

**Obsessive-Compulsive Disorder:
Serotonergic and dopaminergic system involvement in
symptom generation and treatment response**

Paul D Carey



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Promoter: Professor Dan Stein

Co-Promoter: Professor Kurt Audenaert

Declaration

I, the undersigned, hereby declare that the work contained in this dissertation is my own original work and that I have not previously in its entirety or in part submitted it at any university for a degree.

Signed

Date

If therefore anyone wishes to search out the truth of things in serious earnest, he ought not to select one special science; for all the sciences are conjoined with each other and interdependent; he ought rather to think how to increase the natural light of reason, not for the purpose of resolving this or that difficulty of scholastic type, but in order that his understanding may enlighten his will to its proper choice in all contingencies of life. In a short time he will see with amazement that he has made more progress than those who are eager about particular ends, and that he has not only obtained all that they desire, but even higher results than fall within his expectation.

- Descartes -

SUMMARY

Investigations into the neurobiology of obsessive-compulsive disorder (OCD) have provided useful insights into this prevalent and disabling disorder in recent decades. Encouraging advances have also been made in the pharmacological treatment of OCD. This has improved the quality of life for many who typically endure chronic unremitting symptoms. Despite the widespread use of first-line agents selective for the serotonergic system in OCD, relatively little is known about the neurobiology of treatment response, the specific components of the serotonin system involved in symptom modulation, and the overlapping and distinct brain regions impacted by alternative treatment options. Despite the advance that selective serotonin re-uptake inhibitors have been, a significant proportion of patients still fail to respond adequately to these agents, and alternative pharmacological interventions are required. The use of dopamine antagonists, a strategy which until recently has had only limited supporting data, presents one such alternative. Little however, is known about which subsets of patients are most likely to respond to these agents.

In this thesis, I will present a series of six studies that use pharmacological treatments and single photon emission computed tomography (SPECT) to make contributions to three primary areas in OCD namely; neurobiology, treatment and the intersection of the two. First, I address OCD neurobiology by examining the impact of OCD on resting brain function. I then examine the effects of pharmacological challenge of the serotonin 1B receptor using sumatriptan on regional cerebral blood flow (rCBF) and clinical symptomatology. Second, I examine the intersection of neurobiology and treatment as I explore the changes in rCBF in response to treatment with inositol, a precursor of the phosphoinositol second messenger system. I then examine the distinct and overlapping effects on rCBF of treatment for 12 weeks with the selective serotonin re-uptake inhibitor (SSRI) citalopram across anxiety disorders. Third, I address treatment of OCD by examining the efficacy of controlled augmentation of serotonin re-uptake inhibitors with quetiapine, a dopamine antagonist, in treatment refractory OCD. I then combine this data with a second similar dataset to derive a predictive model for treatment outcome with quetiapine augmentation of SRIs.

I demonstrate that rCBF in OCD differs significantly from normal controls, is correlated with severity in frontal brain regions, and remains an important line of investigation for OCD pathophysiology that has yet to fully delineated. Pharmacological challenge of the 5HT1B autoreceptor with the selective agonist sumatriptan results in heterogeneous behavioural and regional brain perfusion changes in OCD. Attenuation of pre-frontal perfusion following 5HT1B agonist administration is in line with the effects of SRIs. This work suggests that direct or indirect effects of SRIs on the 5HT1B receptor may be involved in mediating a clinical response in OCD.

In the section exploring the intersection of neurobiology and treatment, I show that changes in rCBF partially parallel treatment response to SSRIs across a range of anxiety disorders. These data suggest that a degree of overlap exists in the neurobiology of treatment response or indeed core neurobiology across different anxiety disorders. I then show that effective treatment with inositol in OCD results in rCBF changes that are partially in line with the effects of SRIs on brain perfusion. These data support suggestions that second messengers may form part of the common pathway of action for effective anti-obsessional compounds.

In the study in which we augmented SRIs with quetiapine, no advantage over placebo was found. This data has, however, recently been combined with similar data in meta-analyses and demonstrated a benefit over placebo. Finally, we found that patients who have failed fewer SRI trials, have more severe illness, and clinical dimensions with a putative dopaminergic underpinning, may derive preferential benefit from serotonin/dopamine antagonist augmentation of SRIs.

Through this series of clinical treatment and functional brain imaging studies in OCD, I have contributed to the neurobiological understanding of OCD, and its treatment in refractory populations. In addition I have explored the intersection of these two domains using novel as well as conventional treatment across other anxiety disorders. Treatment and pharmacological challenges used, either directly or indirectly impacted the monoamine systems serotonin and dopamine and advanced our understanding of their involvement in symptom generation.

Future work should focus on the functional intersection of brain function, treatment response, and functional genetic polymorphisms within the monoamine systems of the brain.

OPSOMMING

Onderzoek na die neurobiologie van obsessief-kompulsiewe steuring (OKS) het in die afgelope dekades sinvolle bydraes gelewer tot die begrip van hierdie algemene en verminkende steuring. Bemoedigende vordering is ook in die farmakologiese behandeling van OKS gemaak. Dit het tot 'n verbetering in kwaliteit van lewe van meeste pasiënte gelei wat normaalweg kronies en onophoudelike simptome moet verduur. Ten spyte van die uiteenlopende gebruik van eerste-linie behandeling wat spesifiek inwerk op die serotonien sisteem in OKS, is relatief min bekend oor die neurobiologie van respons op behandeling. So ook is min bekend oor; eerstens die spesifieke komponente van die serotonien sisteem wat betrokke is by simptome modulatie, en tweedens die gedeeltelik samevallende en afsonderlike brein streke wat deur alternatiewe farmakologiese behandelings beïnvloed word. Ten spyte van die vooruitgang wat die selektiewe serotonien heropname inhibeerders tot gevolg gehad het, is daar nog altyd 'n betekenisvolle proporsie van pasiënte wat nie voldoende repondeer op hierdie behandelings opsie nie. Dus word alternatiewe opsies benodig. Een so 'n opsie is die klas dopamien reseptor blokkeerders wat tot onlangs min ondersteunende data gehad het. So ook, is min bekend oor die subgroepe van pasiënte wat die meeste voordeel uit hierdie alternatiewe sal trek.

In hierdie proefskrif sal ek 'n reeks van ses studies wat farmakologiese middels en enkel foton emissie rekenaar tomografie (EFERT) gebruik om 'n bydra tot kennis in drie primêre areas van OKS te maak. By name; neurobiologie, behandeling, en die kruispunt van die twee. Eerstens spreek ek neurobiologie aan deur middel van 'n studie wat rustende brein bloed vloei (rBBV) in OKS ondersoek. Hierna ondersoek ek veranderinge op rBBV en simptome na eenmalige toediening van 'n serotonien 1B reseptor agonis, sumatriptan. Tweedens ondersoek ek die kruispunt van neurobiologie en behandeling deur die effek van behandeling met inositol, 'n voorloper van die fosfoinositol tweedeboods-kapper sisteem, op rBBV. Ek ondersoek dan die rBBV patroon van veranderinge in brein streke wat deur twaalf weke van behandeling met die selektiewe serotonien heropname inhibeerder citalopram in verskeie angversteurings bewerkstellig word. Laastens, spreek ek behandeling van OKS aan deur middel van 'n

gekontroleerde studie wat ondersoek instel na die effektiwiteit van die byvoeging van quetiapien, 'n dopamien reseptor antagonist, tot serotonien heropname inhibeerders in behandelingsweerstandige OKS. Ek kombineer dan hierdie data met 'n soortgelyke datastel om 'n model af te lei wat kliniese uitkoms vir hierdie behandelings opsie voorspel.

Ek het gedemonstreer dat rBBV in OKS betekenisvol verskil van gesonde vergelykbare kontroles. Hierdie verskille het gekorreleer met ernstigheid van OKS in frontale brein streke. Dus bly hierdie tipe studies 'n belangrike rigting van ondersoek in OKS patofisiologie wat tot op hede nie tenvolle uitgewerk is nie. Eenmalige toediening van sumatriptan, het heterogene gedrags en rBBV veranderinge in OKS tot gevolg gehad. Pre-frontale verhogings in rBBV voor behandeling is met 5HT1B sumatriptan toediening verminder, 'n effek wat in lyn staan met die effek van selektiewe serotonien heropname inhibeerders. Hierdie werk stel voor dat direkte of indirekte effekte van selektiewe serotonien heropname inhibeerders op die 5HT1B reseptore betrokke mag wees by die meganisme van behandelingsrespons in OKS.

In die afdeling waarin ek die kruispunt van neurobiologie en behandeling ondersoek, demonstreer ek dat rBBV veranderinge gedeeltelik oorvleuel met dié wat deur selektiewe serotonien heropname inhibeerders veroorsaak word in verskeie angstversteurings. Hierdie data stel voor dat oorvleueling in die neurobiologie van beide behandelingsrespons en kern neurobiologie van hierdie angstversteurings 'n waarskynlikheid is. Ek wys ook dat effektiewe behandeling met inositol in OKS ook veranderinge in rBBV bewerkstellig wat gedeeltelik in lyn staan met dié van die selektiewe serotonien heropname inhibeerders. Hierdie data ondersteun dus hipoteses van 'n gemeenskaplike meganisme, wat tweede boodskapper sisteme insluit, wat in die behandelings respons van effektiewe anti-obsessie middels betrokke is.

Die finale deel van hierdie proefskrif handel oor behandeling van OKS. Ten spyte van die onvermoë om 'n verskil tussen quetiapien en plasebo te demonstreer, het ons onlangs met hierdie data in 'n reeks meta-analises wel 'n voordeel vir hierdie intervensie getoon. Ten slotte, het ons gevind dat (1) pasiënte wat minder kursusse selektiewe serotonien heropname inhibeerders gefaal het; (2) voor behandeling 'n erger vorm van OKS gehad het, en (3) ook voordoen met simptome dimensies wat oënskynlik 'n

dopaminerge basis het, die grootste waarskynlikheid toon om met quetiapien byvoeging tot selektiewe serotonien heropname inhibeerders te respondeer.

Met hierdie reeks behandelings en funksionele breinbeeldings ondersoeke, lewer ek 'n bydra tot die begrip van OKS. Spesifiek dra ek by tot die begrip van die neurobiologie, hantering van behandelingsweerstandige OKS asook die kruispunt van die twee. Farmakologiese middels wat ons óf eenmalig óf vir 'n volle behandelingskursus toegedien het, het direkte of indirekte uitwerkings op die serotonien and dopamien sisteme gehad, en dus dra hierdie werk ook by tot kennis oor dié se betrokkenheid al dan nie in simptoom modulاسie in OKS.

Toekomstige werk in die area sal in die breë fokus op die kruispunt van breinfunksie, behandelingsrespons en funksionele genetiese polimorfismes van die monoamien sisteem.

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TABLE OF CONTENTS

Preamble		1
Chapter 1	General Introduction	5
	1.1 General Introduction	5
	1.2 Introduction to Part I	
	1.2.1 Regional brain perfusion in OCD compared to normal controls – a basis for establishing the impact of treatments on functional status	13
	1.2.2 Acute effects of the Serotonin 1B auto-receptor agonist Sumatriptan on Regional Brain Perfusion SPECT in OCD	17
	1.2.3 Functional brain changes in response to citalopram serotonergic treatment across anxiety disorders: Similarities and distinctions	20
	1.2.4 Functional brain perfusion SPECT in OCD: Changes in response to treatment with Inositol	22
	1.3 Introduction to Part II	26
	1.3.1 Treatment effects of combined dopamine and serotonin receptor blockade in OCD	26
	1.3.2 Clinical and demographic determinants of response to treatment with combined dopamine and serotonin receptor blockade in OCD	28
	1.4 Hypotheses	30

Part I		44
Chapter 2	Regional Brain perfusion in OCD compared to normal controls – a basis for establishing the impact of treatments on functional status	45
	2.1 Abstract	46
	2.2 Background	47
	2.3 Methods	49
	2.4 Results	53
	2.5 Discussion	58
Chapter 3	Clinical and regional brain perfusion changes in response to acute challenge with a serotonin 1B/D receptor agonist in OCD	66
	3.1 Abstract	67
	3.2 Background	68
	3.3 Methods	70
	3.4 Results	74
	3.5 Discussion	78
Chapter 4	Functional brain changes in response to serotonergic treatment across anxiety disorders: Similarities and distinctions	86
	4.1 Abstract	87
	4.2 Background	88
	4.3 Method	89
	4.4 Results	92
	4.5 Discussion	98
Chapter 5	Functional brain perfusion measured with single photon emission computed tomography (SPECT) in obsessive compulsive disorder: Changes in Response to treatment with Inositol	104
	5.1 Abstract	105
	5.2 Background	106
	5.3 Methods	107
	5.4 Results	110
	5.5 Discussion	116
	5.6 Conclusions	118

Part II		122
Chapter 6	Treatment effects of combined dopamine and serotonin receptor blockade in obsessive-compulsive disorder	123
	6.1 Abstract	124
	6.2 Background	125
	6.3 Methods	126
	6.4 Results	129
	6.5 Discussion	135
	6.6 Conclusions	137
Chapter 7	Clinical and demographic determinants of response to treatment with combined dopamine and serotonin receptor blockade in obsessive-compulsive disorder	141
	7.1 Abstract	142
	7.2 Background	143
	7.3 Methods	144
	7.4 Results	145
	7.5 Discussion	146
Chapter 8	Summary and Conclusions	154
	8.1 Executive Summary	155
	8.2 Detailed Summary	156
	8.3 Conclusions and future directions	161

LIST OF TABLES

- Table 2.1** Whole brain group-wise contrast with OCD<controls
- Table 3.1** Paired t-tests for changes in scale scores for sumatriptan and placebo and RMANOVA for within subject treatment comparisons.
- Table 4.1** Clinical parameters for all the groups (mean \pm SD), (paired t-test)
- Table 4.2** Localisation of significant clusters of deactivation following treatment for the combined group of OCD,SAD, & PTSD.
- Table 4.3** Clusters in which responders had significantly lower perfusion following treatment
- Table 5.1** Clinical measures for group as a whole
- Table 5.2** Localisation of significant clusters for deactivation where responders demonstrated greater reductions in rCBF than non-responders after treatment
- Table 5.3** Side-effects reported for by the entire study cohort
- Table 6.3** Percentage of subjects for each treatment group reporting adverse events

LIST OF FIGURES

- Figure 1.1** Representation of the Inositol cycle
- Figure 2.1** Resting rCBF in OCD higher than controls. Two clusters were identified in the left frontal cortex (a), and the orbito-frontal cortex (b)
- Figure 2.2** OCD participants displayed lower resting rCBF in left lingula (a), superior orbito-frontal cortex (b), the cerebellum (c), the left medial hippocampus (d), left anterior cingulate (e), right precuneus (f), and left superior parietal cortex (g)
- Figure 2.3** For the OCD group alone, total YBOCS scores were inversely correlated with rCBF in the mid-temporal region (a), and the left pre-central region (b)
- Figure 2.4** OCD demonstrated higher rCBF compared to controls, which correlated with OCD severity in the Left pre-frontal region
- Figure 3.1a,b** Reduced right mid cingulate (a) and left superior medial frontal (b) rCBF in participants with improved OC symptoms in response to sumatriptan challenge
- Figure 3.2** Right mid-occipital region in which participants who responded to sumatriptan challenge demonstrated higher rCBF relative to those who did not.
- Figure 3.3** Lower anxiety symptoms in response to sumatriptan challenge correlates with lower rCBF in the left fusiform (a) and the right precuneus region (b).
- Figure 3.4** Left lingual rCBF was increased in participants in whom anxiety symptoms improved compared to those who did not improve in response to the sumatriptan challenge.
- Figure 4.1** Regions of deactivation for the combined group of OCD, SAD and PTSD following treatment with citalopram. Significant grey matter clusters are seen in the left superior cingulate (a), right thalamus (b), anterior cingulate (c), left medial temporal region (hippocampus) (d)
- Figure 4.2** Pattern demonstrating where responders showed greater reductions in rCBF compared with non-responders in left precentral (a), right mid-frontal (b), right inferior frontal (c), left prefrontal (d), and right precuneus (e)
- Figure 5.1** Areas of greater reduction in rCBF in responders compared to non-responders.
- Figure 5.2** Baseline rCBF patterns showing significantly greater rCBF in the left anterior superior frontal gyrus for responders compared to non-responders
- Figure 6.1** YBOCS change for treatment groups

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PREAMBLE

It is “without doubt” that our post-modern world can assert it has made considerable advances in understanding and treating complex psychiatric disorders. Equally, it is “with doubt” that many questions in relation to underlying biology and treatments remain unanswered. Uncertainty and doubt arguably remain critical ingredients to continued evolution in thinking and understanding. However, in a minority of people, this uncertainty and doubt can pervade thinking, influence actions, and occasionally result in paralysing ineffectiveness.

Pervasive uncertainty and doubt were first described as “délire du doute” (obsessive doubt) and “folies du toucher” (contamination fears) by Falret in the late nineteenth century [1]. His and shortly thereafter others’ recognition of an imbalance of certainty and doubt began a journey that has led to the current understanding of the complex neuropsychiatric disorder we now refer to as obsessive-compulsive disorder (OCD).

The first half of the twentieth century witnessed a dramatic shift in thinking from pre-modernism with a spiritual understanding of illness, to a post-modern view that integrates biological, emotional and spiritual components into disease conceptualisation. The shift to post-modern approaches in scientific investigation of mental illness required a fundamental shift in thinking in relation to disease and also disability. Needless to say, this kind of transition brought with it considerable conceptual and methodological challenges embodied in comments by CP Emerson in his Wesley M. Carpenter Lecture (1929):

“This new field of medical research where hithertofore quacks and fanatics had blindly, though profitably, ranged, promises to be most important, but certainly would seem to be far more difficult than those through which we have worked.”

Undoubtedly buoyed by a transitioning thinking of his day, Emerson could not have known the resonance his prophetic words would continue to have early in the 21st century. Though not without considerable success since this statement was made, clinicians and neuroscientists a century later continue the struggle to uncover the fundamental changes that underlie disorders such as obsessive-compulsive disorder and by implication how best to treat it.

Epidemiological data suggesting OCD is highly prevalent transnationally has been accompanied by increasing awareness among clinicians of the considerable burden OCD places on many patients. This in turn is translating to increased recognition of OCD in primary care. Neurobiological research in OCD was fuelled by the discovery of the selective treatment benefit of the serotonergic agent, clomipramine. Together these advances mean that many patients now enjoy relief from symptoms and the burden of OCD.

Despite these advances, a significant proportion of OCD sufferers still continue to have an inadequate response to available treatments. This reflects our incomplete understanding of OCD psychobiology. Specifically, our understanding of the effects of treatment on brain function remains poorly understood. In addition, we know relatively little about the specific effects of modulation of specific neurotransmitter components on symptoms of OCD. Developing an understanding of the points of intersection of OCD neurobiology and the effects of a variety of treatments will potentially contribute to the development of more effective treatment for OCD.

This thesis explores the psychobiology of treatment in OCD using a variety of brain imaging and treatment studies. I have used these to demonstrate both distinct and overlapping effects of disparate treatments on brain function as well as specific symptoms in OCD. These studies demonstrate that technological advances in the assessment of brain function can be usefully applied to advance our understanding of the biology of OCD.

As a clinician I am privileged to have shared in part of the journey of the exploration of OCD with many like-minded clinicians around the world. I have come to appreciate the hope of relief from OCD through more effective treatment my patients have. I have also come to appreciate that a universally effective treatment for OCD is likely to remain elusive as this disorder impacts every person it afflicts in profoundly different biological and psychological ways. The latter suggests that subtle differences in neurobiology underlie variable phenomenology and treatment response in OCD. From work in this thesis and a number of other ongoing lines of investigation in this field, I am confident that better tolerated, more effective, and accessible treatment options for obsessive-compulsive disorder will be forthcoming.

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CHAPTER 1

Introduction and Background

1.1 General Introduction

Obsessive-compulsive disorder (OCD) is a disorder characterized by obsessions (recurrent or persistent unwanted thoughts, images or impulses) and compulsions (repetitive behaviours or mental acts performed to relieve tension or anxiety induced by obsessions) [1]. Thought at one time to be relatively rare, it is now recognized to affect 2-3% of the general population [2]. In the majority of cases OCD tends to run a chronic, fluctuating, unremitting and highly co-morbid course [3,4]. As such it is one of the most costly and disabling of psychiatric disorders [5]. Encouragingly, significant advances have been made in our understanding of the neurobiological underpinnings of OCD in recent decades. Equally significant advances in effective treatment strategies have also been seen. Despite this, however, considerable work is still required to address the precise intersection of treatment and neurobiology.

The selective efficacy of compounds that inhibit the re-uptake of serotonin has underpinned a serotonergic hypothesis in OCD for some time [6,7]. While it is worth noting that evidence for the effectiveness of these treatments does not specifically implicate the serotonin system in the pathophysiology of OCD, effects on this system would seem to be an essential ingredient to treatment response in most patients. Peripheral receptor binding studies, a possible marker of CNS serotonergic status, have failed to reliably implicate this system in OCD [7]. Somewhat more promising are indications that mutations within the serotonin transporter are involved in numerous neuropsychiatric disorders including OCD [8]. Genetic association studies have implicated the 5HT1B receptor [30] (see detail in section 1.2.2) in some but not all studies. Also, an association with female gender and the promoter region of the 5HT2a encoding gene has also been found, but not replicated [9-11]. 5HT2A receptor density has been shown to be increased in brain receptor binding studies, an effect that is attenuated with effective treatment response to SRIs [9]. While not directly implicating 5HT2A receptors in the pathophysiology of OCD, at the very least, these data lend support to their involvement in mediating treatment response.

Numerous studies have explored the neurochemistry of OCD, but as yet have not demonstrated a consistent pattern of difference from controls. Specifically, concentrations of cerebrospinal fluid serotonin metabolites have suggested that 5HIAA may predict treatment response, but these too have been inconsistent [12]. Animal models of OCD also strongly suggest that the serotonin system is involved in mediating symptoms and the response to treatment [13].

The administration of pharmacological compounds directed at the serotonergic system has also been explored [14]. This work has included agents with varying specificity for the serotonin system, often making clear dissection of the specific serotonergic effects difficult to delineate. Behavioural and neuroendocrine responses to serotonergic challenges using agents including MK212, m-CPP, sumatriptan, and zolmitriptan, have been demonstrated [44-54] (see section 1.2.2). These however have not shown consistent effects on OCD symptoms even when the same compound is used. While pharmacological challenge studies and genetic association studies certainly lend some indirect support to the serotonin hypothesis in OCD, their precise interactions remain poorly understood.

The most obvious explanation for the inability of the serotonergic hypothesis to fully delineate the neurobiology of OCD is that it is not the only viable hypothesis. From treatment studies we know that a substantial proportion of patients either fail treatment with an SRI or respond inadequately to these first-line interventions. Clinicians have known for some time that the addition of drugs that modulate the dopamine system through D2 receptor antagonism brings some clinical benefit to patients who have failed to respond to first-line SRI treatment [15]. Combining this knowledge with the hypothesized role of striatal and orbitofrontal brain regions in mediating repetitive behaviours [12], a dopaminergic hypothesis in OCD has become increasingly defensible [16].

Animal studies have suggested that potentiation of specific sub-populations of D1 receptors in the prefrontal cortex and amygdala results in compulsive behaviours akin to human OCD [17]. Similarly chronic pharmacological challenge of D2/3

receptors with the agonist quinoprole, results in compulsive behaviour in rats [18]. Post-mortem, these animals were found to have increased levels of dopamine rich tissue in limbic (accumbens) and prefrontal cortex [19]. These findings lead to development of the deficient response feedback mechanism theory in which reward seeking with repetitive behaviours is not sought despite the discontinuation of external feedback [20]. D1 receptor agonist administration in these animals, in turn reduces repetitive lever-pressing [13]. Together, as summarized by Denys et al [16], this work suggests a role for D1/2 receptors in mediating compulsive behaviours in animal models of OCD.

Neurochemical investigations of dopaminergic metabolites such as homovanillic acid (HVA) in CSF have for the most part yielded very limited evidence of differences compared to normal controls [16,21-23]. Recently a small patient series suggested reduced HVA levels correlated with treatment response, however, this did not hold for MHPG levels [24]. Marazziti et al [25] have previously investigated sulfotransferase activity as an indirect measure of catecholamine catabolism including dopamine. They found increased levels in OCD patients compared to controls, again suggesting higher levels of dopamine turnover in OCD. Taken together, however, only very limited neurochemical evidence supports the notion of dopaminergic changes in OCD.

A wide range of genetic association studies have now been reported in OCD, with some evidence to suggest an association with components of the dopamine system. Increased allele frequency of DRD4 in OCD [26,27] has been shown, but a range of negative studies have also been reported [9,28]. Interestingly, in a homogenous population of Afrikaners, an association with early onset OCD and DRD4 has been demonstrated [29]. Only negative studies have been reported for DRD3 [30,31] and DRD2 [30,32].

Arguably the most interesting findings in relation to the dopamine system in OCD genetics have been the reports of the association with catechol-O-methyltransferase (COMT). Associations with the presence of the low-activity COMT allele in

males [33] and females [34] have been separately reported. The former was replicated recently by Denys et al [35]. Other positive studies, however, have not replicated the gender findings [36], but found an association with homozygosity at the COMT locus [37]. Negative studies in smaller samples have been reported [38,39]. Despite these positive indications, a recent meta-analysis of COMT association studies was negative [40].

Numerous brain imaging studies using a variety of ligands for different aspects of the dopamine system have been investigated in OCD. PET studies using ^{18}F -6-Fluorodopa have found lower striatal uptake suggesting reduced numbers of dopaminergic neurons [41]. Increased binding of dopamine transporters (DAT) has been reported with ^{123}I IPT SPECT [42]. A similarly designed, but negative study has also been reported [43]. A similar, but different line of investigation has explored D2 receptor binding in OCD using ^{123}I IBZM SPECT. Denys et al [44] reported lower caudate binding of D2 receptors. Together DAT and D2 findings suggest an up regulation of dopamine neurotransmission [16]. Emerging evidence for the functional differences in DAT allele function may suggest that while functional polymorphisms may not be easily recognizable, differential functioning DAT alleles may mediate symptoms and treatment responsivity despite negative genetic association studies.

Together the serotonin and dopamine hypotheses in OCD, while not the only recognized neurotransmitter systems involved in OCD, remain the most compelling. Furthermore, it seems evident that an integrated view of the phenomenology, genetic underpinnings and treatment response in OCD in relation to each of these systems, is likely to remain the most widely applicable.

Despite the availability of numerous tools with which to investigate crucial questions related to the psychobiology of OCD, many remain unanswered. For instance, the precise pattern of resting brain function in OCD is not yet fully delineated. Equally, the resting brain perfusion response to pharmacological challenge of specific components of the serotonin system such as the serotonin 1B autoreceptor has enjoyed only very limited attention to date. At the time of planning this work, no published data

existed for the use of the dopamine antagonist quetiapine in treatment refractory OCD. Also, very little is known about the ability to predict treatment response to augmentation agents in OCD. At the intersection of treatment and neurobiology, very little is known about the effects of novel treatments on brain function. Also it is not known to what extent effective treatment for anxiety disorders including OCD has overlapping or distinct effects on brain function.

Single photon emission computed tomography (SPECT), is arguably the most widely available functional brain imaging modality in nuclear medicine departments across the world. SPECT perfusion imaging uses radio-active tracers with moderately long half lives that when combined with lipophilic compounds readily traverse the blood-brain barrier [45]. Thereafter the tracer is distributed and through incompletely understood cellular processes, becomes “trapped” in the brain. The image of the distribution of this “trapping” indirectly represents the magnitude of regional brain perfusion at the time of cellular interaction. In the studies reported here, I have used technetium-99m labeled hexamethylpropylene amine oxime (Tc-99m HMPAO) which is taken up by astrocytes. Thereafter the ligand undergoes a conformational change through a redox reaction to become hydrophilic. These molecules are now unable to traverse cellular membranes and are retained within the cellular cytoplasm [45]. SPECT perfusion studies using HMPAO to define differences between varied clinical populations are accepted to reflect differences (albeit an indirect measure) in underlying cellular metabolic function.

Imaging itself is performed using a gamma camera. It comprises a gantry designed to detect emitted photons with an energy window between 100 and 400keV. Spatial localisation is possible with the use of collimators that direct photons onto scintillation crystal detectors. Photocathode detection in photomultiplier tubes convert the light into an anode current which after a digital conversion is sampled together with full emission data using computer algorithms to derive a final image series [46].

Reconstruction techniques vary, but in the studies we undertook are simplified as they form a stack of 2D images. These are then combined to calculate a 3D map of

activity distribution across the brain. We used one of a variety of standard analytical reconstruction models, filtered backprojection [47], in which it is assumed that data can be modelled mathematically through a series of transformations. This method is both simple to use and efficient, but has some inherent limitations. These include a limited accounting for noise in acquisitions as well as the possible introduction of minor artefact. Despite this, the method remains widely applied in many settings.

Analytical reconstruction processes inevitably lead to some degree of image degradation. The effect on the energy of photons moving through tissue (attenuation) as well as the possible mispositioning of photons in the final image due to scattering effects both need to be controlled for. Attenuation correction methods used in our SPECT studies use whole brain uniform correction methods as described by Chang [48]. After these steps have been completed with an individual patient data set, images can then be reliably combined with similar acquisitions in a study group.

Being reliably able to combine data following reconstruction to determine tracer distribution requires a number of steps to improve the reliability of the observations. The specific methods used to some extent depend on the study question at hand. Semi-quantitative analysis methods such as voxel-wise statistical parametric mapping (SPM) have been possible for some time [49] and provide an option for reliable comparison of subject groups. These methods begin by spatially re-orientating and standardising images in 3D space. This important step ensures that similar voxels across a series of acquisitions reliably represent the same brain region. The coordinates of these brain regions can then be reliably located on standard brain atlases. In the studies presented here we used the Montreal Neurological Institute (MNI) standards.

In general, rigid transformations in three dimensions (affine) with rotations, translations and scaling are performed. Depending on the situation, non-linear transformations or warps can be applied to improve image registration. This step, however, can mask image effects, and will vary according to the study and the effect of interest. Finally, similarity tests or tests of normalisation need to be performed in order

to determine the degree of fit of images. This process uses data from all voxels to compute an image dependent normalisation factor. Each voxel count is then divided by this factor to standardise voxel intensity across the volume and render a voxel-wise semi-quantitative map.

Previously, volume of interest (VOI) or region of interest (ROI) analyses provided for relatively accurate “by volume” analysis of rCBF. These techniques are constrained in part by limited anatomical definition in SPECT imaging. Also, the reliance on predominantly operator dependent determination and placement of volumes may be considered a limitation. Brain regions not falling within the VOI are not examined. Newer voxel-based approaches obviate the need for VOI placement, but in turn introduce a range of challenges including that of multiple comparisons. Gaussian smoothing of images is thus required. The latter reduces anatomical differences between subjects, increases signal to noise ratio based on the normalised data derived as described above. The resulting group maps are amenable to statistical comparison on a voxel-wise basis. Specific tests will depend on the questions being addressed.

Modern SPECT images now have spatial resolution that is comparable to positron emission tomography (PET). The wide range of paradigms lend themselves to SPECT examination and in some cases “real-life” testing situations are more easily mimicked than with PET or indeed functional magnetic resonance imaging. It can however be constrained by its lower temporal resolution compared to PET. In this thesis however, I have confined investigations to resting paradigms. While I will argue that this is not without its challengers, this method is robust and easily replicable across imaging sessions and crucially also across different studies.

In the remainder of this chapter I will provide a brief background and rationale for each of the studies undertaken. I use this section on the one hand to introduce the reader to the specific questions addressed in each of the studies, and on the other to point out how each of these studies contributes to an integrated understanding of the psychobiology of OCD. It should come as no surprise that no single study can be

considered definitive in this area. Nevertheless, this body of work makes a meaningful contribution to our understanding of the impact of treatments in mediating or ameliorating symptoms of OCD through both direct and indirect effects on the serotonergic and dopaminergic systems.

1.2 Introduction to Part I

1.2.1 Regional brain perfusion in OCD compared to normal controls – a basis for establishing the impact of treatments on functional status

Resting brain perfusion studies have repeatedly demonstrated a capacity to distinguish OCD from normal controls. As such they have the potential to provide useful information on the brain function of patients with symptomatic OCD. One advantage of resting studies is that they are theoretically more easily comparable with similar studies and across disorders compared to activation studies. A series of resting perfusion studies have however, produced often inconsistent results that have served to highlight the complexity of OCD, in part related to a high degree of symptom heterogeneity.

Functional brain imaging tools continue to grow in sophistication with passing years. So too do the methods with which this data is analyzed. Current capacity to examine the entire brain without the constraints of limited computing power, has transformed this field. With VOI approaches the need to specify *a priori* all regions of interest may have limited the completeness of information derived from previous studies in this area. In OCD for example, modern approaches enable investigators to examine a range of brain regions that until recently were largely ignored. As such most literature to date has focused on brain regions believed to be the primary mediators of OCD symptoms. Even in these brain regions, recent meta-analyses have shown that the strength of evidence supporting their involvement is relatively limited [50]. As such resting brain perfusion in OCD represents one area of investigation where the full value of contribution using these methods may not have been fully exhausted.

The apparently robust construct of OCD delineated in DSM-IV belies the clinical heterogeneity that exists across clinical populations. Symptoms of OCD are held by some to exist on a spectrum of disorders [51]. Disorders putatively represented on this spectrum share aspects of symptomatology, responsivity to treatment, neurogenetic and neurochemical underpinnings [52]. Within this spectrum, significant overlap of symptoms occurs, that presumably reflects an overlapping

psychobiology. As such, in recent years we have witnessed an emergence of a literature that seeks to define homogenous clinical sub-groups in OCD and OC spectrum disorders [53] in the hope that this will lead to a clearer understanding of both the shared and distinct aspects of psychobiology underlying them. Numerous methods have been employed to define sub-groups with specific symptom dimensions in OCD. Factor analysis of symptoms derived from the YBOCS symptom checklist [54], and more recently the Dimensional YBOCS [55], have been associated with specific brain changes [56,57]. These in turn have been associated in some studies with predicting treatment outcome [58,59].

Work on OC spectrum of disorders has also implicated a wider range of brain regions than were initially described in the cortico-striatal-thalamic-cortical loop model of OCD. These include extra-striate regions [56] as well as the amygdala [60]. The role that studies of this kind are poised to play in delineating the underlying biology of specific symptoms cannot be underestimated. Particularly as these techniques now permit reliable dissection of specific sub-regions within the prefrontal and limbic cortices that are believed to mediate specific symptoms. In time, these lines of investigation will be useful when used in conjunction with studies that correlate specific receptor binding profiles and allelic variants with these functional brain changes.

Despite the heuristic appeal of a dimensional approach, some fundamental characteristics of OCD are likely to mean that this cannot be considered the only valid line of investigation of brain function in OCD. Importantly, the typically waxing and waning course of symptoms implies that within an individual, brain functional patterns may vary considerably over time [61]. By implication, biological investigations of symptom dimensions, whether brain functional (imaging, neuropsychological), genetic or neurochemical, are likely to reflect a symptom “state” rather than an underlying pattern of the enduring neurobiological effects of OCD as currently defined in DSM-IV.

This line of thinking has two primary implications for investigating functional brain imaging patterns in OCD. First, studies that explore resting brain function are likely to continue to be useful in examining the biology of OCD. It is already clear that a range of different brain regions may be implicated when compared to symptom

provocation studies. Second; evidence that more symptomatic disease is associated with higher brain activation may suggest that studies using symptom provocation or activation are likely to reflect brain changes of an order of magnitude greater than might be expected in the resting state. With this later point in mind, resting state studies should be designed to detect very much smaller changes overall. One explanation for the inconsistency across studies using this approach is that they are essentially underpowered. In fact there are indications that disorder severity does influence brain imaging findings at rest [62,63], However, this question has not been consistently explored across studies using similar methodologies.

As such, I question whether, in the face of inconsistency of results in previous resting brain perfusion studies, this approach still help inform our understanding of the underlying neurobiology of OCD? In what now constitutes a reasonably large body of literature, Whiteside et al recently conducted a meta-analysis which included data from 13 studies comparing OCD with controls at rest [50]. Significant challenges were noted by the authors in combining these data and may well have had a significant impact on study outcome. Despite the reasonable sample size in the combined analysis, only the findings within the area of the caudate head achieved levels of significance set by the authors. Furthermore, this finding was derived from only 3 of the 13 studies included in the analysis and as such should also be considered preliminary. While the authors acknowledge the existence of a range of data that support the involvement of the frontal-sub-cortical (striatal)-thalamic circuit in OCD, the findings of their meta-analysis suggest that data from rCBF studies do not, as has been strongly contended in the past [64,65], reinforce the involvement of these brain regions OCD. As such, I believe that with increasingly consistent analysis methods now being employed across studies, this line of investigation will benefit from the addition of studies that use whole brain methods to examine brain function in the resting state of patients with OCD.

In the context of this thesis then it is worth questioning to what extent a resting perfusion SPECT study can contribute to our understanding of the serotonergic and dopaminergic systems' contribution to OCD psychobiology? I have already mentioned that these monoamine systems are very widely distributed throughout the central nervous system (CNS). In studies that involve pharmacological challenge of these systems at rest, it seems is important to provide

a foundation for understanding the basis of changes resulting from modulation of either or both of these systems.

In this section (Chapter 2) I explore the resting brain perfusion patterns of participants with OCD using whole-brain voxel wise analysis and compare them to matched healthy controls. In addition, I examine the impact of disorder severity, a putative predictor of treatment response to serotonergic and dopaminergic treatments, on brain perfusion patterns.

What follows then, is a series of three studies in which the symptomatic resting state of patients with OCD is interrogated with (1) chemical challenge of the serotonin 1B (5HT_{1B}) autoreceptor (Chapter 3), (2) serotonergic treatment across anxiety disorders to examine the overlapping and distinct effects on brain function (see Chapter 4), and (3) direct activation of the putative final common pathway of effective treatments for anxiety disorders, namely the second messenger systems using inositol (Chapter 5).

1.2.2 Acute effects of the Serotonin 1B auto-receptor agonist Sumatriptan on Regional Brain Perfusion SPECT in OCD

We have noted that the selective response of OCD symptoms to first-line treatments with specific effects on the serotonin system is arguably the most consistent, albeit indirect, evidence for the involvement of the serotonin system in OCD [66]. Despite this, it is also clear that this advance in the treatment of OCD does not implicate specific components of the serotonin system. It does however implicate the serotonin system in mediating the symptom response to serotonergic treatment. Guided by increasingly sophisticated genetic, molecular and brain imaging tools, it has become possible to examine specific aspects of neurotransmitter systems in a variety of clinical conditions.

The identification of the 5HT1B receptor on chromosome 6 in humans in the early nineties [67-69], has led to considerable interest in these genes and their potential role in many disorders including OCD. The 5HT1B receptor was first identified in rats and pigs [69], and then the 5HT1D receptor in humans and rabbits [70] was reported. Subsequent receptor amino-acid sequencing has confirmed high degrees of similarity between rat and human receptors which lead to the classification of these receptors as the human (h) 5HT1B (formally 5HT1D β) and the rat (r) 5HT1B [71]. Despite this, there is still some evidence of variable pharmacological effects following interaction with these receptors [72]. More recently, evidence that the formally rat 5HT1B receptor has been detected in humans suggests that an accurate sub-classification of this receptor is still some way off [73]. 5HT1B receptors have now been mapped using autoradiography. These studies have found a predominance of 5HT1B receptors in the basal ganglia and the frontal cortex, however, receptors in varying concentrations are detected throughout the brain [74,75].

Three primary lines of evidence provide partial insights and an ongoing rationale to explore the role of the serotonin 1B receptor in the psychobiology of OCD. These include genetic association studies, pharmacological challenge studies and finally clinical treatment response to 5HT1B agonists. Gene association studies have found positive associations with the preferential transmission of the G-allele of the gene encoding for 5HT1D on chromosome 6q13 in some [76,77], but not all

[11,78] studies in OCD. The difference from the C-allele of the gene is conferred by a single base-pair difference, and is believed to have functional significance. In a single study presence of the G-allele was associated with higher YBOCS scores [78].

Drug challenge studies have for some time provided the ideal setting in which to explore the functional role specific receptor-drug (ligand) interactions have in mediating symptoms of a particular disorder. In OCD, this approach has been used for some time to explore the role of the serotonin system. Initially the use of less specific compounds such as m-Chlorophenylpiperazine (m-CPP), a compound with non-specific agonist action on 5HT_{2c}, 5HT_{1b}, and 5HT_{2a} receptors lead to mixed results [79]. For instance, acute administration results in OC symptom exacerbation in some [80-83], but not all studies [84,85]. The more specific 5HT_{1a} and b receptor agonist, MK-212, appeared to have little impact on OCD symptoms when administered acutely [86]. The results of these studies, suggest that while some impact on symptoms may be mediated through acute manipulation of serotonin receptors, the specific receptors involved could not be accurately deduced.

The introduction of the 5HT_{1B} auto-receptor agonist sumatriptan, and subsequently the wider family of triptans [87] for the treatment of migraine, has afforded investigators the opportunity to explore the role of this receptor in OCD symptomatology. Initially studies used acute administration of sumatriptan to patients with OCD to explore immediate changes in OC symptomatology. This line of investigation produced mixed clinical results with a transient exacerbation of symptoms [81,88,89] before a moderate reduction with more chronic treatment [88,89] was reported. The relatively low bio-availability and low lipophilicity lead some to speculate that a central action for sumatriptan seems unlikely. Subsequent studies with newer triptans including zolmitriptan, a compound which more readily crosses the blood-brain barrier, also found no significant difference in measures of behavioural change in OC and anxiety symptoms [90]. I will discuss a number of lines of evidence that now support a central action for the triptans including sumatriptan. Together they suggest that alternative explanations should be sought to clarify the reasons for the mixed response to acute challenge with 5HT_{1B} agonists. In a recent review of this work, Zohar et al [66] encourage the use of functional brain imaging tools, and in time to combine this with genotyping data to elucidate the specific functional response of the 5HT_{1B} receptor in OCD.

Taken together, clinical, genetic, and functional brain imaging data can be usefully combined to provide a rationale for exploring the impact of acute pharmacological challenge with a specific 5HT_{1B} receptor agonist on functional brain perfusion patterns in OCD. We have previously reported on a preliminary study with 14 subjects to whom a single dose of sumatriptan was administered in a double-blind, placebo-controlled, cross-over design [91]. We found heterogeneous OC symptom responses to sumatriptan challenge, with nearly a third of patients experiencing a worsening of OC symptoms. In the analysis of the SPECT perfusion data, we used manually placed regions of interest in areas putatively involved in the functional neurocircuitry of OCD. We found increased thalamic perfusion in sumatriptan relative to placebo challenge using cross-over design. Worsening of OC symptoms was associated with decreased perfusion in inferior and medial frontal brain regions while symptom exacerbation correlated with reduced inferior frontal and putaminal perfusion. We did not detect any significant differences in this study between responders and non-responders to acute sumatriptan challenge.

In this section, I build on the strengthening hypothesis for the involvement of the 5HT_{1B} receptor in OCD and extend the study mentioned above to examine the effects of sumatriptan challenge and OC symptom responses using a whole-brain voxel wise approach to image analysis. This approach will potentially yield information on brain changes outside of the putative functional OCD circuit.

1.2.3 Functional brain changes in response to citalopram serotonergic treatment across anxiety disorders: Similarities and distinctions

The introduction of the selective serotonin re-uptake inhibitors into routine practice and their subsequent adoption as first line agents in all of the major anxiety disorders in addition to OCD [92], including posttraumatic stress disorder (PTSD) [93] and social anxiety disorder (SAD) [94], still represents one of the major advances in the treatment of this highly prevalent and costly group of disorders. Numerous lines of investigation suggest distinct genetic, neurochemical and brain functional patterns exist for all the major anxiety disorders. Despite this, the response of these apparently different anxiety disorders to the same treatment raises a number of questions regarding the overlapping and distinct effects of these drugs on the underlying brain dysfunction across the anxiety disorders.

In obsessive-compulsive disorder, the superior response to serotonergic compounds such as clomipramine is now well known. Available evidence would suggest that the same cannot be said for some of the other anxiety disorders including social anxiety disorder (SAD) and post-traumatic stress disorder (PTSD) where a consistent advantage of SRIs over drugs that also incorporate noradrenergic re-uptake and monoamine oxidase inhibiting effects has not been clearly shown. In SAD strong effects also exist for the monoamine oxidase inhibitors [94], a fact that has not been convincingly shown in OCD [95,96]. Overall, the superior tolerability of SRIs along with its similar efficacy to other drug classes continues to support their use as first-line agents in these disorders.

In OCD, attenuation of pre-treatment regional activation has been shown to correlate with treatment response in the anterolateral orbitofrontal cortex (OFC), caudate nucleus, thalamus, and temporal regions [97-102]. Results for studies assessing pre-treatment cerebral perfusion as a predictor of response, have, however, yielded mixed results. In some, an inverse relationship appears to exist with pre-treatment regional activation of the OFC [103], anterior cingulate, caudate [6] and subsequent responses to treatment. Conversely findings of higher prefrontal, cingulate and basal ganglia activation correlating with subsequent treatment response have also been reported [104,105]. In OCD co-morbid with depression, substrates of response to the SSRI, paroxetine, appear to differ based on

pretreatment [106] activation patterns. Also, differences in rCBF are seen in response to SSRI treatment in both depression and OCD when each condition exists on its own [107].

In SAD, prefrontal and insula activation in response to public speaking as well as with anticipation anxiety related to public speaking [108,109] have been demonstrated. In response to treatment, attenuation of frontal, anterior and lateral temporal cortex, cingulate, and thalamic activity has been demonstrated by our own and other groups [110,111]. There are also additional indications that higher anterior and lateral temporal cortical perfusion at baseline correlated with subsequent treatment response in the former study. Unpublished data from our group also demonstrates evidence of functional connectivity of brain regions impacted by SRI treatment (Warwick et al, unpublished). In an interesting paper in SAD, the SSRI citalopram and cognitive behavioural therapy resulted in overlapping changes in regional brain metabolism. This finding suggests that different (pharmacological and non-pharmacological) interventions result in similar regional attenuation of activity despite employing apparently different underlying mechanisms of action [111].

In PTSD, a single study by our group has demonstrated attenuated medial temporal lobe perfusion in response to treatments irrespective of observed clinical response. Further, attenuation of medial prefrontal cortex activation did correlate with treatment response [112]. Also, in a case series of female rape survivors with PTSD, I have recently found that similar medial and superior prefrontal attenuation in perfusion was associated with improvement in PTSD symptoms following 12 weeks of exposure therapy (Carey et al, unpublished data). Taken together, it is hypothesized that symptomatic pretreatment prefrontal and medial prefrontal increased perfusion, is attenuated as the effective treatment aids in restoring “top-down” control of temporo-limbic hyperperfusion when compared to controls.

Modern brain imaging techniques have been sparingly employed in exploring the possible overlap in the functional neurocircuitry that underlies individual anxiety disorders [113,114]. These studies do suggest that while there is overlap among anxiety disorders, particularly in respect of fear-processing, there are distinct effects on regional brain perfusion related to each. The evidence suggests that there are similar overlapping and distinct brain regions impacted by effective treatments.

Indeed, higher resolution of modern imaging techniques used to examine brain function such as f-MRI, now allow us to recognise different effects within relatively small sub-regions of the brain including the amygdala, accumbens and cingulate cortex. In these brain regions it is becoming increasingly clear that distinct neuropsychological function and emotional processing is mediated by specific sub-regions.

In this section I report on a study undertaken to examine the response to SSRI treatment in a combined group of subjects with OCD, PTSD, and SAD. On the basis of previous findings, I hypothesized that changes in rCBF affecting primarily limbic and related prefrontal regions would be shared by all of the disorders. I also hypothesized that pretreatment regional brain perfusion would differentiate responders to subsequent treatment with citalopram across the anxiety disorders.

1.2.4 Functional brain perfusion SPECT in OCD: Changes in Response to treatment with Inositol

The crucial contribution of the SRIs to the treatment armamentarium of modern psychopharmacologist is in no doubt. In general it is held that increased transmission of serotonin through desensitization of 5HT₂ and 5HT_{1B} auto-receptors in prefrontal and limbic brain regions is responsible for the therapeutic effects of SRIs [115]. It was shown some time ago that SSRIs enhance 5HT release in the orbitofrontal cortex of guinea pigs after 8 weeks of treatment, an effect not seen at week three of treatment [116]. The time delay required for this desensitization is consistent with the longer lag in therapeutic response in OCD compared to depression [117].

The primary action of the SRIs on the pre-synaptic re-uptake pump inhibits the clearance of serotonin from the synaptic cleft, an effect that in time leads to the desensitization of post-synaptic receptors [118]. Interestingly, in the same sample of guinea pigs, altered serotonergic transmission was not noted in the caudate nucleus [116]. It therefore seems that receptor desensitization in response to treatment may occur either through direct effects in the region of interest, or in a remote brain region that is linked through functionally connected neuronal circuitry [119]. It is also

noteworthy that the effectiveness of SSRIs in OCD is only produced at higher doses than are conventionally required for depression. In the prefrontal cortex, it has been shown that similar doses of different SSRIs produce significantly different levels of reuptake pump inhibition [116]. Blier et al [119] have shown that higher doses are necessary in most cases to produce a treatment effect. As such, not only do regional differences in serotonin autoreceptor desensitization exist, but different affinity of various SSRIs for re-uptake pumps. This implies a quite distinct mechanism of action of these agents in depression and OCD [120]

The serotonin (5HT₂) and dopamine systems (D₁, D₂) are involved in mediating action in the the GABA-ergic system in the regulation of motor behaviour through the cortico-striatal-thalamo-cortical circuit [121]. Within this circuit, 5HT₂ receptor stimulation results in attenuated DA release with downstream consequences on motor function mediated by the GABA system [122]. Work from our group has previously found that administration of inositol, a precursor in the phosphatidylinositol (PI) second messenger system, resulted in reduced D₂ receptor density with a much smaller effect on 5HT₂ receptors [123]. These findings suggested that the effect of inositol is less likely to be mediated by serotonergic than dopamine action.

Despite this, there is widespread support for involvement of second messenger system activation in the action of effective antidepressants. Action follows specific drug-receptor interactions on the neuronal membrane. Conformational changes of transmembrane G-proteins then activate a variety of second messenger systems including inositol triphosphate (IP₃), calcium, diacylglycerol (DAG) and protein kinase C (PKC). The subsequent effects of these intracellular signaling pathways on gene transcription and translation in turn impacts protein receptor expression.

The PI cycle acts as the second messenger system to a variety of neurotransmitter systems including monoamines [124]. More specifically, myo-inositol (MI) serves as a precursor to receptor-activated phosphatidyl inositolbisphosphate (PIP₂) hydrolysis by phospholipase-C (PLC) [124]. This interaction produces inositol triphosphate (IP₃) and diacylglycerol (DAG) (Fig 1.1). In addition to the direct effect on these systems, phosphoinositides (PI) are seemingly involved in regulating the interaction of signalling proteins [125], neurotransmitters and membrane receptors [124]. The specific contribution of each of these effects of

inositol to the mechanism of action in exerting behavioural effects, however, remains unknown.

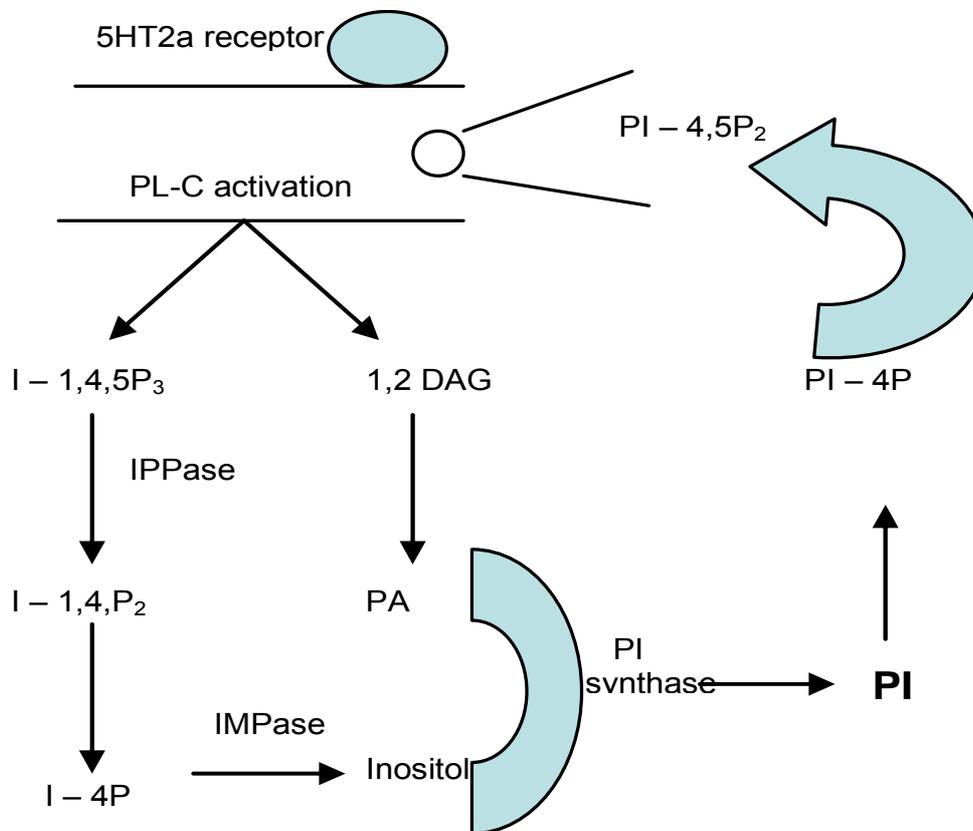


Fig 1.1. Representation of the inositol cycle. The figure depicts metabotropic receptor (e.g., 5HT₂) activation of PLC, the subsequent hydrolysis of membrane PIP₂ leading to the formation of IP₃ and DAG, and the cycle concluding with the replenishment of PIP₂ via the linkage between MI and DAG degradative pathways through the action of PI synthase. Abbreviations: PLC: phospholipase C; PI-4,5P₂: phosphatidylinositol bisphosphate (PIP₂); I-1,4,5P₃: inositol trisphosphate (IP₃); I-1,4P₂: inositol bisphosphate (IP₂); I-4P: inositol monophosphate (IP); IMPase, inositol-1-monophosphatase; IPPase: inositol polyphosphate 1-phosphatase; 1,2-DAG: 1,2 diacylglycerol (DAG); phosphatidylinositol (PI); PI-4P: phosphatidylinositol 4-phosphate (PIP).

Revised from Harvey BH et al, 2002

The behavioural effects of inositol have been known for some time [126]. Controlled evidence of its effective use in treating obsessive-compulsive disorder (OCD) [127], panic disorder [128,129] and depression [130] has been shown. Inositol was, however, found to be ineffective as an augmentation strategy to SSRI non-responsive OCD [131]. In addition, disorders such as premenstrual dysphoric disorder [132], schizophrenia [133], autism [134], Alzheimer's disease [135] and attention deficit hyperactivity disorder (ADHD) [136] have not responded to inositol.

These data may suggest that the clinical efficacy of inositol is limited largely to disorders that respond preferentially to drugs that modulate the serotonergic system [126]. This is interesting in the light of the animal data from Harvey et al cited above. As such, it remains unclear what the reasons for the preferential effect of SRI responsive disorders is. Evidence from genetic studies has emerged in which genes encoding for inositol-mono-phosphatase have been identified on chromosome 8q21.13-21.3 (IMPA1) as well as 18p11.2 (IMPA2). The latter is located close to or on the same site as a susceptibility locus for bipolar disorder [137]. While no specific genetic evidence implicates this gene in OCD, there is evidence of altered activity in the PLC pathway in OCD [138].

Functional brain imaging data has demonstrated an attenuation of activity in regions within the cortico-striatal-thalamo-cortical (CSTC) following a response to treatment with SRIs [65,104,139,140]. Given the limitations of some of this data, and the capacity to examine the whole brain using voxel-wise analysis methods, investigating the effects of inositol on regional brain perfusion before and after a course of therapy with orally administered inositol is warranted. Given the suggestion that there may be an overlapping mechanism of action between inositol and downstream effects of the SSRIs, we hypothesized that clinical efficacy of inositol would translate to similar attenuation of perfusion that has been demonstrated with SSRI's.

In this section I report on a study in which we used SPECT (as a measure of cerebral perfusion and examined the effects of inositol treatment on regional cerebral perfusion before and after 12 weeks of open-label treatment in subjects with OCD.

1.3 Introduction to Part II

1.3.1 Treatment effects of combined dopamine and serotonin receptor blockade in OCD

Recognition that the tricyclic antidepressant clomipramine has predominantly serotonergic modulating properties, and demonstrates preferential benefit for patients with OCD, constituted a major advance in the pharmacological treatment of OCD [96]. Prior to this, OCD had been considered to be relatively difficult to treat

contributing to the conceptualisation that it typically runs a chronic and fluctuating and predominantly unremitting course [141,142]. Subsequently, the introduction of the selective serotonin re-uptake inhibitors rapidly established this class as the first-line treatment in OCD [15,143-145].

Despite the considerable benefit brought by the widespread use of SRIs, this class of agents has unfortunately not brought the desired degree of relief from symptoms that was originally envisaged or hoped for. While the majority of patients will experience some relief of symptoms of OCD [141], currently some 40-80% still fail to respond adequately to an initial trial of therapy with an SRI [141,142,146,147]. Still fewer will experience complete remission from their symptoms [148]. Recent systematic reviews suggest that there is some support for switching to an alternative SRI [96], however some 30% of patients will still fail to respond adequately to this strategy [149]. In addition, alternative augmentation strategies that may enhance the serotonin system have in the main been disappointing [150]. These include lithium, and buspirone [151,152].

Brain imaging, genetic and clinical evidence now provides relatively robust support for the involvement of the dopamine system in the pathophysiology of OCD [16]. In line with this, augmentation of SRI treatment with dopamine receptor antagonists has enjoyed considerable attention in recent years. A wide variety of open-label studies have suggested that augmenting SRI's with atypical antipsychotics is likely to be a promising strategy for treatment-refractory OCD. These include support for risperidone [153-155], olanzapine [156-161], and more recently amisulpride [162] and quetiapine [163-166]. A single open-label study using quetiapine as augmentation showed lack of effect in a small sample using low doses [167].

The outcome of the first controlled studies in this area with the antipsychotic haloperidol demonstrated preferential benefit for refractory OCD subjects with comorbid tic disorder [168]. Haloperidol is a potent and reasonably selective antagonist of the dopamine 2 receptor with negligible binding of the post-synaptic serotonin 2A receptor. Most subsequent studies of augmentation with antipsychotics have used a variety of second generation antipsychotics, which have amongst others a dual action at D2 and 5HT2a receptors. In two of these, efficacy of risperidone in SRI

refractory OCD has been reported [169,170]. Interestingly the former study [169], did not replicate the particular advantage for subjects with co-morbid tic disorder. At the time this study was conceptualised, no controlled published data for quetiapine existed. Subsequently, efficacy has been shown for quetiapine [171] and olanzapine [172] using similar designs, but the effect on co-morbid tic disorders was not reported. In contrast a recent controlled study using olanzapine failed to demonstrate efficacy over placebo in a six week study [173]. Despite there being mixed evidence in this area, in general the available literature appears to support the use of relatively short trials of low doses of antipsychotic agents as augmentation to SRIs in refractory OCD.

Quetiapine, is a second generation antipsychotic with moderately low affinity and highly transient binding to dopamine 2 receptors in addition to moderate 5HT_{2a} and 5HT_{1D/B} receptor binding. Combined with the open label evidence supporting its use and subsequent to the initiation of this work, the reported efficacy of this strategy in a controlled trial suggests this is a reasonable and hypothetically appealing treatment alternative that deserves further exploration in augmentation of SRIs in refractory OCD. Demonstration of its efficacy would contribute to a growing body of literature supporting a role for the serotonin and dopamine systems in OCD.

In this study I report on the effects of flexible dose quetiapine augmentation of SSRIs in subjects with OCD who had failed to respond adequately to a minimum 12 week trial of an SRI using a double-blind placebo controlled study design.

1.3.2 Clinical and demographic determinants of response to treatment with combined dopamine and serotonin receptor blockade in OCD

While OCD is a replicable and robust construct with obsessions and compulsions being present in most patients, there is considerable clinical heterogeneity in most study populations. This heterogeneity is reflected in the variability in response to treatment with evidence-based interventions. Also, genetic, functional brain imaging, and neurochemistry studies in OCD have produced characteristically heterogeneous findings in many disorders including OCD. For some time this heterogeneity in clinical features and consequent variability in biological

investigations has posed a significant challenge to advances in our understanding of the underlying neurobiology of OCD.

Using clinical tools such as the Yale-Brown Obsessive-Compulsive Scale (YBOCS) Symptom checklist [54,174] to delineate the considerable phenomenological heterogeneity in OCD has led to investigations that explore the variety of symptom dimensions and their possible biological correlates [50,52,175]. Useful as these have been, this line of investigation is not without its limitations as I argue in the section on resting brain perfusion in OCD (Chapter 4). As such, much work remains to gain a full understanding the role symptom dimensions might have in increasing the predictive power of response to treatments.

Numerous studies have attempted to reconcile the presence of particular symptoms with prediction of response to predominantly serotonergic treatment such as the SRIs in OCD. To date, findings from this line of investigation remain incomplete [176,177]. It has, however been shown that behavioural dimensions may have different neuronal substrates [57] with different genetic variants [178,179]. Further evidence suggests symptom dimensions may be associated with differential outcome to treatment [58,180].

A superior response to treatment has been associated with washing symptoms and exposure therapy [181,182], compared to poorer response to SRIs [183,184]. Other clinical dimensional predictors of better response to SRIs have included checking compulsions [185], and overall greater severity of obsessions [186]. Poorer response to treatment has been associated with hoarding [187,188], symmetry and hoarding, contamination and cleaning [189], cleaning [190,191], somatic obsessions [192], and sexual/religious obsessions [190]. As such it is clear that specific symptoms impact significantly on the natural course and outcomes in OCD.

In addition, a range of other descriptive variables in the context of SRI treatment have been associated with better SRI response rates. These include fewer previous courses of SRIs [186], female gender [185,193], later life onset [194], co-morbid depression [195,196] and, higher YBOCS sub-scores [197,198]. Taken

together, this literature remains variable, and in some cases conflicting. This is likely due to a range of issues including heterogeneity of samples and methods.

In one of the few studies to develop a model for predicting treatment outcome, Denys et al [199] used key findings from the literature cited above to guide the choice of variables they entered into a multivariate regression in a double-blind placebo-controlled study of venlafaxine and paroxetine [200]. They found that YBOCS scores <23, HAM-D depression ratings >6, and fewer than two previous treatments for OCD together predicted treatment response with an ROC-area of 0.71, a model with reasonable discriminative capacity despite its simplicity.

Data from the controlled studies of antipsychotic augmentation of OCD including data from the work presented in Chapter 6 of this thesis have recently been combined in several separate meta-analyses. Considering the three most recent of these, Bloch et al [150], systematically reviewed data from all available controlled studies using a variety of antipsychotics and found an overall positive effect for this treatment alternative. Interestingly, this meta-analysis confirmed earlier indications of a preferential benefit for patients with co-morbid tic disorders first described by McDougle [168]. In a Cochrane analysis by Ipser et al [201] we looked at the effects of antipsychotic augmentation across anxiety disorders. Not unexpectedly, we confirmed a positive effect for this strategy. In addition, we found that the largest part of this effect was produced by the body of evidence in OCD. Thirdly, in a meta-analysis by Fineberg et al, we combined data from three placebo-controlled studies [171,202,203], including my own, in which quetiapine was used to augment SRI therapy in OCD. Using less conservative criteria ($\geq 25\%$ reduction in YBOCS score) for treatment response than the Bloch analysis ($\geq 35\%$ reduction in YBOCS score), we found a significant treatment effect in favour of quetiapine [204]. In a separate analysis of the same dataset, we found somewhat surprisingly that lower doses of SRIs were associated with superior clinical response to subsequent augmentation with quetiapine [205].

Data like these are responsive to the need for evidence-based alternatives in OCD pharmacotherapy, but as yet there is little indication as to which refractory patients are likely to derive the most benefit from these interventions. In the present study we pool data for a total of 80 subjects from two studies, including our own

described in Chapter 6 of this thesis that used compatible methods. We then used available clinical and demographic variables to derive a model that together provides the highest predictive power for treatment outcome for augmentation of SRIs with atypical antipsychotics in refractory OCD.

1.4 Hypotheses

In conclusion, a summary of the core hypotheses for each of the studies to follow is given.

The overall aim of this thesis is to use available clinical, brain imaging and treatment tools to contribute to our understanding of the psychobiology of OCD its treatment and intersection with treatment response.

Central Hypotheses:

- Resting brain perfusion differences exist in OCD compared to normal controls and that the difference correlates with symptom severity. I also hypothesise that whole-brain voxel-wise analysis will demonstrate differences in brain regions located outside the cortico–striatal-thalamo-cortical circuitry (Chapter 2)
- Brain perfusion changes in response to a single dose challenge with a specific 5HT_{1B} receptor agonist, sumatriptan, in OCD will be present, and (1) will attenuate OC symptoms while (2) implicating cortico-striatal brain regions in this response (Chapter 3).
- Brain perfusion changes before and after treatment with a single SSRI will primarily involve limbic and related prefrontal brain regions across anxiety disorders (OCD, PTSD, and SAD). I also hypothesize that pretreatment regional brain perfusion will differentiate responders to subsequent treatment with citalopram across the anxiety disorders. (Chapter 4)
- Brain perfusion changes in prefrontal and striatal regions following treatment with inositol in OCD will overlap with those of the SRIs. This might suggest an overlap in the mechanism of action and imply a single common pathway in the downstream effects of these two treatments (Chapter 5)

- The efficacy of controlled augmentation of SRIs in treatment refractory OCD with quetiapine will demonstrate a benefit over placebo after 6 weeks of treatment (Chapter 6).
- That clinical and demographic factors can be used to predict treatment response following augmentation of SRIs with quetiapine (Chapter 7).

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PART I

CHAPTER 2

**Regional Brain perfusion in OCD compared
to normal controls – a basis for
establishing the impact of treatments on
functional status**

2.1 Abstract

Background

Considerable evidence suggests that obsessive-compulsive disorder (OCD) is mediated by frontal-subcortical circuits. Nevertheless, recent meta-analysis of data from functional brain imaging studies at rest suggests considerable inconsistency across studies. Also, exploration of the relationship between resting perfusion and symptom severity is limited. We therefore examined between group differences between OCD and normal controls, and the impact of illness severity on resting cerebral blood flow (rCBF) in OCD.

Methods

Participants recruited from our anxiety disorders clinic (OCD n=18) and the community (normal controls n=19) were free of psychotropics and matched for age and gender. Resting Tc-99m HMPAO single photon emission computed tomography (SPECT) was completed in all subjects, and Yale-Brown Obsessive-Compulsive Scale (YBOCS) severity scores were used for correlation analysis with resting brain perfusion in a voxel-wise whole brain statistical parametric (SPM) analysis.

Results

Compared with healthy controls, OCD subjects had significantly increased resting perfusion in left frontal (pre-central) and right mid orbito-frontal cortices. In the left frontal cluster, perfusion correlated with YBOCS severity ($p < 0.001$). Conversely, significantly ($p < 0.001$) lower perfusion in OCD compared to controls was evident in the lingual gyrus, superior orbito-frontal cortex, cerebellum, hippocampus, anterior cingulate, precuneus, and superior parietal cortex. All these clusters, except the lingual gyrus and the anterior cingulate clusters, correlated negatively with YBOCS scores.

Conclusions

Our study demonstrates that: (1) there are significant differences in resting brain perfusion between participants with OCD compared to healthy controls, and (2) that differences correlate both positively and negatively with disease severity across a range of brain regions which are inconsistently implicated in mediating OCD. Further studies using resting perfusion SPECT and PET using consistent image acquisition and analysis methods are likely to provide valuable information on the neurobiology of OCD that is distinct from the information gained by dimensional approaches which target symptoms that are changeable over the course of the illness.

2.2 Background

Obsessive-compulsive disorder (OCD) is a chronic and disabling psychiatric disorder characterized by obsessions and compulsions [1]. Despite this apparently simple definition of OCD, there is a considerable degree of clinical heterogeneity in relation to its phenomenology, severity, and course [2]. Inconsistent and non-replicable findings in brain imaging and genetic studies of OCD, may be accounted for in part by this underlying clinical heterogeneity [3]. The recent emergence of studies that delineate distinct biological substrates of specific symptoms dimensions in OCD may give us some indication as to the reasons for the frequently divergent findings [4]. However, a number of other possible explanations including differences in imaging technology used, and patient related factors probably act in concert to render the available data as variable as it is.

In the particular context of functional brain imaging, many have argued that the available literature supports the involvement of frontal-sub-cortical (striatal)-thalamic circuit in mediating OCD symptoms [5,6]. In a recent meta-analysis of the functional brain imaging data in single photon emission computed tomography (SPECT) and positron emission tomography (PET) in OCD, however, the authors question whether available data in fact supports a number of the conclusions that have previously been assumed to have been well substantiated [3].

In particular, meta-analytic findings suggest that a wide range of brain regions are probably involved in mediating OCD, and concur that there is a lack of consistency across studies, making conclusions difficult to draw at this time. A wide range of brain regions are to greater or lesser degrees specifically involved in OCD, including frontal (orbital, anterior, superior; and cingulate), striatal; and thalamic areas. However, in the analysis of the 13 studies included in the meta-analysis mentioned above, only a single finding in the head of caudate region (drawn from only 3/13 studies) reached the specified level of significance in studies of resting perfusion. In line with the conclusions of this meta-analysis, this extensive and important literature has not delivered the levels of insight that may previously have

been hoped for. Consequently, the question arises as to when and if this data can be expected to be meaningfully combined to advance our understanding of OCD.

Combining studies in meta-analyses that use different imaging platforms, subtly different patient cohorts and varied methods of analysis makes comparisons challenging. Dividing the literature into smaller groups of studies has the effect of reducing the power to detect and explain perfusion abnormalities present in OCD at rest. Many investigators have reasoned that symptom activation paradigms are likely to yield more robust and specific findings in a particular disorder. However, given that activation of a single symptom/dimension occurs in the context of significant symptom heterogeneity across any given sample, the specificity of the resulting imaging findings may also be sub-optimal.

As mentioned above, attempts to minimize clinical variance within samples have emerged in recent years in both clinical (phenomenological) and functional brain imaging studies with symptoms being classified on a dimensional and not a purely categorical basis [4,7-9]. While intuitively appealing, the value of this approach in OCD is only partly helpful for two primary reasons. First, many of these dimensions are also present to some degree in healthy volunteers though clearly to a less severe degree [4]. As such the findings may be fallaciously assumed to occur on a continuum of symptom severity between those with behavioral traits and those severely impacted by the presence of the symptom in question. Second, while dimensional investigations do demonstrate clear brain functional changes related to the presence of a particular symptom dimension, there is evidence for limited temporal stability and indeed interchangeability of symptoms over the course of the disorder. As such, findings cannot be assumed to represent a core neurobiological “substrate” for OCD, but merely a specific functional state within the broader definition of OCD. Resting brain perfusion studies thus seem likely to reflect a *different* measure of brain function in OCD that is broadly symptomatic and temporally relatively more stable than the “provoked” state of OCD. Thus relatively small changes anticipated in resting brain perfusion in OCD compared to normal controls, would translate to a need for relatively larger samples before firm conclusions can be drawn from the findings. As such, it seems important that resting and activation studies using both a dimensional and categorical approaches to define

participant cohorts should remain parallel yet complementary lines of investigation in the functional imaging of OCD.

The present study presents a moderately large cohort of subjects with OCD in whom we compare resting brain perfusion using SPECT with those of normal controls and correlate differences with disorder severity using whole brain voxel-based analysis.

2.3 Methods

Study population

Study participants were recruited from our teaching hospital anxiety disorders clinic. Eligible participants were required to have a primary diagnosis of Obsessive-compulsive disorder (OCD) (n=18, 13 males, 5 females), and be between the ages of 18-65 years. A group of age and gender matched participants (n=19, 14 males, 5 females) without current DSM-IV Axis I disorders were recruited to act as normal controls. Data for educational status is not available, however, on clinical examination no participants in either group demonstrated a history of showed current signs of cognitive impairment. Controls were originally recruited for a separate SPECT perfusion study in our group. Recruitment for this study occurred at a similar time to the OCD participants in this study, and criteria to define normals were similar across studies. Structured diagnostic psychiatric interviews to determine current psychiatric status were conducted by a board certified psychiatrist using the Structured Clinical Interview for the Diagnosis of Axis-I Disorders (SCID-I [10] on all prospective participants (OCD and normal control). Any other current primary Axis-I disorder, current use of psychotropic medicine, medical illness deemed to be significant according to the clinical judgment of the investigating clinician, previous head injury with loss of consciousness exceeding 10 minutes, history of seizure disorder, refusal to consent to procedure or any other condition that might have rendered a participant unable to undergo or complete a SPECT study, were grounds for exclusion from participation. Previous use of psychotropics was not an exclusion, but all participants had psychotropics washed out for a minimum of two weeks before the study. Patients on fluoxetine were the only exception where this time was extended to four weeks.

Approval for the study was obtained from the relevant Institutional Review Board of the University of Stellenbosch. All participants were provided with a patient information and consent form prior to inclusion in the study. Inclusion followed detailed explanation from the investigating clinician and signed informed consent from the participant. The study was conducted in line with international guidelines guiding ethical conduct in research on human participants.

Clinical measures

The Yale Brown Obsessive-Compulsive Scale (YBOCS) [11,12] was administered to all participants with OCD on the day of SPECT imaging to determine illness severity.

SPECT Imaging

Single photon emission computed tomography (SPECT) was performed in the resting state for all participants in the study. Participants were required to lie supine in a quiet dimly lit room for 30 minutes prior to injection of the radiopharmaceutical. Apart from administration of the injection by a physician, they remained alone in the room during this period. Subjects were asked to remain at rest for 10 minutes after the injection of the radiopharmaceutical to allow uptake of the radiopharmaceutical in the brain.

An injection of 555 MBq (15 mCi) of technetium-99m hexamethylpropylene amine oxime (Tc-99m HMPAO) was given into an arm vein through an intravenous cannula positioned in an ante-cubital fossa prior to the initiation of the rest period. After completion of the minimum 10 minute rest period following the radiopharmaceutical injection, SPECT imaging of the brain was performed. We supported the subject's head with a standard headrest lined with sponge to maximize comfort. SPECT imaging was performed using a dual detector gamma camera (Elscint Helix, GE Medical Systems, USA) equipped with fan beam collimators.

Data were acquired in the step-and-shoot mode using a 360° circular orbit, with the detectors of the gamma camera positioned as close as possible to the

subject's head. Data were acquired using a 128 x 128 image matrix in 3 degree steps of 15 seconds per step.

Data were reconstructed by filtered back-projection, using a Metz filter (power=5, FWHM=14mm). The Chang method ($\mu = 0.11/\text{cm}$) was used for attenuation correction [13]. The final reconstructed voxel size was 1.7x1.7x3.9 mm³. Image files were converted from interfile to analyze format using conversion software (Medcon, Erik Nolf, UZ Ghent, Belgium).

Image Spatial Pre-processing

Statistical analyses were conducted on a voxel-by-voxel basis using Statistical Parametric Mapping (SPM2, Wellcome Department of Cognitive Neurology, UK) [14]. The images of each subject were normalized to the Montreal Neurological Institute (MNI) standard anatomical space with 4x4x4 mm³ voxels, and to a value of 50 using proportional scaling. This was achieved using 12 affine transformations and 7x8x7 non-linear basis functions. The normalized images were then smoothed using a 3D Gaussian kernel with a FWHM of 12mm.

SPECT Image Analysis

1) A multi-group study design was first selected using 2 groups (OCD and control group). Contrasts were designed to detect in the first instance areas of significantly *increased* resting perfusion in OCD participants compared to controls, and in the second instance areas of significantly *decreased* resting perfusion in OCD participants compared to control participants.

2) In a second analysis we performed a correlation analysis between YBOCS scores as a measure of OCD severity and resting brain perfusion as measured with SPECT. Areas of significant (i) positive and (ii) negative correlation were sought.

3) In a third and final analysis, we took clusters reaching our significance threshold specified in the positive and negative correlation analyses (2) above and fitted these to group contrasts (1) above for resting perfusion in OCD > controls and OCD < controls respectively. Here we report only on clusters from the correlation analyses that were spatially located within 20mm of the clusters from the group-wise contrasts using a threshold of $p < 0.05$ uncorrected. This was done to increase the reliability of the assertion that cluster from the two analyses were located in the same brain regions.

We only report here on clusters of five or more (4X4X4mm) voxels in extent, as clusters smaller than this in extent are more likely to yield spurious results on the basis of the spatial resolution limitations of SPECT. Unless specified, a threshold p-value of $p < 0.001$ uncorrected was used to denote statistical significance in all analyses. The precise anatomical location of significant clusters is described using the anatomical regions using MRlcro software (Chris Rorden, Nottingham University, UK).

2.4 Results

Our study sample comprised participants with OCD (n=18, 14 male, 5 female), with a mean age of 33.1yrs (SD11.0), and controls (n=19, 15 male, 5 female), mean age 36.9yrs (SD 7.9) (p=0.231). YBOCS scores for the OCD group were in the moderate to severe range with a mean of 27 (SD 3.7). No specific measure of symptom dimensions with which symptom heterogeneity could be better understood was available in this sample.

In the first contrast of OCD>controls, two small clusters met predefined threshold criteria. The first of these, 5 voxels in extent, was located in the left frontal cortex (L-pre-central, x,y,z = -56,4,36) (Fig 2.1a). The second was located in the orbito-frontal cortex (Mid-orbito-frontal x,y,z = 0,28,-8) (Fig 2.1b).

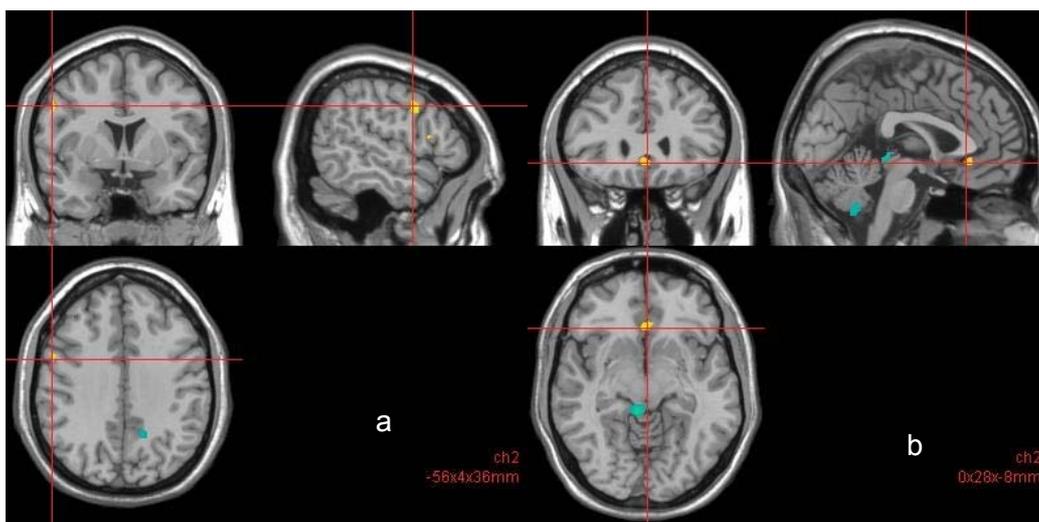


Fig 2.1 Resting perfusion in OCD > controls. Two clusters were identified in the left frontal cortex (x,y,z = -56,4,36) (a), and the orbito-frontal cortex (x,y,z = 0,28,-8) (b)

In the reverse contrast (OCD<controls), 7 clusters emerged with the two most significant of these being in the lingual gyrus and the orbito-frontal cortex. Other clusters were found in the cerebellum, hippocampus, cingulate and precuneus. (See Table 2.1 for full results)

Cluster extent (n-voxels) = n (4x4x4mm)	Z-score	x,y,z co-ordinates	MNI anatomical localization
33	4.2	-8,-36,0	L – lingual
11	3.75	-8,44,-32	sup orbito-frontal
17	3.72	-4,-56,-40	cerebellum
13	3.61	-12,-8,-16	L- med to hippocampus
7	3.56	-8,8,28	L anterior cingulate
6	3.29	12,-52,36	R-precuneus
6	3.27	-24,-56,52	L superior parietal

Table 2.1: Whole brain group-wise contrast with OCD<controls

Height threshold $T=3.34$, $P=0.001$, extent threshold 5 voxels

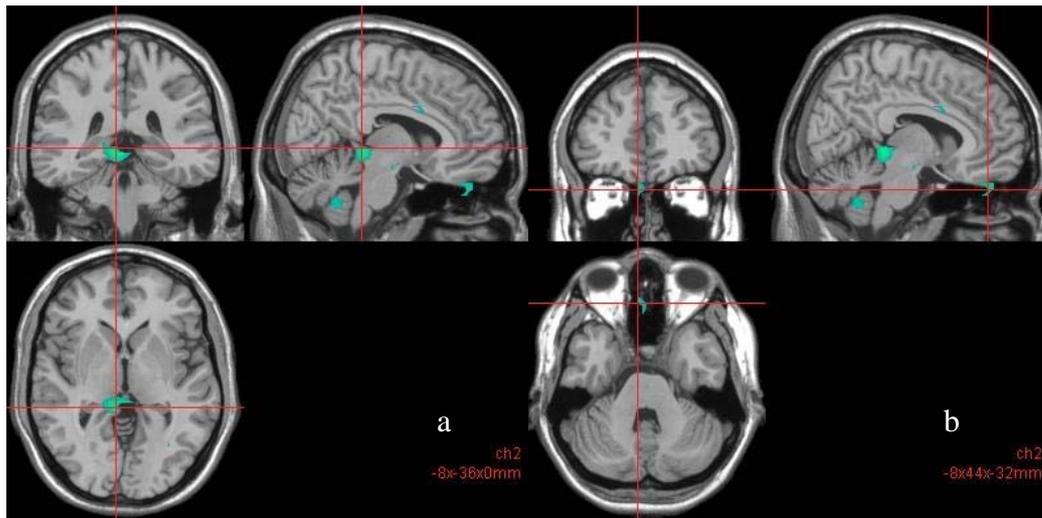


Fig 2.2: OCD participants displayed lower resting brain perfusion in left lingula (a), superior orbito-frontal cortex (b)

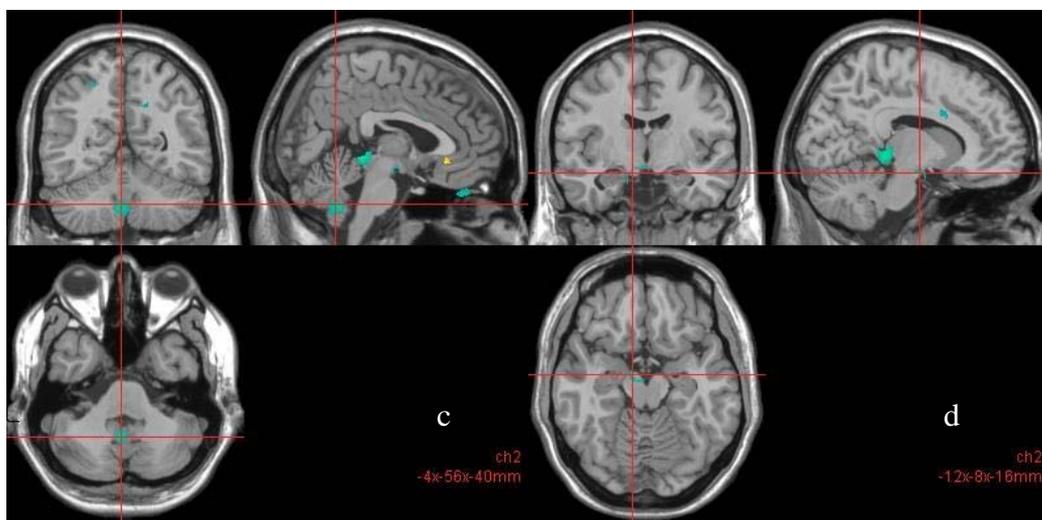


Fig 2.2 OCD participants displayed lower resting brain perfusion in the cerebellum (c), and left medial hippocampus (d)

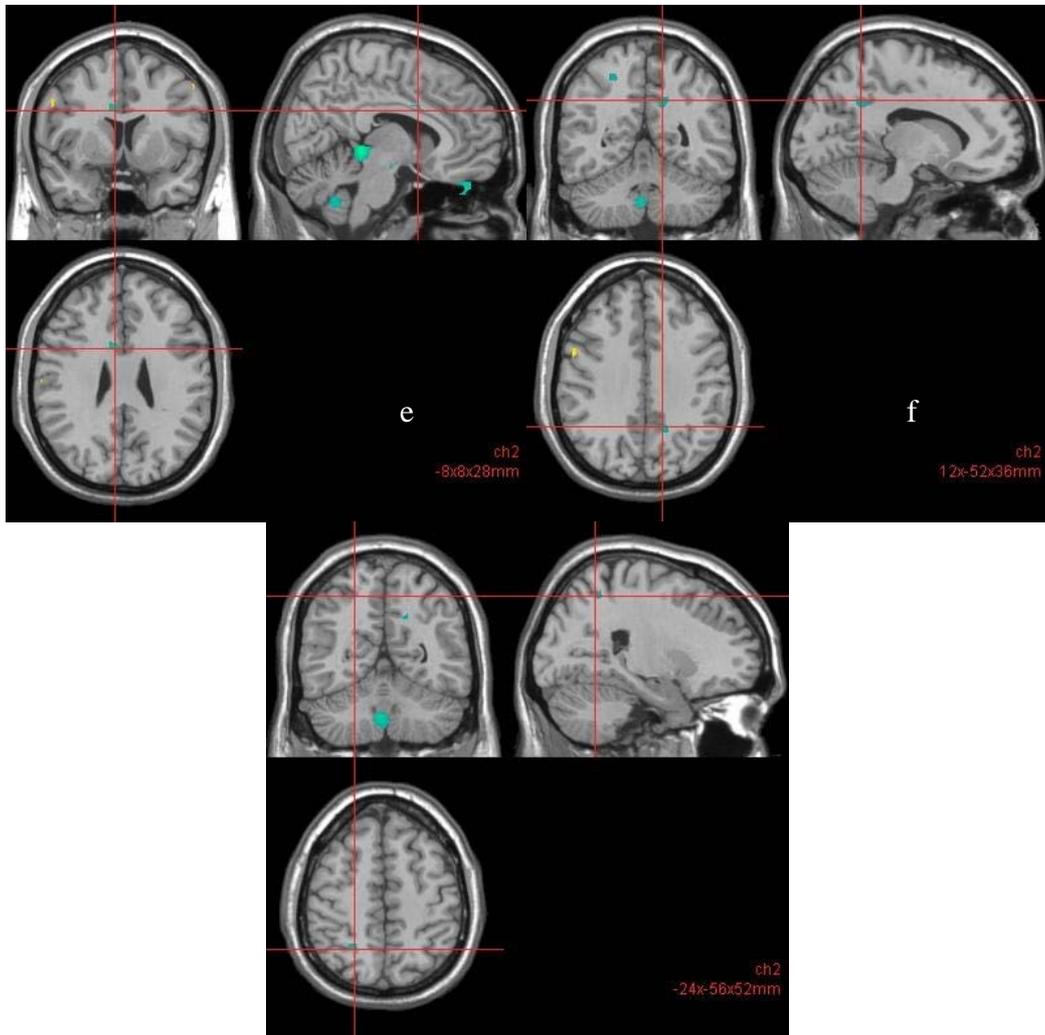


Fig 2.2 OCD participants displayed lower resting brain perfusion in the, left anterior cingulate (e), right precuneus (f), and left superior parietal cortex (g)

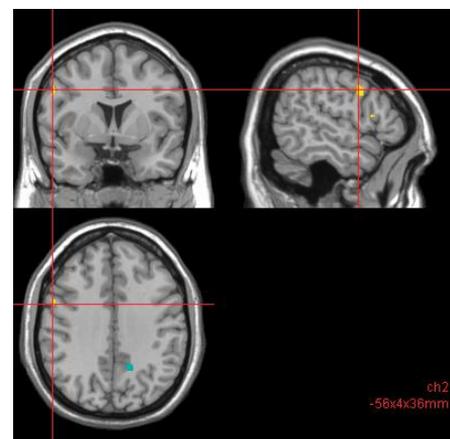
In the correlation analyses of resting cerebral perfusion with YBOCS scores in the OCD group alone, we found no positive correlations at the $p=0.001$ level. In the reverse contrast, significant clusters for negative correlations of perfusion with YBOCS scores emerged as follows. These were located in the right mid temporal cortex (19 voxels, located at 48, -72,8) (Fig 2.3a), and the left pre-central region (15 voxels located at -52, -16,48) (Fig 2.3b).



Fig 2.3: For the OCD group alone, total YBOCS scores were inversely correlated with regional perfusion in the mid-temporal region (a), and the left pre-central region (b)

Given that with the group-wise contrast we had defined “regions of interest” for use in the comparison of regions with the correlation analysis, we used a lower threshold for height equivalent to $p=0.05$. For the contrast of $OCD > controls$ we found one cluster in the left frontal region (-64, 8, 32, distance 9mm) correlated positively with YBOCS scores. (Fig 2.1)

Fig 2.4: OCD demonstrated higher rCBF compared to controls, which correlated with OCD severity in the Left pre-frontal region



In a similar analysis for the reverse contrast of OCD<controls we found 5 clusters that correlated negatively with YBOCS scores in the OCD group. These were located within the superior orbito-frontal (16,36,-20 within 17mm), left cerebellum (-8,-44,-36 within 13mm), medial to hippocampus (90,-16,-8 within 17mm), right precuneus (12,-60,48 within 14mm), and left superior parietal region(-28,-56,56 within 6mm).

2.5 Discussion

In this study we compared SPECT resting brain perfusion in a moderately large cohort of participants with OCD compared to normal controls. Our main findings included (1) higher perfusion in OCD relative to controls in right mid orbito-frontal and left pre-central frontal brain regions, and a positive correlation with a left pre-central frontal cluster and illness severity, 2) lower perfusion in OCD versus normal controls in more widespread brain regions including left lingual, superior orbito-frontal, cerebellar, right precuneus, anterior cingulate, left superior parietal cortex, and left hippocampus. 3) an inverse correlation with disorder severity in all the aforementioned brain regions with the exception of the left lingual and the anterior cingulate cortex clusters.

In line with our hypothesis, these data confirm that differences in brain perfusion are present when comparing OCD and normal controls at rest. The opposite direction of the observed differences in some brain regions when compared to normal controls adds to the complexity of understanding these data. Symptom heterogeneity has long been suggested to represent underlying biological variability. We show that some frontal regions (left pre-central) demonstrate increased perfusion that correlates with disorder severity, while others (superior orbito-frontal) showed the reverse. The mixed findings here, however, are consistent with the variability seen in much of the resting SPECT literature to date in OCD [15-19]. Reasons for this plausibly include clinical heterogeneity [20,21], sub-regional changes that are not equally well explored across studies that use variably sensitive analysis methods, imaging methodology, and disorder severity. Many of these hypotheses are difficult to test.

Our finding of lower perfusion in a number of brain regions is however in line with some previous work. An overlap exists with findings incorporating temporal and parietal brain regions such as the right precuneus and left superior parietal regions [22-24]. Our findings however differ from others in respect of the direction of change in these temporal [16,17,25-27] and parietal regions [16,17,25,27]. Emerging evidence has suggested a role for parietal (precuneus) involvement in OCD through its connections with striatal, thalamic and frontal brain regions. Parietal regions mediate a range of functions including memory processing, and self awareness among others [18,28,29]. Particularly interesting in this context is a reported association of fronto-parietal deactivation in the conscious resting state possibly accounting for the finding here [30]. How this explains the difference between OCD and controls however remains unclear.

In our study involvement in the lingual gyrus did not correlate with symptom severity. This region of the occipital cortex is involved in mediating response to unpleasant stimuli [31-33] and selective attention [33]. It is possible that despite an apparent resting state, participant's anticipation of injection of a radiopharmaceutical and subsequent SPECT scanning may have an impact on brain perfusion and consequently brain regions that mediate processing of unpleasant stimuli. If this is worse in OCD than in normal controls, this may account for greater deactivation in OCD compared to controls.

The impact of symptom dimensions on the "ability to rest" prior to injection of the radiopharmaceutical may be affected by underlying symptoms. A period of 30 minutes rest in an environment devoid of bright light, noise, pain or otherwise uncomfortable sensory stimuli may not induce comparable resting states across subjects and studies. Depending on the nature and severity of OC symptoms of OCD, participants could plausibly respond with some variability to the instruction to rest. Nevertheless, differences in resting state are likely to be of some significance and should be considered as possible reasons for discrepant findings across studies [17,19].

Another possible explanation for the variability we see might be explained in the findings from the recent meta-analysis by Whiteside et al [3]. Data from 13 studies were combined which included comparisons of OCD versus normal controls.

By computing the effect size of differences between OCD and normal controls they found that only the left and right head of caudate and the left orbital gyrus differed significantly from no effect. They also note that very few of the studies actually examined these regions. The head of caudate findings are derived from 3/13 studies [34-36] and the orbito-frontal findings from 2/13 studies [34,35]. As alluded to in their paper, Whiteside et al express concern at the assertions made in previous comprehensive narrative reviews [5,6], that current data strongly support the involvement of the orbito-frontal cortex and the caudate in the pathophysiology of OCD [3]. Meta-analyses have the advantage of accurately quantifying data acquired in comparable ways, and in so doing increase the power to detect meaningful differences between study groups. While this approach has some appeal in imaging literature, caution should be exercised when interpreting pooled data that combines studies acquired under different resting conditions. In addition, the effect of different imaging equipment and indeed different imaging modalities such as PET and SPECT may introduce significant confounds to interpreting these data.

Whiteside et al [3] do argue that based on their findings, a more specific focus on smaller brain regions may be more fruitful. The authors cite the need to create so-called “super-groups” of brain regional findings in order to generate sufficient power for meta-analysis as a potential confound to their results. In so doing they needed to some extent to disregard emerging evidence suggesting that sub-regional functional differences are likely to exist in orbito-frontal and cingulate cortices in OCD. Increasingly sophisticated whole brain, voxel-wise analysis may have an advantage over some region of interest (ROI) approaches in that *a priori* knowledge on expected change is not an absolute requirement. As such studies using ROI analyses with larger regions of interest may have been set up so that areas believed to be central to OCD were prioritized over less well studied areas. Also, larger regions of interest, as suggested, may entirely overlook changes in opposite directions that occur within an ROI, effectively canceling each other out.

We turn now to the question of the potential of underlying differences in core symptom dimensions to influence variability of imaging findings. An emerging literature has focused on defining increasingly specific symptom dimensions within OCD cohorts [2,4,9] It is anticipated that in time this approach will contribute to analyses that combine clinical correlates of symptom dimensions with more sensitive

neuro-cognitive and functional neuroimaging patterns. Barriers to this approach, however, lie in the natural course of OCD. Symptoms in OCD typically run a waxing and waning course. This approach seeks to classify participants on the basis of the presence and severity of specific symptom dimensions. To do this they rely on the categorization of symptoms of obsessions and compulsions as (1) present or not, and (2) whether a symptom is regarded as primary or not at the time of assessment. The typical course of OCD thus suggests that core symptoms without temporal stability may be absent at a future assessment and be superseded by other symptoms entirely. It is therefore conceivable that a particular individual may at another time display a considerably different if not quite distinct pattern of brain function as a result of the primacy of a distinct obsession or compulsion. Dimensional descriptions, while undoubtedly valuable for a number of other reasons, probably capture a specific symptom “state” when using activation techniques as imaging paradigms. These data may thus represent a distinct and possibly more replicable brain functional state that is OCD. While theoretically appealing, however, this remains to be shown in studies using a similar methodology.

Finally, the correlation we found with differences in disorder severity (YBOCS) and changes in prefrontal regional brain perfusions in line with a number of previous studies. In this area to, it has been argued that variability across studies may be accounted for at least in part, by variability in symptom severity both in respect of general anxiety at rest as well as specific OC symptoms [17]. For instance, frontal abnormalities are frequently seen [3,6] and are likely to mediate a range of cognitive and affective dysfunction in part impacted by severity in OCD. Sub-regional differences in the direction of that change, whether primary or compensatory may account for variability and requires further clarification [19].

Limitations of the present study should be noted. First, we did not objectively measure anxiety at the time of the HMPAO injection, and as such we acknowledge that anxiety levels may have differed to some degree across subjects and accounted for some of the regional differences we see compared to other studies. However, we believe that the effect of moderate to severe symptoms of OCD, as was the case in our cohort, is likely to be the major determinant of the between-group differences we observe. Despite some of the limitations of SPECT examination, the advent of increasingly reliable and comparable analysis methods will in time aid in meaningful

comparisons across studies. For this accessible technology such as SPECT can still be expected to make a meaningful contribution to this literature. Larger, more easily comparable samples will in time move us closer to addressing crucial questions in OCD neurobiology.

We have argued that both categorical and dimensional approaches as well as activated and resting state investigations to pursue the biological underpinnings of OCD seem justified. In future studies, consistency in analysis methods should be pursued. In particular, the advantage that whole brain voxel wise analysis, allows examination of smaller sub-regional volumes that in time may provide us with a clearer indication of the brain functional changes that underlie OCD.

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CHAPTER 3

**Clinical and regional brain perfusion
changes in response to acute challenge
with a serotonin 1B receptor agonist in
OCD**

3.1 Abstract

Background

Treatment data, genetic findings, and some previous pharmacological challenge data suggest a potential role for the serotonin 1B autoreceptor in mediating symptoms in obsessive-compulsive disorder (OCD). A previous acute sumatriptan challenge found heterogeneous clinical responses. Frontal brain perfusion attenuation correlated with exacerbation of OCD symptoms when measured with single photon emission computed tomography (SPECT). Here we expand this previous sample and examine brain perfusion effects of acute sumatriptan challenge in OCD using whole-brain voxel-wise SPM analysis.

Methods

Sumatriptan or matching placebo was administered in a double-blind, cross-over, counterbalanced design on separate days to 25 consenting, treatment free participants with primary diagnosis of OCD. Participants had no other primary psychiatric co-morbidity including depression. SPECT imaging followed a standardized rest period and injection with Technetium-99m HMPAO. Repeated measures of OC and general anxiety symptoms were performed by trained clinicians to assess changes in response to sumatriptan.

Results

Behavioural responses of OC and anxiety symptoms did not differ significantly between placebo and sumatriptan. This however, masked considerable heterogeneity of OC symptom responses. The majority (n=14) of participants had an improvement in symptoms of anxiety. Five subjects each reported either worsening or improvement in OCD symptoms while the rest were unchanged. Improvement in OC symptoms was associated with attenuated regional perfusion in the right mid-cingulate, and left superior medial frontal cortex. Increased perfusion was also noted in the occipital region. Improved anxiety symptoms correlated inversely with perfusion in the left fusiform gyrus, right precuneus, and left lingual gyrus.

Conclusions

Drug challenge of the 5HT_{1D/B} autoreceptor complex in OCD in the present study produced mixed responses in obsessive-compulsive symptoms and anxiety in OCD. In general, brain regional perfusion responses to sumatriptan challenge were seen in brain regions implicated in the functional neurocircuitry of OCD. In addition, whole brain voxel-wise analysis has enabled us to detect and speculate on the involvement of regions outside of this circuit. Our data also suggest that the change in frontal regional perfusion may be specific to OC symptoms following sumatriptan challenge.

3.2 Background

A range of investigations into the neurobiology that mediates symptoms of obsessive-compulsive disorder (OCD) have been undertaken in recent decades. Much of this work has focussed on the involvement of neurotransmitter systems which are implicated in the pathophysiology of OCD. The selective response to treatment with drugs that target the serotonin system have underpinned a serotonergic hypothesis in OCD for some time.

The identification of the 5HT_{1B} receptor on chromosome 6 in humans in the early nineties [1-3], lead to positive associations with preferential transmission of the G-allele of the gene encoding for 5HT_{1B} in some [4,5], but not all [6,7] studies in OCD. Along with a number of other lines of evidence, the 5HT_{1B} hypothesis in OCD began to develop [8]. This hypothesis has been particularly strengthened by the contribution of pharmacological challenge studies.

Challenge studies with drugs acting on specific components of receptor systems have been informative regarding the involvement of the serotonin system in OCD. These began with studies using m-Chlorophenylpiperazine (m-CPP), a ligand with non-specific agonist action on 5HT_{2c}, 5HT_{1b}, and 5HT_{2a} receptors. Acute administration results in OC symptom exacerbation in some [9-12], but not all studies using m-CPP [13,14]. MK-212, a specific agonist of 5HT_{1a} and b receptors does not seem to have an impact on OCD symptoms when administered acutely [15]. Together with the neuroendocrine blunting of cortisol and prolactin responses to MK-212 in OCD, these data may suggest a degree of hypo-responsivity of components of the serotonin system [15]. Due, however to the relative lack of specificity of these agents, the involvement of particular receptor subtypes in OCD is still not deducible from these data.

The use of triptans such a sumatriptan in clinical practice, introduced a potential to investigate the role of the 5HT_{1B} auto-receptor in challenge studies using the selective auto-receptor agonist, sumatriptan [16]. Acute administration of sumatriptan to patients with OCD has produced mixed clinical responses. In some, a transient exacerbation of symptoms [10,17,18] before a moderate reduction with

more chronic exposure [17,18] has been reported. In another study, similar exacerbation was found with sumatriptan, but this did not differ significantly from placebo [14]. In a study using zolmitriptan, a derivative which traverses the blood brain barrier more effectively than sumatriptan, no behavioural effects on measures of OCD and anxiety were found [19]. In collating this work, Zohar et al [8] note the difficulty in interpreting inconsistent challenge data and call for further clinical studies in this area.

Functional brain imaging tools such as single photon emission computed tomography (SPECT) along with specific drug challenges provide the ideal opportunity to examine regional brain perfusion and drug interactions. Hollander et al [20] using an m-CPP challenge found increased whole brain cortical blood flow correlated with increased symptoms of OCD. Ho Pian et al [21] compared responses to m-CPP challenge in OCD with SPECT and found reduced rCBF in frontal, caudate, putamen and thalamic regions. These changes were, however, did not accompany changes in OCD symptoms compared to healthy controls. As mentioned, both of these studies used the non-specific serotonin receptor agonist m-CPP, leaving some doubt as to the specific involvement of the 5HT1B receptor in this context.

Our group have previously reported on a small SPECT study with a sample of patients (n=14) with OCD to whom a single dose of sumatriptan was administered in a double-blind, placebo-controlled, cross-over design [22]. We found heterogeneous OC symptom responses to sumatriptan challenge, with nearly a third of patients (n=4) experiencing a worsening of OC symptoms. Using an ROI approach to the analysis, we demonstrated perfusion increases in the thalamus and putamen with sumatriptan relative to placebo challenge. A worsening of symptoms was associated with decreased activity in inferior and medial frontal brain regions. We also found that symptom exacerbation correlated with reduced inferior frontal and increased putaminal perfusion. Post-hoc analysis of those with and without symptom exacerbation did not demonstrate significant rCBF differences.

In the present study, we extend our previous work in this area and now report on a moderately large OCD sample in which we examine the behavioural correlations

of acute sumatriptan challenge with SPECT findings using whole brain voxel-wise analysis methods.

3.3 Methods

Study Participants

Potentially eligible study participants were screened in our teaching hospital anxiety disorders clinic. Suitable participants had a primary DSM-IV diagnosis of Obsessive-compulsive disorder (OCD) [23]. The sample (n=25) comprised 19 males and 6 females between the ages of 18-65 years. Structured psychiatric diagnostic interviews to determine current psychiatric status were conducted by a board certified psychiatrist using the Structured Clinical Interview for the Diagnosis of Axis-I Disorders (SCID-I [24]. Any other current primary Axis-I disorder, medical illness deemed to be significant according to the clinical judgment of the investigating clinician, previous head injury with loss of consciousness exceeding 10 minutes, history of seizure disorder, refusal to consent to procedure or any other condition that might have rendered a participant unable to undergo or complete a SPECT study, were grounds for exclusion from participation. All patients had been free of any psychotropic medication for a minimum of two weeks (or as appropriate for drugs with longer washout times) at the time of the first scan.

Approval for the study was obtained from the relevant Institutional Review Board of the University of Stellenbosch. All participants were provided with a patient information and consent form prior to inclusion in the study. Inclusion followed detailed explanation by the investigating clinician and signing of the informed consent document. The study was conducted in line with international guidelines guiding ethical conduct in research on human participants.

Study design and clinical measures

Matching sumatriptan/placebo tablets (100mg) were administered to patients in a double-blind, placebo-controlled, counterbalanced, cross-over design. On each of two scan days (72 hours apart), medication was administered at 08:30, with a standardized period of rest beginning at t=60. Radiopharmaceutical injection 30 minutes later at t=90 (see imaging methods below for detail). We used clinically

trained raters with good inter-rater reliability, to assess obsessive-compulsive and general anxiety symptoms at regular intervals throughout the 4-hour period of the clinic visit. We used the Clinician Challenge Obsessive-Compulsive scale (CC-OCS) [12] to measure obsessive-compulsive symptoms at all protocol specified time intervals. The CC-OCS is derived from the Yale-Brown Obsessive-Compulsive scale (YBOCS) [25,26]. This 9 item scale assesses both obsessions (time spent, anxiety, control, overall severity) and compulsions (time, anxiety, control, indecisiveness, overall severity), and was designed with the drug challenge environment in mind. Measures of state anxiety were also taken using the Acute Panic Inventory [27], a 27-item version of the scale designed to measure the effects on general anxiety and panic in the context of drug challenge studies. Behavioral measures were taken at $t=-30$ min, time of drug administration ($t=0$), and again at $t=30$, $t=90$, $t=150$, and $t=210$. To derive a baseline measure of anxiety, we summed the scores of $t=-30$, $t=0$, and $t=30$. Similarly, to derive a measure of anxiety over the period of maximal uptake of the sumatriptan, we summed behavioral scores from $t=90$, $t=150$, and $t=210$.

Overall measures of OCD severity included the YBOCS which was measured on each of the scan days. While no participant met criteria for depression at the time of the study, we used the Montgomery Åsberg Depression Rating Scale (MADRS) [28] to assess symptoms of depression.

SPECT Imaging

Single photon emission computed tomography (SPECT) was performed in the resting state for all participants on two separate days with a minimum of 72 hours separating examinations of an individual participant. Randomization of medication was counterbalanced across the two imaging sessions to ensure blinding of symptom raters. For the rest period beginning at $t=60$, participants were required to lie supine in a quiet, dimly lit room for 30 minutes prior to injection of the radiopharmaceutical. Apart from administration of the injection by a physician, they remained alone in the room during this period. Subjects were asked to remain at rest for 10 minutes after the injection of the radiopharmaceutical to allow uptake of the radiopharmaceutical in the brain.

An injection of 555 MBq (15 mCi) of technetium-99m hexamethylpropylene amine oxime (Tc-99m HMPAO) was given into an arm vein through an intravenous cannula positioned in the right ante-cubital fossa prior to the initiation of the rest period. After completion of the minimum 10 minute rest period following the radiopharmaceutical injection, SPECT imaging of the brain was performed. While on the scanner bed, the participant's head was supported with a standard headrest lined with sponge to maximize comfort. SPECT imaging was performed using a dual detector gamma camera (Elsint Helix, GE Medical Systems, USA) equipped with fan beam collimators.

Data were acquired in the step-and-shoot mode using a 360° circular orbit, with the detectors of the gamma camera positioned as close as possible to the subject's head. Data were acquired using a 128 x 128 image matrix in 3 degree steps of 15 seconds per step.

Data were reconstructed by filtered back-projection, using a Metz filter (power=5, FWHM=14mm). The Chang method ($\mu = 0.11/\text{cm}$) was used for attenuation correction [29]. The final reconstructed voxel size was 1.7x1.7x3.9 mm³. Image files were converted from interfile to analyze format using conversion software (Medcon, Erik Nolf, UZ Ghent, Belgium).

Image Spatial Pre-processing

Statistical analyses were conducted on a whole brain voxel-by-voxel basis using Statistical Parametric Mapping (SPM2, Wellcome Department of Cognitive Neurology, UK) [30]. The images of each subject were normalized to the Montreal Neurological Institute (MNI) standard anatomical space with 4x4x4 mm³ voxels, and to a value of 50 using proportional scaling. This was achieved using 12 affine transformations and 7x8x7 non-linear basis functions. The normalized images were then smoothed using a 3D Gaussian kernel with a FWHM of 12mm.

Behavioural symptom analysis

Clinical behavioural data were collated and analysed using the Statistical Package for Social Sciences (SPSS Version 14). To assess within subjects change

in response to placebo and medication, we used paired sample t-tests to assess change in API scores from baseline (t -30+0+30) to the end point defined as the sum of scores from t = 90+150+210 for both the sumatriptan and the placebo scan days. To assess differences between treatments within subjects we used general linear model and a repeated measures analysis of variance (RMANOVA) using the baseline and endpoint API, and CC-OCS respectively as factors, and treatment (sumatriptan/placebo) as the between subjects factor.

SPECT Image Analysis

1) A single group, within subjects design was employed to compare placebo versus sumatriptan scans. Contrasts were designed to examine in the first instance areas of significantly *increased* resting perfusion in sumatriptan scans compared to placebo, and in the second instance areas of significantly *decreased* resting perfusion in OCD participants compared to control participants.

2) In a second analysis we examined areas with significant (i) positive and (ii) negative correlations between a) the change in API score, and b) the CC-OCS in response to sumatriptan/placebo and resting brain perfusion as measured with SPECT.

3) In a third and final analysis, using only the sumatriptan scans, we used a simple between subjects design to examine the resting SPECT perfusion differences between participants who had symptom improvement versus participants who did not on the API measure of anxiety, and the CC-OCS. Contrasts for (i) responders>non-responders, and (ii) responders<non-responders were designed.

We only report here on clusters of four or more voxels (4X4X4mm) in extent, as clusters smaller than this in extent are more likely to yield spurious results on the basis of the spatial resolution limitations of SPECT. We used a threshold p-value of $p < 0.001$ uncorrected to denote statistical significance in all analyses. The precise anatomical location of significant clusters is described using the anatomical regions using MRIcro software (Chris Rorden, Nottingham University, UK).

3.4 Results

Study sample characteristics

Our study cohort comprised 25 subjects (19 male, 6 female). Of those who were eligible and consented to participate, all completed both imaging sessions. No adverse effects from either the sumatriptan or placebo were reported. The mean age of participants was 33.5 years (SD 12.21). The mean YBOCS score was 23.15 (SD 5.06) suggesting participants were moderately ill overall. As co-morbid depression was an exclusion criterion and MADRS mean scores were predictably low (11.03, SD 4).

Behavioural outcomes

Results of paired sample t-tests assessing within-group (placebo and sumatriptan) changes in 1) obsessive-compulsive symptoms (CC-OCS), and 2) overall anxiety (API) (see Table 3.1) suggest that overall, participants did not demonstrate significant changes. Within subject treatment differences of OC symptoms were also not significant ($p=0.48$). This however masks what was essentially a heterogeneous response to sumatriptan. Five subjects reported improved symptoms of OCD while 5 reported a worsening, and the rest remaining unchanged. On overall measures of anxiety, however, both sumatriptan ($p=0.04$) and placebo ($p=0.03$) challenges were accompanied by reduced symptoms. Here 14 participants improved, 10 were worse and 1 was unchanged in response to the sumatriptan challenge. The magnitude of the differences, however, did not differ significantly between sumatriptan and placebo ($p=0.77$).

Behavioral Measure	Sumatriptan (mean, SD)	Paired t-test Mean (df,(SD), p)	Placebo (mean, SD)	Paired t Mean df (df,(SD), p)	RMANOVA Sumatriptan vs placebo (F, p)
API Baseline	25.28 (25.58)	3.92 (9.07)	24.08 (22.53)	3.30,(10.68) p=0.03	0.089, p=0.77,
API Peak	21.36 (21.17)	p=0.04	20.78 (20.67)		
CC-OCS Baseline	11.06 (5.87)	0.06 (4.30)	11.92 (5.74)	-0.74 (5.49) p=0.507	0.516, p=0.48
CC-OCS Peak	11.00 (7.25)	p=0.95	12.66 (7.62)		

Table 3.1: paired t-tests for changes in scale scores for sumatriptan and placebo and RMANOVA for within subject treatment comparisons.

API – Acute Panic Inventory, CC-OCS – Clinician Challenge Obsessive-Compulsive Scale

SPECT imaging results

In the first analysis which contrasted sumatriptan and placebo in a paired design, there were no differences in brain regional perfusion that cleared the height and extent threshold set *a priori* in either the sumatriptan>placebo or sumatriptan<placebo contrasts. As we may have anticipated from the absence of meaningful overall change in OC behavioral findings, we found neither positive nor negative regional correlations of perfusion with change in CC-OCS scores.

Despite the small overall change in OC symptoms, the heterogeneous clinical response to sumatriptan warranted further exploration of this group for possible differences in brain perfusion between participants in whom symptoms improved and those in whom symptoms worsened. We found a cluster within the right mid-cingulate region (7 voxels, x=4,y=24,z=36, Z=3.97, p=0.001)(Fig 3.1a) in which those with

symptom improvement had lower regional perfusion than non-responders following sumatriptan challenge. Another small cluster (4 voxels) was noted in the left superior medial frontal cortex ($x=-8, y=56, z=28, Z=3.81, p=0.001$) (Fig 3.1b).

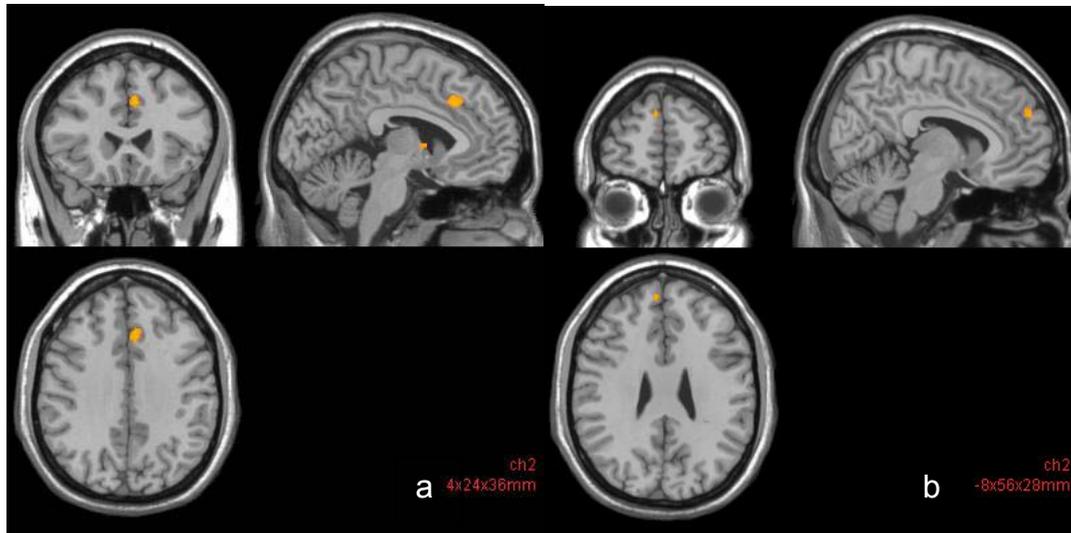
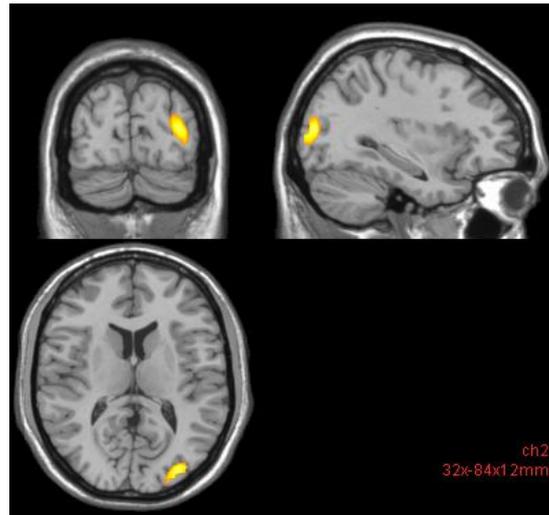


Fig 3.1: Reduced right mid cingulate (a) and left superior medial frontal (b) perfusion in participants with improved OC symptoms in response to sumatriptan challenge

For the reverse contrast (Responders>non-responders) we found a single large cluster (42 voxels) located within the right mid-occipital cortex at MNI coordinates $x=32, y=-84, z=12$ ($Z=5.3, p<0.001$) (Fig 3.2).

Fig 3.2: Right mid-occipital region in which participants who responded to sumatriptan challenge demonstrated higher perfusion relative to those who did not.



In line with the overall improvement in anxiety, improved anxiety correlated positively with reduced brain perfusion in two small clusters; these were 1) the left fusiform gyrus (6-voxels; $x=-36, y=-12, z=-32$ [$Z=3.87, p<0.001$] (Fig 3.3a), and 2) the right precuneus (4 voxels; $x=16, y=-44, z=8$ [$Z=4.59, p<0.001$]) (Fig 3.3b).

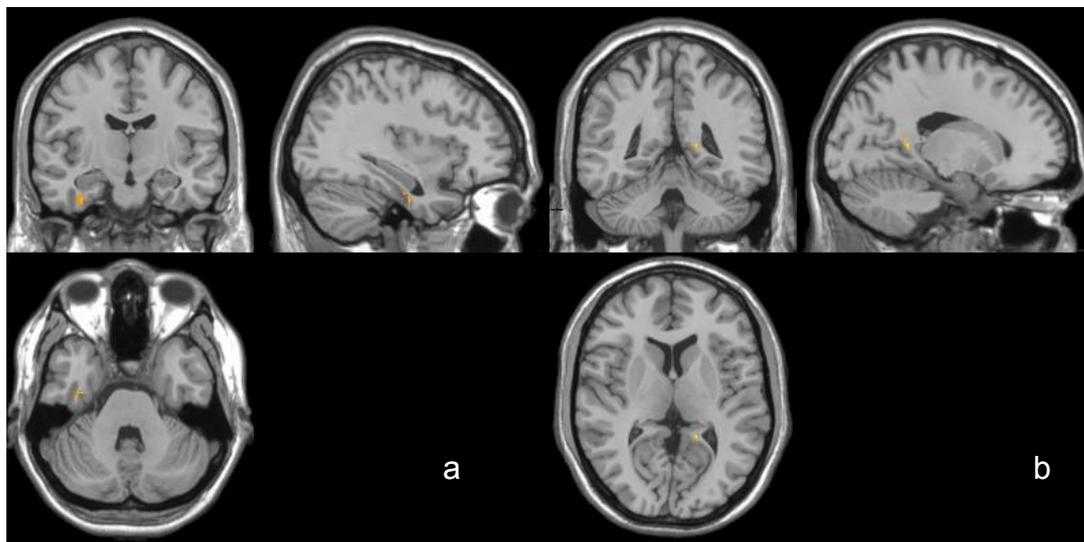


Fig 3.3: Lower anxiety symptoms in response to sumatriptan challenge correlates with lower regional perfusion in the left fusiform (a) and the right precuneus region (b).

We found no negative correlations with perfusion and changes in anxiety. A single small cluster (4 voxels) in the left lingual gyrus using one-way ANOVA ($x=-16, y=-72, z=-8$ [$Z=3.91, p<0.001$]) (Fig 3.4) demonstrated a significant increase in perfusion in participants who had improved anxiety symptoms relative to those who did not respond or worsened in response to sumatriptan.

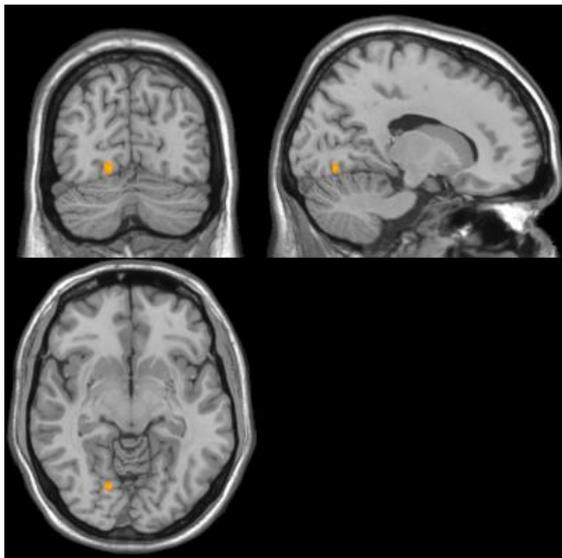


Fig 3.4: Left lingual perfusion was increased in participants in whom anxiety symptoms improved compared to those who did not improve in response to sumatriptan

3.5 Discussion

We found that overall, behavioural responses to sumatriptan did not differ significantly from placebo. The main clinical imaging findings of the present study are that those with OC symptom improvement in response to a single dose challenge with sumatriptan had significantly lower right mid-cingulate, superior medial frontal, and higher right mid-occipital rCBF than those who had no change in OC symptoms. We found that more than half the participants experienced improvements in anxiety in response to sumatriptan challenge and that these changes (lower symptom scores) correlated with reduced brain perfusion in the left fusiform gyrus and the right precuneus. When we contrasted those in the sumatriptan group with improved anxiety symptoms had lower left lingual perfusion than non-responders. Finally, we found that response to sumatriptan on measures of both OCD and anxiety symptoms were variable. A sizeable minority of participants ($n=10$) had a measurable response

to sumatriptan, and that numbers showing improvement (n=5) and exacerbation (n=5) were evenly divided.

Our findings are in line with other functional imaging data in OCD [31], including our own unpublished data, in which resting perfusion is higher in frontal brain regions in more symptomatic OCD patients compared to controls (See Chapter 2). Our main finding that participants who experienced a response to sumatriptan challenge differs from the findings in our previous work in which lower putaminal perfusion was noted in the same group. These data did not replicate this finding. Also, in our previous data we found that frontal inferior-anterior perfusion increased with symptom response to sumatriptan. Here we see that right inferior frontal perfusion was attenuated in response to a reduction on OC symptoms following sumatriptan challenge. At the time we hypothesized that the lower frontal perfusion with increased symptoms may have resulted from decreased compensatory frontal activity in this subgroup of patients. In general, brain perfusion data in OCD suggests pre-treatment increases in frontal perfusion relative to controls [32] and that with treatment this effect is attenuated [33,34]. Our findings suggest therefore that serotonergic modulation of clinical symptoms through either an SRI or more specifically with the acute administration of a 5HT_{1B} autoreceptor agonist results in partial attenuation of frontal perfusion. Agonist activity at the autoreceptor has the effect of acutely reducing serotonin levels within the synapse. This might be seen to be akin to the effect of receptor desensitization that occurs with chronic treatment [9,12,17]. While this explanation has some appeal it does not account for the heterogeneity of the clinical response in our study.

We speculate that different clinical responses may be the result of a number of factors. Those at a receptor level may include receptor density, distribution, function or allelic composition. A limitation of the present study is the absence of allele data. At present the lack of available SPECT ligands for the 5HT_{1B} receptor limits our ability to address the questions of receptor density, distribution and function. We did note however that for changes in general anxiety, we found no specific frontal area in which perfusion was attenuated. As such the specificity of these frontal findings with respect to change in OC symptoms and lends weight to the distinctiveness of OCD and general symptoms of anxiety.

The response to sumatriptan challenge of overall anxiety symptoms in our cohort is less heterogeneous than is seen for specific OC symptoms. While we found an overall reduction in symptoms in both the sumatriptan and placebo conditions, these did not differ significantly from one another. Nevertheless, the effects are interesting due to the differences in regional brain perfusion that we demonstrated between those with differing anxiety responses. We found a correlation with improved anxiety and reduced brain perfusion in the left fusiform gyrus and the right precuneus, when comparing sumatriptan and placebo.

The fusiform gyrus within the inferior temporal cortex extending to the base of the occipital cortex has primarily been implicated in higher order visual object processing. More recently though, this area has also been implicated in the amount of retrieved information related to visually perceived objects [35]. Also, this region has been implicated in processing of OC dimensions of aversion, hoarding and aggression/checking [36]. In the case of aggression/checking, and aversion symptoms, controls demonstrated greater activation than OCD subjects. In hoarding the reverse was true. These data suggest that not only do different symptoms when provoked result in distinct patterns of rCBF, but that brain regions outside of the putative CSTC circuit may be important determinants of OCD symptoms and treatment response.

Lower perfusion in the right precuneus correlated with reduced levels of anxiety in response to sumatriptan challenge in our study. Preliminary evidence has previously suggested that the precuneus within the temporo-parietal region may also be involved in OCD [36]. This region is richly connected with sub-cortical and frontal brain regions to mediate memory processing (spatial working memory), and self awareness among a range of other functions [37-39]. In the light of the association with the precuneus and fusiform regions in relation to anxiety in our data, we speculate that higher levels of anxiety are generally associated with higher regional brain perfusion most notably in frontal and temporal cortices. However, the precise regional specificity of these changes still needs to be worked out.

In addition to receptor effects accounting for heterogeneity, is the likelihood that heterogeneity could plausibly reflect different responses in the “resting” state to radiopharmaceutical administration. Entry of the investigator to administer

the HMPAO after a period of 30 minutes rest, may have effects on brain activity. Variability in the “ability” of participants to rest when instructed to do so has been cited as an additional confound of resting brain imaging studies. Also, less anxious subjects would probably be less likely to respond with increased activation as they use all available recalled information/recognition of investigator to “reassure” themselves in the face of a subtle change in their environment [14,31]. Depending on the specific symptoms of OCD, it would thus seem reasonable to believe this may translate to differential effects on attention, self awareness and memory.

While we recognize that the effects cited above may be significant in conventional resting perfusion studies, they would seem to be less of a significant factor in the present study for reasons of the design we used. A blinded cross-over study design (ie within subjects) counterbalanced for sumatriptan and placebo between imaging sessions would seemingly minimize these differences. Thus, the heterogeneity in clinical response we see here is more likely to be mediated by the impact of underlying differences in core symptoms and response to sumatriptan.

A number of limitations of our study preclude more definitive conclusions being drawn from our findings. First, the absence of a clinical response to sumatriptan in a proportion of our cohort might reflect relatively low or even insignificant effects of sumatriptan in the CNS. Our finding, however is in line with the clinical findings of Ho Pian et al [14] where minimal clinical response to sumatriptan challenge was reported. The authors speculated that sumatriptan’s low potential to cross the blood brain barrier, may have accounted for this lack of effect. While it is known that bio-availability and blood brain barrier penetration of sumatriptan is generally low [40], there are several sets of data indicating that sumatriptan does indeed have central actions. First, centrally mediated effects on growth hormone [14], 2) our own data on clinical responses in patient subgroups to sumatriptan challenge [22] , 3) evidence of disruption of the blood brain barrier (BBB) in OCD with consequently higher levels of BBB penetration by sumatriptan [41,42], and 4) the demonstration of an overall effect to reduce SPECT rCBF in non-human primates [43] all support this notion. These data challenge the argument that no response reflects a failure by sumatriptan to cross the blood-brain barrier. In addition, sumatriptan also has direct effects on brain tissue by acutely affecting diffusion coefficients in the cat brain after intra-peritoneal administration measured with

diffusion weighted magnetic resonance imaging [44]. Further clinical evidence for a direct and central action of sumatriptan comes from a small case series in which it was chronically administered to patients with severe treatment refractory OCD. Moderate OC symptom improvement was demonstrated, and the effect was lost when sumatriptan was withdrawn [17].

Second, the fact that we did not measure peak plasma sumatriptan levels. This would have enabled us to control for the effect of differences in drug levels in the context of response heterogeneity. While this may have accounted for some of the effects, we have already alluded to the equally variable response to treatment in OCD for a variety of reasons including genetic determinants that stand aside of variability in drug levels [45]. Third, data on allelic status of the 5HT1B receptors in our cohort was not collected precluding findings on the impact of allelic variations in 5HT1B on differential responses to sumatriptan challenge.

In conclusion, the present study confirms that the 5HT1B auto-receptor complex in OCD is variably responsive to acute challenge with OCD. In general, brain regional perfusion responses to sumatriptan challenge are seen in brain regions implicated in the functional neurocircuitry of OCD. In addition, whole brain voxel-wise analysis has enabled us to detect and speculate on the involvement of regions outside of this putative circuit that deserve further investigation [32]. Our data also suggest that regions likely to mediate aspects of the anxiety response may differ from those that are impacted with direct 5HT1B challenge to mediate changes in OC symptom severity. Future studies in this area could make further contributions to our understanding whether OC dimensions combine with differences in 5HT1B autoreceptor alleles to produce clinical heterogeneity in response to sumatriptan.

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CHAPTER 4

Functional brain changes in response to serotonergic treatment across anxiety disorders: Similarities and distinctions

4.1 ABSTRACT

Background

Several studies have now examined the effects of selective serotonin reuptake inhibitor (SSRI) treatment on brain function in a variety of anxiety disorders including obsessive-compulsive disorder (OCD), posttraumatic stress disorder (PTSD), and social anxiety disorder (social phobia) (SAD). Regional changes in cerebral perfusion following SSRI treatment have been shown for all three disorders. The orbitofrontal cortex (OFC) (OCD), caudate (OCD), medial prefrontal/cingulate (OCD, SAD, PTSD), temporal (OCD, SAD, PTSD) and, thalamic regions (OCD, SAD) are some of those implicated. Some data also suggests that higher perfusion pre-treatment in the anterior cingulate (PTSD), OFC, caudate (OCD) and, antero-lateral temporal region (SAD) predicts subsequent treatment response. This paper further examines the notion of overlap in the neurocircuitry of treatment and indeed treatment response across anxiety disorders with SSRI treatment.

Methods

Single photon emission computed tomography (SPECT) using Tc-^{99m} HMPAO to assess brain perfusion was performed on subjects with OCD, PTSD, and SAD before and after 8 weeks (SAD) and 12 weeks (OCD and PTSD) treatment with the SSRI citalopram. Statistical parametric mapping (SPM) was used to compare scans (pre- vs post-medication, and responders vs non-responders) in the combined group of subjects.

Results

Citalopram treatment resulted in significant deactivation ($p=0.001$) for the entire group in the superior ($t=4.78$) and anterior ($t=4.04$) cingulate, right thalamus ($t=4.66$) and left hippocampus ($t=3.96$). Deactivation ($p=0.001$) within the left precentral ($t=4.26$), right mid-frontal ($t=4.03$), right inferior frontal ($t=3.99$), left prefrontal (3.81) and right precuneus ($t= 3.85$) was more marked in treatment responders. No pattern of baseline activation distinguished responders from non-responders to subsequent pharmacotherapy.

Conclusions

Although each of the anxiety disorders may be mediated by different neurocircuits, there is some overlap in the functional neuro-anatomy of their response to SSRI treatment. The current data are consistent with previous work demonstrating the importance of limbic circuits in this spectrum of disorders. These play a crucial role in cognitive-affective processing, are innervated by serotonergic neurons, and changes in their activity during serotonergic pharmacotherapy seem crucial.

4.2 Background

Significant advances in our understanding of the mediating psychobiology and the development of effective treatments for anxiety disorders have been made in recent years. Modern brain imaging techniques have proved useful in exposing specific albeit overlapping neurocircuitry that underlies individual anxiety disorders [1,2]. However, relatively little work has focused on the extent to which the anxiety disorders overlap with respect to changes in brain perfusion that accompany response to first-line treatment that is after all pharmacologically similar for different disorders.

The selective serotonin reuptake inhibitors (SSRIs) are currently recommended as first line medications for most anxiety disorders, including obsessive-compulsive disorder (OCD) [3], posttraumatic stress disorder [4] and social anxiety disorder [5]. A number of imaging studies have now examined the effects of SSRI's on brain perfusion in individual anxiety disorders. In OCD, attenuation of pre-treatment regional activation has been shown to correlate with treatment response in the anterolateral orbitofrontal cortex (OFC), caudate nucleus, thalamus, and temporal regions [6-11]. Results for studies assessing pre-treatment cerebral perfusion as a predictor of response, have, however, yielded mixed results. In some, an inverse relationship appears to exist with pre-treatment regional activation of the OFC [12], anterior cingulate, caudate [6] and subsequent responses to treatment. Conversely findings of higher prefrontal, cingulate and basal ganglia activation correlating with subsequent treatment response have also been reported [13,14]. In OCD co-morbid with depression, substrates of response to the SSRI, paroxetine, appear to differ based on pretreatment [15] activation patterns as well as changes that accompany treatment response when an SSRI is given in identical doses for either of the two conditions separately [16].

In social anxiety disorder SSRI treatment response accompanies attenuation of frontal, anterior and lateral temporal cortex, cingulate, and thalamic activity [17,18]. Higher anterior and lateral temporal cortical perfusion at baseline correlated with subsequent treatment response in the former study. The latter study also demonstrated some overlap of regions demonstrating attenuation of activity for both cognitive and pharmacotherapy interventions.

In PTSD, a single study by our group demonstrated medial temporal lobe deactivation with treatment irrespective of clinical response and medial prefrontal cortex activation correlated with treatment response. In addition, no baseline differences distinguished responders and non-responders to subsequent SSRI treatment [19].

In this present study, we hypothesised firstly, that response to SSRI treatment in this combined group of subjects with anxiety disorders (OCD, PTSD, SAD) would effect shared changes in rCBF affecting primarily limbic and related prefrontal regions and thus suggest some overlap between disorders in the mechanism of their response to effective treatment with SSRI's. Secondly, pre-treatment differences in regional perfusion would likely differentiate responders to subsequent treatment with citalopram across the anxiety disorders.

4.3 Methods

Subjects

Adult subjects with a primary diagnosis of OCD (n=11), PTSD (n=11) or SAD (n=15) were recruited from the Anxiety Disorders Clinic of our tertiary hospital. All subjects were interviewed with the Structured Clinical Interview for the Diagnosis of Axis-I Disorders [20] to ascertain diagnosis according to DSM-IV criteria. Results for the PTSD group have been reported previously [19].

Comorbid major depression was an exclusion criterion in the OCD and SAD, but not in the PTSD subjects. Nevertheless, in all cases comorbid disorders were considered secondary in terms of temporal course, symptom severity, and associated distress. Patients previously treated with SSRI's had been free of medication for a minimum of four weeks for fluoxetine and two weeks for other SSRI's. In total 30 (81%) of the group were SSRI naïve. Subjects with other central nervous system disorders including previous head injury or epilepsy were excluded. The Institutional Review Board of our University approved the protocol

and all patients gave informed written consent after a full explanation of the possible risks and benefits.

Pharmacotherapy and measures

All patients underwent treatment with citalopram, the most selective of the currently available selective serotonin reuptake inhibitors (SSRIs). The duration of the trial of treatment was 12 weeks for OCD and PTSD, and 8 weeks for SAD.

Dosage was initiated at 20mg daily for the first two weeks and then maintained at 40mg daily for the remainder of the study. Measures of symptom improvement were made bi-weekly by clinicians using the Clinical Global Impressions (CGI) scale [21]. Subjects with a CGI change score of 2 or less post-treatment were defined as responders, while those with scores greater than 2 were defined as non-responders.

Anxiety symptoms were also rated using disorder specific scales including the Liebowitz Social Anxiety Scale (LSAS) [22], the Yale Brown Obsessive-Compulsive Scale (YBOCS) [23] and the Clinician Administered Scale for PTSD [24]. Depressive symptoms were rated using the Montgomery-Asberg Depression Rating Scale (MADRS) [25].

SPECT Imaging

Single photon emission computed tomography (SPECT) was conducted before and after pharmacotherapy. Subjects lay supine in a quiet dimly lit room for 30 minutes prior to injection of the radiopharmaceutical. Apart from administration of the injection by a physician, they remained alone in the room during this period. Subjects were asked to remain at rest during the 30 minute period and for 10 minutes after injection of the radiopharmaceutical.

An injection of 555 MBq (15 mCi) of technetium-99m hexamethylpropylene amine oxime (Tc-99m HMPAO) was given into an arm vein through a previously placed intravenous cannula. After completion of the rest period, SPECT imaging of the brain was performed, with the subject's head supported by a headrest, using a

dual detector gamma camera (Elscint, Helix, GE Medical Systems, USA) equipped with fan beam collimators.

Data were acquired in the step-and-shoot mode, using a 360 degree circular orbit, with the detectors of the gamma camera as close as possible to the subject's head. The height of the imaging table and radius of rotation were noted for each subject and the same measurements were used for the follow-up study. Data were acquired using a 128 x 128 image matrix in 3 degree steps of 15 seconds per step.

Data were reconstructed by filtered backprojection, using a Metz filter (power=5, FWHM=14mm) and a zoom factor of 2.29. The Chang (1978) method was used for attenuation correction. Scatter correction was not performed. The final reconstructed pixel size was 3.87mm by 3.87mm. Image files were converted from interfile to analyze format using conversion software (Medcon, Erik Nolf, UZ Ghent).

Statistical analyses were conducted on a voxel-by-voxel basis using the Statistical Parametric Mapping (SPM99, Wellcome Department of Cognitive Neurology, UK)[26]. The realign function was used to co-register baseline and post-treatment SPECT images for each subject and to generate a mean image for each subject. Realigned images were then normalised to the Montreal Neurological Institute (MNI) standard anatomical space to a value of 50 using proportional scaling. For this the transform function from the mean image for each subject to the normalised image with 4mm³ voxels using 12 affine transformations and 7x8x7 non-linear basis functions was used. Standardised images were then smoothed using a Gaussian kernel with a FWHM of 12mm³.

A multi-group study design was performed using 2 groups (responders and non-responders) with 2 conditions each (pre- and post-treatment). Contrasts were applied to look for areas of significant change post-treatment compared to pre-treatment. Contrasts were also used to search for areas of relative change in treatment responders compared to non-responders. A second design was employed to compare the baseline scans of responders to SSRI pharmacotherapy

with those of non-responders. Contrasts were used to search for regions of significant differences on the baseline scans of responders compared to non-responders.

In view of *a priori* knowledge suggesting involvement of the cingulate, hippocampus, inferior frontal cortex, and striatum in the anxiety disorders, an uncorrected p-value of $p < 0.001$ corresponding to a t value of 3.34, was chosen for the analysis of these regions in order to minimize type I errors. Given the relative paucity of data in this area, we chose this uncorrected p-value, based on work using a similar methodology [19]. In order to minimize type I errors a significance level of $p < 0.05$ corrected for Gaussian Random Field Theory was used for the remainder of the brain. A spatial extent threshold of 5 voxels was also used at all times. Masking using a threshold proportional to 0.4 times the mean voxel value was used to minimize the analysis of voxels not located in grey matter. Furthermore, clusters were ignored if co-registration with a SPECT template demonstrated that they were located outside of grey matter.

4.4 Results

Twenty-two males and fifteen females with a mean age of 33.5 years (SD 9.8) completed the study. Clinical changes with pharmacotherapy for each disorder are provided in Table 4.1 This shows that for each of the anxiety disorders being studied, citalopram was effective in significantly reducing clinical measures of severity as determined by a CGI change score of 2 or less (much or very much improved). As such, 20 of 37 patients (54%) were responders to citalopram.

		Baseline	Endpoint	p
OCD (n=11)	YBOCS	26.6 ± 4.7	23.7 ± 5.8	0.001
	MADRS	13.64 ± 9.6	9.9 ± 6.4	0.119
	CGI-severity	4.7 ± 0.647	4.18 ± 1.1	0.025
	CGI-improvement		3.1 ± 0.7	
SAD (n=15)	LSAS	79.2 ± 30.2	63.1 ± 28.5	0.003
	MADRS	15 ± 4.9	9.1 ± 5.9	0.004
	CG -severity	4.6 ± 0.8	3.3 ± 1.1	0.001
	CGI-improvement		2.7± 1.2	
PTSD (n=11)	CAPS	78.1 ± 16.9	45.5 ± 23.9	<0.01
	MADRS	25 ± 6.7	15.9 ± 8.0	<0.01
	CGI -severity	4.5 ± 0.5	2.5 ± 0.7	<0.01
	CGI-improvement		1.9 ± 0.7	

Table 4.1: Clinical parameters for all the groups (mean ± SD), (paired t-test)

Legend: YBOCS, Yale Brow Obsessive-compulsive scale; MADRS, Montgomery Asberg Depression Rating scale; CGI-s, Clinical global impressions severity; CGI-I, Clinical global impressions – improvement; LSAS, Liebowitz Social Anxiety Scale; CAPS, Clinician Administered PTSD scale.

Comparison of pre- and post-treatment scans for the whole group showed decreased activity in 4 significant clusters in grey matter (Figure 6.1): These included the superior cingulate, right thalamus, anterior cingulate, and the left hippocampus (Table 6.2). Comparison of pre- and post-medication scans showed no significant areas of activation.

Cluster size (voxels)	t	MNI co-ordinates (x,y,z)	Brain region
44	4.78	-4,12,36	Superior cingulate
19	4.66	24,-28,12	Right thalamus
10	4.04	0,48,8	Anterior cingulate
7	3.96	-24,-12,-20	Left hippocampus

Table 4.2: Localisation of significant clusters of deactivation following treatment for the combined group of OCD,SAD, PTSD. Z_{max} set to threshold of $t=3.34$ corresponding to $p<0.001$

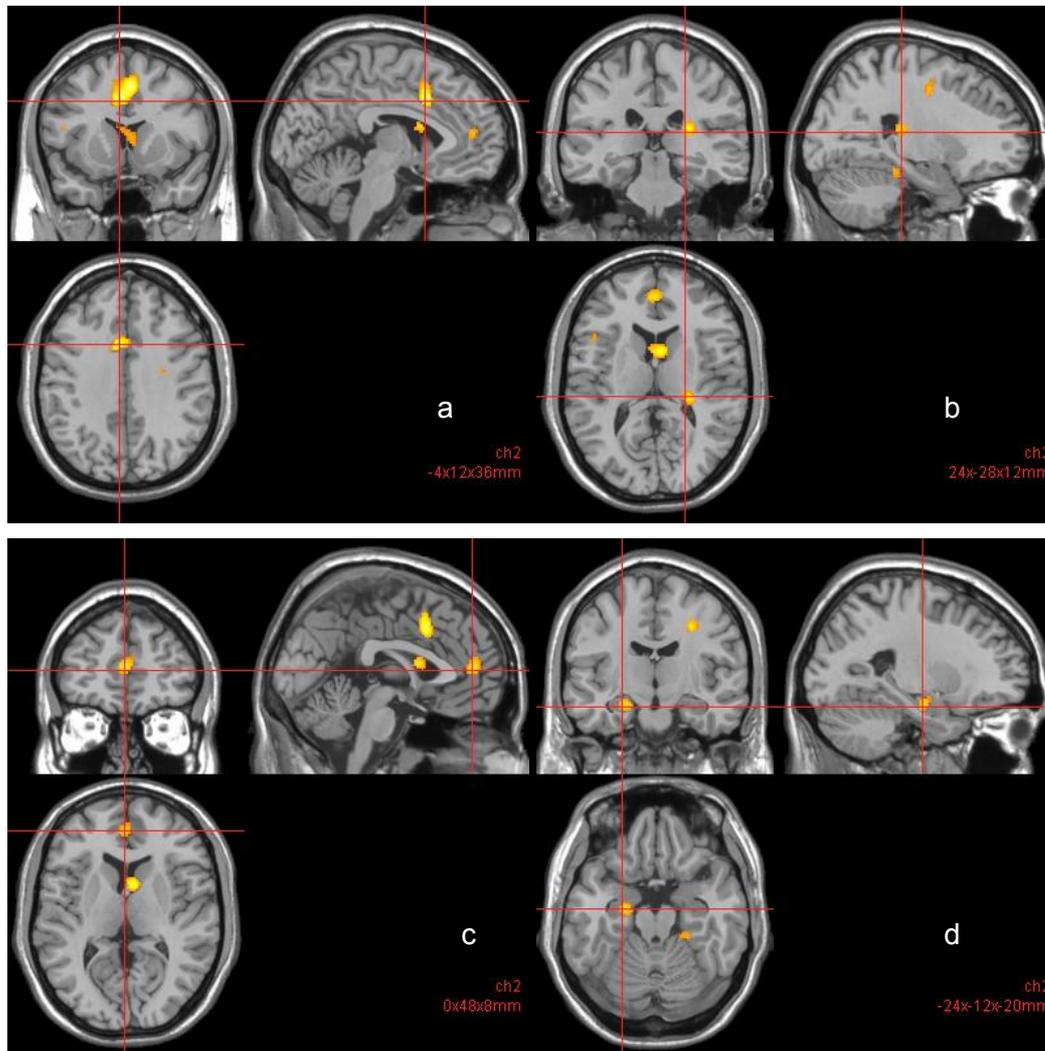


Figure 4.1: Regions of deactivation for the combined group of OCD + SAD + PTSD following treatment with citalopram. Significant grey matter clusters are seen in the left superior cingulate (a), right thalamus (b), anterior cingulate (c), left medial temporal region (hippocampus) (d).

Cluster size (voxels)	t	MNI co-ordinates (x,y,z)	Brain region
21	4.26	-24,-20,56	Left precentral
33	4.03	12,64,-8	Right mid-frontal
17	3.99	36,32,-20	Right inferior frontal cortex
5	3.85	8,-48,16	Left prefrontal
18	3.81	28,60,-8	Right precuneus

Table 4.3: Clusters in which responders had significantly lower perfusion following treatment

Comparison of responders with non-responders demonstrated that responders had a significantly greater decrease of activity in 4 clusters (Figure 4.2). These clusters were localised to the left precentral, right middle frontal, right inferior frontal and, left prefrontal and right precuneus regions (Table 4.3). Comparison of baseline scans of responders and non-responders did not reveal any significant differences.

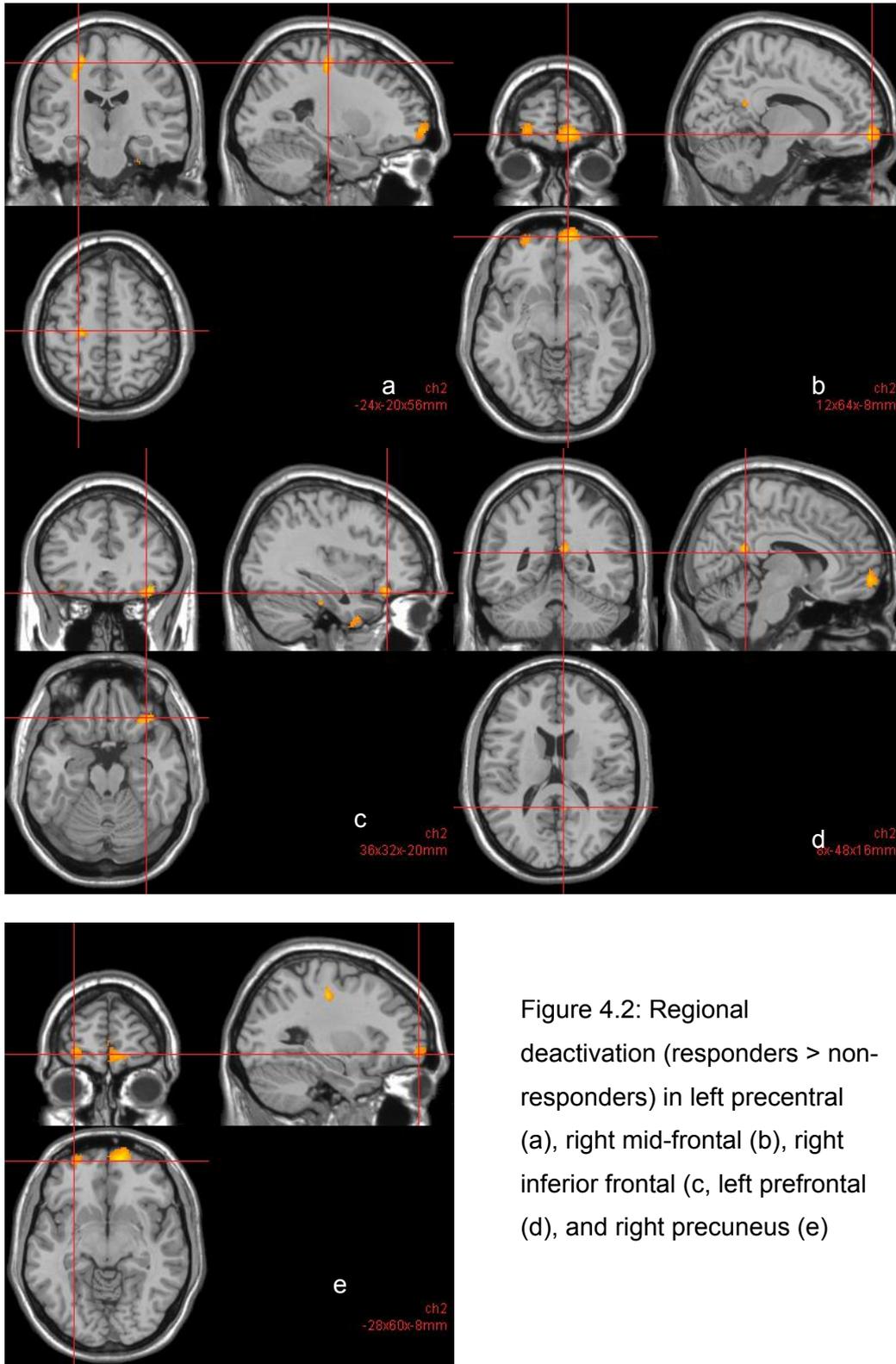


Figure 4.2: Regional deactivation (responders > non-responders) in left precentral (a), right mid-frontal (b), right inferior frontal (c), left prefrontal (d), and right precuneus (e)

4.5 Discussion

The main finding in this study is that citalopram pharmacotherapy resulted in significant deactivation within anterior and superior cingulate cortex, the left hippocampus and the right thalamus in a combined group of patients with different anxiety disorders (OCD, PTSD, and SAD). Furthermore, deactivation was significantly more apparent in responders than in non-responders to SSRI treatment within precentral, right inferior, middle frontal and left prefrontal regions. Interestingly, no pre-treatment differences in regional perfusion between subsequent treatment responders vs non-responders were found.

Although there are important differences in the symptomatology of the anxiety disorders, these conditions do share certain aspects of their phenomenology, including heightened anxiety and avoidance behaviour. Furthermore, previous functional brain imaging work has demonstrated overlapping neurocircuitry across different anxiety disorders with activation of paralimbic circuitry and right inferior frontal cortex in a combined group comprising subjects with OCD, PTSD, and specific phobia [1]. Results in the present study now also point to an overlap in the functional neuroanatomy, primarily implicating paralimbic neurocircuitry, in treatment response to the same SSRI, citalopram, across anxiety disorders. In citalopram responders, effects across disorders were most pronounced in the mid, inferior and prefrontal cortex. In other regions, such as the striatum, data on treatment response and symptom provocation seems to indicate less overlap across anxiety disorders, which may suggest only partial and regionally specific overlap between disorders [1,2].

Specific limbic regions are well-known to play a role in broadly mediating anxiety. Early observations of epileptogenic cingulate lesions support its role in regulating affect [27]. Furthermore, recent work has suggested a role for the anterior cingulate in integrating cognitive and motivational processes. These include evaluating environmental cues and monitoring performance [28]. On the other hand, a central role for the hippocampus in contextual aspects of fear conditioning has been demonstrated [29,30].

The findings here complement previous studies of OCD, PTSD, and SAD that have demonstrated a specific role for the cingulate and hippocampus in these conditions. Studies in OCD have shown increased anterior cingulate activity at baseline, or deactivation during pharmacotherapy with serotonergic agents [31]. In PTSD, anterior cingulate activity is also increased in some, although not all, studies of PTSD [32,33]. Further, the anterior cingulate is deactivated during citalopram treatment of SAD patients [17]. Dysfunction of the hippocampus, as indicated by smaller hippocampal volume and declarative memory deficits, may play an important role in PTSD [34].

The medial prefrontal cortex comprises several related areas including anterior cingulate cortex. Lesions of this area are associated with suboptimal responses to stress, and the area has important inhibitory inputs to the amygdala which mediate extinction of fear conditioning [29]. The middle and inferior frontal cortex, on the other hand, is involved in encoding and retrieval of verbal memories. Our finding that the right inferior frontal cortex was more deactivated in responders is perhaps consistent with previous findings showing increased activity pre-treatment in this region across different anxiety disorders [2] and in some, but not all, studies of PTSD [35].

Serotonergic circuits innervate the medial prefrontal cortex and other limbic structures, and chronic administration of a serotonin reuptake inhibitor may lead to an increase in their neurotransmission. It is possible that the medial prefrontal cortex deactivation during serotonergic pharmacotherapy indicates that a compensatory increase of activity in this region is no longer needed after symptom improvement. Along these lines, a number of functional and electrophysiological imaging studies of depression have found that anterior cingulate hyperactivity predicts a positive response to pharmacotherapy, a finding that has also been interpreted as indicating the baseline presence of an adaptive compensatory response [36]. In addition changes in cognitive processing of frontal cortex may be secondary to symptom reduction caused by primary drug-induced changes within the limbic system. We have previously demonstrated similarly higher pre-treatment prefrontal perfusion in subsequent responders relative to non-responders using inositol in OCD [37]. Interestingly, inositol responsive disorders overlap with those responsive to SSRI's which may suggest that it is serotonergic components of

these disorders that account for at least some of the overlap in perfusion patterns demonstrated here.

In contrast, however, increased activity in anterior cingulate or orbitofrontal region in OCD has also been shown to predict a poorer response to pharmacotherapy [9]. Perhaps increased activity in particular limbic circuits plays a different functional role in different psychiatric disorders. Only limited functional imaging studies of pharmacotherapy effects have involved provocation paradigms [38] and such differences in design may account for certain inconsistencies across studies. Alternatively, it is feasible that different effects in different disorders may also help explain inconsistencies. In the current dataset, however, we were unable to demonstrate any associations between baseline activity and pharmacotherapy response for the combined group.

This study is limited by the slightly different inclusion criteria (inclusion of secondary depression in PTSD group) and pharmacotherapy duration for different disorders. While the absence of untreated controls may to some extent limit the conclusions we can draw, comparing non-responders to responders we believe serves as a reasonable evaluation of changes that result from treatment response. The lower spatial resolution of SPECT may be considered a limitation nevertheless this study usefully emphasizes the importance of limbic regions (amygdala, hippocampus) in mediating anxiety. Furthermore, deactivation within these regions as well as richly connected frontal regions following SSRI treatment, particularly in responders, is clearly demonstrated. Further research combining pharmacological interventions and functional methodologies, and using tracers tailored to specific neurotransmitter receptors, will undoubtedly lead to increased understanding of the pathogenesis of the anxiety disorders and the mechanisms of response to treatment in the future.

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CHAPTER 5

Functional brain perfusion measured with single photon emission computed tomography (SPECT) in obsessive compulsive disorder: Changes in response to treatment with Inositol

5.1 Abstract

Background

Inositol, a glucose isomer and second messenger precursor, regulates numerous cellular functions and has demonstrated efficacy in obsessive-compulsive disorder (OCD) through mechanisms that remain unclear. The effect of inositol treatment on brain function in OCD has not been studied to date.

Methods

Fourteen OCD subjects underwent single photon emission computed tomography (SPECT) with Tc-99m HMPAO before and after 12 weeks of treatment with inositol. Whole brain voxel-wise SPM was used to assess differences in perfusion between responders and non-responders before and after treatment as well as the effect of treatment for the group as a whole.

Results

There was; 1) deactivation in OCD responders relative to non-responders following treatment with inositol in the left superior temporal gyrus, middle frontal gyrus and precuneus and the right paramedian post-central gyrus, 2) no significant regions of deactivation for the group as a whole post treatment, and 3) a single cluster of higher perfusion in the left medial prefrontal region in responders compared to non-responders at baseline. Significant reductions in the YBOCS and CGI – severity scores followed treatment.

Conclusions

These data are only partly consistent with previous functional imaging work on OCD. They may support the idea that inositol effects a clinical response through alternate neuronal circuitry to the SSRI's and may complement animal work proposing an overlapping but distinct mechanism of action.

5.2 Introduction

Selective serotonin re-uptake inhibitors (SSRI's) are currently accepted first-line therapies for obsessive compulsive disorder (OCD) [1,2]. However 40-50% of patients fail to respond to a first trial of an SSRI [3]. There is therefore strong interest in developing novel pharmacological approaches. Inositol, a single isomer of glucose has proved effective in treating obsessive-compulsive disorder (OCD) [4] panic disorder [5,6] and depression [7] in small controlled studies. Inositol was, however, found to be ineffective as an augmentation strategy to SSRI non-responsive OCD [8,9]. In addition, disorders such as premenstrual dysphoric disorder [10], schizophrenia [11], autism [12], Alzheimer's disease [13] and attention deficit hyperactivity disorder (ADHD) [14] have not responded to inositol.

The mechanism of action of inositol remains an interesting question. Previous work suggests that the efficacy of inositol is limited to the most SSRI responsive disorders [15] with medium to high effect size (ES) of 0.73 [15]. Similarly, effect size for inositol (0.97) in OCD seems to indicate at least comparable efficacy to SSRI's (0.69-0.35) [3]. The selective responsivity of OCD to serotonergic compounds makes it a useful exemplar for examining the mechanisms of action of inositol. Perhaps a common mechanism is able to account for the efficacy of both SSRI's and inositol in this disorder, and may shed more light on the sub-cellular neurobiology of the disorder.

Myo-inositol (MI) serves as a precursor to receptor-activated phosphatidyl inositolbisphosphate (PIP_2) hydrolysis by phospholipase-C (PLC) [16] that produces inositol triphosphate (IP_3) and diacylglycerol (DAG). Monoamine ligands for postsynaptic receptors, including serotonin, couple with G-proteins and trigger post-synaptic signal transduction pathways through activation and synthesis of the second messenger, IP_3 . While this may suggest some overlap in functioning of treatments, animal work has demonstrated that phosphoinositides (PI) are also involved in regulating the interaction of signalling proteins [17], neurotransmitters and membrane receptors [16] some of which suggests a contribution from other mechanisms to the action of inositol.

The cortico-striatal-thalamo-cortical (CSTC) functional neuro-circuit is believed to be central to the cerebral changes that characterise OCD . Hyperactivity within this circuit is attenuated following administration of SSRI's [18-20]. The use of inositol as a treatment strategy in OCD is novel in that most other precursor strategies have employed neurotransmitters as precursors. The question arises as to whether the clinical efficacy of inositol is reflected in similar patterns of attenuation of activation that have been demonstrated with SSRI's.

We report on a single photon emission computed tomography (SPECT) study undertaken to examine the effects of inositol treatment on regional cerebral perfusion before and after treatment in subjects with OCD. We hypothesised that: 1) attenuation of activation on SPECT in responders would differentiate them from non-responders following 12 weeks of treatment with inositol, 2) that attenuation of activation from baseline to endpoint would be most pronounced within the CSTC functional circuitry known to mediate OCD, 3) lower activation pre-treatment of the orbito-frontal cortex would predict poorer treatment response.

5.3 Methods

Subjects

Fourteen patients (7 male, 7 female) were recruited from the outpatient clinic of our research unit which is attached to a tertiary referral hospital. The diagnosis of OCD was made using the Structured Clinical Interview for DSM IV (SCID-I) [21]. Subjects were excluded if they met criteria for alcohol/substance abuse/dependence currently or in the six months preceding the study. One subject had a single previous depressive episode and another subject had a recurrent major depressive disorder, neither subject was depressed when the study started. All subjects were treatment free having completed adequate washout periods for psychotropic medications prior to commencing inositol. Subjects were required to provide written informed consent prior to the commencement of any study related procedures. The study protocol was approved by the Pharmaceutical Advisory Committee of the University of Stellenbosch Institutional Review Board (IRB) (Cape Town, South Africa).

Treatment and measures

Inositol was administered to subjects as a powder dissolved in water or tea in a fixed dose of 18 grams per day in three divided doses for twelve weeks. Subjects were assessed at two weekly intervals for efficacy, safety and tolerability. Clinical measures were performed at two weekly intervals for the duration of the study and included the Yale-Brown-Obsessive-Compulsive Scale (YBOCS) [22,23], the Montgomery-Asberg Depression Rating Scale (MADRS) [24] and the Clinical Global Impression Scale - severity and improvement (CGI) [25]. The Y-BOCS was used as the primary outcome measure with treatment response defined as a 50% or greater decrease in the YBOCS. Adverse events were also documented at the 2-weekly study visits.

SPECT Acquisition

Prior to administering the radiopharmaceutical an intravenous cannula was placed in an arm vein and a solution containing 200mg of sodium perchlorate was administered orally to minimise uptake of free pertechnetate by the salivary glands. Subjects then remained supine with their eyes open in a quiet, dimly lit room for 30 minutes. At this point 555MBq (15mCi) of technetium-99m hexamethylpropylene amine oxime (Tc-99m HMPAO) was injected via the indwelling cannula. Subjects remained basal for a further 10-minute period post-injection. SPECT images of the brain were acquired with the subject's head supported by a headrest and bandage using a dual detector gamma camera (Elscint Helix, General Electric Medical Systems, USA) equipped with fanbeam collimators. Acquisition of data was done in step-and-shoot mode using a 360 degree circular orbit with the detectors of the gamma camera as close as possible to the subject's head. Data was acquired using a 128 by 128 matrix with 3 degree steps of 15 seconds per step. For quality control raw images were inspected using a cine display to ensure that no subject movement had occurred. If patient movement was noted, the imaging was repeated. The height of the imaging table and radius of rotation were noted for each subject and also used for the post-treatment SPECT study.

SPECT reconstruction

Data was reconstructed by filtered backprojection, using an Xpert workstation (General Electric Medical Systems, USA). A Metz filter (power=5,

FWHM=14mm) and a zoom factor of 2.29 were used. The image reconstruction matrix was 64 by 64. The Chang method [26] was used for attenuation correction. The final reconstructed pixel size was 3.87mm². Reconstructed images were converted from interfile to ANALYZE format using Medcon (Erik Nolf, UZ Ghent, Belgium).

SPECT Pre-processing

Spatial pre-processing and statistical analysis of the images was performed using Statistical Parametric Mapping (SPM99, Wellcome Department of Cognitive Neurology, UK) [27]. The realign function was used to co-register the baseline and post therapy SPECT images for each patient. A single mean image was then created from these two realigned images for each patient. All of the SPECT scans were normalised to a standard brain of the Montreal Neurological Institute, using the ICBM152 template. Due to its improved statistical quality, the mean image of each patient was first normalised to the standard space. Transformation was performed to 4mm³ voxels using 12 affine transformations and 7x8x7 non-linear basis functions. The normalised SPECT images were then smoothed using a Gaussian kernel with a FWHM of 12mm³. The intensity of all SPECT scans was scaled to a global value of 50. An analysis threshold of 0.8 was used.

Statistical analysis

Paired t-tests were used to define the mean change scores for the clinical measures. Responders were defined using a conservative YBOCS change score of greater than or equal to 50% reduction from baseline. Two study designs were utilised. The first with two groups (treatment responders and non-responders) and two conditions (baseline and post therapy) used contrasts to search for regions of deactivation post therapy across all subjects, and to search for regions of deactivation that was more marked in treatment responders compared to non-responders. The second design compared the baseline perfusion of treatment responders to that of non-responders using an unpaired t-test. Only clusters achieving an uncorrected height threshold of $p < 0.001$ and an extent threshold of at least 5 voxels are discussed.

5.4 Results

Fourteen subjects with a mean age of 32.4 years (SD 12.3), mean age of onset of OCD symptoms of 17.3 years (SD 9.3), and mean illness duration of 14.6 years (SD 12.6) completed the study. The lag time to initial treatment was long (mean 10.1 years, SD 12.9). Five patients (35%) in the sample reported having had at least one previous trial with an SSRI.

Clinical measures

Inositol treatment over twelve weeks yielded a response (YBOCS \leq 50% of baseline score) in 8/14 (57%) of subjects. The overall reduction in the YBOCS score for the group as a whole was significant (paired t-test $t=5.75$, $p<0.0001$). Similarly the CGI-severity scores were significantly different between baseline and endpoint ($t=6.27$, $p<0.0001$) (Table 5.1). Notably no significant differences were found between responders and non-responders with respect to current age, duration of illness, gender, lag time to treatment initiation, and previous history of treatment. Furthermore no significant differences in clinical measures of illness severity (YBOCS, CGI) were noted between responders and non-responders at baseline.

Clinical measure	Mean score	t (two-tailed)(p value)
YBOCS (Week 0)	24.5	5.75 (p<0.0001)
YBOCS (Week 12)	13.78	
MADRS (Week 1)	12.42	3.95 (p<0.001)
MADRS (Week 12)	4.5	
CGI – severity (Week 1)	4.35	2.785 (p<0.0001)
CGI – severity (Week 12)	2.78	

Table 5.1: Clinical measures for group as a whole

SPECT Imaging

In our first design a comparison of baseline and post-treatment SPECT scans for the group as a whole demonstrated no statistically significant deactivation. Responders however demonstrated significantly greater deactivation in a number of clusters compared to non-responders (Fig 5.1). These include primarily the left antero-lateral temporal cortex (x=-40, y=12,z=-32), two clusters in the antero-lateral prefrontal cortex on the left side (x=-36, y=60,z=8 and x=-24, y=40,z=36) and finally two small clusters in the left superior parietal region (x=40, y=-20,z=52) and left paramedian occipital cortex (x=-4, y=-60,z=32) (Table 5.2)

Cluster size (voxels)	Z _{max}	MNI co-ordinates (x,y,z)	Brodmann Area	Brain Region
25	4.40	-24, 40, 36	9	Left antero-lateral
5	3.55	-36, 60, 8	10	prefrontal cortex (middle frontal gyrus)
11	4.30	-40, 12,-32	38	Left superior temporal gyrus
6	3.65	-4,-60,32	7	Left Parietal (precuneus)
5	3.52	40,-20,52	3	Right post-central gyrus

Table 5.2: Localisation of significant clusters for deactivation in responders > than non-responders after treatment

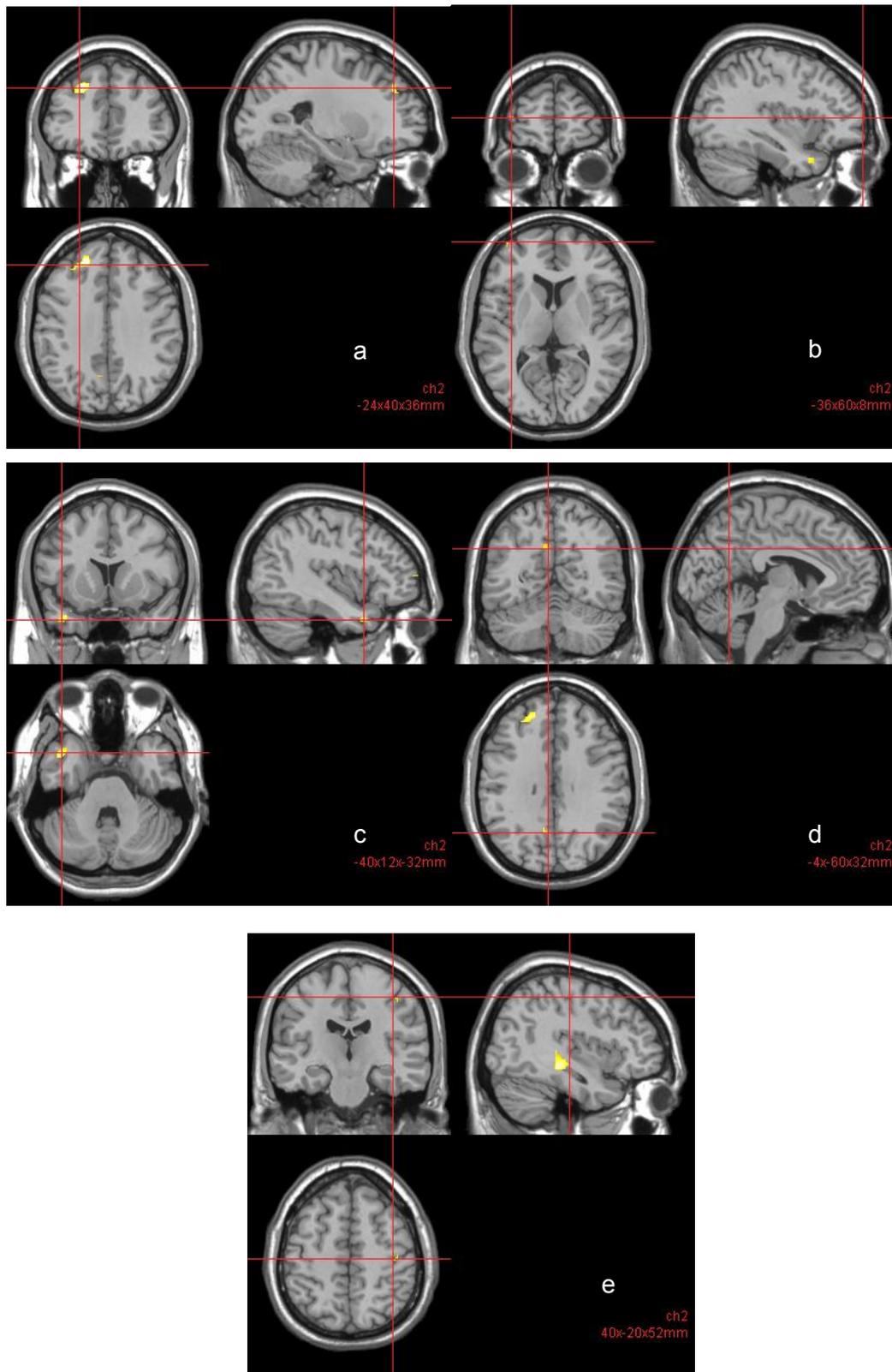


Figure 5.1: Areas of deactivation in responders compared to non-responders. Clusters of significance are noted in the left antero-lateral temporal cortex (a), antero-lateral prefrontal cortex (mid-frontal gyrus) (b), left superior temporal region (c), left parietal (precuneus), and right post-central gyrus (e)

In our second design, responders demonstrated significantly greater baseline activity in the left anterior frontal cortex (superior frontal gyrus) ($x=8$, $y=44$, $z=48$, Z_{\max} , 3.67) (Figure 5.2).



Figure 5.2: Baseline perfusion showing significantly greater perfusion in the left anterior superior frontal gyrus region for responders compared to non-responders

Safety and tolerability

Inositol was generally well tolerated. All patients enrolled completed the 12 week study. No serious adverse events were reported. Side-effects were generally mild and resolved within two weeks of initiation of treatment (Table 5.3).

Side-effect	N (%)
Diarrhoea	8 (57%)
Flatulence	5 (36%)
Bloating	4 (28.5%)
Nausea	3 (21%)
Abdominal cramps	2 (14%)
Fatigue/Lethargy	2 (14%)
Dizziness	2 (14%)
Headache	1 (7%)
Increased appetite	1 (7%)

Table 5.3: Side-effects reported for entire cohort

5.5 Discussion

In summary we report: 1) deactivation in OCD responders relative to non-responders following treatment with inositol in the left antero-lateral temporal cortex (superior temporal gyrus), antero-lateral prefrontal cortex (middle frontal gyrus), left superior parietal cortex (precuneus) and right paramedian post-central gyrus, 2) no significant regions of deactivation for the group as a whole post treatment, and 3) a single cluster of higher perfusion in the left medial prefrontal region in responders compared to non-responders at baseline. To our knowledge this is the first study to assess the effects of inositol treatment on brain perfusion SPECT in OCD and findings are preliminary, but interesting.

The cortico-striatal-thalamic cortical (CSTC) functional loop is now widely accepted to mediate the symptoms of OCD [18]. Within this loop regions most consistently activated at rest and accentuated on symptom provocation, include the orbitofrontal cortex, anterior cingulate cortex and the sub-cortical caudate nucleus. In addition attenuation of activation in similar regions follows effective treatment with fluoxetine [28], clomipramine [29], paroxetine [30], and behaviour therapy [31,32]. This suggests that response specific patterns are likely in disorders irrespective of treatment type.

We hypothesised that inositol would be similar to SSRI's in attenuating activation in regions specific to OCD incorporating the CSTC circuit. The apparent deactivation in the anterior dorsolateral prefrontal cortex (middle frontal gyrus) and the antero-lateral temporal cortex (superior temporal gyrus) in treatment responders, may, however, suggest that inositol has a different mechanism of action and ultimately affect different neuronal circuits to SSRI's in effecting a clinical response in OCD.

The findings are not completely inconsistent with previous work. The frontal cortex has been associated with OCD [33] and more recently implicated in mediating specific symptom dimensions [34] and neuropsychological dysfunction [35]. In addition a recent study using MR spectroscopy [36] in children with OCD found evidence for N-acetyl-aspartate increases in the DLPFC of subjects,

suggesting neuronal hypertrophy/hyperplasia possibly indicative of abnormal development and or neuronal pruning in children with OCD. Similarly the temporal lobe has previously been implicated in OCD [37,38]. Furthermore, animal work has shown that temporal structures play an important role in anxiety, and that inositol is anxiolytic [39]. The precuneus of the parietal lobe, in which our data demonstrates attenuation of regional perfusion following treatment response, has also been implicated in OCD with regional activation appearing to correlate with symptom severity [35,40] .

Demand for inositol and substrates amenable to its effects are widespread in the brain. Our data demonstrate a pattern of brain perfusion following a clinical response to inositol that is different from that of SSRI's and apparently links regions that have been previously implicated in OCD. As such it is conceivable that specific neuronal circuitry may mediate the clinical response to inositol that incorporates the prefrontal cortex, the superior temporal, gyrus and the precuneus of the parietal lobe. Furthermore, our data found no significant effect of treatment alone on brain perfusion SPECT for the group as a whole.

The current data demonstrate a small cluster in the anterior medial prefrontal cortex with significantly higher perfusion pre-treatment correlating with subsequent treatment response in OCD. Saxena et al [41] recently demonstrated disorder related changes in activation in response to SSRI treatment. Relationships have been found between pre-treatment regional brain activation and subsequent response to SSRI's ([42] 2002) and behaviour therapy [43]. However, the direction and localisation of the change is neither consistent between studies nor treatment types within the same disorder. This may lend support to the idea that the neuronal circuitry involved in response may differ between treatments. In this regard, we have recently found that inositol acts by decreasing the receptor signaling capacity through G proteins, and is thus able to modify serotonergic 5HT_{2a} and muscarinic receptor signaling ([44]. Since cholinergic dysfunction has been described in anxiety states [45,46], this may represent a novel site of action for inositol. Moreover, that this property was shared by fluoxetine, but not imipramine, possibly explains why inositol is effective exclusively in SSRI sensitive disorders. Further exploration of the value of functional brain imaging to predict response to treatment

is necessary and may in future allow tailoring of treatment options to particular patients.

Our present study may have been limited by the high (10.72 or 44%, $p < 0.0001$) mean change in YBOCS score for the whole group coupled with the small sample size to reduce the power to detect additional group differences. Furthermore the inclusion of a control group treated with an SSRI would have served to strengthen the debate on the differential effects of disparate, but effective treatment options in OCD [43].

5.6 Conclusions

We have demonstrated reduced brain SPECT perfusion in the prefrontal cortex, the temporal lobe, and the parietal cortex correlating with clinical response to inositol. Furthermore, higher medial prefrontal activation correlated with subsequent treatment response. While this data implicate less well studied regions in OCD, all have been previously implicated in the disorder. As such this data may support the idea that inositol effects a clinical response through different neuronal circuitry to the SSRI's and may complement animal work that suggests an overlapping but distinct mechanism of action. Despite a number of small controlled studies supporting the clinical utility of inositol, it deserves further evaluation.

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PART II

CHAPTER 6

Treatment effects of combined dopamine and serotonin receptor blockade in obsessive-compulsive disorder

6.1 ABSTRACT

Background

Although serotonin reuptake inhibitors are effective in the treatment of OCD, many patients fail to respond to these agents. Growing evidence from open-label and placebo-controlled trials suggests a role for augmentation of SRIs with atypical antipsychotics in OCD. Quetiapine is generally well tolerated and previous open-label data has produced mixed results in OCD and additional controlled data is needed.

Methods

We undertook a double-blind, randomised, parallel-group, flexible-dose, placebo-controlled study of quetiapine augmentation in subjects who had responded inadequately to open-label treatment with an SRI for 12 weeks. Following informed consent and screening, forty-two subjects were randomised to either placebo or quetiapine for six weeks.

Results

There was significant improvement from baseline to endpoint on the Yale-Brown Obsessive-Compulsive Scale in both the quetiapine and placebo groups (quetiapine, $n=20$, $p<0.0001$; placebo, $n=21$, $p=0.001$) with 40% ($n=8$) of quetiapine and 47.6% ($n=10$) of placebo treated subjects being classified as responders. Quetiapine did not demonstrate a significant benefit over placebo at the end of the six-week treatment period ($p=.636$). Similarly quetiapine failed to separate from placebo in the subgroup of subjects ($n=10$) with co-morbid tics. Quetiapine was generally well tolerated.

Conclusions

In this study, quetiapine augmentation was no more effective than placebo augmentation of SRIs. A number of limitations in study design make comparisons with previous studies in this area difficult and probably contributed to our negative findings. Future work in this important clinical area should address these limitations.

6.2 Background

Obsessive-compulsive disorder (OCD) is a prevalent, chronic and disabling disorder [1]. Controlled pharmacotherapy studies have established superiority of serotonin re-uptake inhibitors (SRI's) over noradrenaline reuptake inhibitors and over placebo in OCD and these currently form the cornerstone of pharmacotherapy management [2]. Despite the considerable advances made with the introduction of the SRI's into clinical practice, 40-60% of subjects still fail to respond adequately to initial therapy [3,4].

From this it is clear that a need exists to pursue more effective treatments for those with OCD who fail to respond or respond inadequately to SRI's. To this end, preliminary evidence supports a role for the addition of atypical antipsychotics to SRIs in OCD. These agents combine serotonin-dopamine antagonism with the advantage of being well tolerated including a low potential for inducing motor side-effects.

To date a number of open-label studies have suggested that augmenting SRI's with atypical antipsychotics is an effective strategy for treatment-refractory OCD. These include support for risperidone [5-7], olanzapine [8-13], and more recently amisulpride [14] and quetiapine [15-18]. A single open-label study using quetiapine as augmentation showed lack of effect in a small sample using low doses [19].

The outcome of the first controlled study in this area with the antipsychotic haloperidol demonstrated preferential benefit for refractory OCD subjects with co-morbid tic disorder [20]. In two subsequent studies the efficacy of risperidone in SRI refractory OCD has also been reported [21,22]. Interestingly the former study [21], did not replicate the particular advantage for subjects with co-morbid tic disorder. Efficacy has also been shown for quetiapine [23] and olanzapine [24] using similar designs, but the effects on co-morbid tic disorders were not reported. In contrast a recent controlled study using olanzapine failed to demonstrate efficacy over placebo in a six week study [25].

Despite some mixed evidence in this area, in general the available literature appears to support the use of relatively short trials with low doses of antipsychotic agents as augmentation to SRIs. Quetiapine has a particularly interesting profile in that it is the only available antipsychotic with significant 5-HT_{1D} effects and this serotonin receptor subtype has been implicated in OCD [26,27].

Our objective was to examine the effects of quetiapine augmentation in subjects with OCD who had failed to respond adequately to a 12 week trial of an SRI, employing a double-blind, placebo-controlled, six week study design.

6.3 METHODS

Patients

Forty two subjects aged 18-65 years inclusive were recruited in our multi-centre study comprising five sites in South Africa and one in Canada. Recruitment took place between May 2002 and November 2003. Prior to commencement, all sites in the study received approval from their relevant Research Ethics committees/Institutional review boards and regulatory authorities. All subjects provided written informed consent prior to the commencement of any study-related procedures. Diagnosis was confirmed using the MINI Neuropsychiatric Interview (Version 5.00, 1998) [28] to ensure compatibility with the Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition (DSM-IVTR)[29] criteria for OCD. Subjects with any co-existing Axis I disorder were excluded unless the co-morbid condition was deemed to be secondary to the OCD. Female subjects of childbearing potential were required to use adequate contraception and were not permitted to breastfeed while on the study. Subjects were excluded if they suffered from unstable medical conditions including renal or hepatic insufficiency, epilepsy or had suffered previous brain injury or undergone brain surgery. Taking medication that was deemed likely to interact with quetiapine or any other psychoactive substance was grounds for exclusion.

Study Design

All subjects were treated and monitored by investigators for the minimum twelve week duration of SRI-alone treatment phase before inclusion into this study. This was to ensure that patients met criteria for duration of SRI treatment which included at least 6 weeks on the maximum tolerated dose of the relevant SRI. Sample size calculations were based conservatively on similar work in this area [20,21]. Accordingly, for the primary outcome variable (YBOCS), clinically meaningful differences between treatment groups of 6.67 with a standard deviation (SD) of 6 would be detected with a power of 80% at a 5% significance level with a sample size of 14 in each of the treatment groups. The larger sample recruited reflects the anticipation of a 33% drop-out rate in the double-blind treatment phase.

A double-blind, randomised, parallel-group six-week augmentation with quetiapine or matching placebo of the SRI to which participants had not responded adequately, was undertaken. Specific SRI's, mean doses and dose range are provided in Table 1. Non-responsiveness to an SRI was defined as either an improvement score on the clinical global impression scale of minimally improved (3) or worse (4,5,6), or less than 25% reduction in Yale Brown Obsessive-compulsive score following twelve weeks of treatment. Inadequate response, as defined above, to at least one SRI administered for a minimum of 12 weeks of which 6 weeks was either at the maximum tolerated dose or alternatively the manufacturer's recommended maximum daily dose. SRI doses were maintained at the same level throughout the double-blind treatment phase. For assignment to either quetiapine or placebo groups, we used a computer generated randomization schedule supplied by the sponsoring pharmaceutical company which also packaged the medication. This procedure ensured blinded, balanced allocation to each treatment group across all the study sites. All investigators remained blind to this schedule until closure of the study. No incidents requiring investigators to break the blind occurred through the course of the study.

Treatment

At baseline participants were randomly allocated to receive treatment with either quetiapine or placebo using a computer generated schedule and numbered dispensing wallets. A flexible dosing schedule was initiated at 25mg per day for one week and then doubled weekly to the start of week 4. Based on Clinical Global

Impression of Improvement (CGI-I) scores of minimally improved or worse, clinicians were permitted to increase the dose to a maximum of 300mg per day for the final two weeks of the study. In addition to clinical measures of improvement, clinicians also considered patient tolerability in their decision to adjust doses. Following completion of the treatment phase, subjects were withdrawn from study medication while continuing their SRIs. All subjects were then followed up for any adverse effects.

Ratings

Patients were assessed by clinicians at baseline and on completion of weeks 2, 4 and 6. Telephonic assessments were performed on completion of weeks 1 and 3. Symptoms of obsessive-compulsive disorder were measured by the same clinician where possible at all study visits using the Yale Brown Obsessive Compulsive Scale (YBOCS) [30,31]. A global assessment of severity and improvement was made by clinicians at all assessment points using the Clinical Global Impressions scale of Severity (CGI-S) and Improvement (CGI-I) [32]. Depression was rated using the 10-item Montgomery-Asberg Depression rating scale (MADRS) [33]. For a measure of patient-rated disability we used the Sheehan Disability scale (SDS) [34]. For subjects with tics, frequency and severity were rated using the Yale Global Tic Severity Scale (YGTSS) [35].

Our primary outcome measures for OCD symptoms were (1) the change in YBOCS score from baseline to endpoint and (2) the clinical global impression of improvement (CGI-I) at endpoint. In the final analysis, treatment response was defined as a 25% or greater reduction in YBOCS score and a CGI-I of 1 (very much improved) or 2 (much improved) from baseline to endpoint. Secondary outcome measures included the MADRS, SDS and YGTSS (in subjects with co-morbid tics).

Statistical analysis

Thirty-nine of the forty-two randomised subjects successfully completed the six-week treatment phase. Two subjects withdrew from the study prematurely (Week 1 and Week 4) due to severe levels of sedation. In both of these cases at least one week of study medication had been taken and at least one post-baseline clinical assessment was completed. Both of these subjects were included in the final analysis using data from the last observation carried forward (LOCF). The single subject not included in the efficacy analysis completed the study, but was found not to have correctly fulfilled the study definition of treatment refractoriness and was excluded. Twenty subjects were allocated to the quetiapine arm and twenty-one to the placebo arm. Student's t-tests were used to determine any baseline differences in the groups for age, gender, number of previous trials of SSRI's, severity of symptoms in relation to OCD, depressive symptoms, and CGI-S. Analysis of variance was undertaken with group and tics as factors. All tests were two-tailed with p-values of less than 0.05 considered significant.

6.4 Results

Study sample characteristics

For the final analysis, our sample comprised 19 men and 22 women. Baseline characteristics of two treatment groups did not differ with respect to age (years) (quetiapine group 33.8(SD 9.66), placebo group 31.81 (SD 12.14); $p=0.57$), gender ($p=0.29$), number of previous adequate SRI trials (quetiapine 1.55 (SD 1), placebo 1.62 (SD 1.02) ($p=0.83$), baseline severity of OCD (CGI-severity, $p=0.47$; YBOCS, $p=0.33$), depressive symptoms ($p=0.91$), patient-rated disability ($p=0.28$) or the presence ($n=11$, $p=0.66$) and severity ($p=0.87$) of co-morbid tics.

Treatment outcomes

For the primary outcome measure of severity (YBOCS), quetiapine ($p<0.0001$) and placebo ($p=0.001$) augmentation of an SRI significantly improved symptoms of OCD. However quetiapine did not demonstrate significant benefit over placebo at the end of the six-week treatment period ($F=.19$; $p=.636$) (Figure 2.1).

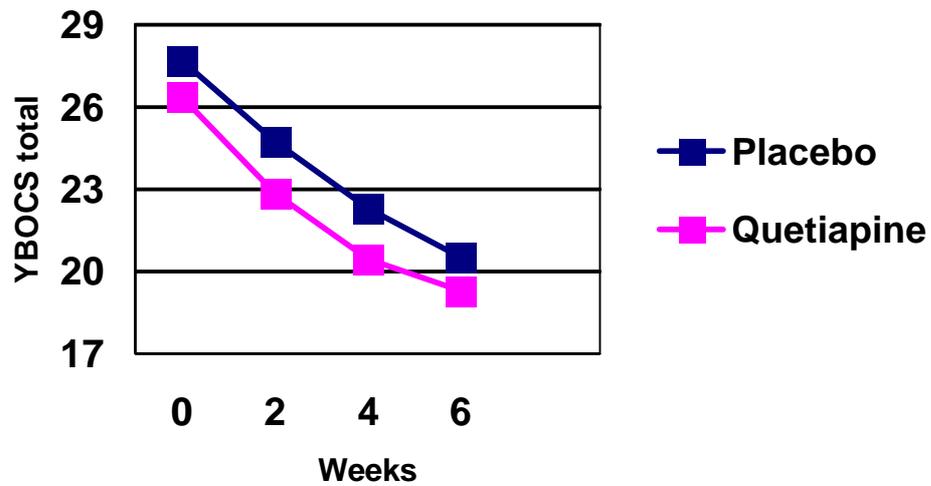


Figure 6.1 - YBOCS change for treatment groups

The mean reduction in YBOCS scores for the combined group was 7.15 points (quetiapine = 7.10; placebo 7.19). Forty percent (n=8/20) of subjects on quetiapine were classified as responders (YBOCS reduction of >25% from baseline and CGI-improvement score of 1 or 2) while 47.6% (n=10/21) of subjects on placebo were classified as responders. A higher number of previous SRI trials for the each treatment group did not correlate with the degree of change on the YBOCS or the response status. Table 6.1 provides details of individual subject SRI doses, baseline clinical severity ratings and response status. Table 6.2 provides a summary of baseline and change scores for each of the primary and secondary outcome variables.

Treatment Group		SRI baseline	SRI Dose baseline (mg/day)	Prev SRI trials	Total YBOCS Baseline	Total YBOCS Week 6	Endpoint dose (mg/day)	% CHANGE	CGI – Improvement	Response status
Quetiapine	1	Paroxetine	60	1	33	29	50	-12.00	3	N/R
	2	Citalopram	60	2	25	23	200	-8.00	4	N/R
	3	Fluvoxamine	300	1	32	27	300	-16.00	3	N/R
	4	Citalopram	70	1	27	25	25 (E/W)*	-7.00	4	N/R
	5	Clomipramine	250	2	22	27	100	23.00	5	N/R
	6	Paroxetine	60	5	35	32	300	-9.00	4	N/R
	7	Fluoxetine	80	3	25	16	300	-36.00	2	R
	8	Sertraline	200	1	18	3	50	-83.00	1	R
	9	Fluoxetine	20	1	21	20	300	-5.00	4	N/R
	10	Fluoxetine	60	1	22	17	300	-23.00	2	N/R
	11	Citalopram	60	1	32	17	300	-47.00	1	R
	12	Fluoxetine	80	1	32	14	300	-56.00	1	R
	13	Fluvoxamine	300	1	30	12	50	-60.00	1	R
	14	Fluoxetine	60	1	25	7	50	-72.00	1	R
	15	Citalopram	60	1	27	24	200	-11.00	4	N/R
	16	Fluvoxamine	300	1	24	12	150	-50.00	2	R
	17	Fluvoxamine	200	2	22	22	50	.00	4	N/R
	18	Fluvoxamine	300	2	25	22	25	-12.00	4	N/R
	19	Fluoxetine	60	2	24	25	25 (E/W)*	4.00	4	N/R
	20	Clomipramine	250	2	27	12	300	-56.00	2	R
Placebo	1	Fluvoxamine	300	2	32	25	300	-22.00	3	N/R
	2	Fluvoxamine	300	1	30	28	300	-7.00	3	N/R
	3	Fluoxetine	80	2	34	38	300	12.00	4	N/R
	4	Paroxetine	60	1	22	18	300	-18.00	1	N/R
	5	Citalopram	60	1	28	26	300	-7.00	4	N/R
	6	Fluoxetine	60	5	26	24	300	-8.00	3	N/R
	7	Fluoxetine	60	1	23	23	300	.00	4	N/R
	8	Fluoxetine	60	1	27	10	300	-63.00	1	R
	9	Fluoxetine	40	1	32	18	300	-44.00	2	R
	10	Citalopram	60	2	24	23	300	-4.00	4	N/R
	11	Citalopram	60	1	35	23	300	-34.00	2	R
	12	Fluvoxamine	300	3	22	14	300	-36.00	2	R
	13	Citalopram	60	1	28	10	50	-65.00	2	R
	14	Fluoxetine	60	1	28	4	50	-86.00	2	R
	15	Citalopram	60	1	26	19	100	-27.00	2	R
	16	Fluoxetine	60	1	27	12	100	-56.00	1	R
	17	Fluoxetine	20	1	26	18	200	-31.00	2	R
	18	Fluvoxamine	300	2	23	35	200	52.00	6	N/R
	19	Citalopram	60	2	26	9	100	-65.00	2	R
	20	Paroxetine	80	1	32	29	300	-9.00	3	N/R
	21	Fluvoxamine	300	3	31	25	100	-19.00	2	N/R

Table 6.1: Baseline characteristics of treatment groups

*E/W = Early withdrawal

	Quetiapine	Placebo
YBOCS (baseline)	26.4 (SD4.6)	27.7(SD3.9)
YBOCS (change at week 6)	-7.1(SD7.2)	-7.2(SD8.4)
YBOCS % change	-26.9%	-26%
CGI-Severity (baseline)	5.2 (SD0.8)	5.3 (SD0.8)
CGI-Severity (week 6)	4.1 (SD1.4)	4.1(SD1.5)
MADRS (baseline)	10.6 (SD 4.8)	10.71 (SD 9.8)
MADRS (change at week 6)	-2.6 (SD 6.5)	-3 (SD 8.3)
SDS (baseline)	17.9 (SD 5.3)	19.6(SD4.7)
SDS (change at week 6)	-5.3(SD5.6)	-6.1 (SD4.8)
YGTSS (baseline)	24.7 (SD 19.3)	22.6(SD 22.3)
YGTSS (change at week 6)	-4.5(SD 5.1)	-9.4 (SD 14.6)
YGTSS % change	-18.2%	-41.6%

Table 6.2 - Summary scores (baseline) and change scores for primary and secondary outcome variables.

Of the 11 subjects with co-morbid tics, six were randomised to quetiapine. Endpoint data was missing for one subject on quetiapine. Of the remaining 10 subjects, 3 (quetiapine n=2 (33%); placebo n=1(20%)) were classified as YBOCS responders. The reduction in the YGTSS did not differ significantly between treatment groups with tics (quetiapine -4.5, placebo -9.4; $F=2.8$, $p=.46$).

Severity ratings for depressive symptoms (MADRS) were low at baseline (mean 10.6, SD 4.8), showed little change over the study period, and at week 6 remained similar for both groups (quetiapine = 8.2, SD 4.8; placebo = 7.7, SD 6.1).

The mean daily dose at week 6 for the quetiapine group was 168.75mg (SD 120.82) compared to 228.57mg (SD 99.46) per day for those on placebo. Quetiapine responders (187.5mg, SD 124.6) did not differ significantly from quetiapine non-responders (156.25mg, SD 122.1) in their mean daily dose at Week 6 ($p=.585$). Furthermore, within the quetiapine group, participants receiving ≥ 200 mg/day (10/20 at week 6 demonstrated non-significant differences ($F=6.837$, $p=.988$) and a marginally lower percentage reduction in YBOCS at endpoint (26.7%, SD 20.34) compared to those receiving a dose ≤ 200 mg/day (26.9%, SD 36.24) at endpoint.

Tolerability

Quetiapine was generally well tolerated and no serious adverse events (SAE's) were reported through the course of the study period. Two patients on quetiapine withdrew from the study due to severe sedation (Week 1 and Week 4) that was judged to be drug related. Otherwise adverse events were in the mild to moderate range and were mostly self-limiting. No subjects on placebo withdrew from the study. Table 6.3 provides a list of the adverse events and their frequencies in the respective study groups.

Adverse event	Quetiapine (% , n)	Placebo (% , n)
Sedation	75% (15)	33.3%(7)
Dry mouth	15% (3)	0
Headache	15% (3)	38% (8)
Fatigue	15% (3)	19% (4)
Irritability	10% (2)	4.7% (1)
Impaired concentration	10% (2)	0
Dizziness	5% (1)	14.3% (3)
Nausea	5% (1)	9.5% (2)
Increased appetite	5% (1)	9.5% (2)
Delayed ejaculation	5% (1)	0
Weight gain	5% (1)	0
Worsening mood	5%(1)	4.7%(1)
Memory difficulties	5%(1)	0
Muscle aches	5%(1)	0
Abdominal tenderness	5%(1)	0
Slurred speech	5%(1)	0

Table 6.3: Percentage of subjects for each treatment group reporting adverse events

6.5 Discussion

Our findings indicate that both quetiapine and placebo significantly reduced symptoms in subjects with OCD who had failed to respond adequately to 12 weeks of an SSRI and, that the difference between groups was not significant. Similarly in the subgroup with co-morbid tics, no preferential benefit was noted for quetiapine. Interestingly, the high placebo response was similar to that seen in a recent failed controlled trial of olanzapine [25], but stands in contrast to the positive studies in this area in which low placebo response rates were seen when demonstrating efficacy of quetiapine [23], risperidone [21], and olanzapine [24]. It is likely that features of study design or specific study population characteristics may have contributed to this finding and these are discussed below.

First, the duration of a therapeutic trial of an SRI prior to augmentation with an antipsychotic should be of adequate dose and duration. In our study the majority of participants had failed only the single trial of an SRI on which they continued during the study (63.4% mean 1.59). Notably only six weeks of this treatment was required at the maximum tolerated dose. Despite the notion that an optimum trial of pharmacotherapy in OCD is 12 weeks, it may be argued that higher and ultimately effective doses of an SRI had not been maintained for an optimum duration prior to randomization. Given that therapeutic doses of SRIs in OCD are usually on the upper end of the dose range, it seems feasible that the high placebo response rate may reflect a response to SRI's once they had been administered at these higher doses for the additional six weeks of the study. It seems possible that the recent study by Shapira et al [25] may have been impacted by similar factors.

In a second and related point; the number of previous SRI trials in the subgroup receiving quetiapine did not predict a poorer response to treatment. This effect is probably related to the lack of statistical power to detect these differences in a group in which the low number of previous SRI trials was a distinguishing characteristic. Certainly, previous positive studies in this area have used relatively more refractory groups based on the number of previously failed SRI trials. Taken together with the first point above, we suggest that future work in this area should

consider longer periods at maximum tolerated doses of SRI's prior to categorisation of subjects as treatment refractory.

Third, the use of a slow up-titration resulted in a relatively low mean daily dose being administered for the majority of the study. For instance, a mean daily (week 6) dose of 168mg/day in the quetiapine group (median 175 mg) had only been achieved for the final two weeks of the study. These doses are comparably low to those used in the negative single-blind study using low dose quetiapine by Sevincok et al [19]. In contrast the positive study using quetiapine by Denys et al [23] employed a more rapid up-titration and a fixed-dose design. This meant that subjects were exposed to 200mg daily doses that were generally well tolerated, from the start of week 3. The authors of this study were able to show significant YBOCS differences between groups from the end of week 4. Similarly Mc Dougle et al [21], using risperidone, began treatment on 1mg per day for one week and permitted weekly 1mg incremental increases for 6 weeks. They found that by the beginning of week 2, most subjects were on or around the mean daily dose for treatment responders (2.2mg). Despite the significant improvement in the quetiapine group demonstrated in our study, the apparent lack of benefit of doses higher than 200mg per day may seem surprising, however, we cannot rule out the possibility that administering these higher doses for an adequate duration would have changed the outcome. In addition it must be noted that in our study the quetiapine group reported high rates of sedation (n=15, 75%) and a 10% (n=2) rate of premature withdrawal was experienced. As such it seems likely that a more aggressive up-titration schedule might have resulted in even higher rates of withdrawal. By comparison, rates of sedation were equally high, but did not appear to restrict use of the more rapid up-titration in the study by Denys et al [23]. Certainly evidence of efficacy using lower doses has been demonstrated in studies of 6 and 8 weeks duration [21,23,24], and it seems that therapeutically adequate doses should probably be reached earlier than week 4 in a 6 week study.

Fourth, the impact of repeated clinical assessments and rating of relatively small changes in clinical severity combined with regular dose increases, may conceivably have increased the placebo response rates resulting from increased optimism, a tendency to over-report improvements and belief that higher doses are more likely to be more effective than lower doses. This may be particularly true for

the placebo-treated group that were considerably less likely to report sedation as an adverse event and as such were more likely to have their treatment dose increased at each visit. Our results differ, with respect to placebo response, from a considerable literature that suggests a consistently lower placebo response rate in treatment trials in OCD than in other mood and anxiety disorders. While we believe that the reasons (1-3) discussed above probably provide the main reasons for our finding, the impact of repeated assessments and the potential effect thereof cannot be entirely discounted.

6.6 Conclusions

Despite significant improvement in each of the study groups, response to quetiapine augmentation in SRI non-responders, failed to separate from placebo treated subjects at the end of the six week treatment phase. A number of limitations in study design make comparisons with previous studies in this area difficult and probably contributed to our negative findings. Future work in this important clinical area should address these limitations.

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CHAPTER 7

Clinical and demographic determinants of response to treatment with combined dopamine and serotonin receptor blockade in obsessive-compulsive disorder.

7.1 Abstract

Background

Treatment response to serotonin re-uptake inhibitors (SRIs) in OCD remains unsatisfactory in a high proportion of patients. Recent meta-analyses have demonstrated a benefit for the addition of quetiapine to SRIs in treatment refractory obsessive-compulsive disorder (OCD). Numerous studies have investigated a range of clinical and demographic variables that may predict response to SRI treatment, but fewer data are available on the predictors of response in this context. We aimed to delineate predictors of response to quetiapine augmentation in refractory OCD.

Methods

Data for 80 subjects was combined from two previously published placebo-controlled augmentation studies. In both studies, quetiapine augmentation followed inadequate response to a minimum of 12 weeks SRI treatment. We combined data derived from the Yale-Brown Obsessive-Compulsive Scale (YBOCS) checklist with a variety of clinical and demographic variables previously shown to predict treatment outcome in OCD. We then derived a model to best predict treatment outcome using best-subset logistic regression. Clinical and demographic variables were measured against YBOCS change and YBOCS endpoint scores as dependent variables for outcome.

Results

In univariate analyses, a lower number of previous SRI treatment trials was associated with YBOCS response. In our model, 45% of the variance for better treatment response (YBOCS change) was explained by subjects having failed fewer previous SRI treatments, and having higher baseline obsession scores as well as ordering and arranging compulsions. In a separate analysis using YBOCS endpoint scores we found a lower number of previous SRI trials, higher baseline compulsion scores, counting/ordering and arranging compulsions together predicted 50% of the variance in treatment outcome.

Conclusions

Despite the relatively small sample size, the data here provide a number of preliminary predictors of clinical response to quetiapine augmentation of SRIs in treatment refractory OCD. These include fewer previously failed SRI trials and generally higher overall baseline scores for obsessions and compulsions as well as ordering, arranging, and counting compulsions. Together the predictive value of these data suggest that other as yet unidentified factors may also contribute to predicting treatment outcome to augmentation with antipsychotics in treatment refractory OCD.

7.2 Background

Obsessive-compulsive disorders are not only highly prevalent [1,2], but are considered one of the most disabling of all medical illnesses [3]. The introduction of compounds with selective serotonergic reuptake inhibition represented a major step forward in the treatment of obsessive-compulsive disorder (OCD), up to 40% of patients still fail to respond adequately to this first-line strategy [4,5]. A further sizeable proportion retain significant symptoms even after switching to alternative drug treatments [6,7]. The ensuing chronicity contributes to the disease burden of OCD so that patients and physicians perceive a need for more effective and better tolerated alternatives to the serotonin re-uptake inhibitors (SRIs).

To this end, the most widely used alternative in recent years has become adjunctive treatment with typical and atypical antipsychotics. The first evidence to support this treatment strategy was published by McDougle using haloperidol [8]. Since then the introduction of a range of the second generation antipsychotics, this class of drugs has been tested as augmentation to first-line treatments for refractory OCD in a number of studies.

Data from these controlled studies of antipsychotic augmentation of OCD have recently been combined in several separate meta-analyses and reviews. All consistently demonstrate an overall benefit for this strategy. Bloch et al [9], systematically reviewed data from all available controlled studies using a variety of antipsychotics. Using response criteria of a minimum 35% reduction in Yale Brown Obsessive-Compulsive Scale (YBOCS) [10,11], scores from baseline to endpoint, they found an overall positive, albeit small, effect with absolute risk difference of 0.22 (95% CI 0.13, 0.31). Consistent with the favourable effect noted by McDougle in his early study [8] for patients with tic disorders, an overall benefit for this strategy was also found. A specific benefit in those with tic disorders as well as schizotypal personality disorder was also highlighted in review by Keuneman et al [12]. Fineberg et al pooled data from three placebo-controlled studies [13-15] that used quetiapine to augment SRI therapy. Using less conservative criteria for treatment response (>25% reduction in YBOCS), they found a significant treatment effect in favour of quetiapine ($p=0.008$) with the clinical effect falling in the range of “only limited clinical benefit” on a forest plot of overall effect [16]. Ipser et al [17] in a recent Cochrane

analysis of antipsychotic augmentation across anxiety disorders, also demonstrated an overall benefit for this strategy, a result conferred largely through the contribution of controlled augmentation studies in OCD.

An initial response to the question of which patients respond best, Denys et al [18] found that lower doses of SRIs predicted a more robust response to quetiapine augmentation. This finding together with the meta-analytical data mentioned above is interesting and responsive to the need for evidence-based alternatives in OCD pharmacotherapy. As yet, however, there is very little indication as to which refractory patients are likely to derive the most benefit from these interventions.

In the context of SRI monotherapy for OCD, an extensive literature now exists in which clinical and demographic variables have been combined in a variety of ways to derive a series of clinical predictors of treatment outcome [19-27]. In these studies a wide range of dimensional symptom factors have been shown to be predictive of poorer response to treatment. These include hoarding [25,27] symmetry and hoarding [21], cleaning [26,28], somatic obsessions [23], and sexual/religious obsessions [26]. Clinical symptom predictors of better response to SRIs have included checking compulsions [29], and overall greater severity of obsessions [30].

With respect to other descriptive variables in the context of SRI treatment, fewer previous courses of SRIs [30], female gender [29,31], later life onset [19], co-morbid depression [32,33] and, higher YBOCS sub-scores [20,34] have been associated with better treatment outcome. In one of the few studies to develop a model for predicting treatment outcome, Denys et al [35] used key findings from the literature cited above to guide the choice of variables they entered into a multivariate regression in a double-blind placebo-controlled study of venlafaxine and paroxetine [36]. They found that YBOCS scores <23, HAM-D depression ratings >6, and fewer than two previous treatments for OCD predicted treatment response with an ROC-area of 0.71. This represents a reasonable discriminative capacity of this simple three-variable model.

In the present study we pool data for 80 subjects from two previously published studies which used a similar design. We used available clinical and

demographic variables to derive a model that together provides the highest power to predict treatment outcome for augmentation of SRIs with atypical antipsychotics in refractory OCD.

7.3 Methods

Data from two studies using a double-blind placebo-controlled, parallel group, flexible dose, augmentation with quetiapine of continued selective serotonin re-uptake inhibitors (SRIs) [14,15] was pooled. In the study by Denys et al participants had to have failed at least two adequate (12 week) trials of an SRI [15]. Efficacy for quetiapine over placebo augmentation in a sample of 40 patients was shown from as early as the 4th week of double-blind treatment. Mean YBOCS improvements of 32% from baseline compared to 6.8% improvement on placebo were seen at the week 8 treatment endpoint. In the second study reported in Chapter 6 of this thesis [14], we studied a sample of 42 subjects who had responded inadequately to a minimum of 12 weeks of SRI treatment of which six weeks needed to be at maximum tolerated doses. We found quetiapine (YBOCS reduction of 26.9%) and placebo (YBOCS reduction 26%) groups improved significantly, but not significantly differently over the 6 week treatment period.

Here we use data derived from the YBOCS symptom checklist [10,11] to define the primacy and presence or not of each of the symptom domains. Scores were assigned as follows: “1” for being present and “0” for being absent. Further to this, study participants were asked to specify for each of the broad domains of obsessions and compulsions which of the symptom domains was primary or most prominent. For symptom domains in this category, a score of 2 was assigned. The result is a description of the main obsession and compulsion symptom dimensions in OCD, with scores for their presence and primacy now presented in a semi-ordinal fashion for use in subsequent analyses [37].

Clinical symptom dimensions included contamination, sexual, hoarding, religious, symmetry, and somatic obsessions and cleaning/washing, checking, repeating/ritual, counting, ordering/arranging, hoarding, and mental compulsions. These were combined with a range of previously identified clinical and demographic

variables including age, gender, previous number of failed SRI trials, YBOCS obsession and compulsion scores separately and together at baseline, and the presence of tics. Despite previous indications that higher depression scores may predict response to SRIs in OCD, the data sets combined in this study used different measures of depression (HAM-D and MADRS), making direct comparison difficult.

In the first instance all variables were employed in univariate chi-square analyses with YBOCS responder status (>25% reduction in YBOCS), as the dependent variable. Two multivariate best subset regression analyses formed the basis of this study. Using all possible combinations of predictor variables in best-subsets multiple logistic regressions, we derived the best “subset” of variables that most strongly predict for; (1) the change in YBOCS score from baseline to endpoint, and (2) the YBOCS score at week 6 endpoint [38]. Finally, in both instances we then used the best subset combination of derived variables and used them into a “best of subsets” logistic regression to determine the overall predictive value of each of these dependent variables. From this a measure of the overall predictive value of our models was derived.

7.4 Results

Results of univariate analyses of demographic and symptom dimensional characteristics showed that fewer previous failed SRI trials were significantly associated ($p < 0.01$) with response status as defined by a 25% reduction in YBOCS from baseline to endpoint. No other clinical/demographic variables of interest were significantly associated with response status on chi-square (gender, $p = 0.81$, presence of tics, $p = 0.938$) or one-way ANOVA (age, $p = 0.61$; YBOCS total at baseline, $p = 0.5$; YBOCS baseline obsession score ($p = 0.17$), and YBOCS baseline compulsion score ($p = 0.67$). Similarly, univariate analysis of individual symptom dimensions showed that no one dimension on its own was significantly associated with a treatment response.

For the combined study dataset, the quetiapine group’s mean YBOCS percentage reduction was 25.66% (SE 4.33), while in the placebo group’s the reduction was 14.94% (SE 4.22). The “best subsets” regression analysis method

used percentage change in YBOCS as the dependent variable without predetermined criteria for treatment response. This revealed that 9 of the independent variables provided the best model for predicting the percentage YBOCS change over the treatment course. These were treatment group, number of previous failed SRI courses, the presence of tics, YBOCS obsession score at baseline, symmetry obsessions, somatic obsessions, checking compulsions, counting compulsions, and ordering/arranging compulsions. This group of independent variables was then combined in a logistic regression against a dependent variable of percentage change in YBOCS score. Of the 9 variables, 3 remained significant. These included having failed fewer previous SRI trials ($p < 0.01$), higher baseline YBOCS obsession sub-score ($p < 0.01$), and ordering/arranging compulsions ($p < 0.01$). Together these predictive variables explain 45% of the variance in respect of treatment response ($R^2 = 0.45$).

In a second analysis we also undertook a best-subsets and stepwise linear regression using the 9 most significant variables with the week 6 YBOCS score as the dependent variable. In this case, treatment group, number of previous failed SRI courses, the presence of tics, YBOCS compulsions score at baseline, symmetry obsessions, somatic obsessions, checking compulsions, counting compulsions, and ordering/arranging compulsions were then entered into the model for the linear regression. In this model, fewer failed SRI trials ($p < 0.01$); higher YBOCS baseline compulsion score ($p < 0.01$), counting ($p = 0.03$), and ordering/arranging ($p < 0.01$) compulsions were the only significant predictors of a lower endpoint YBOCS score (better treatment outcome) in our model. This model predicted 50% of the variance for the week 6 YBOCS score in our sample ($R^2 = 0.50$). A tendency to treatment group being a significant predictor of outcome was seen for both YBOCS change ($p = 0.09$) and YBOCS endpoint scores ($p = 0.07$).

7.5 Discussion

The main findings of the present study were; (1) that failure of fewer previous trials with an SRI, (2) higher baseline obsessions (for YBOCS change), (3) higher baseline compulsions (for YBOCS endpoint), (4) higher counting compulsions (YBOCS endpoint), and (4) ordering/arranging compulsions (YBOCS change and endpoint) predicted a greater likelihood of improved outcome to antipsychotic

augmentation of patients poorly responsive to initial SRI treatment. Together, these factors combine in a regression model and account for 45% of the YBOCS change score and 50% of the YBOCS endpoint score respectively.

Our findings suggest that previous treatment history and more severe disease predict a positive treatment outcome. The levels of variance explained by our model, however, suggests one or a number of other as yet unknown factors may also be important contributors to treatment outcome. Larger samples and increased attention to alternative clinical and biological variables would be required to more accurately predict treatment outcome in antipsychotic augmentation studies in OCD.

The results of the present study are nevertheless informative. Our finding that fewer previous failed trials of SRIs were associated with superior response rates in univariate as well as regression analyses is consistent with data from predictors of SRI response. This may suggest that the factors underlying poor response to serial SRI trials and antipsychotic augmentation overlap.

We recently published data from an expanded cohort derived in part from the same data-set we used here suggesting that lower SRI doses were associated with more robust changes in response to quetiapine augmentation [39]. As such, it seems possible that treatment responsiveness in OCD lies on a continuum. Within OCD populations, a biologically distinct sub-group who have failed fewer SRI trials may specifically benefit from augmentation with atypical antipsychotics. On the other hand, it is possible that this finding simply reflects a reality that in those who fail two or more SRI trials, the likelihood of responding to either an alternative SRI trial or antipsychotic augmentation is low, irrespective of the mechanism of action. In the clinic, our data raises the question as to whether there is not potentially more to be gained from augmenting with an atypical antipsychotic prior to switching to an alternative SRI after failure of a first trial?

In the meta-analysis by Bloch et al [9], the maximum effect of treatment was noted in the first 4-6 weeks of augmentation. This suggests that the time to onset of action may be significantly faster than is conventionally, though not universally held to be the case for SRIs in OCD [7]. This has implications for the underlying biology of

treatment response, as it suggests that the time-delaying process of receptor desensitization is either not necessary or is significantly accelerated with antipsychotic augmentation. At a clinic level, these data suggest that a potential for time (faster onset of action), therapeutic (more likely to respond robustly) and ultimately cost advantages exists in favor of augmentation earlier in the treatment course of refractory OCD. This notion deserves further exploration. This will be required before it can be considered reasonable to influence current treatment guidelines of first switching to an alternative SRI for 12 weeks prior to antipsychotic augmentation being considered as the third-line option [7,40].

In respect of the specific predictive value of individual symptoms, we found that higher baseline scores for obsessions predicted lower YBOCS scores. We also found that higher baseline compulsion scores predicted total YBOCS scores at week 6 of treatment. In previous studies, higher baseline scores have been found to predict a poorer response to treatment with SRIs [41]. In this study, Shetty et al examined a cohort in which non-responders had significantly higher baseline YBOCS scores (25.3) than responders (18.96). Denys et al [35] derived a model for SRI response prediction in OCD and found that moderately high (<23) total YBOCS scores were associated with a superior response to SRI therapy. In functional brain imaging studies, higher frontal regional perfusion has been associated with more severe OCD [42]. Also higher regional perfusion has been shown to predict response to subsequent treatment with an SRI. Our data here would seem to be in line with the data that suggests higher pre-treatment YBOCS scores predict better outcome. In our data, however, total YBOCS scores were not predictive of outcome. We also found no obsessions or compulsions that occurred with significantly higher frequency than any other.

We did find that symmetry obsessions, counting and ordering/arranging compulsions predicted better response to augmentation with quetiapine. There is evidence to suggest partial convergence of these symptoms with aspects of OCPD. While we did not collect data from which details of personality disorders could be extrapolated, this overlap is interesting in the light of recent arguments for understanding OCD with co-morbid OCPD as a subgroup of its own [43,44]. It seems that if OCPD is co-morbid with OCD, obsessions and compulsions such as symmetry, ordering, repeating, cleaning and hoarding are more likely to occur [44].

In the Baer study, associations were also found with tic disorders and hoarding. Both of these dimensions have been linked with dopamine as a possible factor in mediating these “behaviours” in OCD. While tic disorders have been associated with superior responses to dopamine blocking augmentation in OCD [8,9], hoarding has demonstrated a poor response to SRI treatment [25,27], though not all data are consistent (Stein et al, unpublished).

The association of ordering with response is interesting in the light of data suggesting an overlap with dimensions with an apparent dopaminergic basis. These include for instance the association with checking and symmetry/ordering with tics [25,37,45]. Aspects of our data, however mitigate the argument for dopamine involvement here with the absence of a predictive value of tics and behavioural dimensions such as hoarding which are believed to have a dopaminergic basis [46]. In the review by Bloch et al, co-morbid tics demonstrated preferential benefit to antipsychotic augmentation suggesting that the absence of a finding in the present study is possibly the effect of small sample size. The same could be argued for symptoms such as hoarding, which in trials of purely serotonergic compounds, predict poor treatment outcome.

Returning then to the main finding of the present study that failure of fewer trials of SRIs is predictive of response to antipsychotic augmentation. Aside of the point made above in relation to treatment resistance as a position a subgroup of patients will enter irrespective of treatment type, it is possible that true differences do underlie the differential responsivity to dopamine antagonists in some patients. We can only speculate on the potential for underlying differences in dopaminergic neurotransmission in “less refractory” OCD patients compared to those who have failed two or more SRI therapy trials to exist. It may of course be true that a lack of evidence for the efficacy of antipsychotic earlier in the course of OCD treatment reflects a masking effect by the larger effect size of SRIs over the small effect of antipsychotic augmentation. Whatever the underlying mechanism for the efficacy of antipsychotic augmentation in OCD, the present study provides some preliminary indications of the clinical and demographic variables that predict a response to quetiapine augmentation.

In conclusion, we have found that a number of clinical variables appear to predict response to augmentation with quetiapine, but that the psychobiological basis for refractoriness to SRIs remains unknown. Recent meta-analyses that support the use of antipsychotic augmentation in OCD do suggest that a dopaminergic contribution to treatment is needed in a sub-group of patients with OCD. It is notable that failed trials of SRIs predict worse response to both SRIs and quetiapine augmentation, and may suggest distinct, as yet to be defined psychobiological factors that characterize treatment refractoriness that lies in the interaction of the serotonergic and dopaminergic systems. While our findings must be regarded as preliminary that requiring further confirmation, they do begin to suggest that the currently accepted notion that switching to an alternative serotonergic antidepressant should precede a trial of an atypical antipsychotic in patients who fail to respond adequately to first-line treatment with an SRI.

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CHAPTER 8

Summary and Conclusions

8.1 Executive Summary

The role effective treatments have played in driving scientific exploration of the serotonin and more recently the dopamine systems in OCD are significant. Despite emerging evidence for the involvement of neurotrophic factors, immune modulators, functional genetic polymorphisms and a range of other neurochemical systems in the pathogenesis of OCD, the prominence of investigations into the role of serotonin and dopamine persists. Despite this, the specific mechanisms through which components of these systems are involved in mediating OCD has not been clearly delineated. This fact is probably a testimony to the complexity of these and other central nervous system neurotransmitter systems.

The series of studies comprising this thesis represent an effort to explore three important and interlinked study areas. First, we explored an aspect of neurobiology with two studies. In the first of these we examined resting brain perfusion compared to healthy controls and in the second rCBF in response to a specific serotonin 1B autoreceptor agonist challenge. These were followed by two further studies in which we first examined the differential impact of the selective serotonin re-uptake inhibitor (SSRI), citalopram on rCBF across anxiety disorders to examine the intersection of treatment with neurobiology. This was achieved through the delineation of distinct and overlapping brain effects of this single effective treatment strategy. In the second study in this area, we explored the impact of a novel second messenger precursor, inositol, on rCBF when administered as treatment for OCD. This enabled us to examine the intersection of brain functional responses to an effective treatment in OCD that arguably targets a downstream common pathway also activated by conventional SRIs.

Finally, in a series of two studies we explored treatment of OCD using a dopamine-serotonin antagonist, quetiapine, in SSRI refractory patients. While our study did not demonstrate a benefit for quetiapine, we have subsequently combined our data with other similar studies in a meta-analysis and together demonstrated efficacy for this strategy. We then proceeded to combine our data with another similar dataset to derive a best subsets model with the highest predictive value for a favourable outcome to augmentation with quetiapine in refractory OCD.

In summary, this body of work has primarily contributed to our understanding of the neurobiology of OCD, its treatment and the intersection of the two. To this end, both the serotonin and the dopamine systems were impacted directly and indirectly through the range of treatments we administered to patients. Taken together, these studies lend further support to both the serotonin and dopamine hypotheses in OCD.

8.2 Detailed Summary

Part I:

In the first in this series (Chapter 2), we examined the differences in regional brain perfusion in OCD compared to matched healthy controls. Similar studies over a number of years have yielded highly variable results, such that evidence for the putative cortico-striatal-thalamic circuit in OCD, is not convincingly reinforced by this work. In most previous studies, analysis has focused on regions hypothesized to be involved in OCD, with relatively little attention being given to other brain regions. In this study we showed that patients with OCD have substantially different brain perfusion patterns compared to normal controls. These differences are most pronounced in orbito-frontal and pre-central frontal brain regions with increased perfusion correlating in the prefrontal region with illness severity. While this data is in line with previous findings that have gone on to show that serotonergic treatments attenuate frontal perfusion, we also found a number of brain regions, outside of the putative functional circuit in OCD, in which the pattern was reversed. These include the lingula, superior orbito-frontal cortex, cerebellum, precuneus, anterior cingulate, superior parietal cortex, and left hippocampus.

While anxiety circuitry implicates some of these regions, robust explanations for all of these findings have yet to be delineated. Together however, they do suggest that in OCD with characteristic clinical heterogeneity, clear evidence for the involvement of brain regions other than the frontal-striatal circuit requires further investigation. Furthermore, this line of investigation only seems likely to yield meaningful results if methods of imaging and analysis are increasingly standardized to enable more reliable pooling of data. This in turn will

provide a useful neurobiological foundation for understanding the functional brain patterns of the resting state in OCD and also the brain functional patterns of treatment response. It is conceivable that in combination with pharmacogenetic data, this approach may assist in understanding the action of future treatment for OCD *in vivo*.

In the second study in this series of four in Part I (Chapter 3), we considered clinical, genetic, and pharmacological challenge data underpinning the serotonin 1B autoreceptor hypothesis in OCD. Specifically we examined the neurobiology of the clinical and brain functional responses to pharmacological challenge with sumatriptan, a specific 5HT1B autoreceptor agonist. This was executed using a double-blind, cross-over, and counterbalanced design with placebo. We then examined the rCBF in participants on placebo and compared this to the responses on sumatriptan.

We found that behavioural responses of obsessive-compulsive (OC) and anxiety symptoms did not differ significantly overall between placebo and sumatriptan. However, this masked a characteristically heterogeneous behavioural response in our cohort. A little over half of the participants had improved anxiety ratings while the remainder reported symptom exacerbation. For OC symptoms on the other hand improvement in around 20%, exacerbation in 20%, and no change in the balance was found. A clinical improvement following sumatriptan was associated with lower cingulate, superior and medial frontal, and higher occipital perfusion. Improved anxiety in response to sumatriptan challenge correlated with reduced brain perfusion in the fusiform gyrus and the precuneus. We argue that pre-treatment frontal perfusion which is attenuated with sumatriptan and clinical improvement is in line with published work suggesting similar findings in response to SSRI treatment. While SSRIs do not primarily target the 1B autoreceptor, these data are suggestive of a role for the 5HT1B autoreceptor in mediating the clinical response in OCD that correlates with brain functional changes in frontal brain regions.

In Chapter 4, the third study in Part I, we asked to what extent anxiety disorders that are held to have distinct neurobiological underpinnings, but that respond similarly well to SRIs, share changes in brain perfusion as a function of

treatment response. To this end we studied a group of participants with one of OCD, posttraumatic stress disorder (PTSD), or social anxiety disorder (SAD). We found no pre-treatment perfusion pattern helped distinguish subsequent responders to the SSRI citalopram in the group as a whole. Citalopram treatment resulted in attenuated perfusion for the combined group in the anterior superior cingulate, the thalamus, and hippocampus. Clinical responders to treatment demonstrated greater attenuation of perfusion in pre-central, mid, inferior and prefrontal regions as well as the precuneus.

These data suggest that despite phenomenological and neurochemical evidence for the distinctiveness of anxiety disorders, that overlap in functional neurocircuitry involved in mediating a treatment response to an SSRI is noteworthy. The involvement of brain regions that include limbic circuits known to mediate cognitive-affective dimensions of these disorders are also known to be richly innervated by serotonergic neurons. It is possible that across the group, only changes in regions that mediate shared phenomenological aspects of these disorders such as the limbic and paralimbic cortices are detectable. As such we should be cautious about over-interpreting data suggesting an overlap in disorders with quite distinct core phenomenology.

In the fourth study in Part I (Chapter 5), we examined the impact of treatment with myo-inositol, a glucose isomer and crucial precursor to the phosphoinositol second messenger system on regional brain perfusion measured with SPECT in OCD. Inositol has been shown to have effects at many levels of the signal transduction pathway. It has also been shown to be preferentially effective in disorders that are responsive to serotonergic drugs including OCD. This seemingly suggests that Inositol may mediate postsynaptic processes that overlap with those of the SSRIs, though the specific mechanisms of this interaction remain unclear.

We demonstrated that attenuated brain perfusion in the prefrontal, temporal and parietal cortices correlated with clinical response to inositol. Furthermore, higher medial prefrontal perfusion at baseline correlated with subsequent treatment response. The same has been shown to be true with treatment with SSRIs. Together with our finding here, these data would seem to

support the notion of an overlap in the function of SRIs and inositol that is most likely to lie beyond the level of receptor-neurotransmitter interaction at the level of the second messenger and beyond in the signal transduction pathway. These data also implicate brain regions that have been less well studied in OCD, such as the temporal and parietal cortex. This finding may suggest that inositol effects a clinical response through activation of functional circuitry that is distinct from the frontal-striatal circuit. These interesting data and the suggested efficacy of inositol in OCD deserve further examination that will further delineate both overlapping and distinct mechanisms through which it works to effect a clinical response.

Part II:

In Chapter 6, we examined the efficacy of augmentation of SRIs with a dopamine antagonist quetiapine under double-blind placebo-controlled conditions for six weeks in patients who had failed to respond adequately to first-line therapy with a serotonin re-uptake inhibitor (SRI). We were not able to demonstrate superiority over placebo in this study; however, a significant treatment effect was noted in both treatment groups. Our cohort was required to have failed only a single trial of an SRI, of which only six weeks was required at the maximum tolerated dose. We argued that the large and unexpected placebo response we observed was possibly due to a “delayed” effect of the SRIs. This may have been the case as the later were only required to have been at the maximum tolerated doses for a minimum of six weeks. This delayed effect, may therefore have rendered the relatively small effect anticipated with the dopamine modulating drug quetiapine, difficult to detect.

We have subsequently combined these data with two similar data sets in a meta-analysis and an overall positive effect has been shown for this strategy in refractory OCD. Together with another meta-analysis this strategy has been found to be effective for drugs including haloperidol, risperidone and olanzapine, suggesting that this is a class effect, and one that strongly supports a dopaminergic basis for resistance to treatment with SRIs in OCD.

In the final study (Chapter 7) we combined two of the three available data-sets of quetiapine augmentation mentioned above to address the primary questions of whether a model of clinical and demographic variables could be derived to reliably predict treatment outcome in this refractory population. We chose to use the primary outcome variable YBOCS change and endpoint scores respectively as dependent variables in two separate best-subsets regression analyses. We found that fewer previous failed SRI trials, higher baseline obsession scores, and having ordering and arranging compulsions, predicted better treatment outcome explaining some 45% of the variance in YBOCS change. Using YBOCS endpoint scores we found a lower number of previous SRI trials, higher baseline compulsion scores, counting/ordering and arranging compulsions together predicted 50% of the variance in treatment outcome. We argued that some convergence with clinical dimensions believed to have a dopaminergic basis is evident in our sample. The evidence suggests that less refractory patients (defined by a lower number of failed SRI trials) are more likely to respond to quetiapine. This may suggest a specific role of dopamine modulating drugs in more symptomatic patients with “dopaminergic” symptoms that are partially refractory to SRIs. This effect, however, appears to diminish in parallel with lower response rates to SRIs seen with successive therapy trials. This may suggest that with “increasing” refractoriness, symptoms of OCD seem equally intransigent to both serotonin and dopamine modulating therapies.

8.3 Conclusions and future directions

Through this series of clinical treatment and functional brain imaging studies in OCD, I have contributed to the neurobiological understanding of OCD, its treatment in refractory populations and explored the intersection of these two domains using novel treatments and treatment across other anxiety disorders. Treatment and pharmacological challenges studies all directly or indirectly impacted the monoamine systems serotonin and dopamine and advanced our understanding of their involvement in symptom generation through:

- 1) Demonstrating that resting brain perfusion in OCD differs significantly from normal controls, is correlated with severity in frontal brain regions, and remains an important line of investigation for OCD pathophysiology that has yet to fully delineated. Future studies should encourage standardized approaches to image processing to ensure that small studies can be meaningfully combined using original data. In time, larger sample sizes using whole brain approaches to analysis will provide useful and reliable insights into resting brain function in OCD and how this differs from the provoked symptomatic state. Future work will also then be able to focus on sub-regional differences in brain function.
- 2) Demonstrating that the 5HT1B autoreceptor agonist sumatriptan results in heterogeneous behavioural and regional brain perfusion changes in OCD. Pre-frontal increases in pre-treatment perfusion are attenuated following 5HT1B autoreceptor agonist challenge, a finding that is in line with SSRI effects. This is suggestive of direct or indirect effects of SRIs on the 5HT1B receptor in mediating a clinical response in OCD. Future pharmacological challenge studies such as this will benefit from detailed symptom dimension data complemented by 5HT1B allelic composition. In addition, the development of a specific labeled ligand for the 5HT1B receptor would make a significant contribution to our understanding of the role of 5HT1B in OCD.
- 3) Demonstrating that brain functional changes parallel treatment response to an SSRI across a range of anxiety disorders. This suggests a degree of overlap in the neurobiology of treatment response across anxiety disorders, or indeed a component of shared neurobiology per se in these disorders.

Future studies across anxiety disorders would also benefit from the use of ligands for the serotonin transporter as well as the serotonin 2a receptor in order to delineate the specific impact of treatment on these components in each of the disorders alone and combined.

- 4) Effective treatment with an alternative treatment inositol which results in brain functional changes in line with the effects of SRIs on brain perfusion. This suggests that second messengers may form part of the common pathway of action for effective anti-obsessional compounds. Future studies using inositol should also examine its impact on the 5HT2a receptor, the putative membrane receptor crucial to the activation of inositol derived second messenger pathways.
- 5) Demonstrating an overall benefit for augmentation of SRIs with a serotonin/dopamine antagonist in refractory OCD in pooled analyses. Future studies should more carefully examine the time to treatment response as well as the long-term outcomes in patients who initially benefit from this intervention. Alternative treatments that target the dopamine and serotonin systems indirectly should also be explored in controlled studies.
- 6) Demonstrating that apparently less refractory to treatment patients with more severe illness and clinical dimensions with a putative dopaminergic underpinning may derive preferential benefit from serotonin/dopamine antagonist augmentation of their SRI treatment. Future studies should include larger sample sizes and would be strengthened by the addition of detailed neuropsychological and genetic data.