Neural Circuitry in Obsessive Compulsive Disorder: an fMRI Study of the Effect of IV Citalopram

by

Tracy Prema Bhikram

A thesis submitted in conformity with the requirements for the degree of Master of Science

Institute of Medical Science
University of Toronto

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Master of Science
Institute of Medical Science
University of Toronto
2012

Abstract

**Background:** Functional imaging studies have examined the neural circuitry of subjects with obsessive compulsive disorder (OCD), and the changes associated with oral treatment. However, the effect of intravenous (IV) serotonin reuptake inhibitors (SRIs) on neuronal activation has not been investigated in OCD subjects, even though IV SRIs have been shown to be more effective than oral pharmacotherapy.

**Methods:** Six OCD and 6 control subjects underwent functional magnetic resonance imaging while receiving infusions of citalopram and placebo, in a randomized, crossover design.

**Results:** Compared to controls, OCD subjects exhibited hyperactivation of the orbitofrontal cortex and anterior cingulate cortex while looking at symptom provoking pictures at baseline. However, after the citalopram infusion, patients displayed attenuations of these regions, which correlated with reductions in subjective anxiety ratings.

**Conclusion:** The effects observed after the IV citalopram infusion are similar to modulations observed after prolonged oral pharmacotherapy trials, illustrating the benefits of IV SRIs.
Acknowledgments

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<th>Description</th>
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<tbody>
<tr>
<td>5-HIAA</td>
<td>5-Hydroxyindoleacetic acid</td>
</tr>
<tr>
<td>5-HT</td>
<td>5-hydroxytryptamine/serotonin</td>
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<tr>
<td>ACC</td>
<td>Anterior cingulate cortex</td>
</tr>
<tr>
<td>BDI-II</td>
<td>Beck Depression Inventory II</td>
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<tr>
<td>BOLD</td>
<td>Blood oxygen level-dependent</td>
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<tr>
<td>CAMH</td>
<td>Centre for Addiction and Mental Health</td>
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<tr>
<td>CBT</td>
<td>Cognitive behaviour therapy</td>
</tr>
<tr>
<td>dACC</td>
<td>Dorsal anterior cingulate cortex</td>
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<tr>
<td>Deoxy-Hb</td>
<td>Deoxygenated hemoglobin</td>
</tr>
<tr>
<td>DLPFC</td>
<td>Dorsolateral prefrontal cortex</td>
</tr>
<tr>
<td>DS</td>
<td>Disgust Scale</td>
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<tr>
<td>DSM-IV-TR</td>
<td>Diagnostic and Statistical Manual of Mental Disorders IV – Text Revision</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
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<tr>
<td>fMRI</td>
<td>Functional magnetic resonance imaging</td>
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<td>Abbreviation</td>
<td>Full Form</td>
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</tr>
<tr>
<td>Hb</td>
<td>Hemoglobin</td>
</tr>
<tr>
<td>hrf</td>
<td>Hemodynamic response function</td>
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<tr>
<td>IV</td>
<td>Intravenous</td>
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<tr>
<td>mCPP</td>
<td>meta-Chlorophenylpiperazine</td>
</tr>
<tr>
<td>MDD</td>
<td>Major depressive disorder</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear magnetic resonance</td>
</tr>
<tr>
<td>OCD</td>
<td>Obsessive compulsive disorder</td>
</tr>
<tr>
<td>OFC</td>
<td>Orbitofrontal cortex</td>
</tr>
<tr>
<td>Oxy-Hb</td>
<td>Oxygenated hemoglobin</td>
</tr>
<tr>
<td>PET</td>
<td>Positron emission tomography</td>
</tr>
<tr>
<td>Q-LES-Q</td>
<td>Quality of Life Enjoyment and Satisfaction Questionnaire</td>
</tr>
<tr>
<td>rACC</td>
<td>Rostral anterior cingulate cortex</td>
</tr>
<tr>
<td>rCBF</td>
<td>Regional cerebral blood flow</td>
</tr>
<tr>
<td>REB</td>
<td>Research ethics board</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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</tr>
<tr>
<td>RF</td>
<td>Radiofrequency</td>
</tr>
<tr>
<td>ROI</td>
<td>Region of interest</td>
</tr>
<tr>
<td>RRI</td>
<td>Rotman Research Institute</td>
</tr>
<tr>
<td>SCID-I</td>
<td>Structured Clinical Interview for Diagnosis for DSM-IV Axis I Disorders</td>
</tr>
<tr>
<td>SPECT</td>
<td>Single photon emission computed tomography</td>
</tr>
<tr>
<td>SPP</td>
<td>Symptom provocation paradigm</td>
</tr>
<tr>
<td>SRI</td>
<td>Serotonin reuptake inhibitor</td>
</tr>
<tr>
<td>SSRI</td>
<td>Selective serotonin reuptake inhibitor</td>
</tr>
<tr>
<td>TSH</td>
<td>Thyroid stimulating hormone</td>
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<tr>
<td>Y-BOCS</td>
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Chapter 1 – Scientific Background

The purpose of this chapter is to:

- Describe obsessive compulsive disorder (OCD) and review its causes, impact and course of illness
- Review the efficacy of the main treatment forms for OCD
- Review neuroimaging studies in OCD
- Review proposed neurobiological models of OCD

1.1 Obsessive Compulsive Disorder

Obsessive Compulsive Disorder (OCD) is a debilitating disorder characterized by the recurrent presence of obsessions and/or compulsions, which cause significant distress and functional impairment. Obsessions are recurrent, intrusive, unwanted ideas, thoughts or impulses that cause anxiety or distress, and are regarded as repugnant and/or unacceptable by the person experiencing them. They are extremely difficult to dismiss and are more than simple worries about real-life problems. Compulsions are ritualistic behaviours that are performed physically and/or mentally, often according to a set of rules. They are performed to reduce the anxiety engendered by the obsessions, even though these behaviours or acts are clearly excessive, or not connected in any realistic way to what they are trying to prevent or avoid. Certain compulsions are concomitant with particular obsessions and thus may have a ‘logical connection’ (eg. excessive hand washing accompanying contamination fears), whereas other instances may involve magical thinking.
in order to connect the obsession to the compulsive acts (eg. counting to a certain number to prevent harm befalling a loved one) (Evans et al. 2002).

The obsessions and compulsions characteristic of OCD are often viewed as a negative feedback loop that is extremely difficult to break. Even though compulsions can be quite troubling, they become reinforced and fixed due to the tension reducing aspect of these learned behaviours. In turn, these compulsions reinforce the obsessions by preventing habituation of the fear evoking thoughts or stimuli. Avoidance behaviour is a central feature of the disorder because individuals with OCD often avoid certain situations or items that trigger their obsessive and/or compulsive behaviours. Some patients with OCD report that they must engage in compulsions a certain amount of times, whereas others repeat the behaviours until it feels ‘just right.’ OCD is a significant public health concern, and the identification of the factors that contribute to its onset, persistence and effective clinical management remain extremely important.

Etiology and Pathophysiology

The pathophysiology of OCD remains unclear, although genetic, environmental and neurobiological factors have been shown to confer vulnerability. It is believed that OCD is most likely caused by an interaction of these factors, however, for the purposes of clarity, they will be described separately.

Psychological Theories

Cognitive-behavioral models of OCD propose that obsessions arise from unwanted cognitive intrusions that are experienced by most people in the general population. These
intrusions develop into troublesome obsessions when they are appraised as being personally important, highly unacceptable or immoral, or as posing a threat for which the individual is personally responsible. Such appraisals evoke distress and motivates the individual to suppress the unwanted intrusion (Sachdev et al., 2005). Compulsive rituals develop as efforts to remove intrusions and to prevent any perceived harmful consequences. The compulsions become reinforced by the immediate and temporary reduction in distress, causing the behaviours to persist. However, performing the compulsions reminds the individual of the intrusions, thereby triggering their reoccurrence (Sachdev et al., 2005).

An evolutionary psychology view of OCD is that moderate versions of compulsive behaviors may have had evolutionary advantages. Supporters of this theory argue that numerous species exhibit behaviours such as checking for danger, avoiding contamination, and hoarding food, and a dysfunction in these strategies could lead to the expression of OCD (Abramowitz et al., 2009). Indeed, animals have been observed engaging in excessive and repetitive motor actions, such as digging, pecking and grooming, that are inappropriate to the context in which they are performed, similar to some compulsions. It has been proposed that these ‘displacement behaviours’ are triggered by conflict over territory, frustration, or when specific goal-directed behaviours are thwarted (Abramowitz et al., 2009).

**Genetic Contribution**

Pauls (2010) reviewed the literature on the heritability of OCD, and in general, there is convincing evidence that supports the importance of genetic factors for the
expression of OCD. Studies have shown that probands with OCD are more likely to have first degree family members who suffer from the disorder than are matched controls who do not have the disorder (Micallef et al., 2001). Furthermore, studies investigating differences in concordance rates between monozygotic and dizygotic twins suggest that obsessive-compulsive symptoms are moderately heritable, with genetic factors influencing OCD symptoms by approximately 27-47% and the remaining 53-73% of the variance attributed to environmental factors (Pauls 2010). While the literature provides evidence supporting the heritability of OCD within families, the genetic model that best fits this transmission differs between studies, suggesting that OCD is an oligogentic disorder (expression of the disorder is due to numerous genes). Specific attention has been paid to the genes important in the serotinergic, dopaminergic and glutaminergic systems, however, none have been consistently reported as being a risk factor of OCD (Micallef et al., 2001). Nevertheless, studies have reported that homozygosity for the serotonin transporter 5-HTT gene may confer susceptibility for the disorder (Abramowitz, 2009). Additionally, a recent meta-analysis of the relationship between OCD and all previously examined polymorphisms concluded that OCD is associated with polymorphisms in the serotonin transporter (HTTLPR) and receptor (HTR2A) genes (Taylor, 2012). However the author stated that more studies with large sample sizes are needed to confirm these findings.

**Neurochemical Models**

The hypothesis that OCD involves an abnormality in the serotonin neurotransmitter system is called the serotonin hypothesis. Serotonin, 5-hydroxytryptamine (5-HT), is a monoaminergic neurotransmitter known to mediate mood and emotion, as well as a host of
other basic functions (Dell’Osso et al., 2006). Serotonergic neurons project to most regions of the brain, with primary targets including the amygdala, caudate nucleus, substantia nigra, putamen, nucleus accumbens and multiple cortical areas (Dell’Osso et al., 2006). Most of the evidence supporting the role of a serotonin malfunction in OCD comes from treatment studies pointing to the anti-obsessional effect of selective serotonin reuptake inhibitors (SSRIs). Other antidepressants with less specific effects on the 5-HT system (eg. nortriptyline) do not appear to have significant anti-obsessive benefits (Bareggi et al., 2004). There is additional evidence that dysregulation of the serotonin system is involved in the pathophysiology of OCD. Studies have found that decreases in platelet serotonin levels, which is an indirect measure of neuronal reuptake, is highly correlated with clinical improvement due to clomipramine, a serotonin reuptake inhibitor (SRI) (Flament et al. 1987). As well, decreased levels of cerebrospinal 5-hydroxyindoleacetic acid (5-HIAA), a serotonin metabolite that is reduced with serotonin reuptake inhibition, has also been correlated with clinical improvements after treatment (Thoren et al. 1980). These various studies generally support the association between improvement of OCD symptoms with an SRI and acute alterations of serotonin in the brain.

Studies investigating serotonin receptor function also provides evidence for the role of this neurotransmitter in OCD. Zohar et al. (1987) found that OCD patients experienced an increase in obsessive–compulsive symptoms following administration of meta-chlorophenylpiperazine (mCPP). However, mCPP, a serotonin 5-HT \textsubscript{2C} and 5-HT \textsubscript{1D} receptor agonist, had no effect on normal controls, a finding replicated by Hollander et al. (1992). Similarly, Stein et al. (1999) found that administration of sumatriptan, also a 5-HT \textsubscript{1D} receptor agonist, resulted in a worsening of symptoms. The increase in obsessions
caused by mCPP can be blocked with pretreatment of the serotonin receptor antagonist metergaline (Pigott et al. 1991), or by chronic treatment with clomipramine (Zohar et al. 1988). More recently, Adams et al. (2005) found evidence of increased 5-HT2A receptor binding in the caudate nuclei of untreated OCD patients. These researchers speculate that the upregulation of 5-HT2A receptors may occur to compensate for deficient serotonin in the feedback loop between the thalamus, orbitofrontal cortex (OFC), caudate nuclei, and globus pallidus (Bartz and Hollander 2006). However, the exact role of serotonin in OCD and how SRIs improve symptoms remain unclear.

It should be pointed out that not all studies support the hypothesis that serotonin has a singular role in OCD. There is some evidence to support the role of the dopamine and glutamate system in the pathogenesis of the disorder, however, research focusing on these systems are minimal and often inconsistent.

**Neuroanatomical Correlates**

Neuroimaging techniques have advanced the search for brain abnormalities in OCD patients at rest and with symptom provocation. A majority of these studies have implicated the orbitofrontal cortex, anterior cingulate cortex, caudate and thalamus, as key regions involved in the etiology and maintenance of OCD. Neuroimaging studies investigating structural and functional brain abnormalities in OCD, as well as proposed neuropathway models of the disorder, will be summarized in greater detail in the neuroimaging section of this thesis.
Epidemiology and Impact of OCD

Although OCD was originally considered to be rare, findings from the Epidemiological Catchment Area survey demonstrated that OCD is a common psychiatric disorder (Myers et al. 1984). It has a lifetime prevalence of 1-3% (Rector et al. 2002) and has an approximately equal male:female gender ratio. (Lochner and Smith, 2001). Age at onset is usually during late adolescence, with males making up a disproportionate majority of early onset cases; nearly a quarter of males experience symptoms before age 10. Females, in contrast, show a much more rapid accumulation of new cases after age 10, with the highest slope occurring during adolescence (Ruscio et al. 2010). Onsets after the early thirties among both males and females are rare (Rasmussen and Eisen 1998).

For OCD sufferers, obsessions and compulsions can be very time consuming, often significantly interfering with occupational and social functioning. Respondents in one study estimated that over the past year, they spent an average of 5.9 hours/day occupied by obsessions and 4.6 hours/day engaging in compulsions (Ruscio et al. 2010), while Koran et al. (1996) estimated that having OCD is associated with a fourfold risk of unemployment. In severe cases, which may define upwards of 50% of those with the diagnosis (National Advisory Mental Health Council, 1993), obsessions and compulsions can occupy the entire day and result in profound disability. Family functioning may also be impaired due to the large burden assumed by spouses and parents. OCD patients are more likely to remain single and have an elevated risk for divorce and/or marital separation (Amir et al. 2000). It is of note that OCD sufferers have a lower quality of life of not only the general population, but also of patients with serious illnesses such as major depressive disorder (MDD),
schizophrenia, and organ transplantations. This is particularly true in the areas of mental health, vitality and social functionality (Jobes et al. 2001).

OCD is frequently comorbid with other DSM-IV-TR Axis 1 disorders, further impeding and worsening the sufferer’s quality of life. The most commonly co-morbid condition is MDD (Rasmussen and Eisen 1998), which was found to be ten times more prevalent in an OCD population compared to the general population (Alonso et al., 2010). Importantly, OCD often predates depression, suggesting that OCD increases vulnerabilities to mood conditions (Roberts et al., 2003). The immense toll that OCD has on people’s lives can be further demonstrated by the high rates of suicidal behavior, with studies reporting that 10–27% of those suffering from OCD may attempt suicide at least once in their life (Hollander et al., 1998; Torres et al., 2006). Due to the impairing nature of OCD and its high prevalence, the World Health Organization named OCD among the top 10 leading causes of disability, and the disorder occupies the 5th position for women aged 15-49 years (Murray & Lopez, 1996).

Symptom Subtypes

OCD patients experience widely varying obsessions and compulsions that contribute to the disorder’s high heterogeneity. The most common obsessions relate to fears of safety, contamination, pathological doubt, a need for symmetry and aggressive impulses (Abramowitz et al. 2003). Common compulsions include ritualistic checking, washing, arranging, the need to ask or confess and counting. Most patients have multiple obsessions and compulsions with a particular fear or concern dominating the clinical picture at any one time. Due to the many different types of obsessions and compulsions,
researchers have attempted to reclassify the disorder into dimensional subtypes, rather than classifying patients into mutually exclusive subgroups. Mataix-Cols et al. (1999) critically reviewed the evidence supporting a multidimensional model of OCD. The authors identified 12 factor analytic studies involving more than 2000 patients with OCD. They found that the most consistent factorial solutions consisted of five symptom dimensions: symmetry/ordering, hoarding, contamination/cleaning, aggressive obsessions/checking and sexual/religious obsessions. It appears that these symptom dimensions are stable over time; any new obsessions and compulsions that may develop are often within the same symptom dimension as previous symptoms (Mataix-Cols et al., 2002). These dimensions, which may be present in varying degrees and combinations in any given patient, have been found to be differentially related to variables such as sex, age of onset, comorbidity with other disorders, treatment response, and regional blood flow in various brain systems (Mataix-Cols et al. 2000). For instance, a functional magnetic resonance imaging study reported that hoarding, washing and checking dimensions were mediated by partially overlapping but distinct neural systems (Mataix-Cols et al., 2004). As well, it has been shown that increased scores on the hoarding dimension predict poorer outcomes to treatment (Lochner et al., 2005; Rufer et al., 2006; Mataix-Cols et al., 1999). Future research into elucidating the putative relationship between symptom dimensions and treatment response may eventually help to reduce the percentage of treatment failures.

The most common symptom dimension is contamination/cleaning (eg. fear of contracting an illness by contacting germs, resulting in excessive handwashing), which was found to have an incidence rate of 63.7% among those with OCD (Rufer et al. 2006). This is followed by the aggressive obsessions/checking dimension (eg. fear of harming a loved
one, causing one to repeatedly check to make sure the oven is off), with an incidence rate of 57.7% (Rufer et al. 2006). Patients with these symptom subtypes represent a significant population of OCD patients, and contribute to the debilitating nature of the disorder.

**Role of Disgust**

Many studies have looked at the role of disgust in OCD, and more specifically, the role it plays in the different symptom subtypes. Disgust is a basic emotion that is believed to constitute an evolutionary function of contamination and disease avoidance. It has been hypothesized that individuals with OCD tend to have elevated disgust sensitivities (the overestimation of the negative impact of experiencing disgust) (Berle et al. 2006). It is reasonable to expect elevated disgust-sensitivity in the contamination/washing subtype, where the obsessional theme is typically about being contaminated by some pathogen or disease, and the function of compulsive washing is to prevent transmission of disease. Indeed, OCD patients with contamination fears often describe contaminated objects as ‘disgusting’ rather than ‘frightening,’ leading some researchers to believe that disgust plays a prominent role in the etiology and maintenance of the contamination/washing subtype (Husted et al. 2006).

Olatunji (2010) suggests that given the emphasis on disease avoidance, contamination-based OCD may represent a dysfunction in the appraisal and processing of disgust. Studies have demonstrated that disgust sensitivity significantly predicts contamination fears and correlates with OCD severity (Olatunji et al. 2011). In a study by Olatunji et al. (2011), changes in disgust propensity (the heightened frequency/intensity of disgust emotions) were associated with decreases in OCD symptoms after a sample of 40
OCD patients completed an exposure and response prevention treatment program. While the link between disgust and the contamination/washing subtype is understandable, research has also shown that disgust sensitivity significantly correlates with OCD symptoms of checking, although it is unclear as to why this is (Berle et al. 2006). Other studies have found associations between disgust sensitivity and religious obsessions, especially among the morality-based disgust domains (Husted et al. 2006). This may indicate that highly religious people are more likely than others to experience self-directed disgust, guilt and shame in response to impure thoughts/obsessions. Identifying the role that disgust and other basic emotions have in the preservation of OCD will allow for a better understanding of the disorder and may better guide treatment interventions.

1.2 OCD Treatments

The first-line pharmacological and psychological treatments in combating symptoms of OCD are serotonin reuptake inhibitors (SRIs) and cognitive behaviour therapy (CBT). Unfortunately, in a significant proportion of patients, first line medications and psychotherapy does not bring any relief of symptoms and more complex pharmacological interventions, as well as neurosurgical treatments, may be warranted.

Cognitive Behaviour Therapy

CBT entails prolonged exposure to obsessional cues that induce discomfort, and response prevention of ritualizing behaviors until the discomfort abates. Exposure techniques focus on in vivo exposure and to a lesser extent, imaginal exposure, and typically proceeds from stimuli that produces moderate distress to stimuli that produce
greater distress (Dreessen et al. 1997). Patients are also instructed to practice exposure exercises between sessions, upwards of 2 hours per day, and are encouraged to apply the techniques as new situations arise (Nakatani et al. 2009). The goal of CBT is to teach patients to identify and correct their dysfunctional beliefs about feared situations, allowing them to habituate to the anxiety caused by the obsessions and to extinguish the compulsions. It is estimated that 60-90% of patients benefit from CBT, experiencing a reduction of 50-80% of symptoms, with long term remission seen in 45% of patients (Warren and Thomas 2001). In a meta-analysis conducted by Abramowitz (1998), 84% of patients who received CBT were classified as treatment responders, with a 48% improvement in the Yale Brown Obsessive-Compulsive Scale (Y-BOCS). Despite its efficacy, CBT has limitations. Approximately 15-25% of patients refuse CBT or drop out early because they are not willing to expose themselves to situations that are anxiety provoking (Greist 1994). As well, poor homework compliance on the part of the patient often leads to unsuccessful treatment results. Furthermore, the lack of CBT availability often results in long waiting lists, causing patients to turn to pharmacotherapy (Cottraux et al. 2001).

**Serotonin Reuptake Inhibitors**

Pharmacological agents classified as serotonin reuptake inhibitors (SRIs) have been shown to be efficacious in controlling OCD symptoms, and are usually the first line of treatment prescribed to OCD patients. Selective serotonin reuptake inhibitors (SSRIs) and the tricyclic agent, clomipramine, inhibit the function of serotonin reuptake pumps allowing serotonin to remain in the synaptic cleft longer to exert its effects (Mataix-Cols et
al. 1999). Initial clinical trials demonstrated that patients with OCD symptoms responded to clomipramine, which was originally marketed as an antidepressant (Pato and Phillips, 2003). This led to the investigation of other antidepressants, specifically SSRIs, due to their even greater selectivity in inhibiting serotonin reuptake. Since then, the efficacy of SSRIs, which includes fluoxetine (Wood et al., 1993), fluvoxamine (Jenike et al., 1990), citalopram (Montgomery et al., 2000), sertraline (Greist et al., 1995), and paroxetine (Tollefson et al., 1994) in treating OCD patients have been demonstrated in a number of placebo controlled trials. SSRIs can reduce symptoms by 30-60%, with a clinically meaningful reduction unlikely to occur within the first 6-12 weeks (Pigott and Seay 1999). The need for medication is often long term, with discontinuation of treatment associated with relapse (Matlby and Tolin 2003).

A number of studies have directly compared the efficacy of the different SSRIs. These comparison studies have involved clomipramine, fluoxetine (Pigott et al., 1990), fluvoxamine (Koran et al., 1996), paroxetine (Zohar and Judge 1996), sertraline (Bisserbe et al., 1997), and citalopram (Mundo et al., 1997). These studies all found that the SSRIs were equally efficacious in reducing OCD symptoms. However, meta-analyses of OCD trials (Greist and Jefferson, 1998; Jenike et al., 1990), comparing SSRIs across large placebo-controlled multi-center studies, support the superiority of clomipramine over the SSRIs in the treatment of OCD. Clomipramine has been the most extensively studied medication in the treatment of OCD but is not used as a first line pharmacotherapy because of its unfavourable safety profile. Because clomipramine possesses significant affinity for muscarinic and histaminergic receptors, it is frequently associated with troublesome side effects. These include weight gain, sexual dysfunction and more severe adverse events.
including cardiac arrhythmias and in some cases, even death (Pigott and Seay 1999).
Nonetheless, many meta-analyses support the use of clomipramine in patients who do not respond to SSRIs.

**Treatment Resistance in OCD**

Even though SRIs have been shown to be superior over placebo, approximately 40-60% of patients with OCD do not gain significant benefits and are classified as treatment resistant (Denys et al. 2003) and often need more complex interventions. The definition of ‘treatment resistant’ is not consistent among the literature, however, it is generally defined as failure to respond to several (2-4) adequate SRI trials (10-12 weeks at an appropriate dose) without at least a 25-35% improvement in the Y-BOCS. The failure to respond to one SRI has been shown to predict poor response to subsequent SRIs, further exacerbating the difficulty of treating patients effectively (Pallanti et al., 2004). As well, OCD may require higher dosages than typically needed for other psychiatric disorders, and may have longer lag times before onset of improvement occurs (Pigott and Seay 1999). Several predictors of pharmacological non-response have been proposed, and include early age of onset, longer illness duration, and greater illness severity. (Mataix-Cols et al., 1999; Ackerman and Greenland, 2002; Stein et al., 2001). In addition, co-morbidity of personality disorders, attention deficit hyperactivity disorder, oppositional defiant disorders and the presence of tic disorder have also been shown to predict comparatively poorer outcomes (Mataix-Cols et al., 1999; Geller et al., 2003).
**Interventions for Treatment Refractory OCD Patients**

For patients who are treatment resistant to first-line agents, other interventions, such as combination of anti-obsessive agents and/or augmentation with CBT, antipsychotic agents and non-antidepressants, may be warranted. Intravenous administration of anti-obsessive agents is also a relatively unused but effective strategy for treatment refractory OCD. Very severe refractory illness may lead to consideration of psychosurgery.

**Switching to non-SSRIs**

One strategy for patients resistant to SSRI treatment is to switch them to serotonin-norepinephrine reuptake inhibitors (SNRIs) because some patients respond better to agents that target multiple systems. To date the majority of the research on the efficacy of SNRIs in OCD has been conducted with venlafaxine, which has been shown to be effective in reducing OCD symptoms at doses >225 mg/day, in open label studies (Pato et al., 2003). More studies investigating the efficacy of SNRIs are needed.

**Combination Strategies**

Combining SSRIs or adding clomipramine to an SSRI regimen is a common and effective combination strategy for patients unresponsive to SSRI monotherapy. However, this strategy should be approached with caution because pharmacokinetic interactions on the hepatic cytochrome P450 isoenzymes may lead to an accumulation of clomipramine which can cause adverse events (Marazziti et al., 2008). It is therefore recommended that lower mean doses of SSRIs and clomipramine are prescribed when using this combination strategy. There are no controlled studies examining the efficacy of the co-administration of
two or more SSRIs, but augmentation with clomipramine has been investigated. Significantly larger improvements in Y-BOCS scores were reported in patients treated with citalopram plus clomipramine when compared to patients on citalopram monotherapy (Marazziti et al., 2008). As well, this combination was well tolerated, as it did not alter clomipramine’s metabolism.

**Augmentation Strategies**

Patients who have not responded to at least 2 adequate SSRI trials may benefit from an augmentation strategy or treatment with an unconventional agent. However many questions about augmentation remain unanswered, including optimal duration, predictors of response and mechanism of action (Maltby et al. 2003). Augmentation with antipsychotics have been studied, and while the results are not consistent, there is evidence of efficacy for this approach. Double-blind, placebo-controlled studies have supported the efficacy of augmenting SRIs with haloperidol, risperdone, olanzapine, quetiapine, and aripiprazole, as reported in a review by Sahib et al (2011). However, meta-analyses support the use of risperidone over other antipsychotic agents in treating refractory OCD patients (Skapinakis et al., 2007; Bloch et al., 2006). The combination of atypical antipsychotics to SSRIs are generally well tolerated, and have been shown to be especially effective in patients with poor insight (Sahib et al., 2011).

**Intravenous Anti-Obsessive Agents**

The literature on the efficacy of intravenous (IV) anti-obssessive agents has been previously reviewed (Ravindran et al., 2008) and evidence indicates that the use of IV
SRIs, rather than oral forms, can be effective when treating treatment refractory patients. The majority of studies examining the efficacy of IV anti-obscene agents in OCD patients have done so using clomipramine. The efficacy of IV clomipramine in reducing symptoms has been demonstrated in double blind, placebo controlled trials (Koran et al., 2006; Koran et al., 1997; Fallon et al., 1998). Koran et al. (1994) administered IV clomipramine 6 days/week to treatment refractory patients who were considered to have severe OCD. At the end of the 7 week treatment phase, there was a mean reduction of 71% in the Y-BOCS score from baseline. In an additional study, patients who were refractory to oral clomipramine received clomipramine infusions and experienced a significant reduction in symptoms compared to patients on placebo, maintaining the improvement at 1 month after treatment (Fallon et al. 1992). Intravenous medications may also prove to have a more long term prognostic value than immediate end of treatment response, as demonstrated in a study where responders at 1 month after receiving IV clomipramine had eight times higher odds of doing better years later at follow-up than non-responders (Ross et al. 2008).

Citalopram is the only SSRI available in IV formulation, and has only been studied once in OCD populations. The results by Pallanti et al. (2002) were encouraging with 59% of refractory patients on IV citalopram showing a decrease of more than 25% on the Y-BOCS. Additionally, the majority of patients experienced further post-infusion improvement gains while on oral maintenance therapy. The authors suggest that patients who have previously received no benefit from oral pharmacotherapy may experience reductions of greater than 35% if first started on IV citalopram and then continued on oral citalopram (Pallanti et al., 2002). Given the need for effective treatments for OCD, further research with IV citalopram would be of great clinical value.
Studies directly comparing IV agents to oral agents have demonstrated that significantly more OCD patients respond to IV clomipramine than oral clomipramine, and the extent of symptom reduction is significantly greater (Ross et al., 2008). In a study where OCD patients were randomized to receive either pulse loading of oral clomipramine or IV clomipramine, 85% of patients who received IV infusions were classified as treatment responders (>25% reduction in Y-BOCS rating) compared to only 13% of those taking oral tablets. Furthermore, there was an approximately 25% difference in symptom reduction between the two groups, with more than half of the patients who received IV clomipramine maintaining their improvement scores 8 weeks after treatment (Koran et al. 1997). The onset of improvement has also been found to be faster for IV agents. In a study where patients were pulse loaded with IV clomipramine, a clinical response was observed within 4.5 days, compared to oral tablets which usually takes a minimum of 6-12 weeks to produce a clinically significant response (Koran et al., 1997). Earlier onset of therapeutic effects could result in an earlier reprieve from suffering, which is an incentive to follow-up IV treatment with oral therapy and may result in shortened hospital stays for patients.

Intravenous anti-obssessive agents may also be more desirable than oral forms, not only because of its faster onset and its greater degree of effectiveness, but also because it has a better safety profile (Ravindran et al. 2008).

The significant differences between the two routes of administration is often attributed to the fact that intravenous agents bypass first-pass hepatoenteric and gastrointestinal metabolism, allowing for greater bioavailability of the drug and higher plasma levels to be achieved more quickly (Bigos et al. 2008). The infusion guarantees the direct supply of the active agent to the brain and may in turn play a role in rapidly
desensitizing serotonergic receptors or initiating changes in postsynaptic serotonergic neurons, bringing about a more rapid clinical response (Bigos et al. 2008). Intravenous formulations of clomipramine and citalopram are not approved for sale by Health Canada, but are available through special request programs (Ravindran et al., 2008).

Citalopram

Of specific relevance to this thesis is the SSRI citalopram, which is one of the most commonly prescribed antidepressants, and will be reviewed in greater detail. Citalopram is marketed under the trade names Celexa®, Cipramil®, Seropam® and Cipram®. It is available orally and parentally, with a recommended starting dose of 20 mg/day, and a maximum dose of 60 mg/day. (However, Health Canada has recently indicated that Celexa® should no longer be taken at doses greater than 40 mg/day due to the risk of abnormal heart rhythms at higher doses). The efficacy of citalopram at each available dose was investigated in a 12 week, double-blind, placebo-controlled trial where approximately 400 OCD patients were treated with either placebo, 20 mg, 40 mg, or 60 mg/day of citalopram. A total of 57% of patients in the 20 mg group, 52% in the 40 mg group and 65% in the 60 mg group responded to treatment, and all three doses were significantly superior to placebo (Montgomery et al., 2000). Pharmacological studies have shown that IV infusions of 20 mg citalopram results in peak plasma concentrations between 20-30 minutes from the start of the infusion and that the elimination half life is 30-35 hours (Bareggi et al., 2004).

Of the SSRIs, citalopram is one of the most selective, having negligible effects on noradrenaline and dopamine reuptake (Stahl 1998). Citalopram also demonstrates little to
no affinity for a range of neurotransmitter targets including acetylcholine, histamine, γ-aminobutyric acid, muscarinic, opioid and benzodiazepine receptors (Hyttell et al., 1995; Sanchez and Hyttel 1999). This lack of significant secondary receptor activity defines citalopram as one of the purest SSRIs. The metabolites of citalopram, demethylcitalopram (DCT) and didemethylcitalopram (DDCT), weakly inhibits serotonin reuptake and is present at much lower concentrations than the parent compound at steady state. However, since these metabolites are less lipophilic than citalopram they do not readily cross the blood-brain barrier and hence do not contribute significantly to the pharmacological effect of citalopram (Baumann and Marsen 1995).

Due to citalopram’s selectivity, it is generally well-tolerated by adults, including the elderly. Side effects are mild and include dry mouth, nausea, somnolence, and increased sweating (Muldon 1996). For most studies, the incidence of side effects in excess of those experienced on placebo were less than 10% (Feighner et. al., 1998; Montgomery et al., 1994). After the first few weeks of treatment, these effects decline in frequency and intensity. As well, citalopram’s minimal effect on liver metabolism makes it safer than other SSRIs when combined with other drugs (Pollock 2001), as is often the case with OCD patients, who may take more than one medication.

**Neurosurgery**

For patients with severe, intractable, and debilitating OCD symptoms who have failed to respond to CBT and at least 3 adequate medication trials, neurosurgery may be an option. Current surgical techniques involve the creation of 10-20 mm lesions to interrupt specific brain tracts involved in the serotonin system and implicated in the pathophysiology
of OCD (Pato and Phillips 2003). This is usually accomplished with radio-frequency heated electrodes or gamma knife techniques, which focuses individual gamma rays deep in the brain without causing damage to the skull or surrounding brain tissue (Pato and Phillips 2003). These surgical procedures aim to interrupt the connections between the cortex, the basal ganglia and related structures, and can be accomplished by anterior capsulotomy, cingulotomy, subcaudate tractotomy and combined orbitomedial/cingulate lesions (Maltby and Tolin 2003). This has led many investigators to believe that the regions involved in the neuronal loop connecting the basal ganglia to the cortex plays an important role in the etiology of OCD. Success rates of 25-84% have been reported with neurosurgical treatments, however many patients require more than one operation (Rasmussen et al., 2001; Hollander et al., 2002). A recent study reported clinical improvements in 45% of patients who received cingulotomy, an effect size comparable to that seen in some pharmacotherapy trials (Dougherty et al., 2002). However, these improvements were usually only apparent months after the operation. Preliminary studies involving deep brain stimulation (DBS) which uses electrical stimulation rather than ablation of nerve cells, has also shown promising results, but more research is needed (Cosyns et al., 2003).

**Course and Outcome of Treatment**

Often, in spite of treatment, OCD follows a chronic course; obsessions and compulsions are continuously present with varying degrees of intensity over time (Ravindran et al. 2008). Symptoms can sometimes be significantly controlled with the use of psychotherapy and/or pharmacological agents, but unfortunately, with most patients
there is no complete and sustained remission. However, even patients who respond to medication, often continue to experience significant residual symptoms that are clinically relevant and disabling. In at least a third of cases, symptoms remain despite long-term treatment with optimal pharmacotherapy (Cottraux et al. 2001). It is estimated that the average patient who responds to treatment experiences an approximately 35% reduction in symptoms after 12 weeks of treatment with pharmacotherapy (Pato and Phillips 2003). Demal et al. (1993) found over 60% of patients with OCD to have a continuous course without improvement and a further 25% to have an episodic illness with partial remission. In a study conducted by Dendler (1992), only 12% of patients receiving treatment achieved full remission with a 48% probability of relapse, demonstrating the long-term disability inflicted on patients and their families. The profound impact of OCD is further exacerbated by the tendency for patients to delay seeking treatment. Respondents to one survey reported that professional help was not sought until approximately 10 years after their symptoms first occurred, primarily because they felt ashamed and tried to hide their symptoms (Micallef and Blin 2001). While there are many treatment options for OCD, the effective clinical management of symptoms is difficult, contributing to the debilitating nature of the disorder.

1.3 Neuroimaging Techniques

Neuroimaging techniques allow for the detection of brain regions that may be implicated in the etiology of certain psychiatric disorders. Their unique ability to capture the structural and functional integrity of distributed neural circuitries within individuals provides a powerful approach in identifying abnormalities and regional effects of drugs.
Numerous studies in OCD have been conducted with both structural imaging (Magnetic Resonance Imaging) and functional imaging (Positron Emission Tomography, Single Photon Emission Computed Tomography, and Functional Magnetic Resonance Imaging). While the research in this thesis will utilize fMRI, a brief description of the above listed functional neuroimaging techniques are included in this section.

**Positron Emission Tomography (PET)**

PET technology uses radiolabelled molecules with positron-emitting isotopes of carbon, nitrogen, oxygen or fluorine to assess different metabolic processes occurring in the brain, such as receptor density, receptor binding potential and regional cerebral blood flow (rCBF). Tracing the emission of gamma rays from the radiolabelled molecules, investigators can determine the position and concentration of the compounds and make conclusions about the metabolic activity being investigated (Choi et al., 2009).

**Single Photon Emission Computed Tomography (SPECT)**

SPECT techniques require the injection of gamma-emitting radioisotopes into a peripheral vein. The radioisotope is attached to a specific ligand, and is rapidly taken up by the brain, reflecting cerebral blood flow at the time of injection. Gamma emissions of the radioisotopes are detected by a gamma camera and the results are reflective of the amount of brain activity in the various regions of the brain (Choi et al., 2009).
**Magnetic Resonance Imaging (MRI)**

Magnetic Resonance Imaging (MRI) signals are ultimately dependent on the nuclear properties of water, with each molecule containing 2 hydrogen nuclei, also called protons. Each proton has a spin, causing the hydrogen nuclei to act as a polarized magnet. In the normal physical state, protons are oriented randomly in such a way that the individual magnetic moments sum to cancel each other out. However, these protons align in one of 2 possible nuclear spin states when placed in an external magnetic field, with more than half aligning in a low energy state, and the others in a high energy state (Logothetis 2002). Application of a radiofrequency (RF) pulse causes transitions between the two nuclear spin energy states. In the absence of another RF pulse, the spins of the protons return to thermodynamic equilibrium (a process called relaxation). The difference between the energy absorbed and emitted during the transition between the 2 energy states represents the nuclear magnetic resonance (NMR) signal (Logothetis 2002). Functional magnetic resonance imaging (fMRI) techniques uses this principle to detect changes in the magnetic properties of blood due to brain activation.

**Blood-Oxygenation Level Dependent (BOLD) Signal**

When a tissue is metabolically active it requires a greater supply of oxygen from the surrounding vasculature. It is this fundamental principle on which researchers rely to relate fMRI signal to neuronal activation, as the change in oxygenation provides the mechanism by which brain function can be evaluated. Oxygen is carried through the bloodstream by hemoglobin, Hb, and when bound together it is referred to as oxygenated hemoglobin or oxy-Hb, whereas Hb that does not have bound oxygen is referred to as deoxyhemoglobin,
or deoxy-Hb. When a cerebral region becomes metabolically active there is an increase in oxygenated blood recruited to the site of increased brain activity. However, oxygen consumption (conversion of oxy-Hb \(\rightarrow\) deoxy-Hb) does not increase to the same extent, resulting in excess oxy-Hb compared to deoxy-Hb in the region in which cerebral blood flow has been increased (Howseman and Botwell, 1999).

The BOLD signal is dependent on the magnetic properties of hemoglobin which differ depending on whether it is bound to oxygen or not. Deoxy-Hb is a paramagnetic compound, while oxy-Hb is a diamagnetic compound. Deoxy-Hb is attracted to, and interacts with the applied magnetic field, resulting in magnetic field inhomogeneities and a shortening of the relaxation time, whereas oxy-Hb does not interfere with the magnetic field (Rajagopalan et al. 1995). When an area of the brain becomes metabolically active, there is an increase in the concentration of oxy-Hb relative to deoxy-Hb, resulting in a longer relaxation time and a concomitant increase in local signal (Howseman and Botwell, 1999).

Many factors including increased blood volume and increased oxygen consumption affect the production of the BOLD signal, which is an indirect measure of neuronal activity. Because of this, there is a time delay from the onset of stimulus presentation until a measurable change in the BOLD response can be observed. Following stimulation onset, there is a small negative dip in the BOLD signal lasting approximately 1-2 seconds. This initial dip results from a delay in time before the vasculature responds to the increase in oxygen consumption. This is followed by an increase in the BOLD response, which peaks between 4 and 8 seconds after stimulation. Upon reaching the peak value, the BOLD response remains elevated until the stimuli is removed. After cessation of the stimulus, the
BOLD response decreases to below baseline levels and then recovers back to the baseline level (Howseman and Botwell, 1999). The above outlined vascular response to increased neuronal activity is called the hemodynamic response function (hrf).

1.4 Neuroimaging studies in OCD

Structural Imaging Studies in OCD

Volumetric Magnetic Resonance Imaging (MRI) has demonstrated significant baseline differences in OCD subjects compared to controls, namely, volume increases in the thalamus (Atmaca et al., 2007; Christian et al., 2008) and the amygdala (Szeszko et al., 2004). Increases in thalamic volumes have been found to correlate with higher Y-BOCS scores (Gilbert et al., 2000). Volume reductions have been found in areas such as the pituitary (Jung et al., 2009), putamen (Rosenberg et al., 1997) and caudate nucleus (Robinson et al., 1995). In one study, Lazaroo et al. (2009) detected an approximately 35 ml reduction of gray matter in OCD patients, with substantial deficits in both parietal lobes.

MRI data regarding the orbitofrontal cortex (OFC) has been conflicting, with most of the evidence in support of decreased volumes compared to healthy controls (Friedlander and Desrocher 2006), including a study by Pujol et al.(2004) that found a significant reduction in OFC grey matter in a sample of 72 OCD patients when compared to 72 healthy controls. However, increased grey matter in the OFC has been reported as well (Christian et al., 2008). A meta-analysis from 14 case-control studies reported reduced volumes of the left anterior cingulate cortex (ACC) and OFC (bilaterally) in OCD patients, along with increased bilateral thalamic volumes (Rotge et al., 2009).
Studies have also looked at structural differences among patients in different symptoms dimensions. A study by van den Heuvel et al. (2009) found that symmetry/ordering was associated with lower global gray and white matter volumes; contamination/washing with lower gray matter volumes in the bilateral caudate; harm/checking with lower bilateral temporal lobe gray matter; and hoarding with decreased left insula and left parietal cortex gray matter volumes. These findings highlight the distinct structural abnormalities relating to different symptom dimensions.

Functional Imaging Studies in OCD

Positron Emission Tomography (PET) Studies

PET studies have found that when compared to normal controls, OCD subjects exhibit hypermetabolism of the caudate nucleus (Baxter et al., 1988), putamen (Perani et al., 1995), thalamus (Swedo et al., 1989), OFC (Sawle et al., 1991; Kang et al., 2003), and the ACC (Perani et al. 1995). Rauch et al. (2002) reported increased rCBF in the OFC of OCD subjects at resting state and in the context of a symptom provocation paradigm, which correlated with symptom severity. These results were similar to those found by Swedo et al. (1989); patients with childhood onset OCD exhibited increased glucose metabolism in the OFC and ACC compared to controls, with the degree of activation correlating with the Y-BOCS score. The right cerebellum and right thalamus, were also found to be hyperactive in this sample. As well, decreased glucose metabolism has been reported in the lateral prefrontal cortex of OCD patients compared to healthy volunteers (Martinot et al., 1990).
Saxena et al. (2001) investigated glucose metabolism in patients with OCD, MDD, and concurrent OCD and MDD. In patients with OCD and MDD alone, thalamic metabolism was significantly elevated, however, subjects with concurrent OCD plus MDD had lower metabolism in the thalamus. The authors suggest that different thalamic abnormalities may mediate depressive episodes experienced by OCD patients. A PET study investigating patients by subtype, found significant reductions in regional blood flow levels in the thalamus in checkers, and right amygdala hyperactivity in washers (Cottraux et al., 1996).

PET imaging has been frequently used to predict patients’ response to treatment. Studies have reported that non-responders to treatment have especially high metabolic activity in the OFC, ACC and thalamus, noting that these patients have more severe functional abnormalities (Saxena et al., 1999; Perani et al., 1995). Lower rCBF values in the OFC and higher rCBF values in the posterior cingulate cortex were detected in contamination-subtype OCD subjects, and predicted a better treatment response to SSRIs (Rauch et al., 2002). In another study, Brody et al. (1998) investigated whether PET could be used to predict response to pharmacotherapy, as well as CBT. They found that decreased left OFC metabolic activity was associated with better responses to fluoxetine treatment, but higher activity predicted better response to CBT, further demonstrating the neural complexity of OCD.

Single Photon Emission Computed Tomography (SPECT) Studies

Controlled studies of rCBF utilizing SPECT technology have also reported increased blood flow in the thalamus, OFC, and the medial frontal cortex in OCD subjects
compared to normal controls (Hendler et al. 2003; Stein 2000). Similarly to PET studies, SPECT studies have highlighted the OFC as a key region in OCD, even when the direction of reported activity is in conflict. Machlin et al. (1991) found increased rCBF bilaterally in the OFC in a sample of OCD patients compared to controls, while Bussatto (2000) reported significant hypoactivity in the right OFC and the left ACC in patients.

A few studies have reported hypoactivation in the caudate nucleus of OCD subjects compared to controls (Rubin et al., 1992; Lucey et al., 1997), while both increased (Perani et al. 1995) and decreased activation (Busatto et al., 2000) of the ACC has been reported. Taken together, the results of PET and SPECT studies provide evidence for the occurrence of fronto-subcortical hyper-perfusion in OCD patients, and provide insight into the underlying neural abnormalities in the etiology of OCD.

**Functional Magnetic Resonance Imaging (fMRI) Studies in OCD**

Functional Magnetic Resonance Imaging (fMRI) is unique in its ability to detect functional abnormalities in real time, without the use of contrast agents or harmful ionizing radiation, thus enabling repeated imaging without risk to the patient. Several studies using fMRI have consistently found increased activation in the caudate, OFC, dorsolateral prefrontal cortex (DLPFC), thalamus and ACC in OCD patients compared to controls (Friedlander and Desrocher 2006; Adler et al. 2000). In a study by Breiter et al., (1996) OCD patients were exposed to innocuous stimuli (eg. a tissue soaked in water) and disorder-relevant stimuli (eg. a tissue soaked in toilet water). During the exposure to disorder-relevant stimuli, patients demonstrated increased blood oxygenation in the insula, OFC, ACC, caudate nucleus and the amygdala. Adler et al (2000) reported similar results
when unmedicated OCD patients were exposed to an individualized symptom provocation paradigm. During the exposure to provoking stimuli, hyperactivation was observed bilaterally in the OFC, the ACC and the visual association cortex, as compared to neutral stimuli.

Mataix-Cols et al. (2004) used fMRI to investigate the distinct neural correlates of the different symptom dimensions, within the same patients. When looking at pictures depicting contamination scenes, patients exhibited hyperactivation of the OFC, caudate, and ventromedial prefrontal cortex. Checking scenes triggered increased activation of the thalamus, putamen, global pallidus and dorsal cortical areas. In addition, positive correlations were detected between subjective anxiety scores caused by the pictures and the corresponding neural responses. In a similar study comparing OCD patients with mainly checking symptoms to those with washing symptoms, washers demonstrated activation in the insular cortex, whereas checkers showed activation in the frontrostratal regions and the thalamus (Choi et al. 2009).

fMRI studies have largely supported the results garnered from PET and SPECT studies, further reinforcing the OFC, thalamus, ACC and basal ganglia as key regions in OCD.

**Neuroimaging Studies of Treatment Effects in OCD**

The structural and functional brain abnormalities detected by neuroimaging studies have prompted researchers to investigate if these abnormalities normalize with oral pharmacotherapy. These investigations have examined the effect of oral SRIs and have consistently found a reduction in the hyperactivation of the OFC among OCD patients after
PET studies have shown that after receiving clomipramine, OCD patients exhibited reductions in the hypermetabolism of the OFC compared to baseline (Swedo et al., 1992; Benkelfat et al., 1990), results which were mirrored in studies using fluoxetine (Kang et al., 2003), paroxetine (Saxena et al., 1999) and sertraline (Kang et al., 2003). These studies report that more exaggerated reductions in OFC activation were observed in treatment responders and correlated with symptom reductions. In an fMRI study by Nakao et al. (2005), patients were randomly assigned to receive either fluvoxamine (200 mg/day) or behavior therapy for 12 weeks. After improvement of OCD symptoms, activation of the OFC, DLPFC and cerebellum decreased compared to baseline scans. The regional dysfunctions in the OFC and subsequent improvements after SSRI treatment has led investigators to believe that it may be a key site mediating the pathology of OCD (Swedo et al. 1992).

Altered activation caused by pharmacotherapy in the striatal regions have also been reported. For example, using PET imaging, Hansen et al. (2002) found that the increased levels of cerebral blood flow observed in the caudate nucleus at baseline in OCD patients, reduced after treatment with paroxetine, and the effect was more significant in treatment responders. Furthermore, the changes in caudate activation correlated with reductions in the Y-BOCS score after treatment. Other PET studies have reported similar metabolic reductions in the caudate nucleus and subsequent correlations with symptom improvement after treatment with paroxetine (Saxena et al. 1999), and fluoxetine (Baxter et al. 1992). Decreased metabolism in the caudate was also detected in a PET study after clomipramine treatment, with treatment responders exhibiting more exaggerated reductions, as well as metabolic increases in other areas of the basal ganglia, including the putamen (Benkelfat et
al., 1990). In an fMRI study investigating the effect of a 6 month fluoxetine (20-60 mg/day) trial, attenuated responses in the putamen were observed (Lazaro et al., 2008), findings replicated with a 12 week fluoxetine trial (Nakao et al., 2005) and a PET study investigating paroxetine (Kang et al, 2003). The results of these studies suggest that the pathophysiology of OCD may be related to a dysfunction in the cortico-striato-thalamic circuitry.

Studies employing MRI have reported that amygdala volumes that were increased in OCD patients compared to controls at baseline, decreased by 15% after paroxetine treatment (Szeszko et al. 2004). Similarly, thalamic volumes reduced by 19% compared to baseline scans after treatment with paroxetine, (Gilbert et al. 2000) approximating the volumes of controls (Jung et al. 2009). Lazaro et al. (2008) reported that reductions in grey matter volume in OCD patients compared to healthy volunteers at baseline, were no longer detectable after 6 months of treatment with fluoxetine and CBT.

Studies examining the effects of SRIs on the neural circuitry of OCD patients in different symptom dimensions, have reported differences in these subgroups. After treatment with clomipramine, OCD patients with primarily checking symptoms were found to have decreased activation of the thalamus and hypothalamus compared to baseline, resembling the activation of normal controls and correlating with the extent of symptom improvement recorded (Zitterl et al. 2008). In another study, sertraline treatment was found to decrease activation in the ACC among patients in the washing symptom dimension (Mataix-Cols et al. 2004). The above studies have led researchers to believe that SRIs ameliorate OCD symptoms by modulating functional activity in the key regions implicated in the etiology of the disorder.
Table 1. Main Pre-Post Treatment Neuroimaging Studies in OCD

<table>
<thead>
<tr>
<th>Reference</th>
<th>Technique</th>
<th>Participants</th>
<th>Intervention</th>
<th>Main Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lazaro et al. 2009</td>
<td>MRI</td>
<td>15 drug naïve pediatric OCD subjects and 15 matched controls</td>
<td>Patients received fluoxetine (20-60 mg/day) and behaviour therapy for 6 months. All participants were scanned at baseline, and at 6 months follow-up.</td>
<td>Gray matter volume in OCD subjects were significantly reduced by ~35 ml, when compared to controls, specifically in the lateral surface of both parietal lobes. After treatment with fluoxetine and behaviour therapy, there were no significant differences between controls and patients.</td>
</tr>
<tr>
<td>Gilbert et al. 2000</td>
<td>MRI</td>
<td>21 drug naïve pediatric/adolescent OCD subjects and 21 matched controls</td>
<td>All participants were scanned at baseline. Ten of the 21 OCD subjects were scanned again after receiving paroxetine treatment (40-60 mg/day) for 12 weeks.</td>
<td>Baseline thalamus volumes of OCD subjects were significantly increased when compared to controls. However, post treatment volumes were reduced by 19%, approximating the volumes of controls. This reduction in thalamic volume correlated with symptom improvement.</td>
</tr>
<tr>
<td>Szeszko et al. 2004</td>
<td>MRI</td>
<td>11 pediatric OCD subjects and matched controls</td>
<td>OCD subjects received paroxetine (60 mg/day) for 16 weeks and were scanned before and after treatment. Controls were scanned at baseline and at follow-up, but did not receive any medication.</td>
<td>MRI scans before treatment showed increased amygdala volume in OCD subjects, compared to controls. However, after treatment, amygdala volumes decreased by approx. 15% in the OCD group, resembling the amygdala volumes of controls.</td>
</tr>
<tr>
<td>Zitter et al. 2008</td>
<td>SPECT; [(123)I]beta-CIT</td>
<td>24 OCD subjects with primarily checking symptoms</td>
<td>Subjects were treated with clomipramine (150 mg/day) for 12 weeks. Participants were scanned before and after treatment.</td>
<td>Mean post-treatment radioligand binding was significantly reduced by 47.82% in the thalamus and hypothalamus when compared to baseline. Pretreatment β-CIT binding predicted treatment response.</td>
</tr>
<tr>
<td>Benkelfat et al. 1990</td>
<td>PET; FDG</td>
<td>8 OCD subjects</td>
<td>Subjects received clomipramine (125-300 mg/day) for 12 weeks. Participants were scanned before and after treatment.</td>
<td>Compared to baseline, OCD subjects displayed decreased metabolism in the OFC, and increased metabolism in the basal ganglia after treatment. Subjects who responded well to clomipramine had lower overall metabolic glucose rates than poor or partial treatment responders.</td>
</tr>
<tr>
<td>Saxena et al. 1999</td>
<td>PET; FDG</td>
<td>20 OCD subjects</td>
<td>Subjects received paroxetine (40 mg/day) for 12 weeks and were scanned before and after treatment.</td>
<td>Compared to baseline, there were greater reductions in glucose metabolism in the anterolateral OFC and the right caudate, among treatment responders.</td>
</tr>
<tr>
<td>Reference</td>
<td>Technique</td>
<td>Participants</td>
<td>Intervention</td>
<td>Main Findings</td>
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<tr>
<td>Hansen et al. 2002</td>
<td>PET; FDG</td>
<td>20 OCD subjects</td>
<td>Subjects received paroxetine (40-80 mg/day) treatment for 12-20 weeks and were scanned before and after treatment.</td>
<td>Post treatment, reduced glucose metabolism was observed in the right caudate nucleus, but there were no differences in global cerebral metabolism.</td>
</tr>
<tr>
<td>Kang et al. 2003</td>
<td>PET; FDG</td>
<td>10 OCD subjects</td>
<td>Subjects received 4 months of therapy with either paroxetine (40 mg/day), sertraline (100 mg/day), or fluoxetine (40 mg/day). Participants were scanned before and after treatment.</td>
<td>When comparing baseline to post-treatment scans, there were significant reductions in cerebral glucose metabolism in the right hippocampus, lateral and medial cerebellum, lateral and medial OFC, and right putamen. Metabolic increases were observed in the superior parietal lobe and the superior occipital gyrus.</td>
</tr>
<tr>
<td>Nakao et al. 2005</td>
<td>fMRI, Stroop and SPP</td>
<td>10 OCD subjects</td>
<td>Subjects were randomly assigned to receive either fluvoxamine (200 mg/day) or behaviour therapy for 12 weeks. Participants were scanned before and after treatment.</td>
<td>Pre-treatment scans illustrated increased activation of the left dlPFC, left parietal cortex, the cerebellum and the left OFC, and decreased activation of the ACC. After improvement of symptoms with either fluvoxamine or behaviour therapy, activation of the OFC, dlPFC, putamen, insula, cerebellum and basal ganglia decreased, while the ACC increased.</td>
</tr>
<tr>
<td>Lazaro et al. 2008</td>
<td>fMRI, performance of simple and complex sequences</td>
<td>12 pediatric/adolescent OCD subjects and 12 controls</td>
<td>OCD subjects received fluoxetine (20-60 mg/day) and behaviour therapy for 6 months. All participants were scanned at baseline, and at 6 months follow-up.</td>
<td>When compared to controls, OCD subjects exhibited hyperactivation of the middle frontal gyrus at baseline and in the inferior parietal lobe post-treatment. When compared to baseline, activation of the insula and putamen significantly decreased in the patient group, after treatment.</td>
</tr>
<tr>
<td>Nabeyama et al. 2008</td>
<td>fMRI, Stroop task</td>
<td>11 OCD subjects and 19 controls</td>
<td>OCD subjects underwent CBT for 12 weeks and were scanned before and after treatment. Controls were only scanned once.</td>
<td>Compared to controls at baseline, OCD subjects exhibited hypoactivation of the ACC and cerebellum. After treatment, patients displayed reductions in the OFC, fusiform gyrus, middle frontal gyrus, and left precuneus, and exhibited increases in the right precuneus and cerebellum, when compared to baseline.</td>
</tr>
</tbody>
</table>

FDG = $^{18}$F-Fluorodeoxyglucose; ACC = anterior cingulate cortex; CBT = cognitive behaviour therapy; dLPFC = dorsolateral prefrontal cortex; fMRI = functional magnetic resonance imaging; MRI = magnetic resonance imaging; OCD = obsessive compulsive disorder; OFC = orbitofrontal cortex; PET = positron emission tomography; SPECT = single photon emitted computed tomography; SPP = symptom provocation paradigm
1.5 Neuroimaging Studies with Intravenous SSRIs

Neuroimaging studies investigating the effect of IV SRIs have not been conducted in OCD patients; however IV antidepressant infusion studies have been conducted in healthy controls and in patients with depression. A PET investigation reported that when compared to placebo, cerebral glucose metabolism decreased in the anterior cingulate gyrus, thalamus, and cerebellum after a single citalopram infusion, while increased glucose metabolism in the occipital cortex was detected in normal controls (Smith et al. 2002). In another PET study, patients with geriatric depression demonstrated greater metabolic increases in the putamen and occipital cortex after IV citalopram administration, compared to the elderly control subjects (Bauman and Nil 1998). A more recent PET study compared a sample of geriatric depressed patients to control subjects after receiving placebo and citalopram infusions. Smith et al. (2009) reported greater decreases in the middle temporal gyrus, postcentral gyrus, and supramarginal gyrus in controls subjects when compared to depressed patients, after the citalopram infusion. As well, significant increases in the superior frontal gyrus and middle frontal gyrus were also detected in the controls after IV citalopram. Depressed patients, on the other hand, displayed greater increases in the cuneus, inferior parietal lobule, thalamus and putamen with the citalopram infusion, when compared to controls.

In fMRI studies, healthy volunteers given IV citalopram exhibited attenuated responses in the OFC and amygdala, when compared to BOLD responses during a placebo infusion (Del-Ben et al. 2005). These results are quite different than those reported by other fMRI studies which found IV citalopram led to increased signaling in the thalamus, putamen, caudate nucleus (McKie et al.2005) and amygdala, compared to placebo (Bigos et al.}
The above regions identified, overlap with areas thought to be important in the pathophysiology of anxiety and may indicate important regions for treatment response.

In a placebo-controlled, randomized, crossover fMRI study, 12 male volunteers were infused with IV citalopram (7.5mg) or placebo, 60 minutes prior to a covert face emotion recognition task (Anderson et al., 2009). In response to disgusted faces, citalopram was found to enhance BOLD signals in the left insula and decrease activation in the left amygdala, while right amygdala activation decreased in response to fearful faces. The authors suggest that citalopram modulates a pathway involved in the identification of potentially threatening stimuli. In a follow-up study (Anderson et al., 2011), the investigators infused subjects with placebo for the first scan visit, and (7.5 mg) IV citalopram infusion on the second scan visit, to investigate the functional differences between remitted depressed subjects and matched controls during a covert face emotion task. Irrespective of group, citalopram enhanced left ACC activation in response to happy faces, decreased amygdala activity to fearful faces, and increased insula and prefrontal cortex responses to sad faces. When comparing groups, controls had increased bilateral hippocampal activation in response to happy faces, supporting a role for 5-HT in modulating affective processing. It would be of great clinical value to investigate if such changes seen in controls with IV SSRIs, also occurs in OCD populations.

1.6 Neurocircuitry models of OCD

Meta-analytic results support the conclusions drawn from many studies that the OFC, ACC, thalamus and caudate nucleus are key brain regions in the pathophysiology of OCD (Friedlander and Desrocher 2005). Based on these and other psychological and
neuroimaging investigational findings, several neuroanatomical models of OCD have been proposed. Saxena et al. (1998) proposed a model in which the circuitry of OCD is thought to be comprised of a direct and an indirect pathway, both of which originate in the frontal cortex and project to the striatum. From the striatum, the direct pathway projects to the globus pallidus interna/substantia nigra, pars reticulate complex (the primary output location of the basal ganglia), then to the thalamus and back to the cortex. This pathway is thought to facilitate complex motor programs by activating the thalamic system. In comparison, the indirect pathway projects from the frontal cortex to the globus pallidus externa, the subthalamic nucleus, globus pallidus-substantia nigra pars reticula, thalamus, and back to the cortex. This pathway is thought to suppress complex motor programs by inhibiting activation of the thalamus. These pathways, which serve as positive and negative feedback loops, balance each other out in healthy individuals, allowing for both activation and inhibition of complex motor behaviours. In OCD patients, however, a bias occurs in favor of the direct pathway, leading to increased activity in the OFC, ventromedial caudate, and medial dorsal thalamus, resulting in the characteristic obsessions and compulsions of OCD (Saxena and Rauch, 2000). In general, there is robust evidence for the involvement of the corticostriatal–thalamocortical neural circuit in OCD.

Graybiel and Rauch (2000) further expanded on this 2 pathway model. They proposed the first circuit, composed of the OFC, ACC, the medial prefrontal cortex and the caudate nucleus, is critical for habit learning and in the acquisition of stereotyped behaviours. The second circuit, the corticothalamic loop, is composed of neural inputs from the basal ganglia through the thalamus to the frontal cortex, and is thought to play a key role in conscious information processing. In OCD, parallel processing of information,
which occurs under normal conditions, is compromised and intrudes into consciousness. This results in the manifestation of obsessions, also causing behavioural selection to become narrower and automatic, leading to compulsive acts.

Baxter et al. (1995) also proposed a model in which the OFC, thalamus and caudate nucleus of OCD patients lose metabolic independence, causing them to function as one region. In this model, OCD symptoms are at least partly mediated by these metabolically ‘bound’ together set of regions, with successful treatment associated with the decorrelation of metabolic activity.

Further evidence for the involvement of the OFC, ACC and the frontal–subcortical circuits in OCD comes from reports of symptom improvement following various types of neurosurgical interventions. These procedures include anterior cingulotomy, limbic leucotomy, subcaudate tractotomy and anterior capsulotomy. They often involve various degrees of disconnection of the OFC and/or ACC from the striatum, anterior thalamus, amygdala and other subcortical structures (Pato and Phillips 2003). The complexity of the circuitry involved in OCD may explain symptom heterogeneity and variations in treatment outcomes, as deficits may arise at any point in the pathway, resulting in regional dysfunctions.

1.7 Summary

Obsessive compulsive disorder is characterized by the presence of obsessions and compulsions that cause anxiety due to their distressing content and troublesome, time-consuming nature. OCD is one of the most common psychiatric disorders and causes significant social and functional impairment. While obsessions and compulsions vary
among patients, they can be grouped in different symptom dimensions. The lowered quality of life associated with OCD may in part be due to the high rates of comorbidity with other disorders and/or the tendency for patients to delay seeking treatment because they feel ashamed and embarrassed. However, those that receive treatment still generally experience disabling symptoms, as OCD follows a chronic course with waxing and waning of symptoms. The most common treatments for OCD are CBT, SRIs, and in extreme cases, neurosurgery. SRIs inhibit serotonin reuptake allowing serotonin to remain in the synaptic cleft for longer periods. While SRIs can reduce symptoms by 30-60%, they usually have long lag times before onset of improvement occurs, require higher dosages compared to other disorders, and is often needed on a long term basis. Interestingly, IV SRIs have been shown to be effective, even when oral agents have not improved symptoms, and appear to be safer and well tolerated. Greater degrees of symptom reduction and faster onsets have been reported in studies using IV clomipramine and citalopram (which is the only SSRI available parentally).

Numerous neuroimaging studies of OCD subjects have found increased activation in the OFC, caudate nucleus, thalamus, ACC and putamen compared to normal controls, suggesting involvement of the cortico-striatal-thalamocortical circuit in the pathology of OCD. The activation of these areas have been shown to normalize after treatment with oral pharmacotherapy. Neuroimaging studies examining the effect of IV citalopram in healthy volunteers and depressed patients, have provided early evidence that IV citalopram modulates brain activity in regions that are believed to play a role in the etiology and maintenance of OCD. However, there has not been a previous study investigating the effects of IV anti-obsessional agents on the neural circuitry of OCD patients.
This present study was conducted to examine the changes in neuronal activation of OCD subjects due to an intravenous infusion of citalopram and placebo, compared to matched controls. An understanding of the changes in the neural circuitry caused by IV SSRIs may lead to a better understanding of the underlying pathophysiology of the disorder and may aid in the development of more effective interventions.
1.8 Aims and Hypotheses of Present Study

Specific Aims

1. To evaluate the effects of IV citalopram and placebo on the neuronal circuitry of currently symptomatic OCD patients, using fMRI and a symptom provocation paradigm.

2. To examine the effect of IV citalopram on the neuronal circuitry of a matched normal control population.

Hypotheses

1. Symptomatic OCD patients will exhibit a greater degree of activation in the OFC, caudate, thalamus and cingulate regions of the brain at baseline, compared to normal controls.

2. After receiving IV citalopram, OCD subjects, and not normal controls, will exhibit a reduction in the hyperactivity of these regions as compared to baseline.
Chapter 2 Methods

The purpose of this chapter is to:

- Provide an overview of the study design
- Describe the fMRI task and scanning protocol
- Describe the approach to statistical analysis

2.1 Design and Overview

This study was a randomized, single-blind, placebo-controlled, crossover study of IV citalopram and normal saline solution, administered during 2 fMRI scans while subjects completed a symptom provocation paradigm (SPP). Six OCD patients and 6 healthy volunteers were randomized to receive either citalopram (20 mg infused over 30 min) or placebo (0.9% sodium chloride solution) on their first fMRI scan visit, and the other infusion on their second scan visit. Scans were separated by a minimum washout period of 2 weeks. An overview of the study design is presented in Figure 1.
Figure 1. Overview of study design.
2.2 Recruitment

This study recruited 12 right-handed men and women between the ages of 18-50 (6 subjects diagnosed with OCD, and 6 healthy volunteers with no history of any psychiatric disorders, matched for age, gender and education). OCD subjects were recruited from referrals coming into the Centre for Addiction and Mental Health (CAMH) and from advertisements placed in hospitals located in downtown Toronto and on the CAMH website. Healthy volunteers were recruited from flyers posted around the University of Toronto campus, community boards, and downtown hospitals. Participants responding to flyers were first briefly screened on the phone before being asked to come in. All participants signed a CAMH research ethics board approved consent form prior to study enrollment.

2.3 Screening Visit

The screening visit for the study was conducted at CAMH. Screening included a complete medical history, physical examination (height, weight, blood pressure and heart rate), biochemical and hematological laboratory screen (including complete blood count (CBC), serum electrolytes, liver function tests, thyroid stimulating hormone (TSH) levels), blood alcohol levels, a urine drug test and an electrocardiogram (ECG). All participants received the Structured Clinical Interview for Diagnosis of DSM-IV Axis I Disorders (SCID-I) to confirm diagnosis of OCD for patients, and to rule out psychiatric illnesses for controls. As well, participants completed the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q), the Disgust Scale (DS) and the Beck Depression Inventory II (BDI-II). In addition, subjects with a diagnosis of OCD underwent a psychiatric
assessment to confirm the diagnosis and completed the Y-BOCS to quantify symptom severity.

Subjects were excluded from participating in the study if they had a neurological disorder, a clinically significant laboratory abnormality or medical condition, a positive urine drug test, and/or substance abuse or dependence within the last 6 months. Subjects were also excluded if they were of child-bearing potential and not using an effective contraceptive method, had a previous severe adverse reaction to oral citalopram and/or had electrophysiological abnormalities as detected by the ECG (which can be exacerbated by SSRIs). Subjects with medical implants, bullets or other implanted metallic objects were not eligible to participate in the study due to the risk posed from the magnetic environment of the MRI scanner. Healthy volunteers were excluded from the study if they (or their first degree relatives) had a history of psychiatric illness.

For OCD subjects, current comorbid DSM-IV TR diagnoses of MDD and/or other anxiety disorders were acceptable as long as OCD was their primary diagnosis. However, participants with a diagnosis of bipolar disorder, schizophrenia or other psychotic disorders were excluded. Also, all OCD participants must have had contamination or safety/harm as their primary obsessions, and washing/cleaning or checking behaviours as their primary compulsions. The minimum Y-BOCS score for enrollment was 17. Subjects taking anxiolytics and antidepressants were weaned off of their medication so that they were medication-free for 2 weeks prior to each scan. Patients were weaned off their medication in a step-down manner, under the care of a psychiatrist. This was done to ensure that functional changes detected in OCD patients were due to study interventions, and not patients’ individual OCD medications. However, patients taking fluoxetine were excluded.
due to the drug’s long half life and the impracticality of weaning patients off of it.

Participants receiving CBT were also excluded.

### 2.4 Scan Visits

Subjects arrived at the Brain Health Complex of Baycrest Hospital 1 hour prior to their scheduled scan time. They removed all metal objects (piercings, jewellery, etc.) from their body and changed into a standard hospital gown and pants. Blood pressure was taken and recorded prior to any study interventions. A physician inserted an intravenous catheter into the subjects left forearm and a slow drip of 0.9% sodium chloride was started to ensure the vein was kept open and to prevent backwards blood flow. From the clinic room, participants were escorted to the Rotman Research Institute (RRI) MRI suite where a technologist reviewed the MRI safety screening form with the participant to ensure safety while in the magnet. Participants were then placed in the MRI scanner after being given instructions.

Subjects were in the scanner for approximately 1 hour and 15 minutes. After functional baseline scans were obtained, the physician switched the intravenous bag to a new bag containing either placebo (250 ml of 0.9% sodium chloride), or citalopram (20 mg in 250 ml 0.9% saline) and started the infusion. Participants were not informed of which infusion they received. The infusion lasted 30 minutes, and the physician entered the MRI room at various intervals to monitor the infusion and adjust the drip rate as necessary. When the scan was completed, subjects were escorted back to the clinic room where the physician removed the catheter and measured the subjects’ blood pressure post-infusion. Once the participant changed back into their clothes, they filled out the Symptom Checklist
(a citalopram side effect questionnaire), and the DS. If subjects reported no side effects and the doctor thought it was advisable, subjects were dismissed 1 hour post-infusion. All scan-day procedures were repeated at least 2 weeks after subjects completed their first scan. Subjects were compensated $100 ($50 for each scan) and reimbursed for any travel expenses (ie. tokens, parking fare).

2.5 fMRI Scanning Procedures and Image Acquisition

fMRI scans were conducted at Baycrest Hospital on a 3 Tesla scanner (Siemens Medical Solutions, Erlangen, Germany). Subjects were given earplugs and headphones to dampen the noise of the MRI machine and to enable communication. Foam cushions placed around the subjects’ head were used to restrict movement during the scanning session. Stimulus presentation was performed using Visual Basic (version Visual Studio 2005; Microsoft, Redmond, Washington) on a standard RRI computer, which also collected subjects’ anxiety and disgust ratings. The stimuli were projected on a screen placed in the bore of the magnet, and seen by the participant by means of a mirror attached to the head coil. BOLD functional images were acquired using T2* weighted gradient echo planar imaging (EPI) sequences covering 30 slices (5.00 mm thick, zero gap), aligned oblique axially, and encompassing the entire cerebral cortex (TR = 2000 ms, TE = 30 ms, FOV = 200 mm, flip angle = 70°, matrix = 64 x 64, interleaved acquisition). Anatomical images (TR = 2000 ms, TE = 2.63 ms, FOV = 256, slice thickness= 1mm, 160 slices) were collected after the first two functional runs.

Two 6-minute functional runs were conducted prior to the infusion (-14 to -1 min) while participants completed a SPP, which served as a baseline. Once the infusion was
started (at time 0 min), structural scans were obtained (from 0 to 11 min) and were immediately followed by functional scans measuring resting state activity (from 11 to 16 min). Two additional SPP functional runs were conducted during infusion administration (from 17 to 30 min), and immediately after the infusion ended (from 31 to 43 min). Previous investigations have shown that IV citalopram concentrations peak approximately 30 minutes after the infusion begins, therefore the timing was chosen so we could see the effects of citalopram before and after it reached its maximal concentrations. To aid in the clarity of the presentation of the results, ‘PRE infusion scans’ refers to the baseline scans, or the runs occurring before the infusion started, ‘MID infusion scans’ refers to the scans acquired during the infusion, and ‘POST infusion scans’ refers to the scans acquired after the infusion ended.

2.6 fMRI tasks

A block design was used for the fMRI tasks (see Figure 2). For 6 of the functional runs (each 6 minutes in length), participants completed a SPP. Each SPP run was composed of 7 picture blocks, which were each separated by an arrow task. There were five major categories of pictures used for each block: (i) aversive (ie. disgust inducing), (ii) neutral, and pictures relating to the OCD subtypes of (iii) checking, (iv) washing and (v) hoarding. Each picture block consisted of 5 scenes that were grouped together according to picture content. In total, 225 colour pictures were used (45 scenes for each of the 5 picture categories). Ninety of these pictures were chosen from the International Affective Picture System (IAPS, 2001) to represent the neutral (eg, furniture, nature) and aversive blocks (eg. insects, mutilated bodies, decaying food). The aversive stimuli were chosen to elicit
feelings of disgust in both controls and patients, and to avoid resembling common triggers of OCD symptoms. Scenes depicting the OCD subtypes of washing, checking and hoarding were obtained with a standard digital camera and from an internet search. A psychiatrist confirmed the anxiety arousing nature of the symptom-related pictures, which were previously established as symptom provoking in an OCD sample (unpublished data). Examples of washing scenes included pictures of money, public phones and toilets; checking pictures included scenes of electric appliances and open doors; hoarding scenes included heaps of newspapers, and cluttered homes. Washing related scenes were chosen with the intention that they would not be viewed as very aversive by the normal controls.

Pictures were presented in 20 second blocks. Immediately following the presentation of each block of pictures participants were asked to rate how anxious the pictures made them feel using a 7-point Likert scale (a score of 1 representing no anxiety, a score of 4 representing moderate anxiety and a score of 7 representing maximal anxiety). Participants were also asked to rate how disgusted the pictures made them feel using a similar scale. These questions and their accompanying scales were displayed on the screen for 5 seconds each, and subjects responded via fibre optic response buttons. (See Figures 2 and 3). The order in which the blocks occurred were different for each run.

Arrow blocks separated each picture block and served as a buffer between the picture categories. Arrows pointing either left or right were randomly displayed on the screen and participants were asked to respond to which way they were pointing as quickly and accurately as possible by pressing the appropriate buttons. Each arrow block consisted of 10 arrows and lasted 20 seconds.
Figure 2. A) General overview of fMRI block design, including infusion start and end times. B) An example of a SPP run, which consisted of 7 picture blocks and 7 arrow blocks. C) An example of a ‘washing’ picture block, consisting of 5 pictures and 2 ratings scales.
Figure 3. Timing of fMRI block design
2.7 Data Analysis

fMRI Data Preprocessing

Spatial pre-processing and whole-brain image analysis of MRI images were preformed using Statistical Parametric Mapping 8 (SPM8, University College London, United Kingdom; http://www.fil.ion.ucl.ac.uk/spm/software/spm8). Raw images were imported into SPM as DICOM files and saved as nifti files so images could be preprocessed and analyzed. The first 3 images from each run were excluded from the analyses to eliminate any T2*-equilibrium effects.

Subject movement can cause voxels to contain information from different anatomical locations over the course of a scan, and may lead to misinterpretation of data. While subjects are instructed to remain as still as possible during the scans, precautions are taken to minimize movements. To correct for subject motion, all the images were realigned to the mean image obtained for each participant and coregistered with their T1-weighted structural image. The T1 image was segmented using template (International Consortium for Brain Mapping) tissue probability maps for gray and white matter and cerebrospinal fluid. Parameters obtained from this step were subsequently applied to the functional and structural data during normalization into a standard stereotactic space (Montreal Neurological Institute template) using a 12-parameter affine model. Normalizeation is needed to account for individual differences in brain size, shape and anatomy, among the subjects. Images were then smoothed with a Gaussian filter, set at 6 mm full width at half maximum (FWHM). ‘Smoothing’ is a mathematical process by which a voxel is averaged with surrounding voxels to increase the signal-to-noise ratio
(where signal equals BOLD response to stimulation and noise equals random BOLD intensity changes occurring without stimulation).

**fMRI Data Analysis**

Single subject data were analyzed at the first level with general linear statistical models, and the time series of the images were convolved with a canonical hemodynamic response function. Each model included high-pass filtering to remove low-frequency signal drift (period = 128 sec). Contrasts comparing emotional (washing, checking, hoarding and aversive) picture blocks to neutral blocks were generated for each subject at each time point (eg. PRE wash > PRE neutral, MID wash > MID neutral, POST wash > POST neutral; etc.).

For baseline comparisons, PRE-infusion contrast images were combined according to picture block, (eg. all scans obtained during the PRE-infusion washing blocks were pooled for the OCD group, and likewise for the controls). Two sample T-tests were then used to compare baseline differences between OCD patients and controls for each of the different picture blocks. The MNI coordinates of the most significantly active voxels were used to determine anatomical locations using MRIcon.

To investigate the effect of citalopram, compared to placebo, on brain activation, comparisons were made between the PRE vs. MID infusion scans, and then for the PRE vs. POST infusion scans. To accomplish this, an Infusion x Time ANOVA was performed separately for both groups, for each of the different picture blocks. The regions that were significant at p<0.005 (uncorrected) and greater than 30 voxels were then used to create regions of interest (ROI). ROI images were constructed using the MarsBar toolbox in
SPM8. Once the ROIs were created, they were used as masks to extract signal from each participant using the Rex toolbox. A Greenhouse-Geisser corrected repeated measures analysis using SPSS (IBM corp., Armonk, New York) was then conducted to test for interactions between Group, Infusion and Time. Bonferroni corrected post hoc tests were then performed to ascertain the nature of significant effects and interactions (two-tailed p<0.05).

For the purposes of this thesis, data analysis on the resting state runs were not conducted.

**Behavioural Ratings**

The subjective anxiety and disgust ratings obtained during the SPP were combined in a 2 x 2 x 3 repeated measures Greenhouse-Geisser corrected ANOVA, with factors of diagnostic group (OCD and controls), infusion condition (citalopram and placebo) and time (PRE, MID, and POST). Post hoc tests with Bonferroni correction were conducted between conditions. All statistics were two-tailed with an alpha of 0.05.

**Correlations**

To determine if the changes in neural activity observed after the citalopram infusion in the OCD group were associated with changes in subjective anxiety, correlation analyses were conducted. Kendall’s tau was used to examine the correlation between z scores for PRE-POST changes in brain activity and PRE-POST changes in anxiety ratings.
Questionnaires

Data from questionnaires (BDI-II, Q-LES-Q and DS) completed at screening were subjected to Mann-Whitney U tests to test for statistically significant differences between OCD subjects and controls. Additionally, Wilcoxon signed rank tests were conducted to test for differences in DS scores obtained after the citalopram and placebo infusions, for each group.
Chapter 3 Results

The purpose of this chapter is to:

- Present baseline clinical and demographic characteristics of our study sample
- Present the behavioural data acquired during the SPP
- Present the baseline fMRI data, and make comparisons to changes observed during and after the infusions

3.1 Subjects: Demographic and Clinical Characteristics at Screening

Twenty right-handed subjects provided written informed consent and were screened for this study. Three control subjects were excluded for past or current psychiatric illness, 1 subject was excluded for an abnormal ECG at screening, and 4 participants withdrew from the study. Six healthy controls and 6 OCD patients completed the study.

The subjects’ baseline demographic and clinical characteristics are summarized in Table 2 and Table 3. There were no significant differences between OCD patients and controls for age, gender or education. The mean Y-BOCS score for the OCD group was 21.7 ± 4.1, indicating moderate severity, with mean scores of 10.8 on both the obsession (± 1.6) and compulsion questions (± 2.5). The mean Q-LES-Q scores for OCD patients and controls were 45.5 ± 6.8 and 61.8 ± 13 respectively, with a significant difference between the two groups (U=4.5, p=0.026). The mean age of onset of OCD symptoms in the patient group was 16 ± 6.2 years, with a mean illness duration of 10.3 ± 7.5 years. Only 2 patients had a current comorbid diagnosis of MDD, so BDI-II scores between the two groups did
not differ significantly (9.8 ± 4.76 vs. 1.0 ± 0.89; U = 29.0, p=0.093). Three of the patients were on SSRIs at time of screening, but stopped taking their medication 2 weeks prior to each of their 2 fMRI scans.

Table 2. Demographic and Clinical Characteristics of Subjects at Screening

<table>
<thead>
<tr>
<th>Group</th>
<th>Statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Demographics</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>26.7 (9.7)</td>
</tr>
<tr>
<td>Years of education</td>
<td>16 (1.8)</td>
</tr>
<tr>
<td>Male</td>
<td>3</td>
</tr>
<tr>
<td>Female</td>
<td>3</td>
</tr>
<tr>
<td>Clinical</td>
<td></td>
</tr>
<tr>
<td>Q-LES-Q</td>
<td>45.5 (6.8)</td>
</tr>
<tr>
<td>BDI-II</td>
<td>9.8 (4.76)</td>
</tr>
<tr>
<td>Y-BOCS</td>
<td>21.7 (4.1)</td>
</tr>
<tr>
<td>Obsessions</td>
<td>10.8 (1.6)</td>
</tr>
<tr>
<td>Compulsions</td>
<td>10.8 (2.5)</td>
</tr>
<tr>
<td>Duration of illness, years</td>
<td>10.3 (7.5)</td>
</tr>
<tr>
<td>Age of onset, years</td>
<td>16 (6.2)</td>
</tr>
</tbody>
</table>

BDI-II = Beck Depression Inventory II; N/A = not applicable; OCD = obsessive compulsive disorder; Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire; Y-BOCS = Yale-Brown Obsessive Compulsive Scale
Table 3. Clinical characteristics of OCD subjects

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age (years)</th>
<th>Y-BOCS Score</th>
<th>Duration of illness (years)</th>
<th>Age of onset (years)</th>
<th>Comorbid Diagnoses</th>
<th>Primary OCD symptoms</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>F</td>
<td>21</td>
<td>17</td>
<td>8</td>
<td>13</td>
<td>None</td>
<td>Checking</td>
<td>Sertraline</td>
</tr>
<tr>
<td>M</td>
<td>37</td>
<td>24</td>
<td>9</td>
<td>28</td>
<td>None</td>
<td>Washing</td>
<td>Naïve</td>
</tr>
<tr>
<td>M</td>
<td>41</td>
<td>24</td>
<td>25</td>
<td>15</td>
<td>None</td>
<td>Washing</td>
<td>Naïve</td>
</tr>
<tr>
<td>M</td>
<td>20</td>
<td>21</td>
<td>10</td>
<td>10</td>
<td>Depression</td>
<td>Checking</td>
<td>Sertraline</td>
</tr>
<tr>
<td>F</td>
<td>20</td>
<td>17</td>
<td>5</td>
<td>15</td>
<td>Panic Disorder</td>
<td>Washing</td>
<td>Citalopram</td>
</tr>
<tr>
<td>F</td>
<td>21</td>
<td>27</td>
<td>5</td>
<td>15</td>
<td>Depression</td>
<td>Washing</td>
<td>Naïve</td>
</tr>
</tbody>
</table>
3.2 Tolerability Profile of Citalopram

Subjects completed the Infusion Side Effect Questionnaire before discharge on each scan visit and rated to what extent they felt certain symptoms on a 3-point scale (0 = not at all, 1 = a little, 2 = a lot). Subjects reported mild or no side effects for both drug and placebo visits. Wilcoxon matched pairs tests were performed for each symptom; no significant differences were found between the citalopram and placebo infusion (Table 4).

Table 4. Reported side effects from the citalopram and placebo infusions

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Citalopram</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of appetite</td>
<td>0 (0-1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Tiredness</td>
<td>1 (0-2)</td>
<td>0.5 (0-1)</td>
</tr>
<tr>
<td>Lightheadedness/Feeling faint</td>
<td>0 (0-1)</td>
<td>0 (0-1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>0 (0-1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Headache</td>
<td>0 (0-1)</td>
<td>0 (0-1)</td>
</tr>
<tr>
<td>Tense/Nervous/On edge/Restless</td>
<td>0 (0-1)</td>
<td>0 (0-1)</td>
</tr>
<tr>
<td>Difficulty concentrating</td>
<td>0 (0-1)</td>
<td>0 (0-1)</td>
</tr>
<tr>
<td>Shaky/Tremors</td>
<td>0 (0-1)</td>
<td>0 (0-1)</td>
</tr>
<tr>
<td>Heart racing</td>
<td>0 (0-1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Sweating</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Short tempered/Irritable</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Happy</td>
<td>1 (0-2)</td>
<td>1 (0-1)</td>
</tr>
<tr>
<td>More energetic</td>
<td>0.5 (0-1)</td>
<td>0.5 (0-1)</td>
</tr>
<tr>
<td>Low energy/Fatigued</td>
<td>1 (0-2)</td>
<td>0 (0-1)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>0 (0-1)</td>
<td>0 (0-1)</td>
</tr>
</tbody>
</table>
2.3 Disgust Scale

The Disgust Scale (DS) was completed by all participants at screening and at the end of each scan.

Screening

There were significant differences in the overall mean DS scores between the two groups at screening: OCD patients (27.0 ± 7.7) and controls (16.3 ± 2.7) (U=5, p=0.041). The DS can be divided into 3 subscales: Core Disgust, Animal Reminder Disgust and Contamination-based Disgust. When examining the group differences for each of the subscales, OCD subjects were found to have significantly higher mean values than controls for Core Disgust, 10.7 ± 3.4 vs. 6.3 ± 1.5 (U=4.5, p=0.026); and Contamination-Based Disgust, 5.1 ± 0.98 vs. 3 ± 1.2 (U= 3.0, p=0.015). However, there were no significant differences between OCD subjects (5.8 ± 3.3) and controls (4 ± 1.6) for Animal Reminder Disgust (U=11.5, p=0.310). Baseline subscales and overall scores for the DS are presented in Figure 4.

Comparison Between Infusions

No significant changes were detected in the post-infusion DS scores (ie. post citalopram vs. post placebo) within the OCD group (Z=-1.682, p=0.093) or the control group (Z=-1.342, p=0.180), as displayed in Figures 5 and 6.
Figure 4. Screening Disgust Scale and subscale scores

* Overall Score: U=5, p=0.041

** Core disgust subscale: U=4.5; p=0.026

*** Contamination disgust subscale: U=3; p=0.015
**Figure 5.** Comparisons of control group DS scores after each infusion

![Control Group Graph](image)

Overall Score: $Z = -1.682$, $p = 0.093$

Core Disgust: $Z = -0.962$, $p = 0.074$

Animal Reminder Disgust: $Z = -1.807$, $p = 0.071$

Contamination Disgust: $Z = -1.786$, $p = 0.336$
Figure 6. Comparisons of OCD group DS scores after each infusion

Overall Score: $Z = -1.342$, $p = 0.180$

Core Disgust: $Z = -1.342$, $p = 0.180$

Animal Reminder Disgust: $Z = -0.577$, $p = 0.564$

Contamination Disgust: $Z = 0$, $p = 1.00$
3.4 Behavioural Ratings

Subjective Anxiety Ratings

For the washing picture blocks, OCD subjects had significantly higher anxiety ratings than controls, during the PRE (U=36, p=0.002), MID (U=36, p=0.002) and POST (U=39, p=0.009) infusion scans. A repeated measures ANOVA with a Greenhouse-Geisser correction determined that anxiety ratings differed significantly between time-points \(F_{1,649, 16.494} = 5.94, p=0.015\). The Time x Group interaction effect was significant for the washing block \(F_{1,649, 16.494} = 7.813; p = 0.006\) but the Time x Group x Infusion interaction effect was not \(F_{1,468,14.679} = 1.716; p = 0.208\). Post hoc tests using the Bonferroni correction revealed that with the citalopram infusion, POST infusion ratings were significantly lower than PRE \(p<0.001\) and MID \(p=0.023\) infusion ratings in the patient group. As well, this reduction produced significant differences between the post citalopram and post placebo ratings in the patient group \(p=0.028\). The citalopram infusion did not have the same effect in the control group, as there were no significant changes when comparing ratings across the different time points \(p=1.00\). With the placebo infusion, there were no significant differences in anxiety ratings among the three time points in either the OCD \(p=0.334\) or control group \(p=1.00\). The washing block anxiety ratings for both groups are presented in Figure 7.

For the checking picture blocks, similarly to the washing blocks, OCD subjects had significantly higher anxiety ratings than controls, for the PRE \(U=36.0, p=0.02\) and MID \(U=36.0, p=0.02\) infusion scans. Anxiety ratings were found to differ statistically between time points \(F_{1,733, 17.333}=5.101, p=0.022\) with post hoc tests revealing that with the
citalopram infusion, POST infusion ratings significantly reduced when compared to PRE (p<0.0005) and MID (p<0.33) infusion ratings in the OCD group. Correspondingly, post-citalopram anxiety ratings were significantly lower than post-placebo ratings (p=0.003). As well, for the checking blocks, this POST infusion reduction seen in the OCD group, decreased anxiety ratings to near controls levels, so that there was no longer a significant difference between groups for the citalopram infusion (U=29.0, p=0.093). There were no significant changes in control group anxiety ratings among the three time points for either infusion. The Time x Group interaction effect was significant for the checking blocks (F_{1.733, 17.333} = 5.023; p = 0.023). Anxiety ratings for the checking blocks are presented in Figure 8.

There were no significant differences in anxiety ratings between group, infusion or time, for the aversive, hoarding and neutral picture blocks.

Subjective Disgust Ratings

The washing picture blocks were the only picture blocks in which OCD subjects had significantly higher disgust ratings than controls, during the PRE (U=35, p=0.004), MID (U=33.0, p=0.015) and POST infusion scans (U=36, p=0.002). Significant interactions for the disgust ratings were observed for the effects: Infusion x Time (F_{1.712, 17.12} = 5.172; p = 0.021) and Infusion x Time x Group (F_{1.712, 17.12} = 6.707; p = 0.009). Upon further investigation, significant reductions in disgust ratings were observed when comparing PRE to POST infusion ratings (p<0.0001), and when comparing MID to POST infusion ratings (p<0.027) in the OCD group, with the citalopram infusion. This reduction did not occur with the placebo infusion in the patient group (p=1.00), or in the control
group with IV citalopram (p=0.701) or placebo (p=0.953). Disgust ratings for the washing blocks are presented in Figure 9.

There were no significant differences in disgust ratings between groups, infusions or time-points for the checking, aversive, hoarding and neutral picture blocks.
**Figure 7.** Anxiety ratings for the washing blocks

![Washing Block - Anxiety Ratings](image1)

Time: $F_{1.649, 16.494} = 5.94, p=0.015$

Time x Group: $F_{1.649, 16.494} = 7.813; p = 0.006$

**Figure 8.** Anxiety ratings for the checking blocks

![Checking Block - Anxiety Ratings](image2)

Time: $F_{1.733, 17.333}=5.101, p=0.022$

Time x Group: $F_{1.733, 17.333} = 5.023; p = 0.023$
**Figure 9.** Disgust ratings for the washing blocks

| Infusion x Time: $F_{1,712,17.12} = 5.172$; $p = 0.021$ |
| Infusion x Time x Group: $F_{1,712,17.12} = 6.707$; $p = 0.009$ |
3.5 fMRI results

Differences between OCD and Control Subjects at Baseline

When subtracting neutral from aversive pictures (looking at the Aversive>Neutral contrast) in the baseline condition (PRE infusion), OCD subjects exhibited increased BOLD signals in the left postcentral gyrus, left superior frontal gyrus and right supramarginal gyrus when compared to controls, and hypoactivation in the left calcarine sulcus and the left superior temporal gyrus. These results are presented in Figures 10 & 11 and Table 5.

For the contrast Washing>Neutral, when compared to controls, OCD patients displayed hyperactivation in the left OFC and left rostral anterior cingulate cortex (rACC). Decreased activity was observed in the left and right middle temporal gyrus in the patient group. Figures 12 & 13 and Table 6 display these results.

When examining the contrast Checking>Neutral, OCD subjects exhibited hyperactivation in the left inferior parietal lobe, left dorsal anterior cingulate cortex (dACC), and hypoactivation bilaterally in the caudate nucleus compared to controls, as displayed in Figures 14 & 15 and Table 7. There were no significant differences between the two groups for the Hoarding>Neutral contrast at baseline.
**Figure 10.** Regions where OCD subjects exhibited more activation than controls for the aversive picture blocks at baseline

**Table 5.** Baseline differences between OCD and controls subjects for the aversive blocks

<table>
<thead>
<tr>
<th>Region</th>
<th>Side</th>
<th>Brodmann Area</th>
<th>MNI Coordinates x,y,z (mm)</th>
<th>Cluster size (kE)</th>
<th>Z</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients&gt;Controls</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postcentral gyrus</td>
<td>L</td>
<td>2</td>
<td>-39 -34 49</td>
<td>90</td>
<td>4.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Superior frontal gyrus</td>
<td>L</td>
<td>6</td>
<td>-21 -4 58</td>
<td>40</td>
<td>4.39</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Supramarginal gyrus</td>
<td>R</td>
<td>40</td>
<td>39 -31 37</td>
<td>60</td>
<td>3.43</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Controls&gt;Patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcarine sulcus</td>
<td>L</td>
<td>18</td>
<td>-24 -67 16</td>
<td>403</td>
<td>4.62</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Superior temporal gyrus</td>
<td>L</td>
<td>41</td>
<td>-45 -31 13</td>
<td>36</td>
<td>3.49</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Figure 11.** Regions where controls exhibited more activation than OCD subjects for the aversive picture blocks at baseline
**Figure 12.** Regions where OCD subjects exhibited more activation than controls for the washing picture blocks at baseline

![Figure 12](image)

**Table 6.** Baseline differences between OCD and controls subjects for the washing blocks

<table>
<thead>
<tr>
<th>Region</th>
<th>Side</th>
<th>Brodmann Area</th>
<th>MNI Coordinates x,y,z (mm)</th>
<th>Cluster size (kE)</th>
<th>Z</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients&gt;Controls</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orbitofrontal cortex</td>
<td>L</td>
<td>47</td>
<td>-39 38 -5</td>
<td>39</td>
<td>3.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Rostral anterior cingulate</td>
<td>L</td>
<td>32</td>
<td>-3 32 -8</td>
<td>213</td>
<td>3.82</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Controls&gt;Patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mid temporal gyrus</td>
<td>R</td>
<td>37</td>
<td>60 -58 -2</td>
<td>35</td>
<td>3.85</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mid temporal gyrus</td>
<td>L</td>
<td>37</td>
<td>-48 -52 1</td>
<td>30</td>
<td>3.31</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Figure 13.** Regions where controls exhibited more activation than OCD subjects for the washing picture blocks at baseline

![Figure 13](image)
**Figure 14.** Regions where OCD subjects exhibited more activation than controls for the checking picture blocks at baseline

![Image of brain scans showing regions with increased activation in OCD subjects compared to controls](image)

**Table 7.** Baseline differences between OCD and controls subjects for the checking blocks

<table>
<thead>
<tr>
<th>Region</th>
<th>Side</th>
<th>Brodmann Area</th>
<th>MNI Coordinates x,y,z (mm)</th>
<th>Cluster size (kE)</th>
<th>Z</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients&gt;Controls</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inferior parietal lobe</td>
<td>L</td>
<td>40</td>
<td>-42 -37 43</td>
<td>67</td>
<td>4.39</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dorsal anterior cingulate</td>
<td>L</td>
<td>23</td>
<td>-2 -18 32</td>
<td>81</td>
<td>3.86</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Controls&gt;Patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caudate nucleus</td>
<td>R</td>
<td>-</td>
<td>15 11 7</td>
<td>31</td>
<td>3.52</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Caudate nucleus</td>
<td>L</td>
<td>-</td>
<td>-12 11 7</td>
<td>86</td>
<td>3.64</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Figure 15.** Regions where controls exhibited more activation than OCD subjects for the checking picture blocks at baseline

![Image of brain scans showing regions with increased activation in control subjects compared to OCD subjects](image)
The Effect of Citalopram

**PRE infusion vs. MID infusion**

During the washing picture blocks, OCD subjects exhibited decreased activation in the right angular gyrus, while receiving the citalopram infusion, compared to baseline (Figure 16, Table 8).

During the checking picture blocks, OCD subjects demonstrated decreased activation in the cerebellum, while receiving the citalopram infusion, compared to baseline (Figure 17, Table 9). Increased BOLD signals were not observed in either group during the administration of citalopram in response to the picture block. Also, control subjects did not exhibit any BOLD signal changes throughout the citalopram infusion compared to baseline. No significant BOLD changes occurred during the citalopram infusion, in either group, for the aversive or hoarding picture blocks.
Figure 16. Regions exhibiting decreased activation in the OCD group during the citalopram infusion, for the washing picture blocks

![Brain scan images showing decreased activation areas](image)

Table 8. Regions exhibiting decreased activation during the citalopram infusion for the washing blocks

<table>
<thead>
<tr>
<th>Region</th>
<th>Side</th>
<th>Brodmann Area</th>
<th>MNI Coordinates x,y,z (mm)</th>
<th>Cluster size (kE)</th>
<th>Z</th>
<th>p value</th>
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</thead>
<tbody>
<tr>
<td>Decreases in OCD subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angular gyrus</td>
<td>R</td>
<td>39</td>
<td>60  -55  28</td>
<td>97</td>
<td>3.50</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
**Figure 17.** Regions exhibiting decreased activation in the OCD group during the citalopram infusion, for the checking picture blocks

![Brain images with highlighted regions](image)

<table>
<thead>
<tr>
<th>Region</th>
<th>Side</th>
<th>Brodmann Area</th>
<th>MNI Coordinates x,y,z (mm)</th>
<th>Cluster size (kE)</th>
<th>Z</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreases in OCD subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebellum</td>
<td>L</td>
<td>-</td>
<td>-6 -64 -32</td>
<td>44</td>
<td>3.15</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Table 9.** Regions exhibiting decreased activation during the citalopram infusion in the OCD group for the checking blocks
**PRE infusion vs. POST infusion**

During the washing picture blocks, OCD subjects exhibited decreased activation in the left dACC, the left OFC, the left rACC and the left supramarginal gyrus, after receiving the citalopram infusion, compared to baseline (Figure 18, Table 10). These reductions were not observed with the placebo infusion. Control subjects also demonstrated decreased BOLD responses in the right rACC after the citalopram infusion, however, the reduction was not to the same extent as seen in the OCD group (Figure 19, Table 10). A repeated measures ANOVA with a Greenhouse-Geisser correction revealed a significant Time x Infusion x Group interaction for the activation observed in the supramarginal gyrus ($F_{1,10} = 6.764$, $p = 0.026$).

For the checking picture blocks, after the citalopram infusion ended, OCD subjects demonstrated attenuated BOLD responses in the right OFC and left middle temporal gyrus, compared to baseline (Figure 20, Table 11). Control subjects also demonstrated reduced activity in the left middle temporal gyrus after receiving the citalopram infusion (Figure 21, Table 11). Results of the ANOVA revealed a significant ($F_{1,10} = 5.772$, $p = 0.037$) Time x Infusion interaction for the middle temporal gyrus.

During the aversive picture blocks, OCD subjects exhibited decreased activation in the right calcarine sulcus, after receiving the citalopram infusion, compared to baseline (Figure 22, Table 12). Controls subjects, on the other hand, demonstrated increased BOLD responses in the precuneus and bilaterally in the postcentral gyrus (Figure 23, Table 12). Many regions were discovered as having significant interaction effects, as determined by a repeated measures ANOVA. The precuneus was significant for the interaction Time x Infusion ($F_{1,10} = 10.163$, $p = 0.01$), the calcarine sulcus was significant for the interaction
Time x Infusion x Group ($F_{1,10}=7.918, p=0.018$) and the left postcentral gyrus was significant for the interaction Time x Group ($F_{1,10}=5.337, p=0.018$).

For the contrast Hoarding>Neutral, there were no changes in BOLD response associated with the citalopram infusion, in either group.
Figure 18. Regions exhibiting decreased activation in the OCD group after the citalopram infusion, for the washing picture blocks

![Regions exhibit decreased activation in the OCD group after the citalopram infusion, for the washing picture blocks](image)

Table 10. Regions exhibiting decreased activation after the citalopram infusion for the washing blocks

<table>
<thead>
<tr>
<th>Region</th>
<th>Side</th>
<th>Brodmann Area</th>
<th>MNI Coordinates x,y,z (mm)</th>
<th>Cluster size (kE)</th>
<th>Z</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Decreases in OCD subjects</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dorsal anterior cingulate</td>
<td>L</td>
<td>23</td>
<td>-5 -10 34</td>
<td>33</td>
<td>3.90</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Orbitofrontal cortex</td>
<td>L</td>
<td>47</td>
<td>-42 38 -16</td>
<td>44</td>
<td>3.50</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Rostral anterior cingulate *</td>
<td>L</td>
<td>32</td>
<td>-3 32 -8</td>
<td>172</td>
<td>3.41</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Supramarginal gyrus</td>
<td>L</td>
<td>48</td>
<td>-51 -25 28</td>
<td>36</td>
<td>3.55</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Decreases in Control subjects</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rostral anterior cingulate *</td>
<td>R</td>
<td>32</td>
<td>0 47 10</td>
<td>55</td>
<td>3.26</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Both groups exhibited attenuations in the rACC, however reductions were greater in the OCD group

Figure 19. Regions exhibiting decreased activation in the control group after the citalopram infusion, for the washing picture blocks

![Regions exhibit decreased activation in the control group after the citalopram infusion, for the washing picture blocks](image)
**Figure 20.** Regions exhibiting decreased activation in the OCD group after the citalopram infusion, for the checking picture blocks

![Image of brain scans showing decreased activation](image)

**Table 11.** Regions exhibiting decreased activation after the citalopram infusion for the checking blocks

<table>
<thead>
<tr>
<th>Region</th>
<th>Side</th>
<th>Brodmann Area</th>
<th>MNI Coordinates x,y,z (mm)</th>
<th>Cluster size (kE)</th>
<th>Z</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Decreases in OCD subjects</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orbitofrontal cortex</td>
<td>R</td>
<td>11</td>
<td>30 47 -14</td>
<td>38</td>
<td>3.35</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mid Temporal gyrus</td>
<td>L</td>
<td>21</td>
<td>-57 -55 1</td>
<td>31</td>
<td>3.25</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Decreases in Control subjects</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mid Temporal gyrus</td>
<td>L</td>
<td>21</td>
<td>-48 -52 3</td>
<td>30</td>
<td>3.23</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Figure 21.** Regions exhibiting decreased activation in the control group after the citalopram infusion, for the checking picture blocks

![Image of brain scans showing decreased activation](image)
Figure 22. Regions exhibiting decreased activation in the OCD group after the citalopram infusion, for the aversive picture blocks

![Brain images showing decreased activation regions](image)

Table 12. Regions exhibiting altered activation after the citalopram infusion for the aversive blocks

<table>
<thead>
<tr>
<th>Region</th>
<th>Side</th>
<th>Brodmann Area</th>
<th>MNI Coordinates x,y,z (mm)</th>
<th>Cluster size (kE)</th>
<th>Z</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Decreases in OCD subjects</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcarine sulcus</td>
<td>R</td>
<td>17</td>
<td>12 -82 7</td>
<td>45</td>
<td>3.40</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Increases in Control subjects</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Precuneus</td>
<td>R</td>
<td>7</td>
<td>12 -49 46</td>
<td>32</td>
<td>3.46</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Postcentral gyrus</td>
<td>R</td>
<td>2</td>
<td>46 -28 45</td>
<td>284</td>
<td>4.32</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Postcentral gyrus</td>
<td>L</td>
<td>2</td>
<td>-40 -31 48</td>
<td>90</td>
<td>4.40</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Figure 23. Regions exhibiting increased activation in the control group after the citalopram infusion, for the aversive picture blocks

![Brain images showing increased activation regions](image)
3.6 Correlations between Imaging and Behavioural Data

To determine if the changes in activation observed in the OCD group (from PRE to POST citalopram infusion) were associated with changes in subjective anxiety and disgust ratings, correlations were computed. Changes in OCD subjects’ anxiety ratings for the checking blocks positively correlated with BOLD signal reductions in the OFC (\(\tau=0.745; p=0.047\)) and dACC (\(\tau=0.926; p=0.015\)). As well, the PRE-POST change in rACC activation exhibited after the IV citalopram infusion positively correlated with changes in both the anxiety (\(\tau=0.931; p=0.011\)) and disgust ratings (\(\tau=0.745; p=0.044\)) for the washing blocks. These significant correlations are presented in Figures 24-27. As well, when looking at the PRE-POST changes in BOLD activation observed in the OCD subjects for all of the picture blocks, and correlating it to the changes in anxiety ratings for all of the picture blocks, the OFC was the only region showing significance (\(r = 0.493, p = 0.012\)) (Figure 28).
Figure 24. Correlation between citalopram induced PRE-POST changes in OFC activation and changes in anxiety scores for the checking blocks (OCD subjects only).

![OFC correlation graph]

tau=0.75

Figure 25. Correlation between citalopram induced PRE-POST changes in dACC activation and changes in anxiety scores for the checking blocks (OCD subjects only).

![dACC correlation graph]

tau=0.93
**Figure 26.** Correlation between citalopram induced PRE-POST changes in rACC activation and changes in anxiety scores for the washing blocks (OCD subjects only).

![Graph showing correlation between change in BOLD signal and change in washing anxiety ratings](image)

- Change in BOLD signal (z score)
- Change in washing anxiety ratings (z score)
- tau = 0.93

**Figure 27.** Correlation between citalopram induced PRE-POST changes in rACC activation and changes in disgust scores for the washing blocks (OCD subjects only).

![Graph showing correlation between change in BOLD signal and change in washing disgust ratings](image)

- Change in BOLD signal (z score)
- Change in washing disgust ratings (z score)
- tau = 0.75
Figure 28. Correlation between citalopram induced PRE-POST changes in OFC activation and changes in anxiety ratings for the all of the picture blocks (OCD subjects only).
Chapter 4 Discussion

The purpose of this chapter is to:

- review the main findings of the study and discuss how it relates to the published literature and our hypotheses
- discuss the implications of our results in OCD
- describe the limitations and strengths of the study, and future research perspectives

To our knowledge, this is the first study investigating the changes in neural activity due to the infusion of an IV SSRI in an OCD population. For this study we compared differences in baseline neuronal activation between groups, as well as changes in activation due to the citalopram infusion, compared to placebo, among groups. fMRI data will first be discussed, followed by behavioural data, and how our findings might explain the greater efficacy and faster onset of IV anti-obsessional agents.

4.1 Baseline differences between OCD and control subjects

When examining the baseline differences between the OCD and control group for the washing blocks, we found that OCD subjects exhibited greater activity in the OFC and ACC compared to controls, and less activation bilaterally in the middle temporal gyrus. Hyperactivity of the ACC and OFC is commonly reported in neuroimaging studies of OCD using symptom provocation, and this is in agreement with our findings (Fitzgerald et al., 2005; Adler et al., 2000; Chen et al., 2004; Mataix-Cols et al., 2004). However, contrary to
our results, several groups have previously noted increased activity in the middle temporal
gyrus of OCD subjects during provocation paradigms (Adler et al., 2000; Nakao et al.,
2005). This discrepancy could possibly be explained by the use of different types of
stimuli; while we exposed participants to provoking pictures, other studies have asked
participants to think of provoking and neutral words, or exposed participants to what they
believed to be contaminated stimuli.

During the checking blocks, OCD subjects exhibited greater activation than controls
in the inferior parietal lobe and the dACC, findings that are consistent with reports from
previous studies (Kang et al., 2003; Mataix-Cols et al., 2004). We also observed decreased
activation bilaterally in the caudate nucleus, which is discrepant with several studies
reporting increased caudate activation in OCD subjects. However, symptom provocation
studies have reported reduced activation of the caudate when the OCD sample consisted of
mostly checkers (Cottraux et al., 1996). This may suggest that while increased caudate
activity is associated with other OCD subtypes, decreased activation may be more
characteristic of the checking subgroup. Cottraux and colleagues theorized that reduced
caudate activity in checkers may result from their ability to perform covert and/or overt
rituals at any time (eg. reflect back on whether or not they locked the door) to reduce
feelings of anxiety caused by obsessions. Washers, on the other hand, are not able to
ritualize covertly, causing increased caudate activation (Cottraux et al., 1996). If valid, this
would explain our findings of decreased caudate activity only during the checking block, as
all participants in the OCD group reported some degree of checking symptoms and viewed
the checking stimuli as being anxiety provoking.
When examining differences in BOLD response during the aversive picture blocks, controls displayed greater activation of visual processing areas including the superior temporal gyrus and the calcarine sulcus, when compared to patients. These results are consistent with previous studies (Schienle et al., 2005; Mataix-Cols et al., 2003). Mataix-Cols et al (2004) have suggested that control subjects are better able to direct their attentional resources to the processing of aversive pictures’ visual details rather than their emotional salience, leading to greater activation in visual areas. Interestingly, activation of the insula was not significantly different between the two groups, even though insular hyperactivity has been reported in OCD subjects when viewing aversive stimuli (Shapira et al., 2003; Schienle et al, 2005).

There were no significant differences between the two groups for the hoarding picture blocks. This may be explained by the fact that we purposely excluded OCD subjects with hoarding symptoms from this study, and included only those who belonged to the OCD subtypes of washing and/or checking.

Altogether, our results at least in part confirm our first hypothesis, which proposed that at baseline, OCD subjects would exhibit greater activation of the OFC, caudate, thalamus and cingulate regions compared to controls. While hyperactivity of the OFC and cingulate regions were detected, decreased, rather than increased, activation was observed in the caudate. Furthermore, we were not able to identify any differences in thalamus activity between the two groups, even though it is a common finding in neuroimaging studies of OCD. The thalamus is thought to play a significant role in the corticostriatal–thalamocortical circuitry that is believed to mediate symptomatic expression in OCD.
4.2 Effect of Citalopram on the Neural Circuitry of OCD subjects & Controls

Mid-infusion results

When comparing baseline scans to those acquired during the citalopram infusion, reduced activity was observed in the angular gyrus of OCD subjects during the washing blocks, and in the cerebellum during the checking blocks. (Interestingly, these regions were not hyperactive in OCD subjects at baseline). The citalopram infusion only had an attenuating effect in the OCD group, and did not cause activation increases in any region, for any of the picture blocks.

Most studies investigating the effects of IV citalopram on the neuronal activity of healthy (non-OCD) subjects have done so 30-60 minutes after the infusion ended. However, one study looking at the immediate effects of citalopram in healthy controls, found significant attenuations in the cerebellum, similarly to our findings in the OCD group (McKie et al., 2005). As well, studies have reported increased (Nakao et al., 2005), as well as decreased (Nabeyama et al., 2008) activity of the cerebellum after symptom improvement in OCD subjects. The reason for this discrepancy is unclear, as the cerebellum is not often thought of as a key region mediating OCD symptomatology, and may therefore warrant further investigations regarding its role in the disorder.

It is surprising that when comparing baseline scans to those acquired during the infusions, citalopram only caused significant changes in 2 regions, and not in others. A possible reason for this may be the timing because the MID infusion scans were obtained prior to citalopram reaching its peak plasma and cerebral concentrations. Thus, at the MID
infusion time-point, there may not have been a sufficient concentration of the drug in the brain to cause more significant changes in neural activation. If this reasoning is correct, it would be expected that after citalopram reached its peak concentrations, (ie. at approximately 30 minutes), more exaggerated neural changes would be evident. Indeed, this was observed in the POST infusion scans, as discussed below.

**Post-infusion results**

Once the citalopram infusion was completed, decreased activation in the OCD group was observed in the OFC, ACC and supramarginal gyrus during the washing blocks, when compared to baseline. Interestingly, in the OCD group, the OFC and ACC were hyperactive at baseline, supporting our hypothesis that IV citalopram would attenuate responses of hyperactive regions. Control subjects also exhibited reduced rACC levels post-citalopram, and even though the reductions were not as substantial as they were in the patient group, it signifies that the effects of citalopram may not be specific to the patient population as we had hypothesized.

When viewing the checking picture blocks, OCD subjects exhibited reductions in the OFC and middle temporal gyrus once the citalopram infusion ended, an effect that did not occur with the placebo infusion. These regions did not exhibit altered activation at baseline during the checking blocks, whereas the regions that were significantly different between the 2 groups at baseline (caudate nucleus and inferior parietal lobe) were not influenced by the citalopram infusion. Control subjects also exhibited attenuated responses in the middle temporal gyrus, but not to the same extent as seen in the patient group.
Citalopram decreased activation in the calcarine sulcus of OCD subjects during the POST infusion aversive picture blocks. This is surprising because the calcarine sulcus was hypoactive in the OCD group at baseline, and contrary to what we expected, citalopram further reduced activation in this region instead of normalizing it. Increases in neuronal activation due to IV citalopram were not observed in the OCD group, however increases were detected in the control group. Compared to baseline, control subjects exhibited increased activation bilaterally in the postcentral gyrus and the precuneus after receiving IV citalopram.

In general, the citalopram infusion had an attenuating effect on the neural activity in the OCD group, while it both increased and decreased neuronal activity in the control group, depending on the picture block being viewed. The control subjects exhibited activation reductions in areas similar to the OCD group after the citalopram infusion, however, the effect in the patient group was greater and extended to more regions in the brain. These findings, in part, confirms our hypothesis that IV citalopram would reduce hyperactivity in the patient group, compared to controls. It is possible that citalopram has an affinity to exert its effects in specific brain regions regardless of the population (patients or controls), but produces more exaggerated responses in patients, which would account for our findings.

Neuroimaging studies investigating the neuronal effects of IV citalopram have not been previously conducted in OCD patients, however, we can compare our results to studies performed in healthy control subjects. These studies reported that after receiving IV citalopram, control subjects exhibited decreased activation in the left and right OFC, right ACC, left supramarginal gyrus, and the left middle temporal gyrus (Anderson et al. 2009;
Smith et al. 2009; McKie et al. 2005; Del-Ben et al. 2005). We found very similar
deactivations with IV citalopram in the OCD group. However, these findings have not
been reported consistently, with other studies reporting activation increases in the ACC and
right middle temporal gyrus, contrary to our results (Anderson et al. 2011; Smith et al.
2002). Studies have also reported activation changes in regions that were not detected in
our study, which may be due to the differences in the populations studied and in the tasks
that were used.

Reports from previous neuroimaging studies investigating the effects of treatment
in OCD, can also be used to evaluate our findings. An fMRI study by Nakao et al. (2005)
examined the changes in brain activation of OCD subjects before and after symptom
improvement using a symptom provocation paradigm (SPP). They reported that at
baseline, OCD subjects exhibited activations in the left middle frontal gyrus, OFC, left
temporal cortex, left parietal cortex and right cerebellum. However after treatment,
reductions were observed in the right postcentral gyrus, left ACC, left middle temporal
gyrus, and bilaterally in the cerebellum and the thalamus. These reports are in keeping
with our findings, as similar regions, namely the middle temporal gyrus, cerebellum and
ACC, exhibited decreased activation after treatment (oral fluvoxamine in the Nakao et al.
study and IV citalopram in the present study). In addition, several neuroimaging studies
have reported activation decreases in the OFC and cingulate regions in OCD patients after
SSRI treatment and symptom improvement, findings that are also consistent with our
results (Del Casale et al. 2011; Friedlander et al. 2006; Choi et al. 2009). Reductions in
striatal activity have also been reported in the literature after successful medication trials
(Lazaro et al. 2007; Schwartz et al. 1996; Hendler et al. 2003); however we were unable to identify any significant changes in the striatum after IV citalopram administration.

Even though the effects observed in the present study were relatively immediate and transitory (subjects only received a single dose), it would appear that we replicated findings from long term (12 weeks) treatment studies of oral agents (Nakao et al. 2005) and CBT (Nabeyama et al. 2008). Furthermore, it would seem reasonable to suggest that these effects may persist with a prolonged trial of IV citalopram.

In general, the results confirmed our primary hypothesis, as regions that demonstrated increased activity in the patient group at baseline (OFC, rACC, dACC, supramarginal gyrus) did indeed exhibit activation reductions after the citalopram infusion. However, interestingly, regions that were hypoactive at baseline (middle temporal gyrus, calcarine sulcus) and regions not significantly different between the two groups at baseline (angular gyrus, cerebellum) also exhibited post-citalopram attenuations. Nevertheless, most of the robust changes in activation occurred in regions exhibiting significant differences between OCD subjects and controls at baseline. The attenuations of hyperactivity in these key regions may account for the faster onsets of improvement and greater efficacy associated with IV medications. Thus, it could be argued that IV citalopram specifically targeted these regions (possibly in an attempt to normalize them) and this may explain its therapeutic benefit in reducing anxiety.

4.3 Behavioural Ratings

OCD subjects had significantly higher anxiety ratings for the washing and checking picture blocks compared to controls, confirming that the symptom provocation paradigm
was effective in triggering anxiety in OCD subjects. As expected, there were no significant differences in the ratings for the neutral and aversive blocks, as they were designed to elicit similar responses in both groups. While all subjects rated the hoarding pictures as being mildly anxiety provoking, ratings were not significantly different between the 2 groups. This is most likely due to the fact that our OCD sample consisted of washers and checkers who were free of hoarding symptoms.

OCD subjects reported significant reductions in anxiety for the washing and checking blocks after receiving IV citalopram, suggesting that the infusion may have ameliorated the anxiety triggered by the pictures. It is of note that the reductions in anxiety observed in the OCD group did not occur during the infusion, but only after the infusion ended, which corresponds to when citalopram reaches its peak plasma concentrations. It is can be argued that adequate concentrations of citalopram in the brain were required to manifest behavioural changes, and this occurred during the POST infusion picture blocks. It is unlikely that this reduction in anxiety was due to the relief the subjects felt when the infusions finished, because such changes in anxiety levels were not observed with the placebo infusion. It is of interest that the timing of the observed behavioural changes are similar to our fMRI data, with reductions in hyperactive regions (specifically the OFC and cingulate regions) occurring only after the citalopram infusion ended. Thus it would seem reasonable to argue that the reduced hyperactivity of these regions led to reductions in subjective anxiety experienced by the OCD subjects. Indeed, correlation analyses revealed significant associations between changes in BOLD signal of the OFC and ACC, and changes in anxiety ratings for the checking and washing blocks.
OCD subjects also rated the washing pictures as being significantly more disgusting than the control subjects did. This finding is in line with previous observations that OCD patients view contamination-related pictures as disgusting, rather than fearful, which then is said to trigger feelings of anxiety (Husted et al. 2006). Significant reductions in disgust ratings for the washing block were observed only after OCD subjects received citalopram. Interestingly, similar reductions were not observed for the aversive picture block, suggesting that citalopram only reduced feelings of disgust that were related to OCD symptomatology, rather than general feelings of disgust. We would expect then, to find significant differences in the contamination subscale of the Disgust Scale (DS) after OCD subjects received IV citalopram, compared to placebo. However, this was not the case; there were no significant differences in the contamination subscale, or any other DS subscales, when the infusions were compared. This discrepancy may at least in part be explained by a time lag; reductions in (washing picture block) disgust ratings were observed at the end of the citalopram infusion, whereas the DS questionnaire was completed by subjects an hour afterwards. It is possible (though unlikely due to citalopram’s long half-life), that the beneficial effect of the drug in reducing disgust sensitivity, may have worn off, and therefore did not translate into changes on the contamination subscale.

It is worthy of note, that reductions in subjective anxiety and disgust due to IV citalopram, only occurred in the symptom blocks that were relevant to our OCD sample (ie. checking and washing). This may suggest that citalopram’s benefit is mediated by specific anti-obsessional effects, rather than a non specific reduction in general anxiety. However, it should be noted that we asked participants to rate how anxious the pictures made them
feel, and did not ask if they felt the urge to engage in compulsions, which would have been a more direct method of investigating citalopram’s anti-obsessional effect. It would be interesting to see if IV citalopram also reduces anxiety in other subgroups of OCD, such as those with hoarding and symmetry/ordering symptoms. To our knowledge, this is the first study to observe an almost instant reduction in anxiety after a single dose of IV citalopram in OCD subjects. A previous investigation reported noticeable reductions in anxiety after OCD subjects underwent a 3 week trial of 40 mg IV citalopram administered daily (Pallanti et al. 2002). However, the main outcome variable for this study was a reduction in the Y-BOCS, which is a long-term measure of OCD symptoms and related anxiety, whereas the subjective behavioural ratings that we collected most likely reflect transient changes.

It is important to point out that while the previously discussed PRE-POST reductions in anxiety and disgust that we observed were significant, they were not substantial, with differences not exceeding 0.7 points. However, the differences were statistically significant and correlated with neuroimaging data, thereby, demonstrating the immediate and specific anxiolytic effects of IV citalopram.

### 4.4 Implications in OCD

Our results indicate that anxiety in response to the provocative stimuli, and BOLD signal changes observed after the citalopram infusion, were associated with prefrontal regions (OFC, ACC) and regions involved in visual processing (precuneus, middle temporal gyrus, calcarine sulcus). These regions have been suggested to be a part of the neural circuitry implicated in the pathophysiology of OCD.
The OFC plays an important role in integrating information about rewards and punishments when planning future behaviour, including evaluating the motivational significance of stimuli. Furthermore, it is instrumental in learning appropriate responses to both rewarding and aversive stimuli, as well as switching responses when it is adaptive to do so. The causal relationship between OFC hyperactivity and OCD symptomatology is most-likely bi-directional, and researchers have put forward models explaining their interaction. Evans et al. (2004) have proposed that abnormal reward and punishment perceptions may contribute to the pathophysiology of OCD. When experiencing obsessions, patients are said to be conscious of committing an error, and the relief experienced by engaging in compulsions is said to serve as the reward. Thus, the need to regulate anxiety by engaging in behaviour patterns that are difficult to terminate, results in continuous activation of the OFC. This ‘overstimulation’ detracts the OFC from its role in executing a flexible control process, leading to rigid and stereotypic behaviours (Evans et al. 2004). An alternative model of OFC activation and OCD symptomatology was proposed by Zald and Kim (2001). This model suggests that processing information about aversive expectations is a key function of the OFC, and in OCD subjects, its hyperactivity leads to excessive representations of aversive stimuli, which in turn leads to cognitive intrusions and repetitive behaviours. It is of note that the OFC has been shown to be sensitive to 5-HT modulation (Anderson et al. 2008) adding evidence for its role in the pathophysiology of OCD.

Along with the OFC, hyperactivation of the ACC significantly decreased after the citalopram infusion. The ACC plays a key role in error detection and overriding prepotent response patterns. It is responsible for deciding an appropriate behaviour course under
motivationally ambiguous circumstances and in regulating emotion when behaviours are not achieving a desired outcome. Many of these functions overlap with the OFC, and altered activation of these two regions, (which normalize with oral SSRI treatment), are robust findings in OCD subjects (Nakao et al. 2005; Hendler et al. 2003; Nabeyama et al., 2008). The dorsal area of the ACC (dACC) is referred to as the ‘cognitive division’ and has been implicated in response selection and processing of cognitively demanding information. Conversely, the rostral area of the ACC (rACC) is referred to as the ‘affective’ division and is implicated in affect regulation and motivation (Davidson et al. 2002). ACC related dysfunction of action monitoring and error detection may explain several symptoms of OCD. Del Casale et al. (2011) have suggested that patients with OCD may have a greater sensitivity to errors. This causes them to perceive errors even when a particular behaviour was executed correctly, leading to significant affective responses and a preoccupation to correct the perceived mistakes (Del Casale et al. 2011). Furthermore, the dACC is said to play a key role in self monitoring processes that turns ‘on’ and ‘off’ when appropriate. However, in OCD subjects, there is a failure to turn off this monitoring process even when the desired result is achieved (Shackman et al. 2011). Certain OCD symptoms like constant doubt and the need for repetition has been attributed to malfunctions of the ACC, which may continue to signal a conflict, even when one no longer exists. This proposal may in part explain the baseline hyperactivity we observed in the dACC during the checking blocks in the patient group, as constant doubt is a key feature of the checking subtype.

In this investigation, several other regions including the angular, supramarginal and middle temporal gyri, demonstrated reduced activity after the citalopram infusion in the
OCD group, an effect not seen with the placebo infusion. The angular and supramarginal gyrus are thought to play an important role in the generation of mental movement representations. Schienle et al. (2005) have proposed that dysfunctions in these regions lead to impaired evaluations of whether a compulsive behaviour should be executed and when they should be terminated. This is of particular relevance to contamination related symptoms, as patients constantly evaluate whether they have adequately rid themselves of contaminants. In keeping with the above proposition, we observed reduced activation in the supramarginal and angular gyri of OCD subjects during the washing picture blocks after the IV citalopram infusion. Less is known about the role that the middle temporal gyrus may have in OCD, however, complex partial seizures involving the temporal lobe have been characterized with reported feelings of ‘forced thinking’ that is very similar to obsessional thinking in OCD (Perani et al. 1995).

The observed attenuations of the OFC, temporal cortex, ACC, and supramarginal gyrus after IV citalopram administration, are consistent with a role for 5-HT in the inhibition of unwanted behaviours, as these regions have a rich innervation of 5-HT neurons and loosely matches known 5-HT2C receptor distribution (Anderson et al. 2008). Few studies have examined the association between 5-HT receptors subtypes, treatment response and neuroimaging. Smith et al. (2009) have previously suggested that changes in the cingulate observed after citalopram treatment, are mediated by 5-HT2C receptors, and with chronic treatment these receptors are desensitized, leading to increased 5-HT concentrations following reuptake inhibition. This hypothesis is consistent with the suggestion that acute increases in 5-HT often leads to increased anxiety (Pigott et al. 1992), with subsequent reductions in anxiety occurring after continued treatment produces
adaptive changes in the 5-HT receptors. However we observed opposite findings, or more specifically, decreased anxiety levels after IV citalopram administration, results similar to other studies in OCD (Fabio et al. 2007). Another investigation identified orbitofrontal 5-HT1BRs (a serotonin receptor) as a critical substrate for modulating OCD-like behavior in mice (Shanahan et al. 2011). The authors reported that activating 5-HT1BRs induced repetitive actions in mice, and that chronic treatment with SRI s reduced the expression of these receptors, specifically in the OFC, which corresponded with the return of normalized behaviour. They concluded that orbitofrontal 5-HT1BRs play a critical role in the pathophysiology of OCD, and that desensitizations of these receptors in the OFC (due to chronic SRI treatment) brings about symptom improvement (Shanahan et al. 2011).

However it is unclear if this murine model of OCD pathophysiology is applicable to humans. Several 5-HT pharmacofMRI studies have reported altered activation of numerous brain regions in healthy and depressed subjects; however it is difficult to formulate a cohesive functional model because the hemisphere and direction of activation is often varied, probably due to different types of stimuli and tasks used.

It is suggestive that the results of our study confirm the beneficial effects of IV SSRIs in OCD, and supports their use in clinical settings. The attenuations we observed in previously hyperactive regions, after a single dose of IV citalopram, are similar to effects observed after prolonged oral pharmacotherapy trials. This further demonstrates the quicker onsets associated with IV agents when compared to oral forms. With oral pharmacotherapy, clinically meaningful symptom reductions can take as long as 6-12 weeks. However, studies suggest this lag period could be considerably reduced (to less than 2 weeks) with the use of IV SRI s (Fallon et al., 1998). The faster onsets of IV agents
may be attributed to the relatively immediate deactivations that we detected in key brain regions. It is possible that once significant symptom reductions are achieved by the infusions, oral medication could then be instituted as maintenance therapy. In addition, it is well documented that complete remission is rare in OCD and treatment response is typically defined by a 20–40% reduction in symptoms. Thus, a great number of patients classified as “responders” are still markedly symptomatic (Abramowitz 2009). However, with the use of IV agents, there may be a greater likelihood of attaining complete remission. Furthermore, the benefits of IV anti-obsessional agents may be extended to the treatment of OCD spectrum disorders, including trichotillomania, dermatillomania, and compulsive gambling, which often shows inadequate response to pharmacotherapy and treatment resistance.

The published literature suggests that there are few reliable predictors of treatment response in OCD. Baseline functional and structural abnormalities of the key regions involved in the pathophysiology of OCD may be useful as biomarkers for OCD severity and treatment response. Indeed, several studies have indicated that activation of the OFC, thalamus and cingulate regions may serve to predict treatment response in OCD patients (Saxena et al. 1999; Perani et al. 1998). We would suggest that in addition to this, BOLD responses to IV SSRIs (such as the responses we observed) might also be useful in predicting which patients to select for aggressive oral pharmacotherapy. Patients exhibiting greater attenuations in the OFC, ACC and other key regions may respond to oral SSRIs, whereas patients exhibiting little to no BOLD signal changes after the infusions are less likely to do so. Predicting treatment response can potentially aid in treatment selection, as those predicted not to respond to oral SSRIs may experience faster symptom
relief if they are started with behavioral therapy or combination treatments, instead of the usual first line pharmacotherapy. This may be of significant clinical value because response time and adequate SSRI doses vary widely in OCD patients. The use of objective and reliable biomarkers can be very useful in clinical practice and would validate the emerging trend towards personalized medicine.

Recent research advances have helped to establish some of the key regions implicated in the pathology of OCD, however, further advancements in our understanding of the neurobiology of OCD are needed before effective interventions can be formulated. Elucidating the mechanisms by which IV SSRIs bring about more rapid and effective improvements would be instrumental in developing more effective treatments. This would involve determining where and how IV citalopram exerts its effects, including which receptors/transporters it targets and what neurochemical processes are involved. The use of IV agents could potentially be helpful in this task, as acute citalopram manipulations can be used as a probe to detect activity at different receptor sites.

4.5 Methodological Considerations and Future Studies

An important strength of this study was that subjects were matched for age, sex and education. Furthermore, subjects were all right-hand dominant. As well, the use of a placebo infusion added to the rigor of the investigation and allowed us to determine that changes in neuronal activation were due to the citalopram infusion, and not due to non specific factors, such as the IV procedure. Furthermore, the criteria that OCD subjects on medication had to be drug-free for at least 2 weeks prior to their scan dates ensured that residual effects of their usual medication would not influence the results.
A main limitation of this study is that our samples were small and important differences may have been missed due to lack of power. As well, given the small number of subjects, we needed to utilize lower statistical thresholds for SPM analysis, since more stringent thresholds may have excluded potentially significant findings. One such example is the thalamus, a region repeatedly reported as being hyperactive in OCD, and whose activation was not detected in this study, probably due to lack of power.

The intensity of the stimuli in the SPP may have also had an influencing factor on the extent of neuronal activations we observed. While OCD subjects reported experiencing significantly more anxiety than controls during the SPP, they perceived the stimuli as only mildly to moderately provoking (based on their anxiety ratings). Using stimuli of higher intensity to evoke greater levels of anxiety (and therefore more significant alterations in neuronal activity) may be a useful strategy to explore. Since OCD often presents with heterogeneous symptoms, one possible approach is to use stimuli individually tailored to each subject’s symptoms to ensure sufficient anxiety arousal. However, there are several advantages to using a priori-selected provocative stimuli, as we did for the present study. When using a sample that consists of OCD subjects with similar subtypes, there are usually only a limited number of themes that trigger anxiety. The use of a wide variety of pictures representative of the symptom subtypes ensures the inclusion of the triggers relevant to most patients. Furthermore, differences in activation between subjects are not confounded, as identical pictures are presented to all subjects.

In terms of our participants, half of the OCD subjects had comorbid diagnoses, which may have confounded the results. However, with the exception of 1 patient, these comorbid diagnoses were considered to be mild in severity. As well, controls subjects did
not complete the Y-BOCS, so we can not completely rule out the possibility that they may have had some degree of obsessions and/or compulsions, even though they were screened before study enrollment.

Another potential confound is the possibility that citalopram has direct effects on overall cerebral blood flow and blood volume. These variables can therefore change the magnitude of the BOLD responses, so that effects seen may not necessarily be due to alterations in neuronal activity. However, in general, 5-HT manipulations are not believed to have significant effects on the cerebral vasculature (Anderson et al., 2011).

Bearing the above limitations in mind, we believe the results of the present study adds to the literature regarding the benefits of IV SSRIs as anti-obsessive agents and their impact on the neuronal circuitry of OCD patients. Replication studies using larger samples with increased statistical power are needed to determine the robustness of our results. As well, future studies are recommended to include pharmacokinetic measures, so that BOLD signal changes can be correlated to citalopram concentrations, providing a more comprehensive view of citalopram’s role in modulating neuronal activity. Also, while the present study demonstrated the behavioural effects of acute citalopram administration, how the changes in BOLD response translates into reductions in anxiety, warrants investigation. As well, PET studies using radioligands for 5-HT transporters (eg. \(^{11}\text{C}\text{DASB}\)) and receptors (eg. \(^{11}\text{C}\text{MBL}\)) can be used to detect the molecular changes that occur at the transporter and receptor level due to IV anti-obsessive agents. This would be instrumental in gaining a more comprehensive view of OCD, and how interventions mediate their benefit.
4.6 Conclusion

To the best of our knowledge, this is the first study examining the effects of an IV SSRI infusion on the neural circuitry of an OCD sample. While replication studies are needed to confirm our findings, our results provide evidence that IV citalopram has immediate effects on the neuronal circuitry implicated in OCD, as well as on anxiety related to it. Intravenous anti-obsessive medications have been shown to be more effective and confer quicker benefits than oral medication in treating OCD symptoms. Our findings add to the neurobiological evidence for such benefits, and strengthens the rationale for the use of IV anti-obsessive agents in clinical settings. Furthermore, our research contributes to an evolving and comprehensive neurobiological model of OCD. This may ultimately lead to the development of more effective therapeutic interventions that can better combat OCD symptoms and provides relief to those suffering from it.
References


