mediation (Olley et al., 2007; Purcell et al., 1998b). Poorer performance was reported in OCD samples relative to controls in spatial memory and recognition tasks, where verbal representations may not be applied easily

(Gross-Isseroff et al., 1996; Martin, Wiggs, Altemus, Rubenstein, & Murphy, 1995; Purcell et al., 1998b; Zielinski et al., 1991). Even though this thought could potentially explain for reduced performances observed in non-verbal tasks, the lack of verbal representations alone does not provide an explanation for poorer performances in some verbal tasks such as the CVLT.

Working-memory Explanation. The working memory explanation is based on Baddeley's modified model that consists a central executive, phonological loop, visuospatial sketchpad and episodic buffer (Baddeley, 2000). According to the working memory explanation (Harkin & Kessler, 2011), memory impairments are relevant to executive dysfunction in OCD (Greisberg & McKay, 2003), and the combined load of a task could be understood in three factors: i) executive functioning requirements (low if materials can be maintained successfully or if organization is not interfered); ii) binding complexity (low if stimuli has a single feature); and iii) memory load (low if within the phonological loop capacity of six items, and visuospatial sketchpad of four items; (Baddeley, 2000)). Situations such as rumination (Exner, Martin, & Rief, 2009) and symptom-related stimuli (Coles & Heimberg, 2002) interfere with task encoding in OCD, and divides attention to binding; inappropriate use of strategies decrease binding efficiency and could increase memory load; binding complexity increases with the number of features or multi-modalities (Harkin & Kessler, 2009; Olley et al., 2007). The review indicated that patients with OCD showed deficit performance when the task benefits from some input organization that influence binding efficiency and memory load (Harkin & Kessler, 2011). For instance, comparable group performances among OCD samples and controls were observed in verbal span tasks (Boone et al., 1991; Christensen et al., 1992; Kuelz et al., 2004; Zielinski et al., 1991), where input strategies were minimal, task stimuli were low in binding complexity, and low in memory load; poorer performance in the CVLT in OCD (Deckersbach et al., 2000; Savage et

al., 2000) could be explained by the lack of effective strategy use like chunking, and hence the task was high in binding complexity and high in memory load.

For visuospatial tasks, the authors postulated that OCD patients showed deficits in tasks that exceeded the visuospatial sketchpad capacity (more than six items) were high in executive requirements and high in binding complexity (Harkin & Kessler, 2011). Two studies (Ciesielski et al., 2007; Henseler et al., 2008) did not show group differences in a delayed-match-to-sample task that were low in all three factors. Group differences in spatial search tasks were also not observed when memory load was low (2-4 items), but performances were poorer in OCD samples than controls with increased memory load (6-8 items) (Purcell, Maruff, Kyrios, & Pantelis, 1998a). Consistent with this postulation, OCD samples also showed poorer performances relative to controls on the Corsi-block span (Boldrini et al., 2005; Moritz, Kloss, Jahn, Schick, & Hand, 2003; Zielinski et al., 1991). Performance on these load-dependent tasks suggested that executive functioning could be stressed at high memory loads, that led to poorer performances in OCD (Harkin & Kessler, 2011).

Summary. Behavioural findings of verbal and visuospatial working memory in OCD samples appear inconsistent, especially when findings are considered in a domain-specific approach. Several hypotheses such as the inefficient use of strategies and the working memory explanation could potentially explain for the existing observations. However, most studies that evaluated visuospatial abilities in OCD had typically utilized spatial but not visual paradigms in their investigations, and therefore, knowledge about visual working memory in OCD is still not well understood.

Neuroimaging Findings. Neuroimaging studies evaluating working memory in OCD samples are limited. One study reported comparable task accuracy and reaction times in OCD samples and controls during verbal and spatial working memory tasks (Henseler et al.,

2008) despite neural differences. Compared to controls, OCD samples showed increased activations in regions such as the inferior frontal gyrus and intraparietal cortex during verbal working memory, and the precentral sulcus during both verbal and visual working memory task performances (Henseler et al., 2008). Hyperactivity in these regions have also been viewed as compensatory processing that enabled OCD samples to have comparable performances as the controls (Henseler et al., 2008). Compensatory hyperactivity in the anterior insula, frontal, parietal and striatal regions were also reported in other investigations that purportedly evaluated working memory using verbal and visual n-back tasks (Koch et al., 2012; Nakao et al., 2005; Purcell et al., 1998a; Purcell et al., 1998b). More neuroimaging studies of working memory are required in OCD samples to ascertain neural abnormalities during task performance.

One caveat is that existing tasks that reportedly measured working memory also in effect assessed other cognitive processes. An example is the n-back task that has been regularly used to evaluate working memory. In a typical n-back task paradigm, participants identify whether the current stimulus matched a stimulus presented n-trials previously. Several cognitive processes are required for successful performance: consistent updating and active maintenance of information and their serial order, and inhibiting previously relevant information (n-lag) that has turned irrelevant (non n-lag) as the task progresses. Due to the involvement of multiple executive processes, the n-back task may not be a pure measure of working memory (Chatham et al., 2011; Miller, Price, Okun, Montijo, & Bowers, 2009). Therefore, it is important that tests selected measure the intended cognitive processes.

Cognitive Control

Existing studies utilized neuropsychological tests to investigate cognitive control in OCD, and these cognitive domains include response inhibition, interference, and set-shifting.

Response Inhibition. Relevant to the concept of cognitive control, response inhibition can generally be understood as the ability to suppress pre-potent or automatic behaviours that are inappropriate or no longer relevant (Chambers, Garavan, & Bellgrove, 2009; McGovern & Sheth, 2017). Considering that individuals with OCD experience difficulties inhibiting obsessions and compulsions, response inhibition has been thought to be a suitable measure to investigate neural substrates relevant to dysfunctional inhibitory processes (van Velzen, Vriend, de Wit, & van den Heuvel, 2014). The construct of response inhibition can be differentiated into motor response inhibition and interference control (Schachar et al., 2007). Motor response inhibition refers to inhibition of pre-potent motor responses, with the most common examples include Go/No Go and Stop-signal tasks. Motor response inhibition tasks activate a network of frontal regions such as the orbitofrontal, dorsolateral and medial frontal, temporal and parietal cortices, cerebellum and basal ganglia (Horn et al., 2003; Menzies et al., 2007; Roth et al., 2007; Rubia et al., 2001); and performance on the task were associated with grey matter volumes in the inferior frontal gyrus and pre-supplementary motor area regions (Aron, Robbins, & Poldrack, 2004).

Deficits in response inhibition have been proposed as a behavioral endophenotype for OCD (Chamberlain, Fineberg, Menzies, et al., 2007; Chamberlain & Menzies, 2009; de Wit, de Vries, et al., 2012; Menzies et al., 2007). In one study, 31 OCD patients and their unaffected first-degree relatives ($n = 31$) demonstrated delayed response inhibition on a stop-signal task compared to 31 non-concordant controls (Menzies et al., 2007). The study also reported significant associations between impaired performance and reduced grey matter in the OFC and right inferior frontal regions, and increased grey matter in the cingulate, parietal and striatal regions in the OCD and matched-relative groups (Menzies et al., 2007). However, results were not consistent as some studies failed to find significant patient-control group differences in behavioural performances during a response inhibition task, albeit with neural

differences (Page et al., 2009; Roth et al., 2007). Interestingly, studies that reported significant behavioural performances during response inhibition coincided with larger sample sizes of having more than 20 participants per group (for example: de Wit et al. (2012) – 41 OCD, 17 siblings, 37 controls; Chamberlain et al., 2007 – 20 OCD, 20 relatives, 20 controls) as compared to studies that failed to find significant group differences (Page et al., 2009 – 10 OCD, 11 controls; Roth et al., 2007 – 12 OCD, 14 controls). Nevertheless, some have regarded motor inhibition as a potential biomarker for OCD (Chamberlain et al., 2005; McLaughlin et al., 2016).

Interference Control. Interference control refers to the cognitive control required to prevent interference due to irrelevant competing information (Nigg, 2000); examples include the Stroop task and the Flanker task. Existing studies reported that individuals with OCD have difficulty ignoring irrelevant information (Clayton, Richards, & Edwards, 1999; Enright & Beech, 1990), and this difficulty has been associated to frontal-striatal function (Jentsch & Taylor, 2001; MacDonald, Cohen, Stenger, & Carter, 2000; Pardo, Pardo, Janer, & Raichle, 1990). In terms of behavioural performances, some studies reported greater difficulty in interference control on the Stroop task in patients with OCD compared to controls (Kalanthoff, Henik, Simpson, Todder, & Anholt, 2017; Martinot et al., 1990; Penades et al., 2007), but others failed to observe significant group differences (Hajcak & Simons, 2002; Koçak, Nalçacı, Özgüven, Nalçacı, & Iclal, 2010; Moritz et al., 2004; Page et al., 2009). Neuroimaging findings have generally reported altered functional activations in OCD samples in the cingulate, caudate and cerebellar regions during interference tasks. However, there are inconsistencies in the direction of increased or reduced activations in OCD samples compared to controls (Nabeyama et al., 2008; Nakao, Nakagawa, Yoshiura, et al., 2009; Nakao et al., 2005; Schlosser et al., 2010). Inconsistencies in the findings could potentially be attributed to the different versions of Stroop tasks used, symptom improvements due to

treatment, small sample sizes and heterogeneity of the symptoms (Koçak et al., 2010; Nabeyama et al., 2008).

Set-shifting. Considering the perseverative and repetitive nature of the disorder manifestations, impaired set-shifting abilities have also been proposed as a core neurocognitive feature in OCD (Chamberlain, Fineberg, Blackwell, Robbins, & Sahakian, 2006; Chamberlain, Fineberg, Menzies, et al., 2007). Existing studies seemed to support this notion, with reported observations of set-shifting deficits in patients with OCD (Abbruzzese, Ferri, & Scarone, 1997; Veale, Sahakian, Owen, & Marks, 1996; Watkins et al., 2005). Neuroimaging investigations demonstrated abnormal neural activations in the prefrontal, cingulate, basal ganglia and parietal regions during set-shifting, with reduced activations in these regions during switching in patients with OCD compared to controls (Gu et al., 2008; Page et al., 2009). Interestingly, Chamberlain and colleagues (2008) reported reduced activations of several cortical regions, including the lateral orbitofrontal, lateral prefrontal, and parietal regions during reversal learning in OCD patients without comorbid conditions ($n = 14$) and their unaffected first-degree relatives ($n = 12$) compared to controls ($n = 15$). However, in terms of behavioural performances, relatives had slower response times compared to the patients and controls, but there were no significant differences in response times between patients and controls (Chamberlain et al., 2008). That neural but not behavioural differences were consistently observed in patients and their relatives suggest the plausibility that neural pathogenesis may be more proximal than behavioural expressions to underlying genetic diathesis.

Despite the seemingly abundant information that demonstrated executive impairment in OCD, it remains challenging to pin-point exact mechanisms that are impaired in the disorder as individual studies utilized different tasks that entailed different levels of task processes and difficulties, therefore contributing to varying findings of neural involvement

(Koch et al., 2012). In addition, studies with smaller sample size suffer in statistical power, and may miss observations of behavioural impairments in the patients sample, as evident in several small sample sized studies reviewed above.

Chapter Summary

In this chapter, we first discussed the neural models of OCD, namely the CSTC circuitry, dorsolateral prefrontal cortex-caudate network; the dACC in cognitive control, and affective networks; and considered the involvement of the cerebellum and parietal cortex in OCD pathophysiology. The literature review of networks and regions implicated in OCD pathophysiology appear to involve the OFC, DLPFC, ACC, striatum, cerebellar and parietal regions. Affective networks and dysfunctions in OCD are relatively less understood and would require specific emotive and symptom-provocation paradigms to investigate relevant research questions. As these paradigms are not employed in the current thesis, further discussions on affective networks are out of the scope of the thesis.

In the second part of the literature review, we reviewed existing evidence on verbal working memory, visuospatial working memory, and domains related to cognitive control – response inhibition, interference and set-shifting. Inconsistencies observed in verbal and visuospatial working memory have been attributed to several potential explanations, such as inability to utilize effective strategies and working memory load in terms of executive function requirements, binding complexity and memory load of the tasks. Motor inhibition has been regarded as a potential biomarker for OCD (McLaughlin et al., 2016; Menzies et al., 2007), even though inconsistent findings in behavioural performances of cognitive control have been generally reported. These inconsistent findings could potentially be attributed to factors such as task specifications, and sample characteristics, such as sample size, with larger studies being more sensitive to behavioural differences compared to smaller sample studies.

Neuroimaging evidence generally showed group differences in frontal and parietal regions during verbal and visual working memory, and the OFC, dorsolateral, cingulate, parietal and cerebellar regions in cognitive control. In general, abnormal neural activations observed during these tasks have been postulated to be relevant to the intrusive and persistent obsessive thoughts and dysfunctional behavioural patterns in OCD. Even though the findings seem consistent with the regions included within the OCD networks and hypotheses, different studies utilized different paradigms and had included patient groups with comorbid conditions, hence these findings may have limited clinical utility.

Motivation for the Thesis and Reiteration of Research Aims

Several gaps could be identified based on the review of past studies. Even though past studies have reported altered activations/volumes in the cerebellum, no study has yet investigated the cerebellum specifically. Distinct subregions of the cerebellum occur on a much smaller scale than cerebral cortical regions, and the ICBM152 template from the Montreal Neurological Institute (MNI) typically used in normalisation provides very little anatomical detail of the cerebellum, leading to poor alignment of cerebellar structures (Diedrichsen, 2006). Unlike the ICBM152 template, the SUI template is of higher resolution and provides more accurate normalization of the cerebellum (Diedrichsen, 2006). In addition to analysing alterations of cortical/subcortical regions in grey matter structure and task-related functional activations, we also conducted separate evaluations in this thesis to identify group differences in the cerebellum. Lastly, considering the intricate connectivity between the cerebellum and the subcortical and cortical regions (Buckner et al., 2011), accurate localization of anomalies is important and could inform corresponding involvement of other cortical regions. Therefore, in addition to evaluating alterations of the cerebellum in terms of structure and function, connectivity analyses of resting-state data are also performed

to understand underlying differences in cerebro-cerebellar connectivity and their associations with OCD symptomatology.

Even though much discussion have been made on verbal and visuospatial memory in OCD and in understanding why domain-specific inconsistencies were observed, most studies that evaluated nonverbal/visuospatial tasks often utilized spatial paradigms, while many studies that evaluated verbal working memory had utilized n-back task paradigms that would also require executive functioning involvement. Moreover, it is also important to note that past studies had frequently included OCD samples with significant comorbid conditions, which adds complexity in results interpretation as findings could be complicated by the presence of comorbid conditions.

The current thesis adopts a systematic approach to understand and clarify the neural correlates of OCD. We attempt to address some research gaps via an empirical study by evaluating the involvement of the cerebellum in OCD pathophysiology using a normalization technique that improves the alignment of cerebellar fissures to a high-resolution atlas template of the human cerebellum (Diedrichsen, 2006). We also evaluate functional activations during verbal and visual working memory, and a response-inhibition task. To overcome the shortcomings stated above, the current study has utilized a Sternberg's paradigm, which is a basic working memory paradigm that involves encoding, maintenance and retrieval (Corbin & Marquer, 2013), and included OCD patients without comorbid conditions.

The subsequent chapters are organized in the following sequence: The next chapter presents a meta-analysis (Study 1; Chapter 3) to quantitatively consolidate the existing neuroimaging findings in OCD in terms of structural grey matter volumes (Study 1a), and executive-function task-related brain activations (Study 1b). This is followed with an empirical study (details in Chapter 4), that enabled evaluations of grey matter alterations

(Study 2; Chapter 5), functional activations during verbal and visual working memory and stop-signal task (Study 3; Chapter 6), and resting-state evaluations (Study 4; Chapter 7) that probes intrinsic activity in resting-state networks (Study 4a), and functional connectivity involving the cerebellum (Study 4b) in OCD samples relative to controls. Figure 2-2 presents a more elaborated framework that details the aims and hypotheses for each study that will be further discussed in subsequent chapters.

Figure 2-2. Aims and hypotheses of this dissertation.

CHAPTER 3²: STUDY 1 – META-ANALYSIS

Meta-analysis on structural and executive task-related functional neuroimaging studies in
OCD

² Publication: Study 1 in the thesis has been published in full as a journal article as it appears in “G.K. Eng, K. Sim, & S.H.A. Chen. (2015). Meta-analytic investigations of structural grey matter, executive domain-related functional activations, and white matter diffusivity in obsessive compulsive disorder: an integrative review. *Neuroscience and Biobehavioral Reviews*, 52, 233-257.”

Introduction

The cortico-striato-thalamo-cortical (CSTC) model has been the leading model of OCD pathophysiology and critical in guiding investigations. However, existing reports of neural abnormalities within the CSTC circuitry have been somewhat inconsistent. For instance, some studies have reported increased (Szeszko et al., 2008) and reduced grey matter in bilateral OFC (Hoexter et al., 2012) in OCD, and some others observed increased grey matter only in left OFC (Christian et al., 2008; Kim et al., 2001), and reduced grey matter in right OFC (Pujol et al., 2004; Togao et al., 2010) in OCD patients compared to healthy controls. Variability in these findings could be attributed to the use of region-of-interest (ROI) analytic techniques, comorbid conditions within the patient group, and small sample sizes; or could potentially indicate possible limitations of the existing model in defining abnormalities involved in the disorder.

Past studies have indicated the involvement of other regions outside CSTC network in OCD pathophysiology. For instance, abnormal functional activations in parietal regions were observed in OCD patients during working memory and response inhibition tasks (Roth et al., 2007; Woolley et al., 2008), and altered resting-state connectivity was observed between the inferior and superior cerebellum in patients with OCD compared to controls (Zhang et al., 2011). As noted in the previous chapter, additional involvement of the OFC, DLPFC, ACC, striatum, cerebellar and parietal regions were associated with OCD pathophysiology. These and other existing reports seemed to question the adequacy of the CSTC model in accounting for all abnormalities observed in OCD pathophysiology and suggests the need to clarify the neural correlates of the disorder (Menzies, Chamberlain, et al., 2008; Milad & Rauch, 2012; Millet et al., 2013; Radua & Mataix-Cols, 2009a).

Previous meta-analyses have also highlighted grey matter alterations in OCD (Radua & Mataix-Cols, 2009a; Rotge et al., 2009; Rotge et al., 2010). In general, altered grey matter

volumes were reported within the dorsal prefrontal-striatal model, involving the superior and middle frontal regions, anterior cingulate, thalamus, caudate and putamen (Radua & Mataix-Cols, 2009a; Rotge et al., 2009; Rotge et al., 2010), and within parieto-frontal regions such as the supramarginal gyrus, precuneus, superior parietal lobule and the orbitofrontal regions (Radua & Mataix-Cols, 2009a; Rotge et al., 2009; Rotge et al., 2010). However, findings of altered grey matter volumes were not consistently observed across all three meta-analyses. For instance, altered grey matter of the orbitofrontal cortex was only reported in the meta-analysis conducted by Rotge and colleagues (2009) but not in the other two meta-analyses (Radua & Mataix-Cols, 2009a; Rotge et al., 2010). These could be attributed to limited papers that contributed to low number of foci in data analyses and the inclusion criteria of papers for the meta-analyses.

Executive functioning is generally understood to comprise of three main cores: 1) Inhibitory (such as inhibitory control) and interference control (such as selective attention or cognitive inhibition); 2) working memory; and 3) cognitive flexibility (such as set shifting) (Lehto, Juujärvi, Kooistra, & Pulkkinen, 2003; Miyake et al., 2000). These relatively simple executive function abilities are engaged and built upon to give rise to higher-order executive functions such as planning and problem solving (Collins & Koechlin, 2012; Lunt et al., 2012). To the best of our knowledge, no meta-analysis has yet to consolidate task-related abnormalities for executive function in patients with OCD, and concurrently relate these functional abnormalities with differences in structural grey matter. This is important as dysfunctions in cognitive control, especially response inhibition, interference, and set-shifting abilities have often been proposed as core neurocognitive features in OCD (Chamberlain et al., 2005; Chamberlain & Menzies, 2009; Watkins et al., 2005). A multi-modality approach could enhance understanding about the structural and functional anomalies in OCD samples. In this chapter, we present a meta-analysis to quantitatively consolidate existing information

on grey matter and executive function task-related differences in individuals with OCD compared to controls.

This study aims to employ meta-analytic techniques to summarize and integrate differences observed in structural grey matter (Study 1a), and functional activations during the performance of executive function tasks (Study 1b) in OCD samples compared to controls. We narrowed the scope for Study 1b to consider executive function tasks that measured: Response inhibition [Theme 1]; Interference [Theme 2] and Set-shifting [Theme 3]. Findings from this study would enhance our understanding of the neural circuitry implicated in OCD pathophysiology.

In this regard, activation likelihood estimation (ALE) meta-analyses were conducted using GingerALE 2.3.2 algorithm (Eickhoff, Bzdok, Laird, Kurth, & Fox, 2012; Eickhoff et al., 2009; Turkeltaub et al., 2012) to evaluate differences in grey matter volume, and executive function task-related brain activations among patients with OCD and healthy controls. A qualitative approach is then adopted to discuss findings from separate meta-analyses.

Aims and Hypotheses

Study 1 aims to employ meta-analytic techniques to consolidate neuroimaging literature in: Structural grey matter abnormalities (Study 1a), and functional activations during the performance of executive function tasks (Study 1b) in patients with OCD compared to controls. We narrowed the scope for Study 1b to consider executive function tasks that measured: Response inhibition [Theme 1]; Interference [Theme 2] and Set-shifting [Theme 3].

Compared to controls, we expect patients with OCD to show abnormal activations in the cingulate, inferior frontal, parietal activations during executive tasks. Also, consistent with the general literature, we expect group differences in grey matter in regions within the CSTC

circuitry, such as the orbitofrontal and striatum regions; and additional parietal and cerebellar abnormalities in patients with OCD compared to healthy controls.

Methodology

Data sources

The National Centre of Biotechnology Information (NCBI), PubMed/Medline and ScienceDirect databases were searched for relevant neuroimaging studies in OCD subjects up till July 2014. Potentially useful reports were identified and screened as abstracts for meeting inclusion criteria that follow. Articles were further reviewed as full reports, and their bibliographies were screened for additional references.

Keywords for literature search

Keywords for the literature search for Study 1a (Structural grey matter) included: ‘obsessive-compulsive disorder/OCD’ with ‘structural magnetic resonance imaging/MRI’; and for Study 1b (Executive function task-related functional activations): ‘obsessive-compulsive disorder/OCD’ with ‘functional magnetic resonance imaging/fMRI’, ‘functional neuroimaging’, ‘cognition’, ‘executive function’, ‘executive functioning’.

Inclusion/exclusion criteria

A study was included if it 1) was published in an English-language peer-reviewed journal; 2) included patients who were diagnosed with OCD; 3) reported stereotactic coordinates of group differences between an OCD group and a control group; 4) utilized a sample size of more than 5; and 5) utilized whole-brain analyses -- studies that reported only ROI findings were excluded.

Additional inclusion/exclusion criteria for Study 1b.

The process of article selection for final inclusion into each meta-analysis is presented in a PRISMA flowchart (Figure 3-1)³. Articles were included in Study 1b if subjects underwent fMRI scanning while performing executive function tasks; and if executive function tasks were relevant to the following categories: Theme 1: Response inhibition -- tasks that required the termination of a planned response or withdrawal of a prepotent motor response; Theme 2: Interference -- tasks that involved interference suppression due to the presentation of congruent and incongruent information; and Theme 3: Set switching/shifting - - tasks that required rapid switching between task sets or task rules.

Five articles that evaluated executive functioning in OCD were not included in the meta-analysis as these articles evaluated visual/spatial n-back tasks (de Vries et al., 2013; Nakao, Nakagawa, Nakatani, et al., 2009), verbal working memory (Henseler et al., 2008; Koch et al., 2012), and planning (van den Heuvel et al., 2005) domains, and were therefore, neither not suitable to be included in any of the three themes, nor to be considered as separate domains/themes due to the limited number of papers available in their respective domains.

³ Figures and tables were taken in full from the published journal article as it appears in “G.K. Eng, K. Sim, & S.H.A. Chen. (2015). Meta-analytic investigations of structural grey matter, executive domain-related functional activations, and white matter diffusivity in obsessive compulsive disorder: an integrative review. *Neuroscience and Biobehavioral Reviews*, 52, 233-257.”

Figure 3-1. PRISMA flowchart on articles selection according to Moher et al., 2009.

Procedures involving articles removal (other than the duplicates) were indicated by side arrows (→).

1. This procedure removed articles based on their abstracts. Articles that were not full-text articles and articles that were not conducted on patients with obsessive-compulsive disorder were excluded at this stage.
2. This procedure removed articles after screening through their full-text.

Data extraction

Reported foci in Talairach space were transformed to MNI space by means of `mni2tal` (Brett, Christoff, Cusack, & Lancaster, 2001) or `icbm2tal` function (Lancaster et al., 2007). MNI coordinates were then entered into individual ALE analyses (Laird et al., 2010). Studies published after year 2007 and that did not indicate the transformation algorithm were assumed to have applied the `mni2tal` transformation algorithm (Brett et al., 2001).

Activation-likelihood estimation (ALE)

The ALE algorithm has been widely used for coordinate-based meta-analyses for neuroimaging data (Laird et al., 2005; Turkeltaub, Eden, Jones, & Zeffiro, 2002; Wager, Lindquist, & Kaplan, 2007). The algorithm estimates convergence of activation based on significant foci extracted from selected studies. Extracted foci are not treated as single points but are represented as centers of three-dimensional Gaussian spatial probability distributions. Spatial uncertainty of these probability distributions are modelled using estimates of between-subjects and between-template variances, and are reflected as the width of these spatial probability distributions, i.e. the full-width at half-maximum (FWHM). In the revised algorithm, FWHM is not pre-specified across experiments, but is dependent on the sample size within each experiment. The probability distributions of all extracted foci in each experiment are then combined into a modelled activation (MA) map. MA maps of each experiment are then combined to form a probability distribution of ALE scores for a particular single meta-analysis, and are subjected to further thresholding. Recent revisions to the algorithm enabled a data-driven (rather than arbitrary) approach in determining cluster-extent threshold sizes (Eickhoff et al., 2012). The inference approach at cluster-level considers only the spatial extent of super-threshold clusters, which are handled as a single entity. This is in contrast with other threshold options such as FDR corrections that evaluate ALE scores as individual voxels. In cluster-extent threshold, a cluster-forming threshold is first defined that

identifies contiguous volumes, i.e. "clusters" from the ALE analysis. These clusters are tracked and are subjected to a 2nd level of inference, which compares the size of these clusters against a random/null distribution of clusters. The p-value of the cluster-inference threshold is based on the proportion of clusters from the random data that have equivalent or larger sizes than the tracked clusters. Tracked clusters that are large enough to be exceeded in size by 1 out of 100 clusters formed from the random data is considered to have a p-value of 0.01 ($p=0.01$). A reasonably stringent and less biased threshold is recommended at $p \leq .05$ (Eickhoff et al., 2012) -- only tracked clusters that are significantly large enough to be exceeded in size by a maximum of 5 out of 100 random clusters from the random distribution. Simulations that compared ALE analyses yielded by different threshold criterion concluded that the cluster-inference threshold approach is intermediate between the less stringent uncorrected voxel-level threshold and the more conservative FDR and FWE corrections. An advantage of the ALE algorithm is the option to apply cluster-inference corrections for clusters derived based on the regions of activations (Eickhoff et al., 2012). This is in contrast with other meta-analytic techniques that apply false discovery rate (FDR) corrections, which have been showed to be less ideal (Chumbley & Friston, 2009). The ALE algorithm has also been used in other fields of research to conduct meta-analytic investigations of fMRI studies (Chen, Ho, & Desmond, 2012; Wu, Ho, & Chen, 2012), white matter diffusivity (Liao et al., 2013; Yao et al., 2013), and grey matter (Fusar-Poli et al., 2011; Stoodley, 2014).

In the current study, ALE analyses were conducted using GingerALE 2.3.2 (BrainMap, University of Texas) (Eickhoff et al., 2012; Eickhoff et al., 2009; Turkeltaub et al., 2012). This is available as a Java software application and can be downloaded from BrainMap (<https://brainmap.org/ale/>). Since the publication of the last meta-analysis that utilized the ALE algorithm in OCD research (Rotge et al., 2010), several key modifications have been made to the algorithm to improve detection accuracy of significant clusters and

minimize the influence of single studies with large sample sizes on results of the meta-analysis (Eickhoff et al., 2012; Eickhoff et al., 2009; Turkeltaub et al., 2012).

Data synthesis and meta-analyses

Study 1a (Structural grey matter): A total of 1578 articles were initially identified and collected. A total of 13 articles on adults and 6 articles on adolescents were initially identified for final inclusion, contributing to a total of 250 foci (122 in adults and 128 in adolescents), of which 55 foci corresponded to increased volume (40 in adults and 15 in adolescents), and 195 foci corresponded to reduced volume (82 in adults and 113 in adolescents) in a total of 430 adults and 117 adolescents with OCD as compared to 441 adult and 110 adolescent healthy controls. These articles included studies that adopted whole-brain voxel-wise and region-of-interest analyses in grey matter. These articles were further screened to identify studies that utilized whole-brain analytic approaches. A total of 14 articles were identified, of which 10 were on adults and 4 on adolescents, contributing a total of 216 foci, of which 36 foci corresponded to increased volume (all in adults), and 180 foci corresponded to reduced volume (70 in adults and 110 in adolescents) in a total of 331 adults and 36 adolescents with OCD compared to 334 adult and 40 healthy controls [Studies with adult samples: (Gilbert, Mataix-Cols, et al., 2008; Hoexter et al., 2012; Kim et al., 2001; Koprivova et al., 2009; Matsumoto et al., 2010; Pujol et al., 2004; Tan et al., 2013; Togao et al., 2010; Valente et al., 2005; Yoo et al., 2008)].

Study 1b (Executive-function task-related fMRI studies): A total of 961 articles were initially collected, of which 35 articles employed fMRI scanning during the performance of executive function tasks in OCD. Of the 35 articles, 19 articles employed executive function tasks and contributed studies for inclusion in the three themes: 6 studies in Theme 1 (Response Inhibition), 11 studies in Theme 2 (Interference) and 6 studies in Theme 3 (Set-shifting/switching) (Britton et al., 2010; de Wit et al., 2013; de Wit, de Vries, et al., 2012;

Fitzgerald et al., 2010; Fitzgerald et al., 2005; Gu et al., 2008; Han et al., 2011; Huyser et al., 2011; Kang et al., 2013; Maltby et al., 2005; Marsh et al., 2013; Nabeyama et al., 2008; Nakao, Nakagawa, Yoshiura, et al., 2009; Nakao et al., 2005; Page et al., 2009; Roth et al., 2007; Schlosser et al., 2010; Woolley et al., 2008; Yucel et al., 2007). Notably, 2 articles employed multiple tasks and contributed studies in all three themes (Page et al., 2009; Woolley et al., 2008). Articles that restricted analyses and results to ROIs-only were further excluded. Contrasts conducted by each study were also evaluated. A total of 12 articles finally remained with a total of 187 patients with OCD (177 adults and 10 adolescents) compared to 191 controls (182 adults and 9 adolescents). Of these articles, only 1 was conducted in adolescents (Woolley et al., 2008). Included studies were categorized into three themes of executive function.

Theme 1: ‘Response Inhibition’, comprised of 4 articles (3 on adults; 1 on adolescents) that employed either Go/No-go or Stop-signal tasks, contributing a total of 42 foci (38 from adults, 4 from adolescents), of which 15 foci corresponded to increased activations (all from adults) and 27 foci (23 from adults, 4 from adolescents) corresponded to reduced activations in a total of 40 adult and 10 adolescent patients with OCD compared to 43 adult and 9 adolescent controls.

Theme 2: ‘Interference’, comprised of 7 articles (6 on adults, 1 on adolescents) that utilized stroop, multi-source interference test (MSIT), Simon's or flanker tasks. These studies contributed a total of 41 foci (39 from adults, 2 from adolescents), of which 16 foci corresponded to increased activations and 25 foci (23 from adults, 2 from adolescents) corresponded to reduced activations in a total of 102 adult and 10 adolescent patients with OCD compared to 100 adult and 9 adolescent controls.

Theme 3: ‘Switching and Shifting’ included 5 articles (4 on adults, 1 on adolescents) that adopted switching and shifting paradigms, contributing a total of 54 foci (52 from adults,

2 from adolescents), of which 3 foci (from a single study) (de Wit et al., 2013) corresponded to increased activations and 51 foci (46 from adults, 5 from adolescents) corresponded to reduced activations in a total of 55 adult and 10 adolescent patients with OCD compared to 61 adult and 9 adolescent controls. Separate meta-analyses were conducted in accordance to their individual themes. Meta-analysis was not conducted for 3 foci that corresponded to increased activations during the performance of switching and shifting paradigms (Theme 3) as the 3 foci were contributed from a single study (de Wit et al., 2013).

A general note

We conducted separate meta-analyses for adults and adolescents. Study 1a included a total of 10 articles that utilized adult samples and 4 articles on adolescents samples. Even though separate meta-analyses were conducted for studies with adolescents in Study 1a, interpretation of results derived from the adolescents sample is limited due to the small number of contributing studies. Hence, results derived from the adolescents group in Study 1a will not be interpreted, but are provided in the supplementary materials (Supplementary tables S-Table 3-1, S-Table 3-2). Among the included articles for Study 1b, only 1 was conducted on adolescents (Woolley et al., 2008). Therefore, only meta-analyses based on adult studies could be conducted (Study 1b: 11 articles) and subsequent sections of results and discussion that follow would be based on findings derived from adult samples.

Meta-analyses

Foci that corresponded to increased or reduced grey matter or functional activations in OCD compared with healthy controls were analysed separately. ALE analyses were conducted using the Turkeltaub Non-Additive methodology (Turkeltaub et al., 2012) to reduce inter-subject variability with 1000 permutations. ALE maps were subjected to cluster-inference thresholds, with cluster-forming threshold of $p < .001$ (uncorrected), then subjected to cluster-level threshold of $p < .05$ (Eickhoff et al., 2012). Clusters significant at $p < .05$ cluster

inference threshold were presented in result tables. MRICron software was used to visualize the ALE maps.

Results

Articles included in each meta-analysis are presented in Table 3-1, and results of all meta-analyses are presented in Tables 3-2, 3-3 and Figure 3-2. All presented clusters were significant at $p < .05$ cluster inference threshold.

Study 1a: Structural grey matter

Table 3-2 and Figure 3-2 present grey matter meta-analysis findings based on studies that adopted full-brain analyses on adult samples. Minimum cluster size of significance was 64mm^3 for increased grey matter in OCD compared to controls, and 272mm^3 for reduced grey matter in OCD compared to controls. Compared to controls, patients with OCD demonstrated increased grey matter volumes in cortical regions such as left postcentral gyrus (120mm^3 , Max ALE: 9.83×10^{-3}), right middle frontal (64mm^3 , Max ALE_{Right}: 9.02×10^{-3}), and subcortical regions such as bilateral putamen (R: 120mm^3 , Max ALE_{Right}: 9.91×10^{-3} ; L: 88mm^3 , Max ALE_{Left}: 9.68×10^{-3}) and thalamus (R: 72mm^3 , Max ALE_{Right}: 9.53×10^{-3} ; L: 64mm^3 , Max ALE_{Left}: 8.69×10^{-3}). Increased grey matter volumes were also observed in the left cerebellar lobule IV-V (L: 128mm^3 , Max ALE: 10.21×10^{-3}) and left cingulate gyrus (L: 96mm^3 , Max ALE: 8.82×10^{-3}) in patients with OCD. In contrast, patients with OCD showed grey matter reductions in the right temporal (360mm^3 , Max ALE: 13.69×10^{-3}) and right insula (392mm^3 , Max ALE: 13.86×10^{-3}) regions compared to controls. Results of grey matter analyses based on foci from adolescents samples are presented in the supplement tables S-Table 3-1.

Table 3-1: Studies included in the meta-analyses.

Author	Sample	Age(S.D.)	Age of Onset (S.D.)	Duration of Illness in years (S.D.)	Medication Status	Comorbidities	Y-BOCS	Motion Correction	Threshold for Significance	Direction of Effect: Number of Foci
Meta-Analysis: Grey matter studies in adults										
Kim et al., 2001	25 OCD (17M,8F) 25 Controls (17M,8F)	OCD: 27.4(7.0) Controls: 27.0(6.2)	no data	8.4 (6.7)	8 were drug-naïve; Remaining were medication-free for at least 4 weeks before the scan.	4 had comorbid disorders.	OCD: 24.2 (8.0)	12-parameter affine transformation approach	p<.001, uncorrected, 50 contiguous voxels.	OCD>Controls: 8 OCD<Controls: 2
Pujol et al., 2004	72 OCD (40M,32F) 72 Controls (40M,32F)	OCD: 29.8(10.5) Controls: 30.1(10.2)	17.0 (5.9)	13.0 (10.5)	5 were drug-naïve; 18 were medication-free for at least 4 weeks; Remaining were medicated or currently undergoing treatment.	26 had comorbid disorders.	OCD: 26.7(7.1)	12-parameter affine transformation approach	p<.05, corrected for multiple comparisons.	OCD>Controls: 3 OCD<Controls: 3
Valente et al., 2005	19 OCD (10M,9F) 15 Controls (7M,8F)	OCD: 32.7(8.8) Controls: 32.3(11.8)	14.4 (9.2)	18.3 (10.6)	3 were medication-naïve; 5 were medication-free for at least 3 weeks before the scan; Remaining were medicated	Yes	OCD: 24.6 (7.4)	12-parameter affine transformation approach	p<.001, uncorrected for multiple comparisons for a priori regions; p<.05, corrected for multiple comparisons for unpredicted regions.	OCD>Controls: 3 OCD<Controls: 2
Gilbert et al., 2008	25 OCD (13M,12F) 20 Controls (9M,11F)	OCD: 37.5(10.7) Controls: 29.8(7.86)	29.5 (10.8)	no data	Medicated.	Yes.	OCD: 26.9 (6.3)	not detailed.	p<.001, uncorrected.	OCD>Controls: 2 OCD<Controls: 7
Yoo et al., 2008	71 OCD (47M,24F) 71 Controls (47M,24F)	OCD: 26.61(7.50) Controls: 26.68(6.09)	18.59 (6.52)	8.02 (6.10)	59 were medicated; Remaining were medication-free for at least 4 weeks before the scan.	8 had comorbid disorders.	OCD: 22.84 (8.40)	not detailed.	p<.001, uncorrected, with cluster threshold of 20 voxels.	OCD>Controls: 4 OCD<Controls: 10
Koprivova et al., 2009	14 OCD (5M,9F) 15 Controls (6M,9F)	OCD: 28.6(6.1) Controls: 28.7(6.5)	13.9 (6.6)	15.6 (8.3)	4 were medication-free; Remaining were medicated.	no data	OCD: 16.4 (7.0)	not detailed.	p≤.05, FDR-corrected, cluster threshold of 100 voxels.	OCD<Controls: 30
Matsumoto et al., 2010	16 OCD (7M,9F) 32 Controls (14M,18F)	OCD: 32.8(7.5) Controls: 32.6(8.7)	no data	no data	4 were psychotropic-naïve; Remaining were medicated/receiving therapy.	No other psychiatric disorders other than OCD	OCD: 22 (7.6)	not detailed.	p<.001, uncorrected (T=3.50), and at least 400 contiguous voxels.	OCD<Controls: 4
Togao et al., 2010	23 OCD (9M,14F) 26 Controls (12M,14F)	OCD: 32.6(9.7) Controls: 31.3(7.3)	no data	12.91 (8.5)	5 were drug naïve; All were medication-free for at least 2 weeks before the scan.	No comorbid Axis I disorders.	OCD: 29.8 (2.6)	12-parameter affine transformation approach	p<.05, corrected for multiple comparisons FDR, and at least 25 voxels.	OCD<Controls: 6
Hoexter et al., 2012	38 OCD (15M,23F) 36 Controls (13M,23F)	OCD: 31.5(10.2) Controls: 27.8(7.8)	13.1 (7.6)	18.2 (10.4)	no data	Yes.	OCD: 25.1 (5.2)	12-parameter affine and non-linear transformation approach	For a priori regions: p<.05, FWE-corrected, and with cluster sizes of at least 20 voxels. For unpredicted regions: p<.001, uncorrected for multiple comparisons.	OCD>Controls: 4 OCD<Controls: 6
Tan et al., 2013	28 OCD (19M,9F) 22 Controls (15M,7F)	OCD: 25.4(7.2) Controls: 27.9(8.0)	19.3 (8.1)	4.5 (4.1)	10 were medication-naïve; Remaining were medication-free for at least 8 weeks before the scan.	No comorbid Axis I disorders.	no data	not detailed.	p<.001, uncorrected, with cluster size larger than 100 voxels.	OCD>Controls: 12

Table 3-1 (cont'd): Studies included in the meta-analyses.

Author	Sample	Age(S.D.)	Age of Onset (S.D.)	Duration of Illness in years (S.D.)	Medication Status	Comorbidities	Y-BOCS	Motion Correction	Threshold for Significance	Direction of Effect: Number of Foci	Behavioral Task Performances: OCD vs Controls	Task Category
Meta-Analysis: Functional studies during tasks of executive functioning												
Page et al., 2009	10 OCD (10M,0F) 11 Controls (11M,0F)	OCD: 39.1(10.2) Controls: 34.1(10.1)	no data	no data	6 were medication-naïve; Remaining were medication-free for at least 6 weeks before the scan.	Yes	OCD: 23.5 (3.9) Controls: 0 (0.7)	Rigid body and affine transformation.	ANOVAs at P<.05 for voxel activation. P-values were selected to yield less than one false positive cluster per brain map.	i)Go/No-go Task: No-go>Go: OCD>Controls:6, OCD<Controls:3 ii)Stroop Task: Incongruent>Congruent: OCD>Controls:1, OCD<Controls:4 iii) Switch Task: Switch>Repeat: OCD<Controls:2	All between group comparisons on all measures of accuracy or RT, stroop effect, switch costs were not significant.	Response Inhibition Interference Switching/Shifting
Roth et al., 2007	12 OCD (5M,7F) 14 Controls (6M,8F)	OCD: 37.8(13.2) Controls: 34.9(13.2)	no data	no data	6 were treated with SSRI; Remaining were medication-free at least 6 weeks before the scan.	2 had comorbid disorders.	OCD: 22.3 (6.1)	12-parameter affine approach followed by default nonlinear warping using spatial basis functions.	p<.005, uncorrected with a minimum cluster extent of 25 contiguous voxels.	Go/No-Go Task: No-go>Go: OCD>Controls:4, OCD<Controls:7	No significant between-group differences in percentages and RT for correct responses and errors.	Response Inhibition
Kang et al., 2013	18 OCD (12M,6F) 18 Controls (12M,6F)	OCD: 24.9(5.9) Controls: 24.7(2.7)	no data	6.5 (5.5)	12 were medication-naïve; 6 were medication-free for at least 4 weeks before the scan.	No comorbid Axis I disorders.	OCD: 22.1 (7.6)	realigned to the middle image of 2nd session.	p<.005, uncorrected with cluster size of greater than 27 for whole-brain multiple comparison. Small volume correction for regions of a priori interest (p<.05, FWE corrected in a 5mm radius sphere centered on ROI: Caudate nucleus, putamen, parahippocampal cortex).	Stop-Signal Task: StopSuccess>GoSuccess: OCD>Controls: 5, OCD<Controls: 13	Increased SSRT in OCD than HC (325.1ms VS 275.0ms). No significant differences for median correct GO RT.	Response Inhibition
Nakao et al., 2005	24 OCD (9M,15F) 14 Controls (5M,9F)	OCD: 33.9(8.08) Controls: 30.2(5.13)	no data	no data	All were medication-free for at least 2 weeks before the scan.	No comorbid Axis I disorders.	OCD: 29.4 (4.22)	6-parameter rigid body transformation	p<.001, uncorrected, and clusters with more than 10 voxels.	Chinese Stroop task: Task(mismatch)>Control: OCD>Controls:7, OCD<Controls:1	No significant between-group differences.	Interference
Yucel et al., 2007	19 OCD (10M,9F) 19 Controls (10M,9F)	OCD: 33.7(10.7) Controls: 30.6(7.2)	no data	13.4 (11.3)	11 were receiving stable doses of medication at time of scanning.	No comorbid Axis I disorders.	OCD: 16.3 (5.7)	Motion correction using MCFLIRT	Between-group comparisons: whole brain (uncorrected threshold) of z>3.0, p<.0001.	Multi-Source Interference Task: Incongruent>Congruent: OCD<Controls:2, OCD>Controls:5	No significant group differences in accuracy.	Interference
Nabeyama et al., 2008	11 OCD (4M,7F) 19 Controls (8M,11F)	OCD: 32.4(10.6) Controls: 32.7(7.1)	no data	10.73 (6.95)	4 were medication-naïve; Remaining were medication-free for at least 2 weeks before the scan.	No comorbid Axis I disorders.	OCD: 29.7 (3.0)	6-parameter spatial transformation	p<.001, uncorrected, and clusters with more than 10 voxels.	Chinese Stroop task: Task(mismatch)>Control: OCD<Controls: 2	Higher Stroop Effect (RT of incongruent - RT of congruent trials) observed in OCD. No significant group differences in RT, error rates in congruent and incongruent conditions.	Interference

Table 3-1 (cont'd): Studies included in the meta-analyses.

Author	Sample	Age(S.D.)	Age of Onset (S.D.)	Duration of Illness in years (S.D.)	Medication Status	Comorbidities	Y-BOCS	Motion Correction	Threshold for Significance	Direction of Effect: Number of Foci	Behavioral Task Performances: OCD vs Controls	Task Category
Nakao et al., 2009 (Only short term included)	17 Short-term OCD (5M,12F) 16 Controls (9M,7F)	OCD (Short term): 30.6(9.7) Controls: 30.8(7.9)	Short term: 25.5 (10.2)	Short term: 5.5 (3.1)	8 were medication-naïve; Remaining were medication-free for at least 2 weeks before the scan.	No comorbid Axis I disorders.	Short term: 28.7 (3.8)	6-parameter spatial transformation	p<.001, uncorrected, and clusters with more than 10 voxels.	<i>Chinese Stroop task: Task(mismatch)>Control: OCD(Short-term)<Controls: 7</i>	Longer time spent for task in OCD.	Interference
Schlosser et al., 2010	21 OCD (5M,16F) 21 Controls (5M,16F)	OCD: 31.3(10.2) Controls: 28.8(8.3)	no data	8.6 (7.8)	9 were medication-naïve; 2 were medicated at the time of scan; 10 were medication-free for an average of 5.3 days before the scan.	No comorbid Axis I disorders.	OCD: 20.7 (6.5)	not detailed; realigned to first image of each session.	p<.001, uncorrected, and cluster size greater than 12 voxels.	<i>Stroop Task: Incongruent>Congruent: OCD>Controls:2, OCD<Controls:1; IncongruentConditionOnly: OCD>Controls:7</i>	Higher RT for congruent and incongruent conditions in OCD group than controls, with more pronounced group differences for incongruent condition.	Interference
Gu et al., 2008	21 OCD (18M,3F) 21 Controls (18M,3F)	OCD: 23.6(4.5) Controls: 24.8(3.7)	17.5 (5.0)	6.1 (4.2)	8 were medication-naïve; 2 were non-medicated; 11 were medicated.	3 had comorbid disorders; 18 were without comorbid Axis I or II disorders.	OCD: 20.0 (5.8)	not detailed; realigned to the middle image of 2nd session.	p<.001, uncorrected, and cluster size greater than 20 voxels.	<i>Task-switching: Task-Switch>Task-Repeat: OCD<Controls:21</i>	Higher error rates and RT in task-switch conditions in OCD group.	Switching/Shifting
Han et al., 2011	10 OCD (9M,1F) 20 Controls (18M,2F) *All controls and 4 patients were overlapped with Gu et al., 2008. 6 patients were newly recruited.	OCD: 23.2(4.5) Controls: 24.3(2.9)	18.5 (4.6)	4.4 (3.3)	9 were medication-naïve; 1 medicated.	1 had comorbid disorders; Remaining were without comorbid Axis I or major Axis II disorders.	OCD: 20.9 (4.5)	not detailed; realigned to the middle image of 2nd session.	p<.005, uncorrected at the voxel level with p<.05 at the cluster level. For a priori ROIs, p<.005 uncorrected with cluster size of >30 voxels.	<i>Task-switching: Task-Switch>Task-Repeat: OCD<Controls:22</i>	Higher error rates in task-switch conditions in OCD group.	Switching/Shifting
Remijnse et al., 2013	18 OCD (without MDD) 29 Controls	OCD: 33(Range: 19-54) Controls: 33(Range: 22-53)	no data	no data	All were medication-free for at least 2 weeks.	10 had comorbid disorders.	OCD: 22.7 (4.9)	not detailed.	p<.001, uncorrected.	<i>Switch Task: Switch>Repeat: OCD<Controls:3, OCD<Controls:1</i>	No significant difference in switch costs on RT and error rates.	Switching/Shifting

Table 3-2: Results of meta-analysis in Study 1a.

Study 1a: Meta-Analysis on grey matter [Adults only; Studies that utilized/reported ROI-only analyses were excluded]
(Coordinates are in standardized MNI stereotactic space)

* FWHM Median of OCD>HC: 9.08 (8.65, 9.24). Chosen minimum cluster size: 64mm³

† FWHM Median of OCD<HC: 9.14 (8.65, 9.57). Chosen minimum cluster size: 272mm³

Centered Cluster Regions	BA	Volume (mm ³)	Coordinates			Max ALE (x10 ⁻³)
			x	y	z	
<u>OCD>HC*</u>						
R Frontal, Middle Frontal Gyrus	9	64	48	22	26	9.02
L Parietal, Postcentral Gyrus	5	120	-18	-36	74	9.83
L Parietal, Postcentral Gyrus	3	80	-66	-10	26	9.18
L Inferior Parietal Lobule (overlapping L inferior parietal lobule and L postcentral gyrus)	40	88	-36	-40	60	9.32
L Cingulate Gyrus	31	96	2	-28	40	8.82
R Insula	13	64	36	14	-12	8.31
R Putamen (overlapping R putamen, R caudate)		120	20	14	-8	9.91
L Putamen		88	-30	4	-6	9.68
L Putamen		64	-20	14	-12	9.38
L Cerebellum, lobule IV-V		128	-12	-48	-12	10.21
R Thalamus		72	30	-28	-2	9.53
L Thalamus		64	-4	-24	12	8.69
<u>OCD<HC[†]</u>						
	BA	Volume (mm³)	x	y	z	Max ALE (x10⁻³)
R Temporal, Sub-Gyral	20	360	48	-18	-28	13.69
R Insula (overlapping R Insula and R Inferior Frontal Gyrus)	13	392	46	14	-6	13.86

Study 1b: Executive-task related fMRI studies

Separate ALE analyses were conducted on each executive function domain, and results revealed domain-specific abnormalities in patients with OCD (Table 3-3, Figure 3-2). The minimum cluster size of significance was 224mm³ for increased activations in OCD compared to controls, and 72mm³ for reduced activations in OCD compared to controls in Theme 1 (Response Inhibition); Minimum cluster size of significance for both increased and reduced activations in OCD compared to controls was 160mm³ in Theme 2 (Interference); and minimum cluster size of significance for reduced activations in OCD compared to controls is 16mm³ in Theme 3 (Set Shifting/Switching).

There were no significant clusters of increased activations in OCD compared to controls during response inhibition tasks. Compared to controls, patients with OCD showed significantly reduced activations in the right putamen (128mm^3 , Max ALE: 8.19×10^{-3}) and right cerebellar lobule IV-V (168mm^3 , Max ALE: 8.38×10^{-3}) during response inhibition tasks (Theme 1); increased activations in the right precentral (464mm^3 , Max ALE: 9.48×10^{-3}), left superior frontal (160mm^3 , Max ALE: 8.35×10^{-3}) and cingulate gyrus (160mm^3 , Max ALE: 8.22×10^{-3}), and reduced activations in right caudate (688mm^3 , Max ALE: 15.09×10^{-3}) during interference tasks (Theme 2); and reduced activations in the bilateral inferior frontal gyrus (R: 40mm^3 , Max ALE_{Right}: 6.63×10^{-3} ; L: 24mm^3 , Max ALE_{Left}: 6.57×10^{-3}), cingulate (R: 32mm^3 , Max ALE_{Right}: 6.62×10^{-3} ; L: 24mm^3 , Max ALE: 6.57×10^{-3}) and caudate regions (R: 32mm^3 , Max ALE_{Right}: 6.60×10^{-3} ; L: 32mm^3 , Max ALE_{Left}: 6.47×10^{-3}), and in the left precuneus (32mm^3 , Max ALE: 6.61×10^{-3}) during switching and shifting tasks (Theme 3).

Table 3-3: Results of meta-analysis in Study 1b.

Study 1b: Theme 1: Meta-Analysis on functional studies: Response inhibition (Go/No-go, Stop Signal Task) [Adults only; Studies that utilized ROI-only analyses were excluded] (Coordinates are in standardized MNI stereotactic space)
 * FWHM Median of OCD>HC: 9.76 (9.33, 10.00). Chosen minimum cluster size: 224mm³

† FWHM Median of OCD<HC: 9.76 (9.33, 10.00). Chosen minimum cluster size: 72mm³

Centered Cluster Regions	BA	Volume (mm ³)	Coordinates			Max ALE (x10 ⁻³)
			x	y	z	
<u>Activations: OCD>HC*</u>						
No significant clusters						
<u>Activations: OCD<HC[†]</u>	BA	Volume (mm ³)	x	y	z	Max ALE (x10 ⁻³)
R Putamen		128	28	12	-4	8.19
R Cerebellum, lobule IV-V		168	22	-38	-22	8.38

Study 1b: Theme 2: Meta-Analysis on functional studies: Interference (Stroop Task, MSIT) [Adults only; Studies that utilized ROI-only analyses were excluded]

* FWHM Median of OCD>HC: 9.57 (9.20, 10.00). Chosen minimum cluster size: 160mm³

† FWHM Median of OCD<HC: 9.57 (9.20, 10.00). Chosen minimum cluster size: 160mm³

Centered Cluster Regions	BA	Volume (mm ³)	Coordinates			Max ALE (x10 ⁻³)
			x	y	z	
<u>Activations: OCD>HC*</u>						
L Frontal, Superior Frontal Gyrus	6	160	-22	0	72	8.35
R Frontal, Precentral Gyrus (overlapping Precentral Gyrus and Medial Frontal)	4	464	26	-14	60	9.48
L Cingulate Gyrus	24	160	-2	0	38	8.22
<u>Activations: OCD<HC[†]</u>						
	BA	Volume (mm ³)	x	y	z	Max ALE (x10 ⁻³)
R Caudate		688	12	-2	12	15.09

Study 1b: Theme 3: Meta-Analysis on functional studies: Switching and Shifting (Task Switching, Set Shifting) [Adults only; Studies that utilized ROI-only analyses were excluded]

* FWHM Median of OCD>HC: -

† FWHM Median of OCD<HC: 10.00 (9.33, 10.10). Chosen minimum cluster size: 16mm³

Centered Cluster Regions	BA	Volume (mm ³)	Coordinates			Max ALE (x10 ⁻³)
			x	y	z	
Activations: OCD>HC*						
[Meta-analysis for OCD>HC was not conducted. Only 1 article reported increased activations in OCD VS HC. (Remijnse et al., 2013).]						
Activations: OCD<HC[†]						
R Superior Frontal Gyrus	9	32	36	52	22	6.55
R Frontal, Precentral Gyrus	4	32	18	-18	62	6.58
L Precentral Gyrus	4	32	-36	-14	40	6.55
R Frontal, Medial Frontal Gyrus	6	24	24	10	50	6.57
L Frontal, Middle Frontal Gyrus	10	160	-28	52	-12	7.67
L Frontal, Middle Frontal Gyrus	6	32	-34	12	42	6.62
L Frontal, Middle Frontal Gyrus	10	24	-36	52	2	6.63
L Frontal, Inferior Frontal Gyrus	47	24	-52	22	-8	6.57
R Frontal, Inferior Frontal Gyrus	47	40	34	36	-14	6.63
R Superior Temporal Gyrus	38	32	48	8	-22	6.57
L Parietal, Precuneus	7	32	-6	-42	52	6.36
L Parietal, Precuneus	7	32	-22	-44	54	6.61
R Parietal, Paracentral Lobule	5	32	24	-42	56	6.56
L Cuneus	19	24	0	-90	32	6.60
R Claustrum		32	42	-26	-4	6.57
R Lingual Gyrus	18	32	18	-82	6	6.56
R Caudate Body		32	20	4	20	6.60
L Caudate Body		32	-22	-4	22	6.47
L Caudate Tail		32	-30	-36	10	6.58
R Cingulate Gyrus	31	32	18	-38	32	6.59
R Anterior Cingulate		24	0	30	-4	6.62
L Cingulate Gyrus	32	24	-4	30	26	6.57
L Cingulate Gyrus	23	24	-6	-30	34	6.56
R Uncus	34	24	22	4	-26	6.61

Figure 3-2. Results of all separate meta-analyses.

Regions in red indicate increased activations or grey matter volume in OCD VS HC (healthy controls), while regions in blue indicate reduced values. Clusters were significant at $p \leq 0.05$ cluster-inference threshold.

[Study 1a]: (Minimum cluster size -- OCD>HC: 64mm³; OCD<HC: 272mm³)

A: OCD<HC in R insula (46 14 -6); OCD>HC in bilateral putamen (-30 4 -6; 20 14 -8); **B:** OCD>HC in L cerebellum lobule IV-V (-12 -48 -12); **C:** OCD>HC in L postcentral gyrus (-18 -36 74); L putamen (-20 14 -12).

[Study 1b]:

Theme 1 -- (Minimum cluster size -- OCD>HC: 224mm³; OCD<HC: 72mm³)

D: OCD<HC in R cerebellum lobule IV-V (22 -38 -22); **E:** OCD<HC in R putamen (28 12 -4);

Theme 2 -- (Minimum cluster size -- OCD>HC: 160mm³; OCD<HC: 160mm³)

F: OCD<HC in R caudate (12 -2 12); **G:** OCD>HC in L cingulate gyrus (-2 0 38); **H:** OCD>HC in R precentral gyrus (26 -14 60);

Theme 3 -- (Minimum cluster size -- OCD<HC: 16mm³)

I: OCD<HC in R medial frontal gyrus (24 10 50); **J:** OCD<HC in L cingulate gyrus (-4 30 26); **K:** OCD<HC in bilateral caudate body (-22 -4 22; 20 4 20); **L:** OCD<HC in L caudate body (-22 -4 22) and L precuneus (-22 -44 54).

Study 1 – Discussion

To the best of our knowledge, this is the first meta-analytic study that performed separate meta-analyses on neural changes in grey matter (Study 1a) and functional activations during executive function tasks (Study 1b) in OCD compared to controls.

Summary of results

Compared to controls, patients with OCD showed increased grey matter in the right frontal, left postcentral gyrus, inferior parietal lobule and cerebellar lobule IV-V, and bilateral putamen and thalamus regions, and reduced grey matter in the right temporal gyrus and insula regions extending to the inferior frontal gyrus. Investigations of executive function task-related abnormalities in OCD samples compared to controls showed reduced activations in the right putamen and right cerebellum during inhibition tasks such as stop-signal, and go/no-tasks (Theme 1: Response Inhibition); increased activations in right precentral, left superior frontal and cingulate gyrus, and reduced activations in right caudate during interference tasks such as Stroop task and multi-source interference test (MSIT) (Theme 2); and reduced activations in the bilateral inferior frontal gyrus, cingulate, caudate, and the left precuneus during switching and shifting tasks (Theme 3).

Comparison of results with previous studies (Grey matter volume)

A mega-analysis was recently published by The International OCD Brain Imaging Consortium (de Wit et al., 2013) that combined neuroimaging data from 6 research centers to analyse grey and white matter brain volumes in a total of 412 adult patients with OCD and 368 healthy controls using an optimized VBM approach. Coordinates reported in that article were not included in our grey matter meta-analysis (Study 1a), as its sheer sample size adds significant variability to the meta-analysis.

Consistent with results from the mega-analysis (de Wit et al., 2013), our results also observed reduced grey matter volumes in the right insula extending to the inferior frontal gyrus, and increased volumes in the left cerebellar lobule IV-V in OCD samples compared to controls. The mega-analysis reported additional grey matter abnormalities in OCD samples, specifically, increased grey matter in bilateral cerebellar lobule XI extending to the anterior and posterior lobules, and reduced grey matter in the left insula and dorsomedial prefrontal/bilateral cingulate regions. Results from our meta-analysis in Study 1a reported additional grey matter abnormalities in regions in the right middle frontal, and bilateral thalamus and putamen regions. Even though the mega-analysis utilized a large sample of participants, a substantial proportion of included data have not been published. Therefore, divergence in reported findings could be attributed to methodological differences (de Wit et al., 2013). In addition, the authors also acknowledged that even though the mega-analysis included a large sample size that increased statistical sensitivity, the use of a large sample substantially introduced between-subjects variation in cortical thickness or surface area that might have overshadowed real effects (de Wit et al., 2013).

Results from our study are more consistent with previously published meta-analyses (Radua & Mataix-Cols, 2009a; Rotge et al., 2009; Rotge et al., 2010). In particular, one meta-analysis conducted analyses based on adult studies had similarly demonstrated increased grey matter in the left cerebellar lobule IV-V, bilateral putamen, and postcentral gyrus (Rotge et al., 2010). Our meta-analysis (Study 1a) showed additional grey matter increase in the right middle frontal and bilateral thalamus in OCD. These findings could be attributed to the inclusion of more foci contributed by additional articles in our meta-analysis and use of an updated version of the GingerALE algorithm.

Even though we observed significant grey matter abnormalities in the cingulate region among OCD samples compared to controls, it is important to note that this finding has been inconsistently reported in existing meta-analyses. One meta-analysis did not observe significant differences in cingulate grey matter (Rotge et al., 2010), while three other meta-analysis studies reported reduced cingulate grey matter in OCD samples compared to controls (Peng et al., 2012; Radua & Mataix-Cols, 2009a; Rotge et al., 2009). On close examination of the individual meta-analyses, it appears that there have been some variability in each study's inclusion criteria as two of these meta-analyses (Peng et al., 2012; Radua & Mataix-Cols, 2009a) included unpublished analysis of a published paper (Soriano-Mas et al., 2007), and the meta-analysis conducted by Rotge and colleagues (Rotge et al., 2009) included articles that compared volumetric measurements (means and SD) in ROIs between OCD patients and controls. Therefore, variability in reported findings across different meta-analyses could be attributed to differences in inclusion criteria. More VBM studies and further investigations are required to ascertain the involvement of grey matter abnormalities in cingulate regions in patients with OCD compared to controls.

Interestingly, similar to a previous meta-analysis (Radua & Mataix-Cols, 2009a), results from our meta-analysis did not reveal significant group differences in the OFC. The lack of expected finding could be due to inconsistent reports of the exact directionality of enhanced or reduced grey matter volumes observed in the orbitofrontal region obtained from included studies. Even though the mega-analysis also did not report significant group differences in orbitofrontal grey matter volume, additional analyses conducted by de Wit and colleagues reported age-related preservation of orbitofrontal grey matter volumes in OCD samples compared to controls (de Wit et al., 2013). Henceforth, the authors highlighted the importance of age as a factor in understanding variability of brain abnormalities, and

proposed the concept that age-related neural differences observed in the orbitofrontal region in OCD could be secondary to symptom persistence or compensatory processes related to cognitive dysfunction (de Wit et al., 2013).

Integration of findings

Existing reports described executive function deficits as core deficits in OCD. In this section, we discuss and integrate executive function processes with structural and functional abnormalities reported from our results. Table 3-1 summarised significant differences in behavioural performances observed between OCD samples compared to controls.

Response inhibition (Theme 1)

Response inhibition tasks measure one's ability to withdraw strong response tendencies (Heyder, Suchan, & Daum, 2004). Response inhibition task paradigms typically manipulate proportions of response and no-response trials to train automatic responding (using the larger proportion of response trials); subjects are required to withdraw an already initiated motor response on a small number of trials (no-response trials). The ability to suppress pre-potent behaviours that were no longer appropriate or required has generally been reported to be supported by the frontal and striatal regions (Aron, Fletcher, Bullmore, Sahakian, & Robbins, 2003; Chikazoe et al., 2009; Duann, Ide, Luo, & Li, 2009; Garavan, Ross, & Stein, 1999; Hampshire, Chamberlain, Monti, Duncan, & Owen, 2010). Existing functional neuroimaging studies have also identified an extensive network of regions involved in inhibition that included the orbital, inferior, medial and middle frontal regions, dorsolateral, anterior cingulate, parietal and temporal cortices, and the cerebellum and basal ganglia (Alptekin et al., 2001; Melloni et al., 2012; Menzies, Chamberlain, et al., 2008; Page et al., 2009).

Results from our meta-analysis (Study 1b: Theme 1) showed increased activations in the putamen and right cerebellum (lobule IV-V) during response inhibition tasks in OCD samples. The putamen is part of the striatum in the basal ganglia, and existing evidence appeared to suggest specific role of the putamen in habit learning (de Wit, Watson, et al., 2012; Grahn et al., 2008; Tricomi, Balleine, & O’Doherty, 2009). Aberrant neural activations in these regions concurred with findings of grey matter abnormalities in the putamen and cerebellum in OCD samples. Reduced activations and enhanced grey matter volumes in the putamen in OCD samples (in Study 1a and Study 1b Theme 1) indicate inhibitory deficits and lack of cognitive flexibility for efficient overriding of learned actions, which are also manifestations of OCD symptomatology. These experiences could be speculated to be compounded by abnormal activations and grey matter volume in the anterior cerebellar lobule IV-V, which existing studies have pinpointed specific involvement of sensorimotor-related functions (E et al., 2012; Stoodley & Schmahmann, 2009, 2010).

Out of all included studies, only one study employed the stop-signal task observed longer stop-signal reaction time in OCD samples compared to controls (Kang et al., 2013), while remaining studies that utilized Go/No-Go tasks did not observe group differences in behavioural performances (Page et al., 2009; Roth et al., 2007). The Go/No-go paradigm typically requires participants to make quick button responses to a range of stimuli and withhold response to a specific stimulus (Donders, 1969); the stop-signal paradigm requires participants to respond as quickly as possible to ‘Go’ trials but suppress response on a random small number of trials, during which a stop-signal appears after a short delay following the ‘Go’ stimulus (Logan, Cowan, & Davis, 1984). Both task paradigms measure motor response inhibition, with the Go/No-Go task probing action restraint and stop-signal task probing action cancelation (van Velzen et al., 2014). The apparent lack of significant

group differences in task performances appear to contradict results from our meta-analysis that demonstrated neural abnormalities of reduced activity in the putamen and cerebellar culmen in the OCD sample. It is noteworthy that the Go/No-Go tasks employed in both studies (Page et al., 2009; Roth et al., 2007) were specifically designed to minimise behavioural differences between the two groups (Roth et al., 2007), and prevent large number of errors in patients with OCD that could potentially confound fMRI findings (Page et al., 2009). It is also possible that some compensatory mechanisms were recruited by the OCD samples to maintain comparable performance as the healthy control group. Results from our meta-analysis did not reveal significant clusters of increased activity during response inhibition. However, increased activations were observed in a diffused set of regions involving the cerebellar tonsil, parahippocampus superior parietal lobule and the postcentral gyrus when the analysis threshold was lowered to $p < .001$ (uncorrected) with extent volume of 200mm^3 (Supplementary material: S-Table 3-3). Considering the higher inhibitory load for stop-signal tasks compared to Go/No-Go, compensational mechanisms may be successfully recruited during Go/No-Go paradigms but failed for the more complex stop-signal task. However, further research is required to ascertain this compensation hypothesis. Also importantly, results from a meta-analysis of neuropsychological test performances in OCD samples demonstrated medium effect size for response inhibition deficits in OCD samples and reported seemingly non-clinically meaningful performance differences in neuropsychological tests including tests of response inhibition such as the Go/No-Go test (Abramovitch, Abramowitz, & Mittelman, 2013). These findings prompted a reconsideration of the use of neuropsychological performances and response inhibition deficits in OCD as reliable endophenotypic markers of OCD (Abramovitch et al., 2013). Indeed, neuropsychological tests may lack sensitivity in pin-pointing deficits in specific cognitive

processes in patients with OCD, and therefore, as suggested in a previous study, neural abnormalities during task performance may be more sensitive in detecting cognitive dysfunction in OCD (Page et al., 2009), although, this could be more dependent on the specific behavioural test that is used.

Remaining studies that utilized clinical samples with comorbidities did not report behavioural differences in response inhibition, thereby highlighting potential complications due to comorbid conditions.

Interference (Theme 2).

Tasks such as flanker, stroop, and the MSIT require cognitive control to suppress interference from competing stimuli and characteristics, and are typically associated with prefrontal and cingulate activity. Our results showed increased activations in the precentral gyrus, superior frontal extending to medial frontal regions, the cingulate gyrus, and reduced activations in the caudate in OCD patients. Results from our grey matter meta-analyses also reported grey matter differences among OCD samples and controls in the cingulate and caudate regions. Specifically, the cingulate is involved in error-prediction and during conflict, these error-monitoring processes have been reported to occur even when errors were highly unlikely (Brown & Braver, 2005). These alterations suggest dysfunctional monitoring processes and motor control in OCD, as also manifested in longer reaction times and lower accuracy rates in OCD samples.

Set shifting/switching (Theme 3)

Set shifting/switching involves the self-generation of several task-related actions that are engaged in accordance to task-specific rules and goals (Heyder et al., 2004). During set shifting, cognitive control processes enable flexible shifts of attention from one dimension of the test stimuli to another according to changing reinforcement contingencies, preparation of

an appropriate response, and update stimulus-response rules according to the information derived from the task (Hubner, Kluwe, Luna-Rodriguez, & Peters, 2004). Our results showed reduced activations in the medial frontal, inferior frontal, parietal, cingulate and caudate regions. Abnormal neural activations observed during set switching/shifting tasks concurred with grey matter volume abnormalities observed among OCD samples compared to controls (Study 1a).

Results from Theme 3 appear to again, indicate dysfunctional error detection and monitoring processes in OCD. The right inferior frontal gyrus is highly involved in motor response inhibition, while the middle frontal gyrus is involved in error detection processes (Chevrier, Noseworthy, & Schachar, 2007; Rodrigo et al., 2014). Apart from error detection processes, the middle frontal gyrus is also involved in monitoring processes, and in this context, adopting a top-down control approach in preparing a response set (Aron, Monsell, Sahakian, & Robbins, 2004; MacDonald et al., 2000). The cingulate region is activated during actual or possible detection of errors, the precuneus, during attention and awareness, and the caudate, in action selection during goal-directed behaviours (Brovelli, Nazarian, Meunier, & Boussaoud, 2011; de Wit, Watson, et al., 2012) and is sensitive to rule switches (Crone, Wendelken, Donohue, & Bunge, 2006). According to Beckmann and colleagues' parcellation of the cingulate cortex, the anterior-dorsal cingulate region of the cingulate (as observed in our meta-analysis) was reported to be involved in memory processes, and was most prominently activated amongst other clusters in response to error and conflict (Beckmann et al., 2009), which have been consistently reported to be impaired in OCD. Beckmann and colleagues also reported high probabilities in connectivity between this anterior-dorsal cingulate region and the striatum, premotor, and DLPFC regions, which are also regions of abnormalities observed from our meta-analytic results (Meta-analysis 1a and

Theme 2) (Beckmann et al., 2009). Increased activity of the anterior cingulate gyrus in patients with OCD during shifting tasks (Theme 3) was accompanied by abnormal neural activations, such as in the striatum and the frontal regions. Also observed in our results were anomalies involving the inferior frontal regions, which are highly involved in inhibitory mechanisms (Konishi et al., 1999). These findings, taken together, further support impaired inhibition, conflict and error processes in OCD psychopathology.

Deficits in error monitoring and "not just right experience"

Indeed, dysfunctional responses to conflict and error monitoring processes have been proposed to be key in OCD pathophysiology (Endrass, Klawohn, Schuster, & Kathmann, 2008; Gehring, Himle, & Nisenson, 2000; Ursu, Stenger, Shear, Jones, & Carter, 2003). In a similar way, sensations of "not just right experience" (NJRE) have been reported to be important in the phenomenology of OCD (Coles, Frost, Heimberg, & Rhéaume, 2003). According to this theory, deficits in the error monitoring system generate excessive error signals that are manifested as repetitive thoughts or feelings that things are "not just right" (Pitman, 1987; Schwartz, 1997), and are usually translated to its corresponding corrective actions and compulsive acts until they felt "just right" (Leckman, Walker, Goodman, Pauls, & Cohen, 1994; Miguel et al., 2000). These error signals could be speculated to be generated internally or triggered by external stimuli or when certain actions do not concur with their representations of how it should be, thereby maintaining one's obsessions and compulsions regardless the rational awareness of whether an actual error has been made. The cingulate gyrus has been postulated to be involved in conflict identification and subsequent affective evaluation of the responses (Maltby et al., 2005); existing studies have also associated error monitoring processes with abnormal activations in the cingulate cortex and basal ganglia (D. H. Kang et al., 2013; Maltby et al., 2005; Melloni et al., 2012), with additional work

implicating the insula and middle frontal cortex in error monitoring processes (Chevrier et al., 2007; Taylor, Stern, & Gehring, 2007).

Regions currently not involved in the CSTC circuitry: Cerebellum and the parietal cortex

The existing CSTC circuitry has been subjected to controversy as increasing reports seemed to implicate regions outside the CSTC circuitry in OCD pathophysiology. Results from our meta-analysis showed abnormal grey matter volume (Study 1a) and reduced activations in the anterior cerebellar lobule IV-V during response inhibition (Theme 1), which could indicate abnormal sensorimotor functions in OCD.

Previous meta-analyses have also reported grey matter abnormalities in the parietal regions, specifically in the superior parietal lobule, precuneus and supramarginal gyrus (Radua & Mataix-Cols, 2009a; Rotge et al., 2009). The current study only observed significant grey matter abnormalities in OCD samples in the postcentral gyrus and inferior parietal regions, but not in other parietal regions. Existing studies have postulated the involvement of abnormal white matter in the precuneus and supramarginal gyrus in OCD pathophysiology (Li et al., 2013; Peng, Shi, Shi, Miao et al., 2014). Structural grey matter abnormalities in the supramarginal gyrus have also been associated with symptom severity (Koprivova et al., 2009; Szeszko et al., 2005), and existing reports proposed the involvement of posterior, and inferior parietal regions in attentional set shifting (Hampshire & Owen, 2006), and response inhibition in OCD respectively (Horn et al., 2003; Rubia et al., 2001). Our results did not show abnormalities in parietal regions during response inhibition tasks, but demonstrated abnormalities in the left precuneus during set-shifting. The lack of expected differences in the parietal regions could be attributed to the inclusion of adult-only studies. Consistent with this view, our grey matter findings are comparable with a previous meta-

analysis that also reported increased grey matter volume in the postcentral region in OCD samples compared to controls based on studies that utilized adult samples [(Rotge et al., 2010), supplementary material].

Abnormal functional activations observed in the frontal and inferior parietal regions during set-shifting tasks appear to implicate a dysfunctional fronto-parietal network in OCD (Stern et al., 2012) that has been viewed to be important in attention control. Indeed, abnormal activations observed in the fronto-parietal network have been reported and proposed as an endophenotype of OCD after observing compensatory frontoparietal activity in patients with OCD and their first-degree relatives (de Vries et al., 2013). In addition, dysfunction of the frontoparietal regions has been associated with deficits in sustained attention, set-shifting and response inhibition (Nagahama et al., 1996) (Cabeza & Nyberg, 2000). Even though existing studies seem to demonstrate the presence of parietal anomalies in OCD pathophysiology, its involvement in the CSTC circuitry remains unclear.

Despite the results from our meta-analysis that showed potential cerebellar abnormalities in OCD pathophysiology, this finding is limited to the fact that not all studies included full coverage of cerebellar regions in their scan acquisitions. More investigations are needed to evaluate the role of cerebellar and specific parietal structures in OCD symptomatology.

Limitations of the current meta-analyses

Our study is not without limitations. Although, most of the limitations below are inherent in many of the published meta-analyses with clinical populations that need to be noted.

Number of articles: Inclusion and availability

The developers of the ALE algorithm published a recommendation for ALE analyses to be based on workspaces of 17-20 experiments or more for sufficient power to detect moderately sized effects (Eickhoff & Etkin, 2016; Eickhoff, Laird, Fox, Lancaster, & Fox, 2017). Even though results presented in the meta-analysis conducted in 2015 following the recommendations then provided a preliminary overview of the neural differences in OCD samples compared to controls, we acknowledge that the meta-analyses may be underpowered, and therefore, require more studies and replication. The current study design have excluded articles from the meta-analyses if their analyses were restricted to ROI-only approaches, resulting in the inclusion of a reduced number of articles. In addition, several limitations of the current study could be attributed to the limited availability of published articles. Consequently, investigations of executive functions in OCD were only focused on limited domains, and we were not able to include other cognitive domains such as working memory and planning. We were not able to stratify our meta-analyses to control for OCD symptom severity, duration of illness, age-of-onset and medication dosages, which could potentially confound study findings (Benedetti et al., 2013; Gilbert, Mataix-Cols, et al., 2008; Nakao, Nakagawa, Yoshiura, et al., 2009). Caution should be taken in the interpretation of results for Theme 3: Set shifting/switching, as the presence of large number yet small sizes of clusters in our results suggests that these results may not be reliable, possibly due to the small number of contributing studies.

Characteristics of included studies & ALE algorithm

Studies included in our meta-analyses utilized different thresholds of detection, which directly influenced foci contributed in our meta-analyses. On a similar note, studies also utilized different protocols for motion correction, and included participant samples with varying clinical characteristics. Moreover, many existing studies were conducted on OCD

samples with comorbid conditions. In addition, even though we reported abnormalities in the cerebellum in OCD samples, results from our meta-analyses were at best, only approximations, as not all studies included the cerebellum structure in their imaging acquisitions. Moreover, the ALE algorithm does not enable regressors to be considered in the meta-analyses, which could also confound the true study findings.

Others

Existing evidence have suggested sex differences in neural abnormalities in OCD (den Braber, de Geus, Boomsma, & van't Ent, 2013). However, we were not able to infer brain-related sex differences from our study findings as our meta-analyses were conducted on combined groups of males and female samples. Despite these limitations, our current study showed clear involvement of the subcortical-cortical abnormalities in OCD. Results from our meta-analyses on studies that employed tasks of executive functioning suggest cognitive inflexibility and dysfunctional inhibitory, error detection and monitoring processes in OCD that may be relevant to altered activations observed in the cingulate, frontal and subcortical regions in OCD.

A General Note

Our results appear to support a view of cognitive inflexibility and dysfunctional monitoring and inhibitory system in patients with OCD that hinders efficient attention control and selection of appropriate response to switch trials, resulting in a general slowing of reaction time during switch trials as showed in our included articles (Table 3-1). Notably, variability in behavioural performances observed across studies could be attributed to different medication status and comorbid conditions in patient samples. The lack of consistent behavioural differences in some task performances (recorded in Table 3-1) may tempt one to interpret hyperactivations as compensatory. However, the current analyses are

not able to suggest whether hyperactivations were compensatory or were more relevant to a failure to deactivate. Further investigations using multimodal neuroimaging techniques including resting-state and task-related connectivity could contribute to an improved understanding of neural abnormalities observed in OCD.

Existing studies have also commonly utilized OCD samples with comorbid conditions. Considering the heterogeneity nature of the disorder, utilizing patient samples with comorbid conditions adds complexity to the interpretation of neuropsychology profiles and neural anomalies. In view of the large proportion of patients with OCD who are also diagnosed with comorbid conditions, investigations of patients with comorbid conditions warrant further attention. Future research could examine differences in neuropsychological profiles and neural abnormalities in separate patient groups characterized by different comorbid conditions, and these investigations could better inform about impairments and abnormalities involved in patients with and without these specific comorbid conditions.

Conclusion

In conclusion, results from our meta-analyses suggest extensive cortical and sub-cortical abnormalities in OCD. Consistent involvement of the frontal, cingulum and striatal brain regions across the meta-analyses of functional MRI and grey matter further support the involvement of specific cortical-subcortical pathways in OCD pathophysiology. However, results from our meta-analyses also suggest potential inadequacies of current models in accounting for abnormalities observed in other brain regions, such as the cerebellum and the parietal cortex. Further research is required to clarify the role of cerebellar structures in OCD pathology. Even though our study results did not report significant neural differences in the orbitofrontal regions between OCD samples and controls, we do not exclude the possible role of the OFC in OCD pathophysiology. Further research is required to investigate the role of

the orbitofrontal region in the CSTC network by evaluating the involvement of its subdivisions and associations with the disorder. In addition, further research is required to ascertain the inter-relationships of specific pathways involving structures such as the frontal, cingulum, and basal ganglia regions on the clinical manifestations of the disorder, clinical prognosis, and other neurobiological substrates and resting-state networks that could contribute to a comprehensive understanding of the pathophysiology of the disorder.

Considering existing literature and results from our meta-analyses, it appears that OCD symptomatology could possibly be maintained by dysfunctional monitoring and error detection processes. We speculate that these dysfunctional processes keep the individual at heightened vigilance for possible errors and even during situations when no errors were committed. Indeed, insights for a dysfunctional salience-processing network in OCD has been reported using an interference task to measure task-related intrinsic connectivity in OCD, from which the authors reported increased functional connectivity between the ventromedial frontal cortex and regions of the anterior insula/frontal operculum and the right thalamus (Stern et al., 2011). Further studies could utilize resting-state connectivity techniques to investigate the salience-processing network in OCD to gain better understanding in the neural abnormalities involved in the disorder. Results from our meta-analyses showed abnormal activations in the fronto-parietal regions during switching task, which could potentially indicate some dysfunction of the "executive control" network especially when challenged by tasks. However, this remains to be further investigated.

An Analysis Update

The cluster-inference threshold entails a cluster-forming threshold ($p < .001$, uncorrected) and compares the clusters with those that arise from a null set of random spatial locations, allowing the tracked clusters large enough to be exceeded in size by a maximum of

5 out of 100 random clusters from the random distribution (cluster-level threshold at $p < .05$, FWE-corrected). However, an algorithmic error in versions earlier than GingerALE 2.3.6 resulted in inferences that were based on uncorrected cluster-level p values (Eickhoff et al., 2017). The developers of GingerALE acknowledged that even though the uncorrected cluster-level thresholding may be more conservative than voxel-level uncorrected p values, the use of uncorrected cluster-level may be considered inadequately liberal (Eickhoff et al., 2012). Therefore, it could be expected that small clusters would no longer remain significant when the data is re-analysed using GingerALE 2.3.6.

We re-analysed our meta-analysis using the latest version of GingerALE 2.3.6. Results from the re-analysis are presented in the supplementary materials S-Table 3-3. As expected, small clusters that were previously reported in Tables 3-2 and 3-3 were no longer significant. The re-analysis demonstrated only reduced activations in the right caudate during Interference in patients with OCD compared to controls (Study 1b: Theme 2). There were no group differences in grey matter volumes (Study 1a), and functional activations during response inhibition (Study 1b: Theme 1) and Switching and Shifting (Study 1b: Theme 3).

The lack of results in the re-analysis could be attributed to several reasons. First, ALE analyses have been recommended to be based on 17-20 experiments or more in order to detect moderate effect sizes (Eickhoff & Etkin, 2016; Eickhoff et al., 2017). Therefore, the current study may be underpowered with 10 studies in Study 1a, and 3 studies in Theme 1, 6 studies in Theme 2, and 4 studies in Theme 3 of Study 1b, and therefore require more contributing papers and replication. Second, considering the small number of inclusion experiments in the meta-analyses, it is possible that the FWE-corrected cluster-level thresholding implemented in GingerALE 2.3.6 are too conservative, and hence leaving only the largest effects as significant findings.

It is the view of the current dissertation that the re-analyses do not deem the initial analysis invalid. Findings from the initial meta-analytic investigations are generally consistent with views held in the field – that the disorder implicates involvement of cortical and sub-cortical brain regions, and are in line with the key findings of the thesis, in terms of cerebellar involvement in functional activity and resting-state functional connectivity as we later discuss in subsequent chapters. However, the re-analyses provide additional insights that differences in activations in the right caudate may be most prominent in OCD samples compared with controls during Interference tasks.

Despite our attempts to follow the developers' recommendations for best practices at the time of performing the meta-analyses in 2015, it is unfortunate that the software implementation errors were only discovered later. Though it is noted above, that the analyses conducted using more liberal thresholds than intended do not invalidate our initial results and conclusions, we support open science as encouraged by the authors of GingerALE (Eickhoff et al., 2017). Thus, considering the importance of accurate information dissemination, we will be providing a technical note to the journal for readers to receive correct information about the thresholds applied.

CHAPTER 4: THE EMPIRICAL STUDY & BEHAVIOURAL FINDINGS

Introduction

Past findings that investigated neural differences in OCD samples relative to controls consistently reported abnormalities in several regions outside the CSTC circuitry (de Vries et al., 2013; de Wit et al., 2013). In addition, lack of expected significant group differences in OFC grey matter, and findings of group differences in grey matter and functional activations in the cerebellum and parietal regions in Study 1 (Chapter 3) indicated the necessity to adopt a systematic approach to clarify neural involvement of the disorder. We designed and conducted an empirical study to evaluate structural (Chapter 5), task-related (Chapter 6) and resting-state functional (Chapter 7) neural differences in OCD samples compared to controls. Unlike past investigations, the current study excluded participants with comorbid conditions to enable interpretation of results without additional complexity.

This chapter aims to provide an overview of the procedures and methodology of the empirical study and report clinical and neuropsychological performances of the sample. The empirical study consists two sessions: (1) Neurocognitive testing (behavioral) and (2) MRI session.

In the first session, all participants were administered a series of clinical scales to record information related to OCD, depressive, and anxiety symptoms. Selected neuropsychological scales were also employed to evaluate performance in several neurocognitive domains such as verbal working memory, visual working memory, visuomotor processing speed and set-shifting, and inhibition. In the second session all participants underwent an MRI scan, and performed three tasks in the scanner: a verbal working memory task, visual working memory task, and stop-signal task. The current chapter elaborates details on the design of the empirical study and presents neurocognitive test performances to characterize both patients and controls and understand the relationships

between test performances and clinical indices. Findings from the MRI session are detailed in subsequent chapters (Chapters 5 to 7).

Methods

Participants

21 patients with OCD and 17 controls between the ages of 21 to 47 participated in the study. Patients with OCD were recruited from the outpatient clinics of the National University Hospital (NUH) and Institute of Mental Health (IMH) via referral by the attending psychiatrist. Controls were age-, sex-, and education-matched to the patient sample, and were recruited from the community and by word-of-mouth.

Inclusion/Exclusion Criteria. Participants were included in the study if they were between the ages of 21 to 65 years of age and excluded if they had significant history of alcohol or drug abuse, neurological disease, severe head injury, mental retardation, learning disorders, developmental disorders, visual impairments that cannot be corrected using vision-correcting aids and contraindications for MRI examinations. Patients with OCD fulfilled the Diagnostic and Statistical Manual, 4th Edition (DSM-IV) diagnostic criteria for OCD as assessed using the Structured Clinical Interview for DSM-IV Axis I Disorders (Patient Version) (SCID I-P) (First, Gibbon, Spitzer, & Williams, November 2002 Revision), and were precluded if they had a lifetime history of unipolar or bipolar disorder, psychotic condition, eating disorders, Tourette's disorder, other tic-related conditions, conduct disorder, major depressive disorder that preceded OCD diagnosis, current major depressive disorders and anxiety disorders. As most OCD patients also have some depressive and anxiety symptoms that do not meet criteria for clinical depression or other anxiety disorders, presence of anxiety and depression symptoms were not considered as exclusion criteria if OCD was the primary clinical diagnosis. Controls were assessed using the SCID-I-Non-Patient Version

(SCID-I-NP) (First et al., November 2002 Revision) and were excluded from the study if they had any personal and family history of Axis I psychiatric illness or psychiatric disturbances.

The study was approved by relevant institutional and ethics committees of the Nanyang Technological University Institutional Review Board (NTU-IRB; IRB-2013-11-010) and National Healthcare Group Domain-Specific Review Board (NHG-DSRB; Ref: 2013/01221) (Supplementary Appendix A). All participants provided written, informed consent in accordance prior to any scales administration. All scales and procedures were administered by trained researchers.

Study Procedures

Study procedures consisted of two sessions as presented in Figure 4-1. The neurocognitive testing session consisted of a demographics questionnaire, clinical scales, self-rating questionnaires and neuropsychological tests. Participants who fulfilled the study's criteria were invited to return within seven days for the MRI brain scan in the second session. All scales were administered in the English Language.

Procedures: Session one (Neurocognitive testing). All participants were administered the following scales and neurocognitive tests.

Demographics questionnaire. The demographics questionnaire was used to collect information on basic demographics, medical information and history, education history, family history of psychological disorders, duration of illness, age of onset, medications that the participant was taking at the time of interview, and participant's hand-preference using the Edinburgh Handedness Inventory (Oldfield, 1971).

Clinical scales. These consisted of the SCID-I, Yale-Brown Obsessive Compulsive Scale (Goodman, Price, Rasmussen, Mazure, Delgado, et al., 1989; Goodman, Price, Rasmussen, Mazure, Fleischmann, et al., 1989), 17-item Hamilton Depressive Rating Scale

(Hamilton, 1960), 14-item Hamilton Anxiety Scale (Hamilton, 1959), and 18-item self-rated Obsessive-Compulsive Inventory – Revised (OCI-R; Foa et al., 2002). All scales except the OCI-R (self-report questionnaire) were administered by trained researchers in a semi-structured interview. The following provides a description of the clinical scales.

Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID-I). The SCID-I is a semi-structured interview for making DSM-IV Axis I diagnoses and was used in the current study to confirm the diagnosis of OCD in the patients' sample, and to ensure participants did not meet the exclusion criteria for other current or past Axis I diagnoses. Patients were administered the SCID I-P (P = Patient) and controls were administered the SCID-I-NP (NP = Non-patient) versions.

Yale-Brown Obsessive Compulsive Scale (Y-BOCS). The Y-BOCS is also a semi-structured interview and comprises two primary scales: Symptoms Checklist, and Severity Scale. The Symptoms Checklist is a 64-item rating scale that assesses in detail content of the patient's past and present obsessions and compulsions. Identified symptoms were assessed in further detail using the Severity Scale, where patients were asked to describe characteristics of the symptoms during the past week up. The Severity Scale consists 10 items and each item were scored on a scale of 0 (no symptoms) to 4 (extreme symptoms). Severity score was provided by the sum of ratings on the 10 items. According to the manual (Goodman, Rasmussen, & Price, 1986), a total score of under seven indicates subclinical or mild case of OCD, 16 to 23 as moderate, 24 to 31 as severe, and 32 to 40 as extreme case of OCD. Severity scores were absent for all controls as they did not report obsessive and compulsive symptoms.

Hamilton Depressive Rating Scale (HDRS). The HDRS was administered to all participants to record the presence and severity of depressive symptoms experienced over the

past week. This 17-item rating scale was administered in a semi-structured approach using available interview guides (Williams, 1988). Items were rated on a scale of 0 (not present) to 4 (severe), and the total score ranged from 0 to 68. According to the manual (Hamilton, 1960), a score of 0 to 7 is considered within the normal range or clinical remission, and a score of 20 and above is considered moderate severity and is typically required for eligibility into clinical trials.

Hamilton Anxiety Rating Scale (HAM-A). The HAM-A is a 14-item scale that was administered to assess symptoms and severity of anxiety symptoms (psychic and somatic) experienced over the past week. Administration was semi-structured and interview guides were used (Shear et al., 2001). Items were rated on a scale of 0 (not present) to 4 (severe). The range for the total score is 0 to 56, where a score of less than 17 indicates mild severity, 18 to 24 as mild to moderate severity, and 25 to 30 as moderate to severe (Hamilton, 1959).

Obsessive-Compulsive Inventory—Revised (OCI-R). The OCI-R is an 18-item self-rated questionnaire that evaluates distress experienced due to the obsessions and compulsions experienced over the past month. Items were rated on a scale of 0 (not at all distressed) to 4 (extremely distressed). The total score ranges from 0 to 72. The OCI-R has been validated to be an efficient tool in discriminating between individuals with OCD and nonpatient, with a cutoff score of 21 for optimal sensitivity and specificity (Foa et al., 2002).

Neuropsychological tests. All participants were evaluated on the cognitive domains of: i) verbal working memory (Digit Span Forward and Backward) (WMS-III; (Wechsler, 1997); ii) visual working memory (Symbol Span test) (WMS-IV; (Wechsler, 2009); iii) visuomotor processing speed and set-shifting (Trail Making Test A & B; TMT-A & B) (Reitan & Wolfson, 1993), and iv) inhibition (Colour-Word Stroop Test) (Golden, 1978).

Digit Span – Forward, Backward (WMS-III; (Wechsler, 1997). Digits were verbally read to participants at a rate of one digit per second. Participants were required to repeat the digits in the order that was read to them in the forward condition, and in reverse order in the backward condition. Scores in the forward condition reflect verbal span, and scores in the backward condition reflect span for verbal working memory. This task was administered to evaluate verbal span and working memory.

Symbol Span Test (WMS-IV; (Wechsler, 2009). Participants viewed an array of abstract symbols on a page for five seconds and were asked to select the symbols from a test array in the same order the symbols were presented on the previous array. The symbol span requires recalling of visual details and maintaining sequential information of the symbols in memory. Scores reflect span for visual memory.

Trail-Making Test A & B (Reitan & Wolfson, 1993). In TMT-A, participants drew a line connecting 25 encircled numbers in numerical order, and in TMT-B, drew a line connecting 25 encircled numbers and alphabets in numerical and alphabetical order, alternating between numbers and alphabets. TMT-A reflects speed of processing, and TMT-B assesses cognitive control during task-switching between sequential numbers and letters. Performance for TMT-A and TMT-B were recorded in terms of the time taken for the test, where higher numbers indicate poorer/slower performances. A difference index was additionally computed : $TMT-B - TMT-A$ to evaluate performance in cognitive switching that takes into consideration general processing speed and motor control (Lezak, Howieson, Bigler, & Tranel, 2012).

Colour-Word Stroop Test (Golden, 1978). There were three conditions in the Stroop test: Word-only, Colour-only, and Colour-Word conditions. Participants were presented a list of 100 stimuli per condition, one condition at a time, and were instructed to read aloud as

many items as they can in 45 seconds. There were 3 outcome scores: Word-score (W), Colour-score (C), and Colour-Word score (CW). A global index of interference was computed according to the formula: $CW - (C + W)/2$ (Caffarra, Vezzadini, Dieci, Zonato, & Venneri, 2002; Scarpina & Tagini, 2017). This provides an indication of the ability to inhibit interference relative to performance in a congruent condition, where larger negative values indicate greater Stroop interference.

Information on Prescribed Medications. Information on prescribed medications and dosages were obtain from the patients and their psychiatrists. Medications were classified into categories: i) *antidepressants* were further categorized as selective serotonin reuptake inhibitors (SSRIs), selective non-serotonin reuptake inhibitor (SNRI) and tricyclic antidepressants, and were converted into mean daily dosage equivalents of fluoxetine (Hayasaka et al., 2015); ii) *antipsychotics* were further categorized as typical and atypical antipsychotics, and were converted into mean daily dosage equivalents of olanzapine (Leucht et al., 2014). The information on duration of pharmacotherapy was also noted and cross-checked against the case-notes where available. In instances where such information was not documented, a judgment was made based on details provided by the patient. These information, though approximate, helped to understand the clinical profile of the patients' sample.

Procedures: Session two (MRI scanning). Participants who fulfilled the study's criteria returned for the brain scan session within 7 days. Prior to the day of the scan, participants were informed to have sufficient rest, and not consume caffeine substances at least one hour before meeting.

Pre-scan briefing. The participants were briefed on what to expect during the scan and the tasks to be performed in the scanner. They were given a practice session before

entering the scanner suite to ensure that they understood the instructions and were familiarized with the tasks and response buttons used. This session took approximately an hour. Details of the fMRI tasks are discussed in Chapter 6.

Scanning sequence. A localizer scan to visualize the position of the brain for image prescription was first acquired, followed by a three-dimension (3D) magnetization-prepared rapid gradient-echo (MPRAGE) scan to acquire a high resolution T1 image (Chapter 5), a series of echo-planar imaging (EPI) acquisitions for task-related functional imaging (Chapter 6), diffusion spectrum imaging (not within the scope of the thesis); and lastly, a resting-state EPI scan (Chapter 7). Total scan time was approximately 75 minutes.

General MRI data acquisition. Whole-brain MRI data were acquired on a Siemens 3.0 Tesla MRI scanner (Siemens Prisma, Erlangen, Germany) using a 32-channel head coil. Sufficient foam paddings were inserted around the participant's head to minimize head motion. Participants were provided ear plugs to protect from the scanner sounds, and an alarm ball to squeeze for attention in event of an emergency. Prior to each scan segment, the participant was informed via an intercom system of the upcoming scan, duration, instructions, and reminded to keep their head still. Details of imaging-related tasks and analyses were detailed in later chapters (Chapters 5 to 7).

Figure 4-1. Study procedures of the empirical study.

Participants who fulfilled the study's criteria as assessed in Session 1 were invited to return for Session 2 within 7 days. SCID-I = Structured Clinical Interview for DSM-IV-TR; Y-BOCS = Yale-Brown Obsessive Compulsive Scale; HDRS = Hamilton Depressive Rating Scale; HAM-A = Hamilton Anxiety Rating Scale; OCI-R = Obsessive-Compulsive Inventory (Revised); EPI = Echo-planar imaging.

Behavioural Data Analysis

Means, distribution histogram and indices (skewness and kurtosis) for all variables were presented in Supplementary Appendix S-Figure 4-1. Z-statistics for skewness and kurtosis were greater than 1.96 in magnitude for some variables, indicating violation of the

normality assumption (Kim, 2013). Therefore, non-parametric Mann-Whitney tests were employed to evaluate group differences in the following variables: i) demographic (age, handedness index, total years of education), ii) clinical (HDRS, HAM-A, OCI-R), and iii) neurocognitive tasks within their cognitive domains: a) verbal working memory – digit span forward, digit span backward tests; b) visual working memory – symbol span; c) visuomotor processing speed and set-shifting – TMT-A, TMT-B, difference index; and d) inhibition – Stroop colour/word/colour-word conditions, Stroop index). Effect size was computed by calculating a r statistic. Initially proposed by Cohen (1998), r was computed by dividing the z statistic obtained from Mann-Whitney tests with the square root of the total sample size, N , i.e. $r = z / \sqrt{N}$ (Cohen, 1988). Based on Cohen's guidelines for r , an effect is considered small when r is .1, medium at .3, and large at .5 (Coolican, 2014). Spearman's correlations were also performed to explore associations between the clinical indices, such as Y-BOCS total score, duration of illness, and duration of medication consumption, and with neurocognitive measures that showed significant group differences. Due to the exploratory approach of the correlational analyses, all observed effects were not Bonferroni-adjusted for multiple comparisons.

Considering the small sample size, independent samples t-test were also performed on 1000 bootstrapped samples that were stratified according to patient/controls using bias-corrected 95 percentile confidence interval. Results are presented in Supplementary Appendix S-Table 4-1.

Behavioral Measures Between Groups

Demographic variables

Demographics information are presented in Table 4-1. No significant group differences were observed in age, education and handedness index.

Clinical indices

Information on clinical indices are also presented in Table 4-1. Results from Mann-Whitney U indicated OCD samples had higher scores in total HDRS ($Mdn_{Controls} = 2$, $Mdn_{OCD} = 4$, $U = 108.00$, $p = .04$, $z = -2.09$, $r = -.34$), HAM-A ($Mdn_{Controls} = 2$, $Mdn_{OCD} = 7$, $U = 81.50$, $p = .004$, $z = -2.87$, $r = -.47$), and total OCI-R scores ($Mdn_{Controls} = 3$, $Mdn_{OCD} = 21$, $U = 14.50$, $p < .001$, $z = -4.83$, $r = -.78$). A breakdown of prescribed medications and dosages for the current study's OCD samples are presented in Table 4-2.

Table 4-1: Descriptives of demographics and clinical indices.

	Controls	OCD	χ^2	df	p					
Gender (Male:Female) (count)	9:8	10:11	0.11	1	.74					
	Controls ($n=17$)			OCD ($n=21$)			Mann-Whitney			Effect size
	Mdn	M	SD	Mdn	M	SD	U	p	z	r
<u>Demographics</u>										
Age	27	26.12	1.01	28	28.62	6.89	144.00	.31	-	-
Years of Education	14.5	15.24	0.52	15.0	14.96	2.24	157.00	.52	-	-
Handedness Index [^]	100	76.03	9.70	100	82.71	43.98	152.00	.38	-	-
<u>Clinical Indices</u>										
HDRS	2	2.65	0.46	4	5.52	4.61	108.00*	.04	-2.09	-.34
HAM-A	2	2.47	0.39	7	7.33	5.90	81.50**	.004	-2.87	-.47
OCI-R	3	3.47	0.83	21	25.10	17.40	14.50***	< .001	-4.83	-.78
Age of Onset (years)	-	-	-	-	20.74	4.83	-	-	-	-
Duration of Illness (years)	-	-	-	-	7.88	6.56	-	-	-	-
Duration of Pharmacotherapy (years)	-	-	-	-	5.01	5.01	-	-	-	-
Y-BOCS (Total)	-	-	-	-	20.19	6.58	-	-	-	-
Y-BOCS (Obsessions)	-	-	-	-	10.00	3.54	-	-	-	-
Y-BOCS (Compulsions)	-	-	-	-	10.19	3.78	-	-	-	-

Note. [^] Handedness index is measured using Edinburgh's Handedness Questionnaire. HDRS = Hamilton Depressive Rating Scale. HAM-A = Hamilton Anxiety Rating Scale. OCI-R = Obsessive-Compulsive Inventory (Revised). Y-BOCS = Yale-Brown Obsessive Compulsive Scale. n = Sample size. Mdn = Median. M = Mean. SD = Standard deviation. r = Effect size coefficient, where .1 = small, .3 = medium, .5 = large effects. (* $p < .05$. ** $p < .01$. *** $p < .001$).

Table 4-2: Breakdown of medications prescriptions.

	<i>n</i>	<i>Mdn</i>	<i>M</i>	<i>SD</i>
<u>Medications Name & Mean Dosage (mg)</u>				
<u>SSRIs</u>				
Fluoxetine	10	40.00	39.50	22.42
Paroxetine	1	60.00	60.00	-
Escitalopram	3	5.00	5.00	5.00
Sertraline	5	150.00	150.00	50.00
<u>SNRI</u>				
Venlafaxine	1	300.00	300.00	-
<u>Tricyclic Antidepressants</u>				
Clomipramine	5	100.00	135.00	99.37
<u>Atypical Antipsychotics</u>				
Aripiprazole	2	6.25	6.25	1.77
Risperidone	2	0.75	0.75	0.35
<u>Mean Daily Dosage Equivalents (in mg)</u>				
Fluoxetine Equivalent	19	40.61	52.34	30.69
Olanzapine Equivalent	4	0.40	0.47	0.44

Note. SSRI = Selective Serotonin Reuptake Inhibitor. SNRI = Serotonin-

Norepinephrine Reuptake Inhibitor. *n* = Sample size. *Mdn* = Median. *M* =

Mean. *SD* = Standard deviation.

Neuropsychological Tests

Results are provided in Table 4-3. Mann-Whitney *U* tests demonstrated significant group differences in the following domains and tests: [Visual working memory domain] Symbol Span ($Mdn_{Controls} = 29$, $Mdn_{OCD} = 22$, $U = 80.50$, $p = .004$, $z = -2.89$, $r = -.47$); [Visuomotor Processing Speed and Set-shifting] TMT-A ($Mdn_{Controls} = 21$, $Mdn_{OCD} = 31$, $U = 91.00$, $p = .010$, $z = -2.57$, $r = -.42$) and TMT-B ($Mdn_{Controls} = 41$, $Mdn_{OCD} = 64$, $U = 78.50$, $p = .003$, $z = -2.94$, $r = -.48$), and [Inhibition] Word condition ($Mdn_{Controls} = 110$, $Mdn_{OCD} = 95$, $U = 98.50$, $p = .019$, $z = -2.35$, $r = -.38$), and Colour-Word condition of the Stroop test ($Mdn_{Controls} = 49$, $Mdn_{OCD} = 42$, $U = 98.00$, $p = .018$, $z = -2.37$, $r = -.38$).

Table 4-3: Descriptives of neuropsychological tests.

	Controls (n=17)			OCD (n=21)			Mann-Whitney			Effect size
	<i>Mdn</i>	<i>M</i>	<i>SD</i>	<i>Mdn</i>	<i>M</i>	<i>SD</i>	<i>U</i>	<i>p</i>	<i>Z</i>	<i>r</i>
<u>Verbal Working Memory</u>										
Digit Span Forward	11	11.12	1.90	10	10.67	1.83	156.00	.50	-0.68	-.11
Digit Span Backward	11	10.29	1.90	9	10.05	1.99	162.00	.62	-0.50	-.08
<u>Visual Working Memory</u>										
Symbol Span Total	29	27.65	6.53	22	21.29	5.34	80.50**	.004	-2.89	-.47
<u>Visuomotor Processing Speed & Set-Shifting</u>										
TMT-A (in seconds)	21	25.41	12.90	31	31.95	9.70	91.00*	.01	-2.57	-.42
TMT-B (in seconds)	41	47.88	17.71	64	65.19	17.66	78.50**	.003	-2.94	-.48
TMT-B - TMT-A	22	22.47	12.79	28	33.24	19.11	114.50	.06	-1.88	-.31
<u>Inhibition</u>										
Stroop Word Condition (W)	110	108.65	17.67	95	95.57	16.59	98.50*	.02	-2.35	-.38
Stroop Colour Condition (C)	82	80.53	15.34	73	71.62	11.32	116.50	.07	-1.82	-.30
Stroop CW Condition	49	49.65	11.81	42	41.24	9.30	98.00*	.02	-2.37	-.38
Stroop Index (CW-(C+W)/2)	-47	-44.94	14.03	-39	-42.36	11.49	155.00	.50	-0.69	-.11

Note. *n* = Sample size. *Mdn* = Median. *M* = Mean. *SD* = Standard deviation. TMT-A = Trail-Making

A. TMT-B = Trail-Making B. CW = Colour-Word. *r* = Effect size coefficient, where .1 = small, .3 = medium, .5 = large effects. All findings were not Bonferroni-adjusted for multiple comparisons. (* $p < .05$. ** $p < .01$. *** $p < .001$).

Bivariate Correlations: Clinical Indices

Non-parametric correlations using Spearman's rho were conducted to evaluate correlations between Y-BOCS total score, OCI-R, age of onset, duration of illness, HDRS, HAM-A, duration of pharmacotherapy and fluoxetine equivalents (Table 4-4). Results indicated significant positive correlations between OCI-R scores with Y-BOCS total score ($\rho_s = .64, p = .002$), HDRS ($\rho_s = .65, p = .001$), and HAM-A ($\rho_s = .57, p = .007$); HAM-A with HDRS ($\rho_s = .86, p < .001$); Y-BOCS total with HDRS ($\rho_s = .49, p = .025$); and duration of illness with duration of pharmacotherapy ($\rho_s = .68, p < .001$). Since the duration of illness and duration of pharmacotherapy increase with the patient's age, partial correlations were conducted in attempt to partial out the effects of age. Correlations remained significant after controlling for age, $r = .579, df = 18, p = .008$. No significant associations were observed between performance in neurocognitive tests and clinical indices (all $p > .05$), except for a

negative correlation between performance on Stroop Word Condition with age of onset ($\rho_s = -0.485$, $p = .026$).

It is also observed that several correlations with some medication-related measures, such as duration of pharmacotherapy and/or fluoxetine equivalents have correlations that were close to the significance threshold ($\rho_s = -0.43$ and $\rho_s = -0.37$, compared to $\rho_s = .49$ that were significant at $p < .05$). We conducted supplementary analyses to understand the associations between clinical and neurocognitive variables with effects of pharmacotherapy duration, and fluoxetine equivalents when separately partial out. Key findings remained, with an additional significant negative association between Stroop Colour-Word Condition and pharmacotherapy duration when effects of fluoxetine equivalents were partial out ($\rho_s = -.62$, $p = .006$). Results are presented in the supplementary materials (Supplementary Appendix S-Table 4-3 and S-Table 4-4).

Table 4-4: Spearman correlations between clinical and neurocognitive variables in OCD samples.

	1	2	3	4	5	6	7	8
	ρ_s	ρ_s	ρ_s	ρ_s	ρ_s	ρ_s	ρ_s	ρ_s
TMT-A	.25	.03	.35	-.14	-.13	-.01	-.12	-.09
TMT-B	.09	.13	.09	-.06	-.02	-.13	.10	.19
Stroop Word Condition	-.12	-.07	-.49*	.09	-.03	-.08	-.20	.14
Stroop Colour-Word Condition	-.19	.19	-.19	-.14	.12	.24	-.43	-.19
Symbol Span Test	-.23	.17	.15	-.30	-.08	.07	-.29	-.37
1 Y-BOCS Total	-	.64**	.35	.08	.49*	.33	-.05	.38
2 OCI-R	-	-	.07	-.08	.65**	.57**	-.38	.08
3 Age of Onset	-	-	-	-.34	.13	.06	-.13	-.15
4 Duration of Illness	-	-	-	-	-.01	.11	.68***	.04
5 HDRS	-	-	-	-	-	.86***	-.11	-.04
6 HAM-A	-	-	-	-	-	-	.00	-.14
7 Pharmacotherapy Duration	-	-	-	-	-	-	-	-.07
8 Fluoxetine Equivalents	-	-	-	-	-	-	-	-

Note. Y-BOCS = Yale-Brown Obsessive Compulsive Scale. HDRS = Hamilton Depressive Rating Scale. HAM-A = Hamilton Anxiety Rating Scale. OCI-R = Obsessive-Compulsive Inventory (Revised). TMT-A = Trail-Making A. TMT-B = Trail-Making B. All findings were not Bonferroni-adjusted for multiple comparisons. (* $p < .05$. ** $p < .01$. *** $p < .001$)

Discussion

We presented an overview of procedures and methodology for the empirical study and reported clinical and neuropsychological performances in OCD samples and controls. Relative to controls, OCD samples demonstrated poorer performance in visual working memory (Symbol Span test), visuomotor speed of processing and set-shifting (TMT-A, TMT-B), and inhibition (Stroop word, and colour-word conditions). No significant group differences were observed in tests of verbal working memory. In terms of effect sizes, we reported small effect sizes for digit span forward, digit span backward, TMT-difference (TMT-B – TMT-A) and Stroop indices but medium-to-large effect sizes for Symbol Span test and TMT-A and TMT-B.

Bivariate correlations were conducted to evaluate relationships with clinical indices. OCD patients with higher self-report obsessive-compulsive distress as rated on the OCI-R had greater OCD severity, depressive symptoms and anxiety symptoms; increased depressive symptoms were associated with increased OCD severity and anxiety scores. These relationships remained significant after effects of fluoxetine equivalents or duration of pharmacotherapy were partial out. In addition, duration of illness was also positively correlated with duration of pharmacotherapy, and this relationship remained significant after controlling for age.

The Trail-Making test involves a wide range of cognitive processes, such as attention, visual search, psychomotor speed, flexibility, ability to execute and modify actions online, and to maintain two sets online (Lezak et al., 2012; Salthouse, 2011; Spreen & Strauss, 1998). The difference index (TMT B – TMT A) was computed to assess the relative performance for TMT-B independent of motor speed, visual scanning speed and stimulus complexity, and was thought to be of a purer indicator of “executive control” abilities

(Aronowitz, 1994; Lezak et al., 2012; Sanchez-Cubillo et al., 2009; Schmidtke, Schorb, Winkelmann, & Hohagen, 1998). The current study observed significant group differences in TMT-A and TMT-B performances but not the difference TMT index, suggesting that difficulties in executive control in terms of cognitive flexibility and set-shifting may not be prominent in the current sample. Instead, we propose that there could potentially be some underlying systematic difficulty, perhaps involving motor control, visual scanning/perception that gets cancelled out when the difference index was computed. This argument could also be applied to the results of Stroop tests. Group differences were observed in both congruent (Word) and incongruent (Colour-Word) conditions, but this effect was diminished when we evaluated Interference after discounting processes that were involved in the congruent Word- and Colour- conditions. These patterns in performances were also generally consistent with observations of group differences when evaluated based on bootstrapped confidence intervals (Supplementary Appendix S-Table 4-2).

A meta-analysis evaluated cognitive dysfunction in OCD samples and reported a wide range of cognitive deficits such as visuospatial memory, executive function and verbal fluency in OCD patients, but effect sizes were generally not large (Shin, Lee, Kim, & Kwon, 2014). The largest effect size was observed for tasks that measured visuospatial memory (Hedges' $g = -0.624$, 95% CI -0.752 to -0.495), followed by moderate effect sizes for executive function (interference, set-shifting, and planning) (Hedges' $g = -0.493$, 95% CI -0.553 to -0.432). These findings were somewhat consistent with another meta-analysis that also reported medium effect sizes for visual memory (spatial span) and cognitive flexibility (operationalized as Trail-making B, Stroop Interference) (Abramovitch et al., 2013). The medium-to-large effect size observed for the Symbol Span test in the current study were consistent with findings reported in the meta-analyses. However, both meta-analyses did not

include the difference index in their evaluations as most studies that evaluated cognitive dysfunction in OCD had excluded that computation. Considering that past studies have postulated set-shifting and inhibition as core deficits in OCD, it was somewhat surprising that effect sizes of TMT and Stroop indices observed in the current and past studies were not large.

The lack of consistent findings could be attributed to several factors, such as task differences and sample characteristics. Task differences across studies were apparent for the Stroop task where several variations have been utilized, such as computerized Stroop (Abramovitch et al., 2013; Nakao et al., 2005), modified Stroop (Martinot et al., 1990), Chinese Stroop (Page et al., 2009), motor Stroop (Schmidtke et al., 1998), emotional Stroop (Moritz et al., 2008), Stroop Colour Word Interference test (Aronowitz, 1994), and Colour-Word Stroop amongst others, and outcome measures were also different. The use of different variations of tasks and outcome measures makes it challenging to evaluate cognitive dysfunctions in OCD.

OCD is highly comorbid with other disorders, with lifetime prevalence of 50-80% for mood disorders and about 50% for other anxiety disorders in OCD patients (LaSalle et al., 2004; Perugi et al., 1997; Tükel, Polat, Özdemir, Aksüt, & Türksoy, 2002). Clinically, OCD patients with comorbid conditions had higher depressive, anxiety and Y-BOCS total severity scores compared to those without comorbid conditions, though the symptom typology between the two groups were generally similar in terms of the frequency of obsessions and compulsions (Tükel et al., 2002). It has been argued that inconsistent findings in the literature regarding impairments in executive function in OCD samples were due to comorbid conditions (Basso, Bornstein, Carona, & Morton, 2001; De Geus, Denys, Sitskoorn, & Westenberg, 2007). The impact of comorbid conditions on cognitive functioning were made

apparent from a study that failed to observe performance deficits in executive function in OCD samples relative to controls after taking into account existing depressive and schizotypal symptoms (Aycicegi, Dinn, Harris, & Erkmen, 2003). The lack of significant group differences in the TMT and Stroop difference indices observed in the current study are also consistent with another study that included patients with OCD without comorbid conditions (De Geus et al., 2007). Even though these findings are not within our expectations, these observations could be potentially attributed to the exclusion of participants with comorbid conditions from the current study.

Interestingly, we did not observe significant associations between duration of illness, age of onset and duration of pharmacotherapy with OCD symptom severity. Existing literature that evaluated associations between clinical indices in non-treatment-response paradigms have been limited. Somewhat consistent with our findings, one study also observed lack of significant associations between medication duration and OCD severity score (Feusner et al., 2015). Even within studies that adopted treatment-response paradigms, associations of clinical characteristics have not been consistent: Some studies reported earlier age of onset and increased duration of illness as predictive of greater OCD persistence (Micali et al., 2010; Stewart et al., 2004) and non-responders to treatment (Ravizza, Barzega, Bellino, Bogetto, & Maina, 1995); one study reported that age of onset was associated with response to treatment, independent of the duration of illness (Ackerman, Greenland, Bysritsky, Morgenstern, & Katz, 1994); another study observed longer duration of illness with worse response to pharmacotherapy (Stein, Montgomery, Kasper, & Tanghoj, 2001), and yet another study showed no significant differences between respondents and non-respondents in age at onset and duration of illness (Tükel, Bozkurt, Polat, GenÇ, & Atli, 2006). These findings highlight the inconsistent observations of associations involving

clinical indices. In terms of associations between clinical symptoms and cognitive performances, a meta-analysis did not report significant confounding effects of symptom severity and medication status on executive function and visuospatial memory and perception abilities (Shin et al., 2014), although the authors had acknowledged that not all included studies had reported information on clinical indices. However, the current study observed shorter pharmacotherapy duration with greater interference as measured on the colour-word condition on the Stroop task when effects of fluoxetine equivalents were partial out. Considering that existing evaluations of associations between clinical and cognitive indices are limited, further investigations are required but are out of the scope of the current study. In addition, the sample of OCD patients in the current study were not asked to stop their medications for the study and had continued their treatment as usual. Therefore, the cross-sectional assessment of the symptoms/clinical indices may also reflect different recovery progress among the patients, although this speculation remains to be verified.

Demographic variables such as age, sex and education have been considered potential determinants of neuropsychological function. As controls in our study were well-matched with the patients' in terms of age, sex, and education, the current study evaluated group differences using raw performance scores, similar to the approach adopted in previous studies (Coles, Schofield, & Pietrefesa, 2006; Kang et al., 2013; Menzies et al., 2007).

Lastly, even though we observed medium-to-large effect size for the Symbol Span test, considering that differences of less than two standard deviations may not be clinically meaningful (Lezak et al., 2012), poorer performance in the Symbol Span test may not be considered a good marker for OCD pathophysiology. This position was also supported by a previous meta-analysis that questioned the suitability of neuropsychological functions as reliable endophenotypes of the disorder (Abramovitch et al., 2013). Even though these effects

may not have been considered sufficiently large for the test to be used alone to inform about clinical diagnoses, a medium-to-large effect size is still substantial in terms of informing one's neuropsychological functioning. Therefore, levels of neuropsychological function could still be useful especially when we consider a dimensional-approach to understanding psychiatric disorders.

Conclusion

This chapter detailed procedures of the empirical study and presented clinical and behavioural performances in a sample of patients with OCD without comorbid conditions and controls. We observed significant group differences in visual memory span, but not in verbal memory span. Following an understanding of the patients' clinical profiles and performance in broad cognitive domains, the next few chapters present neural differences in OCD samples relative to controls, with the next chapter on grey matter.

**CHAPTER 5: STUDY 2 – GREY MATTER VOLUMETRIC DIFFERENCES IN OCD
SAMPLES AND CONTROLS**

Exploring structural differences in terms of regional grey-matter volumes in individuals with
OCD and controls using a Voxel-based Morphometry approach

Introduction

Voxel-based morphometry (VBM) evaluates grey/white matter differences between groups of subjects. The technique involves spatially normalizing reoriented high-resolution T1-weighted images to the same stereotactic space, then segmenting grey and/or white matter from the spatially-normalized images using nonlinear image registration procedures. The segmented grey/white matter are then smoothed and subjected to voxel-wise parametric statistical tests to evaluate group differences in the smoothed grey/white matter (Ashburner & Friston, 2000; Mechelli, Price, Friston, & Ashburner, 2005). VBM has been used to evaluate structural differences in several disorders such as schizophrenia (Brown et al., 2011; Kubicki et al., 2002), epilepsy (Keller et al., 2002; Labate, Cerasa, Gambardella, Aguglia, & Quattrone, 2008) and ADHD (Ahrendts et al., 2011; Seidman, Valera, & Makris, 2005).

In Chapter 3, we conducted a meta-analysis to consolidate neuroimaging literature on studies that utilized VBM techniques to evaluate differences in grey matter volume (GMV) in OCD samples relative to controls. Findings from the meta-analysis demonstrated altered GMV in the middle frontal gyrus, postcentral gyrus, inferior parietal lobule, inferior temporal gyrus, cingulate gyrus, insula, putamen, thalamus and the cerebellum in patients with OCD compared to controls. However, we have also noted that existing studies had also included OCD patients with comorbid conditions (Christian et al., 2008; Kim et al., 2001), and this could potentially drive different observed findings.

In this chapter, we evaluate GMV differences in a sample of OCD patients without comorbid conditions relative to controls. Even though it appears that existing studies had observed altered cerebellar GMV in OCD samples, its involvement in OCD pathophysiology is still not well understood. Therefore, the current study also performed SUIT analyses to evaluate cerebellar GMV differences in OCD samples to controls. In general, we expect

observations of altered GMV in regions reported in the meta-analysis (Chapter 3) and in regions of the CSTC circuitry in OCD samples compared to controls. Regions that showed group differences in GMV are also explored to evaluate their associations with cognitive flexibility (difference index of the Trail-Making Test and Stroop index), symbol span, and clinical indices.

Methods

Participants

Data from 21 patients with OCD and 17 healthy controls were included in the study.

Imaging Acquisition

Whole-brain MRI data were acquired on a Siemens 3.0 Tesla MRI scanner (Siemens Prisma, Erlangen, Germany) using a 32-channel head coil. MRI structural data were obtained using a high-resolution sagittal T1-weighted 3D MP-RAGE protocol: TR=1900ms; TE=2.52ms; voxel size=1 x 1 x 1mm; flip angle= 9°; FOV=256mm. The scan lasted approximately five minutes.

Imaging Preprocessing: Whole-brain

All neuroimaging data were processed according to Ashburner's VBM DARTEL protocol (Ashburner, 2015) and analyzed using SPM12 software package (Statistical Parametric Mapping 12; Wellcome Department of Cognitive Neurology, London, UK; revision #6470) (Penny, Friston, Ashburner, Kiebel, & Nichols, 2011). All images were first reoriented to the AC-PC axis (anterior-posterior commissure), then segmented to identify grey and white matter. Segmented grey and white matter images of all participants were imported into the diffeomorphic anatomical registration using exponentiated lie algebra (DARTEL) method of nonlinear image registration procedure. This procedure took the mean of all participants' aligned tissue classes images derived from the segmentation step to

generate a group template. This was achieved by performing six outer iterations, where with each iteration, images were warped to the template, and the template was regenerated from the average of warped images. This process generated a series of flowfields that stored deformation information to normalize images to the Montreal Neurological Institute (MNI) space. In the next step, images were normalized to MNI space and relative voxel volumes before and after warping were preserved and re-sampled at 1.5mm x 1.5 mm x 1.5mm based on recommendations for VBM studies (Ashburner & Friston, 2000). Warped images were smoothed with 6mm full width at half maximum (FWHM) Gaussian kernel. Parametric statistical analyses are based on an important assumption that residuals following model-fitting are normally distributed. However, as grey matter segments as in VBM contain values between zero and one with most values lying at the extremes, the smoothing procedure is essential to render the residuals sufficiently normally distributed (Penny et al., 2011). This increases the validity of parametric tests (Ashburner & Friston, 2000; Salmond et al., 2002), though excessive smoothing reduces accurate localization of change in the brain. In general, a smoothing kernel of 6mm has been recommended for VBM studies (Ashburner & Friston, 2000).

Regions that showed altered GMV in Chapter 3 were used to guide the selection of ROIs - the middle/superior frontal gyrus, postcentral gyrus, inferior parietal lobule, cingulate gyrus, insula, putamen, thalamus, inferior temporal gyrus, and additional regions of the CSTC circuitry (OFC, caudate nucleus) were selected as ROIs and extracted according to the AAL2 template via MRICron (Figure 5-1), with final analysis space of 328578 voxels.

Figure 5-1. Inclusive mask for VBM analyses (non-cerebellar).

Regions in the mask included: middle/superior frontal gyrus, postcentral gyrus, inferior parietal lobule, cingulate gyrus, insula, putamen, inferior temporal gyrus, orbitofrontal cortex, caudate nucleus.

Imaging Preprocessing: Cerebellum

The spatially unbiased infra-tentorial template (SUIT) was developed to provide an atlas template that preserves anatomical details of the cerebellar structure (Diedrichsen, 2006). The SUIT template is of higher resolution and provides better spatial normalization for the cerebellum compared with the standard MNI template (Diedrichsen, 2006). Cerebellar grey matter were evaluated using the SUIT toolbox version 3.0 (Diedrichsen, 2006). AC-PC reoriented T1-weighted images were first cropped to isolate the cerebellum structure. This step provided an isolated cerebellar probability map and a grey-matter segmentation map. The isolated cerebellar probability maps were individually checked and hand-corrected when necessary using MRICron to exclude grey matter outside the cerebellum. The hand-corrected cerebellar maps were then normalized using DARTEL algorithm, resliced at 1mm x 1mm x 1mm based on recommendations of the toolbox, and smoothed using a 4mm isotropic Gaussian kernel. Age, sex and total intracranial volumes were modeled as variables of no interest. Final analysis space included 148993 voxels.

Statistical Analysis

Global volumes of grey matter, white matter and cerebrospinal fluid (CSF) were extracted for each participant using the SPM tissue volume utility. Total intracranial volume was calculated by taking the sum of global grey matter, white matter and CSF volumes. Independent samples t-tests were employed using IBM SPSS Statistics (version 23) to evaluate group differences in these global volumes.

Voxel-by-voxel analysis of covariance (ANCOVA) was conducted to evaluate group differences in whole-brain and cerebellar grey matter with age, sex, and total intracranial volumes specified as covariates of no interest. An inclusive mask containing the ROIs was also specified for the analysis. A threshold of $p < .001$ (uncorrected) with extent threshold of 10 voxels was applied to suppress small and incidental findings.

Regional grey matter volumes of significant clusters were extracted using MarsBaR toolbox in SPM12 (v0.44) (Brett, Anton, Valabregue, & Poline, 2002). Spearman correlations were applied to explore associations between regional grey matter volumes with clinical indices – illness severity (Y-BOCS total/obsessions/compulsions scores), duration of illness, duration of pharmacotherapy and age of onset; and measures of cognitive flexibility such as the difference index from the Trail-Making Test and the Stroop index, and visual memory as assessed by the Symbol Span test. Correlations with $p < .05$ were presented.

Statistical Threshold Justifications

The issue of statistical thresholds in neuroimaging analyses has been an area of controversial debate (Button et al., 2013; Cremers, Wager, & Yarkoni, 2017; Lieberman & Cunningham, 2009). Even though recent reports and simulation studies generally advocated for relatively conservative thresholds to protect against false positive (Type I errors) (Button et al., 2013; Eklund, Nichols, & Knutsson, 2016), doing so inevitably increase Type II errors

(false negative) and reduce power. Conservative p values could potentially hinder important and interesting findings that deserve further evaluations and may be therefore not suitable for studies that are explorative in nature (Cremers et al., 2017; Lieberman & Cunningham, 2009). In addition, as clinical studies are typically considered to be of lower statistical power to begin with, corrected thresholds such as family-wise error (FWE) and false-discovery rates (FDR) may be too stringent for the current sample. Nevertheless, we explored our analyses using two corrected thresholds of $p < .01$ voxelwise with FDR .05 cluster-correction, and $p < .01$ voxelwise with FWE .05 cluster-correction separately, and present results in the Supplementary Appendix S-Table 5-1.

The current chapter utilized a threshold of $p < .001$ (uncorrected) with extent threshold of 10 voxels in attempt to achieve a balance between Type I and Type II errors. Uncorrected $p < .001$ thresholds have been used in previous structural imaging data and were considered reasonable with clear hypotheses (Rüsch et al., 2003; Valente et al., 2005). Several studies that performed VBM analyses in patients with OCD have also utilized uncorrected $p < .001$ thresholds (Gilbert, Mataix-Cols, et al., 2008; Koprivova et al., 2009; Pujol et al., 2004; Valente et al., 2005; Yoo et al., 2008). Effects observed at $p < .001$ (uncorrected) and extent threshold of 10 voxels were then verified using permutations testing via Statistical NonParametric Mapping (SnPM13) (Nichols & Holmes, 2002) with 10000 permutations as based on existing literature that evaluated the optimal number of permutations required for VBM analyses (Dickie et al., 2015). Results obtained from the permutations approach are provided in Supplementary Appendix S-Table 5-2 and S-Figure 5-1. Coordinates of significant clusters were labelled using AAL2 for non-cerebellar coordinates, and SUIF atlas for cerebellar coordinates. The current study also adopted the default criterion for cluster reporting of up to 3 peaks per cluster that are at least 8mm apart.

Results

Global Volumes

There were no significant group differences in all global brain volume indices (Table 5-1).

Grey matter differences

Relative to controls, patients with OCD showed increased GMV in the bilateral postcentral gyrus, and reduced GMV in the right insula (Table 5-2, Figure 5-2). Within the cerebellum, patients with OCD showed reduced GMV in the right cerebellar lobule VI and left lobule VIIa, and increased GMV in the left cerebellar lobule Crus II (Table 5-2, Figure 5-2).

Table 5-1: Group differences in global brain volumes.

	Controls (n=17)		Cases (n=21)		<i>t</i>	df	<i>p</i>
	Mean	S.D.	Mean	S.D.			
Grey matter volume (ml)	712.66	67.85	709.68	62.88	0.14	36	.89
White matter volume (ml)	454.39	46.24	451.77	42.23	0.18	36	.86
Cerebrospinal fluid (ml)	310.64	53.03	334.98	72.52	-1.16	36	.26
Total intracranial volume (ml)	1477.69	133.82	1496.43	127.39	-0.44	36	.66

Associations with regional GMV

Spearman correlations revealed negative correlations between symbol span scores with GMV in the right postcentral gyrus cluster within controls, $\rho_s = -.562$, $p = .019$, and with the right insula cluster within the OCD sample, $\rho_s = -.529$, $p = .014$. In addition, positive associations were observed between GMV in the right cerebellar lobule VI cluster with the Stroop index, $\rho_s = .453$, $p = .039$ and Y-BOCS obsessions score, $\rho_s = .522$, $p = .015$; and between GMV in the left cerebellar lobule VIIa with duration of pharmacotherapy, $\rho_s = .550$, $p = .010$ within the OCD sample. However, associations between GMV in the left cerebellar lobule VIIa and duration of pharmacotherapy was likely contributed by confounding effects

of age, as the association was no longer significant after a partial correlational analysis that controlled for the effects of age, $p > .05$. Due to the exploratory approach of the correlational analyses, all observed effects were not Bonferroni-corrected.

Table 5-2: Group differences from VBM analysis.

								Mean GMV per voxel (ml)				<i>p</i>	Cohen's <i>d</i>
	Hemisphere	<i>k</i>	<i>x</i>	<i>y</i>	<i>z</i>	<i>T</i>	<i>Z</i>	Controls		OCD			
								<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>		
<u>Cerebral Grey Matter</u>													
<i>OCD < Controls</i>													
Insula	R	19	42	-14	6	3.66	3.31	0.69	0.11	0.60	0.12	.02*	-0.75
<i>OCD > Controls</i>													
Postcentral gyrus	R	15	52.5	-14	34.5	3.99	3.55	0.32	0.16	0.40	0.18	.27	0.46
Postcentral gyrus	L	33	-60	-18	22.5	3.94	3.52	0.50	0.14	0.58	0.12	.06	0.58
								Mean GMV per voxel (ml)				<i>p</i>	Cohen's <i>d</i>
	Hemisphere	<i>k</i>	<i>x</i>	<i>y</i>	<i>z</i>	<i>T</i>	<i>Z</i>	Controls		OCD			
								<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>		
<u>Cerebellar Grey Matter</u>													
<i>OCD < Controls</i>													
Lobule VI	R	660	11	-73	-14	4.62	4.00	0.88	0.08	0.79	0.08	.45 x 10 ⁻⁴ ***	-1.17
Lobule VI	R		18	-69	-21	4.24	3.73						
Lobule V	R		10	-64	-18	3.46	3.16						
Lobule VIIa	L	49	-33	-37	-47	4.55	3.95	0.29	0.07	0.20	0.06	.07 x 10 ⁻⁴ ***	-1.27
<i>OCD > HC</i>													
Crus II	L	38	-31	-62	-44	4.63	4.00	0.31	0.05	0.38	0.06	.94 x 10 ⁻³ ***	1.18

Note. Regions that showed differences in cerebral and cerebellar grey matter within the specified

masks. Analysis voxel size: 1.5 x 1.5 x 1.5mm³ (non-cerebellar), 1 x 1 x 1mm³ (cerebellar).

Coordinates are in MNI (non-cerebellar) and SUIT (cerebellar) space. Age, sex and total intracranial volume were modeled as covariates of no interest. Results were thresholded at $p < .001$ (uncorrected)

with $k > 10$. Results were based on 17 Controls, 21 OCD Patients. *M* = Mean. *SD* = Standard

Deviation. L = Left. R = Right. GMV = Grey Matter Volume. (* $p < .05$. ** $p < .01$. *** $p < .001$)

Figure 5-2. Regions that showed differences in cerebral and cerebellar grey matter.

Results were thresholded at $p < .001$, $k \geq 10$. Age, sex and total intracranial volume were modeled as covariates of no interest. Reduced grey matter volume were observed in cases compared to controls in (A): right insula; (B): right cerebellar lobule VI; (C): left cerebellar lobule VIIIa; (D): cerebellar flatmap for OCD < Controls contrast. Increased grey matter were observed in cases compared to controls in (E): right postcentral gyrus; (F): left postcentral gyrus; (G): left cerebellar crus II. Results were based on 17 controls, 21 OCD.

Discussion

Compared to controls, patients with OCD showed increased grey matter in the bilateral postcentral gyrus and left Crus II, and reduced grey matter in the right insula, right cerebellar lobule VI and left cerebellar lobule VIIIA. Within the patients' sample, regional GMV of the right insula was negatively associated with symbol span scores, and GMV of the right cerebellar lobule VI was positively associated with the Stroop index. GMV of the right cerebellar lobule VI cluster was also positively associated with Y-BOCS obsessions scores.

The current study reported relatively modest findings compared to other studies. In addition to the small sample size, the current study had included OCD patients without comorbid conditions and did not request patients to have a medication wash-out period. These characteristics could contribute to a patients' sample that has been remediated to a certain extent, of lower severity and with a less complex clinical prognosis compared to patients' samples of previous studies. One may also speculate that the effects reported could be attributed to clinical factors such as duration of illness and medication effects. The current study is unable to address the speculation directly as the study utilized a cross-sectional design. However, we explored associations between regional GMV of significant findings with clinical factors such as duration of illness, mean daily dosage of fluoxetine equivalents, and duration of pharmacological therapy and did not observe significant associations. An initial association was observed between GMV of the left cerebellar lobule VIIIA and duration of pharmacotherapy, but this relationship did not remain significant after controlling for the effects of age. Therefore, it is unlikely that the marginal findings reported in the VBM analyses were driven by medication effects.

We acknowledged that the current study suffers from small sample size of 17 controls and 21 patients with OCD. To evaluate the consistency of VBM findings, we compared the

findings obtained from the current study with previous studies that utilized similar sample sizes (Valente et al., 2005: 15 controls, 12 OCD patients without major depression; Togao et al., 2010: 26 controls, 23 OCD patients). In general, findings reported from both studies appeared varied. Valente and colleagues reported increased GMV in the left posterior OFC and anterior insula ($Z = 4.79$) and bilateral parahippocampal gyrus regions ($Z_{\text{left}} = 4.69$, $Z_{\text{right}} = 3.66$), and reduced GMV in the right anterior OFC ($Z = 3.43$), left anterior cingulate and medial frontal gyrus ($Z = 4.03$), and in the right angular and supramarginal gyri regions ($Z = 5.33$) in OCD samples compared to controls at $p < .001$ (uncorrected) (Valente et al., 2005). Togao and colleagues reported only reduced GMV in OCD samples relative to controls in the bilateral medial prefrontal cortex ($Z_{\text{left}} = 4.29$, $Z_{\text{right}} = 4.49$), left middle occipital gyrus ($Z = 3.84$), right middle temporal and occipital gyrus ($Z = 4.02$), right dorsolateral prefrontal cortex ($Z = 4.21$), right OFC ($Z = 3.87$) at voxelwise $p < .05$ (FDR-corrected), $k \geq 25$ (Togao et al., 2010). Both Valente et al. (2005) and Togao et al. (2010) reported altered GMV in the OFC but this was not observed in the current study. Even though the OFC is a key region of the CSTC circuitry, reports of altered OFC GMV in OCD have been inconsistent, which contributed to the absence of group differences in the OFC in a previous (Radua & Mataix-Cols, 2009a) and current meta-analysis (Chapter 3). In addition, the mean age of the samples in Valente et al. (2005) (Controls: 32.3, OCD: 32.7) and Togao et al. (2010) (Controls = 31.3, OCD = 32.6) were also older than the samples in the current study (Controls = 26.1, OCD = 28.6). A separate study had postulated age-related preservation of OFC GMV in OCD samples compared to controls. de Wit and colleagues evaluated group-by-age interactions on OFC GMV, and reported relative loss in OFC GMV in OCD patients compared to controls with increased in age (de Wit et al., 2013). Therefore, differences in demographic characteristics could also influence reported findings on OFC. In terms of other

demographics information, the current study comprised of approximately equal numbers of males and females in each group (Controls: 9 males, 8 females; OCD: 10 males, 11 females), but this was not the case for Togao et al. (2010), where there were more females in the OCD group (Controls: 12 males, 14 females; OCD: 9 males, 14 females). In terms of clinical symptoms, the OCD sample in the current study had generally older age of onset ($M = 20.7$), shorter duration of illness ($M = 7.88$), and less severe OCD symptoms ($M = 20.2$) compared to Valente et al. (2005) ($M_{\text{age_of_onset}} = 14.4$, $M_{\text{duration_of_illness}} = 18.3$, $M_{\text{Y-BOCS_severity}} = 24.6$) and Togao et al. (2010) ($M_{\text{age_of_onset}} = \text{no data}$, $M_{\text{duration_of_illness}} = 12.9$, $M_{\text{Y-BOCS_severity}} = 29.8$). In addition, the patients' sample in Valente et al., (2005) had also included patients with comorbid conditions. Lastly, variations in findings across studies could potentially be attributed to small sample sizes that led to either false positive or negative findings, especially when corrections for multiple comparisons were not applied. Therefore, sample differences and sizes could potentially contribute to the inconsistencies in findings observed across studies.

We explored our analyses using two corrected thresholds of $p < .01$ voxelwise with FDR .05 cluster-correction, and $p < .01$ voxelwise with FWE .05 cluster-correction separately (S-Table 5-1). Only a right cerebellar lobule VI finding survived $p < .01$ voxelwise with FWE .05 clusterwise, and no clusters survived $p < .01$ voxelwise with FDR .05 cluster-correction.

Parametric and non-parametric uncorrected analyses yielded similar findings in terms of group differences in GMV, except for a reduced GMV in the insula that was not reported using the non-parametric approach. Even though the current study utilized non-corrected thresholds that may be criticized as being overly liberal, that different methods converged to

similar findings indicate that the reported findings are likely not spurious, although the effects may be small.

Altered GMV in the insula and postcentral gyrus observed in the current study could potentially be speculated as probable involvement of relevant networks in the disorder. The cerebral cortex has been thought to be organized into cortical hubs or functional networks where activity between regions intra-network are disproportionately numerous (Buckner et al., 2009; Sporns, Honey, & Kötter, 2007). The insula and postcentral gyrus are anchors of the salience and sensorimotor networks, respectively (Seeley et al., 2007). The salience network is involved in detecting, identifying and integrating different forms of salience and interoceptive autonomic processing (Menon & Uddin, 2010; Seeley et al., 2007). The sensorimotor network is anchored by the precentral and postcentral gyrus (Biswal, Zerrin Yetkin, Haughton, & Hyde, 1995), and is involved in preparing the brain to perform coordinated motor acts (Nachev, Wydell, O'Neill, Husain, & Kennard, 2007). Altered salience network in OCD could potentially increase the perception of salience to external or internal mental stimuli, and altered sensorimotor network could contribute to the urges and compulsive acts that patients with OCD perform (Peng, Shi, Shi, Yang, et al., 2014; Russo et al., 2014). Investigations and findings on intrinsic network connectivity in OCD samples and controls are discussed in Chapter 7.

A meta-analysis conducted by Stoodley and Schmahmann (Stoodley & Schmahmann, 2009) suggested a dissociation of functional locality of the cerebellar lobule VI and VIIb/VIII regions where motoric processes are located more anteriorly (with y-coordinate between -60 to -70), and cognitive processes more posteriorly (y-coordinate between -70 to -80) (Stoodley & Schmahmann, 2009). Drawing reference from the functional meta-analysis of the cerebellum, we postulate that reduced GMV observed in patients with OCD compared to

controls in the left anterior lobule VIIIa may be relevant to motoric processes, and reduced GMV in right posterior lobule VI and increased GMV in left Crus II indicate relevance to language and executive function processes (Stoodley & Schmahmann, 2009). Reduced GMV in the motoric cerebellum appears consistent with reduced GMV in the sensorimotor lobule IV-V as reported in our meta-analysis (Chapter 3). However, it is noted that the exact cerebellar lobules reported in the current chapter and the meta-analysis may not coincide, and this could be attributed to the way the cerebellar lobule findings were derived. In the current study, cerebellar grey matter were evaluated using the SUI toolbox version 3.0 (Diedrichsen, 2006). The SUI template preserves more anatomical details, and provides higher resolution and more accurate spatial normalization for the cerebellum compared to the standard MNI whole-brain template that existing studies typically use (Diedrichsen, 2006). Therefore, differences in preprocessing steps such as the templates used for normalization could potentially contribute to the reports of different cerebellar lobules.

We note that findings reported in this chapter did not survive corrected thresholds, and this could potentially be attributed to small sample sizes, low power, and perhaps small effects. Therefore, findings from this pilot analysis require replication. Further efforts could utilize publicly available datasets such as those from Nathan Kline Institute and Human Connectome Project for replication purposes.

In the next chapter, we will evaluate structural grey matter difference to investigating group differences in neural activations during working memory and response inhibition tasks.

**CHAPTER 6: STUDY 3 –TASK-RELATED FUNCTIONAL ACTIVATIONS IN OCD
SAMPLES AND CONTROLS**

Exploring neural differences in individuals with OCD and controls during verbal working
memory, visual working memory and stop-signal task

Introduction

Existing studies often discussed neuropsychological deficits in OCD samples involving domains such as working memory and response inhibition. However, these findings were often inconsistent and neuroimaging studies in these domains have been limited.

Most studies that evaluated verbal and visual working memory in OCD had adopted the n-back paradigm and generally reported task-related compensatory hyperactivity in the insula, frontal, parietal and striatal regions (Koch et al., 2012; Nakao, Nakagawa, Nakatani, et al., 2009; Purcell et al., 1998a; Purcell et al., 1998b). However, the n-back task may not be a pure measure of working memory as several cognitive processes are required for successful performance, such as consistent updating of new information, active maintenance of information and their serial order, and consistently inhibiting previously relevant information (n-lag) that has turned irrelevant (non n-lag) as the task progresses (Chatham et al., 2011; Miller, Price, Okun, Montijo, & Bowers, 2009). Compared to the n-back task, the Sternberg's working memory paradigm is a relatively simple working memory task that emphasizes information encoding and maintenance (Corbin & Marquer, 2013). In addition, most studies that purportedly evaluated visual working memory in OCD had effectively measured spatial and/or visuospatial working memory.

Henseler and colleagues evaluated verbal and spatial working memory functioning in OCD and reported compensatory activity in the inferior frontal gyrus, intraparietal cortex during verbal working memory, and in the precentral sulcus during verbal and spatial working memory tasks (Henseler et al., 2008). To the best of our knowledge, no study has yet investigated neural differences during a visual working memory task. This is important,

considering that existing literature appear to indicate some difficulties relating to visual working memory processes (Chapter 2).

Response inhibition has most commonly been investigated using the Stop-signal task. Evidence of altered response inhibition during a stop-signal paradigm in OCD have been mixed – some studies reported significantly slower inhibitory responses (de Wit, de Vries et al., 2012; Kang et al., 2013; Lei et al., 2015; McLaughlin et al., 2016; Menzies et al., 2007), and others observed comparable performances in OCD patients relative to controls (Kalanthoff, Henik et al., 2017; Kalanthoff, Teichert et al., 2017; Morein-Zamir et al., 2016). Out of the five studies that reported slower inhibitory responses in OCD samples, three had included a medication wash-out period prior to the day of assessment (de Wit, de Vries et al., 2012; D. H. Kang et al., 2013; Lei et al., 2015). Of the other two studies (McLaughlin et al., 2016; Menzies et al., 2007), only one had excluded patients due to comorbid conditions (Menzies et al., 2007). Among the studies that did not observe significant group differences in inhibitory responses, both studies had included patients with comorbid conditions (Kalanthoff, Teichert, et al., 2017; Morein-Zamir et al., 2016), and one study had utilized face/house stimuli (Morein-Zamir et al., 2016) and the other employed an auditory stop- signal in their task paradigms (Kalanthoff, Teichert, et al., 2017). Based on the above limited review, it appears that existing studies had utilized different task variations of the stop-signal task, and had different medication and comorbidity statuses in the OCD samples. In addition, delaying strategies are undesirable but common in stop-signal paradigms, as evident by higher than 50% accuracy rate for Stop-trials (Boehler, Appelbaum, Krebs, Hopf, & Woldorff, 2012). Of the above-referenced studies, only three had reported Stop-trial accuracy rates (Lei et al., 2015: OCD – 59.9%, Controls – 60.7%; McLaughlin et al., 2016: OCD – 55%, Controls – 56%; Kalanthoff et al., 2017: OCD – 49%, Controls –

49%), and none had reported using any measures to reduce the use of such strategies. Among the studies that had reported accuracy rates of Stop-trials, both studies with Stop-trials greater than 50% had reported slower inhibitory responses in OCD (Lei et al., 2015; McLaughlin et al., 2016). Therefore, it appears plausible that delaying strategies could contribute to inconsistent findings across studies. Neuroimaging evidence using the stop-signal task in OCD are also limited. A familial study conducted on patients with OCD and their unaffected first-degree relatives showed delayed response inhibition reaction times compared to controls (Menzies et al., 2007), but this finding was not replicated in another study (de Wit, de Vries, et al., 2012). Menzies and colleagues (2007) reported significant associations between slower reaction times and reduced grey matter in the OFC and right inferior frontal regions, and increased grey matter in the cingulate, parietal and striatal regions in OCD and matched-relative groups. In other studies, increased activity in OCD samples relative to controls was also reported in *a priori* regions in the presupplementary motor area, inferior frontal gyrus and the inferior parietal cortex (de Wit, de Vries et al., 2012), the caudate nucleus and precentral gyrus (Morein-Zamir et al., 2016), and in the parietal cortex and cerebellum during inhibition (Kang et al., 2013). Reduced activity in several *a priori* regions were also reported in OCD samples such as the putamen, caudate nucleus and ACC (Kang et al., 2013). These differences in neural activity reported across studies could be attributed to the evaluation of different ROIs amidst other factors mentioned above, such as task variations, and sample characteristics within the patient groups.

In the current study, we evaluate differences in neural activity between OCD patients and controls during Sternberg's paradigm of verbal and visual working memory tasks, and the stop-signal task. The Sternberg's working memory task is a simple working memory task that emphasizes information encoding and maintenance. The current study employed a six-

character encoding array for the verbal working memory task, and a three-item encoding array for the visual working memory task, as adopted from Ng and colleagues (Ng et al., 2016). In a sample of healthy adults, the authors reported activity in several brain regions during both verbal and visual working memory tasks that included the supplementary motor area, cingulate, insula, precentral gyrus, inferior frontal gyrus, hippocampus, superior parietal and cerebellar regions (Ng et al., 2016). The calcarine, putamen, caudate, and angular gyrus were additionally activated during verbal working memory, and the fusiform gyrus, middle frontal gyrus and the thalamus during visual working memory task (Ng et al., 2016). In terms of neural involvement during inhibitory processes, existing findings based on healthy adults and results from our meta-analysis indicated the involvement of the inferior frontal gyrus, pre-supplementary motor area, insula, cingulate, putamen, caudate, dorsolateral prefrontal cortex, inferior parietal, superior frontal-medial, and the cerebellum during inhibition in a stop-signal paradigm (Aron, Robbins, et al., 2004; Chen & Desmond, 2005; Nee, Wager, & Jonides, 2007; Sebastian et al., 2013; van Velzen et al., 2014).

Hypotheses

Considering that stimuli utilized in the Sternberg's verbal working memory task could be internally rehearsed and were within the phonological capacity of between four to six items (Baddeley, 2000), the current study hypothesize no significant group differences in reaction time and accuracy rates for the verbal working memory task. However, taking reference from a previous study (Henseler et al., 2008), we expect to observe altered neural activations during the verbal working memory task in OCD despite no group differences in behavioural performance.

For the visual working memory task, we expect OCD samples to show poorer performance in the high load condition. According to the working memory hypothesis

(Harkin & Kessler, 2011), even though the number of items (three-item array) were well within the capacity of the visuospatial sketchpad, the stimuli were more complex at high load conditions (greater binding complexity) and are limited in verbal mediation, and could therefore be more susceptible to interference and memory decay (Olley et al., 2007). In addition, OCD samples had performed poorer than controls in the Symbol Span test (Chapter 4), which could potentially indicate difficulties in visual memory processes. Therefore, for the visual working memory task, we expect OCD samples to demonstrate poorer accuracy in high load conditions and this observation could possibly be accompanied with slower reaction time.

Lastly, as with previous studies, we hypothesize slower response inhibition as evaluated using the stop-signal task. In terms of the expected neuroimaging findings, we generally hypothesize to observe neural differences within known regions of the respective tasks as elaborated earlier.

Regions-of-Interest

As the CSTC circuitry has been influential in guiding neuroimaging studies in OCD, regions in the CSTC in addition to task-specific regions were included as regions-of-interests in subsequent analyses.

The current study evaluates group differences in neural activity of the cerebellum using the spatially unbiased infra-tentorial template (SUIT) toolbox (Diedrichsen, 2006). SUIT was specifically developed to provide an atlas template that preserves anatomical details of the cerebellar structure (Diedrichsen, 2006). Distinct subregions of the cerebellum occur on a much smaller scale than cerebral cortical regions, and the ICBM152 template from the Montreal Neurological Institute (MNI) typically used in normalisation provides very little anatomical detail of the cerebellum, leading to poor alignment of cerebellar structures

(Diedrichsen, 2006). The SUI template has higher resolution and provides better spatial normalization for the cerebellum compared with the standard MNI template. Considering the intricate connectivity between the cerebellum and the subcortical and cortical regions, accurate localization of anomalies is important and could inform potential corresponding involvement of other cortical regions. Therefore, the current study aims to elucidate group differences in task-related functional activations in the cerebellum.

Methods

Participants

All participants performed three tasks in the scanner: Verbal working memory, visual working memory, and stop-signal task. Data of 21 OCD patients and 17 controls (Controls: 9 males, 8 females; $M_{\text{age}} = 26.12$, $SD_{\text{age}} = 4.15$, Range: 21-47) were obtained from the same set of participants as reported in Chapter 4. Data that did not fulfill data and image quality control criteria were excluded. Subsequent analyses were conducted based on: 1) 18 OCD patients (9 males, 9 females; $M_{\text{age}} = 28.33$, $SD_{\text{age}} = 7.27$) and 17 controls for the verbal working memory task; 2) 19 OCD patients (9 males, 10 females; $M_{\text{age}} = 28.42$, $SD_{\text{age}} = 7.07$) and 17 controls for the visual working memory task; and 3) 20 OCD patients (9 males, 11 females; $M_{\text{age}} = 28.30$, $SD_{\text{age}} = 6.91$) and 17 controls for the stop-signal task. Preliminary Spearman correlations did not reveal significant associations between age with accuracy and reaction time of all three tasks, all $p > .05$. The study was approved by relevant institutional and ethics committees (NTU-IRB 2013-11-010 and NHG-DSRB Ref: 2013/01221) (Supplementary Appendix A).

Procedures

Prior to entering the scanner suite, participants had a pre-scan briefing to understand what to expect during the scan and the tasks to be performed in the scanner. Details on the

pre-scan briefing were discussed in Chapter 4 of the thesis (*Pre-scan briefing*). All participants performed the working memory tasks followed with the stop-signal task. The order of verbal and visual working memory tasks was counterbalanced across participants, with a brief rest period of approximately two minutes in between each task run.

Task Descriptions and Instructions

Stimuli were presented using E-Prime 2.0 software (Schneider, Eschmann, & Zuccolotto, 2002), and were back-projected in the scanner via a magnet-compatible projector. Participants viewed the stimuli from a mirror mounted above their head. The scanning was synchronized with the tasks and were triggered automatically from E-Prime software.

Sternberg's Verbal Working Memory Task

Test stimuli and paradigm for the Sternberg's verbal working memory task in this study were similar as previously reported (Chen & Desmond, 2005; Ng et al., 2016). Events information for the verbal working memory task is presented in Figure 6-1(A). Each trial began with a central fixation cross that was presented for 1200ms. This was followed by an encoding array of either six identical (low-load) or six different (high-load) uppercase letters. Participants were given 3000ms to view the array, during which participants subvocally rehearsed the letters in sequential order and continued to rehearse the letters during a 3000ms maintenance phase. A test probe letter was presented for 2000ms, and participants pressed either of two buttons under the right index and middle fingers to indicate a match or no-match to the encoding array, respectively. To minimize jaw movements, participants were instructed to refrain from moving their lips/mouth during the motoric rehearsal.

The Sternberg's Verbal Working Memory Task was presented in a block design paradigm. Stimuli were presented in blocks that consists two trials of low-load followed by two-trials of high-load per cycle, for 10 cycles per run (Figure 6-1(C)). All participants

performed one run of the task in the scanner, with a total of 40 trials. The task lasted for 6.67 minutes. Participants performed one practice run before entering the scanner suite. All participants performed above 75% overall accuracy in the practice run.

Figure 6-1. Events information for Sternberg working memory tasks.

Stimulus flow for (A) verbal working memory and (B) visual working memory tasks. Two load conditions were presented (high-load, low-load). (C): Timing of one cycle -- Stimuli were presented in blocks consisting of two trials of low-load followed by two trials of high-load conditions, interleaved by 1.6 s of rest interval between blocks. Each run consisted of 10 cycles. Participants performed 1 run of verbal working memory task and 2 runs of visual working memory tasks.

Sternberg's Visual Working Memory Task

Task paradigm for the visual task were similar with the Verbal Working Memory task as shown in Figure 6-1(B). The encoding array consisted of either three identical (low-load) or three different visual patterns (high-load). Participants had 4000ms to view the array,

followed with 500ms of maintenance phase, during which participants remembered and mentally refreshed the images. A test probe image was presented for 2500ms, and participants pressed either of two buttons under the right index and middle fingers to indicate a match or no-match to the encoding array, respectively.

The Sternberg's Visual Working Memory Task was presented in a block design paradigm. Stimuli were presented in blocks of two trials of low-load followed by two-trials of high-load per cycle, for 10 cycles per run. All participants performed two runs of the task in the scanner, with a total of 80 trials. The task lasted for 13.33 minutes. Participants performed one practice run before entering the scanner suite. All participants performed above 75% overall accuracy in the practice run.

Stop-Signal Task

The Stop-signal task adopted an event-related design (Figure 6-2). Each trial began with a fixation cross. Thereafter, two forms of trials (Go, Stop) may be presented. In Go-trials, participants viewed arrows in a white ring that pointed either to the right or left (Go-signals). Participants responded by pressing either of two buttons under the right index and middle fingers to indicate whether the arrow pointed to the left or right, respectively. In a small number of trials (25%), a Stop-signal was presented after a short delay from the presentation of the Go-signal. The Stop-signal involved a change in the colour of the ring from white to blue. When this occurred, the participants had to stop themselves from making a response, and therefore, the correct response in Stop-trials would be no response.

The delay between the Go- and the Stop- signal was manipulated by a tracking algorithm (Logan et al., 1984), where each successful stop increased the next stop delay by 50ms, and each unsuccessful stop reduced the next stop delay by 50ms (Figure 6-2(B)). This delay period is known as the Stop-signal delay (SSD). Simulation studies reported greater

inhibition difficulty with increased SSD (Band, van der Molen, & Logan, 2003). A tracking algorithm was used to keep the probability of correct inhibition at around 50%, which allowed the best approximation in estimating the Stop-signal reaction time (SSRT) (Band et al., 2003) – the time needed to inhibit a prepotent response. Two staircases that start with delay periods of 150ms and 250ms were used, and the staircases were independent from each other and randomly interleaved. The average SSD was computed based on the last 8 SSD values per staircase per run. SSRT, a proxy for response inhibition, was then calculated by subtracting average SSD from the median GO reaction time. The inter-trial interval was jittered between one to five seconds. Participants were reminded not to wait for the stop-signal to appear as the stop-signals are unpredictable and only appear in a small number of trials, and that it is equally important to respond quickly to the arrows in the white ring and withhold responses to the stop-signals. Participants were also reassured that it would be quite normal to fail in some of the stop trials, and it would not be always possible to stop.

The Stop-Signal task was presented in an event-related design, with the sequence of trials optimized using Optseq (Dale, 1999). Each run consisted 84 Go-trials and 24 Stop-trials. All participants performed three runs in the scanner and total task duration was 15 minutes. Participants performed one practice run before entering the scanner suite. All participants performed above 75% overall accuracy in the practice run.

Behavioural Data Analysis

Accuracy rates and reaction times for both high and low load conditions were extracted from participants' responses to both verbal and visual working memory tasks. Outcome indices for the stop-signal task were accuracy rates for Go-, Stop-trials, reaction times for Go-trials (GO-RT), and Stop-trials (SSRT). Non-parametric Mann-Whitney U tests

were conducted to evaluate group differences in each index as the distributions were not normally distributed.

Figure 6-2. Events information for Stop-signal task.

(A): Two trial types may be presented. In Go trials, participants viewed arrows in a white ring that pointed either to the right or left. Participants responded using button presses to indicate the direction of the arrows. In a small number of trials (25%), a stop-signal was presented after a short delay from the presentation of a Go-signal. Participants had to stop themselves from making a response, and the correct response is no response. Each run consists of 75% Go-trials and 25% Stop-trials, with a total of 112 trials per run. A total of three runs were administered.

(B): The delay between the Go-signal and Stop-signal during a stop-trial was manipulated by a tracking algorithm. Each successful stop increased the next stop delay by 50ms, and each unsuccessful stop reduced the next stop delay by 50ms. This delay period is known as the stop-signal delay (SSD). Two staircases with initial delay periods of 150ms and 250ms were used. The staircases were interdependent of each other, and randomly interleaved.

Image Acquisition

Whole-brain MRI data were acquired on a Siemens 3.0 Tesla MRI scanner (Siemens Prisma, Erlangen, Germany) using a 32-channel head coil. MRI structural data were obtained using a high-resolution T1-weighted 3D MP-RAGE protocol: TR=1900ms; TE=2.52ms;

voxel size=1 x 1 x 1mm; flip angle= 9°; FOV=256mm. The structural T1 image was used for anatomical co-registration with the functional volumes in later image pre-processing. A T2-weighted anatomical image was acquired using the following parameters: TR=2660ms; TE=99ms; flip angle=150°; 41 slices with 5% gap; voxel size=3.5 x 3.5 x 3.5mm; FOV=225mm to enable prescription of scanning parameters to subsequent functional MRI images. Functional MRI images were acquired using gradient-echo planar imaging (EPI) sequence: TR=2000ms; TE=29ms; flip angle=90°; 41 slices with 5% gap, interleaved from anterior to posterior; voxel size=3.5 x 3.5 x 3.5mm; FOV=225mm. A total of 200 images for verbal working memory task, 400 images for visual working memory task (200 images per run for 2 runs), and 450 images for stop-signal task (150 images per run for 3 runs) were obtained for each participant.

Data Quality Control Criteria

Several criteria were adopted to ensure neuroimaging data collected were suitable for use in subsequent analyses. First, images at each preprocessing step were randomly checked for distortions before subjecting the images for analysis. Second, neuroimaging data from the specific task procedures were excluded from analyses if average behavioural response accuracies fell below 70% for fMRI tasks (verbal working memory, visual working memory, and Go-trials accuracy from the stop-signal task). These criteria were necessary to help ensure that participants performed the task well above chance level, as it is difficult to interpret low accuracy rates as the participants may not be performing the task as intended and thus the measures may not be valid. This led to the exclusion of 3 patients for the verbal working memory task (due to poor behavioural performance, i.e. < 70% accuracy), 2 patients for the visual working memory task (due to poor behavioural performance, and one of the two participants also had low SfNR of < 80), and 1 patient for the stop-signal task (as

accuracy rates for Go trials in the Stop-signal task was lower than 70%). Neuroimaging data of remaining participants fulfilled other quality control criteria, such as having signal-to-noise ratio of above 80, and head movements less than 3.5mm for translations (x, y, z), and 3.5 degrees for rotations (pitch, roll, yaw). Following these quality control criteria, subsequent analyses were conducted based on: 1) 18 OCD patients and 17 controls for the verbal working memory task; 2) 19 OCD patients and 17 controls for the visual working memory task; and 3) 20 OCD patients and 17 controls for the stop-signal task.

Imaging Preprocessing and Analysis

Imaging Preprocessing – Non-cerebellum. All neuroimaging data were preprocessed and analyzed using SPM12 software package (Statistical Parametric Mapping 12; Wellcome Department of Cognitive Neurology, London, UK; revision #6470) (Penny et al., 2011). All images were first reoriented to AC-PC, functional images were then slice-time corrected to the middle slice (Sladky et al., 2011), and realigned to the first volume of the run to adjust for head movements. Rigid-body movement parameters were produced for each participant and were used as regressors in subsequent first-level analyses. This procedure generated a mean EPI image for the task which was used as a reference image to register the realigned functional images to individual participant's structural T1-weighted image. Using the 'Segment' routine, the structural image was segmented into grey matter, white matter and cerebrospinal fluids, and DARTEL-imported tissue class images for each participant were generated. DARTEL-imported grey and white matter tissue class images from all participants were utilized to obtain a group-specific structural template. This was achieved by performing six outer iterations, where with each iteration, images were warped to the template and the template was regenerated from the average of warped images. This process generated a series of flowfields that stored deformation information to normalize images to the Montreal

Neurological Institute (MNI) space. In the next step, images were normalized to MNI space, resampled at 3.5 x 3.5 x 3.5mm and smoothed with a Gaussian kernel of 6 x 6 x 6mm full-width at half-maximum (FWHM). The smoothed and normalized contrast images were submitted for first level analysis, where task-related differences were evaluated.

fMRI Model Specification and Estimation: Verbal and Visual Memory Tasks.

Following preprocessing, a general linear model approach was used to analyze activations in individual participants as implemented in SPM12. Analyses for both verbal and visual working memory tasks were analyzed using a block design paradigm, where two conditions were modeled: high-load, and low-load conditions. The hemodynamic response during both working memory tasks were then analyzed at the first level by taking the contrast of activations in high-load against low-load conditions (high-load > low-load) to evaluate load-specific neural activations for each working memory task. Signals were high-pass band-filtered at 128s to remove slow drift signals larger than this threshold. The first level analysis step produced one image per contrast for each participant. Six-parameter rigid-body motion parameters were also included in the model as regressors of non-interest to account for variances caused by head movements. Serial correlations in the fMRI time series were accounted for by using an autoregressive AR(1) model. Second level analyses were conducted using random effects methods to evaluate group differences, where the contrast images from all participants within the same group were analyzed using one-sample t-test to generate a group-average activation map for the contrast. Whole-brain within group activations for the contrast conditions (high-load > low-load) were considered significant at voxelwise $p < .001$ (uncorrected) and clusterwise FDR $\alpha = 0.05$, and activation maps were superimposed on the canonical T1-weighted rendered brain.

A task-specific mask that consisted all ROIs was created for each task to limit the search areas for between-group differences in neural activations. ROIs were extracted according to AAL2 template via MRIcron. The following ROIs were specified for each task:

i) Verbal working memory task: precentral gyrus, calcarine, inferior occipital, caudate, pallidum, superior and inferior parietal cortex, insula, supplementary motor area, cingulate gyrus, hippocampus, angular gyrus, inferior and middle frontal, superior frontal (dorsolateral), orbitofrontal cortex, thalamus, caudate nucleus and the putamen, with final analysis space of 33831 voxels; ii) visual working memory task: fusiform gyrus, supplementary motor area, cingulate, precentral gyrus, inferior and middle frontal, superior frontal (dorsolateral), inferior and superior parietal regions, the hippocampus, insula, orbitofrontal cortex, thalamus, caudate nucleus and putamen, with final analysis space of 33698 voxels. These ROIs were selected based on previous literature (Ng et al., 2016), and had also included structures within the CSTC. The inclusive masks are presented in Figure 6-3. Resulting group-average t-maps were contrasted using independent samples t-test and thresholded to evaluate enhanced and reduced activations in OCD samples compared to controls.

fMRI Model Specification and Estimation: Stop-signal Task. In contrast to the verbal and visual working memory tasks that adopted a block design paradigm, the stop-signal task was analyzed using an event-related design paradigm. Intertrial-interval, correct trials and incorrect trials for the Go-signals and Stop-signals were modelled as separate conditions. To model the conditions as accurately as possible, directions of arrows presented (pointing to the left or right) were also modelled as separate conditions in the design matrix. This was done by extracting the onset times for all conditions: i) Right-Go (correct trials for Go-trials with arrows pointing to the right); ii) Left-Go (correct trials for Go-trials with

arrows point to the left); iii) Right-Stop (correct trials for Stop-trials with arrows pointing to the right); iv) Left-Stop (correct trials for Stop-trials with arrows pointing to the left); v) Unsuccessful-RightGo (incorrect trials for Go-trials with arrows pointing to the right); vi) Unsuccessful-LeftGo (incorrect trials for Go-trials with arrows pointing to the left); vii) Unsuccessful-RightStop (incorrect trials for Stop-trials with arrows pointing to the right); viii) Unsuccessful-LeftStop (incorrect trials for Stop-trials with arrows pointing to the left); xi) ITI (Inter-trial interval). Considering the event-related nature of the analyses and the impulse-like duration of the conditions except for the ITI, the durations for all conditions were specified as zero seconds, except for the ITI, where durations ranging from one second to five seconds were extracted and modelled in the design matrix. Considering the fast events in the stop-signal task, time and dispersion derivatives were modelled in the design matrix. Time derivatives allow the canonical response of the HRF to enable peak responses to vary by plus or minus a second and the dispersion derivatives allow the width of the HRF to vary. In effect, modelling time and dispersion derivatives act as deviate terms to allow for inter-subject and inter-voxel responses, thereby increasing the power of the event-related analyses. Serial correlations in the fMRI time series were also accounted for by using an autoregressive AR(1) model. The first level analyses evaluated the contrast in fMRI time series for correct Stop vs correct Go conditions, i.e. correct Stop-Go in each participant. Second level analyses were conducted using random effects methods to evaluate group differences, where the contrast images from all participants within the same group were analyzed using one-sample t-test to generate a group-average activation map for the contrast.

A task-specific mask that consisted all ROIs was created to limit the search areas for between-group differences in neural activations. ROIs were extracted according to AAL2 template via MRICron, and were shown in Figure 6-3. The following ROIs were specified for

the Stop-signal task: superior and inferior parietal, thalamus, inferior frontal gyrus, supplementary motor area, insula, cingulate, putamen, caudate, superior frontal, superior medial frontal gyrus, and the orbitofrontal regions, with final analysis space of 33782 voxels. These ROIs were selected based on previous literature (Aron, Robbins, et al., 2004; Nee et al., 2007; Sebastian et al., 2013; van Velzen et al., 2014; Yang, Deng, Xing, Xia, & Li, 2015). Findings from the meta-analysis in Chapter 3 were also included to help guide the search for between-group neural differences during response inhibition in the stop-signal task. Independent samples t-tests were conducted within the mask to evaluate enhanced and reduced activations in OCD samples compared to controls.

Figure 6-3. Inclusive mask (non-cerebellar) for task fMRI analyses: A) verbal working memory; B) visual working memory; C) Stop-signal task.

Regions included in A) were: precentral gyrus, calcarine, inferior occipital gyrus, caudate nucleus, pallidum, superior and inferior parietal cortex, insula, supplementary motor area, cingulate gyrus, hippocampus, angular gyrus, inferior and middle frontal, superior frontal (dorsolateral), orbitofrontal cortex, thalamus, and putamen.

Regions included in B) were: fusiform gyrus, supplementary motor area, cingulate, precentral gyrus, inferior and middle frontal, superior frontal (dorsolateral), inferior and superior parietal, hippocampus, orbitofrontal, insula, thalamus, caudate and putamen.

Regions included in C) were: inferior and superior parietal, thalamus, inferior frontal gyrus, supplemental motor area, insula, cingulate, putamen, caudate, superior frontal, superior medial frontal, and orbitofrontal.

Imaging Preprocessing and Analysis – Cerebellum. To obtain a spatially unbiased anatomical normalization of the cerebellar structures the spatially unbiased infra-tentorial template (SUIT) toolbox (version 3.0) in SPM12 was applied (Diedrichsen, 2006). The structural T1 image that was co-registered with the functional data was cropped to isolate the cerebellum; isolation maps were checked and hand-corrected using MRIcron where necessary to ensure coverage of the cerebellum. Grey and white matter probability maps generated from the isolation routine were used along with the hand-corrected isolation maps to normalize the individual cerebellum into the SUIT atlas template using the DARTEL pipeline. Resulting deformation parameters and affine transformation matrix were applied to warp the first level contrast images in native space to SUIT space. Normalized contrast images were resampled at $2 \times 2 \times 2 \text{ mm}^3$ following recommendations of the toolbox, and smoothed with a 6mm FWHM Gaussian kernel. The smoothed and normalized contrast images were used to perform random effects analyses in second level analyses using independent samples t tests to evaluate for group differences. Final analysis space included 21141 voxels for cerebellar analyses.

Statistical Thresholding and Justifications. As first discussed in Chapter 5, increasing reports have recommended using relatively stringent statistical thresholds. Lower p values increase protection against Type I errors but increase Type II errors (false negative) and reduce power, hence reduce the probability of recognizing true findings when they are in fact present. The use of conservative thresholds inadvertently increase the bias towards identifying large effects, which may not be a problem for studies with well-known and robust findings such as sensory and motor phenomena, but could potentially nullify important subtle effects in studies of smaller effects such as clinical studies and complex cognition (Lieberman & Cunningham, 2009). Using a series of simulations, Lieberman and

Cunningham (2009) demonstrated that a combination of intensity- and cluster- corrected thresholds of $p < .005$ with 10 voxels extent produced a desirable balance between Type I and Type II error rates, and that an extent threshold of 20 voxels is akin to an effective FDR of .05 in sensory and motor phenomena using similar neuroimaging parameters.

The current study is interested to evaluate neural activations between OCD samples and controls. As these effects may be small and the current study is already underpowered with small sample sizes, conservative thresholds such as FDR, FWE or $p < .001$ (uncorrected) may be too stringent for the current study. Therefore, all group differences in the current chapter were evaluated at $p < .005$ (uncorrected) with an extent threshold of $k \geq 20$ voxels, based on the guidelines reported by Lieberman & Cunningham (2009). Nevertheless, we conducted the analyses using corrected thresholds of $p < .01$ voxelwise with FDR .05 cluster-correction, and $p < .01$ voxelwise with FWE .05 cluster-correction separately for exploratory purposes.

All analyses were contained using *a priori* masks based on past literature and our meta-analytic investigations (Chapter 3) to reduce the search space for group differences. Within-group activations were also reported using one-sample t-tests. As within-group effects are typically larger than between-group effects, within-group activations for each task were considered significant at voxelwise $p < .001$ (uncorrected) and clusterwise FDR $\alpha = 0.05$. Coordinates of significant clusters were labelled using AAL2 for non-cerebellar activations, and SUIT atlas for cerebellar activations. The current study also adopted the default criterion for cluster reporting of up to 3 peaks per cluster that are at least 8mm apart.

Parameter Estimates and Correlations. Parameter estimates of significant regions were extracted using MarsBaR toolbox in SPM12 (v0.44) (Matthew Brett, Anton, Valabregue, & Poline, 2002) to understand the patterns that drove significant differences.

Spearman correlations were applied to explore associations between parameter estimates of the reported regions with clinical indices – duration of pharmacotherapy, OCI-R scores, duration of illness, age of onset, fluoxetine equivalents, and illness severity (Y-BOCS total/obsessions/compulsions scores); and indices of the relevant fMRI tasks.

Results

Behavioural Results

Distributions of outcome variables obtained from the verbal working memory, visual working memory and stop-signal tasks are presented in Supplementary Appendix S-Figure 6-1. Behavioural performances are presented in Table 6-1 and Figure 6-4. OCD samples had lower accuracy in high-load condition of the visual working memory task (Mann-Whitney $U = 92.50, p = .030$).

Within-Group Activation Maps

Whole-brain and cerebellar activation maps of each group during all three tasks are presented in Figure 6-5 and Figure 6-6, respectively. Coordinates of peak activations are presented in Supplementary Appendix S-Table 6-1 to S-Table 6-3.

Table 6-1: Descriptives of in-scanner task performances.

	Controls			OCD			Mann-Whitney			Effect size
	<i>Mdn</i>	<i>M</i>	<i>SD</i>	<i>Mdn</i>	<i>M</i>	<i>SD</i>	<i>U</i>	<i>p</i>	<i>z</i>	<i>r</i>
<u>Verbal Working Memory Task</u> (Controls <i>n</i> = 17, OCD <i>n</i> = 18)										
Accuracy (%)										
High-Load	.95	94.12	3.64	.93	90.28	8.13	118.00	.22	-1.22	-.21
Low-Load	1.00	98.82	2.81	1.00	98.06	3.89	138.00	.50	-0.68	-.11
Reaction time (ms)										
High-Load	946.74	969.78	176.35	1031.05	1023.49	205.90	120.00	.28	-1.09	-.18
Low-Load	641.80	691.39	173.73	651.63	676.47	117.59	146.00	.82	-0.23	-.04
<u>Visual Working Memory Task</u> (Controls <i>n</i> = 17, OCD <i>n</i> = 19)										
Accuracy (%)										
High-Load*	.90	90.41	4.09	.83	83.37	9.53	92.50*	.03	-2.20	-.37
Low-Load	1.00	97.88	2.91	.98	96.58	3.75	120.00	.17	-1.38	-.23
Reaction time (ms)										
High-Load	891.17	916.38	142.10	839.19	901.21	165.84	141.00	.52	-0.65	-.11
Low-Load	714.18	766.78	170.70	708.00	749.38	172.06	153.00	.79	-0.27	-.04
<u>Stop-Signal Task</u> (Controls <i>n</i> = 17, OCD <i>n</i> = 20)										
Accuracy (%)										
Go-Trial	.98	98.29	1.45	0.97	96.15	3.57	109.50	.06	-1.87	-.31
Stop-Trial	.57	57.18	6.10	0.53	55.55	10.03	162.00	.44	-0.78	-.13
Reaction time (ms)										
Go-Trial	560.23	570.69	79.08	556.64	562.43	84.76	160.00	.76	-0.30	-.05
Stop-Trial	282.25	294.71	71.44	281.88	283.27	55.27	162.00	.81	-0.24	-.04

Note. Effect sizes for each condition were also presented. *n* = Sample size. *Mdn* = Median. *M* = Mean. *SD* = Standard deviation. *r* = Effect size coefficient, where small = .1, medium = .3, and large = .5. (* $p < .05$. ** $p < .01$. *** $p < .001$)

Figure 6-4. Graphical representation of mean group performances in verbal working memory, visual working memory and stop-signal tasks.

OCD samples showed lower accuracy in high-load condition of the visual working memory task ($p = .03$). (* $p < .05$. ** $p < .01$. *** $p < .001$)

Figure 6-5. Within-group whole-brain activation maps for during three tasks: verbal working memory, visual working memory, and stop-signal.

Findings were thresholded at voxelwise $p < .001$ (uncorrected) and clusterwise FDR $\alpha = 0.05$.

The colour bar refers to intensity of activations, where lighter colours represent greater T values.

Figure 6-6. Coronal views of cerebellar activations during three tasks: verbal working memory, visual working memory, and stop-signal.

Activations were thresholded at voxelwise $p < .001$ (uncorrected) and clusterwise FDR $\alpha = 0.05$. The colour bar refers to intensity of activations, where lighter colours represent greater T values.

Between-Group Neural Differences

Results are presented in Figure 6-7 and Table 6-2. Compared to controls, OCD samples showed reduced activations in the right fusiform gyrus during visual working memory task, and increased activations in the left superior frontal gyrus (dorsolateral), bilateral medial orbital surface of the superior frontal gyrus, and bilateral cingulate regions during response inhibition. No significant differences in non-cerebellar neural activations were observed during verbal working memory task. Within the cerebellum, relative to controls, OCD samples showed reduced activations in lobule VIIb during verbal working memory, reduced activations in left lobule VI and right crus II during visual working memory, and increased activations in right lobules VIIb and VIIIa during response inhibition in the stop-signal task. Coordinates of peak coordinates are also presented in Table 6-2.

We explored our analyses using two corrected thresholds of $p < .01$ voxelwise with FDR .05 cluster-correction, and $p < .01$ voxelwise with FWE .05 cluster-correction. Patients with OCD showed significantly increased activations in the middle cingulate region at $p < .01$ voxelwise with FDR .05 cluster-correction, and an additional cluster of increased activations in the left superior frontal gyrus at $p < .01$ voxelwise with FDR .05 cluster-correction during the stop-signal task. No clusters of activations survived both corrected thresholds for the verbal and visual working memory tasks (Supplementary Appendix S-Table 6-4).

Parameter Estimates and Spearman Correlations

Parameter estimates were extracted from significant clusters derived from the uncorrected threshold ($p < .005$ (uncorrected) with $k > 20$) and presented in Figures 6-8 and 6-9. Parameter estimates of the fusiform gyrus cluster obtained from the visual working memory task was negatively associated with duration of pharmacotherapy ($\rho_s = -.579$, $p = .009$) and positively associated with OCI-R scores ($\rho_s = .521$, $p = .022$) (Figure 6-10).

Associations between other parameter estimates and clinical indices were not significant. For clusters obtained from the Stop-signal task during the Stop-Go contrast, parameter estimates of the left superior frontal gyrus (dorsolateral) cluster was positively correlated with reaction time for Go-trials ($\rho_s = .532, p = .016$), and negative correlations were also observed between the parameter estimates of the superior frontal gyrus (medial orbital) ($\rho_s = -.562, p = .010$) and right middle cingulate regions ($\rho_s = -.464, p = .039$) with accuracy rates for Go-trials in OCD samples (Figure 6-10). Associations with Stop-signal reaction time and all other task outcomes for verbal and visual working memory tasks were not significant.

Chapter 6: Study 3 – Task-related Functional Activations

Table 6-2: Group differences in non-cerebellar and cerebellar peak coordinates of activation in verbal working memory, visual working memory and stop-signal tasks.

	Hemisphere	k	x	y	z	T	Z	Parameter Estimates						Cohen's <i>d</i>
								Controls		OCD		<i>p</i>		
								<i>M</i>	<i>SE</i>	<i>M</i>	<i>SE</i>			
<u>Non-cerebellar activations</u>														
<u>Verbal Working Memory</u> (High-Load - Low-Load) (Controls <i>n</i> = 17, OCD <i>n</i> = 18)														
<i>OCD < Controls</i> no significant activations														
<i>OCD > Controls</i> no significant activations														
<u>Visual Working Memory</u> (High-Load - Low-Load) (Controls <i>n</i> = 17, OCD <i>n</i> = 19)														
<i>OCD < Controls</i>														
Fusiform gyrus	R	62	31.5	-46	-3.5	4.89	4.22	0.15	0.02	0.04	0.01	1.79 x 10 ⁻⁴ ***	-1.59	
<i>OCD > Controls</i> no significant activations														
<u>Stop Signal Task</u> (Stop - Go) (Controls <i>n</i> = 17, OCD <i>n</i> = 20)														
<i>OCD < Controls</i> no significant activations														
<i>OCD > Controls</i>														
Superior frontal gyrus, dorsolateral	L	37	-24.5	49	42	3.79	3.44	-1.79	0.41	0.61	0.56	2.02 x 10 ⁻³ **	1.10	
Superior frontal gyrus, medial	L		-10.5	45.5	38.5	3.07	2.87							
Superior frontal gyrus, medial orbital	L	24	-3.5	45.5	-11	3.29	3.05	-1.84	0.35	-0.24	0.29	1.04 x 10 ⁻³ **	1.18	
Superior frontal gyrus, medial orbital	R		10.5	49	-7	3.19	2.97							
Anterior cingulate & paracingulate gyri	L		-10.5	42	-3.5	3.13	2.92							
Middle cingulate & paracingulate gyri	R	40	7	28	35	3.68	3.36	0.30	0.26	2.05	0.43	1.48 x 10 ⁻³ **	1.10	
Middle cingulate & paracingulate gyri	R		0	17.5	35	3.09	2.89							
Middle cingulate & paracingulate gyri	R	37	0	-3.5	42	3.43	3.16	-0.85	0.24	0.62	0.33	1.20 x 10 ⁻³ **	1.16	
Middle cingulate & paracingulate gyri	R		7	-14	49	3.15	2.93							
Middle cingulate & paracingulate gyri	L		-14	-18	42	2.89	2.72							
								Parameter Estimates						
								Controls		OCD				
								<i>M</i>	<i>SE</i>	<i>M</i>	<i>SE</i>	<i>p</i>	<i>d</i>	
<u>Cerebellar activations</u>														
<u>Verbal Working Memory</u> (High-Load - Low-Load) (Controls <i>n</i> = 17, OCD <i>n</i> = 18)														
<i>OCD < Controls</i>														
Lobule VIIb	R	26	30	-62	-47	4.32	3.82	0.33	0.04	0.10	0.04	5.07 x 10 ⁻⁴ ***	-1.30	
<i>OCD > Controls</i> no significant activations														
<u>Visual Working Memory</u> (High-Load - Low-Load) (Controls <i>n</i> = 17, OCD <i>n</i> = 19)														
<i>OCD < Controls</i>														
Lobule VI	L	20	-20	-64	-17	3.39	3.13	0.12	0.03	0.00	0.03	2.43 x 10 ⁻³ **	-4.62	
Crus II	R	52	34	-76	-51	3.83	3.47	0.08	0.02	0.01	0.01	6.99 x 10 ⁻⁴ ***	-1.24	
Vermis VIIIb		28	8	-64	-41	3.75	3.41	0.07	0.02	-0.02	0.01	6.53 x 10 ⁻⁴ ***	-1.25	
<i>OCD > Controls</i> no significant activations														
<u>Stop Signal Task</u> (Stop - Go) (Controls <i>n</i> = 17, OCD <i>n</i> = 20)														
<i>OCD < Controls</i> no significant activations														
<i>OCD > Controls</i>														
Lobule VIIb	R	26	34	-62	-53	3.93	3.56	-0.11	0.13	0.57	0.12	4.73 x 10 ⁻⁴ ***	1.27	
Lobule VIIa	R	42	12	-64	-41	3.43	3.16	-0.65	0.21	0.69	0.31	1.43 x 10 ⁻³ **	1.14	

Note. Group differences within the specified task mask. Analysis voxel size: 3.5 x 3.5 x 3.5mm³ (non-cerebellar), 2 x 2 x 2mm³ (cerebellar). Coordinates are in MNI (non-cerebellar) and SUIT (cerebellar) space. Results were thresholded at $p < .005$ (uncorrected) with $k \geq 20$. *M* = Mean. *SE* = Standard Error. L = Left. R = Right. (* $p < .05$. ** $p < .01$. *** $p < .001$)

Figure 6-7. Group differences in neural activations.

Verbal working memory: OCD < Controls in (A) right cerebellar lobule VIIb; Visual working memory: OCD < Controls in (B) right fusiform gyrus, (C) left cerebellar lobule VI, vermis VIIIb, and (D) right cerebellar Crus II. (E) shows cerebellar flatmap for all cerebellar findings in the OCD < Controls contrast. Response inhibition: OCD > Controls in (F) left dorsolateral, (G) middle cingulate, superior frontal gyrus (medial orbital surface), and (H) right cerebellar lobule VIIb and VIIa. (I) shows cerebellar flatmap for all cerebellar findings in the OCD < Controls contrast. All results were thresholded at $p < .005$, $k \geq 20$.

Figure 6-8. Parameter estimates of clusters that were significant from second level analyses for verbal and visual working memory tasks.

Clusters were obtained at $p < .005$, $k \geq 20$. Error bars represent standard errors. ^ indicates clusters with peak activations in the cerebellum.

Figure 6-9. Parameter estimates of clusters that were significant from 2nd level analyses for stop-signal task.

Clusters were obtained at $p < .005$, $k \geq 20$. Error bars represent standard errors. ^ indicates clusters with peak activations in the cerebellum.

Visual Working Memory Task **Stop-Signal Task**

Figure 6-10. Correlations between parameter estimates with task-related outcomes and clinical indices within OCD samples.

Parameter estimates were extracted from regions that showed significant group differences at $p < .005$, $k \geq 20$. Only significant findings were presented. (* $p < .05$; ** $p < .01$)

Discussion

The current chapter investigated neural differences underlying working memory and response inhibition in OCD samples relative to controls. According to expectations, patients with OCD performed comparably as controls in the verbal working memory task but demonstrated poorer accuracy rates during the high-load condition on the visual working memory task. Contrary to our expectations, patients with OCD did not show slower stop-signal reaction time than controls. In terms of neural activity, patients with OCD

demonstrated only reduced cerebral activations during verbal and visual working memory tasks compared to controls. OCD samples showed reduced activations only in the right cerebellar lobule VIIb (high load – low load) contrast during verbal working memory, and in the right fusiform gyrus, left cerebellar lobule VI, right cerebellar crus II and vermis VIIIb regions during (high load – low load) contrast in visual working memory task. On the contrary, OCD samples showed only increased activations during response inhibition (Stop – Go), involving regions such as left dorsolateral and left medial orbital surface of the superior frontal gyrus, bilateral cingulate, and right cerebellar lobules VIIb and VIIIa. We also observed significant negative associations between parameter estimates extracted from a fusiform gyrus cluster in the visual working memory contrast with duration of pharmacotherapy that remained significant after controlling for age.

Verbal Working Memory Task

Henseler and colleagues (Henseler et al., 2008) reported increased activations in left lateralized regions involving the precentral sulcus, intraparietal and inferior frontal regions during a verbal working memory task in 11 controls and 11 patients with OCD. Even though these regions were included within the inclusive mask for analysis, we did not observe group differences in the same regions reported by Henseler and colleagues. Instead, the current study observed neural differences only in the right cerebellar lobule VIIb in OCD samples compared to controls. These differences could be attributed to several reasons. Firstly, the scanning parameters utilized by Henseler and colleagues (2008) may not have included the entire cerebellum in the scans. Group activation maps that were presented in their paper did not show cerebellar activations, which would have been expected as with other studies that utilized the articulatory rehearsal paradigm (Ben-Yehudah, Guediche, & Fiez, 2007; Chen & Desmond, 2005; Gruber, 2001; Ravizza et al., 2005). Secondly, reported results in Henseler

et al (2008) were based on group differences in the contrast between the articulatory rehearsal condition versus a control condition, where the control condition had participants judge whether the probe was lower or uppercase. Reported group differences in the intraparietal and precentral regions could therefore indicate attentional, temporal order and motoric processes in addition to processes relevant to working memory (Gruber & von Cramon, 2003; Killebrew, Mruczek, & Berryhill, 2015; Majerus et al., 2006). Lastly, Henseler and colleagues (2008) adopted a liberal threshold of $p < .005$ (uncorrected) without cluster extent in their evaluations. However, it is unlikely that threshold issues drove the different findings reported across both studies, as we had reanalyzed our data using a threshold of $p < .005$ (uncorrected) without cluster extent (Supplementary Appendix S-Table 6-5), but still did not observe significant group differences in the regions reported by Henseler and colleagues (2008).

The cerebellar lobule VIIb has been reported to be involved in higher cognition, for instance, during executive function (such as go/no-go tasks, planning, and decision-making tasks) (Stoodley & Schmahmann, 2009) and verbal working memory (E et al., 2012). Chen and Desmond (2005) proposed that the inferior cerebellum (which includes the lobule VIIb) is involved in facilitating phonological storage during a Sternberg working memory task. In addition, a cerebello-parietal loop comprised of the inferior cerebellum and the inferior parietal lobule have important roles in information maintenance and storage (Chen & Desmond, 2005). A meta-analysis conducted by Stoodley and Schmahmann (Stoodley & Schmahmann, 2009) suggested dissociation of functional locality of the cerebellar lobule VI and VIIb/VIII regions, where motoric processes are located more anteriorly (with y-coordinate between -60 to -70) and more posterior (y-coordinate between -70 to -80) for processes relevant to working memory (Stoodley & Schmahmann, 2009). Activation maps

presented in Figure 6-6 showed weaker activity in the anterior and posterior cerebellar lobule VIIb in OCD patients than controls, with more emphasized attenuated activity in the anterior region that could be more relevant to motoric processes.

Consistent with our initial expectations, there were no significant group differences in accuracy rates and reaction time in both high and low load conditions of the verbal working memory task. The lack of group differences in behavioural performances could be attributed to the nature of the stimuli, as the stimuli could be internally verbalized and the number of stimuli presented in the memory array were within the capacity of the phonological store. Therefore, stimuli could be sufficiently encoded, rehearsed and then retrieved. Even though activity in the right lobule VIIb appeared reduced in OCD, this altered activity may have been insufficient to impair behavioural performance.

Visual Working Memory Task

The fusiform gyrus has been reported to be involved in a wide range of functions, such as facial recognition (Kanwisher & Yovel, 2006), object features discrimination (Yang et al., 2015), body parts discrimination (Peelen & Downing, 2005; Schwarzlose, Baker, & Kanwisher, 2005), and expert reading (McCandliss, Cohen, & Dehaene, 2003). Based on the findings from a parcellation study, reduced activations observed in the current study in OCD samples coincided with the medial part of the posterior fusiform gyrus (Zhang et al., 2016). Zhang and colleagues evaluated functional connectivity between subdivisions of the fusiform gyrus with functional subnetworks, and reported that the medial posterior fusiform gyrus is functionally connected to several networks, such as the cerebellar, auditory, salience, and visual networks (medial visual, occipital pole, and lateral visual network regions) (Zhang et al., 2016). In view of the connectivity of the medial posterior fusiform gyrus with various low level visual networks, the medial posterior fusiform gyrus has been thought to be involved in

low level visual processing. A separate study evaluated event-related potentials during a word-cued visual search task in a sample of treatment-responding and treatment-refractory OCD samples, and reported altered ERP signal in the (bilateral) fusiform region that the authors attributed to deficit early word processing that led to failure in distinguishing between word-graphemes and meaning during the visual search task (Liu et al., 2017). However, it is unlikely that this explanation applies to our current observation due to several reasons: 1) the current study observed reduced activity in the right but not left (where the visual word form area is localized) nor bilateral fusiform areas; 2) It is unlikely that altered activity in the medial part of the posterior fusiform gyrus directly contributes to poorer accuracy rates in the high load condition as follow-up correlational analyses between parameter estimates of the fusiform gyrus and accuracy rates of high load conditions were not significant. Interestingly, parameter estimates of the fusiform gyrus were significantly correlated with duration of pharmacotherapy, and this finding remained after controlling for effects of age. The role of the fusiform gyrus in OCD has yet to be evaluated in detail, and therefore this finding remains to be replicated and understood.

Follow-up Analyses for Visual Working Memory

The current study observed poorer accuracy rate in the high-load condition of the visual working memory task with reduced activations in the right fusiform gyrus, and cerebellar regions of the left lobule VI, right Crus II, and vermis VIIIb in patients with OCD compared to controls. To the best of our knowledge, this is the first time visual working memory alterations are observed alongside cortical and cerebellar differences in OCD samples. Considering that depressive symptoms are prevalent in patients with OCD, and demographic variables such as age and sex may potentially influence neural and behavioural findings, further analyses were conducted to explore the specificity of the observed findings

to OCD pathophysiology. Distress score associated with obsessive-compulsive tendencies as measured on the OCI-R was treated as proxy for OCD symptoms. Parameter estimates of significant clusters were extracted using MarsBAR.

A series of analyses of covariance (ANCOVA) were conducted to evaluate group differences in the parameter estimates of significant clusters (right fusiform gyrus, left lobule VI, right Crus II, vermis VIIIb) and accuracy rate of high-load condition of the visual working memory task with HDRS, OCI-R scores, age, and sex as covariates. Levene's Test of homoscedasticity were violated for three out of five dependent variables (accuracy rate of high-load condition, and parameter estimates of right fusiform gyrus, right Crus II), $p < .05$. Heteroscedasticity in the dependent variables can potentially contribute to incorrect inferences. Therefore, ANCOVA analyses involving accuracy rate of high-load condition, right fusiform gyrus, and right Crus II as dependent variables utilized parameter estimates with robust standard errors by using Heteroscedasticity-consistent (HC)-3 algorithm according to the guidelines recommended by Long and Ervin (2000), through an option available in SPSS. If findings were specific to OCD, then we would expect OCI-R but not HDRS scores as significant predictor, and accompanied with reduced group effects on the dependent variables.

Results did not show significant effects of covariates across all analyses (Supplementary Appendix S-Table 6-6 to S-Table 6-8). In terms of behavioural performances, we initially observed significant group differences in the high-load condition of the visual working memory task after including demographic variables (age, sex) as covariates, $p = .016$ (Supplementary Appendix S-Table 6-9). Group differences were no longer significant when depressive (HDRS) and/or distress scores associated with obsessive-compulsive tendencies (OCI-R) were included as covariates in the model, $p > .05$ (S-Table 6-

7 to S-Table 6-8); the covariates (HDRS and OCI-R) were also not significant predictors of performance accuracy. For neural findings, all group differences in neural parameter estimates remained significant even when OCI-R and HDRS scores were included as covariates in the model (S-Table 6-6 to S-Table 6-8).

In general, findings from the follow-up analyses did not appear to indicate clear specificity of behavioural and neural findings to OCD, nor to depressive scores. We observed a lack of group effects on behavioural performance when OCI-R and HDRS scores were included into the model, but both OCI-R and HDRS were not significant predictors to behavioural performance. One explanation for this observation could be attributed to ceiling effects of high-load accuracy rates – Even though OCD samples ($M = 83.37\%$, $S.D. = 9.53$) had poorer accuracy rates compared to controls ($M = 90.41\%$, $S.D. = 4.09$) ($p < .001$), the entire sample had generally performed well. The lack of variability in behavioural performance could potentially contribute to the lack of clear relationships among variables.

For ANCOVA results on neural findings, consistent group differences were observed in all neural parameter estimates (right fusiform gyrus, and cerebellar regions of the left lobule VI, right Crus II, and vermis VIIIb), even after demographic (age, sex) and clinical variables (HDRS, OCI-R) were added to the model. Even though OCI-R scores were positively associated with parameter estimates of the fusiform gyrus within the OCD sample (Figure 6-10), the effects of OCI-R were not significant in the ANCOVA model. Considering the significant effect of Group (OCD, controls) and lack of significant associations of the clinical variables on neural parameter estimates, neural alterations observed could potentially be more relevant to an overall patient status rather than OCD symptoms *per se*.

To follow-up on this postulation, we conducted hierarchical regression to evaluate whether variance in the dependent variable explained by OCI-R is significant, and if so,

whether the variance contributed by OCI-R remains after Group (OCD / Control) status is added to the model. Hierarchical regression was conducted with predictors in four blocks: Age and Sex in the first block, HDRS in the second block, OCI-R in the third block, and Group variable in the fourth block, on two dependent variables (vermis VIIIb, and left lobule VI) that did not violate the homoscedasticity assumptions. Results presented in S-Table 6-11 (Supplementary Appendix) showed that OCI-R did not contribute significant variance to both cerebellar parameter estimates even before the Group variable was added to the model. Group status explained the greatest amount of variance in the parameter estimates, above and beyond age, sex, HDRS and OCI-R scores. We do note that discussions of hierarchical regression were only based on results from the two dependent variables.

In addition to postulating a lack of specificity of the findings to OCD condition, it is possible that distress severity associated with obsessive-compulsive tendencies as measured on the OCI-R does not sufficiently represent the entire construct of the OCD, and may not be the ideal proxy for OCD symptoms. We also observed limited variability in OCI-R within both controls ($M = 3.47$, $S.D. = 0.83$) and OCD samples ($M = 25.10$, $S.D. = 17.40$; please also refer to the distribution of OCI-R in S-Figure 4-1 and Figure 6-10). These statistics and distribution plots show a clear differentiation between OCD patients and controls in OCI-R scores. It is possible that limited variability of OCI-R scores restrict observations of within-group relationships between OCI-R scores with dependent variables. This view is somewhat supported as we observed significant correlations between OCI-R scores and behavioural and neural parameter estimates within the combined group (all $p < .05$) (S-Table 6-10), but these findings no longer remained, except for a significant association between OCI-R and parameter estimate in the right fusiform gyrus within the OCD sample (Figure 6-10).

Even though our follow-up analyses indicated lack of specificity of both behavioural and neural activations to OCI-R scores, OCI-R scores are still important in the field of OCD, as the tool can differentiate patients with OCD from controls. We postulated several explanations for the lack of specificity of findings, such as limited variability in behavioural observations and OCI-R scores, and the plausibility that OCI-R may not sufficiently represent the entire construct of the OCD condition. Alternatively, it could also be possible that findings observed were simply more specific to general patient status. Further research is required to evaluate specificity of findings to OCD.

Finally, group differences in neural parameter estimates but not high-load accuracy performance remained significant when clinical variables were included in the model indicates the plausibility of behavioural measures as susceptible to influences of clinical state function, and may support the view that neural pathogenesis are more proximal (and perhaps, more reliable) than behavioural expressions to underlying pathophysiology (Chamberlain et al., 2008).

Stop-signal task

Previous studies reported slower stop-signal reaction time and observed increased activity in *a priori* regions in the presupplementary motor area, inferior frontal gyrus and the inferior parietal cortex (de Wit, de Vries et al., 2012), the caudate nucleus and precentral gyrus (Morein-Zamir et al., 2016), and in the parietal cortex and cerebellum during inhibition in OCD samples (Kang et al., 2013). Reduced activity in several *a priori* regions such as the putamen, caudate nucleus and anterior cingulate were also reported in OCD samples (Kang et al., 2013). Contrary to expectations, the current study did not observe significant group differences in stop-signal reaction time (with small effect sizes) and observed only increased but not reduced activity compared to controls. Increased activity was found in the superior

frontal gyrus and the cingulate and paracingulate gyri for OCD samples relative to controls during response inhibition.

Differences in neural findings reported across studies could be attributed to sample characteristics. Most studies have included OCD patients with comorbid conditions in their investigations. An exception is the study conducted by Kang and colleagues (2013). In addition to excluding OCD patients with comorbid conditions, Kang and colleagues had also adopted similar thresholds ($p < .005$ with 27 extent voxels threshold) as the current study. The authors reported increased activity in the superior parietal cortex, cerebellum and the parahippocampal cortex, but reduced activity in several regions such as the precentral gyrus, fusiform and other *a priori* regions such as the putamen, anterior cingulate, and caudate nucleus in patients with OCD compared to controls. However, Kang and colleagues had utilized male and female faces as stimuli in their stop-signal task, which could be considered as relatively more sensitive than arrows (compared to the stimuli utilized in the current study). Previous studies had indicated altered processing in viewing faces and perceiving facial expressions in OCD samples (Kang, Namkoong, Yoo, Jhung, & Kim, 2012; Lawrence et al., 2007), and therefore, differences in stimuli could potentially explain for the different findings observed.

Existing studies rarely evaluated negative parameter estimates during response inhibition paradigms, and therefore the exact relationship between regions that showed negative parameter estimates and inhibitory processing remained unclear. In addition, the understanding of negative parameter estimates has been controversial. Negative parameter estimates could be contributed by task-related decrease in neural activity (Binder et al., 1999; Lin, Hasson, Jovicich, & Robinson, 2010; Stefanovic et al., 2005), or redistribution of task processing to better suited regions (Rosenbaum, Ziegler, Winocur, Grady, & Moscovitch,

2004). Negative parameter estimates were observed in controls during Stop-trials, Go-trials, and Stop-Go contrast in the left superior frontal gyrus (dorsolateral, and medial orbital) (Figure 6-9). The right inferior frontal cortex has been thought to be critical for inhibitory or self-control processes (Aron & Poldrack, 2006; Bellgrove, Hester, & Garavan, 2004; Garavan, Ross, Murphy, Roche, & Stein, 2002; Liddle, Kiehl, & Smith, 2001), specifically in phasic stopping and braking, and this cognitive process can be activated voluntarily regardless the presence of a stop-signal (Aron, Robbins, & Poldrack, 2014). One potential hypothesis for negative parameter estimates observed in the left superior frontal gyrus in controls could be due to a functional mechanism of reciprocal modulation and attenuation of neural activity (Northoff et al., 2004) in the left-lateralized frontal regions that is concurrent with increased activations in the right-lateralized frontal regions. The purpose of such mechanism may enable adjustment of concurrent processes and adaptation to demands of the task (Nakata et al., 2009; Northoff et al., 2004). According to the reciprocal-modulation hypothesis then, we would expect to observe more positive parameter estimates extracted from the right inferior frontal cortex and more negative estimates in the left-lateralized frontal regions during inhibition. To evaluate the plausibility of this hypothesis, we extracted parameter estimates extracted from the right inferior frontal gyrus and observed that parameter estimates were indeed positive during stop trials (Supplementary Appendix S-Figure 6-2). However, in the current study, OCD samples showed increased activations as noted by positive parameter estimates in the left superior frontal gyrus (dorsolateral part) and less deactivations in the medial orbital part for the Stop versus Go-trials compared to controls in the same regions. These findings potentially indicate some deficient reciprocal modulation of the left frontal region in patients with OCD. Following this argument, it then appears that patients with OCD may have difficulty regulating and adapting to concurrent processes and

could therefore, contribute to altered cognitive processes and impulse control. The superior frontal gyrus has key roles in executive functions such as cognitive flexibility and inhibition (Grahn et al., 2008), and has extensive connections with the middle cingulate, which is also a key region in cognitive control (McGovern & Sheth, 2017). Increased activity observed in the left superior frontal gyrus and the middle cingulate in OCD samples could also be speculated as compensatory mechanisms during response inhibition. Increased activity with increase in parameter estimates were also observed in the right cerebellar VIIb and cerebellar VIIIa during Stop-trials and Stop-Go contrasts, which have been reported as having roles in motor activation and executive function, respectively, and could also potentially contribute to compensatory mechanisms during response inhibition.

Delaying strategies are commonly used in stop-signal designs. This may be observed as high accuracy rates for Go-Trials and higher than 50% accuracy for Stop-trials (Boehler et al., 2012). Boehler and colleagues (2012) recommended an alternate method of calculating the SSRT when participants are suspected of using delay strategies. This involves first rank order the Go-RT, and extract the value of Go-RT that corresponds to the percentile of failed stop-trials. For example, for a participant who failed on 40% of stop-trials, the Go-RT value extracted would one that corresponds to the 40th percentile. This value is then used to subtract the stop-signal delay ($SSRT = Go-RT - delay$). We computed this alternate value of the SSRT but did not find significant group differences in the alternate measure of SSRT, $M_{OCD} = 254.83ms$, $SD_{OCD} = 82.77ms$ VS $M_{Controls} = 270.98ms$, $SD_{OCD} = 76.36ms$, $p > .05$, ns.

Even though there were no significant group differences in the alternate value of the stop-signal task, such finding does not disclaim the use of delay strategies during the task. We observed positive correlations between the parameter estimates of the left superior frontal gyrus (dorsolateral) cluster in the Stop-Go contrast with increased reaction times for Go-

trials. Considering the functions of the dorsolateral region, there still lies the plausibility that participants have utilized delaying strategies during the task. However, further follow-up analyses to evaluate correlations between reaction time during Go-trials with parameter estimates of the left superior frontal gyrus (dorsolateral) extracted over Go-trials were not significant ($p > .05$). Further work is required to probe activity of the superior frontal gyrus (dorsolateral) during Go- and Stop- trials and its relationships with Go- and Stop- reaction time and accuracy rates.

Controls also showed negative parameter estimates in the right middle cingulate (0 -4 42) spreading to the dorsal posterior cingulate region. The posterior cingulate has been considered as part of the default-mode network and has been thought to be deactivated during tasks where attention is externally directed (Buckner, Andrews-Hanna, & Schacter; Gusnard, Akbudak, Shulman, & Raichle, 2001; Raichle et al., 2001; Shulman et al., 1997). The current study observed failure in deactivating the middle-posterior cingulate region in OCD samples during Stop-trials and Stop-Go contrast, which could potentially indicate some abnormal control of the default mode network (Spreng & Schacter, 2011) and the salience network (Bonnelle et al., 2012). In addition, the dorsal posterior cingulate region has connections to the frontal regions and is also involved in controlling attentional focus, possibly by influencing the meta-stability of the brain, with increased activity indicating greater fluctuations in network shifts with reduced synchrony (Leech & Sharp, 2014). Increased activity in the posterior cingulate could potentially indicate underlying task-induced compensatory mechanisms in OCD samples. Considering that failure in deactivating the middle-posterior cingulate appropriately is indicative of network fluctuations with reduced synchrony, it could be hypothesized that OCD samples would show altered network activity

at least in the default mode network, executive control network, and salience network. This hypothesis will be evaluated and discussed in the next chapter (Chapter 7).

We did not observe the expected neural differences as reported in Chapter 3 of the thesis, where meta-analytic findings reported reduced activations in the right putamen and right cerebellar lobule IV-V in OCD samples during response inhibition. These inconsistencies could be attributed to several reasons. Firstly, most studies included in the meta-analysis had utilized OCD samples with comorbid conditions and had a medications wash-out period. The OCD patients in our current study did not have comorbid conditions and they did not discontinue their pharmacological treatment for the neuroimaging studies. However, it is unlikely that medication effects could have influenced the observed findings, as associations between parameter estimates of observed clusters and medication dosages and duration were not significant. Secondly, different studies had utilized different thresholds of significance, which could also contribute to different reported findings. Lastly, the meta-analysis had clustered and analysed all studies that evaluated response inhibition and had included studies that utilized go/no-go tasks and stop-signal tasks. Based on the review by van Velzen and colleagues (van Velzen et al., 2014), even though both the go/no-go tasks and stop-signal tasks are considered to evaluate response inhibition, each paradigm is different in terms of the stage of inhibition required to perform the task.

Due to the small sample size in the current study, data of participants with poor behavioural performances were excluded from the analysis. This was to avoid inflating effects that were contributed by selected participants who might not have performed the tasks as instructed or intended. Nevertheless, for the interest of evaluating all subjects, we conducted additional analyses by including all participants, regardless of their behavioural performances, with the exception of one participant with excessive head motion during visual

working memory where these particular runs were excluded. Compared to the findings reported in Table 6-2, this set of analyses observed slightly inflated group differences in the verbal working memory and stop-signal tasks that might have been driven by selected participants (Supplementary Appendix S-Table 6-12, S-Figure 6-3). More specifically, using data from the entire sample, group differences in accuracy rate for high-load condition in the verbal working memory task approached significance ($p = .06$), with a moderate effect size of -0.30 . This finding was likely to be driven by 3 participants, whose data when excluded from the analysis did not yield significant group differences ($p = .22$, effect size $r = -.21$; Table 6-2). For the stop-signal task, group differences evaluated based on the entire sample showed significantly lower accuracy rate of Go-trials in the patients group compared to controls ($M_{\text{OCD}} = 94.43$, $SD_{\text{OCD}} = 8.62$; $M_{\text{Controls}} = 98.29$, $SD_{\text{OCD}} = 1.45$, $U = 109,50$, $p = .04$). Group differences in the accuracy rate for Go-trials could be attributed to a single patient's data who had been excluded from the main analysis due to high stop-signal accuracy (81%) but low Go accuracy rate (60%). In terms of neuroimaging findings, key clusters of activations across all three tasks largely remained when the analyses were evaluated based on the entire sample, except for a finding in the right cerebellar lobule VIIb that was no longer significant when the entire sample was evaluated (Supplementary Appendix S-Table 6-13). Parameter estimates of significant clusters were extracted to evaluate their associations with behavioural performances. Spearman correlational analyses showed a significant negative correlation between parameter estimates of the left cerebellar dentate and accuracy rate for low-load condition in the verbal working memory task ($\rho_s = -.476^*$, $p = .029$), and between parameter estimates of the superior frontal gyrus (medial orbital surface) with accuracy rate for Go-trials in the stop-signal task ($\rho_s = -.575^{**}$, $p = .006$). However, these significant associations could be driven by the data points of lone participants as indicated in

Supplementary Appendix S-Figure 6-3. Thus, we decided to adopt a more conservative approach to exclude participants' data that fell below our pre-defined cut-off of 70% accuracy rate. Further replication with a larger sample size may still be necessary to elucidate deficits in verbal/visual working memory and stop-signal tasks in patients with OCD.

Lastly, all participants performed the working memory tasks followed with the stop-signal task with a brief rest period of approximately two minutes in between each task run. The order of verbal and visual working memory tasks administration was counterbalanced across participants. Even though we do not anticipate any carryover effects from the preceding task to the next task other than potential fatigue, we would still like to raise this as a potential limitation to the study procedures.

Summary

The current study evaluated group differences in task-related differences in neural activity. We observed poorer accuracies in OCD samples in the high load condition of the visual working memory task, but these observations did not survive Bonferroni correction for multiple comparisons. Neuroimaging findings discussed in this chapter were subjected to non-corrected thresholds of $p < .005$ with 20 extent voxels. Earlier in the chapter, we elaborated on the necessity to strike a desirable balance between Type I and Type II error rates (Lieberman & Cunningham, 2009). Nevertheless, we had also explored the analyses using corrected thresholds (Supplementary Appendix S-Table 6-4). We reported significantly increased activations in the middle cingulate region and the left superior frontal gyrus during the stop-signal task at $p < .01$ voxelwise with FDR .05 cluster-correction in OCD samples compared to controls, and did not find significant group differences in both cerebellar and non-cerebellar regions during verbal and visual working memory tasks. Findings from this study could be considered as pilot and require further replication.

In general, our pilot results observed altered neural activity in regions involved in executive function, specifically in the cerebellar regions such as the left lobule VI, right crus II and vermis VIIIb during visual working memory, and in the superior frontal gyrus, cingulate, and cerebellar lobule VIIIa during response inhibition. In addition, altered neural activity in regions believed to be involved in sensorimotor functions were also observed in OCD, such as the fusiform gyrus and cerebellar lobules VIIb and VIIIb. Spearman correlations demonstrated significant associations between the parameter estimates for the fusiform gyrus with duration of pharmacotherapy. However, the mechanisms behind these relationships are unclear and require further investigations. On a separate note, altered activity reported in this chapter could be task-relevant, and hence could be influenced by task challenges and task-specific requirements. In the next chapter, we will evaluate group differences in connectivity and network activity at resting state. This enables further clarification on altered neural activity without the presence and influence of task.

**CHAPTER 7: STUDY 4 – RESTING-STATE FUNCTIONAL NETWORK
CONNECTIVITY IN OCD**

Exploration of differences in resting-state networks (default mode, executive-control, salience-processing, and sensorimotor).

Introduction

Understanding Aberrations using Network and Functional Connectivity Approaches

Resting-State Networks (RSNs). RSNs refer to communities of highly organized and synchronized patterns of correlated activity across distributed brain regions observed at-rest that overlap with functional networks when cognitive load is present (Calhoun, Adali, Pearlson, & Pekar, 2001; Fransson, 2005; Greicius, Krasnow, Reiss, & Menon, 2003; Ponce-Alvarez et al., 2015; Shirer, Ryali, Rykhlevskaia, Menon, & Greicius, 2012). Several RSNs have been identified that include the visual, auditory, sensorimotor and executive-control networks (Seeley et al., 2007; Yeo et al., 2011).

Findings from previous chapters demonstrated alterations of cortical and sub-cortical structures that coincided with key anchors of several RSNs such as the default mode network (DMN), salience-processing network (SN), executive control network (ECN), and sensorimotor network (SMN). Potentially altered gray matter volume (GMV) were observed in OCD samples in the insula and postcentral gyrus (Chapter 5), which are key anchors of the SN and SMN networks, respectively (Seeley et al., 2007). Aberrant activity in the dorsolateral and medial surfaces of the superior frontal gyrus in OCD samples during response inhibition potentially indicated the involvement of altered activity of the ECN (Chapter 6). In addition, evaluations of parameter estimates of clusters extracted from the Stop-signal task in Chapter 6 revealed that unlike controls, OCD samples did not demonstrate deactivations in the middle-posterior cingulate region during response inhibition. The middle-posterior cingulate region is a key region of the default-mode network. Deficits in appropriately deactivating the default-mode network during externally-directed attention (Buckner et al.; Gusnard et al., 2001; Raichle et al., 2001; Shulman et al., 1997) could potentially indicate some abnormal control of the default mode network (Spreng & Schacter,

2011), salience network (Bonnelle et al., 2012), and in attentional focus, and contributing to reduced network synchrony (Leech & Sharp, 2014).

Key Resting-State Networks of Interest. Results from our previous studies indicate potential involvement of the SN, ECN, DMN, and SMN.

The triple network model proposes that dysfunctions in the organization and functioning of the SN, ECN and DMN underlie key features of several psychiatric disorders, such as schizophrenia, depression, anxiety, dementia and autism (Menon, 2011), and more recently in OCD. Anchored by the dorsal anterior cingulate and frontoinsula cortex, the SN is involved in detecting, identifying and integrating different forms of salience, such as pain, emotion, homeostatic regulation, reward and interoceptive autonomic processing (Seeley et al., 2007). While the SN identifies objects/stimuli of salience in the environment, the ECN operates to direct attention to the identified salience (Menon & Uddin, 2010).

The ECN has key nodes in the dorsolateral prefrontal cortex (DLPFC) and lateral parietal cortex (Habas et al., 2009; Seeley et al., 2007), and show strong coactivations during cognitively demanding tasks that involved sustained attention, response selection and response suppression (Curtis, Cole, Rao, & D'Esposito, 2005; Lau, Christensen, Hawley, Gemar, & Segal, 2007). Regions of the ECN work to maintain representations in mind including exerting control over sensorimotor representations until actions are selected (Seeley et al., 2007), and are also functionally coupled to subcortical regions such as the caudate and thalamus (Seeley et al., 2007; Selemon & Goldman-Rakic, 1988).

In contrast to the SN and ECN, the DMN is typically deactivated during most stimulus-driven cognitive tasks (Greicius et al., 2003) and activated during self-referential and stimulus-independent memory recall (Qin & Northoff, 2011), and has been considered as the baseline functional network when individuals are left to themselves without the influence

of an external task (Shulman et al., 1997). Anchored in the posterior cingulate cortex and medial prefrontal cortex, the DMN also has key nodes in the medial temporal lobe and angular gyrus, and are collectively involved in self-referential mental processes, such as remembering the past, considering thoughts and perspectives of others and future planning (Buckner et al.).

The ECN and SN typically show increased activations during demanding cognitive tasks, are minimally correlated with each other, but inversely correlated with the DMN (Seeley et al., 2007). The SN has important roles in regulating saliency detection and dynamic cognitive control (Menon & Uddin, 2010; Seeley et al., 2007). The anterior insula within the SN is an important hub that initiates appropriate signals to engage regions of the ECN that are important in attention and higher cognition to the detected stimuli, and disengage the DMN during cognitive control (Menon, 2011; Menon & Uddin, 2010). Even during tasks when target and distractor salience are hypothetically balanced, and during working memory maintenance, it is unlikely that SN is not at all involved in these processes. When a stimulus is identified in these tasks, object saliency is present, and accordingly, the ECN applies attention on the identified salience (Seeley et al., 2007). In the context of OCD, it could be reasonably speculated that anomalies in the SN impair the assignment of saliency to external stimuli or internal mental stimuli, hence, alter appropriate engagement and disengagement of the ECN and DMN. Dysfunctions in the ECN could also contribute to the OCD pathophysiology in terms of reduced ability in controlling sensorimotor representations until appropriate behavioural response are selected (Menon, 2011), which jointly manifest in intrusive obsessions and compulsions as observed in the disorder.

The SMN is composed of somatosensory and motor regions, and is anchored by the postcentral gyrus and precentral gyrus with key nodes in the supplementary motor area

(Biswal et al., 1995). Regions in the network are activated during motor tasks and in preparation for performing coordinated motor acts (Nachev et al., 2007). Existing studies appear to also propose dysfunctional sensory gating in OCD. According to this proposal, excessive excitation of sensorimotor regions and reduced inhibitory functions of the frontal regions in OCD impairs the capacity to suppress repetitive behaviours and intrusive thoughts, and modulate sensory inputs during movements (Rossi et al., 2005), leading to repetitive compulsions and obsessions. Considering the ECN exerts appropriate control over sensorimotor representations and that individuals with OCD typically experience strong urges and perform compulsive acts in a repetitive fashion, the SMN could also be a potential network target of investigations in OCD.

Altered Intrinsic Activity in OCD. Limited studies had evaluated intrinsic activity in OCD, and those that did utilize mainly two techniques: i) regional homogeneity (ReHo), to evaluate local brain synchronization of spontaneous activity within neighbouring voxels (Zang, Jiang, Lu, He, & Tian, 2004); and ii) amplitude of low frequency fluctuations (ALFF), to investigate the intensity of regional BOLD activity (Xu et al., 2014; Zuo et al., 2010). Even though the direction of findings were largely inconsistent, altered spontaneous neuronal activity were reported in distributed neural regions in individuals with OCD, including the orbitofrontal, thalamus, insula, anterior cingulate, caudate, inferior occipital and in the cerebellar regions (Hou et al., 2012; Moody et al., 2017 ; Ping et al., 2013; Qiu et al., 2017; Zhu et al., 2016). Other studies have also utilized functional connectivity (FC) approaches to understand intrinsic activity.

Functional Connectivity (FC). FC analytical approaches using resting-state fMRI have often been used as an indicator of neural activity. This approach is task-independent and

evaluates correlations between spontaneous low frequency fluctuations of BOLD signals at resting-state (Greicius, Krasnow, Reiss, & Menon, 2003).

Existing studies have reported aberrant cortical-subcortical connectivity in OCD samples. Decreased FC in OCD were observed between the anterior cingulate with thalamus (Fitzgerald et al., 2011) and anterior operculum (Fitzgerald et al., 2010), temporal pole with ventral cingulate (Moreira et al., 2017), and posterior cingulate with putamen (Jang et al., 2010). Increased FC were reported between the ventral caudate/accumbens with the medial orbitofrontal cortex (Harrison et al., 2013) and anterior cingulate (Anticevic et al., 2014), and anterior prefrontal with anterior cingulate regions (Harrison et al., 2013). Altered cortical-subcortical FC have also been demonstrated through seed-based FC approaches within known resting-state networks, such as the SN, ECN, SMN and DMN.

Aberrant Functional Connectivity in Key Resting-State Networks in OCD

Aberrant intrinsic connectivity reported in OCD had implicated several networks, such as the SN, ECN, and DMN (Fitzgerald et al., 2010; Jang et al., 2010; Koçak, Kale, & Çiçek, 2012; J. Posner et al., 2017; Stern et al., 2012). Posner and colleagues (2017) observed increased FC between the DMN and SN in non-medicated adults with OCD by placing seeds in the posterior cingulate cortex (PCC) and the anterior medial prefrontal cortex (amPFC) of the DMN, and left and right anterior insula of the SN. Somewhat consistent to the findings reported by Posner and colleagues, Stern and colleagues (2012) reported increased FC between a ‘core’ task-set network and the DMN. Seeds in the ‘core’ task-set network were placed in the dorsal anterior insula, posterior medial frontal cortex, DLPFC, and the inferior parietal lobule, and seeds of the DMN in the PCC and the amPFC. Relative to controls, OCD samples showed increased FC between the anterior insula with the PCC and amPFC of the DMN, and with the thalamus and somatosensory regions, and between the DLPFC with the

anterior insula and cerebellum. Altered FC was also reported within the DMN, i.e. reduced FC within the PPC, and between the PCC with regions of the CSTC, such as the anterior cingulate, middle frontal and putamen regions (Jang et al., 2010); and increased connectivity with the right inferior frontal, insula, superior parietal cortex and superior temporal cortex (Peng, Xu, et al., 2014).

Apart from seed-based approaches, one other study also adopted whole-brain FC approaches. Hou and colleagues (2014) evaluated whole-brain resting-state FC in non-medicated individuals with OCD and observed increased FC in the bilateral OFC, ACC, caudate nucleus, putamen, middle frontal gyrus, middle temporal gyrus, parietal lobule and right insula, and reduced FC in the bilateral occipital lobe, cerebellum and right superior temporal gyrus in OCD (Hou et al., 2014). These findings were consistent with an earlier study that placed seeds in 39 brain regions and observed increased FC in the cingulate, precuneus, thalamus and the cerebellum, and reduced FC in the posterior temporal regions in OCD samples compared to controls (Zhang et al., 2011).

Motivation and Hypotheses for Studies 4a and 4b

Taking these findings together, it appears apparent that cortical-subcortical organizational patterns of intrinsic FC are altered in individuals with OCD. Even though techniques such as ReHo and ALFF are local measures that inform about the local FC (within a few mm), and regional local BOLD data, respectively, these measures are not able to evaluate and identify intrinsic activity across sets of brain regions with synchronous activity. To date, no study has yet evaluated altered intrinsic activity using a network approach. This is important, considering that existing FC studies and findings from previous chapters indicate aberrant intrinsic activity in several key RSNs. In Study 4a, we utilized group-based independent component analyses (ICA) on whole-brain resting-state data to evaluate group

differences within the ICA-extracted network components of interest. We expect to identify key resting-state networks of interest (SN, DMN, ECN, and SMN) from group ICA component results, and observe group differences in cortical and sub-cortical intrinsic activity within the identified components.

Next, even though increasing studies have reported the involvement of cerebellar dysfunctions in OCD, no studies have yet specifically evaluated altered FC involving the cerebellum in OCD samples by placing sources in specific parts of the cerebellum. This is important, considering the reciprocal connectivity between the cerebellum with subcortical and cortical regions (Buckner, Krienen, Castellanos, Diaz, & Yeo, 2011). To further understand aberrant connectivity with the cerebellum, Study 4b was conducted to evaluate FC involving cerebellar ROIs. This was achieved by conducting ROI-to-voxel analyses, with source ROIs defined as cerebellar lobules that were known in their involvement in the four networks (Seeley et al., 2007; Shirer et al., 2012). We hypothesized that compared to controls, patients with OCD would show aberrant FC between the cerebellum with regions of the CSTC. Correlational analyses were also conducted to explore associations between aberrant FC with clinical and cognitive indices.

Methods

Participants and Data Quality Check

Data were obtained from the same set of participants as reported in Chapter 4. Resting-state data of 1 patient was excluded from analysis as a lower number of images were acquired due to limited scanning time. Motion indices were evaluated. All remaining participants had head motion below 3.5mm in displacement and 3.5 degrees in rotation. The final dataset included 20 patients (10 males, 10 females; $M_{\text{age}} = 28.80$, $SD_{\text{age}} = 7.02$) and 17 controls (9 males, 8 females; $M_{\text{age}} = 26.12$, $SD_{\text{age}} = 4.15$).

Task Descriptions and Instructions

A fixation-cross was presented during the resting-state procedure. Participants were instructed to rest with their eyes opened for about eight minutes, and were asked not to think of anything in particular except for random thoughts. Participants were further reminded to keep their head still and to stay awake.

Functional Image Acquisition Parameters

Functional MRI images were acquired using gradient-echo planar imaging (EPI) sequence: TR=2000ms; TE=29ms; flip angle=90°; 41 slices with 5% gap, interleaved from anterior to posterior; voxel size=3.5 x 3.5 x 3.5mm; FOV=225mm. A total of 240 images were obtained for each participant.

Imaging Data Preprocessing

Neuroimaging data were preprocessed and analyzed using SPM12 software package (Statistical Parametric Mapping 12; Wellcome Department of Cognitive Neurology, London, UK) using the preprocessing pipeline detailed in Chapter 5. All images were first reoriented to the AC-PC axis, slice-time corrected, realigned, and coregistered to the structural image which was then segmented. Functional images were normalized to the standard MNI template using the DARTEL pipeline, resampled at 3.5 x 3.5 x 3.5mm³ and smoothed with a Gaussian kernel of 8 x 8 x 8mm FWHM. Rigid-body movement parameters were produced for each participant and were used as regressors in subsequent first-level analyses.

Imaging Analysis

Study 4a: Group Independent Components Analysis (Group ICA). Spatial ICA was performed using Group ICA fMRI Toolbox (GIFT, version 3.0b) to isolate independent resting-state component maps. Group ICA was carried out in several stages: i) a two-step data reduction procedure was applied to the data; in the first step, principal component analysis

was applied to reduce the number of dimensions in the dataset to 36 per participant; ii) participants were then concatenated into a single partition and passed through a second data-reduction step, where data was further reduced to 24 dimensions; iii) ICA Infomax algorithm was applied to this further reduced data-set to generate group components; the number of extracted group components were constrained to 24, as estimated using the minimum description length (MDL); iv) ICASSO algorithm was employed, with 20 iterations to validate the stability of the group components; v) individual participants' time courses and spatial maps based on the group components were back-constructed using the GICA-3 algorithm. The component maps were spatially sorted using templates (Allen et al., 2011; Shirer et al., 2012) (Figure 7-1), and were visually inspected to identify their specific networks and noise components. The components were verified by an independent reviewer (AC). Considering existing postulations and literature, the current study was interested to evaluate the SN (comprises the anterior and posterior SNs), DMN (comprises the dorsal and ventral DMNs), ECN (comprises the left and right ECNs), and the SMN. One sample t-tests were performed using SPM 12 to evaluate intrinsic network activations within each group. Results were considered significant at voxelwise $p < .005$ (uncorrected) and extent threshold of $\alpha < .05$ (FDR-corrected). Independent samples t-tests were also performed to evaluate group differences in intrinsic activations within the components. Group differences were explored and were considered significant at $p < .005$, $k \geq 10$. Consistent with attempts in previous chapters to explore our findings using corrected thresholds, we evaluated group differences in intrinsic activations within the networks at $p < .01$ voxelwise with FDR .05 cluster-correction, and $p < .01$ voxelwise with FWE .05 cluster-correction. The current study also adopted the default criterion for cluster reporting of up to 3 peaks per cluster that are at least 8mm apart. Coordinates of significant clusters were labelled using AAL2 atlas.

Figure 7-1. Templates of resting-state networks used for ICA spatial-sorting.

Study 4b: Functional Connectivity with the Cerebellum. CONN-fMRI Functional Connectivity Toolbox for SPM (v17b) was employed to evaluate FC between cerebellar ROIs and the rest of the brain. Cerebellar regions involved in the four resting-state networks (SN, ECN, DMN, SMN) according to the templates by Shirer and colleagues (Shirer et al., 2012) were selected as regions of interests. Masks of specific cerebellar regions: Left and right lobule I-IV, lobule V, lobule VI, lobule IX, Crus I and Crus II were extracted using the SUIT atlas via MRICron.

ROI-to-Voxel analyses. Regional connectivity between the cerebellar ROIs and the rest of the brain were evaluated using ROI-to-Voxel analyses in CONN-fMRI. Functional data were temporally band-pass filtered at $0.008 < f < 0.09$ Hz. Correlation coefficients were converted into Fisher-Z. Positive Fisher-Z values indicate increased functional connectivity relative to the comparison group. Only regions with positive functional connectivity were evaluated. *T*-tests were conducted to evaluate group differences and results were considered significant at voxelwise $p < .005$ (uncorrected) and extent threshold of $\alpha < .05$ (FDR-corrected).

Correlational Analyses. Spearman correlations were applied to explore associations between regional FC that showed group differences with cognitive indices that measure cognitive flexibility (Trail-Making A and B, Trail-Making difference index, Stroop index), inhibition (stop-signal reaction time), and visuospatial processing (symbol span and accuracy rate of high-load condition in the visual working memory task), and clinical indices (Y-BOCS total/obsessions/compulsions scores, age of onset, duration of illness, and mean daily dosage of fluoxetine equivalents). Results at $p < .05$ were presented.

Results

Study 4a: Independent Component Analysis

Exploratory analyses using corrected thresholds did not yield significant group differences in any components. Activation maps and coordinates of peak activations for each network within each control/OCD/combined group and group differences in intrinsic network activity at the uncorrected thresholds are presented in Figure 7-2, Table 7-1 and Supplementary Appendix S-Table 7-1 and S-Table 7-2. Resting-state ICA generated 3 components for SMN, 2 components for DMN (1 dorsal, 1 ventral), 3 components for SN (2 anterior, 1 posterior) and 2 components for ECN (1 left, 1 right). Other resting-state components were also identified but were not the focus of discussion: 2 components for higher visual network, 1 component for language, 1 component for auditory, 1 component for primary visual network, 1 component for precuneus network, and 5 noise components. Altered intrinsic activity were observed in OCD samples compared to controls in regions within and beyond the SMN, DMN, SN and ECN networks.

Sensorimotor Network (SMN). Controls and OCD samples demonstrated intrinsic network activity in expected regions of the SMN, such as the postcentral gyrus, precentral gyrus, and supplementary motor area. Results from one sample t-tests did not show expected intrinsic activity within the SMN in the thalamus in both controls and OCD samples, and cerebellum lobule VI in controls (Supplementary Appendix S-Table 7-1, S-Table 7-2). Within the SMN, OCD samples showed increased intrinsic activity in the bilateral postcentral gyrus and reduced intrinsic activity in the left precentral gyrus. Beyond the SMN, OCD samples showed increased intrinsic activity in mainly fronto-temporal regions and reduced intrinsic activity in bilateral frontal regions compared to controls (Table 7-1, Figure 7-2).

Default Mode Network (DMN). Consistent with the expected regions of the DMN, OCD samples and controls demonstrated significant intrinsic activity in the posterior cingulate gyrus, angular gyrus, precuneus, superior frontal gyrus, middle frontal gyrus,

hippocampal and parahippocampal regions, middle occipital gyrus, and cerebellar lobule IX in (S-Table 7-1, S-Table 7-2). Within the expected regions of the DMN, compared to controls, OCD samples demonstrated increased intrinsic activity in the median cingulate and parahippocampal gyri and reduced intrinsic activity in the superior frontal gyrus, precuneus and cerebellum lobule IX. Beyond the DMN, OCD samples also showed altered activity in cortical regions, such as the postcentral gyrus, supramarginal gyrus, and subcortical regions such as the caudate nucleus and cerebellar lobule VIII (Table 7-1, Figure 7-2).

Salience Network (SN). Controls and OCD samples showed intrinsic activity within expected regions of the SN, such as middle frontal gyrus, precuneus, supramarginal gyrus, inferior parietal regions, supplementary motor area and cerebellar lobules VI and Crus I (S-Table 7-1, S-Table 7-2). Individuals with OCD generally showed increased intrinsic activity in cortical regions and reduced intrinsic activity in both cortical and sub-cortical regions than controls. Compared to controls, OCD samples had increased intrinsic activity in the middle frontal gyrus, middle occipital gyrus and cingulate cortex, and reduced intrinsic activity in the putamen, insula and cerebellum lobule VI. Beyond the SN, OCD samples showed increased activity in the superior frontal gyrus and reduced activity in the inferior and middle temporal gyrus and other cerebellar regions (lobule VIII, VIIb) (Table 7-1, Figure 7-2).

Executive Control Network (ECN). OCD samples and controls generally showed intrinsic activity in regions within the ECN, such as middle and superior frontal gyrus, inferior parietal gyrus, precuneus, angular gyrus, and cerebellar lobules VI, Crus I and Crus II (S-Table 7-1, S-Table 7-2). Group differences were observed in mainly cortical regions. Within the ECN, compared to controls, OCD samples showed increased intrinsic activity in the inferior frontal opercular part and precuneus, and reduced intrinsic activity in the bilateral frontal, bilateral precuneus and the left angular gyrus (Table 7-1, Figure 7-2).

Table 7-1: Group differences in intrinsic activations in network components.

Sensorimotor Network (SMN)		Hemisphere	k	x	y	z	T
<i>OCD < Controls</i>							
	Superior frontal gyrus, dorsolateral	R	19	17.5	10.5	60	4.57
	Superior frontal gyrus, medial orbital	L	13	-3.5	45.5	-7	3.91
	Inferior frontal gyrus, triangular part	L	15	-53	28	11	3.82
	Middle temporal gyrus	R	24	59.5	-42	7	4.12
	Precentral gyrus	L	13	-39	-7	39	4.49
	Paracentral lobule	R	18	3.5	-39	63	3.81
	Supplementary motor area	R		3.5	-28	56	3.21
<i>OCD > Controls</i>							
	Superior frontal gyrus	L	20	0	-11	81	4.91
	Superior frontal gyrus, dorsolateral	L	30	-18	59.5	25	4.08
	Inferior frontal gyrus, orbital part	L	11	-28	31.5	-3.5	4.68
	Inferior frontal gyrus, triangular part	L		-35	28	0	3.15
	Superior temporal gyrus	L	13	-53	-25	7	3.78
	Superior temporal gyrus	L		-60	-28	11	3.46
	Temporal lobe, superior to middle temporal gyrus	L	17	-67	0	-3.5	3.71
	Parietal lobe, postcentral gyrus	R	38	21	-39	46	4.63
	Postcentral gyrus	L	23	-18	-32	53	3.62
Default Mode Network (DMN)		Hemisphere	k	x	y	z	T
<i>OCD < Controls</i>							
	Superior frontal gyrus, dorsolateral	R	12	17.5	-7	56	4.45
	Superior frontal gyrus, medial	R	38	14	35	60	4.14
	Inferior frontal gyrus, triangular part	R	15	45.5	28	3.5	3.63
	Supplementary motor area	L	15	-11	17.5	67	3.42
	Superior frontal gyrus, dorsolateral	L		-21	21	60	3.06
	Postcentral gyrus	L	19	-42	-21	25	3.78
	Supramarginal gyrus	L		-46	-28	32	3.28
	Precuneus	L	16	-14	-42	67	3.61
	Precuneus	L		-7	-49	63	3.18
	Inferior parietal, but supramarginal and angular gyri	L	15	-53	-35	35	3.98
	Paracentral lobule	L	15	0	-32	77	4.56
	Caudate nucleus	L	10	-7	10.5	0	3.28
	Cerebellum, vermis, lobule IX		13	3.5	-56	-39	4.85
	Cerebellum, lobule IX	L		-3.5	-60	-46	3.90
<i>OCD > Controls</i>							
	Median cingulate and paracingulate gyri	L	13	-3.5	3.5	42	4.27
	Median cingulate and paracingulate gyri	L		-11	10.5	39	3.87
	Precuneus	L	28	-14	-70	35	4.09
	Cerebellum, lobule VIII	L	11	-21	-70	-46	3.93
	Superior parietal gyrus	L	11	-14	-63	46	3.63
				-14	-70	60	3.01
Salience Network (SN)		Hemisphere	k	x	y	z	T
<i>OCD < Controls</i>							
	Superior frontal gyrus, dorsolateral	R	11	28	-11	74	5.00
	Superior frontal gyrus, medial	R	16	3.5	49	32	4.14
	Middle frontal gyrus	L	57	-35	35	25	5.02
	Inferior frontal gyrus, triangular part	R	15	45.5	35	3.5	3.70
	Postcentral gyrus	R	36	56	-21	49	3.57
	Supramarginal gyrus	R		56	-32	42	3.27
	Inferior frontal gyrus, opercular part	L	10	-46	10.5	0	3.37
	Insula	R	13	42	7	3.5	3.54
	Inferior frontal gyrus, opercular part	R		52.5	10.5	7	2.84
	Precentral gyrus	L	11	-32	3.5	42	3.45

Table 7-1 (Cont'd): Group differences in intrinsic activations in network components.

Salience Network (SN)		Hemisphere	k	x	y	z	T
<i>OCD < Controls (Cont'd)</i>							
	Inferior temporal gyrus	L	56	-56	-60	-11	4.74
	Inferior temporal gyrus	L		-53	-53	-14	4.59
	Middle temporal gyrus	L	16	-60	-56	3.5	4.15
	Middle temporal gyrus	L		-56	-63	0	3.85
	Angular gyrus	R	17	49	-49	28	4.00
	Postcentral gyrus	L	49	-49	-32	56	4.96
	Inferior parietal gyrus	L		-60	-35	42	3.24
	Inferior parietal gyrus	L		-56	-42	46	3.02
	Putamen	L	12	-14	10.5	3.5	3.18
	Putamen	L		-21	3.5	11	3.10
	Cerebellum lobule VIII	L	20	-11	-67	-35	4.40
	Cerebellum lobule VIIb	L		-14	-77	-42	3.35
	Cerebellum lobule VI	R	11	24.5	-53	-21	4.06
	Cerebellum lobule VI	R		24.5	-63	-25	2.94
<i>OCD > Controls</i>							
	Superior frontal gyrus, dorsolateral	L	55	-25	56	7	3.92
	Superior frontal gyrus, dorsolateral	R	15	17.5	-7	70	4.08
	Superior frontal gyrus, dorsolateral	R	16	28	63	18	3.85
	Superior frontal gyrus, medial	R	46	3.5	45.5	39	3.51
	Superior frontal gyrus, medial	R		7	38.5	46	3.33
	Middle frontal gyrus	R	12	45.5	49	28	4.02
	Middle frontal gyrus, orbital part	L	11	-39	52.5	-3.5	3.47
	Postcentral gyrus	R	23	28	-32	70	3.41
	Middle occipital gyrus	L	20	-21	-84	18	4.68
	Middle occipital gyrus	L		-28	-91	7	3.85
	Anterior cingulate and paracingulate gyri	R	22	3.5	35	18	3.65
	Median cingulate and paracingulate gyri	R	19	10.5	-25	42	4.06
Executive Control Network (ECN)		Hemisphere	k	x	y	z	T
<i>OCD < Controls</i>							
	Superior frontal gyrus, medial	L	54	-7	49	46	5.01
	Middle frontal gyrus	R	34	42	7	60	4.25
	Middle frontal gyrus	L	10	-35	28	42	3.58
	Middle frontal gyrus	L	10	-39	28	49	3.26
	Precuneus	R	20	10.5	-46	60	3.81
	Precuneus	L	10	-7	-53	60	3.44
	Angular gyrus	L	13	-42	-63	49	3.76
	Inferior occipital gyrus	R	34	38.5	-84	-11	3.81
	Median cingulate and paracingulate gyri	R	10	7	-11	39	3.65
	Median cingulate and paracingulate gyri	L		0	-18	42	3.03
<i>OCD > Controls</i>							
	Precentral gyrus	R	36	28	-21	56	4.18
	Precentral gyrus	L	10	-18	-25	60	3.63
	Inferior frontal gyrus, opercular part	L	12	-63	10.5	21	3.19
	Precuneus	L	19	-7	-70	53	3.98
	Precuneus	L	16	0	-56	18	3.79
	Precuneus	L		-7	-60	14	3.40
	Superior occipital gyrus	L	16	-25	-70	35	3.62

Note. Two-sample t-test results between controls ($n=17$) and OCD sample ($n=20$), $p < .005$

(uncorrected) and 10 extent voxels. Analysis voxel size: $3.5 \times 3.5 \times 3.5\text{mm}^3$. Coordinates are in MNI space. L = left; R = right.

Figure 7-2. Results from ICA.

The upper three rows showed activation maps of each network for Controls, OCD samples and the combined group. Activation maps are for display purposes only, voxelwise $Z > 0.5$. The last row showed two-sample t-test results between OCD samples and controls, $p < .005$ (uncorrected), $k > 10$.

Study 4b: Regional Functional Connectivity with the Cerebellum

ROI-to-voxel analyses. Results from ROI-to-voxel analyses within controls and OCD samples are presented in Supplementary Appendix S-Figure 7-1 and S-Table 7-3. Group differences in whole-brain connectivity with cerebellar sources are presented in Table 7-2 and Figure 7-3. Supplementary Appendix S-Figure 7-2 presents a breakdown in means and standard errors of each control and OCD group for regional functional connectivity that showed group differences. Means and standard errors of these regional functional connectivity are presented. Only regions with positive functional connectivity were evaluated.

Altered cerebellar connectivity in OCD compared to controls was dominated by reduced FC between the cerebellum with regions of the CSTC such as the thalamus, and the anterior cingulate. Other regions of reduced FC with cerebellar sources were also observed with the superior frontal gyrus, postcentral gyrus, precentral gyrus, superior temporal gyrus, precuneus and the insula. Compared to controls, OCD samples also showed increased FC between bilateral lobule V with the occipital regions, and between left Crus II with medial frontal gyrus to the anterior orbitofrontal region.

Spearman correlational analyses. Regional FC with the cerebellum that showed group differences were extracted and analyzed within each control and OCD group for correlational associations with cognitive and clinical indices. Results are presented in Table 7-3, and scatterplots of these relationships are also presented in supplementary materials S-Figure 7-3. In terms of correlations with cognitive indices, both controls and OCD groups showed significant associations were between FC values involving the cerebellum with inhibition (stop-signal reaction time) and visuospatial processing (visual working memory,

symbol span). Unlike OCD samples, controls did not show significant correlations in cognitive indices with FC involving the cerebellum lobule IX.

In terms of clinical indices, significant associations were observed between FC involving cerebellar sources in right lobule IX, bilateral lobule V, and bilateral crus II with age of onset, duration of illness, mean daily dosage of fluoxetine equivalents, and Y-BOCS total and compulsions scores (Table 7-3). In particular, duration of illness was significantly associated with FC strength between right lobule IX and left precuneus ($\rho_s = -.533, p = .016$), right lobule V and left middle occipital gyrus ($\rho_s = -.524, p = .018$) and right anterior cingulate ($\rho_s = .515, p = .020$), and between right Crus II and right middle cingulate ($\rho_s = -.542, p = .014$). Since duration of illness increases with age, partial correlational analyses were conducted to partial out the effects of age. Significant correlations were observed only for functional connectivity between right crus II and right middle cingulate cluster ($\rho_s = -.465, p = .045$) with duration of illness after controlling for the effects of age.

Table 7-2: Group differences in ROI-to-voxel connectivity between 17 Controls and 20 OCD samples.

ROI Source	k	x	y	z	T	Hemisphere	Connectivity Regions	Controls		OCD		t	df	p	Cohen's
								Mean Z	S.E.	Mean Z	S.E.				d
<u>Source: R Lobule I-IV</u>															
OCD < Controls	497	8	42	2	4.02	R	Anterior cingulate & paracingulate gyri	0.09	0.02	-0.04	0.02	4.06	35	.000	-1.35
		14	34	16	3.80	R	Anterior cingulate & paracingulate gyri								
		2	38	8	3.66	R	Anterior cingulate & paracingulate gyri								
<u>Source: L Lobule V</u>															
OCD < Controls	503	4	24	24	4.86	R	Anterior cingulate & paracingulate gyri	0.11	0.02	-0.03	0.02	4.48	35	.000	-1.51
		8	32	28	3.82	R	Anterior cingulate & paracingulate gyri								
		8	24	32	3.75	R	Middle cingulate & paracingulate gyri								
OCD > Controls	436	28	-84	10	3.91	R	Middle Occipital Gyrus	-0.07	0.03	0.07	0.03	-3.94	35	.000	1.31
		24	-78	14	3.70	R	Cuneus								
		36	-84	6	3.57	R	Middle Occipital Gyrus								
<u>Source: R Lobule V</u>															
OCD < Controls	359	8	24	24	4.50	R	Anterior cingulate & paracingulate gyri	0.09	0.02	-0.03	0.01	5.58	35	.000	-1.82
		4	24	16	4.03	R	Anterior cingulate & paracingulate gyri								
		12	38	16	3.73	R	Anterior cingulate & paracingulate gyri								
	789	4	58	0	4.25	R	Superior Frontal Gyrus, Medial	0.09	0.02	-0.06	0.02	4.06	35	.000	-1.35
		8	52	10	3.92	R	Anterior cingulate & paracingulate gyri								
		-4	60	0	3.65	R	Superior Frontal Gyrus, Medial								
OCD > Controls	2777	26	-56	44	6.10	R	Superior Parietal Lobule	-0.07	0.02	0.08	0.01	-6.52	35	.000	2.14
		26	-64	56	5.04	R	Superior Parietal Gyrus								
		40	-70	2	4.79	R	Middle Occipital Gyrus								
	547	-42	-84	0	4.05	L	Middle Occipital Gyrus	-0.09	0.02	0.05	0.02	-4.37	35	.000	1.43
		-38	-84	-8	3.91	L	Inferior Occipital Gyrus								
		-42	-72	2	3.61	L	Middle Occipital Gyrus								

Table 7-2 (cont'd): Group differences in ROI-to-voxel connectivity between 17 Controls and 20 OCD samples.

ROI Source	k	x	y	z	T	Hemisphere	Connectivity Regions	Controls		OCD		t	df	Cohen's	
								Mean Z	S.E.	Mean Z	S.E.			p	d
<u>Source: L Lobule IX</u>															
OCD < Controls	855	-6	48	6	4.03	L	Anterior cingulate & paracingulate gyri	0.20	0.03	0.05	0.02	4.20	35	.000	-1.36
		12	44	-8	3.94	R	Superior frontal gyrus, medial orbital								
<u>Source: R Lobule IX</u>															
OCD < Controls	920	-16	-22	76	5.11	L	Paracentral Lobule	0.08	0.02	-0.05	0.02	5.57	35	.000	-1.83
		-30	-32	42	4.59	L	Postcentral Gyrus								
	278	-22	-26	72	4.32	L	Postcentral Gyrus								
		-38	-60	16	4.71	L	Middle Temporal Gyrus	0.17	0.02	0.03	0.02	4.49	35	.000	-1.47
		-48	-68	14	4.03	L	Middle Temporal Gyrus								
	737	-40	-68	16	3.48	L	Middle Occipital Lobe								
		18	-42	58	4.56	R	Paracentral Lobule	0.09	0.02	-0.05	0.02	4.71	35	.000	-1.56
		26	-42	70	4.12	R	Postcentral Gyrus								
	593	18	-40	66	3.91	R	Postcentral Gyrus								
		-48	-22	10	4.54	L	Superior Temporal Gyrus	0.13	0.02	-0.01	0.02	4.45	35	.000	-1.46
		-52	-18	2	3.81	L	Superior Temporal Gyrus								
	673	-48	-28	18	3.76	L	Superior Temporal Gyrus								
		-2	-56	28	4.26	L	Precuneus	0.25	0.02	0.12	0.02	3.94	35	.000	-1.30
		8	-56	20	4.11	R	Precuneus								
		8	-48	16	3.99	R	Precuneus								
<u>Source: R Crus I</u>															
OCD < Controls	1098	36	-20	0	4.33	R	Insula	0.01	0.03	-0.14	0.01	5.05	35	.000	-1.82
		36	-18	10	4.32	R	Insula								
	419	-10	-18	2	4.34	L	Thalamus	0.09	0.03	-0.07	0.02	4.74	35	.000	-1.54
		-2	-18	6	4.18	L	Thalamus								
		-14	-18	14	4.00	L	Thalamus								
<u>Source: R Crus II</u>															
OCD < Controls	450	-6	-18	6	4.19	L	Thalamus	0.08	0.02	-0.06	0.02	4.87	35	.000	-1.60
		-20	-28	14	3.83	L	Thalamus								
	644	8	-36	48	4.19	R	Middle cingulate & paracingulate gyri	0.04	0.02	-0.12	0.03	4.54	35	.000	-1.52
		2	-36	54	4.11	R	Paracentral lobule								
		22	-42	70	3.75	R	Postcentral Gyrus								

Table 7-2 (cont'd): Group differences in ROI-to-voxel connectivity between 17 Controls and 20 OCD samples.

ROI Source	k	x	y	z	T	Hemisphere	Connectivity Regions	Controls		OCD		Cohen's			
								Mean Z	S.E.	Mean Z	S.E.	t	df	p	d
<u>Source: L Crus II</u>															
OCD < Controls	638	-10	-18	48	4.84	L	Middle cingulate & paracingulate gyri	0.03	0.01	-0.09	0.02	5.82	35	.000	-1.96
		-24	-26	52	4.17	L	Precentral Gyrus								
	642	50	-18	38	3.86	R	Postcentral Gyrus	0.04	0.02	-0.11	0.02	4.54	35	.000	-1.52
		56	-26	6	3.82	R	Superior Temporal Gyrus								
		54	-26	14	3.61	R	Superior Temporal Gyrus								
	364	-56	-8	42	3.78	L	Postcentral Gyrus	0.01	0.02	-0.12	0.02	4.20	35	.000	-1.39
		-56	0	30	3.40	L	Precentral Gyrus								
		-38	-12	56	3.32	L	Precentral Gyrus								
OCD > Controls	428	-6	52	-18	5.41	L	Rectal Gyrus	-0.02	0.02	0.15	0.02	-4.98	35	.000	1.65
		4	66	-18	4.85	R	Medial Frontal Gyrus								
		-12	56	-14	4.58	L	Anterior orbital gyrus								

Notes. Only findings of significant group differences were presented. Results were significant at voxelwise $p < .005$ (uncorrected) and extent threshold of $\alpha < .05$ (FDR-corrected). Analysis voxel size: $3.5 \times 3.5 \times 3.5\text{mm}^3$. Z = Fisher-Z scores; S.E. = Standard errors; R = Right; L = Left.

Figure 7-3. Significant group differences in ROI-to-voxel functional connectivity.

Figure 7-3 (cont'd). Significant group differences in ROI-to-voxel functional connectivity.

Only significant results are presented. Results were significant at voxelwise $p < .005$ (uncorrected) and extent threshold of $\alpha < .05$ (FDR-corrected). Blue indicates reduced functional connectivity in OCD samples compared to controls (OCD < Controls). Red indicates increased functional connectivity in OCD samples compared to controls (OCD > Controls).

Table 7-3: Significant associations between regional functional connectivity with cognitive and clinical indices within each control and OCD group.

Cerebellar Source and Connectivity Peak	Peak coordinates			Associated index	Group	ρ_s	p
	x	y	z				
Source: Left Lobule IX							
Left Anterior Cingulate	-6	48	6	Stop-Signal Reaction Time	Controls	-.544	.024
Source: Right Lobule IX							
Left Paracentral Lobule	-16	-22	76	Trail-Making Test B	OCD	-.470	.037
				Age of Onset	OCD	-.537	.015
Left Precuneus	-2	-56	28	Duration of Illness	OCD	-.533	.016
Source: Left Lobule V							
Right Middle Occipital Gyrus	28	-84	10	Mean Daily Dosage Fluoxetine Equivalents	OCD	-.526	.025
Source: Right Lobule V							
Right Superior Frontal Gyrus, Medial	4	58	0	Symbol Span	Controls	.583	.014
				Stop-Signal Reaction Time	Controls	-.691**	.002
				Symbol Span	OCD	.476	.034
				Stop-Signal Reaction Time	OCD	-.507	.027
Left Middle Occipital Gyrus	-42	-84	0	Duration of Illness	OCD	-.524^	.018
Right Superior Parietal Lobule	26	-56	44	Symbol Span	OCD	-.449	.047
				Accuracy Rate of High-Load Condition in Visual Task	OCD	-.529	.024
Right Anterior Cingulate	8	24	24	Stop-Signal Reaction Time	Controls	-.583	.014
				Duration of Illness	OCD	.515^	.020
Source: Right Crus I							
Left Thalamus	-10	-18	2	Stroop Index	Controls	.503	.040
Source: Left Crus II							
Left Middle Cingulate	-10	-18	48	Trail-Making Test Index (TMTB - TMTA)	Controls	-.590	.013
				Stroop Index	Controls	.533	.028
Left Postcentral Gyrus	-56	-8	42	Mean Daily Dosage Fluoxetine Equivalents	OCD	-.514	.029
				Y-BOCS Total Score	OCD	-.445	.049
				Y-BOCS Compulsions Score	OCD	-.574**	.008
Source: Right Crus II							
Left Thalamus	-6	-18	6	Accuracy Rate of High-Load Condition in Visual Task	Controls	-.540	.025
				Age of Onset	OCD	.524	.018
Right Middle Cingulate	8	-36	48	Duration of Illness	OCD	-.542	.014

Notes. Only significant correlations were presented, all $p < .05$. Cognitive indices evaluated were: Trail-Making Test A, B, Trail-Making Index, Stroop Index, Stop-Signal Reaction Time, Symbol Span, and Accuracy rate of high-load condition of the Visual task. Clinical indices evaluated were: Y-BOCS total, obsessions, and compulsions scores, age of onset, duration of illness, duration of pharmacotherapy, and mean daily dosage of fluoxetine equivalent. Significant correlations between FC and duration of illness were further evaluated to control for age effects, ρ_s indicates spearman correlations. [^] indicates correlations that were no longer significant when age effects were partial out. Blue = OCD samples. (** $p < .01$)

Discussion

The current chapter utilized a data-driven approach to evaluate altered intrinsic cortical-subcortical connectivity in OCD. In Study 4a, intrinsic activity of cortical and subcortical regions were constrained using four well-known resting-state networks that have been postulated to be involved in OCD pathophysiology based on existing literature and findings from previous chapters. This was followed up with Study 4b, where ROI-to-voxel functional connectivity analyses were conducted to evaluate group differences in cortical-subcortical functional connectivity. This was done by specifying selected cerebellar lobules as ROIs and evaluating significant group differences in functional connectivity between the cerebellar ROIs to the rest of the brain. The approach provided a systematic understanding on aberrant functional connectivity involving the cerebellum in OCD samples relative to controls.

Findings from ICA analyses (Study 4a)

The ICA approach enabled group differences in intrinsic activity to be constrained within the RSNs, and evaluate intrinsic activity across synchronous brain regions. Network activation maps extracted from each controls and OCD group generally demonstrated similar patterns of intrinsic activity within the SMN, DMN, SN and ECN. In terms of group differences, compared to controls, individuals with OCD showed: i) within the SMN, increased intrinsic activity in the postcentral gyrus and reduced intrinsic activity in precentral gyrus; ii) within the DMN, increased intrinsic activity in the median cingulate and reduced intrinsic activity in the precuneus and cerebellum lobule IX; iii) within the SN, increased intrinsic activity in the middle frontal gyrus, anterior cingulate and middle occipital gyral regions and reduced intrinsic activity in the putamen, insula and cerebellar lobule VI, and iv)

within the ECN, increased intrinsic activity in the inferior frontal gyrus and precuneus, and reduced intrinsic activity in the frontal, precuneus and angular gyrus.

Interpretation of ICA findings

Existing studies that evaluated intrinsic differences within networks are relatively limited. According to the dysfunctional sensory gating proposal, excessive excitation of sensorimotor regions and reduced inhibitory functions of frontal regions in OCD impair the capacity to suppress repetitive behaviours and intrusive thoughts (Rossi et al., 2005). Consistent with the proposal, OCD samples showed increased intrinsic activity in the bilateral postcentral gyrus and reduced activity in the precentral and supplementary motor areas within the SMN components. The postcentral gyrus is the site of the primary somatosensory cortex, and is key in perceiving pain, touch, and other bodily sensations (Hyvarinen & Poranen, 1978; Iwamura & Tanaka, 1978; Nelson & Chen, 2008). The precentral region and the supplementary motor areas are located in the frontal cortex, and are involved in the execution of voluntary actions; and control of movements that are internally generated and sequences of movements, respectively (Roland, Larsen, Lassen, & Skinhoj, 1980; Roland, Skinhoj, Lassen, & Larsen, 1980). Therefore, increased intrinsic activity in the postcentral gyrus could potentially increase sensitivity to somatosensory inputs, and altered activity in the frontal regions including the precentral and supplementary motor area contributed to reduced control in internally generated movements and in suppressing repetitive behaviours and thoughts (Gonçalves et al., 2017; Nebel, Eloyan, Barber, & Mostofsky, 2014).

Consistent with findings reported across different studies (Cheng et al., 2013; Zhu et al., 2016), the current study observed increased intrinsic activity in the anterior cingulate and reduced intrinsic activity in the insula – key anchors of the SN (Shirer et al., 2012). The

anterior cingulate is involved in error detection and conflict monitoring, and the insula in physical sensations related to disgust, internal urges and compulsions (Stern et al., 2012). The SN has been thought to influence the salience of external events to facilitate behavioural control in response to the identified salience (Seeley et al., 2007). The insula is also functionally connected with the CSTC, and have been speculated to have key roles in OCD pathophysiology (Harrison et al., 2013; Jung et al., 2013). A separate study had also reported reduced intrinsic activity of the right insula in individuals with OCD where the intrinsic activity of the right insula was also significantly correlated with total Y-BOCS scores (Zhu et al., 2016). The SN is an important hub that appropriately regulates the activity of the ECN and DMN. The DMN is involved in self-awareness and self-referential processing (Cheng et al., 2013; Fan et al., 2017). Altered intrinsic activity within the DMN have been speculated to indicate aberrant recruitment of the DMN in self-referential processing, leading to difficulties in resolving obsessive thoughts (Fan et al., 2017). Taking all information together, dysfunctions in the SN could potentially alter appropriate engagement and disengagement of the ECN and DMN, and collectively influence the control of sensorimotor representations regulated by the SMN.

However, we reiterate that group differences within the components were subjected to considerably liberal thresholds ($p < .005$ (uncorrected) and 10 extent voxels), and that no significant differences were obtained at the corrected threshold ($p < .01$ voxelwise with FDR .05 cluster-correction, and $p < .01$ voxelwise with FWE .05 cluster-correction). This could potentially be attributed to small sample sizes, hence statistical power, and/or that effects were inherently small. Future work is required to replicate our findings using a larger sample.

Study 4b: Findings from cerebellar ROIs-to-voxel functional connectivity analyses

Results from the ICA analyses (Study 4a) demonstrated altered intrinsic activity in cortical and sub-cortical regions. These findings were consistent with that obtained from functional connectivity analyses using cerebellar ROI-to-voxel analyses. Results from functional connectivity analyses (Study 4b) indicated altered cerebellar-to-cortical and -sub-cortical functional connectivity in OCD samples compared to controls at resting-state. In general, OCD samples showed more reduced than increased functional connectivity with cerebellar ROIs than controls. Reduced functional connectivity were observed between cerebellar ROIs with both cortical and sub-cortical regions, such as cingulate, superior frontal gyrus, postcentral gyrus, insula, and thalamus, while increased functional connectivity in OCD samples relative to controls were observed with mainly cortical regions, such as the occipital gyrus, superior parietal gyrus, and orbitofrontal gyrus. Interestingly, altered functional connectivity were observed between the cerebellum and regions within the CSTC.

Interpretation of functional connectivity analyses

Cerebellum. Traditionally thought to be involved in movement-related functions, the cerebellum is also involved in higher cognition (Chen & Desmond, 2005; Lee et al., 2005; Rapoport et al., 2000; Yeganeh-Doost et al., 2011). The cerebellum can be divided into two zones based on its functional connectivity profiles: a sensorimotor zone and a supramodal zone (O'reilly et al., 2009). The sensorimotor zone is functionally connected to the sensory, motor and visual regions, and comprises the anterior lobes including lobules I-V and a secondary representation in lobule VIII. The supramodal zone includes Crus I, Crus II, and lobule VIIa of the posterior cerebellum, and has strong connectivity with prefrontal and inferior parietal regions (O'reilly et al., 2009; Stoodley & Schmahmann, 2010). Lobule IX has also been considered as part of the posterior cerebellum, with key roles in visual guidance of movement (Glickstein et al., 1994), and is involved in the default mode network (Habas et al.,

2009). In the current analysis, cerebellar regions were selected as ROIs for ROI-to-voxel functional connectivity analyses based on their involvement in the key resting-state networks (SN, DMN, ECN and SMN; Shirer et al., 2012). To the best of our knowledge, no study has yet evaluated functional connectivity with cerebellar structures using resting-state neuroimaging in OCD samples.

Functional connectivity between the cerebellum and CSTC regions. Interestingly, results from the ROI-to-voxel functional connectivity analyses revealed significant group differences in functional connectivity strength between cerebellar ROIs with regions of the CSTC, such as the cingulate gyrus, orbitofrontal cortex and the thalamus. The subsequent paragraphs provide a brief discussion on these findings.

Cingulate gyrus. Existing studies have frequently reported altered cingulate activity in OCD samples during symptom-provocation and in tests of executive function (Fitzgerald et al., 2005; Hendler et al., 2003; Maltby et al., 2005; Viard et al., 2005). Nestled within the cingulate cortex are fibers of the cingulum bundle that comprise of long and short fibres that connect far-apart regions and adjacent regions (Y. Wu, Sun, Wang, Wang, & Ou, 2016) . This intricate network of connectivity fibers connects between the cingulate cortex to many regions, such as and not limited to the amygdala, hippocampus, cerebellum, striatum, hypothalamus, and the orbitofrontal cortex (Beckmann et al., 2009). The extensive connectivity of the cingulate cortex gives it important roles in attention and executive functioning, including error monitoring and detection (Braver, Barch, Gray, Molfese, & Snyder, 2001; Lütcke & Frahm, 2008; Yang et al., 2015). Based on connectivity-based parcellations of the cingulate cortex, it appears apparent that cingulate sub-regions have distinctive connectivity profiles (Beckmann et al., 2009).

Our results demonstrated that compared to controls, OCD samples showed reduced functional connectivity between the anterior cerebellum (lobules I-V) and the anterior-cingulate regions. According to the connectivity-based parcellation of the cingulate cortex established by Beckmann and colleagues (2009), the anterior-dorsal cingulate region of the cingulate cortex (as observed in our results) has roles in motor- and conflict-related functions. The dorsal region of the anterior cingulate cortex is distinctively implicated in motor control (Beckmann et al., 2009; Botvinick, 2007; Bush, Luu, & Posner, 2000), and the most anterior cingulate cortex subregion is involved in error-monitoring and conflict (Beckmann et al., 2009). In addition, past research indicated that error-monitoring processes subserved by the anterior cingulate region occurred even during instances when errors were unlikely (J. W. Brown & Braver, 2005). Taken together, the dorsal and anterior cingulate regions are important for reward-guided action selection (Rushworth, Behrens, Rudebeck, & Walton, 2007), and in predicting likelihood of error during conflict (J. W. Brown & Braver, 2005). Results from our meta-analytic investigations reported in Chapter 3 had also observed altered activity in the anterior-dorsal region of the cingulate in OCD samples during shifting tasks. In addition, in Chapter 4, we observed significant group differences in performances within Trail-Making Test A and Trail-Making Test B components but not the difference scores, and had speculated some underlying systematic difficulty such as motor control that gets cancelled out when difference indices were computed. Considering the findings observed in this chapter that involved the dorsal-anterior cingulate region, it appears plausible that abnormal motor control and error-monitoring processes potentially underlie OCD psychopathology.

In terms of altered functional connectivity with the posterior cerebellum, the current study observed reduced functional connectivity between cerebellar Crus I and II with more

middle and middle-posterior regions of the cingulate cortex in OCD samples relative to controls. The anterior regions of Crus I and II are involved in motor processes, while the lateral posterior regions are involved in higher cognition (Stoodley & Schmahmann, 2009). Past research reported the middle cingulate region (observed in results of functional connectivity with left Crus II) to be functionally involved in controlling basic aspects of movement (Beckmann et al., 2009), and had demonstrated high probability of having interconnections with the motor cortex in the precentral gyrus and parietal cortex (Beckmann et al., 2009). This is aligned with results of the current study, where reduced functional connectivity was also observed between left cerebellum Crus II with precentral and postcentral regions. Separately, altered functional connectivity with right Crus II involving the middle-posterior cingulate region corresponded to the middle cingulate sulcal region based on the cytoarchitecture of the middle cingulate cortex (Vogt, Nimchinsky, Vogt, & Hof, 1995). This region of the middle cingulate is engaged in response-outcome functions (Alexander & Brown, 2011; Silvetti, Alexander, Verguts, & Brown, 2014) – in tracking and monitoring outcomes of decisions to temporarily meet higher order needs or abstract goals (Apps, Green, & Ramnani, 2013; Behrens, Woolrich, Walton, & Rushworth, 2007; Botvinick, 2012; Kolling, Behrens, Mars, & Rushworth, 2012). The posterior portion of the cingulate has been associated with episodic memory and self-related processes (Spiers & Maguire, 2007; Vogt, Finch, & Olson, 1992; Whitfield-Gabrieli & Ford, 2012) and is implicated as part of the default mode network.

Even though existing studies frequently implicated the anterior cingulate in OCD pathophysiology, results from Study 4b indicated that alterations of the middle and middle-posterior regions of the cingulate could be potentially important in OCD. Dysfunctional conflict and error monitoring processes have been proposed as key aspects to OCD

pathophysiology. As discussed in Chapter 3, dysfunctional error monitoring system could generate excessive error signals that manifest as repetitive thoughts, feelings, and sensations of “not just right experience” (Coles et al., 2003). These error signals are usually translated to its corresponding corrective and compulsive acts until they felt “just right” (Leckman et al., 1994; Miguel et al., 2000). We speculated in Chapter 3 that the error signals could be generated internally or triggered by external stimuli or when certain actions do not concur with their representations of how it should be, and therefore, maintaining obsessions and compulsions regardless the rational awareness of whether an actual error has been made. In addition to a dysfunctional error monitoring system subserved by the anterior cingulate region, altered middle and middle-posterior cingulate activity could also contribute to ineffective response-outcome tracking, where responses and decisions undertaken had failed to satisfy the temporary need (Botvinick, 2012; Kolling et al., 2012), hence, maintaining the repetitive cycle of obsessions and compulsions as observed in patients with OCD. Interestingly, the current study also observed significant correlations between the functional connectivity strength of right crus II and right middle cingulate region with duration of illness in patients with OCD, and this effect remained significant even after controlling for effects of age. This observation could potentially provide support for the postulation of an ineffective response-outcome tracking that contributed to symptoms maintenance in OCD samples.

Orbitofrontal cortex. The orbitofrontal cortex has traditionally been implicated in the pathophysiology of OCD. Early studies reported increased cerebral perfusion and glucose metabolic rates in the orbitofrontal regions during resting-state and during symptom provocation (Baxter et al., 1987; Rauch et al., 1994; Swedo et al., 1989). Existing studies appear to suggest differentiating roles for each subdivision with different connectivity patterns (Elliott et al., 2000; Kahnt et al., 2012; Kringelbach & Rolls, 2004). In addition to a

medial-lateral distinction within the orbitofrontal cortex, there also appears to be a posterior-anterior distinction of the orbitofrontal cortex (Kringelbach, 2005; Kringelbach & Rolls, 2004). Results from the current study reported increased intrinsic functional connectivity between cerebellar Crus II and anterior-medial orbital gyrus in patients with OCD compared to controls. A previous study had reported associations between subjective ratings of pleasantness with activity in the medial-anterior parts of the orbitofrontal cortex (Anderson et al., 2003; De Araujo, Kringelbach, Rolls, & McGlone, 2003; Hinton et al., 2004). The medial orbitofrontal cortex appears to be relevant to learning, monitoring and decoding representations of reward-value information (Kringelbach & Rolls, 2003; Pauls et al., 2014). Reward-related information involving more complex or abstract reinforcers such as monetary gains and loss were represented and tracked in the anterior orbitofrontal cortex, and these representations can influence subsequent behaviours and subjective hedonic experiences (Kringelbach, 2005); (Kringelbach & Rolls, 2004). These functions are supported by reciprocal information between the orbitofrontal cortex with other regions such as the thalamus (Pandya & Yeterian, 1996), amygdala (Amaral & Price, 1984; Carmichael & Price, 1995), insula (Mesulam & Mufson, 1982), cingulate cortex (Buchanan & Powell, 1993; Petrovic, Kalso, Petersson, & Ingvar, 2002), hippocampus, striatum and dorsolateral prefrontal cortex (Barbas & Pandya, 1989).

To the best of our knowledge, no study has yet reported functional connectivity between the cerebellum with orbitofrontal regions. Existing studies that evaluated and reported whole-brain functional connectivity at resting-state involving the orbitofrontal cortex in OCD have also been limited. Two studies that employed a whole-brain approach had reported increased functional connectivity in OCD samples compared to controls in the bilateral medial (Hou et al., 2014) and anterior orbitofrontal regions (Beucke et al., 2013)

amongst other regions. Hou and colleagues (2014) had also employed seed-based functional connectivity techniques and had reported increased functional connectivity in the left and right caudate nucleus seeds with medial orbitofrontal areas in OCD samples relative to controls. It is noteworthy that OCD samples included in both studies had differed in sample characteristics. Even though both studies had included patients with comorbid conditions, Beucke and colleagues (2013) included patients with a combination of medication status where some were medicated at the time of scanning and others had stopped medications few weeks prior to scanning, and Hou and colleagues (2014) included patients who were either medication-naïve or had stopped taking their medications prior to scanning. Even though the medication status of the patients' group in Beucke et al. (2013) and Hou et al. (2014) had differed from that of the current study where patients were on medication during scan, their findings were somewhat consistent where altered functional connectivity involving the medial orbitofrontal area were demonstrated.

Past studies had reported significant associations between OCD symptom severity and functional activations involving the medial and lateral orbitofrontal cortex during symptom provocation. However, the current study did not observe significant associations between the functional connectivity strength of cerebellar crus II-to- anterior-medial orbitofrontal with OCD symptom severity. This was also consistent with the findings reported by Hou and colleagues (2014), where no significant differences were observed between the functional connectivity strength of the medial orbitofrontal cortex with symptom severity. First, heterogeneity of symptom sub-groups in the patients' sample of the current study and that in Hou et al.'s could contribute to the lack of clear associations between the functional connectivity strength involving the anterior-medial orbitofrontal cortex with symptom severity. Indeed, past studies indicated that combining patients with mixed symptoms could

potentially obscure findings from neuroimaging studies. Limited studies have evaluated neural correlates in patients with predominant symptom types. Rauch and colleagues (1998) reported positive correlations involving checking symptoms and negative correlations involving symmetry/ordering symptoms with cerebral blood flow (rCBF) in the striatum; and positive correlations between washing symptoms and bilateral anterior cingulate and left orbitofrontal cortex rCBF during a sustained attention task (Rauch et al., 1998). Symptom provocation paradigms indicated that OCD patients with predominant washing symptoms showed increased activations in the visual and insula regions (Phillips et al., 2000), and other regions such as the ventrolateral prefrontal cortex and parahippocampal regions (Shapira et al., 2003); OCD patients with predominant checking symptoms had increased activity in the frontostriatal and thalamic regions (Phillips et al., 2000). These findings suggest that although preliminary, different symptoms may be mediated by distinct neural symptoms (Mataix-Cols, do Rosario-Campos, & Leckman, 2005). However, it is out of the scope of this thesis to investigate neural mechanisms of OCD subtypes. Second, the nature of the analysis might have diluted potential associations. Even though adopting a whole brain approach such as whole-brain search of differences (as in Hou et al., 2014) or an ROI-to-whole brain approach for group differences in functional connectivity strength enabled exploration of potential alterations, doing so increases the space available for analysis, and could therefore dilute potential associations. Beucke and colleagues (2013) followed up their whole-brain approach with an ROI-driven approach that evaluated functional connectivity of the orbitofrontal area, and reported greater anterior orbitofrontal connectivity with precentral and superior temporal cortices, and increased degree of local connectivity within the orbitofrontal hub were also observed in patients with OCD compared with controls. In addition, correlational analyses indicated positive associations between the degree of distant connectivity in the

posterior/lateral orbitofrontal cortex and OCD symptom severity in unmedicated patients. This leads to a third possibility – that medication effects could have potentially altered neural signals. The current study had included patients who did not have premorbid conditions and did not require patients to stop their medications for participation in the research study. The current study also did not have a substantial sample of patients who were unmedicated, therefore we were not able to conduct separate analyses to evaluate connectivity patterns of patients who were medication-naïve. However, the current study had conducted correlational analyses between the functional connectivity strength of the cerebellar crus II-to- anterior-medial orbitofrontal with clinical variables such as mean daily dosage of fluoxetine equivalents and duration of pharmacotherapy, but did not observe significant associations. Even though the exact contribution of medication effects on neural connectivity is unclear, our results at least indicates that mean daily dosage and duration of pharmacotherapy may not directly contribute to functional connectivity involving the anterior-medial orbitofrontal cortex in OCD.

Thalamus. The thalamus is a critical structure in CSTC circuitries due to its vast connections with the striatum and the cortex. Projections from the cerebellum to the thalamus can be largely divided into two streams – one via the central thalamus and the other via the motor thalamus that involves the ventral lateral complex and the ventral posterolateral nucleus pars oralis. The central thalamus has been thought to be important in modulating motor preparatory activities and working memory processes. The central thalamus projects to the association cortices, premotor, supplementary motor area and pre-supplemental motor areas (Morel, Liu, Wannier, Jeanmonod, & Rouiller, 2005), hence, supporting its involvement in volitional activity. In terms of its involvement in higher cognition, innervations from the cerebellum reach the central thalamus via the dentate nucleus and are

projected to association areas. These projections increase forebrain arousal via mechanisms of the ascending reticular activation system that provides the thalamic nuclei with cholinergic inputs (Groenewegen & Berendse, 1994; Prevosto & Sommer, 2013), hence mediating working memory functioning. The motor thalamus predominantly targets motor cortical regions such as the premotor cortex, medial intraparietal and posterior parietal cortex via the cerebellar dentate nucleus (Mushiake & Strick, 1993; Prevosto, Graf, & Ugolini, 2009; Prevosto & Sommer, 2013). In addition, virus-tracing studies indicated that neural inputs from many cortical regions (such as the prefrontal, medial frontal and posterior parietal regions) to the cerebellum via the pons also receive cerebello-thalamo-cortical inputs (Prevosto & Sommer, 2013; Ramnani, 2012; Strick, Dum, & Fiez, 2009). Taken together, the thalamus is important in transmitting anticipatory volitional motor activity, self-timed movements via the multiple paths of connectivity between the cerebellum, thalamus and various cortical regions, therefore also giving it important roles in modulating motor behaviours, mediating sub-cortical arousal and overall cortical activation levels (Prevosto & Sommer, 2013).

The current study observed reduced functional connectivity between the right cerebellar crus I and crus II with the thalamus in OCD samples relative to controls. Consistent with the functions of the thalamus in higher cognition aforementioned, the current study observed significant correlations of functional connectivity strength between the right cerebellar crus I and left thalamus with Stroop Index scores, and between the right cerebellar crus II and left thalamus with the accuracy rate of high-load conditions in the visual working memory task, only in controls but not OCD samples. Within OCD samples, only age of onset was significantly associated with functional connectivity strength between the right crus II and left thalamus. In addition, it can be observed that functional connectivity between the

cerebellum and the cortical-subcortical regions are generally reduced in OCD samples compared controls. These observations potentially support previous claims that the thalamus is critical in mediating overall sub-cortical and cortical arousal. It could therefore be speculated that reduced functional connectivity involving the thalamus had contributed to overall reduced functional connectivity between the cerebellum and other cortical-subcortical regions in OCD samples and controls, leading to an imbalance in direct and indirect circuitries.

Lastly, demographic variables such as age and sex can potentially influence neural connectivity. To this extent, we conducted additional analyses to evaluate group differences in neural connectivity when age and sex were modeled as covariates of no interest. Findings observed were similar as the results that were reported and presented in the current chapter (refer to Table 7-2 for the reported results). Compared to controls, patients with OCD showed predominantly reduced connectivity between cerebellar lobules to the rest of the brain and increased cerebellar connectivity with the insula and orbitofrontal cortex. Findings are presented in the supplementary material (Supplementary Appendix S-Table 7-4).

Verifying the involvement of cerebellum in the CSTC, and specificity of these findings to OCD

Study 4B observed altered functional connectivity between cerebellar ROIs and clusters in the CSTC, such as the anterior-medial orbitofrontal, anterior cingulate, and thalamus (Table 7-2). To verify altered cerebellar involvement in the CSTC in the disorder, follow-up ROIs-to-voxel functional connectivity analyses were conducted to evaluate if altered functional connectivity with the cerebellum were observed when CSTC regions were defined as source ROIs, with age and sex as covariates of no interest. If the cerebellum is indeed involved in OCD pathophysiology, then we expected to observe altered functional

connectivity between CSTC ROIs and subregions of the cerebellum in OCD samples compared to controls. CSTC ROIs were selected based on their involvement in the leading neural model (Rauch et al., 1994), and extracted using the AAL2 toolbox via MRIcron. The ROIs included the left and right orbitofrontal subdivisions (lateral, anterior, medial, and posterior orbitofrontal regions), anterior cingulate, thalamus, caudate nucleus, and putamen. Correlational analyses were also conducted to evaluate associations between Fisher Z values extracted from clusters that showed significant group differences in CSTC-cerebellar functional connectivity and clinical indices such as Y-BOCS Total, Y-BOCS Obsessions, Y-BOCS Compulsions, OCI-R, and HDRS, within each patient, control, and combined group.

Results from the follow-up analyses appear to support altered cerebellar involvement in the CSTC circuitry in OCD. Altered functional connectivity were observed between several ROIs and cerebellar clusters in patients with OCD compared to controls (Supplementary Appendix: S-Table 7-5, S-Figure 7-4); complete results of altered functional connectivity between CSTC ROI-to voxel analyses are presented in Supplementary Appendix S-Figure 7-5. Compared to controls, patients with OCD showed reduced functional connectivity involving cerebellar clusters with ROIs in the right posterior orbitofrontal, right anterior cingulate, and bilateral thalamus regions, and increased functional connectivity with the right lateral orbitofrontal cortex (S-Table 7-5, S-Figure 7-4). Interestingly, prominent reduced functional connectivity was observed between bilateral thalamus and the cerebellum in OCD samples compared to controls (S-Table 7-5). Cerebellar efferents projected to the thalamus via the superior cerebellar peduncle communicate with the rest of the cerebral cortex via the cerebello-thalamo-cortical loop (Baumann et al., 2015; Ramnani, 2006; Palesi et al., 2017). In addition, considering that the thalamus is central to the CSTC, altered functional connectivity with the cerebellum could potentially disrupt the thalamus in

modulating motor preparatory activities, working memory processes, and mediating overall sub-cortical and cortical arousal (Prevosto & Sommer, 2013).

There were no significant correlations of functional connectivity between CSTC ROIs and cerebellar clusters with all clinical indices (Y-BOCS Total, Y-BOCS Obsessions, Y-BOCS Compulsions, OCI-R, and HDRS) within each control and patient group. However, when analysed as a single group (controls and patients combined), OCI-R was significantly correlated with all altered functional connectivity between CSTC ROIs and cerebellar clusters – between the right lateral orbitofrontal ROI and brainstem extending to the vermis I-II, right posterior orbitofrontal ROI and anterior cingulate ROI with cerebellar vermis IV-IV, and left and right thalamus ROIs with cerebellar VI. Out of these 5 CSTC ROIs, HDRS was also significantly associated with functional connectivity between the right lateral orbitofrontal ROI and vermis I-II, and between left thalamus ROI and right lobule VI. (Supplementary Appendix S-Table 7-6). These findings indicate some specificity of altered functional connectivity involving the cerebellum and CSTC to OCD symptoms.

Next, we conducted hierarchical regression analyses to evaluate whether variance in the functional connectivity strengths between CSTC ROIs and cerebellar regions could be significantly explained by the OCI-R or HDRS, and whether the variance contributed by OCI-R or HDRS remains after Group (OCD / Control) status is added to the model. As functional connectivity strengths generated from CONN toolbox had already included age and sex as covariates, these demographic variables were not included in the hierarchical regression as predictors. We conducted the hierarchical regression with predictors in three blocks: HDRS in the first block, OCI-R in the 2nd block, and Group variable in the third block, on only 4 dependent variables (ROIs: Posterior orbitofrontal, right anterior cingulate, right thalamus, and left thalamus). Functional connectivity strength between right lateral

orbitofrontal and Vermis I-II regions were not evaluated in the hierarchical regression due to violation of homoscedasticity. Results are presented in S-Table 7-7 (Supplementary Appendix). OCI-R and HDRS were significant predictors for all four, and two dependent variables respectively when only HDRS and OCI-R were in the model. In addition, the OCI-R contributed additional variance over and above significant proportion of variance that was explained by the HDRS for functional connectivity strength of posterior orbitofrontal ROI, right anterior cingulate ROI, and cerebellar regions. However, these effects did not remain significant after the Group variable was added to the model that accounted for the largest proportions of variance. The findings suggest limited specificity of functional connectivity strengths between CSTC ROIs and cerebellar regions to OCD symptoms. In addition, it appears that the variance of the dependent variables specific to OCI-R and HDRS scores overlapped considerably with the Group variable, and that patient / control status accounted for the most variance, above and beyond HDRS and OCI-R scores. Lastly, as with the follow-up analyses for visual working memory (Chapter 6), not all functional connectivity indices (such as, between the right lateral orbitofrontal ROI and cerebellar vermis I-II) were able to be evaluated in the hierarchical regression due to violation of assumptions.

Taking all together, results from the follow-up analyses seem to support altered cerebellar involvement in the CSTC circuitry. However, altered functional connectivity between CSTC ROIs and the cerebellum showed some specificity to OCD symptoms (and for selected ROIs, to depressive symptoms), but this specificity diminished when Patient / Control status was included in the model.

Summary.

In general, results from Study 4A indicated altered intrinsic activations were observed in OCD samples compared to controls in major resting-state networks such the SMN, DMN,

SN and ECN. Results from Study 4B reported altered functional connectivity in OCD samples relative to controls between cerebellar ROIs-to-voxel, involving regions within and beyond the CSTC. Within the CSTC, OCD samples showed reduced functional connectivity between the cerebellum with cingulate and thalamus regions, but increased functional connectivity with the anterior-medial orbitofrontal regions. Beyond the CSTC, altered functional connectivity with the cerebellum were observed in other brain regions, such as the insula, postcentral gyrus, frontal and occipital regions. These findings were largely consistent with that observed in Study 4A. In addition, associations between functional connectivity strength and clinical indices demonstrated potential associations involving the age of onset, duration of illness, Y-BOCS severity scores, mean daily dosage for fluoxetine equivalents within OCD samples such as. In addition, associations were also observed within controls and OCD samples with cognitive indices such as trail-making index scores, stroop index, and performance on the visual working memory task. These associations between functional connectivity strength between cerebellar ROIs and clinical and cognitive indices within OCD samples contributes to the postulation of the involvement of the cerebellum in OCD pathophysiology. Follow-up analyses appeared to support cerebellar involvement in OCD, as indicated by altered functional connectivity between CSTC ROIs and cerebellar subdivisions in OCD samples compared to controls. Lastly, a key obstacle to elucidating connectivity relationships using resting-state activity lies in the difficulty in evaluating mental state without using a stimulus or probe (Sonuga-Barke & Castellanos, 2007; Wang, Ong, Patanaik, Zhou, & Chee, 2016). Tendencies such as increased vigilance or less relaxed states of the patient group may have possibly contributed to the reported group differences, even though most patients reported that they were able to rest in the scanner. Future studies may utilize

eye-tracking techniques during resting-state scanning to evaluate differences in spontaneous eyelid closures as proxy for vigilance (Wang et al., 2016).

CHAPTER 8: OVERALL SUMMARY AND DISCUSSION

Summary of background information

Inconsistent Neural Findings in CSTC

The CSTC model has been the leading model of OCD pathophysiology for the past 2 decades (Cavedini et al., 2006; Christian et al., 2008; Milad & Rauch, 2012), but existing reports of neural abnormalities within the CSTC circuitry have been somewhat inconsistent. Increasing reports indicate neural alterations in OCD beyond the CSTC, involving the cerebellum and parietal regions (Huyser et al., 2010; Page et al., 2009).

Inconsistent Findings in Neuropsychological Functioning in OCD

An abundance of studies evaluated neuropsychological functioning in OCD samples, especially in verbal and visual working memory, and in executive-function domains such as response inhibition, interference and set-shifting. However, existing reports on executive function/dysfunctions in OCD have appeared inconsistent, and some authors have attributed these to comorbid conditions in the patient samples (Basso et al., 2001; De Geus et al., 2007). In terms of memory-related tasks, OCD samples generally display poorer performances compared to controls in tasks that limit verbal mediation, such as tasks involving visuo-spatial processing (Olley et al., 2007; Purcell et al., 1998b). Deficits in memory-related tasks could also be understood in terms of the working memory explanation (Greisberg & McKay, 2003), where OCD samples tended to show reduced performances compared to controls in tasks that were high in executive functioning requirements, binding complexity and memory load. However, neuroimaging studies that evaluated working memory in OCD samples are limited. Existing studies that purportedly investigated working memory paradigms had often utilized the n-back task, which in effect also assesses executive functioning processes rather than working memory processes *per se*. In addition, to the best of our knowledge, no studies

have yet applied neuroimaging techniques to evaluate visual working memory functioning in OCD samples and controls.

Existing studies have evaluated cognitive control in OCD using task paradigms that measure response inhibition, interference and set-shifting. Even though there have been inconsistent findings in behavioural differences between OCD samples and controls (Page et al., 2009; Roth et al., 2007), motor inhibition (evaluated via a stop-signal task) has been proposed as a potential biomarker for OCD. This was based on a study conducted by Menzies and colleagues (2007) that showed delayed response inhibition and altered neural activations in both OCD samples and their relatives compared to controls who were non-concordant for OCD. However, this finding was not replicated by de Wit and colleagues (2012), and hence, questions the reliability of the response inhibition as a potential biomarker endophenotype.

The Problem With Comorbid Conditions In Patient Samples

OCD is highly comorbid with other disorders such as mood and anxiety disorders (LaSalle et al., 2004; Perugi et al., 1997; Tükel et al., 2002). Existing neural and neuropsychological evaluations in OCD often included patient samples with diverse comorbid conditions. Tükel and colleagues (2002) compared clinical symptoms in two groups of patients diagnosed with OCD: 46 patients with uncomplicated OCD, and 101 patients with comorbid conditions (40% had major depression, and the remaining with at least one comorbid Axis I disorder). Patients with comorbid conditions showed more severe depressive and anxiety levels, obsessive and compulsive symptoms (Tükel et al., 2002). Therefore, comorbid conditions potentially contribute to more severe obsessions and compulsions (Tükel et al., 2002), and increase complexity in results interpretation.

Inconsistent findings in the literature regarding impairments in executive function in OCD samples have also been potentially attributed to the presence of comorbid conditions

(Basso et al., 2001; De Geus et al., 2007). This was exemplified though a study that no longer observed performances deficits in executive function (Trail-Making Difference Index, Verbal Fluency) in patients with OCD relative to controls after taking into account existing depressive and schizotypal symptoms (Aycicegi et al., 2003). Indeed, the lack of significant group differences in the TMT difference index and Stroop indices in the current study appeared to be consistent with another study. Including only patients with OCD without comorbid conditions, De Geus and colleagues (2007) did not observe significant differences relative to controls in executive function as defined by the trail-making ratio index (TMT B divided by TMTA) (De Geus et al., 2007). Even though these findings were not within our expectations, these observations could potentially be attributed to the exclusion of participants with comorbid conditions in the current study. Therefore, comorbid conditions could potentially be relevant to the varying results reported in the field.

The cerebellum

The cerebellum was traditionally thought to be involved in mainly motor and coordination functions, but increasing studies indicate its involvement in higher-order cognition such as memory and language (Chen & Desmond, 2005; Lee et al., 2005; Rapoport et al., 2000; Yeganeh-Doost et al., 2011). The cerebellum has reciprocal connectivity to other cortical and sub-cortical functions that enable the diversity of functions (Ito, 2008; Kelly & Strick, 2003; Middleton & Strick, 2000a; Schmahmann & Pandya, 1989). However, in practice, several neuroimaging studies had completely excluded or only included a partial cerebellum during MRI acquisition for several reasons, such as in favour of faster acquisition or for more contiguous slices for the cerebrum. Within the neuroimaging field for OCD, existing studies have reported alterations in the cerebellum in terms of grey matter volume, functional activations during response inhibition, resting-state activity and functional

connectivity (Busatto et al., 2001; Hou et al., 2012; Zarei, 2011; Zhang et al., 2011).

However, to the best of our knowledge, no study has yet evaluated the cerebellum as a key region of interest. This is important, considering that increasing reports indicate the involvement of the cerebellum in OCD pathophysiology.

Intrinsic activity at resting-state

Existing studies that investigated local and ROI-based functional connectivity reported altered intrinsic activity in OCD in key nodes of several resting-state networks, such as the posterior cingulate cortex of the default mode network, insula of the salience network, and medial prefrontal region of the executive-control network (Jang et al., 2010; J. Posner et al., 2014; Stern et al., 2012). In addition to the three networks, the sensorimotor network could also be a potential network that is aberrant in OCD samples due to existing connectivity with the executive-control network (Menon, 2011) and postulation of dysfunctional sensory gating in patients with OCD (Rossi et al. 2005). Existing studies reported altered functional connectivity involving key anchors of the various resting-state networks. However, analytical techniques adopted in those studies did not enable evaluations of intrinsic activity of the resting-state networks. In addition, even though whole brain functional connectivity studies had also reported altered functional connectivity in cortical and sub-cortical regions, and in the cerebellum (Hou et al., 2014; Zhang et al., 2011), no study has yet specifically evaluated intrinsic functional connectivity between cerebellar ROIs with the rest of the cerebrum.

Summary of Study: Aims, Hypotheses, and Key Findings

The overarching aim of this thesis is to clarify the neural correlates involved in OCD. Study aims and hypotheses are presented in Figure 8-1, and key findings and conclusions for each study are summarized in Figure 8-2.

Figure 8-1. Overview of Studies, Aims, Hypotheses, and Methods.

Figure 8-2. Overall key findings and conclusions from the thesis.

Overall Discussion

CSTC circuitry in OCD

Findings from the current thesis appear to indicate some support for CSTC involvement in OCD. Results from resting-state functional connectivity analyses reported altered functional connectivity between cerebellar ROIs with regions of the CSTC, such as the cingulate gyrus, orbitofrontal cortex and the thalamus.

Cingulate gyrus. The current studies found alterations in several subdivisions of the cingulate. Relative to controls, patients with OCD demonstrated increased activations in the median-posterior cingulate region during inhibition in a Stop-signal task (Study 3; Chapter 6). As discussed in Chapter 6, the posterior cingulate is considered part of the default-mode network, and is generally expected to be deactivated during tasks where attention is externally directed (Buckner et al.; Gusnard et al., 2001; Raichle et al., 2001; Shulman et al., 1997). On further evaluations of the cingulate cluster, it was observed that increased activations in the median-posterior in OCD samples relative to controls were driven by negative parameter estimates as demonstrated in the controls sample (S-Figure 6-2). We speculated in Chapter 6 that increased activations observed in the median-posterior cingulate in OCD samples could potentially indicate failure in deactivations during executive control (inhibition – defined as the contrast of Stop-Go), and that failure to deactivate during executive control could potentially indicate some abnormal control of the default mode network (Spreng & Schacter, 2011) and the salience network (Bonnelle et al., 2012). In addition, the dorsal posterior cingulate region has connections to the frontal regions and is also involved in controlling attentional focus, possibly by influencing the meta-stability of the brain, with increased activity indicating greater fluctuations in network shifts with reduced

synchrony (Leech & Sharp, 2014). Increased activity in the posterior cingulate could potentially indicate underlying task-induced compensatory mechanisms in OCD samples. Considering that failure in deactivating the middle-posterior cingulate appropriately is indicative of network fluctuations with reduced synchrony, we initially postulated that OCD samples would show altered network activity at least in the DMN, ECN, and SN. This postulation appeared to be supported by ICA analyses conducted in Study 4a that demonstrated altered activity in the resting-state networks in OCD samples relative to controls.

Results from Study 4a had indicated altered intrinsic activity involving the anterior and median-posterior cingulate regions; results from Study 4b observed reduced functional connectivity between the anterior cerebellum (lobules I-V) and the anterior-cingulate regions; and between cerebellar Crus I and II with more middle and middle-posterior regions of the cingulate cortex in OCD samples relative to controls. These results appear to suggest a dysfunctional error monitoring system (subserved by the anterior cingulate), and ineffective response-outcome tracking (altered middle to posterior cingulate functioning) where responses and decisions undertaken had failed to satisfy the temporary need (Botvinick, 2012; Kolling et al., 2012). Therefore, taking these together, it appears that altered cingulate activity could potentially contribute to the maintenance of the repetitive cycle of obsessions and compulsions as observed in patients with OCD.

Orbitofrontal cortex. Even though the orbitofrontal cortex is traditionally implicated in the pathophysiology of OCD, the current study did not observe significant alterations in the orbitofrontal regions in terms of grey matter volumes and functional activations during verbal and visual working memory and response inhibition tasks.

However, increased intrinsic functional connectivity between cerebellar Crus II and anterior-medial orbital gyrus were observed in patients with OCD compared to controls. Past research had postulated the role of the anterior orbitofrontal area in tracking information related to reinforcers, such as complex or abstract reinforcers that involve money (Kringelbach & Rolls, 2004), and the medial orbitofrontal cortex in learning, monitoring and decoding representations of reward-value information (Kringelbach & Rolls, 2003; Pauls et al., 2014). Therefore, alterations involving the anterior-medial orbital gyrus coupled with that of the anterior and median-posterior cingulate in OCD samples could potentially contribute to ineffective response-outcome tracking and reward-value representations that manifest in symptoms of intrusive and recurrent obsessions and compulsions in patients with OCD.

Subcortical regions: Caudate Nucleus, Putamen, Thalamus. Results obtained from Study 2 (VBM analyses) and Study 3 (task-related fMRI) did not show significant group differences in terms of grey matter volumes and task-related activity in the caudate nucleus, putamen, and thalamus. However, findings from Study 4a revealed altered intrinsic activity involving these sub-cortical regions. In addition, results from Study 4b showed reduced functional connectivity between the cerebellum Crus I and thalamus. The caudate has been thought to be important in action selection during goal-directed behaviours (Brovelli et al., 2011; de Wit, Watson et al., 2012); and the putamen has specific role in habit learning (de Wit, Watson et al., 2012; Grahn et al., 2008; Tricomi et al., 2009). The involvement of altered intrinsic activity of the putamen and caudate nucleus in OCD samples could then be postulated to contribute to impaired ability to effectively override learned actions, resulting in manifestations of OCD symptomatology. The thalamus has important roles in transmitting anticipatory volitional motor activity, self-timed movements via the multiple paths of

connectivity between the cerebellum, thalamus and various cortical regions, therefore also giving it important roles in modulating motor behaviours, mediating sub-cortical arousal and overall cortical activation levels (Prevosto & Sommer, 2013). It can also be observed that functional connectivity between the cerebellum and the cortical-subcortical regions are generally reduced in OCD samples compared controls. These observations potentially support previous claims that the thalamus is critical in mediating overall sub-cortical and cortical arousal. It could therefore be speculated that reduced functional connectivity involving the thalamus had contributed to overall reduced functional connectivity between the cerebellum and other cortical-subcortical regions in OCD samples and controls, leading to an imbalance in direct and indirect circuitries. Lastly, we present a speculation that obsessions and compulsions observed in OCD samples represent compensatory efforts to counter the overall reduced cortical-subcortical functional connectivity, similar to that observed in children and adults with attention-deficit hyperactivity disorder (ADHD) where reduced functional connectivity of fronto-striatal networks were observed (Cubillo et al., 2010).

Altered Salience-Processing Network

Results from the thesis have consistently suggested the involvement of an altered salience-processing network in OCD samples. Compared to controls, OCD samples showed reduced grey matter volume in the insula using VBM methodology (Study 2; Chapter 5) and altered intrinsic activity in an ICA analyses (Study 4a; Chapter 7). The insula is an important hub of the SN that is critical in detecting, identifying and integrating different forms of salience, such as pain, emotion, reward and interoceptive autonomic processing (Seeley et al., 2007), and is key in regulating salience detection and dynamic control by appropriately

engaging and disengaging the ECN and DMN (Menon & Uddin, 2010; Seeley et al., 2007). Consistent with the understanding of the functions of the insula and the SN, existing studies demonstrated altered functional connectivity in OCD samples relative to controls involving the insula with other regions such as the posterior cingulate and anteromedial prefrontal cortex (key anchors of the DMN), and the dorsolateral prefrontal regions (key anchors of the ECN) (Peng, Xu, et al., 2014; Stern et al., 2012). Altered functional connectivity involving the insula could then be speculated to contribute to OCD symptoms via dysfunctional assignment of saliency to external stimuli or internal mental stimuli, and inappropriate engagement and disengagement of the ECN and DMN. In addition, the ECN is also connected to functions of the SMN (Menon, 2011). Considering that the ECN exerts appropriate control over sensorimotor representations until appropriate behavioural responses are selected (Menon, 2011), altered activity of the ECN could potentially contribute to deficits in such control, with effects manifested as intrusive obsessions and compulsions as observed in the disorder.

The Insula

The current results involving the insula have been discussed in terms of its overall structure without paying attention to its subdivisions. Past studies that attempted to perform parcellations of the insula had yielded varying components (Cauda et al., 2012; Cloutman, Binney, Drakesmith, Parker, & Ralph, 2012; Kurth, Zilles, Fox, Laird, & Eickhoff, 2010). The most convergent parcellation that was consistently produced via multiple approaches such as functional connectivity and meta-analyses had identified three subregions within the insula cortex: posterior, dorsal anterior and ventral anterior (Chang, Yarkoni, Khaw & Sanfey, 2013; Mutschler et al., 2009). The posterior insula is functionally connected to the

supplementary motor area, the dorsal anterior insula to the anterior cingulate cortex and dorsolateral prefrontal regions, and the ventral anterior insula to the amygdala, and posteriorlateral orbitofrontal regions (Chang et al., 2013).

The sub-region mask of the insula derived by Chang and colleagues (2013) is available for viewing and download on Neurovault.org (<https://neurovault.org/collections/13/>). Based on this parcellation mask, results from the current study demonstrated involvement of altered posterior and dorso-anterior insula. Specifically, reduced grey matter volume of the insula in Study 2 (Chapter 5) and reduced functional connectivity between right cerebellar Crus I and the right insula in Study 4b (Chapter 7) observed in OCD samples relative to controls had implicated the posterior insula; and results from ICA analyses in Study 4a that demonstrated reduced intrinsic activity of the insula within the SN components in OCD samples relative to controls had corresponded to the dorsal anterior insula. The dorsal anterior insula is implicated in functions related to cognitive control (Dosenbach et al., 2006; Droutman, Bechara, & Read, 2015), and has been reported to be activated in goal-directed tasks and tasks that involve sustained attention, monitoring of goals, and modulation of arousal levels (Chang et al., 2013; Dosenbach et al., 2006; Nelson et al., 2010). The posterior insula has key functions in sensorimotor processing (Craig, 2002; Wager et al., 2004), and also appears to be a convergence zone for sensory information, exteroceptive information, and interoceptive information (Craig, 2002, 2003). Interoception can be understood as the signaling/perception of bodily states and sensations, and is particularly relevant in the maintenance of bodily homeostasis (Namkung, Kim, & Sawa, 2017). A posterior-anterior progression of interoception has been proposed to speculate how interoceptive signals are experienced consciously (Craig, 2009). Specifically,

interoceptive signals first arrive at the posterior insula where lower-level sensory features are first processed. Processed interoceptive signals are then passed to the anterior insula, where these signals integrate with emotional, cognitive and motivational representations contributed from the connecting regions, such as the amygdala, anterior cingulate cortex, dorsolateral prefrontal and the striatum, enabling conscious perception of interoceptive information (Craig, 2009; Namkung et al., 2017). Taking these into the context of the symptomatology of OCD, altered functioning of the insula contributed to dysfunctional perception of interoceptive information, and hence inappropriately directing attention (processed by the dorsal anterior insula) in identifying salient stimuli that could include somatosensory and interoceptive signals (processed by the posterior insula) (Namkung et al., 2017), contributing to intrusive obsessions and “not just right experience” error signals (Coles et al., 2003).

Dysfunctional Sensory Gating

Drawing relevance to dysfunctions of the SMN, a postulation of dysfunctional sensory gating in OCD have also been proposed. According to this proposal, excessive excitation of sensorimotor regions and reduced inhibitory functions of the frontal regions in OCD impair the capacity to suppress repetitive behaviours and intrusive thoughts, and modulate sensory inputs during movements (Rossi et al. 2005), leading to repetitive compulsions and obsessions. Even though the current study did not adopt symptom provocation paradigms to evaluate the plausibility of this theory, results from study 4a appear to indicate some support to this theory. Specifically, increased intrinsic activity of the bilateral postcentral gyrus and reduced activity in the precentral and supplementary motor area within the SMN, and overall reduced intrinsic activity were observed in the frontal regions within the ECN in OCD samples relative to controls. The postcentral gyrus is the site

of the primary somatosensory cortex, and is key in perceiving pain, touch, and other bodily sensations (Hyvarinen & Poranen, 1978; Iwamura & Tanaka, 1978; Nelson & Chen, 2008). The precentral region and supplementary motor areas are involved in the execution of voluntary actions, and control of movements that are internally generated and sequences of movements, respectively (Roland, Larsen, et al., 1980; Roland, Skinhoj et al., 1980).

Alterations involving the postcentral gyrus have been reported across analyses. Results from structural VBM analyses (Study 2; Chapter 5) revealed increased GMV in bilateral postcentral gyrus in patients with OCD compared to controls, and Study 4a reported increased intrinsic activity in the postcentral gyrus. According to the dysfunctional sensory gating hypothesis, increased intrinsic activity in the postcentral gyrus could potentially increase sensitivity to somatosensory inputs, coupled with altered activity in the frontal regions including the precentral and supplementary motor area that contributed to reduced control over internally generated movements and in suppressing repetitive behaviours and thoughts (Gonçalves et al., 2017; Nebel et al., 2014). Interestingly, Study 4b reported significant associations between functional connectivity strength between left Crus II and left postcentral gyrus with Y-BOCS Total, Y-BOCS Compulsions severity scores, and lower mean daily dosage of fluoxetine equivalents. These findings though only correlational had indicated potential implications on symptom severity.

In addition, findings from Study 2 and 4b indicated the involvement of altered posterior insula grey matter volume and functional connectivity in individuals with OCD. The posterior insula has been shown to be functionally connected to the somatosensory cortex, and is involved in sensorimotor processing. Altered posterior insula in OCD samples therefore potentially converge with the postulation of altered sensorimotor processing in

individuals with OCD. These findings taken together seemed to indicate some support for a dysfunctional sensorimotor motor processing and perhaps sensory gating system in OCD pathophysiology, where altered inhibitory functions of the frontal regions influenced the capacity to suppress excessive excitation of intrusive thoughts and repetitive behaviours, potentially leading to the manifestation of symptoms observed in patients with OCD.

Neuropsychology

Findings from the current thesis demonstrated poorer performances in OCD samples compared to controls in Trail-Making B and Symbol Span tests. However, no significant group differences were showed in the Trail-Making Index (B-A). The Trail-Making Index was computed to assess the relative performance for Trail-Making B independent of motor speed, visual scanning speed and stimulus complexity, and was thought to be a purer indicator of “executive control” abilities (Aronowitz, 1994; Lezak et al., 2012; Sanchez-Cubillo et al., 2009; Schmidtke et al., 1998). Based on the existing literature and our findings, it appears that executive control in terms of set-shifting abilities, interference, and cognitive control may not be impaired in the current sample of OCD patients. Significant group differences observed within TMT-A and TMT-B components but not their difference scores could potentially indicate an underlying systematic difficulty, perhaps involving motor control, visual scanning/perception, that gets cancelled out when differences indices were computed.

This postulation appears potentially plausible in light of the findings obtained in the current thesis. In terms of motor control, the current thesis observed altered activity in the precentral and supplementary motor areas, which are key areas involved in execution and control of voluntary actions (Roland, Larsen et al., 1980; Roland, Skinhoj et al., 1980).

Therefore, poorer Trail-Making Test (Trail-Making A and B) but not Index scores in OCD samples potentially indicate altered motor control processes, including gaze control and visual scanning.

It is also important to reiterate key findings of previous major meta-analytic investigations of neuropsychological performance in OCD. These findings were first discussed in Chapter 4. In general, meta-analytic investigations of cognitive dysfunction in OCD samples reported a wide-range of cognitive deficits such as visuospatial memory, executive function and verbal fluency in OCD patients, but the impairments were generally not large. The largest effect size was observed for tasks that measured visuospatial memory, followed by moderate effect sizes for executive function tasks (interference, set-shifting, and planning). Another meta-analysis had also reported medium effect sizes for visual memory and cognitive flexibility (Abramovitch et al., 2013). Taking these findings into consideration, it appears consistent that findings from Chapter 4 reported medium-to-large effect size for Symbol Span test. Interestingly, findings from Chapter 7 had also observed associations of functional connectivity strength between right cerebellar lobule V with the right superior frontal gyrus and right superior parietal lobule with Symbol Span performances within OCD samples, and that GMV of the right insula within OCD samples were also associated with Symbol Span scores (Chapter 5; Study 2).

Associations involving Medications Dosages and/or Duration of Pharmacotherapy

Findings from the current thesis reported several associations with medication dosages and/or duration of pharmacotherapy. Findings from Chapter 7 (Study 4b) reported increased negative associations between functional connectivity strength between left cerebellar lobule V and right middle occipital gyrus; and between left crus II and left

postcentral gyrus with mean daily dosage of fluoxetine equivalents. Duration of pharmacotherapy were significantly associated with duration of illness (Chapter 4) and with parameter estimates extracted from a fusiform gyrus cluster (during the visual working memory task; Chapter 6), and these correlations remained after effects of age were partial out. However, it is noted that associations observed in this study were only associations at best and we were not able to directly imply neural changes as consequences of medication-related factors. Existing studies that evaluated neural effects of selective serotonin reuptake inhibitors (SSRI) with neural changes have indeed reported associations of SSRI treatment with several neural changes, such as reduced activity in the fronto-subcortical regions (Han et al., 2011; Kang et al., 2003; Saxena et al., 2002), and decreased thalamic volumes (Jang et al., 2006).

Conclusion

This thesis adopts a systematic approach to evaluate neural alterations in OCD pathophysiology. Findings observed in the current study do not negate the involvement of altered functioning of the CSTC in OCD, but other findings obtained from the thesis are also noteworthy. In addition to the anterior cingulate that has been often implicated in the pathophysiology of OCD, the current thesis observed alterations involving other subdivisions of the cingulate cortex, such as the dorsal anterior and middle-posterior subdivisions. Findings of the current thesis also reported involvement of the insula in OCD pathophysiology, and this finding was consistent with observations of altered salience-processing network in OCD. Consistent with the connectivity patterns of the insula and the salience-processing network, altered intrinsic activity were also observed in other resting-state networks such as the executive control network, default mode network and the

sensorimotor network. Findings of the current thesis had also reported observations of altered activity in the postcentral gyrus and frontal regions that are involved in motor control, such as the precentral gyrus, and had postulated dysfunctional sensory gating processes in OCD samples that could potentially impair the capacity to suppress repetitive behaviours and intrusive thoughts and modulate sensory inputs appropriately during motor movements (Rossi et al. 2005).

Based on the findings, we speculated that altered cingulate activity contribute to dysfunctional error monitoring system coupled with ineffective response-outcome tracking in OCD samples. Response and decisions undertaken to counter the perceived error signals could have contributed to failure in satisfying the temporary need/urges, potentially contributing to experiences of “not just right” error signals (Coles et al., 2003) and intrusive obsessions. The insula is an important hub of the SN that is critical in detecting, identifying and integrating different forms of salience, such as pain, emotion, reward and interoceptive autonomic processing (Seeley et al., 2007), and is key in regulating salience detection and dynamic control by appropriately engaging and disengaging the ECN and DMN (Menon & Uddin, 2010; Seeley et al., 2007). We speculated that altered functioning of the insula contributed to dysfunctional perception of interoceptive information, and hence inappropriately directing attention (processed by the dorsal anterior insula) in identifying salient stimuli that could include somatosensory and interoceptive signals (processed by the posterior insula) (Namkung et al., 2017), that contributed to manifestations of OCD symptomatology.

Lastly, it was interesting that findings from the connectivity analyses indicated altered functional connectivity between various subregions of the cerebellum with the key regions,

such as the medial orbitofrontal area, thalamus, dorsolateral prefrontal regions, postcentral gyrus, and insula. In addition, the current thesis also reported altered grey matter volumes and functional activations in the cerebellum during working memory and response inhibition tasks. These findings provide strong support for cerebellar involvement in OCD pathophysiology.

Figure 8.3. This model represents a simplified model based on the literature and our study findings.

Black arrows indicate cortico-striato-thalamo-cortical (CSTC) circuitry. Green arrows indicate fronto-ponto-cerebellar pathway, linking frontal regions to the cerebellum. Grey solid arrows indicate cerebello-thalamo-cortical pathway. Grey dashed arrow indicates input pathway from the thalamus to insula. Orange arrows show the pathway of sensory information flow via the insula to eventual perceived interoception.

Figure 8.3 presents a simplified model based on our study findings and literature. Evaluations from the thesis consistently demonstrated alterations of the cerebellum in patients with OCD in terms of grey matter volume, executive-task related functional activations, and functional connectivity with other cortical and sub-cortical regions. The cerebellum communicates with the cortex via efferent cerebello-thalamo-cortical pathway (grey solid arrows) and afferent cortico-ponto-cerebellar pathway (green) (Baumann et al., 2015; Ramnani, 2006). The thalamus also sends innervations to the insula (Reynolds & Zahm, 2005), hence, forming connections between the cerebellum and insula. In terms of the insula, sensory information first converges at the posterior insula (Craig, 2002, 2003) and are subsequently passed to the dorsal anterior insula. The signals then integrate with cognitive and motivational representations from the connecting regions, such as the dorsolateral prefrontal cortex and the striatum, that enabled perception of interoception and modulating attention (Craig, 2009; Namkung et al., 2017). Lastly, the thalamus appears to be central to the model, with major contributions to motor output and higher cognition through pathways that project to the frontal and cortical regions.

The Role of the Cerebellum in OCD

Findings from the thesis consistently demonstrated altered cerebellar involvement in OCD. Increased grey matter volume was observed in the left crus II, and reduced grey matter volumes in the right cerebellar lobule VI, and left cerebellar lobule VIIIa that was also positively associated with Y-BOCS obsessions score in patients with OCD (Study 2). In terms of task-related fMRI (Study 3), reduced activations were observed in the right lobule VIIb during verbal working memory task, and the left lobule VI, vermis VIIIb and right crus II during visual working memory task, and increased activations in the right VIIb and VIIIa

during a stop-signal task in OCD samples compared to controls. We did not report any significant associations between parameter estimates of altered cerebellar clusters with behavioural and clinical indices. In terms of resting-state data (Study 4A), patients with OCD showed reduced intrinsic cerebellar activations within the default mode and salience networks, and generally reduced functional connectivity between cerebellar ROIs with other regions of the brain including key regions of the CSTC (Study 4B). Significant associations between cerebellar ROIs with clinical symptoms such as Y-BOCS scores and duration of illness were also observed within the OCD sample.

A Modulator: Universal Cerebellar Transform

One way to understand the role of the cerebellum in OCD is to derive insights from the theory of universal cerebellar transform (UCT). The notion of the UCT conveys the idea that highly organized brain areas influence the type of information that gets processed in that particular region (Schmahmann, 2000). Sub-regions of the cerebellum have specific roles in sensorimotor, motor, timing, affective, and higher cognitive processes (E et al., 2012; Stoodley & Schmahmann, 2009). According to the UCT, the cerebellum transforms information to which it has access, and modulates projections to subsequent target regions. In line with this explanation, connectivity studies showed support for the functional topographical organization of the cerebellum with evidence of connectivity between respective cerebellar sub-regions and key areas of the cerebral cortex where the projections originated (Buckner et al., 2011; O'reilly et al., 2009). Such patterns of connectivity were also somewhat observed in the findings derived from Study 4B, where for example, altered functional connectivity was observed between motor-related regions of the cerebellum (lobules I-V) and the dorsal anterior cingulate that is also involved in motor control functions.

Unlike damage to the cerebral cortex, damage to the cerebellum does not appear to result in complete loss of function such as aphasia and paralysis, but prominently degrades precision and efficiency in motor and cognitive processing such as disrupted abilities in constructing grammatical sentences, understanding metaphorical expressions, and efficient motor coordination in these contexts (Guell, Gabrieli, & Schmahmann, 2018; Guell, Hoche, & Schmahmann, 2015; Wiig & Secord, 1985). Extending the UCT theory to the role of the cerebellum in OCD, it is possible that the cerebellum is involved in the disorder by modulating interactions with multiple components of the cerebral cortex and brain networks, as is the view of cerebellar involvement in schizophrenia (Andreasen & Pierson, 2008). In addition, considering that information from the cerebral cortex are reciprocally connected to the cerebellum, any alterations involving the cortical, sub-cortical and cerebellar regions could also alter afferents to and efferents from the cerebellum, and thereby, having cascading effects.

Feedforward Controller

The cerebellum has been known to be critical in adaptive motor control that is made possible through its capabilities in learning and refining representations of the motor cortex and skeletomuscular system for efficient and successful movement execution (Luque, Garrido, Carrillo, D'Angelo, & Ros, 2014; Pisotta & Molinari, 2014). As a feedforward controller (Ito, 2013; Wolpert, Miall, & Kawato, 1998), the cerebellum generates predicted sensations based on motor commands generated by the motor cortex and compares the predicted sensations with actual incoming sensations that are carried via mossy fibers to granule cells and then to Purkinje cells (Ito, 2013). When predicted sensations are consistent with actual sensations, the action continues. However, when predicted sensations do not

match the actual sensations, error signals are generated via climbing fibers of the inferior olive that synapse via Purkinje cells or directly on the deep cerebellar nuclei (Chaumont et al., 2013; Ito, 2013; Wang et al., 2008), and innervations are projected back to the cortical and subcortical regions via the cerebello-thalamo-cortical circuitry that allow for quick learning and recalibration of the forward model (Morecraft et al., 2018). These feedforward and feedback loops enable cortico-cerebellar circuits to respond appropriately to erroneous experiences or stimuli (Luque et al., 2014).

According to this understanding and in the context of OCD, alterations of the cerebellum could then potentially lead to deficits in accessing or experiencing actual sensory experiences and proprioception sensory feedback, or erroneous representations of intended sensations that are required for the feedforward controller to perform comparisons with intended sensations. Alterations of the cerebellum could also potentially contribute to inefficient feedback innervations that are important for movement execution. Based on the discussions derived from the study, we postulated altered salience processing and dysfunctional sensory gating in OCD that involved the postcentral gyrus and insula regions. Altered interoception and experience of sensory information could potentially lead to errors in the controller accessing actual sensory experiences, leading to repetitive feedback innervations and recalibration efforts that manifest in recurrent compulsions that are observed in the disorder. In addition, findings of altered functional connectivity between cerebellar ROIs and various cortical and sub-cortical regions (Study 4B) may also potentially indicate some deficits in appropriate access/organization/engagement of the feedback loop that are important in helping the controller learn and perform appropriate motor control. These speculations remain to be investigated.

Clinical Studies

Out of five case reports of different patients who developed OCD symptoms following neural conditions that involved the cerebellum, only two had reported pure OCD symptoms in association with a right posterior cranial fossa meningioma (Takeuchi, Kato, & Kanemoto, 2017), and left cerebellar lesion due to an arachnoid cyst in the left posterior fossa (Tonna, Ottoni, Ossola, De Panfilis, & Marchesi, 2014). Remaining three studies reported development of OCD symptoms along with paranoid ideation in association to a cerebellum venous variant (Palma, Borja-Santos, Trancas, Klut, & Cardoso, 2012), autonomic motor activity that was associated to a right posterior fossa mass (Gonzalez & Philpot, 1998), and dysphasia with infarcts in the right superior peduncle and left basal ganglia (Ward, 1988). It is also interesting to note that neurological conditions were similar in the reports by Tonna et al. (2014) and Gonzalez et al. (1998) where both involved cerebellar displacements in the right posterior fossa, but clinical presentations of the patients were different (please refer to the above). These studies, to some extent indicate the possibility of a primary role of the cerebellum in OCD symptoms, where OCD symptoms develop due to alterations of the cerebellum, or that cerebellar masses in meningioma conditions could have compressed sub-cortical regions such as the basal ganglia and thalamus of the CSTC that contribute to OCD symptoms (Takeuchi et al., 2017). However, the specificity of cerebellar lesions/masses to OCD symptoms is in question, considering that other conditions in addition to OCD symptoms develop following alterations to the cerebellum.

In Conclusion

The cerebellum is an important structure in OCD and deserves greater attention. It is the view of the current thesis that the role of the cerebellum in OCD is unlikely primary,

where dysfunctions in localized areas contribute to OCD symptoms. Rather, we believe that the cerebellum is involved in the pathophysiology of the disorder through modulating interactions with cortical and sub-cortical structures via the cerebello-thalamo-cortical and fronto-ponto-cerebellar pathways. Based on the findings of the current study, limited associations between clinical indices with cerebellar grey matter volumes and task-related functional activations, as well as the diversity of neural findings observed in the current study also potentially support the view of the modulatory role of the cerebellum in the disorder.

A Note on the Specificity of Current Findings

This study adopted a systematic and multi-modality approach to investigate neural correlates of OCD. However, whether these findings are specific to the OCD pathology remains to be directly investigated using machine learning methodologies or pattern analysis on a large sample with various psychiatric conditions. Nevertheless, the current study has attempted to evaluate the specificity of the findings to OCD diagnosis.

Study 3 reported poorer accuracy rate in the high-load condition of the visual working memory task with reduced activations in the right fusiform gyrus, left cerebellar lobule VI, right crus II, and vermis VIIIb in patients with OCD compared to controls. Considering that depressive symptoms are prevalent in OCD patients, follow-up analyses were conducted to explore the specificity of observed findings to OCD pathophysiology, by taking distress scores associated with obsessive-compulsive tendencies (OCI-R) as proxy to OCD symptoms. All group differences in neural parameter estimates but not accuracy of high-load condition in the visual working memory task remained significant when depressive severity (HDRS) and OCI-R scores were included as covariates. Follow-up hierarchical regression approaches performed for vermis VIIIb and left lobule VI showed further support for lack of

specificity of the two investigated parameter estimates to OCI-R, with Group status explaining for the greatest amount of variance in the two parameter estimates, over and above other predictors of age, sex, HDRS and OCI-R scores. Results therefore indicated a general lack of specificity of behavioural and neural findings to OCD symptoms as defined by the OCI-R, although we do note that hierarchical regression analysis was not conducted for the other dependent variables such as visual working memory and parameter estimates for right fusiform gyrus and right Crus II due to homoscedasticity assumption violations.

An additional effort to investigate specificity of the findings to OCD pathophysiology occurred in Study 4B. Study 4B observed altered functional connectivity between cerebellar ROIs and clusters in the CSTC, such as the anterior-medial orbitofrontal, anterior cingulate, and thalamus (Table 7-2). In order to ascertain cerebellar involvement within the leading CSTC network, follow-up functional connectivity analyses were conducted to evaluate whether altered functional connectivity occurred in the cerebellum when source ROIs were defined in regions of the CSTC, with age and sex as covariates of no interest. We observed reduced functional connectivity involving cerebellar clusters with CSTC ROIs in the right posterior orbitofrontal, right anterior cingulate, and bilateral thalamus regions, and increased functional connectivity with the right lateral orbitofrontal cortex (S-Table 7-5, S-Figure 7-4), and all were significantly correlated with OCI-R. Follow-up hierarchical regression analyses demonstrated that even though altered functional connectivity between CSTC ROIs and the cerebellum showed some specificity to OCD symptoms (and to depressive symptoms for posterior orbitofrontal and right anterior cingulate ROIs), this specificity diminished when Group variable was included in the model. Group status appear to account for most variance of functional connectivity strengths above and beyond HDRS and OCI-R scores. Taking all

together, we observed altered cerebellar involvement within the leading CSTC network in OCD samples. However, the status of being a control or a patient may account for substantial variance in parameter estimates for the visual working memory, and resting-state functional connectivity involving the CSTC regions and cerebellum. In addition, based on the observation from the follow-up analyses, it may be plausible to conclude, albeit prematurely, that altered functional connectivity may be more specific to OCD status than functional activations. However, further research is still required as limited variability in OCI-R scores, and plausibility of the OCI-R as a insufficient proxy to OCD symptoms may contribute to the lack of specificity in neural and behavioural findings to OCD, and present as challenges in deriving sound conclusions about disease specificity.

Follow-up analyses discussed above generally appear to indicate limited specificity of behavioural and neural findings to OCD status. Interestingly, emerging studies appear to postulate shared traits among psychiatric conditions. The ‘psychopathology’ factor (*p* factor) is analogous to the *g* factor in general intelligence, and attempts to unite all psychiatric disturbances, taking into account diagnoses, comorbidity conditions, persistence across time and symptom severity (Caspi et al., 2014; Caspi & Moffitt, 2018). A recent study evaluated support for a genetic *p* factor by investigating genetic correlations via principal component analysis on 7026 unrelated individuals (Selzam, Coleman, Caspi, Moffitt, & Plomin, 2018). Results showed strong support for a single genetic dimension across psychiatric conditions. OCD, along with other psychiatric conditions, such as schizophrenia, bipolar disorder and depression loaded positively on the genetic *p* factor (Selzam et al., 2018). A separate study first replicated the *p* factor in a sample of 1246 university students and applied neuroimaging methods to evaluate relevant neural correlates. Interestingly, higher *p* factor scores were only

found to be associated with reduced fractional anisotropy values of white matter pathways within the pons and reduced grey matter volume in the occipital region and left cerebellar lobule VIIb. Broadly speaking, these findings appear to indicate some shared characteristics among psychiatric disturbances that implicate the cerebro-cerebellar circuitries and may contribute to general liability to psychiatric disturbances.

Significance of this Study

Findings from this research study attempt to clarify neural involvement in OCD pathophysiology. It is hoped that findings from this study could serve as a platform for future research studies in terms of methodology and study findings. Lastly, findings from the current study laid a foundation of knowledge that could encourage follow-up studies to explore and refine suitable targets for non-invasive treatment approaches in OCD such as using transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (TDCS) methodologies.

Strengths and Limitations of the Current Thesis

There are several strengths to the research approaches adopted in this thesis. First, the thesis adopted a systematic approach to evaluate neural involvement in OCD pathophysiology. This involved first performing a meta-analysis to quantitatively consolidate neural alterations that were implicated in OCD (Study1). Findings obtained were used to guide several subsequent analyses. A multi-modality approach was adopted to evaluate neural alterations in OCD in terms of grey matter volumes, task-related functional activations and resting-state analyses. This series of evaluations enabled investigations of altered grey matter structure (Study 2) and neural differences when participants experience some cognitive load; participants perform working memory tasks and response inhibition tasks (Study 3). As

neural differences and demands vary according to the task at hand, resting-state data were also analyzed to evaluate neural differences without the influence of task (Study 4a, 4b). To further evaluate the involvement of the cerebellum in OCD pathophysiology, functional connectivity analyses were also performed to evaluate differences among regional functional connectivity strengths (Study 4b). The multi-modality approach enabled conclusions on the neural alterations in OCD to be discussed in several aspects, involving structure, function and connectivity. Secondly, this study adopted a strict recruitment criteria, where patients with comorbid conditions such as major depression were excluded. Past research have indicated that comorbid conditions confound study findings, hence making it challenging in understanding study findings. Even though this approach provides a valuable opportunity to observe neural alterations that are not confounded by the complexities of comorbid conditions, setting a strict recruitment criteria posed challenges to patients' recruitment. Even though the current study had anticipated these difficulties and had therefore expanded recruitment efforts to recruit patient from two sites, recruitment still proved to be challenging.

There are several limitations to this study. Firstly, due to the challenges in recruitment, the sample size obtained in the current study is considered small. Secondly, past literature had reported behavioural and neural differences in patients of different symptom subtypes (e.g. washing VS checking dimension) and symptom onset profiles (early VS late onsets). However, due to the pilot nature of this study, this study did not initially set out to evaluate neural differences among the various subtypes. Moreover, such approaches typically require a larger sample size, and are therefore, not feasible for the current study. Thirdly, past studies on OCD frequently had either recruited patients who are medication naïve or had patients stop their medications for a period prior to the scanning. However, due to ethical

considerations, the current study did not request patients to stop their medications for the research study. Instead, data on mean daily dosage were collected and were used to correlate with significant findings to evaluate the relationships between medication dosages (i.e. fluoxetine equivalents) and observations of neural alterations. Lastly, several analyses in the thesis had adopted non-corrected thresholds. We recognized that increasing studies have advocated for conservative thresholds to protect against false positive findings (Button et al., 2013; Cremers et al., 2017; Lieberman & Cunningham, 2009). However, reducing Type I errors inevitable also reduces power of the analysis, hence lowering the probability of identifying true findings when they are present. Most papers that recommended more stringent thresholds were based on simulation studies or studies with large sample sizes or had within-subject experiments (Cremers et al., 2017; Desmond & Glover, 2002). Such studies have enough power to reliably detect the involvement of large key regions, but are inherently different from most clinical studies. Clinical studies are typically considered to be of lower statistical power due to limited sample size, study effects and between-group analytic approaches. Therefore, conservative p values could potentially hinder important and interesting findings that deserve further evaluations and may not be suitable for studies that are explorative in nature (Cremers et al., 2017; Lieberman & Cunningham, 2009). In weighing on the consequences of committing Type I against Type II errors, some papers argued that findings reported due to Type I errors would fail to replicate in other individual studies anyway and are less likely to converge in meta-analyses (Cremers et al., 2017; Lieberman & Cunningham, 2009; Slotnick, 2017). However, findings that are not reported due to Type II errors would be lost as those were never reported in the first place. Therefore, there appears to be a need to achieve a balance on committing Type I and Type II errors. We

acknowledged that the current study may be underpowered with small sample sizes due to issues of practicality. Therefore, instead of employing whole-brain analyses, ROI approaches were adopted to increase power. In addition, significant findings were followed up with parameter estimates and alternative analyses where appropriate to verify that findings are not spurious. For the interest of the reader, we also presented results that were significant at corrected thresholds (Supplementary Appendix: S-Table 5-1, S-Table 6-4).

Future Directions

Further work may be necessary to replicate and validate the findings of the current study on a larger sample. Group-level analyses typically require large samples and corrections for multiple comparisons, and may therefore, obscure small differences (Kambeitz et al., 2017). Machine learning techniques offer systematic approaches for analyzing high-dimensional data based on multivariate patterns that are more sensitive to subtle neural alterations compared to group-level analyses (Bryan, 2016; Rathore, Habes, Iftikhar, Shacklett, & Davatzikos, 2017). Machine-learning algorithms typically require cross-validation to ascertain the generalizability of predictive models. However, cross-validation are most accurate in large sample sizes ($\pm 3\%$ error in predictive accuracy for a sample size of 1000) and predictive errors increase with small sample sizes ($\pm 15\%$ error in predictive accuracy for a sample size of 30) (Varoquaux, 2018). Therefore, the reliability of conclusions drawn from predictive models based on small sample sizes are limited due to large error bars (Varoquaux, 2018). Even though existing studies that employed machine-learning algorithms in OCD are limited with small sample sizes, reported findings are interesting and potentially important. Support vector machine (SVM) techniques applied on diffusion data based on 28 controls and 28 OCD patients revealed FA values in several

regions such as the bilateral prefrontal and temporal regions, splenium of the corpus callosum, and the left middle cingulum bundle to be most discriminating between controls and patients with OCD (Li et al., 2014); SVM and Gaussian process classifier (GPC) techniques employed on grey and white matter anatomy also demonstrated highest discriminative power in the cerebellum (cerebellum VIIb, VIII and Crus II), fronto-parietal circuit, and temporo-parieto-occipital junction, and mean diffusivity in cerebellar peduncles and cingulum between controls and OCD patients (Hu et al., 2016 – 33 controls and 33 OCD patients; Zhou et al., 2018 – 45 OCD controls and 45 OCD patients). Notably, some of these findings also concurred with altered grey matter volumes in the cerebellum as reported in Chapter 5 of the thesis, such as Crus II and cerebellum lobule VIII. These findings indicate promise in automatic machine learning techniques in identifying biomarkers of the disorder (Wolfers, Buitelaar, Beckmann, Franke, & Marquand, 2015), although replication on larger samples are needed. Future studies may adopt these automatic and objective pattern recognition approaches on multi-modality MRI data to identify ROIs or networks that are critical in classification accuracy.

Next, considering the challenges in evaluating mental states at resting-state, future studies could also employ eye-tracking techniques during resting-state scan to utilize eyelid closures as proxy for vigilance to ensure that group differences in connectivity were not produced due to differing states of vigilance.

In order to understand whether neural alterations are specific to OCD or shared among other psychiatric disorders, further analytic efforts could potentially apply machine learning techniques or pattern analysis on large and publicly available datasets such as those from Nathan Kline Institute and the Human Connectome Project. Alternatively, future studies

and analysis efforts could also benefit from including additional specific diagnostic groups for the purpose of results specificity. However, this approach has its challenges, as variables such as demographic characteristics within each group, variations in clinical severity, and comorbid conditions, amongst others, could complicate results interpretation. Therefore, to overcome these challenges, future efforts could consider evaluating disorders based on symptom dimensions.

Analysis based on symptom dimensions are also helpful in understanding various OCD subtypes. OCD subtype investigations are challenging as the symptomatology of patients with OCD seldom fall neatly into segregated categories. Therefore, a more viable approach could be to evaluate neural differences such as structural, functional and connectivity differences based on symptom dimensions instead of diagnoses (Mataix-Cols et al., 2005)

In terms of analytical approaches, future efforts could perform ICA approaches on task-related functional data to further probe network-related differences during task. Effective functional connectivity approaches could also be conducted to clarify the effect of task on the implicated network. These efforts could further contribute to refining potential targets for non-invasive treatment approaches in OCD.

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SUPPLEMENTARY APPENDICES

Appendix A: Ethics Approval Letters From DSRB and NTU-IRB

NHG DSRB Ref: **2013/01221**

24 February 2014

A/Prof Sim Kang
Department of General Psychiatry
Institute of Mental Health

Dear A/Prof Sim

NHG DOMAIN SPECIFIC REVIEW BOARD (DSRB) APPROVAL

STUDY TITLE: Clarifying the Neural Basis of Obsessive-Compulsive Disorder? A Combined Functional, Structural and Diffusion MRI study

We are pleased to inform you that the NHG Domain Specific Review Board has approved the application as titled above to be conducted in **Institute of Mental Health** and **National University Hospital**.

The approval period is from **24 February 2014** to **23 February 2015**. The NHG DSRB reference number for this study is **2013/01221**. Please use this reference number for all future correspondence.

The documents reviewed are:

- a) NHG DSRB Application Form: **Version No. 1**
- b) Informed Consent Form (Healthy Controls): **Version 2 dated 23 January 2014**
- c) Informed Consent Form (Patient): **Version 2 dated 23 January 2014**
- d) MRI Screening and Data Collection Form (Controls): **Version 1 dated 23 September 2013**
- e) MRI Screening and Data Collection Form (Patients): **Version 1 dated 23 September 2013**
- f) Advertisement for Recruitment of Healthy Controls: **Version 2 dated 23 January 2014**
- g) Advertisement for Recruitment of Patients: **Version 2 dated 23 January 2014**
- h) Instructions for Neuropsychological Tests: **Version 1 dated 13 February 2014**
- i) Table 1: Preliminary findings for VBM studies
- j) Hamilton Anxiety Rating Scale (HAM-A) (Copyright 1959)
- k) Hamilton Depression Rating Scale (HDRS) (Copyright 1960)
- l) Yale-Brown Obsessive Compulsive Scale (Y-BOCS) (Copyright 1986)
- m) The World Health Organization Quality of Life (WHOQOL) – BREF (Copyright 2004)
- n) Obsessive-Compulsive Inventory - Revised (OCI-R) (Copyright 2002)

Continued approval is conditional upon your compliance with the following requirements:

1. Only the approved Informed Consent Form should be used. It must be signed by each subject prior to initiation of any protocol procedures. In addition, each subject should be given a copy of the signed consent form.
2. No deviation from or changes to the study should be implemented without documented approval from the NHG DSRB, except where necessary to eliminate apparent immediate hazard(s) to the study subjects.
3. Any deviation from or changes to the study to eliminate an immediate hazard should be promptly reported to the NHG DSRB within seven calendar days.

4. Please note that for studies requiring Clinical Trial Certificate, apart from the approval from NHG DSRB, no deviation from, or changes of the Research Protocol and Informed Consent Form should be implemented without documented approval from the Health Sciences Authority unless otherwise advised by the Health Sciences Authority.
5. Please submit the following to the NHG DSRB:
- a. All Unanticipated Problems Involving Risk To Subjects Or Others (UPIRTSOs) must be reported to the NHG DSRB. All problems involving local deaths must be reported immediately within 24 hours after first knowledge by the Investigator, regardless of the causality and expectedness of the death. All other problems must be reported as soon as possible but not later than seven calendar days after first knowledge by the Investigator.
 - b. Report(s) on any new information that may adversely affect the safety of the subject or the conduct of the study.
 - c. NHG DSRB Study Status Report Form – this is to be submitted 4 to 6 weeks prior to expiry of the approval period. The study cannot continue beyond **23 February 2015** until approval is renewed by the NHG DSRB.
 - d. Study completion – this is to be submitted using the NHG DSRB Study Status Report Form within 4 to 6 weeks of study completion.
6. Established since May 2006, the NHG Research Quality Management (RQM) Program seeks to promote the responsible conduct of research in a research culture with high ethical standards, identify potential systemic weaknesses and make recommendations for continual improvement. Hence, this research study may be randomly selected for a review by the Research Quality Management (RQM) team. For more information, please visit www.research.nhg.com.sg.

Yours Sincerely

Dr Yip Chee Chew
Deputy Chairman
NHG Domain Specific Review Board A

Cc: Institutional Representative, IMH
c/o Research Division, IMH
Departmental Representative of General Psychiatry, IMH

Cc: Institutional Representative, NUH
c/o Research Office, NUH
Departmental Representative of Psychological Medicine, NUH

(This is an electronic-generated letter. No signature is required.)

Research Support Office

Reg. No. 200604393R

IRB-2013-11-010

28 January 2014

Associate Professor Chen Shen-Hsing Annabel
School of Humanities and Social Sciences

NTU INSTITUTIONAL REVIEW BOARD APPROVAL

Project Title: Clarifying the Neural Basis of Obsessive-Compulsive Disorder—A Combined Functional, Structural and Diffusion MRI study

I refer to your application for ethics approval with respect to the above project.

The Board has deliberated on your application and noted from your application that your research involves collecting brain scan through fMRI. Subjects will be interviewed and asked to perform some neuropsychological tasks.

You have also confirmed that informed consent will be obtained from the participants and you have guaranteed the confidentiality of your participants' biodata obtained from them.

The documents reviewed are:

- a) NTU IRB application form dated **16 January 2014**
- b) Participant information sheet and consent form: version 1 dated **16 January 2014**
- c) Data collection form: version 1 dated **16 January 2014**

The Board is therefore satisfied with the bioethical consideration for the project and approves the ethics application under **Full Board** review. The approval period is from **28 January 2014** to **31 October 2016**. The NTU IRB reference number for this study is **IRB-2013-11-010**. Please use this reference number for all future correspondence.

The following protocol and compliances are to be observed upon NTU IRB approval

1. All research involving procedures greater than minimal risk on minors (individuals who are less than the legal age of 21 years old) requires IRB approved written Parental Consent and assent from the participant to be obtained before any research protocols can be administered. Minimal risk refers to an anticipated level of harm and discomfort that is no greater than that ordinarily encountered in daily life, or during the performance of routine educational, physical, or psychological examination.
2. Only the approved Participants Information Sheet and Consent Form should be used. It must be signed by each subject prior to initiation of any protocol procedures. In addition, each subject should be given a copy of the signed consent form.

Research Support Office

3. No deviation from, or changes of, the protocol should be initiated without prior written NTU IRB approval of an appropriate amendment.
4. The Principal Investigator should report promptly to NTU IRB regarding:
 - a. Deviation from, or changes to the protocol.
 - b. Changes increasing the risk to the subjects and/or affecting significantly the conduct of the trial
 - c. All serious adverse events (SAEs) which are both serious and unexpected.
 - d. New information that may affect adversely the safety of the subjects of the conduct of the trial.
 - e. Completion of the study.
5. Continuing Review Request/ Notice of Study completion form should be submitted to NTU IRB for the following:
 - a. Annual review: Status of the study should be reported to the NTU IRB at least annually using the Continuing Review Request/ Notice of Study completion form.
 - b. Study completion or termination: Continuing Review Request/ Notice of Study completion form is to be submitted within 4 to 6 weeks of study completion or termination.

A handwritten signature in black ink, appearing to read "Lee Sing Kong".

Professor Lee Sing Kong,
Chair, NTU Institutional Review Board
encl.

cc Chair, School of Humanities and Social Sciences
Members, NTU Institutional Review Board

S-Table 3-1: Meta-analysis derived from contributing foci obtained from adolescent studies.

† FWHM Median of OCD<HC: 9.32 (10.00, 10.36). Chosen minimum cluster size: 248mm³

Cluster	Centered Cluster Regions	BA	Volume (mm ³)	Coordinates			Max ALE (x10 ⁻³)
				x	y	z	
<u>OCD>HC*</u>							
No contributing foci.							
<u>OCD<HC</u> [†]							
		BA	Volume (mm ³)	x	y	z	Max ALE (x10 ⁻³)
1	L Middle Frontal Gyrus	46	568	-48	26	20	10.72
2	L Middle Frontal Gyrus	9		-48	22	28	8.69

Note. Inclusion criteria for articles were similar to that of Study 1a. Citations of included studies for this meta-analysis: (Carmona et al., 2007; J. Chen, Silk, Seal, Dally, & Vance, 2013; Gilbert, Keshavan, et al., 2008; Lazaro et al., 2009)

*There were no contributing foci from adolescents for the OCD>HC contrast.

Carmona, S., Bassas, N., Rovira, M., Gisbert, J.D., Soliva, J.C., Prado, M., Tomas, J., Bulbena, A., Vilarroya, O., 2007. Pediatric OCD structural brain deficits in conflict monitoring circuits: a voxel-based morphometry study. *Neuroscience letters* 421, 218-223.

Chen, J., Silk, T., Seal, M., Dally, K., Vance, A., 2013. Widespread decreased grey and white matter in paediatric obsessive-compulsive disorder (OCD): a voxel-based morphometric MRI study. *Psychiatry Res* 213, 11-17.

Gilbert, A.R., Keshavan, M.S., Diwadkar, V., Nutche, J., Macmaster, F., Easter, P.C., Buhagiar, C.J., Rosenberg, D.R., 2008. Gray matter differences between pediatric obsessive-compulsive disorder patients and high-risk siblings: a preliminary voxel-based morphometry study. *Neuroscience letters* 435, 45-50.

Lazaro, L., Bargallo, N., Castro-Fornieles, J., Falcon, C., Andres, S., Calvo, R., Junque, C., 2009. Brain changes in children and adolescents with obsessive-compulsive disorder before and after treatment: a voxel-based morphometric MRI study. *Psychiatry Res* 172, 140-146.

S-Table 3-2: Meta-analysis derived from pooling foci obtained from adult and adolescent studies presented in Study 1a and S-Table 3-1, respectively.

* FWHM Median of OCD>HC: 9.08 (8.65, 9.24). Chosen minimum cluster size: 64mm³

† FWHM Median of OCD<HC: 9.32 (8.65, 10.36). Chosen minimum cluster size: 296mm³

Cluster	Centered Cluster Regions	BA	Volume (mm ³)	Coordinates			Max ALE (x10 ⁻³)
				x	y	z	
OCD>HC* [Contains only foci contributed from adults]							
12	R Frontal, Middle Frontal Gyrus	9	64	48	22	26	9.02
3	L Parietal, Postcentral Gyrus	5	120	-18	-36	74	9.83
7	L Parietal, Postcentral Gyrus	3	80	-66	-10	26	9.18
6	L Inferior Parietal Lobule (overlapping L inferior parietal lobule and L postcentral gyrus)	40	88	-36	-40	60	9.32
4	L Cingulate Gyrus	31	96	2	-28	40	8.82
10	R Insula	13	64	36	14	-12	8.31
2	R Putamen (overlapping R putamen, R caudate)		120	20	14	-8	9.91
5	L Putamen		88	-30	4	-6	9.68
9	L Putamen		64	-20	14	-12	9.38
1	L Cerebellum, Culmen		128	-12	-48	-12	10.21
8	R Thalamus		72	30	-28	-2	9.53
11	L Thalamus		64	-4	-24	12	8.69
OCD<HC†							
		BA	Volume (mm ³)	x	y	z	Max ALE (x10 ⁻³)
4	R Frontal, Sub-gyral	8	360	20	32	42	11.67
2	R Middle Frontal Gyrus	46	504	50	34	20	15.89
3	R Temporal, sub-gyral	20	464	48	-18	-28	16.19
1	R Insula	13	536	46	12	-6	16.50

Note. Even though we are cautious of neurodevelopmental changes in grey matter, the following results are presented to aid comparisons with previous meta-analyses (Radua & Mataix-Cols, 2009b; J.-Y. Rotge et al., 2009; Rotge et al., 2010). *As there were no contributing foci from adolescents for the OCD>HC contrast, results for OCD>HC were identical to that presented in Table 3-2 in the main text.

- Radua, J., Mataix-Cols, D., 2009. Voxel-wise meta-analysis of grey matter changes in obsessive-compulsive disorder. *The British journal of psychiatry : the journal of mental science* 195, 393-402.
- Rotge, J.-Y., Guehl, D., Dilharreguy, B., Tignol, J., Bioulac, B., Allard, M., Burbaud, P., Aouizerate, B., 2009. Meta-Analysis of Brain Volume Changes in Obsessive-Compulsive Disorder. *Biological psychiatry* 65, 75-83.
- Rotge, J.Y., Langbour, N., Guehl, D., Bioulac, B., Jaafari, N., Allard, M., Aouizerate, B., Burbaud, P., 2010. Gray matter alterations in obsessive-compulsive disorder: an anatomic likelihood estimation meta-analysis. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology* 35, 686-691.

S-Table 3-3. Re-analysis of meta-analysis conducted in Study 1a and 1b (Themes 1, 2, and 3) using GingerALE 2.3.6.

Study 1a: Meta-Analysis on grey matter

* FWHM Median of OCD>HC: 9.08 (8.65, 9.52). Chosen minimum cluster size: 416mm³

[†]FWHM Median of OCD<HC: 9.14 (8.65, 9.57). Chosen minimum cluster size: 576mm³

Cluster	Centered Cluster Regions	BA	Volume (mm ³)	Coordinates			Max ALE (x10 ⁻³)
				x	y	z	
<u>OCD>HC*</u>							
No significant clusters							
<u>OCD<HC[†]</u>							
No significant clusters							

Study 1b: Theme 1: Meta-Analysis on functional studies: Response inhibition (Go/No-go, Stop Signal Task)

* FWHM Median of OCD>HC: 9.76 (9.33, 10.00). Chosen minimum cluster size: 640mm³

[†]FWHM Median of OCD<HC: 9.76 (9.33, 10.00). Chosen minimum cluster size: 504mm³

Cluster	Centered Cluster Regions	BA	Volume (mm ³)	Coordinates			Max ALE (x10 ⁻³)
				x	y	z	
<u>Activations: OCD>HC*</u>							
No significant clusters							
<u>Activations: OCD<HC[†]</u>							
No significant clusters							

Study 1b: Theme 2: Meta-Analysis on functional studies: Interference (Stroop Task, MSIT)

* FWHM Median of OCD>HC: 9.57 (9.20, 10.00). Chosen minimum cluster size: 488mm³

[†]FWHM Median of OCD<HC: 9.57 (9.20, 10.00). Chosen minimum cluster size: 520mm³

Cluster	Centered Cluster Regions	BA	Volume (mm ³)	Coordinates			Max ALE (x10 ⁻³)
				x	y	z	
<u>Activations: OCD>HC*</u>							
No significant clusters							
<u>Activations: OCD<HC[†]</u>							
	R Caudate		688	12	-2	12	15.09

Study 1b: Theme 3: Meta-Analysis on functional studies: Switching and Shifting (Task Switching, Set Shifting)

* FWHM Median of OCD>HC: -

[†]FWHM Median of OCD<HC: 10.00 (9.33, 10.00). Chosen minimum cluster size: 464mm³

Cluster	Centered Cluster Regions	BA	Volume (mm ³)	Coordinates			Max ALE (x10 ⁻³)
				x	y	z	
<u>Activations: OCD>HC*</u>							
[Meta-analysis for OCD>HC was not conducted. Only 1 article reported increased activations in OCD VS HC. (Remijnse et al., 2013).]							
<u>Activations: OCD<HC[†]</u>							
No significant clusters							

Note. Coordinates are in standardized MNI stereotactic space. As with the meta-analyses in Tables 3-2 and 3-3, contributing foci were from adult studies only, and studies that utilized/reported ROI-only analyses were excluded.

S-Table 4-1: Descriptives of demographics and clinical indices with bootstrapped (bias-corrected with acceleration) 95% confidence intervals.

	Controls	OCD	χ^2	<i>df</i>	<i>p</i>				
Gender (Male:Female) (count)	9:8	10:11	0.11	1	.74				
	Controls (<i>n</i> =17)			OCD (<i>n</i> =21)			Mean Difference (Controls - OCD)	Bootstrap B.C. 95% C. I.	
	<i>Mdn</i>	<i>M</i>	<i>SD</i>	<i>Mdn</i>	<i>M</i>	<i>SD</i>		<i>Lower</i>	<i>Upper</i>
<u>Demographics</u>									
Age	27	26.12	1.01	28	28.62	6.89	-2.50	-6.35	1.09
Years of Education	14.5	15.24	0.52	15.0	14.96	2.24	0.27	-1.22	1.71
Handedness Index [^]	100	76.03	9.70	100	82.71	43.98	-6.68	-28.76	17.74
<u>Clinical Indices</u>									
HDRS*	2	2.65	0.46	4	5.52	4.61	-2.88	-5.27	-0.98
HAM-A*	2	2.47	0.39	7	7.33	5.90	-4.86	-7.47	-2.50
OCI-R*	3	3.47	0.83	21	25.10	17.40	-21.62	-29.78	-14.42
Age of Onset (years)	-	-	-	-	20.74	4.83	-	-	-
Duration of Illness (years)	-	-	-	-	7.88	6.56	-	-	-
Duration of Pharmacotherapy (years)	-	-	-	-	5.01	5.01	-	-	-
Y-BOCS (Total)	-	-	-	-	20.19	6.58	-	-	-
Y-BOCS (Obsessions)	-	-	-	-	10.00	3.54	-	-	-
Y-BOCS (Compulsions)	-	-	-	-	10.19	3.78	-	-	-

Note. Group differences were evaluated using bootstrapping procedures (1000 samples, stratified by controls/OCD, bias-corrected). [^]Handedness index is measured using Edinburgh's Handedness Questionnaire. HDRS = Hamilton Depressive Rating Scale. HAM-A = Hamilton Anxiety Rating Scale. OCI-R = Obsessive-Compulsive Inventory (Revised). Y-BOCS = Yale-Brown Obsessive Compulsive Scale. *n* = Sample size. *Mdn* = Median. *M* = Mean. *SD* = Standard deviation. B.C. = Bias-Corrected. C.I. = Confidence Interval.

* B.C. 95% C.I. does not include 0.

S-Table 4-2: Descriptives of neuropsychological tests with bootstrapped (bias-corrected with acceleration) 95% confidence intervals.

	Controls (n=17)			OCD (n=21)			Mean Difference (Controls - OCD)	Bootstrap B.C. 95% C. I.	
	<i>Mdn</i>	<i>M</i>	<i>SD</i>	<i>Mdn</i>	<i>M</i>	<i>SD</i>		<i>Lower</i>	<i>Upper</i>
<u>Verbal Working Memory</u>									
Digit Span Forward	11	11.12	1.90	10	10.67	1.83	0.45	-0.74	1.61
Digit Span Backward	11	10.29	1.90	9	10.05	1.99	0.25	-0.85	1.35
<u>Visual Working Memory</u>									
Symbol Span Total*	29	27.65	6.53	22	21.29	5.34	6.36	2.93	9.25
<u>Visuomotor Processing Speed & Set-Shifting</u>									
TMT-A (in seconds)	21	25.41	12.90	31	31.95	9.70	-6.54	-12.83	1.73
TMT-B (in seconds)*	41	47.88	17.71	64	65.19	17.66	-17.31	-29.54	-4.91
TMT-B - TMT-A	22	22.47	12.79	28	33.24	19.11	-10.77	-22.87	.83
<u>Inhibition</u>									
Stroop Word Condition (W)*	110	108.65	17.67	95	95.57	16.59	13.08	3.06	23.27
Stroop Colour Condition (C)*	82	80.53	15.34	73	71.62	11.32	8.91	1.08	17.59
Stroop CW Condition*	49	49.65	11.81	42	41.24	9.30	8.41	2.45	14.08
Stroop Index (CW-(C+W)/2)	-47	-44.94	14.03	-39	-42.36	11.49	-2.58	-11.12	5.26

Note. Group differences were evaluated using bootstrap procedures (1000 samples,

stratified by controls/OCD, bias-corrected). n = Sample size. Mdn = Median. M = Mean.

SD = Standard deviation. B.C. = Bias-Corrected. C.I. = confidence interval. TMT-A =

Trail-Making A. TMT-B = Trail-Making B. CW = Colour-Word. *B.C. 95% C.I. does not include 0.

S-Table 4-3: Spearman correlations between clinical and neurocognitive variables with effects of Pharmacotherapy Duration partial out.

	1	2	3	4	5	6	7
	ρ_s	ρ_s	ρ_s	ρ_s	ρ_s	ρ_s	ρ_s
TMT-A	.20	-.06	.31	-.22	-.08	.09	.09
TMT-B	.08	.15	.03	-.10	-.12	-.21	.19
Stroop Word Condition	-.05	-.11	-.50*	.26	.06	.00	.12
Stroop Colour-Word Condition	-.16	.10	-.22	.37	.03	.26	-.29
Symbol Span Test	-.18	.13	.23	-.26	-.07	.15	-.42
1 Y-BOCS Total	-	.68**	.32	.17	.54*	.34	.39
2 OCI-R	-	-	-.02	.33	.70**	.66**	.06
3 Age of Onset	-	-	-	-.34	.07	.00	-.16
4 Duration of Illness	-	-	-	-	.36	.42	.14
5 HDRS	-	-	-	-	-	.83***	-.06
6 HAM-A	-	-	-	-	-	-	-.15
7 Fluoxetine Equivalents	-	-	-	-	-	-	-

Note. Y-BOCS = Yale-Brown Obsessive Compulsive Scale. HDRS = Hamilton Depressive Rating Scale. HAM-A = Hamilton Anxiety Rating Scale. OCI-R = Obsessive-Compulsive Inventory (Revised). TMT-A = Trail-Making A. TMT-B = Trail-Making B. (* $p < .05$. ** $p < .01$. *** $p < .001$)

S-Table 4-4: Spearman correlations between clinical and neurocognitive variables with effects of Fluoxetine Equivalents partial out.

	1	2	3	4	5	6	7
	ρ_s	ρ_s	ρ_s	ρ_s	ρ_s	ρ_s	ρ_s
TMT-A	.25	-.07	.29	-.09	-.09	.07	.07
TMT-B	.01	.09	.05	.00	-.14	-.20	.12
Stroop Word Condition	-.12	-.04	-.46	-.03	.12	.06	-.22
Stroop Colour-Word Condition	-.08	.29	-.16	-.24	.17	.27	-.62**
Symbol Span Test	-.06	.28	.21	-.43	.01	.14	-.40
1 Y-BOCS Total	-	.65**	.41	.13	.58*	.42	.07
2 OCI-R	-	-	.02	-.04	.73***	.68**	-.32
3 Age of Onset	-	-	-	-.29	.09	-.01	-.10
4 Duration of Illness	-	-	-	-	.05	.19	.75***
5 HDRS	-	-	-	-	-	.83***	-.26
6 HAM-A	-	-	-	-	-	-	-.14
7 Pharmacotherapy Duration	-	-	-	-	-	-	-

Note. Y-BOCS = Yale-Brown Obsessive Compulsive Scale. HDRS = Hamilton Depressive Rating Scale. HAM-A = Hamilton Anxiety Rating Scale. OCI-R = Obsessive-Compulsive Inventory (Revised). TMT-A = Trail-Making A. TMT-B = Trail-Making B. (* $p < .05$. ** $p < .01$. *** $p < .001$)

S-Figure 4-1. Distributions of all measured variables. Values > 1.96 are indicated in red. Values > 2.58 are indicated in red and underlined.

S-Figure 4-1 (Cont'd). Distributions of all measured variables. Values > 1.96 are indicated in red. Values > 2.58 are indicated in red and underlined.

S-Figure 4-1 (Cont'd). Distributions of all measured variables. Values > 1.96 are indicated in red. Values > 2.58 are indicated in red and underlined.

S-Figure 4-1 (Cont'd). Distributions of all measured variables. Values > 1.96 are indicated in red. Values > 2.58 are indicated in red and underlined.

S-Table 5-1: Group differences from VBM analysis at $p < 0.01$ voxelwise and FWE < 0.05 .

	Hemisphere	k	x	y	z	T	Z
<u>Cerebral Grey Matter</u>							
<i>OCD < Controls</i>							
	no significant findings						
<i>OCD > Controls</i>							
	no significant findings						
	Hemisphere	k	x	y	z	T	Z
<u>Cerebellar Grey Matter</u>							
<i>OCD < Controls</i>							
Lobule VI	R	2081	11	-73	-14	4.62	4.00
Lobule VI	R		18	-69	-21	4.24	3.73
Lobule V	R		10	-64	-18	3.46	3.16
<i>OCD > HC</i>							
	no significant findings						

Note. Regions that showed significant differences within the specified masks. Results were thresholded at $p < .01$ (uncorrected) voxelwise and FWE < 0.05 clusterwise. No finding survived corrected thresholds of $p < .01$ (uncorrected) with FDR 0.05 clusterwise. Analysis voxel size: $1.5 \times 1.5 \times 1.5\text{mm}^3$ (non-cerebellar), $1 \times 1 \times 1\text{mm}^3$ (cerebellar). Coordinates are in MNI (non-cerebellar) and SUI (cerebellar) space. Age, sex and total intracranial volume were modeled as covariates of no interest. Results were based on 17 Controls, 21 OCD Patients. L = Left. R = Right.

S-Table 5-2: Group differences from VBM analysis via SnPM permutations.

	Hemisphere	k	x	y	z	T
<u>Cerebral Grey Matter</u>						
<i>OCD < Controls</i>						
	no significant findings					
<i>OCD > Controls</i>						
Postcentral gyrus	L	97	-60	-18	22	3.90
Postcentral gyrus	R	28	53	-13	35	3.73
	Hemisphere	k	x	y	z	T
<u>Cerebellar Grey Matter</u>						
<i>OCD < Controls</i>						
Lobule VI	R	78	11	-73	-14	3.85
Lobule VI	R		15	-70	-21	3.59
Lobule VIIa	L	13	-31	-37	-47	3.80
<i>OCD > HC</i>						
Crus II	L	32	-31	-62	-44	4.21

Note. Regions that showed differences in cerebral and cerebellar grey matter within the specified masks via SnPM with 10000 permutations without variance smoothing. Analysis voxel size: 1.5 x 1.5 x 1.5mm³ (non-cerebellar), 1 x 1 x 1mm³ (cerebellar). Coordinates are in MNI (non-cerebellar) and SUI (cerebellar) space. Age, sex and total intracranial volume were modeled as covariates of no interest. Results were thresholded at $p < .001$ (uncorrected) with $k > 10$. Results were based on 17 Controls, 21 OCD Patients. L = Left. R = Right.

S-Figure 5-1. Regions that showed differences in cerebral and cerebellar grey matter via SnPM with 10000 permutations without variance smoothing.

Age, sex and total intracranial volume were modeled as covariates of no interest. Results were thresholded at $p < .001$ (uncorrected) with $k \geq 10$. Reduced grey matter volume were observed in OCD compared to controls in (A): right cerebellar lobule VI; (B): left cerebellar lobule VIIIa. Increased grey matter were observed in OCD compared to controls in (C): left postcentral gyrus; (D): right postcentral gyrus; (E): left cerebellar crus II.

Results were based on 17 controls, 21 OCD Patients.

S-Table 6-1: Whole-brain results of peak coordinates of activations for controls and cases during the verbal working memory task.

	Hemisphere	k	x	y	z	T
Verbal Working Memory						
<i>Controls</i>						
Middle frontal gyrus	R	134	31.5	3.5	52.5	5.72
Precentral gyrus	R		35	0	45.5	5.40
Precentral gyrus	R		56	-3.5	38.5	4.34
Superior parietal gyrus	L	433	-24.5	-63	52.5	6.40
Middle occipital gyrus	L		-28	-66.5	35	5.86
Parietal lobe	L		-24.5	-42	42	5.61
Angular gyrus	R	93	31.5	-52.5	38.5	4.87
Inferior parietal gyrus, excluding supramarginal and angular gyri	R		28	-45.5	49	4.15
Supplementary motor area	L	3501	-7	3.5	59.5	9.50
Cerebellum, lobule VI	R		14	-59.5	-21	8.36
Calcarine fissure and surrounding cortex	L		-3.5	-84	7	8.01
<i>OCD</i>						
Middle frontal gyrus	R	52	31.5	3.5	52.5	4.8
Middle frontal gyrus	R	25	42	42	38.5	5.2
Precentral gyrus	L	572	-52.5	0	45.5	7.6
Precentral gyrus	L		-38.5	0	59.5	6.3
Insula	L		-31.5	21	0	5.2
Insula	R	79	31.5	21	7	5.6
Supplementary motor area	L	422	-3.5	3.5	59.5	11.4
Supplementary motor area	R		7	21	49	6.0
Middle cingulate & paracingulate gyri	R		7	24.5	38.5	5.3
Calcarine fissure and surrounding cortex	L		-17.5	-77	7	5.8
Calcarine fissure and surrounding cortex	R		10.5	-84	7	5.5
Inferior parietal gyrus, excluding supramarginal and angular gyri	L	181	-28	-56	52.5	5.2
Inferior parietal gyrus, excluding supramarginal and angular gyri	L		-28	-52.5	42	5.2
Inferior parietal gyrus, excluding supramarginal and angular gyri	L		-24.5	-66.5	42	4.7
Inferior parietal gyrus, excluding supramarginal and angular gyri	R	189	35	-49	45.5	6.1
Superior parietal gyrus	R		31.5	-59.5	56	5.7
Superior parietal gyrus	R		14	-63	52.5	3.8
Lenticular nucleus, Putamen	R		21	14	0	4.3
Putamen, overlapping with caudate and thalamus	L	46	-21	0	14	4.8
Lenticular nucleus, Putamen	L		-17.5	7	0	4.5
Sub-lobar	L		-17.5	-7	17.5	4.4
Cerebellum, lobule VIII	R	48	21	-66.5	-56	6.5
Cerebellum, lobule VI	R	1084	24.5	-63	-21	6.2

Notes. Coordinates are in MNI space, labelled according to AAL2 atlas. L/R: left/right.

Results were thresholded at voxelwise $p < .001$ (uncorrected) and clusterwise FDR-corrected $\alpha = 0.05$. Analysis voxel size: $3.5 \times 3.5 \times 3.5\text{mm}^3$. Results were based on 17 controls, 18 OCD Patients.

S-Table 6-2: Whole-brain results of peak coordinates of activations for controls and cases during the visual working memory task.

	Hemisphere	k	x	y	z	T
Visual Working Memory						
<i>Controls</i>						
Superior frontal gyrus, dorsolateral	L	51	-28	56	10.5	5.50
Middle frontal gyrus	R	379	38.5	24.5	31.5	6.08
Insula	R		31.5	28	7	5.54
Precentral gyrus	R		35	0	45.5	5.88
Precentral gyrus	L	458	-42	0	59.5	7.09
Precentral gyrus	L		-42	3.5	35	6.23
Middle frontal gyrus	L		-35	3.5	63	7.07
Supplementary motor area	R	367	3.5	14	63	6.49
Supplementary motor area	R		0	17.5	52.5	6.33
Supplementary motor area	L		-10.5	10.5	52.5	5.83
Cerebellum, lobule VI	R	1275	35	-45.5	-24.5	9.39
Fusiform gyrus	R		31.5	-49	-14	8.83
Fusiform gyrus	R		38.5	-59.5	-14	8.69
Fusiform gyrus	L	1594	-35	-52.5	-17.5	10.54
Fusiform gyrus	L		-38.5	-70	-17.5	10.42
Occipital lobe, cuneus	L		-24.5	-80.5	7	7.90
Caudate nucleus	L	52	-14	3.5	17.5	5.03
Sub-lobar	R		3.5	-3.5	0	4.26
Sub-lobar, thalamus	L		-7	-3.5	7	4.17
Cerebellum, Vermis_IX	R	43	0	-52.5	-35	6.38
Cerebellum, Vermis_VI	R	134	0	-70	-24.5	5.70
Cerebellum, Crus II	R		7	-77	-38.5	5.34
Cerebellum, lobule IV-V	L		-3.5	-49	-14	3.80
<i>OCD</i>						
Inferior frontal gyrus, triangular part	R	46	42	31.5	24.5	4.08
Middle frontal gyrus	R		45.5	38.5	38.5	3.74
Middle frontal gyrus	R	32	38.5	3.5	56	3.87
Superior frontal gyrus, dorsolateral	R		31.5	0	63	3.71
Precentral gyrus	L	97	-35	0	63	5.46
Precentral gyrus	L	156	-42	3.5	31.5	4.27
Frontal lobe, sub-gyral	L		-31.5	17.5	28	4.22
Insula	L		-28	21	7	4.00
Insula to Inferior frontal gyrus, triangular part	R		35	21	10.5	4.46
Frontal lobe, sub-gyral	R		31.5	35	7	4.35
Supplementary motor area	L	271	-7	7	52.5	5.63
Supplementary motor area	R		0	17.5	52.5	5.37
Supplementary motor area	R		0	10.5	59.5	5.29
Superior parietal gyrus	L	181	-28	-59.5	49	5.38
Inferior parietal gyrus, excluding supramarginal and angular gyri	L		-38.5	-38.5	38.5	4.38
Parietal lobe, sub-gyral	L		-28	-42	31.5	3.53
Sub-lobar	R	69	31.5	17.5	0	4.52
Superior parietal gyrus	R	51	31.5	-59.5	56	4.24
Middle occipital gyrus	R	732	24.5	-84	3.5	5.70
Fusiform gyrus	R		38.5	-49	-21	5.30
Fusiform gyrus	R		35	-77	-14	5.28
Fusiform gyrus	L	747	-35	-66.5	-10.5	6.91
Fusiform gyrus	L		-38.5	-59.5	-14	6.87
Fusiform gyrus	L		-35	-52.5	-17.5	6.45

Note. Coordinates are in MNI space, labelled according to AAL2 atlas. L/R: left/right. Results were thresholded at voxelwise $p < .001$ (uncorrected) and clusterwise FDR-corrected $\alpha = 0.05$. Analysis voxel size: $3.5 \times 3.5 \times 3.5\text{mm}^3$. Results were based on 17 controls, 19 OCD Patients.

S-Table 6-3: Whole-brain results of peak coordinates of activations for controls and cases during the stop-signal task.

	Hemisphere	k	x	y	z	T
Stop Signal Task						
<i>Controls</i>						
Middle frontal gyrus	L	100	-35	49	17.5	5.98
Middle frontal gyrus	L	71	-45.5	28	42	5.64
Middle frontal gyrus	L		-35	38.5	42	4.09
Insula	R	1116	35	17.5	0	8.23
Inferior frontal gyrus, opercular part	R		49	17.5	3.5	7.04
Middle frontal gyrus	R		42	7	38.5	6.89
Insula	L	158	-31.5	21	7	8.11
Insula	L		-42	10.5	3.5	5.90
Inferior frontal gyrus, opercular part	L		-52.5	7	28	4.06
Supplementary motor area	L	25	-14	0	63	4.31
Superior frontal gyrus, dorsolateral	L		-21	3.5	70	3.94
Supramarginal gyrus	R	1279	52.5	-42	35	8.97
Supramarginal gyrus	R		49	-38.5	42	8.32
Inferior parietal gyrus, excluding supramarginal and angular gyri	R		38.5	-45.5	42	7.92
Inferior parietal gyrus, excluding supramarginal and angular gyri	L	477	-35	-45.5	42	7.83
Inferior parietal lobule	L		-59.5	-49	42	6.50
Inferior parietal gyrus, excluding supramarginal and angular gyri	L		-52.5	-52.5	52.5	6.34
Fusiform gyrus	L	465	-31.5	-59.5	-17.5	8.29
Inferior occipital gyrus	L		-24.5	-87.5	-7	7.47
Inferior temporal gyrus	L		-42	-63	-7	7.11
Caudate nucleus	R	41	10.5	3.5	14	4.93
Lenticular nucleus, Putamen	R		17.5	7	3.5	4.24
<i>OCD</i>						
Superior frontal gyrus, dorsolateral	L	117	-17.5	3.5	70	5.60
Precentral gyrus	L		-28	0	59.5	5.03
Precentral gyrus	L		-35	-3.5	49	4.92
Middle frontal gyrus	L	226	-42	31.5	42	6.59
Middle frontal gyrus	L		-38.5	31.5	31.5	6.02
Middle frontal gyrus	L		-31.5	52.5	21	5.93
Inferior frontal gyrus, opercular part	L	21	-56	10.5	17.5	4.58
Middle frontal gyrus	R	1770	42	35	38.5	7.01
Inferior frontal gyrus, opercular part	R		49	10.5	24.5	6.97
Insula	R		35	21	3.5	6.75
Insula	L	80	-31.5	21	7	6.23
Insula	L		-31.5	24.5	-3.5	5.57
Inferior temporal gyrus	R	1342	45.5	-70	-3.5	7.44
Inferior parietal gyrus, excluding supramarginal and angular gyri	R		52.5	-38.5	45.5	7.03
Supramarginal gyrus	R		59.5	-38.5	31.5	6.45
Inferior parietal gyrus, excluding supramarginal and angular gyri	L	382	-56	-52.5	42	7.27
Inferior parietal gyrus, excluding supramarginal and angular gyri	L		-45.5	-45.5	45.5	6.80
Inferior parietal gyrus, excluding supramarginal and angular gyri	L		-31.5	-49	42	5.51
Inferior occipital gyrus	L	723	-42	-70	-7	7.98
Inferior occipital gyrus	L		-31.5	-84	-10.5	7.61
Fusiform gyrus	L		-35	-59.5	-17.5	6.61
Cingulate gyrus	R	39	0	-28	28	4.46

Note. Coordinates are in MNI space, labelled according to AAL2 atlas. L/R: left/right. Results were thresholded at voxelwise $p < .001$ (uncorrected) and clusterwise FDR-corrected $\alpha = 0.05$. Analysis voxel size: $3.5 \times 3.5 \times 3.5\text{mm}^3$. Results were based on 17 controls, 20 OCD Patients.

S-Table 6-4: Group differences in activations during stop-signal tasks using corrected thresholds.

	Hemisphere	k	x	y	z	T	Z	Parameter Estimates					
								Controls		OCD		Cohen's	
								M	SE	M	SE		p
<u>Non-cerebellar activations</u>													
Stop Signal Task (Stop - Go) (Controls <i>n</i> = 17, OCD <i>n</i> = 20)													
<i>OCD < Controls</i> no significant activations													
<i>OCD > Controls</i>													
Superior frontal gyrus, dorsolateral	L	155	-24.5	49	42	3.79	3.44	-1.26	0.28	0.77	0.42	3.57 x 10 ^{-4**}	1.27
Superior frontal gyrus, dorsolateral	L		-17.5	52.5	17.5	3.32	3.074						
Superior frontal gyrus, dorsolateral	L		-17.5	14	52.5	3.251	3.018						
Middle cingulate & paracingulate gyri [†]	R	185	7	28	35	3.68	3.36	-0.20	0.22	1.31	0.33	8.17 x 10 ^{-4**}	1.21
Middle cingulate & paracingulate gyri	R		0	-3.5	42	3.43	3.16						
Middle cingulate & paracingulate gyri	R		7	-14	49	3.15	2.93						

Notes. Regions that showed differences in neural activations within the specified task mask at $p < .01$ (uncorrected) voxelwise and FWE $< .05$ clusterwise. Analysis voxel size: 3.5 x 3.5 x 3.5mm³ (non-cerebellar), 2 x 2 x 2mm³ (cerebellar).

[†] indicates finding significant at $p < .01$ (uncorrected) voxelwise and FDR $< .05$ clusterwise.

There were no significant findings at both corrected thresholds for verbal and visual working memory tasks, and cerebellar analyses. Coordinates are in MNI space, labelled according to AAL2 atlas. *n* = Sample size. L = Left. R = Right. (* $p < .05$. ** $p < .01$. *** $p < .001$)

S-Table 6-5: Whole-brain group differences in verbal working memory task. Results were thresholded at voxelwise $p < .005$ (uncorrected) with 0 voxel extent.

	Hemisphere	k	x	y	z	T
<u>Verbal Working Memory</u>						
OCD < Controls						
Superior frontal gyrus, dorsolateral	L	17	-18	24.5	45.5	3.72
Precentral gyrus	L	2	-25	-28	56	3.14
Rolandic operculum	L	1	-46	-3.5	17.5	2.75
Frontal lobe	R	2	24.5	24.5	17.5	3.03
Frontal lobe	R	1	10.5	31.5	7	2.78
Caudate nucleus	L	20	-21	-21	21	4.06
Lenticular nucleus, Putamen	L		-28	-18	10.5	3.56
Caudate nucleus	L	1	-18	7	17.5	2.99
Thalamus overlapping with putamen	L	11	-25	-21	0	4.06
Lenticular nucleus, Putamen	L	1	-32	0	-3.5	2.77
Precuneus	L	2	-7	-67	35	2.94
Precuneus overlapping with hippocampus	L	13	-25	-46	3.5	3.15
Thalamus	L	2	-3.5	-11	3.5	3.16
Thalamus	L	1	-11	-25	3.5	3.03
Thalamus	L	1	-7	-18	17.5	2.81
Limbic lobe	L	1	-11	-39	28	3.48
Amygdala	L	1	-25	-7	-14	2.83
Parahippocampal gyrus	L	5	-25	-39	-7	3.47
Lingual gyrus	L	2	-11	-35	-3.5	2.92
Cerebellar lobule VIII	R	1	24.5	-60	-46	2.93
Cerebellar lobule IV-V	R	2	10.5	-56	-21	3.37
Cerebellar lobule IV-V	L	11	-14	-49	-18	3.65
Cerebellar lobule IX	L	5	-7	-53	-39	3.58
OCD > Controls						
Supramarginal gyrus extending to postcentral gyrus	R	39	66.5	-32	45.5	4.52
Grey matter, sub-lobar	L	1	-25	21	-7	2.89

S-Table 6-6: Group differences in parameter estimates of activations and high-load accuracy rate in visual working memory task with age, sex and depressive symptoms (HDRS) as covariates.

Dependent Variable	Predictors	Homoscedasticity assumed						Robust Standard Errors			
		<i>b</i>	<i>S.E.</i>	<i>F</i>	<i>t</i>	<i>p</i>	η_p^2	<i>S.E. robust</i>	<i>t</i>	<i>p</i>	η_p^2
Accuracy of High-Load Condition	Group (Control / OCD)	.054	.026	4.25	2.06	.048	.121	.027	1.99	.056	.113
	Sex (Male / Female)	.026	.025	1.05	1.03	.313	.033	.026	.983	.333	.030
	Age	.001	.002	.439	.663	.512	.014	.003	.438	.665	.006
	HDRS	-.006	.003	3.44	-1.85	.073	.100	.005	-1.33	.193	.054
P.E. of Right Fusiform	Group (Control / OCD)	.120	.028	18.03	4.25	.000	.368	.028	4.21***	.000	.363
	Sex (Male / Female)	-.006	.027	.052	-.228	.821	.002	.028	-.219	.828	.002
	Age	.000	.002	.002	-.042	.967	.000	.002	-.061	.951	.000
	HDRS	.000	.004	.018	.135	.893	.001	.003	.189	.851	.001
P.E. of Right Crus II	Group (Control / OCD)	.064	.020	9.75	3.12**	.004	.239	.020	3.22**	.003	.250
	Sex (Male / Female)	-.039	.019	4.13	-2.03	.051	.117	.021	-1.83	.077	.097
	Age	-.003	.002	2.70	-1.64	.110	.080	.002	-1.48	.150	.066
	HDRS	-.002	.003	.599	-.774	.445	.019	.002	-.998	.326	.031
P.E. of Left Lobule VI	Group (Control / OCD)	.148	.042	12.18	3.49**	.001	.282				
	Sex (Male / Female)	-.056	.040	1.95	-1.40	.173	.059				
	Age	-.001	.004	.024	-.155	.878	.001				
	HDRS	.006	.005	1.12	1.06	.299	.035				
P.E. of Vermis VIIIb	Group (Control / OCD)	.090	.026	12.46	3.53**	.001	.287				
	Sex (Male / Female)	.003	.024	.019	.138	.891	.001				
	Age	.004	.002	2.77	1.66	.106	.082				
	HDRS	-.002	.003	.419	-.647	.522	.013				

Note. Dependent variables were high-load accuracy rate, and parameter estimates extracted from regions that showed significant group differences at $p < .005$, $k > 20$ during visual working memory task. Where ANCOVA was conducted using robust standard errors using Heteroscedasticity-consistent (HC)-3 algorithm due to the violation of homoscedasticity, statistics are also provided had homoscedasticity been assumed. 'Control', and 'Male' are reference groups for Group, and Sex variables respectively. Analyses were performed on 17 controls and 19 OCD samples. HDRS = Hamilton Depressive Rating Scale; P.E. = Parameter estimates; *S.E.* = Standard error; *S.E. robust* = Robust standard errors; *b* = standard estimate of beta. (* $p < .05$. ** $p < .01$. *** $p < .001$)

S-Table 6-7: Group differences in parameter estimates of activations and high-load accuracy rate in visual working memory with age, sex, and distress associated with Obsessive and Compulsive tendencies (OCI-R) as covariates.

Dependent Variable	Predictors	Homoscedasticity assumed						Robust Standard Errors			
		<i>b</i>	<i>S.E.</i>	<i>F</i>	<i>t</i>	<i>p</i>	η_p^2	<i>S.E. robust</i>	<i>t</i>	<i>p</i>	η_p^2
Accuracy of High-Load Condition	Group (Control / OCD)	.057	.034	2.84	1.68	.102	.084	.043	1.33	.194	.054
	Sex (Male / Female)	.029	.026	1.25	1.12	.273	.039	.027	1.09	.283	.037
	Age	.001	.002	.155	.393	.697	.005	.004	.223	.825	.002
	OCI-R	-.001	.001	.389	-.623	.538	.012	.002	-.386	.702	.005
P.E. of Right Fusiform	Group (Control / OCD)	.133	.034	14.90	3.86	.001	.325	.029	4.53***	.000	.399
	Sex (Male / Female)	-.004	.027	.021	-.146	.885	.001	.028	-.138	.891	.001
	Age	.000	.002	.005	-.067	.947	.000	.001	-.104	.918	.000
	OCI-R	.001	.001	.427	.654	.518	.014	.001	1.131	.267	.040
P.E. of Right Crus II	Group (Control / OCD)	.061	.025	5.81	2.41	.022	.158	.024	2.57*	.015	.176
	Sex (Male / Female)	-.039	.019	3.96	-1.99	.055	.113	.022	-1.77	.086	.092
	Age	-.003	.002	3.04	-1.74	.091	.089	.002	-1.43	.162	.062
	OCI-R	.000	.001	.259	-.509	.614	.008	.001	-.477	.636	.007
P.E. of Left Lobule VI	Group (Control / OCD)	.164	.052	9.92	3.15**	.004	.242				
	Sex (Male / Female)	-.056	.040	1.91	-1.38	.177	.058				
	Age	.000	.003	.003	-.050	.960	.000				
	OCI-R	.001	.002	.897	.947	.351	.028				
P.E. of Vermis VIIIb	Group (Control / OCD)	.093	.032	8.58	2.93**	.006	.217				
	Sex (Male / Female)	.005	.024	.039	.198	.845	.001				
	Age	.003	.002	2.49	1.58	.125	.074				
	OCI-R	.000	.001	.024	-.156	.877	.001				

Note. Dependent variables were high-load accuracy rate, and parameter estimates extracted from regions that showed significant group differences at $p < .005$, $k > 20$ during visual working memory task. Where ANCOVA was conducted using robust standard errors using Heteroscedasticity-consistent (HC)-3 algorithm due to the violation of homoscedasticity, statistics are also provided had homoscedasticity been assumed. 'Control', and 'Male' are reference groups for Group, and Sex variables respectively. Analyses were performed on 17 controls and 19 OCD samples. OCI-R = Obsessive-Compulsive Inventory (Revised); P.E. = Parameter estimates; *S.E.* = Standard error; *S.E. robust* = Robust standard errors; *b* = standard estimate of beta.

(* $p < .05$. ** $p < .01$. *** $p < .001$)

S-Table 6-8: Group differences in parameter estimates of activations and high-load accuracy rate in visual working memory task with age, sex and depressive symptoms (HDRS), and distress associated with Obsessive and Compulsive tendencies (OCI-R) as covariates within a model.

Dependent Variable	Predictors	Homoscedasticity assumed					
		<i>b</i>	<i>S.E.</i>	<i>F</i>	<i>t</i>	<i>p</i>	η_p^2
Accuracy of High-Load Condition	Group (Control / OCD)	.081	.034	.024	2.39	.024	.159
	Sex (Male / Female)	.028	.025	.267	1.13	.267	.041
	Age	.002	.002	.446	.772	.446	.019
	HDRS	-.011	.005	.041	-2.14	.041	.132
	OCI-R	.002	.001	.228	1.23	.228	.048
P.E. of Right Fusiform	Group (Control / OCD)	.140	.037	14.38	3.79	.001	.324
	Sex (Male / Female)	-.004	.027	.025	-.157	.876	.001
	Age	.000	.002	.001	.031	.975	.000
	HDRS	-.003	.006	.328	-.572	.571	.011
	OCI-R	.001	.002	.727	.853	.401	.024
P.E. of Right Crus II	Group (Control / OCD)	.066	.027	5.98	2.44	.021	.166
	Sex (Male / Female)	-.039	.020	3.93	-1.98	.057	.116
	Age	-.003	.002	2.56	-1.60	.120	.079
	HDRS	-.002	.004	.344	-.586	.562	.011
	OCI-R	.000	.001	.017	.132	.896	.001
P.E. of Left Lobule VI	Group (Control / OCD)	.155	.056	7.68	2.77**	.009	.204
	Sex (Male / Female)	-.055	.041	1.83	-1.35	.186	.057
	Age	.000	.004	.018	-.134	.894	.001
	HDRS	.004	.009	.251	.501	.620	.008
	OCI-R	.001	.002	.044	.209	.836	.001
P.E. of Vermis VIIIb	Group (Control / OCD)	.102	.034	9.12	3.02**	.005	.233
	Sex (Male / Female)	.004	.025	.032	.179	.859	.001
	Age	.004	.002	2.84	1.68	.102	.086
	HDRS	-.004	.005	.668	-.817	.420	.022
	OCI-R	.001	.001	.283	.532	.599	.009

Note. Dependent variables were high-load accuracy rate, and parameter estimates extracted from regions that showed significant group differences at $p < .005$, $k > 20$ during visual working memory task. Where ANCOVA was conducted using robust standard errors using Heteroscedasticity-consistent (HC)-3 algorithm due to the violation of homoscedasticity, statistics are also provided had homoscedasticity been assumed. 'Control', and 'Male' are reference groups for Group, and Sex variables respectively. Analyses were performed on 17 controls and 19 OCD samples. HDRS = Hamilton Depressive Rating Scale; OCI-R = Obsessive-Compulsive Inventory (Revised); P.E. = Parameter estimates; *S.E.* = Standard error; *S.E._{robust}* = Robust standard errors; *b* = standard estimate of beta. (* $p < .05$. ** $p < .01$. *** $p < .001$)

S-Table 6-9: Group differences in high-load accuracy rate of visual working memory task performance with age, and sex as covariates.

Dependent Variable	Predictors	Homoscedasticity assumed						Robust Standard Errors			
		<i>b</i>	<i>S.E.</i>	<i>F</i>	<i>t</i>	<i>p</i>	η_p^2	<i>S.E. robust</i>	<i>t</i>	<i>p</i>	η_p^2
Accuracy of High-Load Condition	Group (Control / OCD)	.070	.026	7.54	2.75	.010	.191	.028	2.54*	.016	.167
	Sex (Male / Female)	.032	.026	1.53	1.24	.224	.046	.025	1.28	.210	.049
	Age	.001	.002	.125	.353	.726	.004	.004	.206	.838	.001

Note. Dependent variable was high-load accuracy rate. ANCOVA was conducted with robust standard errors using Heteroscedasticity-consistent (HC)-3 algorithm due to the violation of homoscedasticity (Levene's test $p < .05$). Statistics are also provided had homoscedasticity been assumed. 'Control', and 'Male' are reference groups for Group, and Sex variables respectively. Analyses were performed on 17 controls and 19 OCD samples. P.E. = Parameter estimates; *S.E.* = Standard error; *S.E. robust* = Robust standard errors; *b* = standard estimate of beta.

(* $p < .05$. ** $p < .01$. *** $p < .001$)

S-Table 6-10: Spearman correlations between OCI-R and HDRS with visual high-load accuracy and neural parameter estimates within combined patients and controls sample.

	OCI-R	HDRS
	ρ_s	ρ_s
Visual High-Load Accuracy	-.45**	-.44**
PE Right Fusiform	-.44**	-.09
PE Left Lobule VI	-.45**	-.04
PE Right Crus II	-.45**	-.12
PE Vermis VIIIb	-.48**	-.30

Note. Analyses were performed on the combined sample of 17 controls and 19 OCD participants. HDRS = Hamilton Depressive Rating Scale; OCI-R = Obsessive-Compulsive Inventory (Revised); P.E. = Parameter estimates (* $p < .05$. ** $p < .01$. *** $p < .001$)

S-Table 6-11: Hierarchical regression for parameter estimates for Vermis VIIIb and left lobule VI during visual working memory.

Dependent Variable:	Model	Predictors	Model-level Statistics						Predictor Coefficients		
			df 1	df 2	F	p	R ²	R ² Change	b	t	p
Parameter Estimate for Vermis VIIIb	1	Age	2	36	0.25	.78	.02	.02	.12	.70	.49
		Sex							-.05	-.26	.80
	2	Age							.19	1.07	.29
		Sex	3	36	1.11	.36	.09	.08	-.01	-.04	.97
		HDRS Score							-.29	-1.67	.10
	3	Age							.19	1.11	.27
		Sex							.01	.03	.97
		HDRS Score	4	36	1.53	.22	.17	.07	.05	.17	.87
		OCL_R							-.43	-1.63	.11
	4	Age							.26	1.68	.10
		Sex							-.03	-.18	.86
		HDRS Score	5	36	3.37	.02	.36	.20	-.21	-.82	.42
		OCL_R							.16	.53	.60
		Group							-.62	-3.02**	.005

Dependent Variable:	Model	Predictors	Model-level Statistics						Predictor Coefficients		
			df 1	df 2	F	p	R ²	R ² Change	b	t	p
Parameter Estimate for Left Lobule VI	1	Age	2	36	0.89	.42	.05	.05	-.09	-.55	.59
		Sex							.22	1.29	.20
	2	Age							-.09	-.51	.62
		Sex	3	36	0.58	.63	.05	.00	.23	1.28	.21
		HDRS Score							-.02	-.10	.92
	3	Age							-.09	-.50	.62
		Sex							.24	1.41	.17
		HDRS Score	4	36	1.32	.28	.15	.09	.37	1.36	.18
		OCL_R							-.50	-1.85	.07
	4	Age							-.02	-.13	.89
		Sex							.21	1.35	.19
		HDRS Score	5	36	2.82	.03	.32	.17	.13	.50	.62
		OCL_R							.07	.21	.84
		Group							-.59	-2.77**	.009

Note. 'Control', and 'Male' are reference groups for Group, and Sex variables respectively.

Analyses were performed on 17 controls and 20 OCD samples. Hierarchical regression was not conducted for accuracy of high-load condition, and parameter estimates for right fusiform and right Crus II due to heteroscedasticity. HDRS = Hamilton Depressive Rating Scale; OCI-R = Obsessive-Compulsive Inventory (Revised); *b* = standard estimate of beta. (* $p < .05$. ** $p < .01$. *** $p < .001$)

S-Table 6-12: Mean group performances in verbal working memory task, visual working memory task and stop-signal task based on all participants, regardless of their behavioural performances.

		Controls			OCD			Mann-Whitney			Effect size
		<i>Mdn</i>	<i>M</i>	<i>SD</i>	<i>Mdn</i>	<i>M</i>	<i>SD</i>	<i>U</i>	<i>p</i>	<i>z</i>	<i>r</i>
<u>Verbal Working Memory Task: Controls <i>n</i> = 17, OCD <i>n</i> = 21</u>											
Accuracy (%)											
	High-Load	95.00	94.12	3.64	90.00 [92.50]	83.57 [90.28]	19.76 [8.13]	118.00 [118.00]	.06 [.22]	-1.85 [-1.22]	-.30 [-.21]
	Low-Load	100.00	98.82	2.81	100.00 [100.00]	96.67 [98.06]	7.13 [3.89]	150.00 [138.00]	.28 [.50]	-1.09 [-.68]	-.18 [-.11]
Reaction time (ms)											
	High-Load	946.74	969.78	176.35	1075.53 [1031.05]	1063.54 [1023.49]	217.19 [205.90]	123.00 [120.00]	.10 [.28]	-1.63 [-1.09]	-.26 [-.18]
	Low-Load	641.80	691.39	173.73	680.75 [651.63]	729.92 [676.47]	174.68 [117.59]	149.00 [146.00]	.39 [.82]	-.87 [-.23]	-.14 [-.04]
<u>Visual Working Memory Task: Controls <i>n</i> = 17, OCD <i>n</i> = 20</u>											
Accuracy (%)											
	High-Load	90.00	90.41	4.09	81.50 [83.00]	81.85 [83.37]	11.50 [9.53]	92.50* [92.50*]	.02 [.03]	-2.38 [-2.20]	-.39 [-.37]
	Low-Load	100.00	97.88	2.91	98.00 [[98.00]	95.15 [96.58]	7.36 [3.75]	120.00 [120.00]	.11 [.17]	-1.59 [-1.38]	-.26 [-.23]
Reaction time (ms)											
	High-Load	891.17	916.38	142.10	841.78 [839.19]	914.31 [901.21]	171.71 [165.84]	157.00 [141.00]	.69 [.52]	-.40 [-.65]	-.07 [-.11]
	Low-Load	714.18	766.78	170.70	717.23 [708.00]	761.67 [749.38]	176.24 [172.06]	168.00 [153.00]	.95 [.79]	-.06 [-.27]	-.01 [-.04]
<u>Stop-Signal Task: Controls <i>n</i> = 17, OCD <i>n</i> = 21</u>											
Accuracy (%)											
	Go-Trial	98.00	98.29	1.45	97.00 [97.00]	94.43 [96.15]	8.62 [3.57]	109.50* [109.50]	.04 [.06]	-2.05 [-1.87]	-.33 [-.31]
	Stop-Trial	57.00	57.18	6.10	54.00 [53.00]	56.76 [55.55]	11.25 [10.03]	161.50 [162.00]	.62 [.44]	-.50 [-.78]	-.08 [-.13]
Reaction time (ms)											
	Go-Trial	560.23	570.69	79.08	564.16 [556.64]	572.05 [562.43]	93.64 [84.76]	177.00 [160.00]	.96 [.76]	-.04 [-.30]	-.01 [-.05]
	Stop-Trial	282.25	294.71	71.44	281.38 [281.88]	280.65 [283.27]	55.18 [55.27]	164.00 [162.00]	.67 [.81]	-.43 [-.24]	-.07 [-.04]

Note. Participants were included in these exploratory analyses regardless of their behavioural performances. Effect sizes for each condition were also presented. * $p < .05$. All findings did not survive Bonferroni corrections for multiple comparisons. Group means and group differences in performances based on the reduced sample as presented in the main analysis are also presented here for ease of visual comparison, with their values indicated in []. Values in [] were based on 17 Controls and 18 OCD patients for Verbal Working Memory Task, 17 Controls and 19 OCD patients for Visual Working Memory Task, and 17 Controls and 20 OCD patients for Stop-Signal Task. *n* = Sample size. *Mdn* = Median. *M* = Mean. *SD* = Standard deviation. *r* = Effect size coefficient.

S-Table 6-13: Group differences in non-cerebellar (A) and cerebellar (B) peak coordinates of activations in verbal working memory, visual working memory and stop-signal tasks based on all participants regardless of their behavioural performances (Left) and on the reduced sample as presented in the main analyses (Right).

All Subjects Without Motion Artifact

Reduced Sample in Main Analysis

A)

	Hemisphere	k	x	y	z	T	Z
<u>Non-cerebellar activations</u>							
<u>Verbal Working Memory</u> (High-Load - Low-Load) (Controls $n = 17$, OCD $n = 21$)							
<i>OCD < Controls</i> no significant activations							
<i>OCD > Controls</i> no significant activations							
<u>Visual Working Memory</u> (High-Load - Low-Load) (Controls $n = 17$, OCD $n = 20$)							
<i>OCD < Controls</i>							
Fusiform gyrus	R	61	31.5	-49	-7	4.58	4.03
<i>OCD > Controls</i> no significant activations							
<u>Stop Signal Task</u> (Stop - Go) (Controls $n = 17$, OCD $n = 21$)							
<i>OCD < Controls</i> no significant activations							
<i>OCD > Controls</i>							
Superior frontal gyrus, dorsolateral	L	24	-21	28	56	3.16	2.95
Superior frontal gyrus, dorsolateral	L		-17.5	17.5	56	3.14	2.93
Superior frontal gyrus, dorsolateral	L	52	-21	49	42	3.71	3.39
Superior frontal gyrus, dorsolateral	L		-21	52.5	17.5	3.26	3.03
Superior frontal gyrus, medial	L		-7	45.5	42	2.84	2.68
Middle cingulate & paracingulate gyri	R	44	7	28	38.5	3.71	3.39
Middle cingulate & paracingulate gyri	L		-7	17.5	38.5	3.09	2.89
Superior frontal gyrus, medial orbital	L	35	0	45.5	-11	3.43	3.17
Superior frontal gyrus, medial orbital	R		7	49	-7	3.28	3.05
Superior frontal gyrus, medial orbital	L		-7	42	-7	3.18	2.96
Middle cingulate & paracingulate gyri	L	31	0	-3.5	42	3.56	3.27
Middle cingulate & paracingulate gyri	R		7	-11	49	3.15	2.94
Supplementary motor area	R		3.5	-18	52.5	3.14	2.93

	Hemisphere	k	x	y	z	T	Z
<u>Non-cerebellar activations</u>							
<u>Verbal Working Memory</u> (High-Load - Low-Load) (Controls $n = 17$, OCD $n = 18$)							
<i>OCD < Controls</i> no significant activations							
<i>OCD > Controls</i> no significant activations							
<u>Visual Working Memory</u> (High-Load - Low-Load) (Controls $n = 17$, OCD $n = 19$)							
<i>OCD < Controls</i>							
Fusiform gyrus	R	62	31.5	-45.5	-3.5	4.89	4.22
<i>OCD > Controls</i> no significant activations							
<u>Stop Signal Task</u> (Stop - Go) (Controls $n = 17$, OCD $n = 20$)							
<i>OCD < Controls</i> no significant activations							
<i>OCD > Controls</i>							
Superior frontal gyrus, dorsolateral	L	37	-24.5	49	42	3.79	3.44
Superior frontal gyrus, medial	L		-10.5	45.5	38.5	3.07	2.87
Superior frontal gyrus, medial orbital	L	24	-3.5	45.5	-11	3.29	3.05
Superior frontal gyrus, medial orbital	R		10.5	49	-7	3.19	2.97
Anterior cingulate & paracingulate gyri	L		-10.5	42	-3.5	3.13	2.92
Middle cingulate & paracingulate gyri	R	40	7	28	35	3.68	3.36
Middle cingulate & paracingulate gyri	R		0	17.5	35	3.09	2.89
Middle cingulate & paracingulate gyri	R	37	0	-3.5	42	3.43	3.16
Middle cingulate & paracingulate gyri	R		7	-14	49	3.15	2.93
Middle cingulate & paracingulate gyri	L		-14	-17.5	42	2.89	2.72

S-Table 6-13 (Cont'd): Group differences in non-cerebellar (A) and cerebellar (B) peak coordinates of activations in verbal working memory, visual working memory and stop-signal tasks based on all participants regardless of their behavioural performances (Left) and on the reduced sample as presented in the main analyses (Right).

All Subjects Without Motion Artifact									Reduced Sample in Main Analysis								
B)																	
	Hemisphere	k	x	y	z	T	Z		Hemisphere	k	x	y	z	T	Z		
<u>Cerebellar activations</u>									<u>Cerebellar activations</u>								
<u>Verbal Working Memory</u> (High-Load - Low-Load) (Controls $n = 17$, OCD $n = 21$)									<u>Verbal Working Memory</u> (High-Load - Low-Load) (Controls $n = 17$, OCD $n = 18$)								
<i>OCD < Controls</i>									<i>OCD < Controls</i>								
	Lobule VIIb	R	39	30	-62	-47	4.78	4.18		Lobule VIIb	R	26	30	-62	-47	4.32	3.82
	Crus II	R	29	40	-50	-45	3.85	3.50									
	Dentate	L	37	-16	-54	-35	3.24	3.01									
<i>OCD > Controls</i>									<i>OCD > Controls</i>								
no significant activations									no significant activations								
<u>Visual Working Memory</u> (High-Load - Low-Load) (Controls $n = 17$, OCD $n = 20$)									<u>Visual Working Memory</u> (High-Load - Low-Load) (Controls $n = 17$, OCD $n = 19$)								
<i>OCD < Controls</i>									<i>OCD < Controls</i>								
	Lobule VI	L	21	-20	-64	-17	3.46	3.19		Lobule VI	L	20	-20	-64	-17	3.39	3.13
	Crus II	R	60	34	-76	-51	3.91	3.54		Crus II	R	52	34	-76	-51	3.83	3.47
	Vermis VIIIb		30	8	-64	-41	3.81	3.46		Vermis VIIIb		28	8	-64	-41	3.75	3.41
<i>OCD > Controls</i>									<i>OCD > Controls</i>								
no significant activations									no significant activations								
<u>Stop Signal Task</u> (Stop - Go) (Controls $n = 17$, OCD $n = 21$)									<u>Stop Signal Task</u> (Stop - Go) (Controls $n = 17$, OCD $n = 20$)								
<i>OCD < Controls</i>									<i>OCD < Controls</i>								
no significant activations									no significant activations								
<i>OCD > Controls</i>									<i>OCD > Controls</i>								
	Lobule VIIa	R	37	12	-64	-41	3.42	3.16		Lobule VIIb	R	26	34	-62	-53	3.93	3.56
									Lobule VIIa	R	42	12	-64	-41	3.43	3.16	

Notes. Regions that showed differences in non-cerebellar (A) and cerebellar (B) neural activations within the specified task mask based on the entire sample regardless of their behavioural performances (Left). Group differences in neural activity based on the reduced sample as presented in the main analysis are also presented here for ease of visual comparison (Right). Coordinates are in MNI (non-cerebellar) and SUI (cerebellar) space. Results were thresholded at $p < .005$ (uncorrected) with $k \geq 20$. Analysis voxel size: $3.5 \times 3.5 \times 3.5\text{mm}^3$ (non-cerebellar), $2 \times 2 \times 2\text{mm}^3$ (cerebellar). n = Sample size. M = Mean. SE = Standard error. L = Left. R = Right.

S-Figure 6-1. Distributions of outcome variables. Values > 1.96 are indicated in red. Values > 2.58 are indicated in red and underlined.

S-Figure 6-1 (Cont'd). Distributions of outcome variables. Values > 1.96 are indicated in red. Values > 2.58 are indicated in red and underlined.

S-Figure 6-1 (Cont'd). Distributions of outcome variables. Values > 1.96 are indicated in red. Values > 2.58 are indicated in red and underlined.

S-Figure 6-2. Parameter estimates of right inferior frontal gyrus. ROI was defined by a 10mm sphere with center coordinate at (54,16, 24). Error bars represent standard errors.

S-Figure 6-3: Significant correlations between parameter estimates with task-related outcomes within OCD samples. Parameter estimates were extracted from regions that showed significant group differences at $p < .005$ (uncorrected), $k \geq 20$, based on the entire sample regardless of their behavioural performances. Red arrows indicate data points that were excluded from the main analysis. Three patients' data were removed for the verbal working memory task as all three patients had low accuracy rates of the high-load condition at 65%, 45% and 20%. For the stop-signal task, one participant had high stop accuracy at 81% but low go accuracy at 60%.

(* $p < .05$; ** $p < .01$)

S-Table 7-1: Coordinates of peak activations within ICA network components in controls.

	Hemisphere	k	x	y	z	T
Sensorimotor Network (SMN) -- Components 1, 2, 3						
<u>Controls</u>						
<i>Component 1</i>						
Postcentral gyrus	L	2021	-17.5	-35	66.5	20.67
Postcentral gyrus	R		21	-42	66.5	17.86
Precuneus	R		10.5	-52.5	70	17.21
Insula	L	25	-35	-24.5	17.5	5.29
Superior temporal gyrus	L		-42	-28	10.5	5.01
Rolandic operculum	R	24	45.5	-28	17.5	5.24
Posterior Cingulate Gyrus	L	30	0	-49	17.5	4.95
Fusiform gyrus	L	86	-42	-59.5	-17.5	7.34
Inferior occipital gyrus	L		-42	-73.5	-3.5	5.89
Inferior occipital gyrus	L		-49	-73.5	-14	5.72
<i>Component 2</i>						
Postcentral gyrus	R	1685	42	-35	52.5	13.99
Postcentral gyrus	R		31.5	-45.5	63	13.63
Precentral gyrus	R		49	-14	42	13.46
Postcentral gyrus	L	71	-38.5	-35	45.5	7.14
Postcentral gyrus	L		-45.5	-35	59.5	5.44
Postcentral gyrus	L		-35	-42	63	4.99
Supplementary motor area	L	32	-7	14	63	6.62
Superior frontal gyrus, dorsolateral	R	35	21	10.5	59.5	7.32
Superior frontal gyrus, dorsolateral	L	19	-21	42	38.5	6.03
Superior frontal gyrus, medial	L		-10.5	42	42	5.06
Inferior frontal gyrus, orbital part	L	48	-49	28	-7	6.80
Superior frontal gyrus, medial orbital	L	23	-7	45.5	-7	6.46
Inferior temporal gyrus	R	43	49	-66.5	-3.5	6.55
Middle temporal gyrus	R		45.5	-70	3.5	5.40
Rolandic operculum	R	34	56	-17.5	14	5.30
Rolandic operculum	R		66.5	-3.5	7	4.50
<i>Component 3</i>						
Postcentral gyrus	R	41	45.5	-28	52.5	5.79
Postcentral gyrus	R		38.5	-28	45.5	5.12
Postcentral gyrus	R		35	-35	59.5	4.61
Superior parietal gyrus	L	1999	-24.5	-49	63	13.24
Postcentral gyrus	L		-52.5	-28	59.5	12.59
Postcentral gyrus	L		-42	-31.5	52.5	11.97
Middle temporal gyrus	R	24	56	-56	14	6.40
Default Mode Network (DMN) -- Components 4, 13						
<u>Controls</u>						
<i>Component 4</i>						
Superior frontal gyrus, medial	L	4194	-7	52.5	10.5	25.53
Superior frontal gyrus, dorsolateral	L		-14	52.5	31.5	24.73
Superior frontal gyrus, medial	R		3.5	59.5	10.5	23.92
Inferior frontal gyrus, opercular part	L	18	-38.5	14	21	5.80
Inferior frontal gyrus, opercular part	L		-35	7	24.5	4.36
Precentral gyrus	R	16	0	-31.5	77	6.06
Posterior cingulate gyrus	R	532	3.5	-49	21	16.95

S-Table 7-1 (Cont'd): Coordinates of peak activations within ICA network components in controls.

	Hemisphere	k	x	y	z	T
<u>Controls</u>						
<i>Component 4 (cont'd)</i>						
Angular gyrus	R	90	49	-59.5	28	7.97
Angular gyrus	R		52.5	-63	42	6.39
Angular gyrus	L	186	-49	-59.5	28	11.35
Precuneus	L		-7	-56	31.5	12.37
Precuneus	L		0	-63	28	11.67
Supramarginal gyrus	L	142	-63	-21	38.5	15.07
Postcentral gyrus	L		-59.5	-21	49	8.36
Postcentral gyrus	L		-70	-21	28	5.80
Postcentral gyrus	R	86	56	-17.5	35	6.30
Supramarginal gyrus	R		63	-21	24.5	5.57
Superior parietal gyrus	R	72	24.5	-63	63	8.76
Superior parietal gyrus	R		35	-49	59.5	5.82
Superior parietal gyrus	R		24.5	-70	56	4.50
Superior parietal gyrus	L	49	-28	-59.5	59.5	6.89
Superior parietal gyrus	L		-35	-45.5	63	3.85
Middle temporal gyrus	L	39	-66.5	-7	-14	5.76
Middle temporal gyrus	L		-63	0	-17.5	4.65
Inferior temporal gyrus	R	24	52.5	-59.5	-10.5	5.25
Inferior temporal gyrus	L	49	-45.5	-66.5	-10.5	6.98
Inferior occipital gyrus	L		-52.5	-70	-7	4.88
Superior occipital gyrus	R	28	28	-84	28	5.69
Middle occipital gyrus	L	16	-35	-87.5	7	5.56
Cerebellum lobule IX	L	15	-3.5	-59.5	-45.5	4.60
Vermis IX			3.5	-56	-38.5	3.99
Cerebellum Crus II	L	42	-31.5	-77	-38.5	6.18
Cerebellum Crus I	L		-45.5	-59.5	-38.5	4.81
Cerebellum Crus II	L		-21	-84	-35	4.48
Cerebellum Crus II	R	73	24.5	-87.5	-31.5	9.19
Cerebellum Crus I	R		28	-77	-35	8.37
Cerebellum lobule VI	R		24.5	-77	-21	5.90
<i>Component 13</i>						
Superior frontal gyrus, dorsolateral	R	507	24.5	7	63	11.43
Middle frontal gyrus	R		24.5	14	45.5	9.86
Superior frontal gyrus, dorsolateral	R		24.5	35	45.5	9.24
Middle frontal gyrus	L	590	-38.5	38.5	35	9.81
Middle frontal gyrus	L		-28	14	59.5	9.35
Superior frontal gyrus, dorsolateral	L		-24.5	35	38.5	9.33
Superior frontal gyrus, medial orbital	R	62	7	49	-10.5	9.18
Superior frontal gyrus, medial orbital	L		-7	56	-3.5	4.97
Inferior frontal gyrus, triangular part	R	22	56	38.5	10.5	5.07
Insula (TD)	R	21	38.5	-3.5	-7	5.16
Middle occipital gyrus	L	949	-38.5	-73.5	28	20.31
Precuneus	L		-3.5	-63	59.5	12.99
Precuneus	R		10.5	-52.5	49	12.57
Precuneus	L	585	-14	-49	7	12.51
Precuneus	L		-7	-52.5	14	12.34
Precuneus	R		10.5	-49	10.5	10.02

S-Table 7-1 (Cont'd): Coordinates of peak activations within ICA network components in controls.

	Hemisphere	k	x	y	z	T
<i>Component 13 (cont'd)</i>						
Supramarginal gyrus	L	47	-59.5	-35	38.5	8.60
Supramarginal gyrus	L		-52.5	-31.5	31.5	6.08
Postcentral gyrus	R	39	56	-7	35	8.52
Precentral Gyrus (TD)	R		49	-3.5	24.5	5.99
Postcentral gyrus	R		63	0	24.5	4.93
Superior temporal gyrus	R	15	56	-3.5	-14	5.09
Middle temporal gyrus	R	542	45.5	-59.5	21	15.08
Middle occipital gyrus	R		42	-70	28	13.47
Middle occipital gyrus	R		38.5	-77	35	13.36
Cerebellum Crus I	R	25	38.5	-77	-35	6.78
Cerebellum Crus II	R		38.5	-66.5	-42	4.02
Cerebellum lobule IX	L	33	-7	-45.5	-35	6.71

Salience-Mode Network (SN) -- Components 5, 11, 15Controls*Component 5*

Precentral gyrus	L	238	-52.5	3.5	35	8.50
Inferior frontal gyrus, opercular part	L		-45.5	7	3.5	7.19
Inferior frontal gyrus, opercular part	L		-52.5	10.5	21	7.12
Inferior frontal gyrus, triangular part	L	199	-42	35	14	8.32
Middle frontal gyrus	L		-31.5	35	42	5.42
Inferior frontal gyrus, opercular part	R	463	45.5	10.5	14	12.28
Inferior frontal gyrus, opercular part	R		52.5	10.5	28	12.11
Insula	R		42	7	3.5	11.86
Middle frontal gyrus	R	166	35	45.5	28	6.89
Inferior frontal gyrus, triangular part	R		45.5	38.5	7	6.49
Middle frontal gyrus	R		35	42	17.5	5.54
Superior frontal gyrus, medial	L	51	0	52.5	31.5	6.53
Superior frontal gyrus, medial	L		0	63	17.5	4.02
Middle cingulate & paracingulate gyri	L	235	0	0	35	8.65
Anterior cingulate & paracingulate gyri	R		3.5	21	28	8.62
Cingulate Gyrus (TD)	L		-10.5	-28	38.5	6.75
Middle cingulate & paracingulate gyri	R	66	10.5	-24.5	42	6.18
Middle cingulate & paracingulate gyri	R		3.5	-31.5	45.5	5.86
Precuneus	L		-3.5	-49	59.5	4.94
Precuneus	L	14	-10.5	-66.5	49	5.10
Precuneus	L		-7	-59.5	52.5	4.15
Angular gyrus	L	12	-42	-70	28	4.65
Supramarginal gyrus	R	1103	63	-28	35	25.05
Supramarginal gyrus	R		59.5	-24.5	28	23.76
Postcentral gyrus	R		63	-14	28	21.34
Inferior Parietal Lobule (TD)	L	1034	-66.5	-28	35	20.88
Postcentral gyrus	L		-56	-21	31.5	18.42
Middle temporal gyrus	L	201	-49	-59.5	0	12.93
Middle temporal gyrus	L		-49	-66.5	10.5	5.48
Inferior temporal gyrus	R	66	56	-63	-14	5.93
Inferior temporal gyrus	R		52.5	-52.5	-10.5	5.59
Cuneus	R	26	3.5	-73.5	24.5	6.06
Inferior occipital gyrus	L	21	-28	-87.5	-10.5	5.76
Lingual gyrus	L		-21	-91	-14	4.89

S-Table 7-1 (Cont'd): Coordinates of peak activations within ICA network components in controls.

	Hemisphere	k	x	y	z	T
<i>Component 5 (cont'd)</i>						
Fusiform gyrus	L	50	-38.5	-59.5	-17.5	5.33
Cerebellum lobule VI	L		-28	-52.5	-24.5	5.13
Cerebellum lobule VI	L		-31.5	-42	-38.5	5.04
Cerebellum lobule VI	L	111	-17.5	-70	-24.5	7.85
Cerebellar Vermis VI	L		-3.5	-63	-24.5	6.01
Cerebellum lobule VIIb	L		-17.5	-73.5	-49	5.39
Cerebellum lobule VIII	R	20	14	-73.5	-45.5	6.52
<i>Component 11</i>						
Inferior frontal gyrus, opercular part	L	103	-49	10.5	7	9.05
Inferior frontal gyrus, pars orbitalis	L		-49	21	-7	7.27
Supplementary motor area	R	3676	7	3.5	59.5	20.88
Precentral gyrus	L		-45.5	3.5	38.5	18.09
Middle cingulate & paracingulate gyri	L		-3.5	14	42	16.84
Superior temporal gyrus	R	25	59.5	-45.5	21	5.50
Supramarginal gyrus	R		56	-31.5	35	5.08
Supramarginal gyrus	L	14	-63	-45.5	28	4.58
Middle occipital gyrus	R	83	31.5	-70	31.5	6.40
Postcentral gyrus	R		28	-31.5	56	6.12
Angular gyrus	R		28	-63	42	5.61
Lenticular nucleus, Putamen	L	23	-17.5	7	10.5	5.75
Cerebellum lobule VI	R	109	38.5	-59.5	-24.5	7.03
Cerebellum Crus I	R		38.5	-77	-24.5	4.49
<i>Component 15</i>						
Middle frontal gyrus	R	3266	31.5	45.5	28	20.47
Superior frontal gyrus, dorsolateral	R		24.5	52.5	24.5	18.77
Middle frontal gyrus	L		-35	38.5	28	14.69
Inferior frontal gyrus, opercular part	R	13	56	17.5	0	5.41
Middle cingulate & paracingulate gyri	L	26	0	-10.5	31.5	5.12
Cingulate Gyrus (TD)	L		0	-35	24.5	4.45
Insula	R	13	38.5	10.5	3.5	5.65
Precentral gyrus	R	113	28	-24.5	63	10.69
Superior temporal gyrus	L	116	-63	-42	17.5	6.54
Inferior parietal gyrus, excluding supramarginal and angular gyri	L		-56	-49	38.5	5.89
Supramarginal gyrus	L		-56	-38.5	28	5.36
Precuneus	L	291	0	-45.5	56	9.57
Paracentral lobule	L		0	-21	63	7.16
Precuneus	L		-3.5	-66.5	52.5	6.98
Inferior parietal gyrus, excluding supramarginal and angular gyri	R	40	56	-42	49	6.69
Supramarginal gyrus	R		66.5	-42	35	4.01
Caudate nucleus	R	23	17.5	17.5	3.5	4.89
Thalamus	L	12	-14	-14	17.5	4.67
Middle occipital gyrus	L	248	-35	-94.5	0	6.73
Middle occipital gyrus	L		-45.5	-77	7	6.27
Middle occipital gyrus	L		-24.5	-101.5	-3.5	6.11
Cerebellum lobule VI	L	274	-28	-59.5	-21	8.82
Cerebellum Crus I	L		-45.5	-52.5	-42	7.66
Cerebellum Crus I	L		-24.5	-73.5	-31.5	6.10
Cerebellum lobule VIIb	R	41	38.5	-49	-42	7.13

S-Table 7-1 (Cont'd): Coordinates of peak activations within ICA network components in controls.

	Hemisphere	k	x	y	z	T
Executive-Control Network (ECN) -- Components 19, 20						
<u>Controls</u>						
<i>Component 19</i>						
Inferior parietal gyrus, excluding supramarginal and angular gyri	L	1082	-49	-52.5	49	31.30
Angular gyrus	L		-35	-63	42	23.22
Inferior parietal gyrus, excluding supramarginal and angular gyri	L		-52.5	-56	35	21.93
Angular gyrus	R	404	56	-59.5	35	14.54
Angular gyrus	R		45.5	-59.5	45.5	12.09
Middle temporal gyrus	R		56	-70	28	11.49
Middle frontal gyrus	L	1521	-28	17.5	49	13.83
Superior frontal gyrus, medial	L		0	38.5	35	13.05
Middle frontal gyrus	L		-45.5	24.5	38.5	12.59
Middle temporal gyrus	L	353	-59.5	-35	-3.5	12.58
Middle temporal gyrus	L		-52.5	-38.5	-14	10.90
Middle temporal gyrus	L		-70	-38.5	-7	10.41
Middle cingulate & paracingulate gyri	R	369	3.5	-28	45.5	12.13
Middle cingulate & paracingulate gyri	L		-3.5	-38.5	49	11.79
Middle cingulate & paracingulate gyri	L		-3.5	-38.5	35	9.68
Inferior occipital gyrus	R	96	42	-84	-14	10.07
Middle occipital gyrus	R		31.5	-91	7	5.38
Cerebellum Crus II	R	386	35	-73.5	-42	9.07
Cerebellum Crus II	R		28	-87.5	-42	8.57
Cerebellum Crus I	R		31.5	-63	-38.5	7.94
Rolandic operculum	R	50	49	-24.5	17.5	6.52
Rolandic operculum	R		38.5	-24.5	17.5	4.80
Middle temporal gyrus	R	33	66.5	-24.5	-10.5	6.14
Middle temporal gyrus	R		66.5	-38.5	-14	6.05
Cuneus	R	20	17.5	-84	24.5	5.72
Postcentral gyrus	R	24	17.5	-38.5	70	5.57
Superior parietal gyrus	R		14	-45.5	66.5	4.75
Postcentral gyrus	L	36	-17.5	-35	70	5.51
Precentral gyrus	L		-21	-17.5	63	5.20
Precentral gyrus	L		-14	-21	70	4.94
Cuneus	L	15	0	-84	21	5.10
Middle frontal gyrus	R	18	35	24.5	56	4.88
<i>Component 20</i>						
Middle frontal gyrus	R	2801	45.5	35	35	22.58
Middle frontal gyrus	R		45.5	17.5	49	12.50
Middle frontal gyrus	R		31.5	14	59.5	11.65
Middle frontal gyrus	L	69	-31.5	28	42	7.43
Angular gyrus	R	1187	45.5	-56	38.5	18.07
Inferior parietal gyrus, excluding supramarginal and angular gyri	R		45.5	-49	45.5	17.63
Inferior parietal gyrus, excluding supramarginal and angular gyri	R		52.5	-42	49	17.07
Inferior parietal gyrus, excluding supramarginal and angular gyri	L	359	-45.5	-59.5	45.5	13.78
Precuneus	R	14	7	-73.5	59.5	5.17

S-Table 7-1 (Cont'd): Coordinates of peak activations within ICA network components in controls.

	Hemisphere	k	x	y	z	T
<i>Component 20 (cont'd)</i>						
Precuneus	R	519	10.5	-66.5	38.5	13.75
Middle cingulate & paracingulate gyri	R		3.5	-24.5	38.5	13.24
Precuneus	R		3.5	-42	45.5	12.33
Middle temporal gyrus	R	355	59.5	-28	-10.5	11.07
Middle temporal gyrus	R		56	-38.5	-7	10.43
Inferior temporal gyrus	R		63	-42	-10.5	9.94
Middle temporal gyrus	L	23	-63	-24.5	-10.5	7.06
Middle temporal gyrus	L		-66.5	-35	-10.5	5.47
Cerebellum Crus I	L	172	-38.5	-73.5	-31.5	7.53
Cerebellum Crus II	L		-35	-73.5	-49	7.30
Cerebellum Crus I	L		-42	-59.5	-38.5	6.57
Cerebellum Crus I	L	239	-10.5	-80.5	-24.5	12.86
Hippocampus	R		28	-24.5	-14	6.25

Note. Controls $n = 17$. One-sample t-tests for network components were thresholded at p

$< .001$ (uncorrected) with clusterwise FDR $\alpha = 0.05$. Analysis voxel size: $3.5 \times 3.5 \times 3.5\text{mm}^3$.

Coordinates are in MNI space, labelled according to AAL2 atlas. R = right; L = left.

S-Table 7-2: Coordinates of peak activations within ICA network components in OCD samples.

	Hemisphere	k	x	y	z	T
Sensorimotor Network (SMN) -- Components 1, 2, 3						
<u>OCD</u>						
<i>Component 1</i>						
Postcentral gyrus	L	2279	0	-42	73.5	18.12
Superior frontal gyrus	L		0	-17.5	80.5	17.42
Paracentral lobule	L		-7	-35	77	16.61
Supramarginal gyrus	L	33	-52.5	-31.5	24.5	4.89
Supramarginal gyrus	L		-56	-24.5	17.5	4.76
Superior temporal gyrus	L	82	-63	-7	3.5	5.13
Inferior frontal gyrus, opercular part	L		-63	7	-3.5	5.13
Superior frontal gyrus, medial	R	22	3.5	70	14	4.92
Superior frontal gyrus, medial	L		-3.5	66.5	21	4.02
Posterior cingulate gyrus	L	118	0	-59.5	14	6.85
Posterior cingulate gyrus	L		0	-49	21	6.27
Inferior occipital gyrus	L	67	-45.5	-77	-14	5.53
Cerebellum Crus I	L		-24.5	-87.5	-21	5.07
Inferior occipital gyrus	L		-52.5	-70	-14	4.93
<i>Component 2</i>						
Superior frontal gyrus, dorsolateral	L	106	-14	52.5	31.5	10.79
Superior frontal gyrus, dorsolateral	L		-10.5	45.5	42	5.07
Inferior frontal gyrus, orbital part	L	32	-45.5	28	-7	4.83
Inferior frontal gyrus, triangular part	L		-49	21	7	4.29
Postcentral gyrus	L	151	-42	-35	59.5	8.51
Superior parietal gyrus	L		-28	-45.5	70	5.30
Postcentral gyrus	L		-56	-21	45.5	4.91
Postcentral gyrus	R	1982	45.5	-24.5	59.5	17.00
Postcentral gyrus	R		45.5	-35	56	16.79
Postcentral gyrus	R		42	-31.5	49	16.26
Supplementary motor area	L	31	-10.5	14	63	6.51
Inferior occipital gyrus	R	55	52.5	-66.5	-14	6.76
Middle temporal gyrus	R		42	-56	10.5	4.79
Superior temporal gyrus	R	22	52.5	-10.5	-14	5.06
Middle temporal gyrus	R		59.5	-17.5	-14	4.61
Middle temporal gyrus	R		49	-21	-17.5	3.87
Cerebellum Crus II	R	43	10.5	-84	-38.5	5.38
Cerebellum Crus II	R		28	-84	-49	5.08
Cerebellum Crus I	R		24.5	-77	-35	4.24
<i>Component 3</i>						
Inferior frontal gyrus, triangular part	R	27	52.5	28	10.5	5.73
Inferior frontal gyrus, triangular part	R		42	28	0	4.73
Precentral gyrus	L	2343	-28	-21	59.5	18.21
Superior parietal gyrus	L		-42	-42	56	14.71
Superior parietal gyrus	L		-35	-45.5	59.5	14.48
Postcentral gyrus	R	21	42	-28	52.5	4.56
Postcentral gyrus	R		49	-24.5	49	4.30
Lingual gyrus	L	43	-14	-91	-17.5	6.54
Cerebellum lobule VI	R	25	17.5	-59.5	-21	5.00
Cerebellum lobule VIII	R	41	24.5	-52.5	-56	5.30
Cerebellum lobule VIII	R		17.5	-59.5	-49	4.64
Cerebellum lobule VIII	R		21	-59.5	-59.5	4.47

S-Table 7-2 (Cont'd): Coordinates of peak activations within ICA network components in OCD samples.

	Hemisphere	k	x	y	z	T
Default Mode Network (DMN) -- Components 4, 13						
OCD						
<i>Component 4</i>						
Superior frontal gyrus, medial	L	4597	-10.5	52.5	10.5	26.65
Superior frontal gyrus, medial	L		-14	56	3.5	25.90
Superior frontal gyrus, medial orbital	R		7	56	-3.5	21.93
Posterior orbital gyrus	R	102	38.5	24.5	-21	7.43
Inferior frontal gyrus, orbital part	R		28	38.5	-10.5	7.03
Posterior orbital gyrus	R		38.5	31.5	-14	6.31
Superior parietal gyrus	R	85	28	-66.5	59.5	6.33
Superior parietal gyrus	R		28	-56	63	6.09
Superior parietal gyrus	L	34	-21	-59.5	59.5	6.19
Superior parietal gyrus	L		-31.5	-56	66.5	4.57
Superior parietal gyrus	L		-28	-52.5	56	3.80
Precuneus	L	39	-3.5	-42	70	5.35
Precuneus	L		-7	-52.5	70	5.26
Precuneus	R		3.5	-52.5	70	5.13
Supramarginal gyrus	R	113	49	-28	35	6.26
Postcentral gyrus	R		49	-21	42	5.17
Postcentral gyrus	L	126	-59.5	-21	35	6.72
Postcentral gyrus	L		-52.5	-24.5	52.5	4.90
Postcentral gyrus	L		-49	-24.5	31.5	4.83
Angular gyrus	L	218	-49	-63	28	13.83
Angular gyrus	R	83	56	-63	31.5	6.47
Middle temporal gyrus	R		52.5	-66.5	21	5.19
Middle temporal gyrus	L	93	-59.5	-7	-14	9.24
Middle temporal gyrus	L		-52.5	0	-24.5	3.89
Middle temporal gyrus	R	53	59.5	-7	-17.5	6.52
Middle temporal gyrus	R		66.5	-17.5	-10.5	5.07
Superior temporal gyrus	R		66.5	-7	-7	4.88
Inferior temporal gyrus	R	21	59.5	-52.5	-10.5	5.26
Superior occipital gyrus	R	17	24.5	-84	28	4.98
Calcarine fissure and surrounding cortex	L	14	0	-87.5	3.5	4.92
Calcarine fissure and surrounding cortex	R		3.5	-84	14	4.29
Cerebellum Crus I	L	50	-24.5	-84	-31.5	6.22
Cerebellum Crus I	L		-35	-77	-35	5.34
<i>Component 13</i>						
Superior frontal gyrus, dorsolateral	L	565	-17.5	7	63	12.58
Superior frontal gyrus, dorsolateral	L		-28	3.5	63	11.31
Superior frontal gyrus, dorsolateral	L		-24.5	10.5	66.5	11.28
Middle frontal gyrus	R	446	28	35	38.5	9.07
Middle frontal gyrus	R		31.5	35	49	8.23
Superior frontal gyrus, dorsolateral	R		24.5	14	52.5	7.92
Superior frontal gyrus, medial orbital	L	17	-10.5	45.5	-10.5	4.62
Precentral gyrus	R	14	31.5	-21	63	4.44
Middle temporal gyrus	R	1003	49	-63	21	11.33
Calcarine fissure and surrounding cortex	L		-14	-52.5	10.5	11.04
Middle temporal gyrus	R		45.5	-63	10.5	10.77

S-Table 7-2 (Cont'd): Coordinates of peak activations within ICA network components in OCD samples.

	Hemisphere	k	x	y	z	T
<i>Component 13 (cont'd)</i>						
Superior temporal gyrus	R	28	49	0	-7	5.63
Superior temporal gyrus	R		38.5	3.5	-17.5	4.26
Supramarginal gyrus	L	23	-63	-35	38.5	4.65
Supramarginal gyrus	L		-59.5	-24.5	28	3.84
Parahippocampal gyrus	R	20	21	-21	-17.5	5.14
Hippocampus	R		24.5	-35	-14	3.89
Parahippocampal gyrus	L	68	-28	-42	-7	6.84
Fusiform gyrus	L		-31.5	-35	-14	6.17
Middle occipital gyrus	L	990	-45.5	-73.5	31.5	15.55
Precuneus	R		3.5	-56	52.5	13.76
Middle occipital gyrus	L		-31.5	-80.5	38.5	10.96
Fusiform gyrus	R	18	28	-49	-10.5	4.60
Cerebellum lobule IX	R	75	7	-52.5	-52.5	6.38
Cerebellum lobule IX	R		10.5	-49	-45.5	6.28
Cerebellum lobule IX	L		-10.5	-49	-49	6.25
Salience-Processing Network-- Components 5, 11, 15						
OCD						
<i>Component 5</i>						
Inferior frontal gyrus, triangular part	R	375	52.5	17.5	21	10.68
Inferior frontal gyrus, opercular part	R		49	7	14	9.27
Inferior frontal gyrus, opercular part	R		52.5	14	31.5	8.13
Middle frontal gyrus	R	82	45.5	42	14	8.95
Insula	L	229	-42	0	3.5	7.16
Inferior frontal gyrus, opercular part	L		-45.5	7	21	6.90
Inferior frontal gyrus, opercular part	L		-52.5	10.5	17.5	6.68
Middle frontal gyrus	L	89	-42	42	17.5	5.87
Middle frontal gyrus	L		-38.5	38.5	24.5	5.29
Middle frontal gyrus	L		-42	42	31.5	4.44
Middle cingulate & paracingulate gyri	L	92	-3.5	0	42	5.81
Middle cingulate & paracingulate gyri	L		0	14	31.5	5.73
Supplementary motor area	R		3.5	7	45.5	5.35
Supramarginal gyrus	L	1238	-63	-28	38.5	18.20
Postcentral gyrus	L		-59.5	-21	31.5	16.70
Inferior parietal gyrus, excluding supramargi	L		-52.5	-31.5	49	14.68
Supramarginal gyrus	R	972	66.5	-21	31.5	15.70
Supramarginal gyrus	R		56	-24.5	38.5	14.40
Supramarginal gyrus	R		63	-17.5	24.5	14.37
Middle temporal gyrus	L	184	-52.5	-49	-3.5	8.35
Inferior temporal gyrus	L		-56	-63	-10.5	7.18
Inferior temporal gyrus	R	64	59.5	-56	-3.5	7.63
Inferior temporal gyrus	R		49	-52.5	-3.5	6.36
Middle occipital gyrus	L	23	-35	-70	21	4.90
<i>Component 11</i>						
Supplementary motor area	R	4137	7	14	52.5	21.46
Supplementary motor area	R		10.5	10.5	59.5	18.83
Supplementary motor area	R		3.5	7	63	17.36
Superior occipital gyrus	R	92	21	-70	38.5	4.46
Postcentral gyrus	R		28	-42	59.5	4.25

S-Table 7-2 (Cont'd): Coordinates of peak activations within ICA network components in OCD samples.

	Hemisphere	k	x	y	z	T
<i>Component 11 (cont'd)</i>						
Inferior frontal gyrus, opercular part	L	90	-52.5	14	0	7.97
Inferior frontal gyrus, orbital part	L		-52.5	21	-10.5	5.60
Inferior frontal gyrus, orbital part	L		-45.5	24.5	-7	5.07
Inferior parietal gyrus, excluding supramargir	L	123	-31.5	-59.5	52.5	6.66
Superior parietal gyrus	L		-21	-63	49	5.98
Inferior parietal gyrus, excluding supramargir	L		-28	-45.5	45.5	5.59
Supramarginal gyrus	R	57	66.5	-35	28	6.30
Supramarginal gyrus	R		56	-28	42	4.76
Superior temporal gyrus	R		66.5	-42	21	4.68
Inferior frontal gyrus, triangular part	R	121	56	21	7	5.68
Inferior frontal gyrus, orbital part	R		49	21	-3.5	5.60
Insula	R		35	7	3.5	5.21
Middle temporal gyrus	L	21	-63	-49	10.5	5.13
Middle temporal gyrus	R	19	52.5	-24.5	-7	4.90
Cerebellum Crus I	R	19	28	-80.5	-31.5	4.48
Cerebellum Crus II	R		14	-87.5	-31.5	4.38
<i>Component 15</i>						
Middle frontal gyrus	R	3496	31.5	45.5	35	20.40
Superior frontal gyrus, dorsolateral	R		31.5	52.5	17.5	17.33
Superior frontal gyrus, dorsolateral	L		-24.5	49	21	16.24
Superior frontal gyrus, dorsolateral	L	194	-21	7	66.5	11.32
Superior frontal gyrus, dorsolateral	L		-17.5	21	59.5	4.48
Precentral gyrus	R	55	38.5	-21	63	5.85
Precentral gyrus	R		42	-14	59.5	5.32
Precentral gyrus	R		24.5	-28	70	4.00
Paracentral lobule	R	365	7	-35	49	10.71
Precuneus	R		7	-45.5	56	9.27
Precuneus	L		-3.5	-49	56	8.64
Supramarginal gyrus	R	35	63	-49	38.5	5.63
Supramarginal gyrus	R		59.5	-42	31.5	4.50
Inferior parietal lobule	L	201	-59.5	-49	42	8.73
Inferior parietal gyrus, excluding supramargir	L		-59.5	-38.5	45.5	6.95
Superior temporal gyrus	L		-59.5	-38.5	17.5	6.18
Lenticular nucleus, Putamen	R	94	21	14	0	7.66
Caudate nucleus	R		10.5	0	10.5	6.79
Middle occipital gyrus	L	182	-38.5	-91	0	10.66
Middle occipital gyrus	L		-31.5	-94.5	17.5	6.11
Cerebellum lobule VI	L	240	-24.5	-66.5	-24.5	8.50
Cerebellum lobule VI	L		-35	-59.5	-24.5	7.66
Cerebellum lobule VI	L		-31.5	-42	-31.5	5.57

S-Table 7-2 (Cont'd): Coordinates of peak activations within ICA network components in OCD samples.

	Hemisphere	k	x	y	z	T
Executive-Control Network (ECN) -- Components 19, 20						
<u>OCD</u>						
<i>Component 19</i>						
Middle frontal gyrus	R	3496	31.5	45.5	35	20.40
Superior frontal gyrus, dorsolateral	R		31.5	52.5	17.5	17.33
Superior frontal gyrus, dorsolateral	L		-24.5	49	21	16.24
Superior frontal gyrus, dorsolateral	L	194	-21	7	66.5	11.32
Superior frontal gyrus, dorsolateral	L		-17.5	21	59.5	4.48
Precentral gyrus	R	55	38.5	-21	63	5.85
Precentral gyrus	R		42	-14	59.5	5.32
Precentral gyrus	R		24.5	-28	70	4.00
Supramarginal gyrus	R	35	63	-49	38.5	5.63
Supramarginal gyrus	R		59.5	-42	31.5	4.50
Paracentral lobule	R	365	7	-35	49	10.71
Precuneus	R		7	-45.5	56	9.27
Precuneus	L		-3.5	-49	56	8.64
Inferior Parietal Lobule (TD)	L	201	-59.5	-49	42	8.73
Inferior parietal gyrus, excluding supramargir	L		-59.5	-38.5	45.5	6.95
Superior temporal gyrus	L		-59.5	-38.5	17.5	6.18
Lenticular nucleus, Putamen	R	94	21	14	0	7.66
Caudate nucleus	R		10.5	0	10.5	6.79
Middle occipital gyrus	L	182	-38.5	-91	0	10.66
Middle occipital gyrus	L		-31.5	-94.5	17.5	6.11
Cerebellum lobule VI	L	240	-24.5	-66.5	-24.5	8.50
Cerebellum lobule VI	L		-35	-59.5	-24.5	7.66
Cerebellum lobule VI	L		-31.5	-42	-31.5	5.57
<i>Component 20</i>						
Superior frontal gyrus, dorsolateral	R	2742	28	24.5	52.5	18.21
Superior frontal gyrus, dorsolateral	R		24.5	45.5	38.5	14.43
Superior frontal gyrus, dorsolateral	R		31.5	28	38.5	11.35
Paracentral lobule	R	38	7	-31.5	73.5	5.88
Supplementary motor area	R		10.5	-21	66.5	4.80
Paracentral lobule	L		-7	-28	70	4.24
Inferior parietal gyrus, excluding supramargir	R	1558	56	-49	42	16.55
Angular gyrus	R		38.5	-70	45.5	16.24
Angular gyrus	R		49	-66.5	45.5	15.67
Angular gyrus	L	307	-45.5	-63	42	11.85
Angular gyrus	L		-56	-59.5	38.5	10.01
Precuneus	R	542	3.5	-66.5	35	9.10
Middle cingulate & paracingulate gyri	R		3.5	-31.5	42	8.84
Precuneus	R		7	-49	38.5	8.00
Cerebellum Crus II	L	516	-10.5	-84	-28	8.42
Cerebellum Crus II	L		-42	-66.5	-42	8.30
Cerebellum Crus II	L		-31.5	-73.5	-42	8.06

Note. OCD samples $n = 20$. One-sample t-tests for network components were thresholded at p

$< .001$ (uncorrected) with clusterwise FDR $\alpha = 0.05$. Analysis voxel size: $3.5 \times 3.5 \times 3.5\text{mm}^3$.

Coordinates are in MNI space, labelled according to AAL2 atlas. R = right; L = left.

S-Table 7-3: Peak coordinates of regions showing significant connectivity with cerebellar sources in controls ($n = 17$) and OCD samples ($n = 20$).

	Hemisphere	k	x	y	z	T
Source: L Lobule I-IV						
<u>Controls</u>						
Precentral gyrus	R	416	14	-32	70	5.53
Superior frontal gyrus, dorsolateral	R		14	-14	76	5.22
Postcentral gyrus	R		12	-32	78	4.78
Middle cingulate & paracingulate gyri	R	582	4	-14	44	6.91
Middle cingulate & paracingulate gyri	R		4	-12	34	6.79
Middle cingulate & paracingulate gyri	R		4	-6	40	6.34
Precuneus	L	264	-10	-40	62	6.56
Middle cingulate & paracingulate gyri	L		-2	-36	52	5.58
Middle cingulate & paracingulate gyri	R		4	-30	52	5.36
Rolandic operculum	L	154	-42	-28	20	5.71
Rolandic operculum	L		-34	-28	16	4.27
Cerebellar lobule IV-V	L	10146	-6	-46	-14	40.45
Cerebellar lobule IV-V	L		-6	-54	-12	26.52
Cerebellar lobule IV-V	L		-6	-48	-6	22.60
Cerebellar lobule VIII	R	168	26	-50	-54	7.29
Cerebellar lobule VIII	R		20	-50	-48	4.55
Cerebellar lobule IX	R		14	-40	-46	4.50
<u>OCD</u>						
Inferior temporal gyrus	L	317	-42	0	-14	7.84
Inferior temporal gyrus	L		-44	-8	-8	5.03
Insula	L		-44	-2	-2	5.03
Cerebellar vermis IV-V	L	7597	-2	-50	-12	44.40
Cerebellar lobule IV-V	L		-8	-44	-14	37.70
Cerebellar lobule IV-V	L		-6	-54	-18	24.97
Source: R Lobule I-IV						
<u>Controls</u>						
Postcentral gyrus	R	367	18	-42	72	5.30
Precentral gyrus	R		14	-32	72	5.16
Supplementary motor area	R		8	-14	66	4.75
Paracentral lobule	L	435	-14	-36	70	6.07
Paracentral lobule	L		-10	-30	66	5.60
Paracentral lobule	L		-10	-14	66	5.15
Anterior cingulate & paracingulate gyri	L	257	-2	38	2	5.35
Anterior cingulate & paracingulate gyri	R		4	38	8	5.28
Anterior cingulate & paracingulate gyri	R		8	42	2	4.65
Middle cingulate & paracingulate gyri	R	951	4	0	38	7.21
Supplementary motor area	R		2	0	46	6.15
Middle cingulate & paracingulate gyri	L		-2	-8	38	5.56
Insula	R	402	40	-12	0	6.90
Insula	R		40	-18	14	5.18
Insula	L	147	-34	14	-12	5.16
Insula	L		-44	14	0	4.30
Lenticular nucleus, Putamen	L	685	-28	-4	6	6.15

S-Table 7-3 (Cont'd): Peak coordinates of regions showing significant connectivity with cerebellar sources in controls ($n = 17$) and OCD samples ($n = 20$).

	Hemisphere	k	x	y	z	T
(cont'd)						
Rolandic operculum	L		-42	-14	14	5.28
Lenticular nucleus, Pallidum	L		-16	0	-4	5.22
Inferior temporal gyrus	L		-52	0	-8	4.05
Cerebellar lobule IV-V	R	8739	14	-42	-18	30.52
Cerebellar lobule IV-V	R		8	-54	-14	29.33
Cerebellar lobule IV-V	R		8	-48	-8	28.89
<u>OCD</u>						
Precentral gyrus	L	1264	-14	-14	70	7.72
Paracentral lobule	L		-16	-22	72	7.25
Precentral gyrus	L		-16	-16	78	6.65
Lenticular nucleus, Putamen	L	411	-28	-18	2	6.19
Lenticular nucleus, Putamen	L		-28	-12	-4	6.07
Cerebellar lobule IV-V	R	7504	8	-46	-14	29.38
Cerebellar vermis III			4	-46	-22	25.89
Cerebellar vermis IV-V			2	-50	-10	25.23
Cerebellar lobule IX	R	731	14	-56	-50	7.73
Cerebellar lobule VIII	R		22	-60	-54	7.28
Cerebellar lobule IX	R		6	-56	-54	6.25
Source: L Lobule V						
<u>Controls</u>						
Superior frontal gyrus, dorsolateral	R	564	18	-8	58	6.36
Superior frontal gyrus, dorsolateral	R		22	-2	62	6.34
Precentral gyrus	R		40	-18	42	6.06
Anterior cingulate & paracingulate gyri	R	416	8	28	24	8.05
Anterior cingulate & paracingulate gyri	L		-2	24	24	5.76
Anterior cingulate & paracingulate gyri	R		2	32	20	5.58
Middle cingulate & paracingulate gyri	R	661	4	-4	34	6.41
Supplementary motor area	L		-6	0	48	5.27
Middle cingulate & paracingulate gyri	R		8	-14	42	5.24
Insula	L	238	-34	-18	2	7.41
Heschl's gyrus	L		-40	-18	8	6.06
Insula	L		-40	-18	-4	5.13
Rolandic operculum	L	365	-58	-4	10	6.32
Precentral gyrus	L		-56	4	14	5.56
Rolandic operculum	L		-62	2	2	5.27
Cerebellar lobule IV-V	L	17312	-16	-46	-22	23.34
Cerebellar lobule IV-V	L		-10	-54	-14	22.62
Fusiform gyrus	L		-22	-46	-16	22.61
<u>OCD</u>						
Cerebellar vermis IV-V		7597	-2	-50	-12	44.40
Cerebellar lobule IV-V	L		-8	-44	-14	37.70
Cerebellar lobule IV-V	L		-6	-54	-18	24.97

S-Table 7-3 (Cont'd): Peak coordinates of regions showing significant connectivity with cerebellar sources in controls ($n = 17$) and OCD samples ($n = 20$).

	Hemisphere	k	x	y	z	T
Source: R Lobule V						
<u>Controls</u>						
Postcentral gyrus	L	173	-58	0	14	4.66
Postcentral gyrus	L		-56	-18	20	4.60
Postcentral gyrus	L		-56	-8	14	4.10
Anterior cingulate & paracingulate gyri	R	2477	8	24	28	6.37
Precentral gyrus	L		-38	-12	42	5.84
Lenticular nucleus, Putamen	R	166	32	-8	-4	5.21
Inferior Frontal Gyrus	R		32	10	-14	4.64
Insula	R		40	0	-12	4.52
Cerebellar lobule IV-V	R	13771	18	-54	-18	24.63
Cerebellar lobule IV-V	R		10	-56	-14	23.69
Cerebellar lobule IV-V	R		22	-44	-18	21.41
<u>OCD</u>						
Precentral gyrus	L	3240	-28	-18	66	7.44
Precentral gyrus	L		-24	-26	62	6.25
Superior frontal gyrus, dorsolateral	L		-28	-10	68	6.20
Middle occipital gyrus	R	236	48	-84	10	6.74
Middle occipital gyrus	R		42	-74	10	5.77
Middle temporal gyrus	R		50	-76	10	4.46
Cerebellar lobule IV-V	R	16987	18	-46	-22	19.75
Cerebellar lobule IV-V	R		8	-60	-8	19.33
Cerebellar lobule IV-V	R		12	-56	-18	17.38
Source: L Lobule VI						
<u>Controls</u>						
Middle frontal gyrus	R	309	46	2	58	5.57
Superior frontal gyrus, dorsolateral	R		26	8	66	4.50
Middle frontal gyrus	R	687	40	44	38	7.64
Middle frontal gyrus	R		28	38	28	6.81
Middle frontal gyrus	R		32	38	36	6.17
Middle frontal gyrus	L	188	-38	44	38	6.32
Superior frontal gyrus, dorsolateral	L		-30	34	38	5.44
Middle frontal gyrus	L		-40	44	30	4.98
Supramarginal gyrus	R	358	42	-42	42	4.96
Postcentral gyrus	R		40	-42	58	4.74
Cuneus	R	200	14	-88	42	4.78
Cuneus	R		18	-78	44	4.67
Superior parietal gyrus	R		22	-82	50	4.55
Cuneus	L	287	-16	-74	34	4.54
Cuneus	L		-6	-88	38	4.45
Cuneus	L		-10	-84	30	4.35
Middle occipital gyrus	L	370	-30	-88	6	5.34
Middle occipital gyrus	L		-34	-74	10	5.06
Middle occipital gyrus	L		-28	-80	10	4.88
Cerebellar lobule VI	L	20419	-14	-70	-18	21.44
Cerebellar lobule VI	L		-20	-56	-22	20.47
Cerebellar lobule VI	L		-24	-68	-22	20.45

S-Table 7-3 (Cont'd): Peak coordinates of regions showing significant connectivity with cerebellar sources in controls ($n = 17$) and OCD samples ($n = 20$).

	Hemisphere	k	x	y	z	T
(cont'd)						
<u>OCD</u>						
Middle occipital gyrus	L	497	-42	-88	10	4.83
Middle occipital gyrus	L		-30	-78	10	4.35
Middle occipital gyrus	L		-36	-82	6	4.24
Cerebellar lobule VI	L	23896	-28	-54	-28	19.46
Cerebellar lobule VI	L		-36	-50	-28	16.94
Cerebellar lobule VI	L		-28	-44	-28	15.69
Source: R Lobule VI						
<u>Controls</u>						
Middle Frontal Gyrus	L	180	-38	-4	66	6.41
Precentral gyrus	L		-30	-4	62	4.75
Precentral gyrus	L		-38	-8	58	4.41
Superior frontal gyrus, medial	L	532	-14	62	30	6.00
Superior frontal gyrus, dorsolateral	L		-28	48	20	5.86
Superior frontal gyrus, dorsolateral	L		-30	44	38	5.47
Supplementary motor area	L	156	-6	10	48	5.61
Superior frontal gyrus, dorsolateral	L		-12	10	54	4.25
Thalamus	L	209	-2	-14	10	5.41
Caudate nucleus	L		-16	-18	20	5.37
Thalamus	L		-8	-18	14	4.86
Cerebellar lobule VI	R	17986	32	-56	-26	24.28
Cerebellar lobule VI	R		40	-54	-26	19.66
Cerebellar lobule VI	R		34	-48	-28	18.51
<u>OCD</u>						
Precentral gyrus	L	1087	-24	-22	70	6.19
Precentral gyrus	L		-28	-16	66	5.83
Supplementary motor area	R		8	2	70	5.64
Inferior parietal gyrus, excluding supramarginal and angular gyri	L	415	-38	-54	58	6.28
Superior parietal gyrus	L		-30	-52	58	5.23
Superior parietal gyrus	L		-38	-44	56	4.52
Middle occipital gyrus	L	240	-30	-74	14	5.49
Middle occipital gyrus	L		-28	-78	22	5.22
Middle occipital gyrus	L		-32	-82	14	4.27
Cerebellar lobule VI	R	25478	22	-74	-22	26.30
Cerebellar lobule VI	R		28	-56	-28	23.40
Cerebellar lobule VI	R		20	-66	-22	21.88

S-Table 7-3 (Cont'd): Peak coordinates of regions showing significant connectivity with cerebellar sources in controls ($n = 17$) and OCD samples ($n = 20$).

	Hemisphere	k	x	y	z	T
Source: L Lobule IX						
<u>Controls</u>						
Superior frontal gyrus, dorsolateral	L	267	-20	34	42	5.85
Superior frontal gyrus, dorsolateral	L		-16	34	34	5.42
Middle frontal gyrus	L		-28	24	42	4.77
Middle temporal gyrus	R	240	50	-12	-12	5.89
Middle temporal gyrus	R		64	0	-14	5.02
Middle temporal gyrus	R		62	6	-26	4.51
Middle occipital gyrus	R	1662	42	-64	28	8.64
Middle occipital gyrus	R		38	-82	38	7.52
Angular gyrus	R		46	-58	24	7.19
Middle occipital gyrus	L	915	-38	-78	28	8.61
Middle occipital gyrus	L		-34	-84	32	7.34
Middle occipital gyrus	L		-34	-72	32	6.75
Cerebellar lobule IX	L	19015	-10	-54	-50	40.58
Cerebellar lobule IX	L		-2	-56	-50	35.64
Cerebellar lobule IX	L		-6	-48	-46	30.09
<u>OCD</u>						
Superior frontal gyrus, medial orbital	R	1079	12	62	-4	6.52
Superior frontal gyrus, dorsolateral	R		20	70	14	5.66
Superior frontal gyrus, medial orbital	R		6	68	-4	5.59
Superior frontal gyrus, dorsolateral	R	1545	28	16	56	6.16
Inferior frontal gyrus, triangular part	R		54	28	24	5.87
Superior frontal gyrus, dorsolateral	R		22	16	42	5.73
Middle occipital gyrus	R	8864	46	-68	24	9.77
Middle temporal gyrus	R		50	-60	20	9.66
Angular gyrus	R		54	-64	26	9.52
Middle occipital gyrus	L	815	-42	-82	30	7.26
Middle occipital gyrus	L		-46	-78	24	6.59
Middle occipital gyrus	L		-42	-72	28	6.56
Fusiform gyrus	L	234	-24	-40	-14	5.26
Cerebellar lobule IV-V	L		-20	-42	-22	4.53
Cerebellar lobule IV-V	L		-20	-34	-26	4.43
Cerebellar lobule IV-V	R	253	22	-42	-18	5.94
Parahippocampal gyrus	R		18	-26	-12	5.09
Fusiform gyrus	R		20	-34	-18	4.44
Cerebellar lobule IX	L	8540	-2	-56	-50	45.47
Cerebellar lobule IX	L		-8	-52	-46	36.53
Cerebellar lobule IX	L		-12	-56	-54	31.41
Source: R Lobule IX						
<u>Controls</u>						
Superior frontal gyrus, dorsolateral	R	313	22	42	48	7.93
Superior frontal gyrus, dorsolateral	R		16	46	44	5.99
Superior frontal gyrus, dorsolateral	R		16	42	54	5.56
Superior frontal gyrus, medial orbital	R	2968	4	56	-12	7.33
Superior frontal gyrus, medial orbital	R		12	52	-8	6.77
Superior frontal gyrus, medial orbital	L		-4	52	-8	6.70

S-Table 7-3 (Cont'd): Peak coordinates of regions showing significant connectivity with cerebellar sources in controls ($n = 17$) and OCD samples ($n = 20$).

	Hemisphere	k	x	y	z	T
(cont'd)						
Superior frontal gyrus, dorsolateral	L	1191	-20	16	56	7.93
Superior frontal gyrus, dorsolateral	L		-14	24	48	7.38
Middle frontal gyrus	L		-22	20	48	6.85
Middle temporal gyrus	L	1168	-62	-4	-18	9.09
Middle temporal gyrus	L		-62	-12	-22	7.33
Inferior temporal gyrus	L		-48	-18	0	5.85
Middle temporal gyrus	R	144	60	-4	-26	5.40
Middle temporal gyrus	R		62	6	-26	5.34
Middle temporal gyrus	R		52	2	-26	4.67
Postcentral gyrus	R	231	18	-42	66	5.01
Paracentral Lobule	R		16	-42	58	4.83
Postcentral gyrus	R		16	-34	66	4.39
Thalamus	L	617	-2	-8	6	7.44
Thalamus	R		4	-12	2	6.23
Thalamus	L		-10	-14	14	6.16
Middle occipital gyrus	R	972	42	-64	24	10.86
Middle occipital gyrus	R		42	-74	30	10.56
Middle occipital gyrus	R		50	-68	28	8.84
Middle occipital gyrus	L	2007	-42	-78	28	8.92
Middle temporal gyrus	L		-42	-64	16	8.29
Middle occipital gyrus	L		-34	-78	30	8.22
Fusiform gyrus	L	1015	-34	-36	-18	7.15
Parahippocampal Gyrus	L		-24	-26	-14	6.66
Cerebellar lobule IX	R	11943	4	-54	-46	35.73
Cerebellar lobule IX	R		12	-50	-50	28.72
Cerebellar lobule IX	R		4	-56	-54	24.47
<u>OCD</u>						
Superior frontal gyrus, dorsolateral	L	277	-24	56	0	6.16
Lateral orbital gyrus	L		-38	42	-14	5.29
Superior frontal gyrus, dorsolateral	L		-26	64	0	4.66
Superior frontal gyrus, medial	L	207	-2	58	6	4.82
Anterior cingulate & paracingulate gyri	L		-2	52	12	4.29
Superior frontal gyrus, medial	L		-8	52	6	4.23
Middle frontal gyrus	L	1187	-30	14	62	7.80
Middle frontal gyrus	L		-24	20	42	6.31
Middle frontal gyrus	L		-28	26	46	6.08
Angular gyrus	R	944	50	-70	38	8.85
Angular gyrus	R		44	-74	34	6.97
Angular gyrus	R		46	-70	46	6.14
Cerebellar lobule IX	R	18992	8	-56	-54	33.86
Cerebellar lobule IX	R		2	-56	-48	31.72
Cerebellar lobule IX	R		12	-52	-48	27.75

S-Table 7-3 (Cont'd): Peak coordinates of regions showing significant connectivity with cerebellar sources in controls ($n = 17$) and OCD samples ($n = 20$).

	Hemisphere	k	x	y	z	T
Source: L Crus I						
<u>Controls</u>						
Middle frontal gyrus	R	3685	46	30	42	8.56
Middle frontal gyrus	R		42	20	44	7.59
Middle frontal gyrus	R		42	20	54	6.90
Inferior parietal gyrus, excluding supramarginal and angular gyri	R	1128	54	-42	48	7.43
Angular gyrus	R		54	-56	30	7.13
Angular gyrus	R		50	-64	38	6.97
Cerebellar Crus I	L	15033	-34	-70	-36	26.25
Cerebellar Crus I	L		-42	-74	-36	25.42
Cerebellar Crus I	L		-34	-78	-32	24.49
<u>OCD</u>						
Anterior orbital gyrus	R	4825	28	44	-18	8.77
Anterior orbital gyrus	R		20	44	-14	7.81
Middle frontal gyrus	R		40	58	0	7.81
Angular gyrus	R	1270	46	-60	42	5.48
Inferior parietal gyrus, excluding supramarginal and angular gyri	R		50	-56	56	5.42
Inferior parietal gyrus, excluding supramarginal and angular gyri	R		54	-54	48	5.19
Middle temporal gyrus	R	652	64	-32	-8	5.28
Middle temporal gyrus	R		60	-18	-14	5.22
Middle temporal gyrus	R		64	-24	-10	5.06
Calcarine fissure and surrounding cortex	R	241	0	-96	-4	4.52
Calcarine fissure and surrounding cortex	R		0	-104	2	4.11
Middle occipital gyrus	L		-10	-102	0	3.90
Cerebellar Crus I	L	15734	-24	-78	-28	25.51
Cerebellar Crus I	L		-34	-70	-32	24.99
Cerebellar Crus I	L		-40	-74	-28	21.53
Source: R Crus I						
<u>Controls</u>						
Supplementary motor area	L	3175	-4	14	72	10.41
Superior frontal gyrus, dorsolateral	L		-20	62	28	8.98
Superior frontal gyrus, dorsolateral	L		-24	56	24	6.87
Angular gyrus	L	661	-42	-64	44	5.73
Inferior parietal gyrus, excluding supramarginal and angular gyri	L		-34	-68	48	5.50
Cerebellar Crus I	R	9959	40	-74	-36	31.13
Cerebellar Crus I	R		34	-78	-32	23.46
Cerebellar Crus I	R		38	-66	-36	22.45
<u>OCD</u>						
Superior frontal gyrus, medial	L	3077	-2	28	58	10.23
Supplementary motor area	L		-4	24	68	9.10
Supplementary motor area	L		-4	16	70	8.12

S-Table 7-3 (Cont'd): Peak coordinates of regions showing significant connectivity with cerebellar sources in controls ($n = 17$) and OCD samples ($n = 20$).

(cont'd)		Hemisphere	k	x	y	z	T
	Middle Frontal Gyrus	L	728	-38	62	-4	6.56
	IFG pars orbitalis	L		-38	54	-14	5.83
	Gyrus rectus	R	315	0	52	-22	6.40
	Gyrus rectus	R		4	48	-16	4.66
	Gyrus rectus	L		-6	44	-18	4.51
	Angular gyrus	L	1427	-38	-56	30	6.25
	Angular gyrus	L		-44	-56	38	6.04
	Inferior parietal gyrus, excluding supramarginal and angular gyri	L		-34	-70	48	5.80
	Middle temporal gyrus	L	676	-56	-40	-8	5.94
	Middle temporal gyrus	L		-62	-46	-4	5.64
	Middle temporal gyrus	L		-64	-38	-8	4.99
	Caudate nucleus	R	170	18	-4	20	5.50
	Cerebellar Crus I	R	14907	28	-74	-32	27.37
	Cerebellar Crus I	R		36	-78	-36	24.17
	Cerebellar Crus I	R		26	-82	-28	22.91

Source: L Crus II

Controls

	Middle frontal gyrus	R	5726	46	14	48	10.43
	Middle frontal gyrus	R		40	10	44	9.59
	Middle frontal gyrus	R		42	30	34	8.97
	Inferior parietal gyrus, excluding supramarginal and angular gyri	R	2631	60	-50	38	9.79
	Supramarginal gyrus	R		56	-44	34	9.03
	Inferior parietal gyrus, excluding supramarginal and angular gyri	R		52	-54	38	8.30
	Middle temporal gyrus	R	780	60	-36	0	7.26
	Middle temporal gyrus	R		56	-30	-4	6.87
	Middle temporal gyrus	R		54	-22	-12	6.71
	Precuneus	R	370	12	-64	38	5.23
	Posterior cingulate gyrus	R		4	-40	20	4.92
	Precuneus	R		12	-54	38	4.78
	Cerebellar vermis IV-V		340	4	-54	-12	5.36
	Cerebellar lobule IV-V	R		12	-60	-14	5.16
	Cerebellar lobule VI	R		18	-60	-22	5.13
	Cerebellar Crus II	L	10803	-14	-82	-40	27.15
	Cerebellar Crus II	L		-38	-70	-46	22.91
	Cerebellar Crus II	L		-34	-78	-46	21.15

OCD

	Middle frontal gyrus	R	2051	46	28	42	6.72
	Middle frontal gyrus	R		38	24	38	6.22

S-Table 7-3 (Cont'd): Peak coordinates of regions showing significant connectivity with cerebellar sources in controls ($n = 17$) and OCD samples ($n = 20$).

	Hemisphere	k	x	y	z	T
(cont'd)						
Anterior orbital gyrus	R	4177	26	44	-18	9.27
Middle frontal gyrus	R		36	56	-12	8.79
Superior frontal gyrus, dorsolateral	R		28	66	10	8.00
Middle cingulate & paracingulate gyri	R		12	-48	34	7.93
Angular gyrus	L	1076	-48	-68	42	7.90
Angular gyrus	L		-56	-56	30	6.79
Angular gyrus	R	2811	56	-60	30	12.84
Angular gyrus	R		50	-64	38	12.76
Angular gyrus	R		48	-58	30	10.45
Precuneus	R	1656	8	-54	38	9.40
Precuneus	R		2	-48	38	8.29
Middle temporal gyrus	R	2271	56	-18	-14	8.71
Middle temporal gyrus	R		64	-32	-12	7.80
Inferior temporal gyrus	R		56	0	-32	7.69
Inferior temporal gyrus	L	344	-52	-12	-28	5.28
Middle temporal gyrus	L		-48	-8	-22	5.22
Middle temporal gyrus	L		-44	-2	-18	4.74
Middle temporal gyrus	L	411	-70	-32	-14	6.52
Middle temporal gyrus	L		-66	-28	-8	5.50
Middle temporal gyrus	L		-66	-36	-6	4.81
Cerebellar Crus II	L	12877	-34	-78	-46	25.57
Cerebellar Crus II	L		-30	-74	-40	23.75
Cerebellar Crus II	L		-16	-78	-40	23.26

Source: R Crus II

Controls

Middle frontal gyrus	L	6245	-34	10	44	9.86
Middle frontal gyrus	L		-44	16	38	9.60
Precentral gyrus	L		-42	10	46	8.61
Posterior cingulate gyrus	L	434	-2	-46	22	4.98
Posterior cingulate gyrus	R		0	-40	28	4.88
Angular gyrus	L	2965	-44	-68	30	9.29
Angular gyrus	L		-38	-70	44	8.58
Angular gyrus	L		-42	-62	42	8.52
Middle temporal gyrus	L	1497	-52	-40	-8	7.52
Middle temporal gyrus	L		-60	-32	-8	7.01
Inferior temporal gyrus	L		-62	-60	-12	6.96
Cerebellar Crus II	R	10767	18	-84	-42	29.30
Cerebellar Crus II	R		36	-74	-42	21.76
Cerebellar Crus II	R		14	-82	-34	21.11

OCD

Lateral orbital gyrus	L	6186	-38	48	-14	9.29
Middle frontal gyrus	L		-42	58	-8	8.84
Middle frontal gyrus	L		-38	62	-2	8.80
Lateral orbital gyrus	R	266	42	42	-18	5.17

S-Table 7-3 (Cont'd): Peak coordinates of regions showing significant connectivity with cerebellar sources in controls ($n = 17$) and OCD samples ($n = 20$).

	Hemisphere	k	x	y	z	T
(cont'd)						
Anterior orbital gyrus	R		32	48	-14	4.54
Middle frontal gyrus	R		50	52	-8	4.32
Middle cingulate & paracingulate gyri	L	320	-6	-36	34	6.70
Middle cingulate & paracingulate gyri	L		-6	-42	40	6.01
Middle cingulate & paracingulate gyri	L		-2	-46	34	5.60
Angular gyrus	L	2809	-38	-64	42	11.64
Angular gyrus	L		-42	-56	38	10.64
Angular gyrus	L		-42	-58	46	9.86
Middle temporal gyrus	L	2245	-52	-40	-8	8.09
Middle temporal gyrus	L		-62	-46	-4	7.94
Middle temporal gyrus	L		-60	-38	-8	7.72
Middle temporal gyrus	R	206	68	-36	-12	4.96
Inferior temporal gyrus	R		66	-54	-14	4.35
Middle temporal gyrus	R		70	-36	-2	4.23
Inferior occipital gyrus	R	168	28	-98	-4	4.59
Middle occipital gyrus	R		28	-100	4	4.50
Inferior occipital gyrus	R		22	-102	-12	4.22
Cerebellar Crus II	R	14576	32	-74	-46	21.84
Cerebellar lobule VIII	R		24	-72	-46	19.40
Cerebellar Crus II	R		40	-72	-46	18.88

Note. Within-group ROI-to-voxel connectivity were thresholded at $p < .001$ (uncorrected) with clusterwise FDR $\alpha = 0.01$. Analysis voxel size: $3.5 \times 3.5 \times 3.5\text{mm}^3$. Coordinates are in MNI space, labelled according to AAL2 atlas. R = right; L = left.

S-Table 7-4: Results of regional connectivity between cerebellar ROIs and the rest of the brain, with age and sex modeled as covariates of no interest.

ROI Source	k	x	y	z	T	Hemisphere	Connectivity Regions
<u>Source: L Lobule I-IV</u>							
OCD > Controls	384	-42	48	-8	3.92	L	Middle Frontal Gyrus
		-34	50	-8	3.84	L	Middle Frontal Gyrus
		-42	58	0	3.83	L	Middle Frontal Gyrus
<u>Source: R Lobule V</u>							
OCD < Controls	534	8	58	0	4.22	R	Superior Frontal Gyrus, Medial
		8	52	10	3.64	R	Anterior cingulate & paracingulate gyri
OCD > Controls	2184	26	-56	44	7.10	R	Superior Parietal Lobule
		28	-60	52	5.06	R	Superior Parietal Lobule
		20	-54	50	4.90	R	Precuneus
<u>Source: L Lobule IX</u>							
OCD < Controls	598	-6	42	2	3.92	L	Anterior cingulate & paracingulate gyri
		-8	50	2	3.88	L	Anterior cingulate & paracingulate gyri
		-2	46	8	3.71	L	Anterior cingulate & paracingulate gyri
<u>Source: R Lobule IX</u>							
OCD < Controls	721	-16	-22	76	4.76	L	Paracentral Lobule
		-30	-32	42	4.48	L	Postcentral Gyrus
		-22	-26	70	4.14	L	Postcentral Gyrus
	501	18	-42	58	4.29	R	Paracentral Lobule
		26	-42	70	3.90	R	Postcentral Gyrus
		18	-36	66	3.58	R	Postcentral Gyrus
	398	-44	-26	6	4.19	L	Superior Temporal Gyrus
		-50	-26	12	4.11	L	Superior Temporal Gyrus
		-50	-20	6	3.94	L	Superior Temporal Gyrus
	355	-2	-56	28	4.01	L	Precuneus
		8	-56	20	3.68	R	Precuneus
		8	-60	28	3.60	R	Precuneus
<u>Source: L Crus I</u>							
OCD > Controls	496	-14	28	-28	5.35	L	Medial Orbital Gyrus
		-2	56	-22	4.24	L	Rectus
<u>Source: R Crus I</u>							
OCD < Controls	669	36	-22	0	4.83	R	Insula
		32	-14	6	4.15	R	Putamen
<u>Source: L Crus II</u>							
OCD > Controls	418	-6	52	-18	5.26	L	Rectal Gyrus
		4	66	-18	4.95	R	Superior Frontal Gyrus, Medial-Orbital
		-12	56	-14	4.41	L	Anterior Orbital Gyrus

Note. Correlational coefficients were converted into Fisher-Z connectivity analyses. ROI-to-voxel connectivity were thresholded at $p < .001$ (uncorrected) with clusterwise FDR $\alpha = 0.05$. Analysis voxel size: $3.5 \times 3.5 \times 3.5\text{mm}^3$. Coordinates are in MNI space, labelled according to AAL2 atlas. R = right; L = left.

S-Table 7-5: Results of regional connectivity between CSTC ROIs and the rest of the brain, with age and sex as covariates of no interest.

	k	x	y	z	T	Hemisphere	Connectivity Regions
Source: R Medial Orbitofrontal Cortex							
OCD > Controls	404	56	-42	-14	4.40	R	Inferior temporal gyrus
		64	-56	-12	4.35	R	Inferior temporal gyrus
		56	-34	-12	3.91	R	Middle temporal gyrus
Source: R Lateral Orbitofrontal Cortex							
OCD > Controls	446	-2	-28	-18	4.53	L	Brainstem
		-6	-14	-32	4.39	L	Brainstem
		0	-36	-18	4.29		Cerebellar vermis I-II
Source: R Posterior Orbitofrontal Cortex							
OCD < Controls	391	4	-46	-4	5.67		Cerebellar vermis IV-V
		22	-36	-14	3.96	R	Parahippocampal gyrus
		4	-54	0	3.88		Cerebellar vermis IV-V
	813	38	-18	72	5.51	R	Precentral gyrus
		30	-22	72	4.38	R	Precentral gyrus
		32	-14	52	4.30	R	Precentral gyrus
OCD > Controls	2821	56	-40	24	5.41	R	Supramarginal gyrus
		40	-42	44	4.91	R	Inferior parietal, but supramarginal and angular gyri
		60	-42	0	4.91	R	Middle temporal gyrus
	656	42	6	48	4.63	R	Precentral gyrus
		46	10	42	4.25	R	Middle frontal gyrus
		38	12	42	4.19	R	Middle frontal gyrus
	705	8	-60	44	3.72	R	Precuneus
		4	-54	52	3.66	R	Precuneus
		-2	-64	44	3.41	L	Precuneus
Source: L Posterior Orbitofrontal Cortex							
OCD > Controls	595	46	-42	38	4.20	R	Supramarginal gyrus
		44	-42	46	4.16	R	Inferior parietal, but supramarginal and angular gyri
		46	-46	54	4.05	R	Inferior parietal, but supramarginal and angular gyri

S-Table 7-5 (cont'd): Results of regional connectivity between CSTC ROIs and the rest of the brain, with age and sex as covariates of no interest.

	k	x	y	z	T	Hemisphere	Connectivity Regions
<u>Source: R Anterior Cingulate</u>							
OCD < Controls	586	4	-46	-4	5.92		Cerebellar vermis IV-V
		8	-46	-12	4.48	R	Cerebellar lobule IV-V
		0	-54	-8	4.46		Cerebellar lobule IV-V
OCD > Controls	405	8	-32	58	4.77	R	Paracentral lobule
		-2	-18	70	3.71	L	Paracentral lobule
		2	-32	64	3.46	R	Paracentral lobule
<u>Source: L Anterior Cingulate</u>							
OCD > Controls	611	-34	44	28	6.29	L	Middle frontal gyrus
		-30	44	20	4.75	L	Middle frontal gyrus
		-34	54	28	4.69	L	Middle frontal gyrus
<u>Source: R Thalamus</u>							
OCD < Controls	1682	0	-68	-8	5.35		Cerebellar vermis VI
		-28	-68	-18	4.16	L	Cerebellar lobule VI
		12	-68	-22	3.99	R	Cerebellar lobule VI
<u>Source: L Thalamus</u>							
OCD < Controls	1910	18	-74	-26	4.60	R	Cerebellar lobule VI
		42	-68	-40	4.50	R	Cerebellar crus II
		22	-82	-46	4.26	R	Cerebellar crus II
<u>Source: R Caudate</u>							
OCD < Controls	395	-42	-50	-18	5.23	L	Inferior temporal gyrus
		-42	-60	-14	4.02	L	Fusiform gyrus
<u>Source: L Caudate</u>							
OCD < Controls	553	0	-50	28	4.13	L	Posterior cingulate gyrus
		4	-44	32	4.08	R	Median cingulate and paracingulate gyri
		0	-60	28	4.00	L	Precuneus

Note. Results were significant at voxelwise $p < .005$ (uncorrected) and extend of $\alpha < .05$ (FDR-corrected). Analysis voxel size: $3.5 \times 3.5 \times 3.5\text{mm}^3$. Sections in green indicates significant group differences in altered functional connectivity between CSTC ROIs with cerebellar regions. Coordinates are in MNI space, labelled according to AAL2 atlas. OCD = OCD samples; R = Right; L = Left

S-Table 7-6: Associations between CSTC ROIs-to-voxel functional connectivity involving the cerebellum and OCI-R and HDRS in the entire sample.

CSTC Source and Connectivity Peak	Peak coordinates			Associated index	ρ_s	p
	x	y	z			
Source: Right Lateral Orbitofrontal						
Brainstem to Cerebellar Vermis I-II	-2	-28	-18	OCI-R	.711***	<.000
				HDRS	.366*	.026
Source: Right Posterior Orbitofrontal						
Cerebellar Vermis IV-V	4	-46	-4	OCI-R	-.609***	<.000
Source: Right Anterior Cingulate						
Cerebellar Vermis IV-V to right Lobule IV-V	4	-46	-4	OCI-R	-.489**	.002
Source: Right Thalamus						
Cerebellar Vermis VI	0	-68	-8	OCI-R	-.591***	<.000
Source: Left Thalamus						
Right Cerebellar Lobule VI	18	-74	-26	OCI-R	-.638***	<.000
				HDRS	-.345*	.037

Note. Sample size = 37 participants (17 Controls, 20 OCD). Spearman correlations significant at $p < .05$ (without Bonferroni corrections) are presented. Clinical indices included in the analysis were the Obsessive-Compulsive Inventory (Revised; OCI-R), and the Hamilton Depressive Rating Scale (HDRS). Coordinates are in MNI space, labelled according to AAL2 atlas. (* $p < .05$; ** $p < .01$; *** $p < .001$)

S-Table 7-7: Hierarchical regression for functional connectivity strengths between CSTC ROIs and cerebellar regions.

			Model-level Statistics						Predictor Coefficients		
Dependent Variable:	Model	Predictors	df 1	df 2	F	p	R ²	R ² Change	b	t	p
Functional connectivity between posterior orbitofrontal and Vermis IV-V	1	HDRS	1	36	0.64	.43	.02	.02	-.13	-.80	.43
	2	HDRS	2	36	8.94	<.001	.31	.33	.59	2.64*	.01
		OCI-R							-.93	-4.12***	<.001
	3	HDRS	3	36	14.81	<.001	.54	.23	.30	1.52	.14
		OCI-R							-.25	-1.02	.32
		Group							-.68	-4.213***	<.001
			Model-level Statistics						Predictor Coefficients		
Dependent Variable:	Model	Predictors	df 1	df 2	F	p	R ²	R ² Change	b	t	p
Functional connectivity between right anterior cingulate and Vermis IV-V to right lobule IV-V	1	HDRS	1	36	0.19	.67	.01	.01	-.07	-.44	.67
	2	HDRS	2	36	4.73	.02	.22	.21	.51	2.09*	.04
		OCI-R							-.75	-3.04**	.005
	3	HDRS	3	36	13.35	<.001	.55	.33	.16	.79	.44
		OCI-R							.07	.27	.79
		Group							-.81	-4.91***	<.001
			Model-level Statistics						Predictor Coefficients		
Dependent Variable:	Model	Predictors	df 1	df 2	F	p	R ²	R ² Change	b	t	p
Functional connectivity between right thalamus and Vermis VI to Left Lobule VI	1	HDRS	1	36	3.34	.08	.09	.09	-.30	-1.83	.08
	2	HDRS	2	36	4.42	.02	.21	.12	.14	.58	.56
		OCI-R							-.56	-2.26*	.03
	3	HDRS	3	36	11.12	<.001	.50	.30	-.19	-.90	.38
		OCI-R							.21	.80	.43
		Group							-.77	-4.44***	<.001
			Model-level Statistics						Predictor Coefficients		
Dependent Variable:	Model	Predictors	df 1	df 2	F	p	R ²	R ² Change	b	t	p
Functional connectivity of Left thalamus and Right Lobule VI to Crus II	1	HDRS	1	36	6.34	.02	.15	.15	-.39	-2.52*	.02
	2	HDRS	2	36	7.51	.002	.31	.15	.11	.46	.65
		OCI-R							-.63	-2.74**	.010
	3	HDRS	3	36	12.10	<.001	.52	.22	-.18	-.87	.39
		OCI-R							.03	.10	.92
		Group							-.66	-3.88***	<.001

Note. 'Control', and 'Male' are reference groups for Group, and Sex variables respectively.

Analyses were performed on 17 controls and 20 OCD samples. Hierarchical regression was not conducted for functional connectivity between right lateral orbitofrontal ROI and Vermis

I-II due to heteroscedasticity. HDRS = Hamilton Depressive Rating Scale; OCI-R =

Obsessive-Compulsive Inventory (Revised); *b* = standard estimate of beta. (* $p < .05$. ** p

< .01. *** $p < .001$)

S-Figure 7-1. Results of ROI-to-voxel connectivity analyses within control and patient groups superimposed on canonical rendered brain. Voxelwise $p < .001$ (uncorrected) and clusterwise FDR $\alpha = 0.01$.

S-Figure 7-1 (Cont'd). Results of ROI-to-voxel connectivity analyses within control and patient groups superimposed on canonical rendered brain, voxelwise $p < .001$ (uncorrected) and clusterwise FDR $\alpha = 0.01$.

S-Figure 7-1 (Cont'd). Results of ROI-to-voxel connectivity analyses within control and patient groups superimposed on canonical rendered brain, voxelwise $p < .001$ (uncorrected) and clusterwise FDR $\alpha = 0.01$.

S-Figure 7-2. Significant group differences in ROI-to-voxel connectivity analyses. Voxelwise $p < .005$ (uncorrected) and extent threshold of $\alpha < .05$ (FDR-corrected). Error bars represent standard errors. Significant group differences in ROI-to-voxel connectivity were observed the following ROI sources – A) Left lobule V; B) Right lobule V; C) Right lobule I-IV; D) Left lobule IX; E) Right lobule IX; F) Right Crus I; G) Left Crus II; H) Right Crus II.

S-Figure 7-2 (Cont'd). Significant group differences in ROI-to-voxel connectivity analyses. Voxelwise $p < .005$ (uncorrected) and extent threshold of $\alpha < .05$ (FDR-corrected). Error bars represent standard errors. Significant group differences in ROI-to-voxel connectivity were observed the following ROI sources – A) Left lobule V; B) Right lobule V; C) Right lobule I-IV; D) Left lobule IX; E) Right lobule IX; F) Right Crus I; G) Left Crus II; H) Right Crus II.

■ Controls ■ OCD

S-Figure 7-3. Scatterplots of Spearman correlations between functional connectivity values and cognitive and clinical indices within Controls and OCD samples.

■ Controls ■ OCD

S-Figure 7-3 (Cont'd). Scatterplots of Spearman correlations between functional connectivity values and cognitive and clinical indices within Controls and OCD samples.

■ Controls ■ OCD

S-Figure 7-3 (Cont'd). Scatterplots of Spearman correlations between functional connectivity values and cognitive and clinical indices within Controls and OCD samples.

■ Controls ■ OCD

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S-Figure 7-3 (Cont'd). Scatterplots of Spearman correlations between functional connectivity values and cognitive and clinical indices within Controls and OCD samples. Only scatterplots of significant correlations were presented. Cognitive indices evaluated were: Symbol Span, Trail-Making Test B (TMTB), Trail-Making Test Index (TMTB – TMTA), Stroop Index, Accuracy rates of high-load conditions of the Visual task, and Stop-signal reaction time. Clinical indices evaluated were: Y-BOCS total/obsessions/compulsions scores, age of onset, duration of illness, duration of treatment, and mean daily dosage of fluoxetine equivalent. * $p < .05$; ** $p < .01$.

S-Figure 7-4. Group differences in CSTC ROIs-to-voxel functional connectivity involving the cerebellum, with age and sex as covariates of no interest. Results were significant at voxelwise $p < .005$ (uncorrected) and extend threshold of $\alpha < .05$ (FDR-corrected). Blue indicates reduced functional connectivity in OCD samples compared to controls (OCD < Controls). Red indicates increased functional connectivity in OCD samples compared to controls (OCD > Controls). Results were based on 17 Controls and 20 OCD samples. 339

S-Figure 7-5. Significant group differences in all CSTC ROI-to-voxel functional connectivity, with age and sex as covariates of no interest.

S-Figure 7-5 (Cont'd). Significant group differences in all CSTC ROI-to-voxel functional connectivity, with age and sex as covariates of no interest. Results were significant at voxelwise $p < .005$ (uncorrected) and extend threshold of $\alpha < .05$ (FDR-corrected). Blue indicates reduced functional connectivity in OCD samples compared to controls (OCD < Controls). Red indicates increased functional connectivity in OCD samples compared to controls (OCD > Controls).

Results were based on 17 Controls and 20 OCD samples.