THE NEUROBIOLOGY OF OBSESSIVE-COMPULSIVE DISORDER: NEUROANATOMY, NEUROCHEMISTRY, AND PHARMACOTHERAPY

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DECLARATION

I, the undersigned, declare herewith that the work in this dissertation is my own original research and that it has not previously been submitted for degree purposes, in whole or in part, at any University.

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SUMMARY

Obsessive-compulsive disorder (OCD) is characterized by intrusive thoughts (obsessions) and repetitive mental acts or behaviours (compulsions). For many years, it was considered a rather uncommon condition, caused by unconscious conflict, and somewhat resistant to treatment. In recent decades, however, it has emerged that OCD is a highly prevalent disorder, mediated by particular neuroanatomical circuits (e.g. striatal pathways) and neurochemical systems (e.g. the serotonin system), and responsive to treatment with serotonin reuptake inhibitors (SRIs). Nevertheless, many questions remain; about the specificity of neuroanatomical findings to OCD, about the role of the multiple serotonin (5-HT) receptor subtypes (e.g. 5-HT_{1D}), and about the appropriate pharmacotherapy for patients resistent to SRI treatment? In a series of studies, 1) the neuroanatomy of OCD was assessed by means of magnetic resonance imaging and neuropsychological testing, 2) the neurochemistry of OCD was assessed by means of functional brain imaging after administration of a 5-HT_{1D} agonist, and 3) the pharmacotherapy of OCD was explored in a series of treatment-refractory OCD and OCD spectrum disorder patients using SRI augmentation with a dopamine blocker. Although no significant difference was found in the volume of the caudate in women with OCD and controls, there was a significant correlation between caudate volume and neuropsychological dysfunction in patients, consistent with evidence of striatal involvement in OCD. Functional imaging demonstrated behavioural heterogeneity, but brain-behaviour correlations were positive, consistent with preclinical evidence of a role for the 5-HT_{1D} receptor in the mediation of OCD. Finally, preliminary treatment findings with dopamine blocker augmentation of a SRI were promising, consistent with preclinical understandings of the interactions between the dopamine and serotonin systems. Although

OCD is a complex disorder, a number of future research avenues hold promise for providing a thorough delineation of its pathogenesis.

OPSOMMING

Obsessief-kompulsiewe steuring (OKS) word gekenmerk deur indringende gedagtes (obsessies) en herhalende gedagtes of gedrag (kompulsies). Vir baie jare is dit beskou as 'n redelik seldsame toestand wat veroorsaak word deur onbewustelike konflik, en wat in 'n mate teen behandeling weerstandig is. Meer onlangs het dit egter na vore getree as 'n toestand wat baie dikwels voorkom, wat deur spesifieke neuroanatomiese siklusse (bv. striatale bane) en neurochemiese sisteme (bv. die serotonien-sisteem) teweeg gebring word, en wat op behandeling met serotonien heropname inhibeerders (SHIs) reageer. Nogtans is daar steeds baie vrae; oor die spesifisiteit van neuroanatomiese bevindinge vir OKS, oor die rol van die veelvuldige serotonien (5-HT) reseptor subtipes (bv. 5-HT_{1D}), en oor die toepaslike farmakoterapie vir pasiënte wat weerstandig is vir SHI behandeling. In 'n reeks van navorsingstudies, is 1.) die neuroanatomie van OKS deur middel van magnetiese resonans beelding en neurosielkundige toetse ondersoek, 2.) die neurochemie van OKS deur middel van funksionele breinbeelding na toediening van 'n 5-HT_{1D} agonis bepaal, en 3.) die farmakoterapie van OKS in 'n reeks van behandelingsweerstandige OKS en OKS-spektrum steuring pasiënte - waar gebruik gemaak is van SHI aanvulling met 'n dopamien-blokker - ondersoek. Alhoewel daar geen beduidende verskil in die volume van die caudata in vroue met OKS en kontroles gevind is nie, was daar 'n beduidende korrelasie tussen die caudata volume en neurosielkundige wanfunksionering in pasiënte, in ooreenstemming met striatale betrokkenheid in OKS. Funksionele beelding het heterogeneïteit in gedrag demonstreer, maar brein-gedrag korrelasies was positief, in ooreenstemming met pre-kliniese bewyse vir 'n rol vir die 5-HT_{1D} reseptor in die bemiddeling van OKS. Ten laaste, voorlopige behandelingsbevindinge oor dopamien-blokker aanvulling van 'n SHI is belowend, in ooreenstemming met

die pre-kliniese begrip van die interaksies tussen die dopamien- en serotoniensisteme. Alhoewel OKS 'n komplekse steuring is, is daar talle toekomstige navorsingsrigtings wat belofte inhou vir die deeglike uiteensetting van die patogenese daarvan.

For Heather, Gabriella, and Joshua

PREVIOUS PUBLICATIONS

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CONTENTS

ABBREVIATIONS

5-HIAA - 5-hydroxyindoleacetic acid
5-HT - serotonin
5-HTTP - serotonin transporter protein
ANOVA - analysis of variance
CGI - Clinical Global Impressions
CSF - cerebrospinal fluid
CSTC - cortical-striatal-thalamic-cortical
CT - computed tomography
DALY - disability adjusted life year
DSM - Diagnostic and Statistical Manual of Mental Disorders
DSM-IV - DSM, Fourth Edition
ECA - Epidemiological Catchment Area
ECT - electroconvulsive therapy
HMPAO - hexamethylpropylene amine oxime
MADRS - Montgomery-Asberg Depression Rating Scale
mCPP - m-chlorophenylpiperazine
MRI - magnetic resonance imaging
OCD - obsessive-compulsive disorder
OCF - Obsessive-Compulsive Foundation
PET - positron emission tomography
rCBF - regional cerebral blood flow
RMANOVA - repeated measures analysis of variance
ROI - region of interest
SPECT - single photon emission computed tomography
SRI - serotonin reuptake inhibitor
SSRI - selective serotonin reuptake inhibitor
Tc-99m - technecium-99m
TS - Tourette's Syndrome (Tourette's disorder)
TTM - trichotillomania
VBR - ventricular-brain ratio
YBOCS - Yale-Brown Obsessive-Compulsive Scale

WHO - World Health Organization

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1. INTRODUCTION: THE PHENOMENOLOGY AND NEUROBIOLOGY OF OCD

Obsessive-compulsive disorder (OCD) has long been considered a rather uncommon condition, caused by unconscious conflict, and somewhat refractory to treatment. In recent decades, however, a paradigm shift has occurred, and OCD is now viewed as one of the most prevalent and disabling of psychiatric disorders, mediated by specific neuronal circuits and neurochemical systems, and responsive to certain pharmacotherapeutic and psychotherapeutic interventions. This chapter provides the background for the studies undertaken here, by reviewing the definition and diagnosis of OCD, its epidemiology and impact, and its neurobiology.

1.1. Definition and Diagnosis

1.1.1. Obsessive-Compulsive Disorder

Obsessions are recurrent and persistent thoughts, impulses, or images that the person typically regards as intrusive and inappropriate (American Psychiatric Association, 1994). Characteristically they increase levels of anxiety. An example is the mother who is horrified by a recurrent image of herself stabbing her new-born child, or the boy who is distressed by repeated thoughts that he will be contaminated if he comes into contact with dirt.

Compulsions are repetitive behaviours or mental acts that the person feels driven to perform in response to an obsession, or according to rules that must be followed rigidly (American Psychiatric Association, 1994). Characteristically they

temporarily diminish levels of anxiety. The mother with aggressive obsessions may, for example, act to prevent the stabbing by repeatedly checking that her kitchen knives are locked away. Similarly, the boy with contamination obsessions may repeatedly wash his hands to reduce distress about contact with dirt.

While various habits may be present in normal people, obsessions and compulsions in OCD cause marked distress or interfere significantly with academic, occupational, or social function. People with OCD are typically aware that symptoms are excessive or unreasonable, but note that they are simply unable to resist these repetitive thoughts and actions. A range of obsessions and compulsions may be present in any one patient (TABLE 1.1), and these symptoms may also evolve over time with one set of obsessions and compulsions replacing another (Rasmussen and Tsuang, 1986; Swedo et al, 1989a).

The diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM) (TABLE 1.2) are invariably used in current research on OCD, including the series of studies described herein. These criteria, most recently updated on the basis of extensive field research (Foa and Kozak, 1995), clearly distinguish OCD from lay concepts of "obsessive love" or "obsessive neatness", as well as from other psychiatric disorders, so allowing for rigorous and reliable diagnosis.

1.1.2. Obsessive-Compulsive Spectrum Disorders

Advances in the field of obsessive-compulsive disorder have led also to increased attention to a series of possibly related conditions, the so-called OCD spectrum disorders (Jenike, 1989;

Hollander, 1993; McElroy et al, 1994; Yaryura-Tobias and Neziroglu, 1997). While this spectrum can be defined in various ways, a consistent theme in the literature has been the presence of phenomenological and neurobiological overlaps between OCD and disorders such as Tourette's syndrome (TS), body dysmorphic disorder (BDD), hypochondriasis and trichotillomania (TTM) (Stein and Hollander, 1993).

Nevertheless, the characterization of various disorders as OCD related remains contentious, with some authors warning against premature and overinclusive classifications Rasmussen, 1994). Certainly there are considerable differences in the phenomenology of the various putative OCD spectrum disorders. For example, although unwanted repetitive motor symptoms are characteristic of both OCD and trichotillomania (hair-pulling), in the latter disorder there do not appear to be preceding obsessions. Other phenomenological features also differ; for example, trichotillomania appears considerably more common in women than men (Christenson et al, 1991).

On the other hand, the idea that OCD and putative OCD spectrum disorders are in someway related would seem to be a useful heuristic both in clinical practice (where anti-OCD medication, for example, may be effective in a range of conditions) and in research (where similar mechanisms may be found to mediate diverse disorders). There has been a gradual accumulation of neurobiological data suggesting a number of different, but partially overlapping, approaches to this spectrum (Stein, 2000).

Indeed, the notion of an OCD spectrum begs the question of the dimension along which the various conditions differ. Freud and subsequent psychoanalysts contrasted obsessive-compulsive neurosis, obsessive-compulsive character, and normal obsessive-compulsive defenses (Stein and Stone, 1997). Some contemporary

clinicians have suggested that obsessive-compulsive disorders lie on the spectrum of affective disorders (McElroy et al, 1994). Others have, however, emphasized the contrast between OCD (where insight is usually retained) and psychotic disorders where insight is usually lost) (Klein, 1993).

As the neurobiology of OCD and of putative OCD spectrum disorders is increasingly understood it may be possible to begin to resolve some of these questions. In the series of studies that comprise this thesis, in addition to using healthy controls, patients with trichotillomania are at times used as psychiatric controls. The rationale is to provide a way of simultaneously assessing the specificity of the neurobiology of OCD, and also contributing to understanding the psychobiology of one of the putative OCD spectrum disorders.

1.2. Epidemiology and Impact

1.2.1. Community Surveys

The Epidemiological Catchment Area (ECA) study was the first definitive study of the prevalence of OCD using a structured diagnostic instrument based on DSM diagnostic criteria. The ECA found that OCD was the fourth most common psychiatric disorder, present in 2-3% of the population (Karno et al, 1988). The disorder had a roughly equal male to female ratio, and was present equally in all socioeconomic groups.

Earlier, less systematic studies, had suggested that OCD was a rather uncommon disorder. Furthermore, the interview procedure used in the ECA study may have led to a degree of overestimation

of prevalence. Nevertheless, it is now generally accepted that in the past OCD prevalence has been significantly underestimated, partly because patients frequently do not inform clinicians of their symptoms (Hollander et al, 1997).

Another limitation of the ECA study is that work was done in the developed world and in a single country. However, a cross-national community survey based on the methodology of the ECA was subsequently undertaken (Weissman et al, 1996). There was a surprizingly uniform prevalence of OCD in both the developed and developing world. These data strongly suggest that the pathogenesis of OCD involves universal rather than culture-specific psychobiological mechanisms (Stein and Rapoport, 1996).

2.2 Morbidity

In recent years, there has been growing awareness of the morbidity of OCD and its substantial negative impact on quality of life (Stein et al, 2000a). The term "quality of life" has both subjective elements, as well as objective components (role functioning, living conditions) (Katschnig et al, 1997). Furthermore, the construct of QOL covers a range of different domains, including family and social relations, scholastic and work functioning, financial and health status, and living situation.

One of the most remarkable datasets demonstrating the negative impact of OCD is the Global Burden of Disease study undertaken by the World Bank and the World Health Organization (WHO) (Murray and Lopez, 1996). One measure employed by this study was the DALY - disability adjusted life year. Of the 10 most disabling medical

conditions worldwide, 5 are neuropsychiatric disorders, and one of these (the 10th most disabling condition) is OCD.

Studies using epidemiological and clinical data are consistent with the general tenor of the World Bank study. Dupont and colleagues (1995), for example, estimated the annual costs of OCD on the basis of data collected in the Epidemiological Catchment Area (ECA) study. They calculated that reduced or lost productivity from OCD was $5.9 billion a year in the United States in 1990 - 70.4% of OCD's total economic costs. Leon et al (1995) also highlighted the burden of OCD by focusing on unemployment and disability findings contained in the ECA dataset.

Two parallel surveys of obsessive-compulsive consumer organizations in South African (Stein et al, 1996) and the United States (Hollander et al, 1997) similarly demonstrate the enormous costs of OCD. Although arguably limited by ascertainment bias, the United States survey found a surprisingly long mean time from onset of symptoms to appropriate treatment of 17 years. Inappropriate outpatient treatment was estimated to cost $2 billion a year.

A number of clinical studies have emphasized the burden of OCD across different domains, including instrumental role functioning (work, school, and homemaking). Koran et al (1996) noted that unemployment was twice as high in their sample of medication-free OCD outpatients as in the general population, and that subjects' mean scores for role limitations due to emotional problems, social functioning and mental health were all below the 25th percentile. Similarly, in their survey of work eligible OCD patients, Eisen et al (2000) found that 32% had severe impairment in their ability to work, and that similar frequencies were found at 1-year and 2-year follow-up.

Domains other than instrumental and social functioning are also affected by OCD. Several recent studies, for example, have emphasized the disruption to families caused by OCD. The ECA survey found that OCD subjects had higher rates of divorce and separation than subjects without OCD (Karno et al, 1988). OCD symptoms often intrude on family life, and conversely family members may become involved in rituals (Emmelkamp et al, 1990; Calvocoressi et al, 1995; Shafran et al, 1995; Black et al, 1998a).

1.3. Neurobiology

1.3.1. Neuroanatomy

1.3.1.1. Evidence for Cortico-Striatal Mediation of OCD

The earliest evidence that OCD had a specific anatomical basis emerged during the encephalitic pandemic early this century. Patients with post-encephalitic parkinsonism demonstrated involuntary movements as well as obsessive-compulsive symptoms. At post-mortem, brain pathology included basal ganglia lesions (van Economo, 1931; Cheyette and Cummings, 1995). Certainly, this early clinical evidence is consistent with modern understandings of the role of cortico-striatal-thalamic-cortical (CSTC) loops in the development, maintenance, and selection of motoric and cognitive procedural strategies (Cummings, 1993).

A subsequent literature has demonstrated that many patients with neurological conditions involving the basal ganglia, such as Tourette's syndrome (Hollander et al,1989), Sydenham's chorea

(Swedo et al, 1989b), and Huntington's disease (Cummings and Cunningham, 1992), may have co-morbid OCD. Conversely, patients with OCD may have comorbid tics (Pitman et al, 1987), or increased involuntary movements on neurological soft sign examination (Hollander et al, 1990; Bihari et al, 1991),suggestive of basal ganglia pathology.

Occasionally patients with frontal lobe lesions present with OCD symptoms, and OCD patients may show evidence of frontal lobe impairment on electrophysiological studies(Khanna, 1988; Ames et al, 1994). Furthermore, magnetic resonance imaging (MRI) studies have demonstrated frontal abnormalities in OCD (Garber et al, 1989; Grachev et al,1998; Szeszko et al, 1999). Finally, surgical lesions to frontal-striatal pathways may result in improvement in OCD symptoms in refractory patients (Martuza et al, 1990; Baer et al, 1995).

Brain imaging studies provide the most important evidence of cortico-striatal involvement in OCD. An early study indicated that patients with OCD had reduced volume of the basal ganglia on computed tomograph (CT) (Luxenberg et al, 1989), although not all subsequent volumetric studies have been consistent (Kellner et al, 1991; Scarone et al, 1992) (TABLE 1.3). Functional imaging studies have, however, often demonstrated hyperactivity in orbitofrontal cortex, anterior cingulate, and caudate nucleus; further increase in these structures during exposure to feared stimuli; and decreased activity after treatment (Rauch and Baxter, 1998) (TABLE 1.4-1.6). This patterns of findings differs notably from that in other anxiety disorders (TABLE 1.7).

Innovative recent research in brain imaging in OCD has employed novel methodologies and populations. For example, N-acetyl aspartate levels may represent a measure of neuronal density, and have been found reduced in two studies of OCD (Ebert et al, 1997;

Bartha et al, 1998).Rosenberg and colleagues have published a series of intriguing reports on brain imaging in pediatric OCD,further emphasizing the role of CSTC circuits in OCD(Rosenberg and Keshavan, 1998).

1.3.1.2. Conceptualizing CSTC Mediation of OCD

The development, maintenance, and selection of motoric and cognitive procedural strategies mediated by CSTC circuits has been given various terms including the habit system (Mishkin and Petri, 1984), response set (Robbins and Brown, 1990),and procedural mobilization (Saint-Cyr, 1990). Certainly, some form of malfunctioning feedback or feedforward circuit might well explain the repetitive nature of OCD symptoms. Furthermore, the basal ganglia may be a repository for repetitive motor programmes, akin to the repetitive behavioural sequences seen in OCD. It is as if there is excessive release of such sequences as a consequence of basal ganglia pathology (Wise and Rapoport,1989).

Baxter and colleagues have pointed out that the different CSTC circuits have both a "direct" and an "indirect" pathway (Saxena et al, 1998). The direct pathway facilitates striatal-thalamic outflow, perhaps promoting the execution of procedural strategies. In contrast, the indirect pathway inhibits thalamic activity, perhaps allowing the cortex to respond to different stimuli and to shift sets. In OCD, it may be postulated that there is hyperactivation of the direct pathway relative to the indirect pathway.

Of the different CSTC circuits, the one that is arguably most central to OCD is the ventral cognitive circuit, involving anterior and lateral orbitofrontal cortex,ventromedial caudate,

and dorsomedial nuclei of the thalamus. This system appears to play a particularly important role in response inhibition, particularly in relation to socioemotional and contextual cues (Rauch and Baxter, 1998). Indeed, on neuropsychogical testing,patients with OCD demonstrate executive dysfunction, which then has a negative impact on immediate nonverbal memory(Savage et al, 1999).

Rauch and colleagues have shown that during brain imaging of an implicit sequence learning task, normal controls show striatal activation, but patients with OCD instead appear to recruit medial temporal regions (Rauch et al,1997). These latter regions are typically involved in conscious cognitive-affective processing; thus, whereas normals are able to process procedural strategies outside of awareness, in OCD there instead appears to be intrusion of information and emotion into consciousness.

A "striatal topography" model of OCD spectrum disorders suggests that whereas the ventral cognitive system is involved in OCD, in Tourette's syndrome (TS) and perhaps trichotillomania (O'Sullivan et al, 1997), there is rather involvement of the sensorimotor cortex and putamen (Rauch and Baxter, 1998). On the other hand, there is also evidence that OCD patients have involvement of the range of different CSTC circuits (Rosenberg and Keshavan, 1998), and it is possible rather that specific projection fields or cell types are involved in specific kinds of symptoms. Certainly, further work is necessary to delineate precisely the contribution of CSTC circuits to OCD and to OCD spectrum disorders.

1.3.1.3. Mechanisms Underlying CSTC Pathology in OCD

How does damage to CSTC circuits occur in primary OCD (OCD that is not secondary to an obvious neurological lesion)? Non-specific injury has long been hypothesized in OCD, With an early study reporting an increasing incidence of birth trauma in OCD (Capstick and Seldrup, 1977). Interestingly, the basal ganglia are especially vulnerable to prenatal and perinatal hypoxic-ischemic injury (Hyde and Weinberger, 1995). Disruption of striatal circuitry is also seen after social deprivation during development (Martin et al,1991).

In the last few years, a more specific neuroimmunological hypothesis of OCD has gained steady ground. After noting the high incidence of OCD symptoms in Sydenham's chorea,Swedo and colleagues began to explore patients who presented with OCD symptoms and/or tics in the aftermath of Streptococcal infection, a condition they have termed pediatric autoimmune neuropsychiatric disorder associated with streptococcus (PANDAS) (Swedo et al, 1998). Their description of 50 cases with this picture suggests that autoimmune mechanisms may lead to disruption of CSTC circuits, and so to obsessive-compulsive symptoms in at least a subset of OCD patients.

Additional recent findings from this group include the demonstration that patients with PANDAS respond to immunomodulatory interventions such as plasma exchange and intravenous immunoglobulin (Perlmutter et al, 1999). Although they have been unable to show that penicillin prophylaxis prevents OCD, given that penicillin administration did not in fact prevent streptococcal infection further studies with a more effective prophylactic agent are required (Garvey et al, 1999).

What remains unclear is the extent to which Streptococcal infection is important in OCD patients in general. A number of interesting recent papers have contributed to this question by focusing on neuroimmunological abnormalities in OCD. Abnormal auto-antibodies, as well as range of less specific neuroimmunological dysfunctions, have been found in OCD (Black et al, 1998b; Marazziti et al, 1999; Mittleman et al, 1997).

Of particular interest in this regard, the B lymphocyte antigen D8/17, a marker for susceptibility to auto-immune complications in the aftermath of Streptococcal infection, appears increased in patients with OCD (Swedo et al, 1997; Murphy et al, 1997; Chapman et al, 1998). Further work is, however, necessary to determine whether this finding is specific to OCD;D8/17 expression was, for example, also increased in autism (Hollander et al, 1999).

1.3.2. Neurochemistry

1.3.2.1. Serotonin and Dopamine

Early anecdotal reports that OCD responded to treatment with a predominantly serotonergic reuptake inhibitor, clomipramine (Fernandez-Cordoba and Lopez-Ibor Alino, 1967) were the first evidence that the serotonin neurotransmitter system might play a role in OCD. Subsequent investigation demonstrated that OCD responded to clomipramine, but not to desipramine, a predominantly noradrenergic reuptake inhibitor, a finding that differentiates OCD from many other psychiatric disorders,which respond to a range of antidepressants (Zohar and Insel, 1987). More recently, clinical trials of selective serotonin reuptake inhibitors (SSRIs)

have invariably shown efficacy in the treatment of OCD (Greist et al,1995; Stein et al, 1995a).

Recent research has provided additional evidence that the serotonin system plays an important role in OCD. First, in at least some studies, a subset of patients with OCD is found to have elevated cerebrospinal fluid (CSF)levels of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) (Zohar and Insel, 1987), and these levels may fall during successful treatment with a SRI (Thoren et al, 1980a). Second, at least some groups of researchers have found that administration of the serotonin agonist, m-chlorophenylpiperazine, results in exacerbation of OCD symptoms in a subset of patients with OCD (Zohar et al, 1987; Hollander et al, 1992a). Such a response is no longer seen after treatment with clomipramine or a SSRI (Zohar et al, 1998; Hollander et al, 1991).

Nevertheless, other patients with OCD do not appear to have elevated CSF 5-HIAA, show no symptom exacerbation after mCPP, or do not respond to treatment with SRIs.While some of these findings may reflect methodological limitations of the relevant research, another explanation of the data is that neurochemical systems other than serotonin also play a role in OCD. The fact that tics are common in OCD (Pitman et al, 1987), and that OCD symptoms are frequent in patients with Tourette's syndrome(Hollander et al, 1993), suggests that the dopamine system may also mediate OCD symptoms.

Indeed, serotonin and dopamine are known to have significant functional interactions, and both pre-clinical and clinical findings provide support for the hypothesis that dopamine is also involved in OCD (Goodman et al,1990). Administration of dopamine agonists may result in stereotypies in animals and in increased compulsive behaviours in humans (Frye and Arnold, 1981;

Borcherding et al, 1990). Patients with OCD and co-morbid tics who fail to respond to an SRI may respond to the combination of a SRI and a dopamine blocker (McDougle et al, 1994).

Additional neurochemical systems also appear to contribute to the mediation of OCD symptoms. Administration of the opiate antagonist, naloxone, for example, may exacerbate OCD symptoms (Insel and Pickar, 1983). CSF studies of vasopressin, arginine, oxytocin, and somatostatin in OCD have led some authors to suggest that these neuropeptides may also be implicated in the disorder (Altemus et al,1992; Leckman et al, 1994). The fact that OCD often begins at the time of pregnancy suggests that hormonal factors may also play a role (Neziroglu et al, 1992).Clearly further work is necessary in order to elucidate fully the neurochemical underpinnings of OCD.

1.3.2.2. Functional Polymorphisms of Monoamine Genes

The importance of monoamine neurotransmitters in OCD,taken together with growing evidence from family studies that inherited factors contribute to the pathogenesis of OCD (Pauls et al, 1986), one avenue of recent research has been to investigate functional polymorphisms of the serotonin and dopamine systems, as well as of other possibly relevant neurochemical systems in this disorder.

Early studies provided some evidence to suggest that polymorphisms of the serotonin transporter protein gene(5-HTTP) might contribute to OCD (McDougle et al, 1998;Bengel et al, 1999). Notably, there is an association between the l/l and l/s polymorphism of this gene and higher serotonin (5-HT) blood levels (Hanna et al, 1998),and 5-HT transporter binding (as assessed by 3H-paroxetine binding to platelet membranes) has been found decreased in OCD.

Nevertheless, in an attempt to replicate this work in the Afrikaner population of South Africa, we were unable to do so (Kinnear et al, in press), consistent with a view that polymorphisms in the 5-HTTP gene may account for only a small portion of the variance in predicting OCD.

There are now also several findings indicating that dopamine system genetic polymorphisms may play a role in OCD. Two studies have found an increased number of the 7 repeat allele of the DRD4 gene in patients with tics(Cruz et al, 1993; Billett et al, 1998). There may also be other differences in dopamine polymorphisms in patients with and without tics (Nicolini et al, 1996). While several studies on various genetic findings in OCD have been inconsistent or negative (Stein et al, 2000), data on genetic differences between OCD patients with and without tics is promising insofar as it supports the literature on differences in phenomenology and treatment response in these two OCD groups.

1.3.3. Integration of Neuroanatomy and Neurochemistry

An immediate question is that of the relationship between the neurochemical considerations reviewed here and the neoroanatomical research discussed earlier. It is noteworthy that the striatum has significant serotonergic and dopaminergic innervation. Furthermore, after administration of the serotonin agonist, mCPP, there is increased cerebral blood flow in the frontal region in those OCD patients who demonstrate symptom exacerbation(Hollander et al, 1995), but not in other subjects (Hott Pian et al, 1998), perhaps suggesting a link between CTSC hyperactivity, serotonergic activation, and OCD symptoms.

Conversely, as mentioned earlier, treatment of OCD with a SRI results in a significant decrease in pre-frontal/orbito-frontal and caudate activity on functional brain imaging (Rauch and Baxter, 1998). Furthermore, working with paediatric OCD, Rosenberg and colleagues have noted decreased serotonin synthesis in ventral prefrontal cortex and caudate (Rosenberg et al, 1998), and caudate glutamatergic changes after SSRI treatment (Moore et al, 1998). Such work illustrates how the combination of neurochemical and neuroanatomical methodologies is able to advance an integrated approach to the neurobiology of OCD.

In addition, recent studies have begun to explore functional imaging predictors of response to treatment in OCD. Increased prefrontal metablism has previously been asociated with worse response to clomipramine (Swedo et al, 1989d). However, Brody et al (1998) reported that while increased left OFC cortex metabolism at baseline did correlate with worse outcome after medication, it correlated with greater improvement after behaviour therapy. The underlying mechanisms which explain these kinds of correlations are currently unclear.

1.3.4. Neurobiology of Putative OCD Spectrum Disorders

Another question that emerges from a review of the neuroanatomy and neurochemistry of OCD is whether the systems apparently responsible for the mediation of OCD are also important in the putative OCD spectrum disorders. The amount of information available to address this issue varies, however, from disorder to disorder; some have been well-researched, in others there continues to be a paucity of data.

Tourette's syndrome (TS) (Tourette's disorder) is perhaps the best researched of the putative OCD spectrum disorders. OCD and TS appear to have not only important phenomenological overlap, but also significant neurobiological intersection; CSTC circuits play a crucial role in TS, auto-immune mechanisms may be involved, serotonergic and dopaminergic systems are important, and there appears to be significant familial and genetic overlap with OCD (Hyde and Weinberger, 1995; Stein, 2000).

In trichotillomania, on the other hand, there is only limited neurobiological data. A structural imaging study suggested that the caudate is not involved, but that left putamen may be smaller in trichotillomania than in controls (O'Sullivan et al, 1997). Given evidence of putamen abnormalities in TS, it is tempting to suggest that both TS and trichotillomania are characterized by predominantly motoric symptoms whereas OCD and other spectrum disorders may involve the caudate and more cognitive symptoms (TABLE 1.8).

A number of studies have explored neuropsychological aspects of trichotillomania. In general, these have attempted to demonstrate similarities in the neuropsychology of OCD and trichotillomania and evidence of cortico-striatal involvement in both these disorders.

Rettew et al (1991) compared trichotillomania, OCD patients, and controls on a neuropsychological battery which included the Stylus Maze and the Money Road Map test. Trichotillomania patients had significantly more errors than normal controls on two subtests of the Stylus Maze, a test of visual-spatial memory, while OCD patients differed significantly from normals on one subtest. The authors concluded that differences between trichotillomania patients and controls on the Stylus Maze were consistent with spatial processing difficulties in this disorder.

Keuthen and colleagues (1996) found group differences between trichotillomania patients and normal controls in the Odd Man Out Test, a measure of ability to maintain mental set, and on the Rey-Osterreith Complex Figures Test immediate-recall, a test of nonverbal memory. While there were no group differences on the Rey-Osterreith Complex Figures Test copy score, a test of visuospatial function, dysfunction on the Odd Man Out Test was found for the stimuli of shapes but not letters. The authors wondered whether this finding reflected greater difficulty in maintaining a mental set when dealing with shapes, which are less likely to be subject to verbal mediation strategies.

Coetzer and Stein (1999) compared neuropsychological functioning in females with trichotillomania, OCD, and normal controls. While, there were no significant differences between the three groups on any of the measures studied, exploratory t-tests indicated that the combined OCD and TTM group differed significantly from normal controls in accuracy and planning on the Rey-Osterreith copy score. Again it is possible to speculate that disruption of visual-spatial coordination and sequencing tasks may reflect damage to cortico-striatal pathways in these conditions. Nevertheless, it seems that to date neuropsychology research findings have been too inconsistent to clearly support such a conclusion.

On functional imaging patients with trichotillomania were found to have increased cerebellar and right superior parietal glucose metabolic rates compared to normal controls (Swedo et al, 1991). These authors also found that anterior cingulate and orbital-frontal metabolism correlated negatively with clomipramine response, a result they previously found in OCD. Increased orbital-frontal metabolism may conceivably comprise a compensatory response in both disorders.

In terms of the pathogenesis of CSTC damage in the putative OCD spectrum disorders, the neuroimmunology of conditions other than TS has also received little attention. Swedo et al (1992) have, however, suggested that hair-pulling may develop in the context of Streptococcal infection. Stein et al (1997) have documented a case of hair-pulling associated with Sydenham's chorea. However, it is currently unclear how important auto-immune mechanisms are in general samples of hair-pulling patients.

In a series of fascinating studies, Rapoport and colleagues showed that clomipramine was superior to desipramine in a range of repetitive symptoms other than OCD. These symptoms included hair-pulling (Swedo et al,1989c) as well as a range of other stereotypic behaviours (Leonard et al, 1991; Gordon et al, 1992; Castellanos et al, 1996). Nevertheless, the data on SRIs in hair-pulling have been inconsistent, with a number of studies indicating loss of response during SRI treatment (Pollard et al, 1991), or lack of efficacy (O'Sullivan et al,1999). Similarly, mCPP challenges result in different behavioural and neuroendocrine responses in OCD and trichotillomania (Stein et al, 1995b).

As noted earlier, there is increasing evidence that dopamine plays a role in OCD and putative OCD spectrum disorders (Goodman et al, 1990), perhaps particularly in those with a marked motoric component. There is some preliminary data that dopamine also plays a role in trichotillomania. A recent report noted exacerbation of hair-pulling by methylphenidate in a series of children(Martin et al, 1998). Furthermore, preliminary open data suggests that augmentation of SRIs with classical antipsychotics (dopamine blockers) may be useful in the treatment of hair-pulling (Stein and Hollander, 1992; van Ameringen and Mancini, 1996). Nevertheless, many questions about the neurobiology of the

putative OCD spectrum disorders in general, and of trichotillomania in particular, remain unanswered.

1.4. Questions for Further Study

Indeed, several questions are raised by this review of the neurobiology of OCD for further study. In this thesis three questions in particular are explored in more detail.

First, although there is good evidence that CSTC circuits are involved in OCD, the nature and specificity of striatal volumetric changes in OCD remains unclear. To date structural imaging studies have been inconsistent, have seldom correlated imaging findings with neuropsychological data, and have not included psychiatric control groups (such as patients with a putative OCD spectrum disorder). A study was undertaken of patients with OCD, patients with trichotillomania, and normal controls using magnetic resonance imaging (MRI) and neuropsychological testing. The study rationale, methods, and results are detailed in Chapter Two.

Second, although it seems clear that the serotonin system is involved in the mediation of OCD, an immediate question regards the role of specific serotonin sub-receptors, as well as the nature of their contribution in different regions of the CSTC circuit. Given evidence from preclinical and clinical research that orbitofrontal 5-HT_{1D} receptors might be involved in mediating OCD,using sumatriptan challenge together with single photon emission tomography (SPECT). The study rationale,methods, and results are detailed in Chapter Three.

Third, although SRIs are a first line of pharmacotherapy of OCD and a number of putative OCD spectrum disorders,the question

arises of the appropriate pharmacotherapy for OCD patients who are refractory to these agents. Although there is a rationale for using dopamine blockers, the classical antipsychotics run the risk of important adverse events, including tardive dyskinesia. The introduction of the atypical neuroleptics may, however, provide an alternative option, and an augmentation study using risperidone was therefore undertaken. The study rationale, methods, and results are detailed in Chapter Four.

2. NEUROANATOMY OF OCD: A STUDY OF MAGNETIC RESONANCE IMAGING AND NEUROPSYCHOLOGICAL FUNCTION

2.1. Background

As noted in Chapter One, structural brain imaging studies in OCD have been inconsistent. Both a computerized tomography study (Luxenberg et al, 1988) and a magnetic resonance imaging study (Robinson et al, 1995) found decreased volume of the caudate in OCD patients, but there have also been a number of contrary findings, including no change in volume (Kellner et al, 1991; Stein et al, 1993),and increased volume (Scarone et al, 1992).

Furthermore, volumetric studies in OCD have not employed psychiatric controls; there is particularly little evidence on whether hypothesized abnormalities in OCD are specific, or are also seen in putative OCD spectrum disorders such as trichotillomania (TTM). A "striatal topography" model of OCD (Rauch and Baxter, 1998) would suggest that the caudate is involved in OCD, but that the putamen is involved in disorders characterized by more motoric symptoms, such as Tourette's syndrome (Singer et al, 1993) and trichotillomania.

Finally, the question of whether structural and volumetric findings in OCD are related to neuropsychological findings as not been well explored. This question is important given an early study demonstrating that only OCD patients with increased neurological soft signs had increased ventricular-brain ratios (VBR) (Stein et al, 1993). Although the majority of OCD patients do not have as many neurological soft signs as those assessed in that study, the question of heterogeneity in OCD should not be ignored.

A magnetic resonance imaging (MRI) study was undertaken in OCD patients, TTM psychiatric controls, and healthy normal controls. All patients also received a neurological soft sign examination and neuropsychological testing. In the clinical setting, TTM is seen predominantly in women (Christenson et al, 1992), and the study was therefore confined to females. The hypothesis was that OCD patients and TTM patients would differ from controls on brain imaging and neuropsychology.

2.2. Methods

2.2.1. Subjects

13 OCD and 17 TTM adult patients were recruited from the OCD Clinic of our tertiary hospital. All subjects were interviewed with the Structured Clinical Interview for the Diagnosis of Axis-I Disorders (First et al, 1994). Patients met DSM-IV criteria (American Psychiatric Association, 1994) for either OCD or TTM. In the OCD patients, mean score on the Yale-Brown Obsessive-Compulsive Scale (YBOCS) (Goodman et al, 1989) was 25.4 $\pm$ 6.9, while in the TTM patients, mean score on the compulsions sub-scale of the YBOCS was 9.3 $\pm$ 1.6. Patients who met DSM-IV criteria for major depression or a psychotic disorder, who had a history of substance abuse, or who had a significant medical or neurological disorder were excluded from the study. 12 healthy controls were volunteers from the hospital's laboratory service. All subjects gave informed written consent after the protocol had been accepted by the University of Stellenbosch Medical School ethics committee.

2.2.2. Magnetic Resonance Imaging

Magnetic resonance images were acquired with the South African Medical Research Council's Elscint 0.5 T Gyrex V imager. Routine spin-echo technique protocols were used to demonstrate the brain parenchyma (T1-weighted) and cerebrospinal fluid spaces (T2-weighted). The following multislice sequences were performed: 1) a T1-weighted axial study (TR500/TE10ms, slice width 6mm, slice gap 3mm); 2) a T2-weighted axial study (TR2600/TE20,90ms, slice width 6mm, slice gap 3mm); and 3) a T1-weighted axial interleaved study (TR500/TE30ms, slice width 3mm,slice gap 0mm) of the basal ganglia. All axial slices were planned parallel to the orbito-meatal line.

2.2.3. Volumetric Measures

Interleaved studies of the basal ganglia were examined using the scanner's automatic region-of-interest procedure. On each slice in which the caudate nucleus was clearly seen (typically 4 slices), this procedure was used to measure total brain volume, right and left ventricular volume, and right and left caudate volume. All scans were rated by two raters, who were blind to patient diagnosis. The lentiform nucleus was not included in the study as it soon became apparent that acceptable inter-rater reliability for measurements of this structure was not possible on our scans.

2.2.4. Neuropsychology and Neurological Soft Signs

All subjects were assessed by a single neuropsychologist who was blind to diagnosis. The assessment aimed to measure set-shifting and visual-spatial function, which have previously been shown to be impaired in OCD (Stein,1994) and TTM (Rettew et al, 1991). The battery comprised 1) four subscales of the South African Weschler Adult Intelligence Scale (comprehension, similarities, picture completion, and block design) (Human Sciences Research Council, 1969), 2) the Stroop test (Stroop, 1935) and the Austin maze (Walsh, 1985), 3) the Rey-Osterreith (Osterrieth, 1944; Lezak, 1983) and the Hooper Visual Organization (Hooper, 1983) tests. A neurological soft sign examination previously studied in OCD and TTM patients (Hollander et al, 1990; Stein et al, 1994a) was also administered.

2.3. Results

2.3.1. Demographics

Mean ages and number of years of education of the 3 group were calculated (TABLE 2.1). On analysis of variance (ANOVA), there was a significant group difference ($F=5.35$, $p=.009$), with OCD patients significantly older than both TTM patients ($t=2.75$, $p=.01$) and healthy controls ($t=2.84$, $p=.01$). There was also a significant difference in number of total years of education ($F=5.57$, $p=.008$), with OCD patients having significantly less education than healthy controls ($t=3.65$, $p=.002$).

2.3.2. Volumetric Measures

Mean volumes of the caudate and lateral ventricles (expressed as a percentage of total brain) and ventricular-brain ratio (VBR) were calculated (Table One) Correlation of volumetric measures obtained by the two readers for the right caudate (r=.99), left caudate (r=.96), right ventricle (r=.97), left ventricle (r=.93), and VBR (r=.94) were all significant (p<.001).

On analysis of variance (ANOVA) (three group comparison) there were, however, no significant differences between groups on these measures. Co-varying the ANOVA for age and for education yielded the same negative result. Repeated measures analysis of variance (RMANOVA) of bilateral measures was again not significant.

2.3.3. Correlations

Pearson's correlations were calculated in order to assess the association between caudate and lateral ventricles (expressed as a percentage of total brain) and ventricular-brain ratio and neuropsychological and neurological soft sign measures in all subjects. Decreased left caudate volume was significantly associated with decreased intelligence quotient (r=.37, p=.04), was significantly associated with increased impairment on the Rey-Osterreith test (i.e. copy dysfunction) (r=.37, p=.04) and with increased impairment in the Stroop test (i.e. difference between time for reading with and without interference) (r=.41, p=.02), as well as with total neurological soft signs (r=.33, p=.05). The Rey-Osterreith test involves copying a complex figure and therefore assesses visuoperceptual and visuomotor skills, while the Stroop test involves reading words which are printed in a

color other than the one spelled and therefore assesses ability to shift set.

2.4. Discussion

The main findings of this study were that 1) adult women with OCD, TTM, and healthy controls did not differ on MRI volumetric measures of the caudate and ventricles and 2) decreased left caudate volume correlated significantly with increased impairment on some neuropsychological tests of set-shifting and of visual-spatial function and with increased neurological soft signs.

Although perhaps disappointing, the failure to find group differences here is consistent with previous research which has shown no significant differences between women with OCD, TTM, and normal controls on neurological soft signs (Stein et al, 1994a). It is notable that males are more likely than females to exhibit developmental neurological dysfunction and this may account for increased numbers of males with early-onset OCD (Swedo et al, 1989a). Females may develop OCD at other developmental periods such as pregnancy, when different causal mechanisms are involved (Neziroglu et al, 1992).

Another possibility is that the measures used in this study were not sufficiently robust to obtain differences. The magnet of the MRI used had relatively low power, and we were unable to measure accurately structures such as the lenticular nucleus, although putamen volume may be reduced in patients with trichotillomania (O'Sullivan et al, 1997) and other OCD spectrum disorders such as Tourette's syndrome (Singer et al, 1993).

A final consideration is that abnormalities in the caudate in patients with OCD and trichotillomania may not be homogenous. Caudate volume has been reported to be reduced (Luxenberg et al, 1988; Robinson et al, 1995), normal (Kellner et al, 1991; Stein et al, 1993) or increased (Scarone et al, 1992) in OCD. Different pathogenic mechanisms may differentially affect caudate size - for example, auto-immune reactions after streptococcal infection may result in increased caudate volume (Giedd et al, 2000).

It is of interest that correlations were obtained between low left caudate volume and increased neuropsychological dysfunction and increased neurological soft signs. The hypothesis that the caudate mediates OCD symptoms is supported by findings of a relationship between neurological disorders involving the caudate and these symptoms, and by caudate abnormalities on structural and functional imaging studies of OCD (Wise and Rapoport, 1989). Interestingly, a previous study found correlations between dysfunction on the Stroop test and caudate metabolic activity on positron emission tomography (Martinot, 1990). However, caudate abnormalities are not necessarily specific to OCD, but rather may be associated with a variety of psychopathological processes (McHugh, 1989).

The relationship between OCD and TTM remains a subject for further consideration and research (Swedo, 1993; Stein et al, 1994b). The negative findings obtained here are clearly not the last word on the subject. Future investigation, perhaps combining functional brain imaging and neurochemical challenges, may be useful in clarifying the role of the striatum not only in OCD, but also in putative OCD spectrum disorders.

3. NEUROCHEMISTRY OF OCD: A STUDY COMBINING SPECT WITH PHARMACOLOGICAL CHALLENGE

3.1. Background

As noted in Chapter One, evidence that serotonin plays a crucial role in OCD includes pharmacotherapeutic dissection studies and pharmacological challenge studies. High doses of serotonin reuptake inhibitors administered for relatively long periods of time have frequently (although not invariably) proven more effective than equivalent regimes of noradrenergic reuptake inhibitors in the treatment of OCD (Zohar and Insel, 1987; Leonard et al, 1989). In addition, administration of serotonin agonists such as m-chlorophenylpiperazine (mCPP) (Zohar et al, 1987; Charney et al, 1988; Hollander et al, 1992; Piggott et al, 1992) and sumatriptan (Zohar, 1993; Stern et al, 1998) have often (although again not invariably) resulted in symptom exacerbation or a relatively blunted neuroendocrine response in OCD patients, and after treatment with serotonin reuptake inhibitors there is a normalization of these responses (Zohar et al, 1988; Hollander et al, 1991).

As also discussed earlier, evidence that cortico-striatal circuits play an important role in underpinning OCD symptoms includes studies of OCD in patients with neurological lesions of the basal ganglia and frontal regions, research on involuntary movements in OCD patients, investigation using structural and functional brain imaging techniques, and treatment of refractory OCD patients with neurosurgical disruption of cortico-striatal circuits. In general, functional studies have shown increased baseline activity in the orbito-frontal cortex and caudate, with increased activity during behavioural provocation and decreased activity after

treatment (Rauch and Baxter, 1998). One study combined pharmacological challenge and brain imaging techniques in a determination of regional cerebral blood flow (rCBF) during mCPP administration, and found that patients who demonstrated acute exacerbation of OCD symptoms after mCPP administration had relatively increased cortical perfusion (Hollander et al, 1995). In a second study mCPP did not lead to OCD symptom exacerbation, and was accompanied by global reduction in rCBF (Hott-Pian et al, 1998).

Despite these studies, much remains to be understood about the neurobiology of OCD. One important question concerns the role of specific serotonin sub-receptors in different brain regions in OCD. Pre-clinical data has shown that the serotonin auto-receptor may play a particularly important role in OCD. The serotonin reuptake inhibitors (SRIs) are the only antidepressants that act to desensitize the terminal serotonin auto-receptor ($5\text{-}HT_{1B}$ in rats, $5\text{-}HT_{1D}$ in guinea pig and humans) in rat hippocampus. Furthermore, Blier and colleagues (El Mansari et al, 1995) found that treatment of guinea pigs with high doses of SSRIs for 8 weeks resulted in desensitization of $5\text{-}HT_{1D}$ receptors in orbitofrontal cortex. Such desensitization was not, however, seen after only 3 weeks of treatment, after use of lower SSRI doses, or after electroconvulsive therapy (ECT) - paralleling clinical findings in OCD.

Interestingly, the main difference in the biochemical profile of mCPP, which exacerbated OCD symptoms in some clinical studies, and MK-212, which did not appear to do so (Bastani et al, 1990), is that mCPP also has $5\text{-}HT_{1D}$ agonist properties. A possible role for this sub-receptor in OCD is supported by the reported exacerbation of OCD symptoms shortly after administration of sumatriptan (Zohar, 1993), an agent with specific $5\text{-}HT_{1D}$ agonist effects (Ferrari and Saxena, 1993; Peroutka, 1993).

In this study, the functional role of the serotonin terminal auto-receptor in OCD was investigated by undertaking single photon emission computed tomography (SPECT) with technecium-99m hexamethylpropylene amine oxime (Tc-99m HMPAO) during sumatriptan and placebo challenge. The hypothesis was that, as in the case of mCPP challenge (Hollander et al, 1995), exacerbation of OCD symptoms would be accompanied by increased cortical metabolism and thus blood flow, and more specifically by increased activity in the orbitofrontal-striatal circuit. There was also the expectation that as in the case of mCPP challenge (Hollander et al, 1993), exacerbation of OCD symptoms would be associated with a relatively poor response to subsequent treatment with SRIs.

3.2. Methods

3.2.1. Subjects

A number of subjects (mean age 35.8 ñ 13.3 years, 10M/4F) were recruited from the OCD Clinic of our tertiary hospital. All subjects were interviewed with the Structured Clinical Interview for the Diagnosis of Axis-I Disorders (First et al, 1994). All subjects met DSM-IV diagnostic criteria for OCD and did not meet criteria for co-morbid depression. Mean score on the Yale-Brown Obsessive- Compulsive Scale (YBOCS) (Goodman et al, 1989) was 24.2 $\pm$ 3.4, while mean score on the Montgomery-Asberg Depression Rating Scale (MADRS) was 11.2 $\pm$ 3.8. Medication free interval prior to the procedure was sufficiently long to ensure that level of medication was zero. Subjects with significant medical or neurological illness were excluded from the study. All patients

gave informed written consent after the protocol had been accepted by the University of Stellenbosch Medical School ethics committee.

3.2.2. Sumatriptan Challenge

Sumatriptan (100mg orally) or placebo were administered at 8:30 a.m. according to a randomized counter-balanced double-blind design. Obsessive-compulsive symptoms were rated by a trained clinician at -30, 0, 30, 60, 90, 180, and 240 minutes using the Clinician Challenge Obsessive-Compulsive Scale (Hollander et al, 1992a). This is a clinician-rated scale for OCD severity. It rates time, anxiety, and control over obsessions; and time, anxiety, and control over compulsions. With appropriate training, as was undertaken prior to this study, inter-rater reliability is very high (Hollander et al, 1992). After completion of each set of challenges, this scale was used to determine whether OCD symptoms had decreased, increased, or remained constant on the sumatriptan day.

3.2.3. SPECT Imaging

To achieve a baseline state of cerebral metabolism, subjects were placed supine in a quiet, dimly lit room for 30 minutes prior to injection of the radiopharmaceutical. At 90 minutes after administration of sumatriptan or placebo, 555 MBq (15 mCi) Tc-99m HMPAO was injected in an arm vein through a previously placed intravenous cannula. The baseline state was continued for 10 minutes after injection, whereafter SPECT imaging commenced. SPECT imaging of the brain was performed with the subject's head supported by a head rest, using a dual detector gamma camera

(Elscint, Helix) equipped with a pair of fanbeam collimators. A laser alignment system was used to ensure accurate and reproducible positioning of the patient's head. 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 distance of the camera detectors from the centre of the camera were noted for each subject and the same measurements were used for the second study. Data were acquired in a 128 x 128 image matrix in 3 degree steps at 15 seconds per step.

3.2.4. SPECT Analysis

Data were reconstructed by filtered backprojection, using a Metz (5, 14) filter. The Chang method was used for attenuation correction. Thirty-two transaxial tomographic slices, with a slice thickness of 1 pixel, were reconstructed parallel to a line drawn from the inferior aspect of the frontal lobe through the middle of the cerebellum on a sagittal slice at mid-cerebellar level. This line approximates the orbito-meatal line. Using these internal landmarks for generating the transaxial slices ensured reproducible and comparable slicing of the two studies performed on each subject. A set of 16 coronal slices (perpendicular to the angle of the transaxial slice) and 16 sagittal slices were also generated for each study.

Semi-quantitative analysis of the imaging data was performed using a set of 278 cortical and sub-cortical regions-of-interest (ROI) (139 ROI for each brain hemisphere), using the transaxial slices. These ROI were placed as follows (FIGURE 1): 6 ROI for each cerebellar hemisphere (on two different slices), 5 ROI for each mesial temporal lobe, 2 for each anterior temporal lobe, and 6 for

each lateral temporal lobe. The frontal lobes were caudo-cranially divided into inferior frontal (below the level of the thalami and basal ganglia), mid frontal (at the level of the thalami and basal ganglia) and superior frontal (above the level of the thalami and basal ganglia) regions. Each of these regions was again subdivided antero-posteriorly into anterior, lateral and posterior frontal regions. Two of the inferior frontal slices were used for the placement of 4 anterior frontal, 6 lateral frontal and 6 posterior frontal cortical ROI on each side. Three mid- frontal slices were used for placing 6 anterior frontal, 9 lateral frontal and 9 posterior frontal cortical ROI pm each side. Six contiguous slices were used for the placement of a total of 18 ROI (3 per slice) on each side of the anterior cingulate gyrus. The rest of the ROI were placed in a similar fashion on the inferior parietal and occipital cortex (single slice below the level of the thalami and basal ganglia), mid-parietal and occipital cortex (single slice at the level of the thalami and basal ganglia) and superior parietal cortex (single slice above the level of the thalami and basal ganglia). Two slices were used for placing ROI on the primary visual cortex. Subcortical ROI were placed on the caudate nucleus and putamen on each side, using 3 contiguous slices. Three contiguous slices were also used for the bilateral placement of thalamic ROI.

With the exception of an irregular ROI used in the lateral temporal region, all other ROI were rectangular. The rectangular ROI were all of a 2 x 2 pixel size, with the exception of 6 ROI on each side of the anterior cingulate (2 x 1 pixel size each) and one ROI on each side of the lateral temporal cortex (5 x 2 pixel size) and one on each side of the superior parietal cortex (5 x 2 pixel size).

An automated computer algorithm was used to determine the counts per pixel in each ROI. The counts per pixel of all ROI in a

specific anatomic region (e.g. lateral temporal, inferior-anterior frontal) were averaged to obtain the mean counts per pixel for each anatomical region. A total of 23 anatomical regions on each side of the brain were eventually available for analysis (cerebellum, temporal cortex (anterior, mesial, and lateral), inferior frontal cortex (anterior, lateral, and posterior), mid frontal cortex (anterior, lateral, and posterior), superior frontal cortex (anterior, lateral, and posterior), anterior cingulate gyrus, inferior and mid occipital cortex, primary visual cortex, caudate nucleus, putamen, and thalamus). The mean counts per pixel for each anatomical region were subsequently expressed as a ratio of the mean whole brain counts (region-to-whole brain ratio), as well as a ratio of the mean cerebellar counts per pixel (region-to-cerebellar ratio). The mean whole brain counts were determined according to the method described by Harris et al (1994).

After placing the ROI, all ROI were stored as a template and subsequently transferred to the transaxial slices of the second study performed on that subject. All ROI were placed by a single observer, who was blind to the challenged clinical status of subjects.

3.2.5. Pharmacotherapy

Subsequent to scanning, subjects underwent treatment with a selective serotonin reuptake inhibitor (SSRI). 11 patients were treated with citalopram, the most specific of the SSRIs currently available, for 12 weeks. Dosage was initiated at 20mg daily, titrated upward by 20 mg every 2 weeks if the medication was tolerated and if clinical response was inadequate. Obsessive-compulsive symptoms were rated at 2 weekly intervals using the Y-

BOCS and a Clinical Global Impressions (CGI) change score. Also included in the analysis, however, were the results of the 3 remaining patients - one who was treated with sertraline 200mg for 12 wks after scanning, one who was treated with fluoxetine 60mg for 12 wks after scanning, and one who was lost to follow-up but who had previously been treated with sertraline 200mg for 12 wks.

3.2.6. Data Analysis

Data was transferred to a statistical package for analysis. To minimize inflation of Type I errors, analysis focused a priori on the oribitofrontal-striatal circuit. Thus, repeated measures analysis of variance (RMANOVA) was undertaken with drug (sumatriptan, placebo) as the between factor, while hemisphere (left, right), anatomical area (orbitofrontal, basal ganglia, thalamo-cingulate), and anatomical regions were the within factors. Post-hoc 2-tailed t-tests were then calculated. Pearson's correlations were also conservatively 2-tailed. All analyses were performed using the region-to-whole brain ratio and the region-to-cerebellar ratio.

3.3. Results

3.3.1. Behavioural Response

Behavioural response to the sumatriptan challenge was heterogenous. 4 patients experienced an exacerbation of symptoms, 4 patients experienced an improvement of symptoms, and 6 patients experienced no change. Consistent with this finding, comparison

of peak change in OCD symptoms after administration of sumatriptan and placebo, with paired t-tests, revealed no significant differences. There were no differences in behavioural response (ratio of patients showing exacerbation, no change, or worsening) between male and female patients.

3.3.2. SPECT Findings

RMANOVA showed no significant effect for drug, but did show a significant hemisphere by anatomical area by anatomical regions by drug effect (TSQ=7.85, F=3.77, df=2,25, p=.04), using the region-to-whole brain ratio. This result remained significant when using the region-to-cerebellar ratio (TSQ=7.59, F=3.65, df=2,25, p=.04).

On paired t-tests of anatomical areas using region-to-whole brain ratio, there was a significant increase in right putamen activity after sumatriptan in comparison with placebo (t=2.12, p=.05), and a tendency towards increased activity in right thalamus (t=2.10, p=.06). On paired t-tests of anatomical areas using region-to-cerebellar ratio, there was a significant increase in right thalamus activity (t=2.31, p =.04) after sumatriptan, and a tendency towards increased activity in right caudate (t=1.94, p=.07) and in left inferior-anterior frontal lobe (t=1.76, p=.10) (FIGURE 2).

3.3.3. Correlation of Behavioural and SPECT Findings

On sumatriptan challenge, there was a significant association between increase in OCD symptoms and decreased activity in some frontal areas (using region-to-whole brain activity), namely the

left inferior-posterior frontal area (r=.55, p=.04) and medial-posterior frontal area (r=.58, p=.03). There was also a significant correlation between increase in OCD symptoms and increased activity in the right cerebellum (r=.62, p=.02). None of these associations was present during placebo challenge.

3.3.4. Correlation of Pharmacotherapy and SPECT Findings

On sumatriptan challenge there was a significant association between response to SSRI treatment (on the CGI) and activity in certain brain areas (using region-to-whole brain activity). Specifically, on sumatriptan challenge, decreased response to treatment was associated with decreased activity in the right inferior-posterior frontal area (r=.55, p=.04) and with increased activity in the right putamen (r=.54, p=.05). On placebo challenge, there was an association of decreased response to treatment with decreased activity in the left inferior-lateral frontal area (r=.56, p=.04) and with increased activity in the right lateral temporal area (r=.63, p=.01). These associations remained when patients treated with SSRIs other than citalopram were excluded from the analysis (although one correlation, that of decreased response to treatment with decreased inferior- lateral frontal area on placebo challenge, no longer reached statistical significance).

3.3.5. Comparison of Patients with Symptom Relief and Symptom Exacerbation

One way analysis of variance (ANOVA) was used to compare activity in anatomical areas (using region-to-whole brain ratio) in

patients with symptom exacerbation, no change, and symptom relief after sumatriptan. With the sumatriptan challenge data, there was a significant group difference in the right putamen (F=4.4, df=13, p=.04) and superior parietal area (F=4.0, df=13, p=.05), and a trend towards a significant difference in the left inferior-anterior frontal area (F=2.8, df=13, p=.10) and left cerebellum (F=3.6, df=13, p=.06). Compared to patients with symptom relief (Table 2), patients with symptom exacerbation had significantly increased activity in the right putamen (t=2.57, p=.04) and significantly decreased activity in the right inferior-anterior frontal area (t=3.41, p=.01). Using the placebo challenge data, there was a significant group difference in the right cingulate (F=4.0, df=13, p=.05), and a trend towards significance in the left thalamus (F=3.3, df=13, p=.07) and right cerebellum (F=3.4, df=13, p=.07). However, post-hoc t-tests did not reveal significant differences in activity between patients with symptom exacerbation and symptom relief. Finally, there was also a trend towards a significant difference between groups in response to treatment (F=3.0, df=13, p=.09). Compared to those with symptom relief, patients with symptom exacerbation after sumatriptan had significantly poorer response to treatment (t=2.78, p=.03).

3.4. Discussion

The main findings of this study were 1) that behavioural response to sumatriptan challenge in OCD was heterogenous; 2) that on sumatriptan challenge there was a significant association between increase in OCD symptoms and decreased activity in some frontal areas; 3) that there was an association between decreased activity in an inferior frontal area and worse response to treatment with a SSRI and also patients with symptom exacerbation after sumatriptan had poorer response to treatment.

While a number of previous studies of serotonin agonists in OCD have shown exacerbation of symptoms after their administration (Zohar et al, 1987; Hollander et al, 1992a), there has also been a good deal of heterogeneity within studies (for example, only 50% of patients in one study had exacerbation (Hollander et al, 1992a)) as well as inconsistency between studies (for example, several studies have failed to find that oral mCPP exacerbates OCD symptoms (Charney et al, 1988; Piggott et al, 1992; Goodman et al, 1995)). While these inconsistencies may reflect methodological difficulties with challenge studies, they may also indicate variation in the underlying neurobiology of OCD. Certainly, variation in behavioural response to serotonin agonists is consistent with variation in response rate of OCD to treatment with SSRIs (about 50% in some studies). Indeed, there is a growing body of literature on the heterogeneity of symptoms, associated features, family history, and treatment response in OCD (Baer, 1994). Furthermore, responses to serotonergic challenges in OCD may also vary across gender (Hollander et al, 1992a).

It is currently unclear what the neurobiological basis for such differences in behavioural response to serotonin agonists in OCD is. One possibility is that neurochemicals other than serotonin are particularly important in some subgroups of OCD patients (for example, dopamine may play a crucial role in patients with comorbid tics, or hormonal factors may determine differential responses in males and females). Alternatively, differences in compensatory processes to an underlying dysfunction may play a role; Swedo et al (1989D) for example, have suggested that on functional imaging a subgroup of OCD patients with increased baseline compensatory orbitofrontal activity can be demonstrated, and that this pattern of activity predicts subsequent poor responses to pharmacotherapy with a SRI. Certainly, a number of

studies have replicated this predictive association (Brody et al, 1998; Saxena et al, 1999).

Along these lines, it is possible that sumatriptan challenge resulted in increased activity in the terminal auto-receptor, with subsequent decrease in compensatory frontal activity, and an increase in OCD symptoms in a sub-group of challenged patients. Conversely, ongoing pharmacotherapy with SSRIs seems to be associated with desensitization of the serotonin terminal auto-receptor (El Mansari et al, 1995), 5-HT neuronal activation, and ultimately normalization of functional activity in orbitofrontal-striatal circuits and improvement in OCD symptoms (Baxter et al, 1992; Insel, 1992; Swedo et al, 1989d).

Previous work (Hollander et al, 1993) and the data here indicate that OCD patients who demonstrate behavioural exacerbation in response to a serotonin agonist have poorer outcome during treatment with a SSRI. Perhaps such patients have increased baseline compensatory orbitofrontal activity and serotonergic systems that are less able to respond to pharmacological manipulation. Analysis of a larger sample would, however, be necessary in order to reach definitive conclusions about sub-types of OCD and their responses to sumatriptan challenge and to subsequent pharmacotherapy (Stern et al, 1998).

The correlation between exacerbation of OCD symptoms and decreased frontal activity was different from that which we had expected given the previous finding of increased cortical flow in patients with exacerbation of OCD symptoms after mCPP adminstration (Hollander et al, 1995). Although sumatriptan may act on $5\text{-}HT_{1D}$ heteroreceptors, it is possible that sumatriptan differs from mCPP in acting primarily as an agonist at pre-synaptic 5HT-1D receptors, while mCPP has important effects at post-synaptic serotonin receptors. There may, however, also be significant

differences in the response of adjacent brain areas to behavioural and pharmacological challenges. For example, Rauch et al (1994) found that left anterior orbitofrontal cortex correlated positively with OCD symptoms after behavioural provocation, while left posterior orbitofrontal cortex correlated negatively with such symptoms.

Additional work combining functional brain imaging with different serotonergic pharmacological challenges will be necessary in order to dissect fully the functional neuroanatomy of the serotonin system in OCD. Studies using 5-HT_{1D} agonists with greater blood-brain penetration than sumatriptan may be particularly useful. Given a recent report of sumatriptan induced panic attacks in anxious patients (Loi et al, 1996), the specificity of the response to sumatriptan in different anxiety disorders as well as in healthy controls requires investigation.

The findings here are, however, consistent with a growing body of literature pointing to the importance of the serotonin terminal auto-receptor in OCD. While it is undoubtedly the case that too narrow a focus on one neuroreceptor or another in OCD will result in oversimplification (Goodman et al, 1990), further attention to the 5-HT_{1D} receptor in OCD may be particularly fruitful. The convergence of clinical and pre-clinical data on a possible role for this receptor in OCD is noteworthy.

4. PHARMACOTHERAPY OF OCD: A STUDY AUGMENTING SRI WITH A DOPAMINE BLOCKER

4.1 Background

As noted in Chapter One, since early reports of the efficacy of the serotonin reuptake inhibitor clomipramine in the treatment of obsessive-compulsive disorder (OCD) (Fernandez-Cordoba and Lopez-Ibor Alino, 1967), a range of research has confirmed the selective value of the serotonin reuptake inhibitors in this disorder (Zohar and Insel, 1987; Greist et al, 1995; Stein et al, 1995a) as well as in some of the putative OCD spectrum disorders (Swedo et al, 1989c; Leonard et al, 1991; Gordon et al, 1992; Castellanos et al, 1996; Hollander et al, 2000).

Nevertheless, serotonin reuptake inhibitors are effective in only around 50-60% of patients with OCD (Greist et al, 1995; Stein et al, 1995a), and the response may be even less robust in certain putative OCD spectrum disorders such as trichotillomania (Pollard et al, 1991; O'Sullivan et al, 1999), suggesting that other neurochemical systems may also be important in these conditions. McDougle and colleagues (1994) reported that OCD patients refractory to serotonin reuptake inhibitors may respond to augmentation of these agents with classical neuroleptics, particularly if tics are present. Similarly, this combination of agents has been reported effective in trichotillomania (Stein and Hollander, 1992; van Ameringen and Mancini, 1996) and Tourette's syndrome (Hawkridge et al, 1996).

These findings are consistent with a range of pre-clinical and clinical evidence indicating that dopamine plays a role in OCD and possibly related disorders such as Tourette's syndrome (Goodman et

al, 1990; Hollander et al, 1992b). Furthermore, the recent introduction of atypical neuroleptics with favorable adverse effect profiles, such as risperidone, has encouraged the use of augmentation strategies with these agents in the treatment of OCD (Jacobsen, 1995; Kopala and Honer, 1994; Koran et al, 1999; McDougle et al, 1995a; Saxena et al, 1996), as well as in the treatment of trichotillomania (Jacobsen, 1995) and Tourette's syndrome (Giakas, 1995).

Here we review data collected on patients who failed to respond to a serotonin reuptake inhibitor, and who were treated with risperidone augmentation.

4.2 Methods

Patient details are tabulated (TABLE 4.1). All patients received at least 12 weeks of treatment of a SSRI at maximally tolerated doses, before being given risperidone. Risperidone was initiated at 1mg daily, and titrated up according to symptom response and tolerability. Patients were assessed after 4 weeks of augmentation treatment using the Yale-Brown Obsessive Compulsive Scale (Goodman et al, 1986) as well as with a Clinical Global Impression (CGI) change score. Effect of treatment on these measures was also tabulated (TABLE 4.1).

4.3. Results

Eight patients who met DSM-IV criteria for OCD had received augmentation of serotonin reuptake inhibitors with risperidone. None of these patients had tics or a history of tics. None of

these patients met diagnostic criteria for schizotypal personality disorder. After risperidone augmentation, three patients reported very much or much improvement in OCD symptoms, one patient noted minimal to much improvement, three patients had no change in symptoms, and one patient was unable to tolerate side effects of increased anxiety and irritability. Two of the three responders (CGI change score $\leq$ 2) elected to continue the medication, and improvement has been maintained for 10 and 3 months respectively. The patient with minimal to much response elected to discontinue risperidone two months later after experiencing significant "slowing down" of thought processes.

Five patients who met DSM-IV criteria for trichotillomania, but not for OCD, had received augmentation of serotonin reuptake inhibitors with risperidone. None of these patients had tics or a history of tics. On this regime, three patients reported significant clinical improvement, a fourth reported minimal to much improvement, and a fifth patient experienced no change. Two of the responders have maintained improvement for some months on this regime, but a third elected to discontinue risperidone three months later after noticing increased symptoms of depression.

Three patients who met DSM-IV criteria for Tourette's syndrome, and who had co-morbid OCD symptoms, had received augmentation of serotonin reuptake inhibitors with risperidone. In one patient, there was significant improvement of both tic and OCD symptoms after addition of risperidone. However, after two months of treatment, the patient noted dramatic worsening of mood, and the risperidone was discontinued. In the second patient, OCD symptoms were already fully controlled when risperidone was used in place of pimozide. On this regime, the patient experienced no change in OCD symptoms and further improvement in tics. In the third patient, OCD symptoms had shown some improvement on the

combination of a SSRI and pimozide, and replacement of pimozide with risperidone did not result in any further change.

4.4. Discussion

Given the advantageous adverse effect profile of risperidone compared with classical neuroleptics (Chouinard et al, 1993), evidence that this agent is similarly effective in the augmentation of serotonin reuptake inhibitors in treatment refractory OCD would have obvious clinical importance. A review of a series of cases of patients with OCD, trichotillomania, and Tourette's syndrome, suggests that in patients refractory to treatment with serotonin reuptake inhibitors, risperidone augmentation may indeed be effective for some within a relatively short space of time. At the relatively low doses of risperidone used extrapyramidal side effects were not problematic, but other adverse effects such as increased depression did at times lead to discontinuation of this agent.

Clearly there are significant limitations to the data presented here. These include the limited sample size, and the lack of a placebo-or dose-controlled treatment design. It might be argued that increased duration of exposure to serotonin reuptake inhibitors rather than risperidone augmentation was responsible for clinical improvement, although in all patients duration of monotherapy was at least 12 weeks. Alternatively, it is possible that risperidone alone has anti-OCD effects, although there is little data to suggest that neuroleptic monotherapy is effective in this disorder (McDougle et al, 1995b; Bruun and Budman, 1996; Lombroso et al, 1995). In addition, early response to pharmacotherapy, perhaps particularly in trichotillomania (Pollard et al, 1991), is not always long-lasting. Nevertheless, data here

is consistent with a very recently reported controlled trial of risperidone in treatment-refractory OCD (McDougle et al, 2000). It is theoretically possible that risperidone augmentation results in increased blood levels of the serotonin reuptake inhibitor so leading to a therapeutic response (Byerly and DeVane, 1996). However, in their studies of neuroleptic augmentation, McDougle et al (1994, 2000) found no relationship between serotonin reuptake inhibitor blood level and treatment response. Furthermore, response to the combination of a serotonin reuptake inhibitor and an atypical antipsychotic is consistent with preclinical data indicating involvement of both serotonergic and dopaminergic systems in stereotyped movements (Goodman et al, 1990). In addition, this finding is consistent with reports of the use of serotonin reuptake inhibitors with classical antipsychotics in OCD (McDougle et al, 1994), trichotillomania (Stein and Hollander, 1992; van Ameringen and Mancini, 1996), and Tourette's syndrome (Hawkridge et al, 1996) as well as with previous anecodotal reports of risperidone augmentation in these disorders (Kopala and Honer, 1994; McDougle et al, 1994; Saxena et al, 1996; Jacobsen, 1995). As in this study, this previous literature has indicated that the response to dopaminergic augmentation occurs relatively quickly.

There are, however, also several anecdotal reports of exacerbation of OCD symptoms by atypical neuroleptics (Hwang et al, 1993; Patel and Tandon, 1993; Remington and Adams 1994). Experimental administration of metergoline (Benkelfat et al, 1989), a 5-$HT_{1/}$/5-HT_2 antagonist, or of ritanserin (Ergovesi et al, 1992), a 5-$HT_{2A/2C}$ antagonist, during SRI treatment can reverse the therapeutic effects of SRI treatment. It is similarly possible that clozapine and risperidone, both of which are 5-HT_2 antagonists, may on occasion exacerbate OCD. In our patients, although risperidone did not worsen obsessive-compulsive symptoms, a number of subjects experienced increased depression after addition of this agent. 5-

HT_2/D_2 affinity ratios are higher for clozapine than for risperidone, perhaps accounting for differences in the effects of these agents. Alternatively, there is evidence that particular effects of combined serotonergic-dopaminergic blockade are observed in only a narrow dose range (Kapur and Remington, 1996), perhaps accounting for these apparently differences in the data.

In conclusion, additional research is necessary to determine the indications for, and optimal dose and duration of, risperidone and other atypical antipsychotics in the augmentation of serotonin reuptake inhibitors in OCD and putative OCD spectrum disorders. It is possible that this augmentation strategy may be most effective in patients with both OCD and tics (McDougle et al, 1994), although this has not clearly been shown here or elsewhere (Saxena et al, 1996; McDougle et al, 2000). Atypical antipsychotic augmentation may also be useful in OCD spectrum disorders characterized by stereotypical kinds of symptoms. Nevertheless, attention to the possible adverse affects of these agents is also warranted.

5. CONCLUSION: DIRECTIONS FOR FUTURE RESEARCH ON OBSESSIVE-COMPULSIVE DISORDER

In this chapter the neuroanatomy, neurochemistry, and pharmacotherapy of OCD are briefly reconsidered in light of the studies in Chapters Two to Four, and areas that require future research are addressed. In general, it would seem that future work on OCD should make use of a range of neuroanatomic, neurochemical, neurogenetic, and neuroimmunological data in order to assess the variance contributed by multiple different factors to the pathogenesis and outcome of this complex and heterogenous disorder.

5.1. Neuroanatomy

In Chapter One, evidence that cortico-striatal-thalamic- cortical (CSTC) circuits play a crucial role in mediating both OCD and putative OCD spectrum disorders was outlined. In Chapter Two a study of magnetic resonance imaging (MRI) in OCD patients, trichotillomania patients, and healthy controls was described. The study was unable to find a signficant group difference, and potential methodological reasons for this were considered.

Indeed, despite the negative study described herein, there is no reason to revise the hypothesis that OCD is mediated by CSTC circuitry. Although the role of other circuits should not be neglected in future work (Jenike et al, 1996), there is a growing realization of the importance of different CSTC loops in mediating a range of psychiatric symptoms including those of OCD (Cummings, 1993). In particular, striatal function has increasingly been associated with the development, maintenance, and selection of

motoric and cognitive procedural strategies. Cortico-striatal dysfunction may result in inappropriate release of behaviours such as washing, hoarding, and so on.

A crucial question for future research will be that of ascertaining how putative damage to the CSTC circuits in OCD comes about. The possibility that anti-striatal antibodies may play a role has been strengthened by the description of the syndrome of pediatric autoimmune neuropsychiatric disorder associated with streptococcus (PANDAS) (Swedo et al, 1998). Such patients appear to respond to immunomodulatory interventions such as plasma exchange and intravenous immunoglobulin (Perlmutter et al, 1999).

Notably, in PANDAS basal ganglia volumes are increased during symptom exacerbation, but decrease following symptom attenuation (Giedd et al, 2000). This finding may explain the broad range of findings in previous work, including the study described herein, on basal ganglia volumes in OCD. Similarly, a previous study found that structural brain imaging findings were crucially dependent on neuropsychiatric sub-type of the disorder, with increased ventricular-brain ratio correlating with increased neurological soft signs (Stein et al, 1993). Thus, in exploring the neuroanatomy of OCD in the future, it will be crucial to focus on questions of heterogeneity, including differences in the timing of the brain scan in relation to the development of the disorder.

Similarly, further exploration of differences and overlap in neuroanatomical, neuroimmunological, and other factors in OCD and OCD spectrum disorders may be useful. In a study of the B lymphocyte antigen D8/17, a marker of susceptibility to developing complications after Streptococcal infection, for example, our group found that OCD patients differed from normal controls, but that trichotillomania subjects did not (Niehaus et al, 1999). The paucity of literature on structural brain imaging in some of the

putative OCD spectrums disorders (such as trichotillomania, body dysmorphic disorder, and hypochondriasis) is remarkable, and presents an opportunity for further work.

5.2. Neurochemistry

In Chapter One, evidence that the serotonin system is crucial in mediating OCD was described. In Chapter Three, preclinical evidence that the 5-HT_{1D} auto-receptor might play a particularly important role was presented, and clinical data that were consistent with this hypothesis were presented. Once again, however, the heterogeneity of the findings was emphasized.

Clearly further work on specific 5-HT sub-receptors in OCD is important (for example, using newly available radiopharmaceuticals with affinity for specific 5-HT sub-receptor), and may well lead to therapeutic advances. In addition to work on the 5-HT_{1D} receptor, the 5-HT_2 receptor also deserves additional as a potential locus for therapeutic agents (Delgado and Moreno, 1998). Nevertheless, it should also be emphasized that despite frequent discussion of the "serotonergic mediation of OCD", there is to date little evidence that serotonergic dysfunction per se plays a causal role in the disorder. The serotonin system is in close interaction with many any other systems, and it is quite possible that more primary lesions lie elsewhere.

Indeed, given recent advances in human genomics, a crucial next step is to determine the role of various functional polymorphisms in a range of different neurochemical systems in contributing to OCD and putative OCD spectrum disorders. Indeed, recent work confirms evidence from early family studies (Pauls et al, 1986) that specific genetic factors can play a crucial role in OCD (De

Marchi et al, 1998; Devor and Magee, 1999). There is also preliminary polymorphism evidence underlining the validity of the distinction between OCD patients with and without tics (Cruz et al, 1993; Billett et al, 1998; Nicolini et al, 1996).

Nevertheless, there are also inconsistent and negative findings. Data in Afrikaner OCD patients from our group, for example, has not been consistent with work elsewhere (Niehaus et al, in press; Kinnear et al, in press), suggesting either that previous findings account for only a small percentage of the genetic variance in OCD, or that there are significant ethnic differences in the genetic mediation of OCD. An important milestone, however, was the publication of a complete genome screen in TS, which yielded 2 suggestive regions (4q and 8p) (The Tourette Syndrome Association International Consortium for Genetics, 1999). It is unlikely to be long before similar work is published in OCD.

5.3. Pharmacotherapy

In Chapter One, the value of serotonin reuptake inhibitors (SRIs) in OCD and putative OCD spectrum disorders was reviewed; the introduction of these medications was clearly a significant advance. Nevertheless, many patients are refractory to these agents, and in Chapter Four data was presented to suggest the potential value of augmentation of an SRI with an atypical antipsychotic. These data suggest that additional studies on other more recently available atypical antipsychotics be undertaken, and that questions of optimal dose and duration be addressed. Augmentation strategies using agents with other mechanisms of action should also be explored (Cora-Locatelli et al, 1998; McDougle et al, 1999).

In addition, particularly given the small sample sizes of available augmentation studies, a focus in future work on the heterogeneity of OCD and on determining the value of augmentation strategies for different sub-groups would seem valuable. It seems clear that OCD patients with comorbid tics are less likely to respond to SRIs than patients without tics (McDougle et al, 1993). In contrast, early trials found no association between other potential predictors such as age, sex, severity of OCD, and duration of illness, and response to clomipramine (Thoren et al, 1980b; De Vaugh-Geiss et al 1991).

Subsequent studies have not, however, been entirely consistent. Predictors of non-response of OCD to SRIs in some work have included male gender (Steiner et al, 1996), increased severity of OCD (Alarcon et al, 1993), a longer (Alarcon et al, 1993; Ravizza et al, 1995) or shorter (Steiner et al, 1996) duration of illness. A re-analysis of the multicentre clomipramine trial found that those with the best chance of responding had onset at a later age and were not significantly depressed (Ackerman et al, 1994).

In a study of the citalopram data, we found only that subjects with longer duration of OCD, more severe OCD symptoms, or previous SSRI use were less likely to be responders in the citalopram trial (Stein et al, submitted). In contrast, subjects who received higher medication doses for longer periods of time in the citalopram trial were more likely to be responders. These points are in some ways obvious; they do not advance an understanding of the pathogenesis of OCD, but only underline the importance of efforts to prevent the all to long lag between symptom onset and clinical diagnosis of OCD (Hollander et al, 1997; Stein et al, 1996), and the potential value of appropriate psychoeducation for people with OCD (Stein et al, 1997; Stein et al, in press).

5.4 Combining Approaches

A flaw in the studies presented here is that we were unable to study the same patients with different methodologies (MRI, SPECT, D8/17, etc). We have several times emphasized the heterogeneity of OCD. In all likelihood, as in other complex psychiatric disorders defined currently only by diagnostic convention, there will turn out to be significantly different kinds of OCD mediated in part by different factors. In our present state of relative ignorance it seems that a "shotgun approach" in which a range of different factors are assessed in multiple patients cannot be avoided.

Of course there may be significant overlap in different factors; genetic factors contribute to OCD and TS, CSTC dysfunction is seen in both OCD and putative OCD spectrum disorders, and such dysfunction may be caused by particular neurogenetic and neuroimmunologial factors. On the other hand, there are likely to be significant differences in underlying neurobiology between, say, the child who develops OCD and tics immediately after Streptococcal infection, the adolescent with a significant family history of both OCD and TS who develops hoarding during adolescence, and the women with no family history of OCD or tics who develops compulsive washing during pregnancy.

In short, and in summary, there have been significant advances in OCD; we now understand more about the neuroanatomy, neurochemistry, and pharmacotherapy of OCD and the way in which these overlap. At the same time, however, there are significant gaps in our understanding; there is much that we do not know about what appears to be a complex and somewhat heterogenous disorder, and a good deal of future research will be necessary in order to delineate its neurobiology more completely. The work undertaken

herein is presented in the hope that it will help encourage such research to proceed.

TABLE 1.1 COMMON OBSESSIONS AND COMPULSIONS IN OCD

Obsession	Compulsion
Contamination	Washing, cleaning
Danger to self/others	Checking locks, stove, switches
Symmetry concerns	Lining up, straightening
Blasphemy, morality	Praying, confession
Saving concerns	Hoarding

TABLE 1.2 DIAGNOSTIC CRITERIA FOR OCD (adapted from DSM-IV)

A Either obsessions or compulsions: Obsessions as defined by (1), (2), (3), and (4): (1) recurrent and persistent thoughts, impulses, or images that are experienced, at some time during the disturbance, as intrusive and inappropriate and that cause marked anxiety or distress (2) the thoughts, impulses, or images are not simply excessive worries about real-life problems (3) the person attempts to ignore or suppress such thoughts, impulses, or images, or to neutralize them with some other thought or action (4) the person recognizes that the obsessional thoughts, impulses, or images are a product of his or her own mind (not imposed from without as in thought insertion) Compulsions as defined by (1) and (2): (1) repetitive behaviors (e.g., hand washing, ordering, checking) or mental acts (e.g., praying, counting, repeating words silently) that the person feels driven to perform in response to an obsession, or according to rules that must be applied rigidly (2) the behaviors or mental acts are aimed at preventing or reducing distress or preventing some dreaded event or situation; however, these behaviors or mental acts either are not connected in a realistic way with what they are designed to neutralize or prevent or are clearly excessive

B. At some point during the course of the disorder, the person has recognized that the obsessions or compulsions are excessive or unreasonable.

C The obsessions or compulsions cause marked distress, are time consuming (take more than 1 hour a day), or significantly interfere with the person's normal routine, occupational (or academic) functioning, or usual social activities or relationships.

D. If another Axis I disorder is present, the content of the obsessions or compulsions is not restricted to it.

E. The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

TABLE 1.3 STRUCTURAL BRAIN IMAGING FINDINGS IN OCD

Study	Modality	Findings
Insel et al, 1983	CT	No caudate differences
Behar et al, 1984	CT	↑ ventricle:brain ratio (VBR)
Luxenberg et al, 1988	CT	↓ caudate volume
Kellner et al, 1991	MRI	No striatal differences
Scarone et al, 1992	MRI	↑ R caudate volume
Stein et al, 1993	CT	↑ VBR with ↑ neurological soft signs
Robinson et al, 1995	MRI	↓ caudate volume
Jenike et al, 1996	MRI	R caudate shift
Aylward et al, 1996	MRI	No caudate differences

CT = computerized tomography
MRI = magnetic resonance imaging
VBR = ventricular-brain ratio

TABLE 1.4 FUNCTIONAL BRAIN IMAGING FINDINGS IN OCD: RESTING STATE

Study	Modality	Brain Activity
Baxter et al, 1987	PET	↑L orbital gyrus, caudate
Baxter et al, 1988	PET	↑ orbitofrontal
Swedo et al, 1989	PET	↑ anterior cingulate
Nordahl et al, 1989	PET	↑ orbitofrontal
Benkelfat et al, 1990	PET	↑ frontal, caudate, putamen
Perani et al, 1995	PET	↑ cingulate, lenticulate, thalamus
Machlin et al, 1991	SPECT	↑ medial frontal
Rubin et al, 1992	SPECT	↑orbitofrontal, ↓ caudate
Lopez-Ibor, 1995	SPECT	↑basal ganglia, hippocampus

PET = positron emission tomography
SPECT = single photon emission tomography

TABLE 1.5 FUNCTIONAL BRAIN IMAGING FINDINGS IN OCD: SYMPTOMS PROVOCATION

Study	Modality	Caudate	A/LOFC	Paralimbic
Rauch et al, 1994	PET	Yes	Yes	Yes
McGuire et al, 1994	PET	Yes	Yes	Yes
Breiter et al, 1996	PET	Yes	Yes	Yes

PET = positron emission tomography
A/LOFC = Anterior/lateral orbitofrontral cortex

TABLE 1.6 FUNCTIONAL IMAGING FINDINGS IN OCD AND OCD SPECTRUM: PRE/POST TREATMENT

Study	Modality	Treatment	↓Activity
Baxter et al, 1997	PET	Trazodone	Caudate (?)
Benkelfat et al, 1990	PET	Clomipramine	Orbitofrontal, caudate
Hoehn-Saric et al, 1991	SPECT	Fluoxetine	Medial frontal
Baxter et al, 1992	PET	Fluoxetine/Behavioral	Caudate
Swedo et al, 1992	PET	Mostly clomipramine	Orbitofrontal
Perani et al, 1995	PET	SSRIs	Cingulate
Mollina et al, 1995	SPECT	Clomipramine	Orbitofrontal, ant. cingulate, R caudate
Schwartz et al, 1996	PET	Behavioral	Caudate

PET = positron emission tomography
SPECT = single photon emission computerized tomography

TABLE 1.7 STRUCTURAL BRAIN IMAGING FINDINGS IN OTHER ANXIETY DISORDERS

Study	Diagnosis	Modality	Findings
Potts et al, 1994	Social Phobia	MRI	↓basal ganglia volume (?)
Myslobodsky, 1995	PTSD	MRI	↑cavum septum pellucidum
Canive et al, 1997	PTSD	MRI	↑focal white matter lesions
Gurvitz et al, 1996	PTSD	MRI	hippocampus volume negatively correlated with symptom severity
Bremner et al, 1995	PTSD	MRI	↓R hippocampus (negatively correlated with memory deficits)
Bremner et al, 1997	PTSD (child abuse)	MRI	↓ L hippocampus
Schuff et al, 1997	PTSD	MRI	↓R hippocampus
Stein et al, 1997	PTSD (child abuse)	MRI	↓L hippocampus (negatively correlated with symptom severity)

TABLE 1.8 STRUCTURAL BRAIN IMAGING FINDINGS IN OCD SPECTRUM DISORDERS

Study	Diagnosis	Modality	Findings
Peterson et al, 1993	TS	MRI	R lenticulate shift
Singer et al, 1993	TS	MRI	R lenticulate shift
Hyde et al, 1995	TS twin pairs	MRI	↓ caudate volume
O'Sullivan et al, 1997	TTM	MRI	R putamen shift

TS = Tourette's syndrome
TTM = trichotillomania

TABLE 2.1 COMPARISON OF MRI VOLUMES IN WOMEN WITH OCD, TTM, AND HEALTHY CONTROLS

	OCD (n=13)	**TTM** (n=17)	**CONTROLS** (n=12)	**ANOVA**
Age	42.2 ± 10.9	32.5 ± 8.4	36.1 ± 9.9	p=.03
Education	12.9 ± 1.7	14.1 ± 1.7	15.6 ± 1.	p=.002
Right caudate	0.79 ± 0.11	0.80 ± 0.11	0.82 ± 0.12	ns
Left caudate	0.78 ± 0.07	0.82 ± 0.18	0.85 ± 0.07	ns
Right ventricle	0.64 ± 0.19	0.75 ± 0.26	0.62 ± 0.20	ns
Left ventricle	0.76 ± 0.17	0.87 ± 0.35	0.71 ± 0.25	ns

MRI = magnetic resonance imaging
OCD = obsessive-compulsive disorder
TTM = trichotillomania

TABLE 3.1 COMPARISON OF ACTIVITY IN REGIONS OF INTEREST AFTER SUMATRIPTAN AND PLACEBO CHALLENGE (REGION-TO-WHOLE BRAIN RATIO)

	Sumatriptan (n=14)	**Placebo** (n=14)	**p**
Right Hemisphere			
Cerebellum	1.98	1.99	ns
Temporal - Anterior	1.17	1.21	ns
- Median	1.28	1.28	ns
- Lateral	1.34	1.34	ns
Frontal - Inferior-anterior	1.53	1.54	ns
-lateral	1.60	1.61	ns
-posterior	1.54	1.56	ns
- Medial-anterior	1.50	1.51	ns
-lateral	1.64	1.64	ns
-posterior	1.56	1.57	ns
- Superior-anterior	1.52	1.53	ns
-lateral	1.64	1.64	ns
-posterior	1.62	1.64	ns
Cingulum	1.61	1.60	ns
Parietal - Inferior	1.53	1.50	ns
- Medial	1.58	1.56	ns
- Superior	1.58	1.57	ns
Occipital - Inferior	1.41	1.42	ns
- Medial	1.38	1.39	ns
- Superior	1.65	1.63	ns
Thalamus	1.80	1.74	.04
Caudate	1.64	1.69	ns
Putamen	1.59	1.55	.07

Left Hemisphere

Cerebellum	1.96	1.99	ns
Temporal - Anterior	1.19	1.18	ns
- Median	1.32	1.29	ns
- Lateral	1.28	1.27	ns
Frontal - Inferior-anterior	1.53	1.56	ns
-lateral	1.59	1.58	ns
-posterior	1.55	1.50	ns
- Medial-anterior	1.51	1.49	ns
-lateral	1.66	1.65	ns
-posterior	1.57	1.56	ns
- Superior-anterior	1.53	1.52	ns
-lateral	1.62	1.61	ns
-posterior	1.64	1.64	ns
Cingulum	1.65	1.62	ns
Parietal - Inferior	1.53	1.50	ns
- Medial	1.53	1.52	ns
- Superior	1.55	1.55	ns
Occipital - Inferior	1.38	1.42	ns
- Medial	1.34	1.32	ns
- Superior	1.64	1.63	ns
Thalamus	1.78	1.78	ns
Caudate	1.70	1.66	ns
Putamen	1.56	1.53	ns

TABLE 4.1 RISPERIDONE AUGMENTATION OF SEROTONIN REUPTAKE INHIBITORS (SRIs)

Sex	Age	Dx	SRI trial	YBOCS pre-risperidone	Risperidone trial	YBOCS post-risperidone	CGI
F	54	OCD	Paroxetine 60mg daily x 14 wks	24	2mg daily x 4 wks	16	2
F	28	OCD	Paroxetine 60mg daily x 12 wks	28	1mg daily x 1 wk	28	4
M	43	OCD	Paroxetine 60mg daily x 9 mnths	20	1mg daily x 4 wks	16	2.5
M	27	OCD	Clomipramine 200mg daily x 6 mnths	28	2mg daily x 4 wks	28	4
M	19	OCD	Fluoxetine 40mg daily x 12 wks	28	1mg daily x 4 wks	29	4
F	59	OCD	Clomipramine 250mg daily x 7 mnths	14	1mg daily x 4 wks	4	1
M	33	OCD	Citalopram 60mg daily x 3 mnths	18	1mg daily x 4 wks	8	1
F	40	OCD	Clomipramine 250mg daily x 9 mnths	18	1mg daily x 4 wks	18	4
F	22	TTM	Clomipramine 200gm daily x 8 mnths	5	1mg daily x 4 wks	3	2

M	45	TTM	Clomipramine 50mg daily x 12 mnths	5	1mg daily x 4 wks	3		2.5
F	43	TTM	Citalopram 40mg daily x 36 mnths	8	1mg daily x 4 wks	8		4
F	31	TTM	Clomipramine 175mg daily x 12 wks	8	1mg daily x 4 wks	4		2
F	23	TTM	Clomipramine 100mg daily x 6 mnths	6	1mg daily x 4 wks	3		2
M	20	TS	Citalopram 60mg daily x 10 mnths	24	4mg daily x 4 wks	14	OCD - 2 tics - 2	
M	16	TS	Fluoxetine 40mg plus pimozide 4mg daily x 12 mnths	0	4mg daily x 4 wks	0	OCD - 4 tics - 2	
M	24	TS	Citalopram 60mg plus pimozide 8mg daily x 18 mnths	20	3mg daily x 4 wks	20	OCD - 4 tics - 4	

YBOCS=Yale-Brown Obsessive-Compulsive Scale (Compulsion scale only in trichotillomania patients)
CGI=Clinical Global Impression Change Scale (1=very much improved, 2=much improved, 3=minimally improved, 4=no change)

TTM=trichotillomania
TS=Tourette's syndrome

Figure 1: Cortical and sub-cortical regions-of-interest (ROI) on transaxial slices.

Temporal ROI, 2 mesial, 1 anterior an 3 lateral on each side.

Cerebellar ROI, 3 on each side

Inferior parietal ROI, 4 on each side.
Occipital ROI, 3 on each side.
Visual Cortex ROI, 3 on each side.

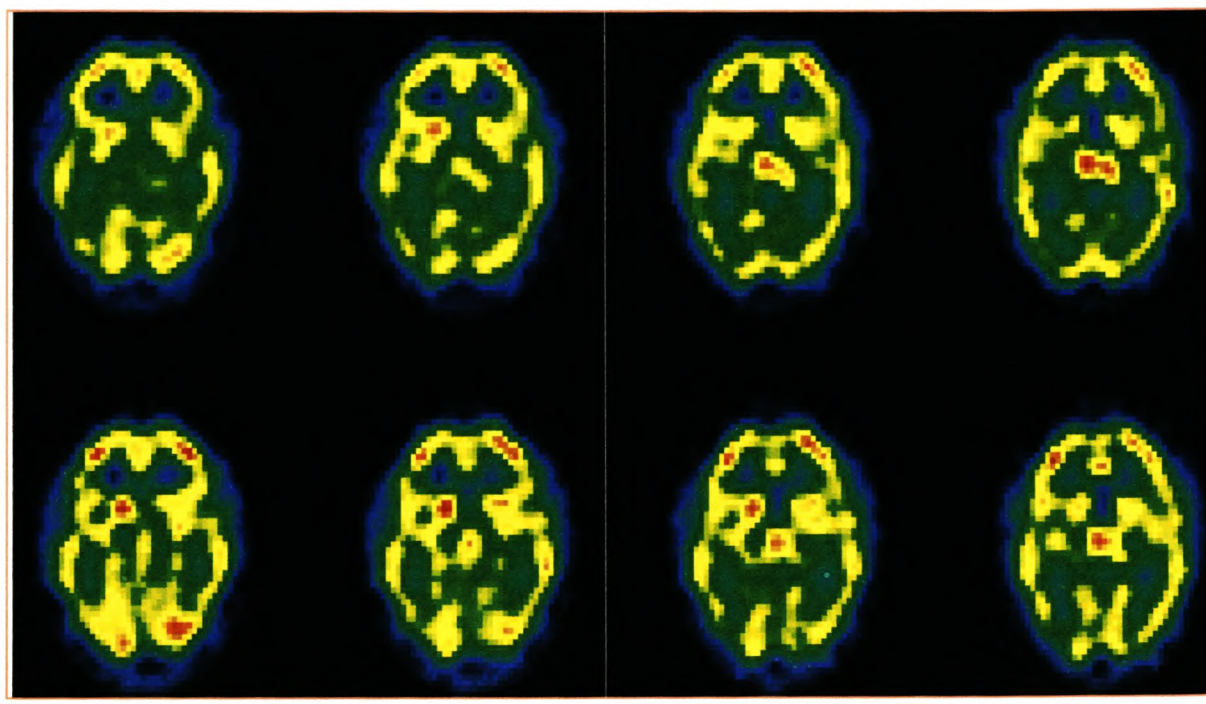
Superior parietal ROI, 4 on each side

Inferior frontal ROI, 2 anterior,
3 lateral and 3 posterior on each side

Mid frontal ROI, 2 anterior, 3 lateral and 3 posterior, on each side.
Cingulate gyrus ROI, 3 on each side.
Basal ganglia ROI, 4 on each side.
Thalamic ROI, 2 on each side.

Superior frontal ROI, 2 anterior,
2 lateral and 2 posterior on each side

FIGURE 2: EXAMPLE OF DIFFERENCES IN ACTIVITY ON BRAIN IMAGING AFTER PLACEBO (TOP ROW) AND SUMATRIPTAN (BOTTOM ROW) SEEN IN ONE SUBJECT



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