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Introduction

Obsessive-compulsive (OC) symptoms occur in a variety of clinical conditions including psychiatric disorders such as tic and impulse control disorders, developmental disorders such as autism and Asperger's Disorder, or as acquired phenomena in neurological disorders such as epilepsy, frontotemporal dementia, Huntington's and Parkinson's diseases, and following brain injury (Alegret et al., 2001; Anderson, Louis, Stern& Marder, 2001; Berthier, Kulisevsky, Gironell& Lopez, 2001; Isaacs, 2004; Russell, Mataix-Cols, Anson& Murphy, 2005; Sharma & Gupta, 2002; Tonkonogy, Smith& Barreira, 1994). Not surprisingly, investigations of OC symptomatology have primarily focused on idiopathic Obsessive-Compulsive Disorder (OCD), which has been investigated from clinical, pathophysiological and neuropsychological perspectives. To date, few neuropsychological investigations have compared idiopathic OCD to patient groups in whom OC symptoms are acquired.

Several lines of evidence link OCD to a disturbance of the frontal lobes (particularly the orbitofrontal cortex) and the basal ganglia (Kwon et al., 2003). The sites of cerebral pathology of frontotemporal dementia (FTD) overlap considerably with the areas of pathophysiology thought to be implicated in OCD. Mendez, Perryman, Miller, Swartz and Cummings (1997) comment on the intriguing nature of the presence of compulsive behaviours in FTD given the association of OCD with metabolic changes in orbitofrontal cortex and in frontal-subcortical circuits in the caudate nuclei.

Indeed, there does appear to be overlap in both the sites of cortical disruption, as well as the nature of the compulsive phenomena in OCD and FTD. In FTD, the OC symptoms reported in the literature include, but are not limited to, motor stereotypies and tic-like movements. FTD patients have been reported to produce compulsive behaviours that are both complex as well as highly individual to the sufferer. The degree of overlap in the sites of cortical disruption between these two very different clinical conditions may end with this propensity towards engaging in compulsive behaviours. However, there may also be neuropsychological predictors of OC symptoms common in both groups.

Obsessions in OCD are thought to be directly related to a state of high anxiety (a fear of contamination, for instance) rarely seen in FTD. Thus the presence of OC symptoms in FTD seems paradoxical, as damage to the frontal lobes results in reduced anxiety and concerns (Snowden, Neary & Mann, 2001). Anxiety alone cannot entirely explain the pathogenesis of OC symptoms, as not all individuals who experience clinical levels of anxiety exhibit OC symptoms. An understanding of OC symptoms in the presence versus the absence of anxiety may shed light on the underlying aetiology of OC symptoms. Unlike OCD, the compulsive symptoms seen in FTD are less commonly preceded by obsessions (although it is perhaps the difficulty in assessing obsessions which may explain the lack of research investigating their presence in patients with dementia) and they are not often reported as ego-dystonic or senseless to the sufferer, though they may cause the family and carers distress.

Neuropsychological models attempt to account for how "the surface features of the disorder relate to underlying information processing deficits" (Frampton, 2003, p.39). It has been argued that the repetitive behaviours and intrusive thoughts characteristic of OCD make the disorder a prime candidate for neuropsychological modelling, while helping our understanding and treatment of OCD. The significant cognitive disturbance associated with FTD may help to highlight the role of less obvious neuropsychological deficits associated with OC symptoms in OCD. Additionally, investigations of compulsive symptoms in FTD could lead to further insights into the neurological underpinnings of OCD. With treatment response rates estimated at only 50% across treatment strategies (Gedanke, Bravo, Belotto & Miguel, 2001) and OCD achieving tenth place in the leading causes of disability in the world (World Health Organisation [WHO], 1996), novel treatment strategies that take into account any underlying neuropsychological deficits warrant attention.

Chapter 1

Literature Review I: Obsessive-Compulsive Disorder

1.1 Clinical characteristics of Obsessive-Compulsive Disorder

Obsessive-Compulsive Disorder (OCD) is a chronic, disabling anxiety disorder. It is the fourth most common psychiatric disorder (Pigott, 1998), affecting approximately 2-3% of the population (Abramowitz, Brigidi & Roche, 2000; Karno, Golding, Sorenson & Burnam, 1988). Clinically, it is characterised by the presence of persistent and recurrent intrusive and senseless ideas, thoughts, urges, and images (obsessions) that cause marked anxiety, as well as by cognitive and physical activities that are performed in a repetitive and/or ritualistic way (compulsions), usually in an attempt to neutralize anxiety caused by an obsession (American Psychiatric Association [APA], 2000). Both obsessions and compulsions are generally recognised as excessive or unreasonable by the patient, who frequently attempts to ignore or suppress them (APA, 2000).

The Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV; APA, 2000) diagnostic criteria for (idiopathic) OCD are as follows:

The patient has obsessions or compulsions, or both.

1. Obsessions: The patient must have *all* of:

   (i) Recurring, persisting thoughts, impulses or images inappropriately intrude into awareness and cause marked distress or anxiety

   (ii) These ideas are not just excessive worries about ordinary problems.

   (iii) The patient tries to ignore or suppress these ideas or to neutralize them by thoughts or behaviour.

   (iv) There is insight that these ideas are a product of the patient's own mind.

2. Compulsions. The patient must have *all* of:

   (i) The patient feels the need to repeat physical behaviours (checking the stove to be sure it is off, hand washing) or mental behaviours (counting things, silently repeating words).

   (ii) These behaviours occur as a response to an obsession or in accordance with strictly applied rules.

(iii) The aim of these behaviours is to reduce or eliminate distress or to prevent something that is dreaded.

(iv) These behaviours are either not realistically related to the events they are supposed to counteract or they are clearly excessive for that purpose.

3. During some part of the illness the patient recognizes that the obsessions or compulsions are unreasonable or excessive.
4. The obsessions and/or compulsions are associated with at least one of:
    - Cause severe distress
    - Take up time (more than an hour per day)
    - Interfere with the patient's usual routine or social, work or personal functioning
5. If the patient has another Axis I disorder, the content of obsessions or compulsions is not restricted to it.
6. The symptoms are not directly caused by a general medical condition or by substance use, including medications and drugs of abuse.
7. DSM-IV specifies if insight is poor. That is, during most of this episode the patient does not realize that these thoughts and behaviours are unreasonable or excessive.
8. DSM-IV specifies preoccupations typical of other Axis I disorders that must be ruled out: appearance (Body Dysmorphic Disorder); food (Eating Disorders); being seriously ill (Hypochondriasis); guilt (Mood Disorders); sexual fantasies or urges (Paraphilias); drugs (Substance Use Disorders); hair pulling (Trichotillomania) (APA, 2000).

Both obsessions and compulsions can take a variety of forms. The most common obsessions, according to the DSM-IV (APA, 2000) are fear of contamination, thoughts of aggression, pathological doubt, excessive focus on bodily functions, need for order, and sexual imagery. The most common compulsions are washing and cleaning, counting, checking, requesting or demanding assurances, repetition of previously performed actions, and ordering.

Most often obsessions occur with associated compulsions, however less commonly, compulsions can occur in the absence of an obsession and vice-versa (Menzies & de Silva, 2003). An example would be the compulsion to count squares on a tile floor

whenever a tile floor is encountered, in the absence of a precipitative obsession. Temporal and cultural factors are sometimes incorporated into patients' OC symptoms, such as obsessions related to a fear of contracting AIDS is common in the present day, though was not reported 20 years ago. Specific religious ideas and behaviours such as praying and other symbolic rituals are also incorporated into some patients' OC symptoms (Menzies & de Silva, 2003).

OCD occurs equally in men and women and with a similar prevalence in children and adults (March & Mulle, 1998). OCD first occurring in later life is relatively uncommon, with an annual incidence of 0.6% in the over 65s (Eaton et al., 1989). The symptomatic expression of OCD also differs in children and adults, with children showing higher rates of compulsive rituals without clearly delineated obsessions (Savage & Rauch, 2000).

The disorder may co-occur with other psychiatric illnesses such as major depression, other anxiety disorders, and eating disorders (Crino & Andrews, 1996). Of note is the high incidence of OCD (30-50%) in patients with Gilles de la Tourette syndrome, a tic disorder characterised by involuntary motor and vocal tics. There is a higher concordance of OCD in monozygotic than in dizygotic twins, and there is a higher incidence of OCD in first-degree relatives of both OCD and Tourette's syndrome patients than in the general population (Rubin & Harris, 1999).

Despite its phenotypic heterogeneity, the DSM-IV and other standard nomenclatures (e.g., International Classification of Diseases-10; WHO, 1994) have treated OCD as a unitary nosological entity (Mataix-Cols, Rosario-Campos & Leckman, 2005). This is at odds with the fact that distinct OCD subtypes have been identified, with both investigators and clinicians routinely describing "washers," "checkers," "hoarders" amongst other symptom-based differentiations. Studies suggest different OCD symptom profiles across participants. For example, Goodman et al. (1989) conducted a factor analysis of the Yale-Brown Obsessive-Compulsive Scale (YBOCS) in more than 300 OCD patients. Four factors emerged, accounting for the 60% of the total variance: obsessions and checking, symmetry and order, cleaning and washing, and hoarding (Leckman et al., 1997). Calamari, Wiegartz & Janeck (1999) found five stable patient subgroups when assessing 106 OCD patients with the YBOCS symptom checklist: harming, hoarding, contamination, certainty and obsessional. These studies

and the clinical presentation of OCD, point to "subtypes" of OCD, producing clinically differentiated types of obsession and compulsions.

The clinical presentation of OCD can resemble some features of organic mental disorders, especially those related to "frontal syndrome," characterized by deficits in executive abilities, including the ability to flexibly shift cognitive set, along with cognitive rigidity in problem solving, and poor impulse control and response inhibition as important features (Dolan et al., 1993; Grafman et al., 1996; Lacerda et al., 2003).

1.2 Cerebral pathology in Obsessive-Compulsive Disorder

Current neurobiological models of OCD based on in vivo functional and structural brain imaging studies implicate dysfunction of the frontal-basal-thalamo-cortical circuitry in the pathophysiology of idiopathic OCD (Cummings, 1993; Kwon et al., 2003; Modell, Mountz, Curtis & Greden, 1989; see Figure 1.2). Examination of glucose metabolism in OCD patients by means of positron emission tomography (PET) has indicated increased metabolism in the orbitofrontal gyri and caudate nucleus relative to control samples of non-patients or depressed patients (Baxter et al., 1987; Baxter, Schwarzt & Mazziotta, 1988; Nordahl et al., 1989). Increased metabolism in the orbitofrontal gyri has been replicated consistently, whereas disruption in the caudate nucleus has not been as consistently reported. Regions of activity in the subcortical areas of patients with OCD have differed across studies, implicating the caudate nucleus in some (Insel & Winslow, 1992), and in others the putamen (Perani et al. 1995), and the thalamus (Kwon et al., 2003; Perani et al., 1995; Swedo et al., 1989). One study found no significant changes in any of subcortical regions (Nordahl et al., 1989).

A study by Kwon et al. (2003) measured cerebral glucose metabolic rates (using PET) to determine whether the clinical features and cognitive deficits of OCD can be explained by frontal-subcortical dysfunction. Fourteen OCD patients and 14 matched controls completed clinical and cognitive evaluation, including four sets of neuropsychological tests that assessed the two areas of neuropsychological dysfunction that have most often been reported as being impaired in this population: Executive function (EF) and visual memory. EF is a broad term used to describe

higher-order cognitive abilities, including set shifting, mental flexibility, abstract reasoning, concept formation, response inhibition, self-monitoring and planning ability. Three tests measured EF (Trail Making Test, Wisconsin Card Sorting Task, word fluency) and one measured visual memory (Rey-Osterreith Complex Figure Test). In OCD patients, the right orbitofrontal cortex showed increased metabolic activity and the left parietal-occipital junction showed decreased metabolic activity. The study also found executive and visual memory dysfunction in the OCD group, the regional metabolic rate revealing that a variety of brain regions, including prefrontal cortices, the putamen and the cerebellum, were involved in poor processing of executive control and visual memory in the OCD patients (Kwon et al., 2003). Such correlations were not observed in the normal control group. Despite the small sample size, these preliminary results point to distinct features of cerebral metabolic activity for performing cognitive tasks, as well as the presenting OC symptoms. The authors conclude, "these abnormal features are particularly apparent in the frontal sub-cortical circuits [for both symptomatic expression and the cognitive deficits in OCD] and are also possible in the parietal-subcortical circuits" (Kwon et al., 2003, p.45).

A meta-analysis of in vivo structural magnetic resonance imaging (MRI) studies in psychiatric disorders differentiated areas of brain anatomy in a number of anxiety disorders (Brambilla, Brale, Caverzasi & Soares, 2002). The authors concluded that the structure of the orbitofrontal and basal ganglia regions are reported to be anatomically abnormal in OCD, differentiating OCD from other anxiety disorders where the temporal lobe has been found to be reduced (in Panic Disorder) and abnormal hippocampal shrinkage was shown (in Post Traumatic Stress Disorder).

Interventions that provoke obsessive-compulsive symptoms have been found to activate orbitofrontal and basal ganglia brain regions (McGuire et al., 1994; Rauch et al., 1994; Breiter et al., 1996). For instance, Breiter et al. (1996) investigated the pattern of positive activation during functional magnetic resonance imaging (fMRI) of 13 non-depressed OCD patients and six normal controls during symptom provocation. Symptom provocation for participants with a fear of contamination was acquired by asking them to hold an innocuous stimulus (e.g., tissue soaked in tap water) in their hand while imagining it and its innocuous implications, and then substituting the stimulus with a provocative one. Provocative stimuli were developed for the OCD

participants such that they also provoked normal subjects: a tissue soaked in toilet water, plastic bags from contaminated waste barrels, and tissue with nose effluvium. Innocuous stimuli were "clean" versions of the same objects (eg, tissue soaked in tap water, new plastic bags). It was found that 70% of patients with OCD showed increased activation in medial orbitofrontal, lateral frontal, anterior temporal, anterior cingulate, and insular cortex, as well as caudate, lenticulate, and amygdala (Breiter et al., 1996). Normal subjects exhibited no increase in activation in any brain region.

In another symptom provocation study Cottraux et al. (1996) used PET scans to investigate cerebral blood flow in ten nondepressed patients with OCD who were characterised by predominant checking rituals in comparison to ten age- and sex-matched control subjects. Unlike the Breiter et al. (1996) study, participant's medication was stopped 15 days prior to the study. Symptoms were provoked using cognitive techniques whereby subjects were read scenarios of potentially aversive events. Under obsessive stimulation, superior temporal and orbitofrontal activities were correlated in OCD subjects but not in controls. Although this study only used cognitive symptom provocation, the findings suggest that the orbitofrontal cortex is involved in actively mediating the expression of OC symptoms (Kwon et al., 2003). Indeed, experimental and clinical studies have provided evidence that the orbitofrontal cortex is involved in the mediation of emotional response to biologically significant stimuli as well as in the inhibition of behavioural responses in OCD patients (Zald & Kim, 2001).

The most consistent pharmacological finding has pointed to reduced serotonergic neurotransmission in individuals with OCD (Murphy et al., 1999; Wetzel & Szegdi, 1993; Zohar & Kindler; 1992). Findings suggest that OCD responds best to selective serotonin reuptake inhibitors (SSRIs; e.g., clomipramine, fluoxetine, paroxetine, setraline and fluvoxamine), which block the serotonin transported and increase synaptic serotonin concentrations (Rubin & Harris, 1999). More evidence for orbitofrontal dysfunction comes from the finding that "preferential metabolic decreases have been found in the orbitofrontal cortex in response to pharmacotherapy (Benkelfat et al., 1990; Saxena, Brody, Schwartz & Baxter, 1998; Saxena & Rauch, 2000), suggesting that 'hyperfrontality' in OCD as a state marker can be modified by the therapeutic interventions" (Kwon et al., 2003, p.44).

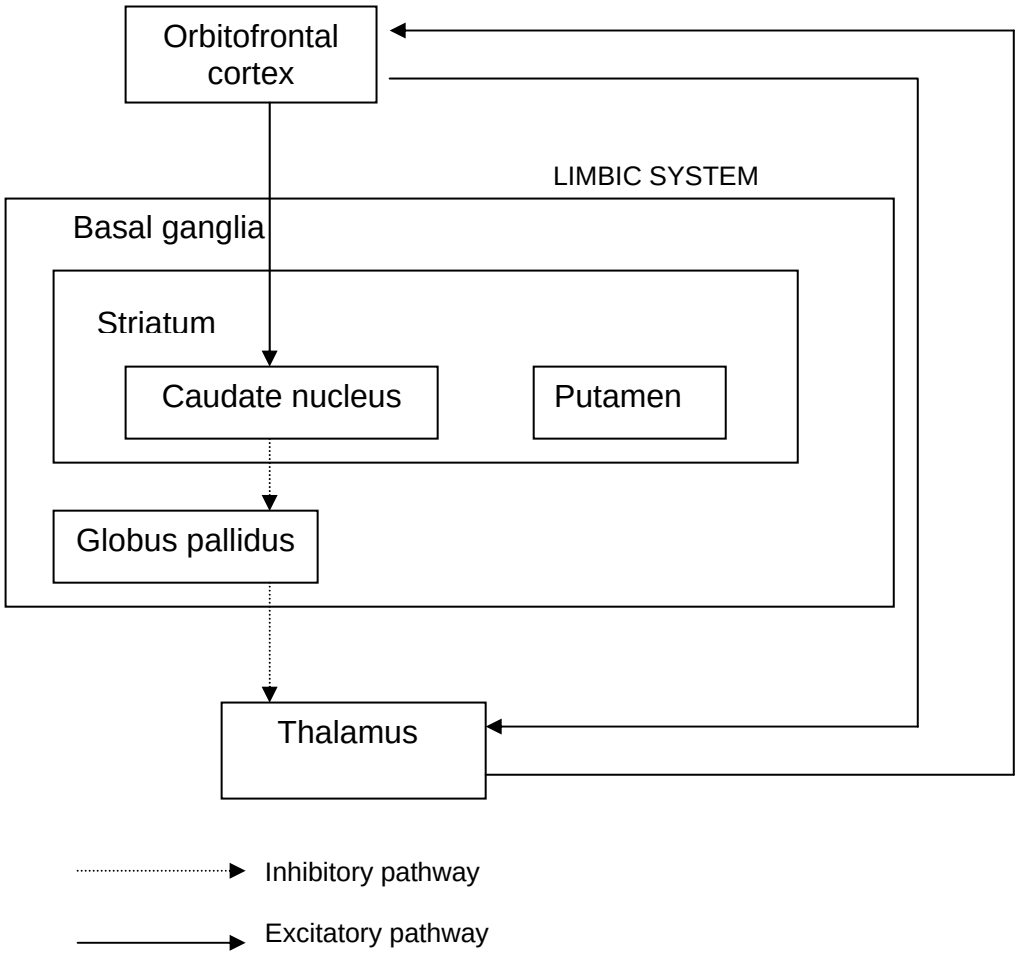

Figure 1.1. Schematic representation of the connections between the orbitofrontal cortex and basal ganglia implicated in OCD (adapted from Frampton, 2003, p.54).

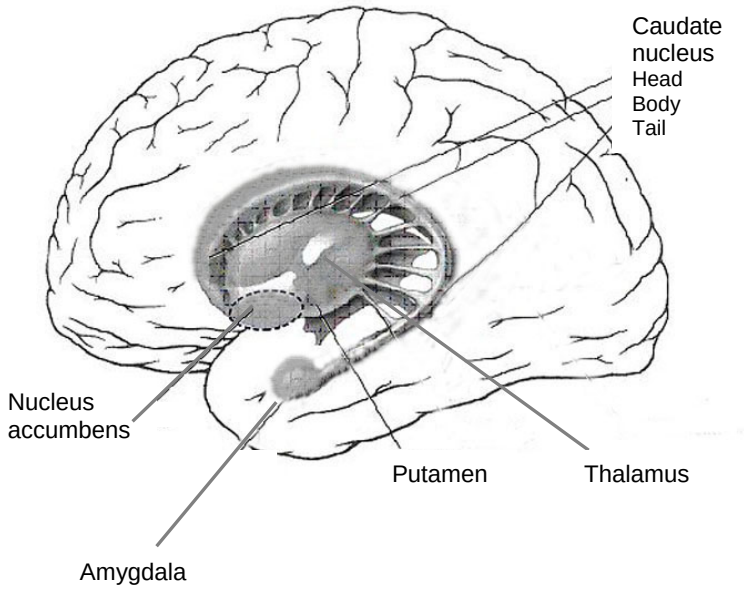

Figure 1.2. The subcortical areas implicated in OCD: caudate nucleus, putamen and nucleus accumbens (areas of the basal ganglia) and the thalamus.

1.3 Obsessive-compulsive symptomatology & the basal ganglia

The basal ganglia, a brain region typically associated with motor function, has received increasing attention in terms of its role in cognition (Saint-Cyr, Taylor & Nicholson, 1995). As described above, abnormalities in the basal ganglia has been found in OCD (Baxter, Phelps & Mazziotta, 1987; Robinson, Wu & Munne, 1995; see Figure 1.2). Pathology in the basal ganglia are associated with organic diseases including Huntington's Disease (Anderson et al., 2001; Cummings, 1993), Parkinson's Disease (Alegret et al., 2001; Daniele, Bartolomeo & Cassetta, 1997; Sharma & Gupta, 2002) and Frontotemporal dementia (Gregory & Hodges, 1996; Honig, Bell & Chin, 2003; Rosso et al., 2001). Interestingly, these neurological diseases are also characterised by increased incidence of OCD diagnosis and/or OC symptomatology (Sano, Marder, Dooneief, Robertson & Yakeley, 2000).

Only one study has explored the cognitive correlates of acquired OC symptomatology. Anderson, Louis, Stern & Marder (2001) examined the frequency and type of OC symptoms in patients with Huntington's disease. As mentioned above, pathology in the basal ganglia (particularly in the caudate nucleus) has been associated with an increased incidence of OCD in patients with Huntington's disease (Cummings & Cunningham, 1992; Rosenblatt & Leroi, 2000). The YBOCS symptom

checklist was administered to 27 Huntington's disease patients. Neuropsychological test performance of 14 patients who endorsed at least one obsessive symptom and 7 patients with at least one compulsive symptom was compared with the performance of the patients without such symptoms. More than half the patients with Huntington's endorsed at least one OC symptom. Patients with obsessive or compulsive symptoms showed significantly greater impairment on tests of EF than those without any OC symptomatology. Functional impairment and stage of illness were not related to the number or presence of OC symptoms.

1.4 Brain lesions & obsessive-compulsive symptomatology

OCD has also been associated with lesions of the frontal lobe. OC symptoms have been observed with frontal lobe tumours, trauma and epileptic foci (Andy et al., 1981; MeKeon et al., 1984; Seibyl et al., 1989; Ward 1988). Such findings are particularly intriguing given the compromise to frontal lobe function and alterations in frontal region activation in patients with OCD described previously.

Group comparisons between patients with brain lesions and associated or acquired OCD (due to either ischaemic changes or head injury) and idiopathic OCD (e.g., Berthier, Kulisevsky, Gironell & Heras, 1996; Berthier, Kulisevsky, Gironell & Lopez, 2001) have found commonalities in the areas of neuroanatomic and neuropsychological disruption, and in the clinical presentation of the OC symptoms.

Berthier et al. (1996) examined the clinical phenomenology, cognitive function, and anatomic correlates in a consecutive series of 13 patients with a diagnosis of OCD and a focal brain lesion. This group was compared to 25 participants with idiopathic OCD and 13 normal controls, matched for age, sex and education. No significant difference was found between the acquired and idiopathic OCD groups on OC symptom severity (YBOCS) but patients with idiopathic OCD had significantly higher levels of depression and anxiety than patients with acquired OCD. Of the two OCD groups, all patients had mixed obsessions and compulsions. The idiopathic OCD group had a significantly higher number of obsessions than the acquired OCD group; but mean number of compulsions was not significantly different.

On neuropsychological testing, there were no significant differences between the acquired OCD and the idiopathic OCD groups on most measures. Both OCD groups performed significantly worse than controls on IQ scores, memory quotient scores of the Wechsler Memory Scale, recent verbal memory, verbal attention span, verbal fluency, spatial shifting, and finger tapping. In fact, the only measure on which the acquired OCD group performed significantly worse than the idiopathic group was in a finger tapping (right hand) task. Interestingly, only the acquired OCD group performed significantly worse than controls on other frontal lobe tests (Wisconsin Card Sorting Test and Trail Making Test) as well as on word retrieval and recent nonverbal memory (Berthier et al., 1996). The authors do note that the presence of significantly higher scores on depression and anxiety rating scales in the idiopathic OCD group compared to the acquired OCD group may have worsened the performance on various tasks in the former group, attenuating potential between-group differences. Nonetheless, these findings suggest similarities in the pattern of cognitive impairment (indicative of bilateral frontal dysfunction) and the clinical phenomenology between patients with idiopathic and acquired OCD. Neuroimaging revealed that a "single or multiple lesion in the [frontal-basal-thalamo-cortical] circuits, whether cortical or subcortical, may produce similar behavioural and cognitive deficits" (Berthier et al., 1996, p.361). Given the small number of reports of patients with OCD following focal brain lesions, it is notable that nearly all such case reports involve patients with basal ganglia or frontal lobe lesions.

1.5 Neuropsychology of Obsessive-Compulsive Disorder

OCD has historically been associated with more profound processing deficits than those associated with a mood disturbance. Freud (1913) and Janet (1903) described memory impairments in their OCD patients. Reed (1968) maintained that obsessional symptoms were related to an inability of OCD patients to organise and integrate experience.

Renewed interest in investigating cognitive deficits in idiopathic OCD has been encouraged by positive findings with brain imaging studies as described above. Clinical observation also justifies examination of neuropsychological functioning in this population. For example, although the majority of individuals with OCD report that they recognise the senselessness of their obsessions, they are still compelled to

engage in compulsions or cannot dismiss the obsessional idea. This difficulty has been plausibly linked to problems in cognitive control, further pointing to impairment in frontal lobe functioning.

Neuropsychological studies do suggest that cognition is impaired in OCD, although the precise nature of these cognitive deficits remains contentious, and there is ongoing debate concerning which functions are compromised.

In general, "the assessment of OCD from a neuropsychological perspective has supported the hypothesis of frontal lobe or caudate dysfunction" (Berthier et al., 1996, p.353), with deficits reported on tasks involving trial and error learning, and set shifting. The most consistent results reflect deficits in aspects of EF (Cox, 1997; Christensen et al, 1992; Cox, Fedio & Rapoport, 1989; Fontenelle, Marques, Engelhardt& Versiani, 2001; Head, Bolton & Hymas, 1989). As stated above, EF describes higher-order cognitive abilities which include set shifting, mental flexibility, abstract reasoning, concept formation, response inhibition, self-monitoring and planning ability.

The Wisconsin Card Sorting Test (WCST) has been employed extensively in studies focusing on the shifting of mental sets in OCD patients (Christensen et al, 1992; Cox, Fedio & Rapoport, 1989). Head, Bolton and Hymas (1989) found that patients with OCD maintained deficits in ability to shift cognitive set, in particular with non-verbal material, as measured by the Short WCST. The Money Road Map Test has also been used as a measure of directional orientation and set shifting. Poor performance on this task in participants with OCD has been reported in both adolescents (Cox, Fedio & Rapoport, 1989) and adults (Head, Bolton & Hymas, 1989). Veale, Sahakian, Owen and Marks (1996) assessed 40 patients with OCD and matched controls on tests thought to be sensitive to frontal lobe dysfunction. It was found that on a computerised version of the Tower of London test of planning, OCD patients were no different to controls in the accuracy of their solutions but, when they made a mistake, they spent significantly more time than controls in generating alternative solutions or checking the next move would be correct. These results suggested that OCD patients have a selective deficit in generating alternative strategies when they make a mistake.

Studies have also reported impaired word fluency in patients with OCD in comparison to normal controls (Christensen et al., 1992; Head, Bolton & Hymas, 1989). However, obsessional slowing on this task, rather than deficits in attentional planning may be responsible for this result. Indeed, the use of timed tests in this population has been criticised, as some authors note that overcautiousness, or frequent interruption of task performance by intrusive cognitions, in OCD patients may be responsible for a general "slowing" of performance, rather than any neurological factor (Tallis, 1997).

Deficits in EF, however, have not been found consistently across the literature, and other deficits seemingly unrelated to the current neuroanatomic theories, have been demonstrated in this population. For instance, in a review of the literature, Otto (1992) points to Zielinski, Taylor and Juzwin. (1991) and Boone, Ananth, Philpott, Kaur and Djenderedjian. (1991). These studies examined the performance of OCD patients relative to matched normal controls on tests sensitive to frontal lobe as well as verbal and nonverbal memory tests. Both studies found decreased performance on tests of visuospatial memory, in contrast with performance on tests of EF, and attention and verbal memory. Simpson et al. (2006) also compared patients with OCD patients and healthy controls on measures of EF, visual memory and motor speed. They found that OCD patients differed significantly form controls on the Benton Visual Retention Test, a visual memory test. Visuospatial processing deficits and/or visual memory deficits are thought to be most consistent with temporo-parietal dysfunction, though imaging studies in OCD have not supported this assumption.

It must also be noted that some studies havereported no specific deficits in cognition in OCD other than a slowing of responses (e.g., Gross-Isseroff et al., 1996; Martin, Wiggs, Altemus, Rubenstein & Murphy, 1995; Purcell, Maruff, Kyrios & Pantelis,1998) or only small differences in cognitive functioning between patients with OCD and healthy controls (Schmidtke, Schorb, Winkelmann & Hohagen, 1998).

Moritz et al. (2001) investigated the effects of comorbid depression on EF test performance of 36 OCD patients and 36 matched healthy controls. The computerised WCST, the Trail Making Test (Part A and B), Digit Span and a verbal fluency task were administered. It was found that patients with high Hamilton Rating Scale for Depression (HRSD) scores performed significantly worse than controls and patients

with low HRSD scores. Moreover, patients with high HRSD scores exhibited deficits on the verbal fluency task, indicating that comorbid affective conditions can exacerbate and/or compromise performance on tests of EF in OCD.

Purcell et al. (1998a) recognised that the neuropsychological dysfunction associated with OCD is similar to deficits reported in other affective or anxiety disorders. Purcell et al. (1998a) therefore compared cognitive function with the Cambridge Automated Neuropsychological Test Automated Battery (CANTAB) in patients with OCD, Panic Disorder, and unipolar depression. Patients with depression were impaired on a measure of attentional set shifting. OCD patients were found to be impaired on measures of spatial working memory, spatial recognition, motor initiation and execution, as well as some aspects of EF and visual memory- they demonstrated normal recognition and recall of pattern material, however recognition of spatial locations was impaired (a task that required participants to recognise the spatial location of white boxes previously presented at different locations on the computer screen) (Purcell et al., 1998a). Patients with Panic Disorder or depression did not differ from controls on these measures. The authors suggested that the deficits found in OCD might point towards an impaired ability to use internal representations to guide ongoing behaviours. Medication status varied but post-hoc analysis revealed medication status, however, did not affect performance scores (Purcell, Maruff, Kyrios & Pantelis, 1998b).

Also utilising a clinical control group, Boldrini et al. (2004) tested patients with OCD, Panic Disorder with agoraphobia and healthy controls. It was found that visual constructive abilities (as measured by the Rey Complex Figure Test [RCFT]) and verbal fluency deficits were specific to the OCD group, while a spatial learning deficit (as measured by the Corsi Block Tapping Task) was shared with the Panic Disorder group. It was concluded that a spatial learning deficit may not be disorder-specific, but anxiety-related (Boldrini et al., 2004).

Lacerda et al. (2003) compared patients with OCD to matched (age, gender, handedness and level of education) controls on several neuropsychological tests. OCD patients performed significantly worse than controls on verbal fluency, the RCFT and the WCST (perseverative errors). All subjects were medication-free for at least 30

days prior to testing and strict inclusion and exclusion criteria were used. However, comorbid depression was not assessed.

Deficits have even been detected in sub-clinical OCD populations. Mataix-Cols, Junque, Sanchez-Turet, Verger and Barrios (1999) investigated performance on the Tower of Hanoi planning task in 71 college students. Thirty-five subclinical OC subjects were identified on the basis of their high scores on the Padua Inventory, but none met the clinical DSM-IV criteria for OCD. Subclinical OC subjects needed significantly more moves to reach the solution criteria on the Tower of Hanoi puzzle than controls, and the number of moves needed on the Tower of Hanoi puzzle was positively correlated with the Padua's checking subscale.

Patients with structural lesions of the basal ganglia (as in Huntington's disease) have not only been reported to exhibit acquired OC symptomatology, they have a pattern of neuropsychological deficits which resonates with those reported in OCD: deficits include slowed processing, reduced verbal fluency, difficulty switching set, impaired spatial ability, poor recall and impaired acquisition of motor skills (Martin et al., 1993). As described previously, patients with OCD have performed poorly on measures of spatial working memory, spatial recognition, and motor initiation/execution (Zielinski, Taylor & Juzwin, 1991; Christenson et al., 1992; Insel et al., 1983; Purcell et al., 1998), similar to patterns in the early stages of Huntington's disease (De Marchi & Mennella, 2000).

Martin et al. (1993) tested the hypothesis that patients with OCD would have a similar pattern of cognitive dysfunction as that found in Huntington's disease. Seventeen unmedicated patients with OCD, 11 patients with trichollomania (a compulsive hair pulling impulse control disorder) and 16 age- and education-matched normal controls were given a battery of neuropsychological tests thought to be sensitive to basal ganglia disruption (Martin et al., 1993). Contrary to expectations, neither the OCD nor the trichollomania patients were significantly impaired on any of the measures included in the battery. The conclusion that the OCD patients in this study do not have fronto-striatal dysfunction was reported as "untenable given the accumulation of evidence that firmly establishes a biological basis for OCD" (Martin et al., 1993, p.350). The authors argue that the areas of the basal ganglia associated with OCD

symptoms and the cognitive deficits associated with Huntington's disease may not overlap. One weakness in this study relates to the choice of tests. For instance, the measure of ability to switch set was a word generation task, where subjects were required to alternate with words beginning with "t" and words beginning with "s". It could be argued that this measure was too easy for subjects and hence not sensitive enough to detect dysfunction associated with set shifting in OCD. Another limitation of this study was the lack of a Huntington's disease control group.

In a review of the literature, Greisberg and McKay (2003) comment that the accumulated research points to deficits in organisational strategies in general, suggestive of problems with EF in OCD. There are inconsistencies in identifying memory deficits, however, memory problems are most evident when tests that require an implicit organisational strategy are used (Greisberg & McKay, 2003).

There is, however, also convincing evidence to suggest that more attention needs to be paid to comorbid mood disorders in OCD (Moritz et al., 2001). Further, the heterogenous nature of OCD, frequently neglected, may account for some of the discrepancies that exist; different syndromatic patterns (e.g., washers and checkers) may produce differential patterns of cognitive functioning. Finally, small sample sizes, differences in inclusion and exclusion criteria among studies, lack of appropriate clinical controls, and confounds such as medication status, treatment status, and length of illness have all complicated the search for a reliable neuropsychological profile of OCD.

Furthermore, few studies to date have related neuropsychological findings to symptomatic expression in OCD. It has been argued that proposed neuropsychological deficits should correlate with symptom severity (unless the model predicts that the deficit reflects an underlying trait) (Frampton, 2003; Mataix-Cols et al., 1999). With an increased understanding of the cognitive deficits associated with OCD, and perhaps the detection of differential cognitive profiles for "subtypes" of the disorder, the clinical presentation of OCD will be better understood, and implications for novel treatment strategies may follow.

1.6 Obsessive-Compulsive Disorder & the orbitofrontal cortex

The orbitofrontal cortex and its connections constitute a distinct component of the prefrontal cortex separate from the dorsolateral prefrontal cortex (see Figure 1.3). It has been associated with a number of functions including the evaluation of the emotional significance of stimuli, learning appropriate responses to rewarding and aversive stimuli, and switching responses when it is advantageous to do so (Evans, Lewis & Iobst, 2004).

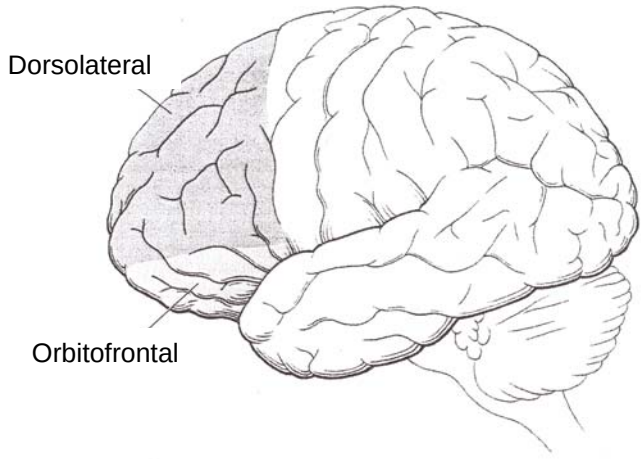

Figure 1.3. The orbitofrontal cortex in relation to the dorsolateral prefrontal cortex (Image adapted from Devinsky & D'Esposito, 2004, p.314)

The orbitofrontal cortex has also been linked to response inhibition. Patients with lesions to the orbitofrontal cortex demonstrate a selective disturbance in the ability to suppress responses to irrelevant stimuli (Luria, 1966; Stuss & Benson, 1993; Diamond, 1990). Clinically, patients with OCD are impaired in the natural inhibition of repetitive thoughts and behaviours. Rosenberg, Dick, O'Hearn and Sweeney (1997) evaluated response inhibition in 12 unmedicated patients and nondepressed patients with OCD and 12 matched controls, using oculomotor tests (visually guided saccade task and an antisaccade response inhibition task). Patients with OCD demonstrated deficits in response suppression on the antisaccade response inhibition task. That is, they were unable to keep their eyes fixated on a central visual target when peripheral targets were also presented. No effects of comorbid anxiety or depression were observed.

A study by Whitney, Fastenau, Evans and Lysaker (2004) hypothesised that OCD patients would perform worse than schizophrenia patients (without OC symptoms) on an orbitofrontal task (the Bechara Gambling Task) because of the differential involvement of the orbitofrontal cortex in OCD not seen in schizophrenia. However, no difference was found between the groups. The researchers raised the question: "Are the neuropsychological tests employed to assess [orbitofrontal function]… sensitive and specific to the neurological substrates they are purported to assess?" (Whitney et al., 2004, p.81). The difficulty with the assessment of orbitofrontal function is becoming apparent in the literature, and other aspects of orbitofrontal function not associated with response inhibition are gaining attention.

Perhaps the most important aspects of orbitofrontal functioning involve registering and regulating emotional states (Carlson, 1999) and Theory of Mind (ToM). ToM is the ability to attribute independent states of mind to others in order to explain and predict behaviour. Its emergence occurs later in development, and appears to be independent of EF (Happaney, Zelazo & Stuss, 2004). ToM tasks are thought to be a sensitive measure of orbitofrontal disruption.

There is a difficulty in obtaining a "pure" measure of ToM or orbitofrontal function. Martin and McDonald (2003) have suggested that any measure of frontal lobe function is affected by "pragmatic language ability," the interaction between linguistic and non-linguistic cognitive systems (Perkins, 1998). The influence of broader executive function on tests of ToM, while not discussed in the literature to date, also warrants investigation. That is, any measure of ToM requires not only the subject to attribute independent states of mind to others and social reasoning skills, but problem solving and abstract thought outside the realm of interpersonal judgments are necessary.

Nevertheless, no research has investigated the performance of patients with OCD on ToM tasks, despite imaging findings that consistently implicate the orbitofrontal cortex in OCD.

Chapter 2

Literature Review II: Frontotemporal dementia

2.1 Clinical characteristics of frontotemporal dementia

The term frontotemporal dementia (FTD) describes a spectrum of non-Alzheimer's neurodegenerative dementias involving frontotemporal atrophy (The Lund and Manchester Groups, 1994). FTD accounts for approximately 20% of cases of dementia with presenile onset (Harvey, 2001). It is sometimes also termed "Pick's Disease" or "frontal lobe degeneration of the non-Alzheimer's type" (Neary et al. 1998). Cases may be either familial or sporadic, and the clinical onset of FTD is generally slow and insidious. It is the third most common cause of cortical dementia, following Alzheimer's disease and Lewy body disease, comprises about 10% of all dementias and is particularly prevalent among those with onset before age 65 (The Lund and Manchester Groups, 1994; Mendez, 1997; Ratnavalli, Brayne, Dawson & Hodges, 2002).

Two variants of FTD exist: frontal variant FTD and temporal variant FTD (commonly termed "semantic dementia.") Frontal variant FTD is marked by dramatic changes in personality, behaviour and some thought processes. Changes in personal and social conduct occur in early stages of the disease, including disinhibition, apathy, social withdrawal, loss of empathy, impulsiveness and hypersexuality (The Lund and Manchester Groups, 1994). Frontal variant FTD patients are more likely to present initially to medical services with behavioural or psychiatric disturbance rather than cognitive decline (Gregory & Hodges, 1996). Temporal variant FTD is marked by a progressive fluent aphasia secondary to a breakdown in semantic knowledge.

The Lund and Manchester Groups (1994) produced clinical guidelines for the neuropsychiatric and pathological diagnosis of FTD, based on clinical evaluation of several hundreds of patients and upon pathological examination of more than 60 brains, helping to decrease previous nosological difficulties in this population. With the aim to further improve clinical recognition and provide research diagnostic criteria, Neary et al. (1998) subsequently developed consensus criteria building on the 1994 clinical guidelines, which specify core and supportive features for a diagnosis of

FTD, both frontal and temporal variants, for use in clinical and research settings (see Appendix D for consensus criteria for FTD).

2.2 Frontotemporal dementia & obsessive-compulsive symptomatology

Among core clinical features of FTD are ritualistic and stereotypic behaviours (Lawrence, Ronca, Tyrrell & Rossor, 1994; Liu, et al., 2004; Nyatsanza, Shetty, Gregory, Lough, Dawson & Hodges, 2002). Such behaviours may include: checking locks, doors and clocks (Mendez et al. 1997), rituals relating to toileting and dressing; wandering and pacing in a fixed route; perseverative responses and stereotyped use of words/phrases (Neary, Snowden & Mann, 2000), superstitious rituals (e.g., avoiding walking on cracks in the pavement) (Snowden, Neary & Mann, 1996); compulsive and ritualistic cleaning (Mendez et al., 1997); and drinking and eating in a specific sequence (Mendez et al., 1997; Miller, Darby, Swartz, Yener & Mena, 1995). The nature and extent of these behaviours have been likened to those found in OCD, previous studies have argued that many patients with FTD meet diagnostic criteria for OCD (Ames, Cummings, Wirshing, Quinn & Mahler, 1994; Brun & Gustafson, 1999; Tonkonogy, Smith & Barreira, 1994).

Nyatsanza et al. (2003) investigated the prevalence and pattern of stereotypic and ritualistic behaviours in frontal variant FTD, temporal variant FTD, and Alzheimer's disease. Patient carers were asked to answer questions from the Neuropsychiatric Inventory (NPI; Cummings, 1997), a measure of psychiatric disturbance commonly used in dementia populations, as well as a newly devised addendum - the Stereotypic and Ritualistic Behaviour subscale (SRB; Nyatsanza et al., 2003). Patients were administered the Mental State Examination (MMSE), Addenbrooke's Cognitive Examination (ACE), and the Clinical Dementia Rating Scale (all measures of cognitive impairment associated with dementia). The overall NPI was significantly higher in the frontal variant group compared with temporal variant FTD and Alzheimer's disease, but frontal and temporal variant FTD showed a similar, and significantly higher prevalence and complexity in compulsive behaviours, as measured by the SRB subscale, when compared with Alzheimer's patients. They also found that ritualistic and stereotypic behaviours were not correlated with either disease severity or the extent of cognitive impairment in the frontal variant FTD

group, although severity was positively correlated with cognitive impairment in the temporal variant and Alzheimer's disease groups.

Snowden et al. (2001) explored the behavioural profiles in both frontal and temporal variant FTD. Using an informant based behavioural interview which covered behavioural domains thought to associated with FTD and including questions around repetitive behaviours, rituals and compulsions. Interestingly, repetitive behaviours were found to be equally common in both temporal and frontal variants of FTD, but these behaviours had a more compulsive quality among the temporal variant FTD patients. The compulsive symptoms in the temporal variant FTD patients were predominantly characterised by clock watching, rigid adherence to a fixed routine, carrying out tasks in precisely the same way, and preoccupation with a limited range of topics leading to repetitive conversational themes. The symptoms did not commonly have the quality of a superstitious ritual. Snowden et al. (2001) speculate that in the temporal variant, the "imbalance between poorly functioning temporal lobes and normally functioning frontal lobes results in a similar state of relative frontal overactivity" to the orbitofrontal hyperactivity found in OCD (Snowden et al., 2001, p.329). Prototypical OCD symptoms such as checking and washing behaviours are not generally reported in temporal variant FTD, such OC phenomena are thought to be more likely to occur in frontal variant FTD. The authors concluded that orbitofrontal dysfunction might play a crucial role in more OCD-like repetitive and stereotypic behaviours.

A study by Rosso et al. (2001) also found that complex compulsive behaviours (in contrast with simple motor and verbal repetitions) occurred in 21% of FTD patients. In the 18 patients that exhibited complex compulsive behaviours, 4 patients showed visual compulsive preoccupation, 2 patients showed ritualistic completion of jigsaw puzzles, one patient copied embroidery patterns in detail, and one patient would produce hundreds of identical drawings. Preoccupation with certain ideas (health, religion, financial status and environment), and coercive behaviour directed at family members who did not adhere to these ideas, was found. Lastly, extreme fixation to daily routines was a common feature, as was repetitive checking behaviour (time, locks, clothing) and arranging objects in a particular order (Rosso et al., 2001).

Interestingly, temporal atrophy was significantly correlated with complex but not simple compulsive behaviours.

Miller et al. (1995) compared 14 patients with frontal lobe degeneration with 14 patients with dementia of the Alzheimer's type and found that severe and persistent compulsions were found in 64% of patients with frontal lobe degeneration, whereas only 14% of patients with Alzheimer's disease exhibited compulsive phenomena. Furthermore, in all instances of the compulsions seen in the Alzheimer's disease group, they were considered mild, and in none were the compulsions considered disabling by the family. On the other hand, the compulsions found in the frontal lobe degeneration group were intense and often extremely troubling for family members. The types of compulsions reported in this group included repetitive trips to the bathroom and toileting, frequent shaving, compulsive cleaning, collecting of coupons, entering into multiple contests and drinking beverages in a specific sequence (Miller et al., 1995).

Ames et al. (1994) reviewed the relationship of repetitive and compulsive behaviours in frontal lobe degenerations. The authors concluded that 78% of 46 proved (upon autopsy) pathological cases of frontal lobe degeneration described in the literature demonstrated repetitive behaviours ranging from motor stereotypies to complex OCD (Ames et al., 1994). No systematic differences in gender, age at onset or disease duration were found between those patients who exhibited repetitive and compulsive behaviours and those that did not.

Mendez et al. (1997) investigated compulsive behaviours as the initial presenting symptoms of 29 patients with FTD in comparison to 48 patients with Alzheimer's disease (AD). Obsessive thinking among these patients could not be assessed due to their limited insight and inability to describe obsessional experiences. 38% of FTD patients had presenting compulsive behaviours compared to 10% of AD patients. The compulsive behaviours seen in the FTD group were repetitive checking (locks, doors, rubbish bins), cleaning rituals (recurrent flossing and brushing of teeth, repetitive washing), repetitive dressing and undressing, repetitive trips to the bathroom, organising papers in an exact order on a desk, repetitive videotaping of everything on television, needing to park car in a certain way, needing to arrange prescription

medications in a certain order, picking up coins and various counting rituals, organising dishes and drinking beverages in a certain order, and wearing clothes of a specific colour.

Tonkonogy, Smith and Barreira (1994) described a 34 year-old woman who developed a fear of contamination and compulsive hand washing. She used tissues to touch and pick up everything, did not use her hands to take off her coat, washed credit cards before there use, and washed her hands every 45-60 minutes for 8-15 minutes at a time. Her condition continued to worsen and imaging performed 8 months after the OCD onset showed a pattern of atrophy in the frontal lobes and basal ganglia (caudate). The caudate atrophy progressed to the temporal lobes, however her OCD symptoms lessened as her condition deteriorated. FTD was diagnosed at a later, relatively advanced stage and confirmed upon autopsy.

Compulsive behaviour often occurs at the early stage of the disease and has been found useful in distinguishing FTD from AD (Bathgate, Snowden, Varma, Blackshaw & Neary, 2001; Bozeat et al., 2000a; Mendez et al., 1997; Miller et al., 1995; Miller et al., 1997) and cerebrovascular dementia (Bathgate et al., 2001).

2.3 Cerebral pathology in frontotemporal dementia

FTD arises from degenerative changes to the frontal and/or anterior temporal lobes (The Lund and Manchester Groups, 1994). Classification of frontal variant FTD and temporal variant FTD depends on the predominant locus of cortical pathology (tissue atrophy, spongiosis, neuronal loss and gliosis). In frontal variant FTD, the brunt of the pathology involves the frontal lobes, particularly the orbitofrontal cortex (Hodges & Miller, 2001). In the temporal variant, the brunt of the pathology occurs in the temporal lobes, especially the anterior temporal lobe and amygdala (Hodges & Miller, 2001). In addition to focal cortical atrophy, there is evidence of basal ganglia pathology in both variants of FTD (Neary, Snowden & Mann, 2000). Occipitoparietal regions are spared (Mendez et al., 1996).

Grimmer, Diehl, Drzezga, Foerstl and Kriz (2004) used PET to examine the pattern of glucose uptake and the changes over time of metabolic deficits in 10 patients with FTD, compared with age-matched healthy controls. FTD patients showed significant

metabolic deficits primarily in frontal cortical areas but also in the caudate nuclei and the thalami. At follow-up, a significant progression of metabolic deficit was exclusively observed in the orbitofrontal parts of the frontal lobe and in the subcortical structures.

Low serotonin receptor binding has also been reported in the frontal lobes and temporal lobes, and hypothalamus in autopsy-proven FTD cases (Swartz, Miller, Lesser & Darby, 1997). Swartz et al. (1997) investigated the hypothesis that many of the behavioural symptoms (including compulsions) seen in FTD would respond to serotonin selective reuptake inhibitors (SSRIs). Eleven subjects meeting the Lund-Manchester clinical, neuropsychological and neuroimaging criteria were treated with SSRIs (fluoxetine, sertraline or paroxetine). After three months' treatment, disinhibition, depressive symptoms, carbohydrate craving, and compulsions all improved in at least half of the subjects in which they had been present. Specifically, compulsions were present in 7 of the 11 patients (64%) and improved in four (57%). The authors concluded that the high prevalence of compulsions in FTD (Miller et al., 1995; Tonkonogy, Smith & Barreira, 1994) and the postmortem neurochemical findings of reduced serotonin receptor binding (Swartz, Miller, Lesser & Darby, 1997) "are consistent with the hypothesis that low central serotonin activity may be related to compulsions" (Swartz et al., 1997, p.215). Further studies are needed to clarify and replicate this result.

2.4 Neuropsychology of frontotemporal dementia

While "non-cognitive behavioural changes in FTD usually precede or overshadow cognitive deficits in FTD" (Mendez, 1996, p.1193), cognitive deficits have frequently been reported. A study conducted by Hodges et al. (1999) compared the neuropsychological functioning of patients with early Alzheimer's disease in comparison to patients with the temporal and frontal variants of FTD, matched on the basis of age and length of illness history. The frontal variant FTD group were the least impaired showing mild deficits in episodic memory compared with the Alzheimer's disease group, and verbal fluency, but normal semantic memory compared with the temporal variant FTD group. One limitation of this study was the lack of inclusion of a wider range of tests sensitive to frontal lobe dysfunction (e.g., lack of inclusion of the WCST, a commonly used and sensitive measure of executive function). Gregory

and Hodges (1996) found that in the frontal variant FTD, normal performance on the WCST may be demonstrated, particularly in the early course of the disease, thought to be due to the initial lack of pathology in the dorsolateral cortex. Rather, in frontal variant FTD, the pathology is concentrated in the orbitofrontal cortex, a region that was not tested using cognitive measures in the Hodges et al. (1999) study. When patients with frontal variant FTD exhibit deficits in executive function, it may only be in the later stage of the disease, when pathology extends to dorsolateral prefrontal areas (Bozeat et al., 2000a; Edwards-Lee et al., 1997).

Temporal variant FTD patients perform poorly on verbal cognitive measures (due to their loss of knowledge about the meanings of words, objects and concepts) and usually perform well on measures of episodic memory, visuospatial skills, visual reasoning until very late in the disease (Bozeat et al., 2000b).

No research to date has investigated patterns of cognitive dysfunction in relation to behavioural disturbances inherent in FTD. For instance, it is not known to what extent cognitive deficits relate to the presence of OC phenomena in FTD.

2.5 Theory of Mind, the orbitofrontal cortex & frontotemporal dementia

Theory of Mind (ToM) refers to the ability to attribute independent mental states, thoughts or feelings to self and others in order to explain and predict behaviour (Gallagher et al., 2000). Functional imaging studies have shown that ToM tasks (such as detecting irony and attributing mental states of others in short stories and cartoons) uniquely activate prefrontal cortical areas (Gallagher et al., 2000). Baron-Cohen et al. (1994) using SPECT (single-photon computerised tomography), found that healthy adults showed increased cerebral blood flow in the right orbitofrontal cortex relative to the left frontal-polar region during a simple ToM test requiring recognition of words that have to do with the mind (e.g., ‘remember’, ‘thought’), but not during a test that required recognition of body terms (e.g., ‘jump’, ‘arm’).

Further evidence of the neural basis of ToM comes from studies of brain-injured subjects. Stone, Baron-Cohen and Knight (1998) found that patients with unilateral dorsolateral prefrontal lesions performed normally on first- and second-order false belief tests and tests of faux pas detection. Patients with orbitofrontal lesions passed

first- and second-order false belief questions, but were significantly impaired on tests of faux pas detection and a test that requires recognising complex mental and emotional states from pictures of the eyes (the Reading the Mind in the Eyes test) (Stone, Baron-Cohen & Knight, 1998).

The orbitofrontal cortex is considered to bear the brunt of early pathology in frontal variant FTD, and indeed, frontal variant FTD patients have been shown to fail ToM tasks. Gregory et al. (2002) administered tests of ToM to patients with frontal variant FTD and AD. MRI scans were performed to assess the degree and location of cerebral atrophy. It was hypothesised that deficits in ToM would be impaired in the FTD group, but not in the AD group or healthy controls. In Alzheimer's disease, there is impairment in memory (episodic followed by semantic) and attentional processing, while social conduct and personality are typically preserved. Frontal variant FTD patients failed all tests of ToM, but did not show any deficits on control questions designed to test general comprehension and memory. By contrast, AD patients failed only one ToM task (second-order false belief), a task that places high demands on working memory. On a faux pas test, the FTD patients showed deficits on the ToM components of the tasks, while Alzheimer's disease patients failed only the memory-based questions. Significant correlations were found between the total NPI score and the higher-order ToM tasks in the FTD group. There was also a high concordance between impairment on ToM tasks and the degree of orbitofrontal (ventromedial) atrophy (Gregory et al., 2002).

Lough & Hodges (2002) described a 57 year-old man with frontal variant FTD who presented with gradual changes in personality with disinhibition, over eating and a decline in self-care. He was also over-preoccupied with counting and checking. For instance, compulsive checking of doors and windows arose when he developed paranoid ideation that his wife was trying to harm him and that people were going to steal form him. The most disruptive checking routine was that of car suspension- he would check the suspension by sitting in cars and rocking them. Standard neuropsychological test performance (including tests of executive function) was generally unremarkable, with reasonably preserved memory and cognition. However, he was severely impaired on measures of ToM. Indeed, his behaviour clearly demonstrated a deficit in making inferences about the mental states of others. For

instance, his “unawareness of his actions upon others was evident in his complete obliviousness to the consequences of rocking parked cars” (Lough & Hodges, 2002, p.644).

Chapter 3

Summary, Aims & Hypotheses

3.1 Summary

There are striking similarities in reports on the neuropsychology and clinical presentation of FTD and OCD. In their review of the literature of OC symptoms present in FTD, Ames et al. (1994) noted that frontal, temporal and basal ganglionic structures (particularly the caudate nuclei) showed pathological change in the majority of cases of those with repetitive and compulsive phenomena and concluded that combined damage to the frontal lobe, caudate nucleus and globus pallidus may account for the behaviours seen in both frontal lobe degeneration and idiopathic OCD. It has thus been recognised that "the occurrence of compulsions from frontal and caudate lesions (Berthier et al., 1996) suggests an inability to suppress urges to perform compulsive behaviours in FTD resulting from damage to orbitofrontal-striatal circuits" (Mendez et al., 1997, p.156).

Clinically, the compulsive behaviours seen in both OCD and FTD are repetitive, excessive, performed as if to relieve some sense of uncertainty (Mendez et al., 1997), and may respond to treatment with selective serotonin reuptake inhibitors (Swartz et al., 1997).

Neuropsychological studies indicate that both FTD patients and OCD patients have response suppression and behavioural inhibition difficulties (The Lund and Manchester Groups, 1994; Rosenberg et al., 1997; Miller et al., 1997), and EF deficits are reported in both groups. It is not known, however, how cognitive deficits relate to OC symptomatology in either group.

Unlike OCD patients, FTD patients with compulsive behaviour do not generally report obsessional thinking, display overt distress over their compulsive acts, or recognise their behaviour as irrational or excessive (Mendez et la. 1997). This may, somewhat paradoxically be due to a lack of insight in these patients, and an inability to describe adequately any obsessions (particularly if semantic knowledge is affected). Further, patients with FTD are usually "blissfully" unaware of changes in behaviour

and personality (Greene & Hodges, 2000); anxiety forms no part of their profile. In OCD, the symptoms cause marked distress and insight is generally good.

To date, there have been no group comparisons investigating OC symptoms in OCD and neurological conditions involving the same putative brain regions. Given the behavioural changes seen in FTD, including high rates of OC behaviours, and the similarities in the locus of cortical pathology, an investigation of OCD and FTD, from a neuropsychological and OC symptom-expression perspective is proposed.

3.2 Aims & hypotheses

Based on a review of the literature, the current study aimed:

(a) to investigate the neuropsychological profile of OCD and FTD in comparison to age-, education and estimated IQ-matched healthy controls;
(b) to explore the association of cognitive deficits with OC symptomatology;
(c) to compare the nature and frequency of OC symptoms in the two patient groups, as well as the distress associated with the symptoms;

The following hypotheses were formulated:

i. Participants with OCD will perform significantly worse than matched controls on aspects of executive function, and potentially measures of speed of information processing, working memory and visual memory;
ii. A negative correlation will exist between aspects of cognitive performance and OC symptoms in the OCD group;
iii. Within the OCD group, OC symptom subtypes will correlate differentially with cognitive performance scores;
iv. Participants with FTD will report significantly more OC symptomatology than matched controls, but not more distress associated with these symptoms;
v. Participants with OCD and FTD will perform significantly worse on tests of ToM, a measure of orbitofrontal function than matched controls. (There will also be a difference in scores on ToM and non-ToM tasks in the clinical groups, which will not exist in the control group).

Chapter 4. Method

4.1 Participants

Fifty-six adult volunteers (50% male/50% female) with a mean age of 46.3 years (*age range*= 19-79 years) took part in the study. There were two diagnostic groups (Obsessive-Compulsive Disorder and frontotemporal dementia) and a healthy control group. All participants were able to read and write in English. Participants with a Mini-Mental State Examination (MMSE) score below 18 (for FTD) and 28 (for OCD and control participants), a history of other neurological disorders including stroke, head injury, epilepsy, encephalitis, major psychiatric history such as schizophrenia, chronic substance abuse history, use of strong psychotropic medication (antipsychotic and/or benzodiazepine medication), or OCD as a secondary diagnosis, were excluded from the study. Recruitment procedures varied for each group:

(i) Obsessive-Compulsive Disorder

Twenty-three participants were initially assigned to the OCD group. Four participants were subsequently excluded from the analysis: One participant was currently on antipsychotics and benzodiazepines, 2 had received a previous diagnosis of Bipolar Disorder (and were on antipsychotic medications) and 1 older participant scored 21/30 on the MMSE and was also in the dementia range on the ACE (74/100). Thus, 19 participants were included in the OCD group. One participant was recruited from the University of Sydney Psychology Clinic, 7 participants from Anxiety Disorder Alliance (ADA) support groups around Sydney, and 11 participants from the Anxiety Treatment and Research Unit (ATRU) at Cumberland Hospital. All had a DSM-IV diagnosis of OCD made by a Clinical Psychologist, as well as scoring in the clinical range on the Obsessive-Compulsive Inventory (OCI). The presence and severity of depression was assessed at intake at the Sydney University Psychology Clinic and ATRU, while those participants recruited from the ADA were interviewed by a Clinical Psychologist about any depressive symptomatology prior to participation in the study. Those participants recruited from ATRU were additionally administered the Anxiety Disorders Inventory Schedule (ADIS) as part of the unit's standard intake procedure. If comorbid anxiety and mood disorders were present, OCD needed to be the primary diagnosis.

(ii) Frontotemporal Dementia

Twelve participants were initially assigned to the FTD group. Three participants were subsequently excluded due to nosological difficulties: At a 12-month follow-up assessment, 2 participants were found to have improved on measures of executive function, while still impaired on other measures, making a diagnosis of FTD less clear. The third participant had a history of psychotic phenomena and was on high levels of antipsychotic medications. Five participants were recruited from the Neurology and Movement Disorder Clinics at Westmead Hospital; 3 from the Neuroscience Clinic at Royal Prince Alfred Hospital; and 1 from the University of Sydney Psychology Clinic. All participants had a presumptive clinical diagnosis by a neurologist and/or neuropsychologist of FTD. A presumptive clinical diagnosis of FTD was based on historical information, neurological examination, neuropsychological assessment, findings on imaging, and based on the consensus on clinical diagnostic criteria for FTD were used (Neary et al., 1998; see Appendix D for consensus criteria).

(iii) Controls

Twenty-one age, education and IQ-matched healthy controls were recruited. One participant was excluded from the analysis because he scored below 28 on the MMSE. Controls did not suffer from any neurological condition nor did they have a history of OCD. Demographically similar carers, spouses and friends of the FTD group and demographically similar friends of the OCD group were asked to volunteer.

4.2 Sample description

Table 4.1 shows summary of group demographics. Table 4.2 shows summary of group psychiatric symptom scores.

Table 4.1. Participant demographics (Mean ± SD)

Group	OCD	FTD	Control
Age (years)	37.6 (±13.1)	62.4 (±11.2)	46.2 (±19.4)
Sex (% male)	58	56	35
Education (years)	12.4 (±2.9)	11.9 (±2.3)	13.7 (±2.6)
Handedness (% right)	89	100	90
MMSE score (/30)	29.6 (±0.8)	24.4 (±4.6)	29.7 (±0.6)

Table 4.2. Participant psychiatric measure scores (Mean ± SD)

Group	OCD	FTD	Controls
DASS Depression	15.56 (±13.8)	11.57 (±11.8)	3.26 (±4.4)
DASS Anxiety	10.72 (±9.9)	6.43 (±4.7)	2.63 (±2.8)
DASS Stress	19.94 (±12.5)	11.00 (±10.0)	6.26 (±5.1)
OCI total frequency	67.87 (±25.7)	14.61 (±9.4)	14.01 (±12.4)
OCI total distress	64.76 (±22.7)	5.17 (±3.8)	6.68 (±7.8)
NPI Stereotypic & Ritualistic Behaviours (% prevalence)		78	

4.2.1 Obsessive-Compulsive Disorder

Eleven participants were male, 8 were female and they had a mean age of 37.6 years *(age range*= 19-68 years*)*. Table 4.3 shows OCD group obsessive-compulsive symptomatology, as measured by the OCI. Participants were required to score in the clinical range on at least one frequency and one distress subscale to be included in the study.

While participants taking antipsychotics and/or benzodiazepines were excluded from the analysis (due to the known effect of these medications on aspects of cognition (Stein & Strickland, 1998), participants taking SSRIs or tricyclic antidepressants (TCAs) were not excluded but the use of psychotropic medication was controlled for in statistical analysis. Eleven OCD participants fell in this category. The remaining 8 were either medication naïve or had been medication-free for a period of at least 8 weeks.

Due to the likelihood of OCD remaining undiagnosed for some years, years of significant OCD symptomatology, as judged by the participant, was used as the measure of longevity of the symptoms. The mean number of years of significant OCD symptomatology for the entire group was 19.3 years, with mean age at onset being 17.9 years.

Eight participants were currently undergoing Cognitive-Behaviour Therapy for OCD, 7 had received psychological treatment in the past, and 4 had undergone an assessment but had not received any psychological intervention to date. Irrespective

of treatment status, all met DSM-IV criteria for OCD (primary) at the time of this study.

The OCD group was very heterogeneous, and usually presenting with a range of symptoms, typical of OCD populations (see Appendix B for OCI subscale items). The most common symptoms were related to checking and mental neutralising, followed by obsessing, washing, doubting, ordering, and hoarding (see Table 4.3). One participant scored in the clinical range on just one subscale, the washing subscale. However, the remaining 18 participants scored in the clinical range on at least 2 subscales, the mean number of subscales in the clinical range being 4.5. Four participants scored in the clinical range on all 7 subscales. The distress scores highlight that when a subscale reached clinical significance in frequency, significant levels of distress generally accompanied it. Most distressing were symptoms relating to mental neutralising, followed by checking, doubting, obsessing, washing, ordering and hoarding. One participant reported obsessional sexual imagery and a range of mental neutralising acts such as praying and counting to relieve the anxiety associated with the sexual imagery. However, also in the OCD group was a participant with contamination fear and engaged in a range of repetitive washing and prevention behaviours to relieve her fear of germs killing her grandchildren. While both diagnosed with OCD, it is clear that subtypes of the disorder require differentiation in both clinical formulations and treatment, but also when investigating possible underlying mechanisms.

Table 4.3. OCD participant symptom characteristics

Measures	Number in Clinical range
OCI frequency washing	14 (74%)
OCI frequency checking	16 (84%)
OCI frequency doubting	14 (74%)
OCI frequency ordering	12 (63%)
OCI frequency obsessing	15 (79%)
OCI frequency hoarding	8 (42%)
OCI frequency mental neutralising	16 (84%)
OCI distress washing	14 (74%)
OCI distress checking	16 (84%)
OCI distress doubting	16 (84%)
OCI distress ordering	13 (68%)
OCI distress obsessing	15 (79%)
OCI distress hoarding	10 (53%)
OCI distress mental neutralising	18 (95%)

4.2.2 Frontotemporal dementia

Five participants were male, 4 were female and they had a mean age of 62.4 years *(age range*= 47-79 years*)*. One participant had a diagnosis of temporal variant FTD, while the other 8 participants had been diagnosed with frontal variant FTD. Mean disease duration was 4 years. See Appendix E for individual symptom and neuropsychological profiles.

Can we call the aberrant behaviours of FTD OCD-like at all? Two participants, "DE" and "WP" were selected as illustrative cases. Both displayed significant OC symptomatology. Interestingly, their neuropsychological profiles were quite different from one another. Tests and measures used are described in detail later in the current chapter.

Case One: DE

DE was a 72 year-old, female, right-handed retired teacher with 15 years education. She had a 3-year history of frontal variant FTD and was living in a nursing home at the time of research participation. DE also suffered from insulin dependent diabetes mellitus, hypertension, hypercholesterolemia and osteoarthritis, and took medications to manage these conditions. Hearing difficulties were reported by her daughter, though did not interfere with the assessment. There was no reported positive family history of FTD. In her lifetime, DE had never been diagnosed with a mood or anxiety

disturbance. She had never suffered from OCD. She had always been an avid pianist and singer, as well as very religious; these points are highlighted because they appeared in her compulsive phenomenology.

In terms of OC symptoms, DE scored 1-2 s.d above controls' on the OCI frequency checking subscale. However, it was on the NPI where her daughter's reports indicated significant compulsive phenomena, as measured by the Stereotypic and Ritualistic subscale and aspects of the Aberrant Motor Behaviour subscale. Most of these behaviours were also witnessed over the two occasions DE was assessed. The compulsive behaviours were: pacing; repeatedly walking the same route around the nursing home and garden; singing the same song ("She Had A Wart Upon Her Nose") at particular points in the walk; checking bathrooms repeatedly; opening doors and closets; rummaging; repeatedly taking on and off clothing; being compelled to touch the same rails and surfaces while walking; counting under her breath when walking; and praying and making the sign of the cross when walking past religious symbology. She would repeatedly sing one song for her deceased husband, and another song for her boyfriend. Her compulsive behaviours were described by her daughter as "very frequent" and a "marked" change from her premorbid behaviour. It was reported that, at the onset of her FTD, some hoarding was apparent (newsagency cards) but that it had stopped within a few months.

DE was not distressed by her compulsive behaviours, nor did she try to suppress them (even when they interfered with the testing and interviews). She was not easily redirected from counting, singing, checking, touching or praying when in the presence of a trigger. For instance if she walked down the hall, the presence of the cross on the wall and the rails to her side would produce, what became a very predictable sequence of praying, performing the sign of the cross and touching the rails, regardless of attempts to redirect her. Characteristic of FTD, she did not appear to have insight into her condition and appeared blissfully unaware of the repetitiveness of her behaviours.

As well as the changes in compulsive behaviour described above, DE's daughter rated her highly on the NPI Disinhibition, Apathy/Indifference and Appetite/Eating subscales. High scores on these scales are typical in FTD.

Her neuropsychological profile was highly consistent with frontal variant FTD. She was estimated to have high-average premorbid intellectual ability. At presentation, her MMSE score was 25 and her ACE score 78, showing a reduction in current intellectual function. Verbal memory, visual memory, aspects of visuospatial ability including Matrix Reasoning, word finding ability and ToM were impaired. Most impaired was her performance on measures of EF, failing on all the tests. On the WCST, she was perseverative- she continually matched to form despite verbal feedback indicating her match was incorrect. Visuoconstructional ability, simple attention, working memory, verbal memory, vocabulary and speed of information processing were within normal limits (see Appendix E for individual neuropsychological profile- DE is Case 7).

Case Two: WP

WP was a 68 year-old right handed retired fitter and turner with 12 years education. He had a very long, 8-year history of temporal variant FTD (and was formerly diagnosed 6 years ago). His father was reported to have had a similar dementing condition, though never formerly diagnosed. WP was otherwise healthy. He had been taking sodium valproate to help with low mood and acquired aggressive behaviours. His wife did not think the sodium valproate had changed any compulsive behaviour, just "calmed him down." She denied that her husband had any premorbid history of depression, anxiety or OCD, but thought that he was currently extremely frustrated with his language difficulties, this insight contributing to low mood.

WP scored in the clinical range on the DASS depression and stress scales. This finding is concordant with past research into the temporal variant of the condition (Edwards-Lee et al., 1997) because of greater insight and frustration with language difficulties. In terms of OC symptoms, his score fell at 1-2 s.d. above controls' on the OCI frequency hoarding and distress at ordering subscales. On the NPI and Stereotypic and Ritualistic Behaviour subscale, WP's wife reported that her husband displays rituals around his medication (bottles and tablets must always be in a perfectly straight line and will get very upset if this order is not maintained); is extremely pedantic with his cutlery (must have *his* spoon, *his* knife etc.); appears obsessed with the weather, going outside up to 10 times per day to check it; is preoccupied with time and repetitively clock watches; and repeatedly attempts word

puzzles. These behaviours were described as "very frequent" and a "marked" change from WP's premorbid behaviour.

As well as the changes in behaviour described above, WP's wife rated him highly on the NPI Delusions, Depression/Dysphoria and Appetite/Eating subscales.

WP's neuropsychological profile was characterised with a fluent aphasia, consistent with temporal variant FTD. He was estimated to have average premorbid intellectual abilities. At presentation, WP scored 26 on the MMSE and 60 on the ACE. His cognitive profile was almost in complete contrast with DE's: VIQ was extremely impaired, however PIQ remained intact. WP was impaired on measures of speed of information processing and language, but not visual memory or visuospatial ability. He performed within normal limits on all measures of EF, except one- he failed to maintain set on two occasions on the WCST. He was the only participant in the FTD group to achieve more than 3 categories on the WCST, achieving all 6 (see Appendix E for individual neuropsychological profile- WP is Case 8).

Of note, was the highly specific and individual presentation of OC symptoms in both cases examples. Indeed, this was the case for all FTD participants with OC symptoms. For DE in particular, her own personal history was highly related to the expression of her compulsions (see Appendix E for individual FTD case profiles).

Both cases are differentiated in their neuropsychology: from their cognitive profile it might have been impossible to predict that both would have demonstrated compulsive behaviours. The two cases are also differentiated in the extent of distress associated with OC symptoms- WP was reported to get distressed only if dissuaded from his compulsions. However, OC symptoms themselves were not ego dystonic to WP, rather his language difficulties were the cause of his distress.

4.2.3 Controls

Seven participants were male, 13 were female and they had a mean age of 46.2 years *(age range*= 21-78 years*)*. No control participant scored in the clinical range on the OCI.

4.3 Procedure

The University of Sydney and the Sydney West Area Health Service Human Research Human Ethics Committees approved the study. Informed written consent was obtained from the participant or the appropriate relative (FTD only) prior to testing. All participants were interviewed to consolidate information about their demographic characteristics, clinical symptomatology and medication. For FTD participants, a carer was usually present during the interviews. The neuropsychological testing took between 2 and 4 hours to complete, the latter for the most impaired of the FTD group. On some occasions testing was conducted over 2 sessions due to patient fatigue. Tests were administered in accordance with standardised procedures and the sequence of test administration was the same for all participants. Participants were also asked to complete 3 questionnaires: a Demographics Questionnaire; the Obsessive-Compulsive Inventory (OCI) to assess current OC symptomatology; and the Depression, Anxiety, Stress Scale (DASS) to assess mood (see Appendix B for copies of the questionnaires).

Because FTD participants were expected to have little insight, carers (usually spouses) were additionally asked to confirm their responses to these questionnaires. Also, FTD carers were interviewed using the Neuropsychiatric Inventory (NPI; Cummings, 1997) and the newly constructed Stereotypic & Ritualistic Behaviour subscale (SRB; Nyatsanza et al., 2003) to assess for psychiatric symptoms, as well as the specific presence of compulsive behaviour thought to be most relevant to dementia-related change (see Appendix B for copy of the SRB subscale).

4.4 Tests & Measures

4.4.1 Obsessive-compulsive symptoms

The Obsessive-Compulsive Inventory (OCI: Foa, Kozak, Salkovskis, Coles & Amer, 1998) is valid, reliable and relatively short self-report measure of OC symptoms. There are 42 items composing seven subscales: Washing, Checking, Doubting, Ordering, Obsessing, Hoarding, and Mental Neutralizing. Participants were asked to rate on a 5-point Likert scale for frequency of OC symptom (from 0= *Never* to 4= *Almost always*) and associated distress (from 0=*Not at all* to 4= *Extremely*), thus yielding a profile of frequency and distress for each symptom class. The OCI surveys a broad range of OCD symptoms and reflects the heterogeneous nature of the

disorder. The scale is also sensitive to nonclinical OCD symptoms. Good reliability and validity of the OCI and its subscales have been demonstrated with clinical and nonclinical samples (Foa et al., 1998). The more recent and shorter OCI-R (Foa et al., 2002) was not chosen because an assessment of a wider range of OCD symptoms was desired, particularly when investigating these symptoms in the FTD group (see Appendix B for a copy of the OCI, as well as items listed under their relative subscales).

4.4.2 Mood

The Depression, Anxiety and Stress Scale (DASS) is a 42-item questionnaire that has proven to be a reliable and valid measure of depression, anxiety and stress in adults (Lovibond & Lovibond, 1995). Participants were asked to rate on a 4-point Likert scale (from 0= *Did not apply to me at all* to 3= *Applied to me very much or most of the time*) the extent to which each statement applied to them over the past week (see Appendix B for a copy of the DASS).

4.4.3 Other psychiatric symptoms

The Neuropsychiatric Inventory (NPI; Cummings, 1997) is a short, reliable, structured clinical interview that assesses psychiatric disturbance commonly found in neurology populations (Aalten et al., 2003). The NPI was used as a measure of psychiatric symptoms in the FTD group. The NPI is informant (carer) based and consists of 12 behavioural symptoms: delusions, hallucinations, agitation/aggression, dysphoria/depression, anxiety, apathy, irritability, euphoria, disinhibition, aberrant motor behaviour, night time behaviour disturbances, and appetite and eating abnormalities. A recently devised NPI addendum, the Stereotypic & Ritualistic Behaviour (SRB) subscale (Nyatsanza et al., 2003) was used to assess compulsive behaviours thought to be particularly prevalent in FTD. Carers were asked to answer a series of yes/no questions regarding changes in behaviour psychiatric phenomena. They were also given the opportunity to expand on responses where appropriate. The severity and frequency of each neuropsychiatric symptom is scored and the amount of carer distress related to each symptom is recorded (see Appendix B for a copy of the NPI and SRB subscale).

The neuropsychological test instruments were selected to cover all major cognitive domains and a wide range of cognitive skills and, guided by previous studies, to target areas of cognition and brain regions thought to be compromised in these conditions. Where possible, test instruments in general clinical use were selected. Tests are listed under their relative cognitive domains:

4.4.4 General cognitive status

The Mini-Mental State Examination (MMSE; Folstein, Folstein & McHugh, 1975), a standard screen for dementia and a rough measure of cognitive status was administered to all participants. The Addenbrooke's Cognitive Examination (ACE; Mathuranath, Nestor, Berrios, Rakowicz & Hodges, 2000), which incorporates the MMSE, was also used to assess various aspects of cognitive decline that are particularly sensitive to dementia-related impairments. The ACE was administered to all FTD participants, as well as any participant over 60 years of age to ensure the detection of possible dementia in the OCD and control groups.

4.4.5 Premorbid intellectual function

Premorbid intellectual function was assessed using the National Adult Reading Test-2nd Edition (NART; Nelson, 1991), a word-reading test insensitive to the effects of most neurological conditions. FTD participants were required to pronounce a list of irregularly spelt words printed in a size 24-point font on an A4 card. Based on error rate, a predicted full scale IQ can be ascertained. Responses were audio taped. Because of expressive speech difficulties, the NART is not considered to be a reliable measure of premorbid IQ in temporal variant FTD. To best match any participant with temporal variant FTD to a control, estimates of premorbid IQ were made based on educational and vocational history.

4.4.6 Current intellectual function

The Wechsler Abbreviated Scale of Intelligence (WASI; Psychological Corporation, 1999a) was used to assess current intellectual functioning. It comprises 4 subtests from the Wechsler Adult Intelligence Scales-III (WAIS-III), previously shown to correlate most strongly with general intellectual functioning: Vocabulary and Similarities are used to estimate verbal IQ (VIQ); and Block Design and Matrix Reasoning are used to estimate performance IQ (PIQ) (Kaufman & Lichtenberger,

1999). An overall full-scale IQ (FSIQ) score can be gained from the administration of all 4 subtests.

4.4.7 Speed of information processing

The Digit-Symbol Coding subtest from the WAIS-III (Psychological Corporation, 1997b) was used to measure speed of information processing. Participants were presented with a series of numbers, each of which was paired with its own corresponding hieroglyphic-like symbol. Using a key, the participant was given 120 seconds to write as many symbols under a list of numbers as possible. Participants were encouraged to be as fast and accurate as possible, to avoid skipping any numbers and to continue until the researcher says, "stop."

4.4.8 Attention & working memory

Attention (Digits Forward) and working memory (Digits Backward) were assessed with the Digit Span subtest from the WAIS-III (Psychological Corporation, 1997a). The participant is orally presented a number string, which they must repeat verbatim (Digits Forward) and backwards (Digits Backward).

4.4.9 Language

The Boston Naming Test (BNT; Kaplan, Goodglass & Weintraub, 1978) was used to evaluate language (word finding and confrontation naming). It consists of 60 line drawings of objects ranging from high frequency (e.g. pencil) to low frequency (e.g. trellis), which participants were required to name. Semantic and phonological cues are given when the participant experiences difficulty with any item.

4.4.10 Executive function

The Wisconsin Card Sorting Test (WCST; Heaton, Chelune, Talley, Kay & Curtis, 1993) was used as a measure of EF. Participants were required to match a series of cards to 1 of 4 key cards varying in colour, shape and number, according to "correct/incorrect" feedback given by the researcher. Adequate performance on the WCST requires "strategic planning, organised searching, the ability to use environmental feedback to shift cognitive sets, goal oriented behaviour, and the ability to modulate impulsive responding" (Heaton et al., 1993; in Spreen & Strauss, 1998,

p.219). The test also provides a measure of perseveration (uncontrollable repetition of a response).

Two subtests from the Behavioral Assessment of Dysexecutive Syndrome (BADS; Wilson, Burgess, Emslie, Alderman & Evans, 1996; Wilson, Evans, Emslie, Alderman & Burgess 1998) were used as further measures of executive function: (i) Zoo Map is a timed measure of planning, whereby participants were required to show how they would visit a series of designated locations on a map of a zoo according to certain rules. Time taken to plan and execute the route is recorded; (ii) Rule Shift Cards is a timed measure of shifting cognitive set and response inhibition, using 21 spiral-bound non-picture playing cards. Like the WCST, it examines the participant's ability to respond correctly to a rule, and to shift flexibly from one rule to another. The rules are presented to the participant in size 28-point font on a card. The first rule is presented to the participant and states, "Say yes to red and no to black." The rule is left in full view throughout to reduce memory constraints. The researcher then turns the playing cards over one at a time and records the participant's yes/no responses. The second rule states, "Say yes if the card is the same colour as the last one and no if it is not" and the procedure remains the same. The first rule was designed to establish a pattern of behaviour, which increases the likelihood of perseverative errors in the second part of the test when the rule is changed. Time taken and number of errors is recorded.

4.4.11 Theory of Mind

Both verbal and nonverbal Theory of Mind (ToM) tasks were administered. Test stimuli were drawn from previous published studies in adult populations where the stimuli were developed to study higher-order ToM in autism and following brain injury (Castelli, Frith, Happe & Frith, 2002; Happe, Bronwell & Winner, 1999; Gallagher et al., 2000) (see Appendix C for copies of ToM stimuli). The selected stimuli were piloted on a small group of neurologically normal adults to ensure face validity and ease of comprehension. Verbal stimuli were presented in size 20-point font on A4 white paper in counterbalanced order. Responses were audio taped. There were 2 conditions, 4 stories or cartoons in each condition: ToM (concerned with attribution of mental states- ignorance, false belief, faux pas), and non-ToM (required

general verbal reasoning ability and inferences about practical, rather than ToM issues).

The verbal ToM task consisted of 8 story vignettes, followed by a comprehension question. Participants were asked to read each passage silently until they had understood it, at which point they were to read the comprehension question, and tell their answer to the researcher. Correct answers required inferences about the thoughts, feelings and sometimes intentions of the central character. Answers were scored 0, 1, or 2 (as per Happe, Bronwell & Winner, 1999); with 2 representing a full and explicitly correct answer, 1 a partial or implicit answer. Wrong or "don't know" responses were scored as 0 (see Appendix C for examples of scoring criteria).

On the visual ToM task, participants were shown each of 8 black and white cartoons, one at a time with the instruction to tell the researcher why each was funny. Here, ToM responses involved humour that depended upon what a character mistakenly thought or did not know; and non-ToM involved rather a physical anomaly or violation of a social norm. Answers were scored 0, 1, 2, or 3 (as per Happe, Bronwell & Winner, 1999); with 3 given for a full and explicit answer, 2 for partial/implicit explanation, 1 for reference to relevant parts of the cartoon, and 0 for incorrect or "don't know" answers (see Appendix C for examples of scoring criteria). For both stories and cartoons, order of stimuli presentation was counterbalanced.

4.4.12 Verbal memory

The Logical Memory I and II subtests from the Wechsler Memory Scale-III (WMS-III; Psychological Corporation, 1997) were used as measures of immediate and delayed verbal recall. Two stories are read aloud, the second story is read twice, and the participant is asked to retell as much of the stories from memory as possible both immediately and after a delay. A recognition component also requires the participant to answer yes/no to questions about each story after a delay.

4.4.13 Visual memory

The Rey Complex Figure Test (RCFT; Meyers & Meyers, 1995) measured visuospatial ability (Copy) and memory for complex visual information (3-minute delayed recall). Participants were asked to copy a two-dimensional complex

geometric figure and were timed. After a 3-minute delay, the participant was asked to reproduce the design from memory. A recognition component requires the participant to select the design from amongst distractors.

4.4.14 Visuospatial & visuoconstructional abilities

Visuospatial ability was measured with the RCFT (Copy), described above. Visuoconstructional ability was measured with the Block Design subtest from the WASI which required the participant to manipulate two-colour cubes to replicate a set of modelled or printed two-dimensional geometric patterns under a time constraint.

4.5 Scoring

Raw scores were tabulated for the various neuropsychology tests for comparison across groups. Neuropsychology test scores were calculated in accordance with standard scoring procedures (Lezak, 1995; Spreen & Strauss, 1998). IQ and premorbid IQ estimates were attained by the WASI and the NART based on the normative data available in the manuals (Nelson, 1991).

4.6 Statistical analyses

Statistical analyses were conducted using SPSS, version 12.0. A standard alpha of α=0.05 was chosen. Where Levene's test for homogeneity was significant, that is the variances of the variable were not equal between groups, equality of variance was not assumed when testing for significance. All data are expressed as mean ± standard deviation (s.d.) and all *p*-values are two-tailed. Independent samples t-tests were performed to explore group differences between groups on age, years of education, MMSE, and OCI and DASS scores. Chi-square analyses were performed to explore categorical variables such as handedness, English as a Second Language (ESL), drinking and medication status. Multiple univariate ANOVAs were performed to investigate the difference between the OCD and control group on cognitive variables. Pearson, Spearman-R and partial correlational analyses were performed to investigate relationships between OC symptoms and aspects of cognitive performance. Multivariate ANOVA was performed to investigate differences between the FTD and a matched portion of the control group on cognitive variables and OC symptoms. Pearson correlational analysis was performed to identify the principle

neuropsychological scores related to OC symptoms, illness duration and demographic variables. Paired samples t-tests were used to investigate the difference in ToM and non-ToM performance within each group.

Chapter 5. Results

5.1 Obsessive-Compulsive Disorder results

Independent samples t-tests were conducted to investigate the between group differences in age, years of education, MMSE scores, DASS depression, anxiety and stress scores, as well as OCI subscale and total frequency and distress scores.

No statistically significant differences were found between the OCD and control groups in age, years of education or MMSE scores (see Table 5.1). The groups differed significantly on almost all psychiatric variables with the OCD group scoring higher on DASS depression, anxiety and stress scores, as well as OCI checking, doubting, ordering, obsessing, mental neutralising and total scores (both frequency and distress subscales, $p < .001$ in all cases, $df = 37$). The only measure on which the groups did not differ significantly was the OCI hoarding frequency subscale (see Table 5.2).

Pearson's goodness of fit chi-square analyses was conducted to investigate frequencies in categorical demographic variables to compare the two groups. Fisher's exact test and Cramer's V test was employed when indicated. The analysis showed that there were no significant differences between the groups in sex, handedness, ESL, or present and past alcohol consumption.

A significant difference in psychotropic medication status was found between the two groups with 12 (60%) of the OCD group taking psychotropic medication at the time of the assessment, compared with only two (10%) of the control group ($x^2 = 10.989$, $df = 1$, $p = .001$).

Table 5.1. Means, standard deviations and p-value of age, years of education and MMSE for OCD and healthy controls.

Group	OCD	Controls	T-test (*p*-value)
Age (years)	37.6 (±13.1)	46.2 (±19.4)	0.116
Education (years)	12.4 (±2.9)	13.7 (±2.6)	0.174
MMSE	29.6 (±0.8)	29.7 (±0.6)	0.579

Table 5.2. Obsessive-compulsive symptoms, depression, anxiety & stress in OCD and healthy controls with descriptive and MANOVA overall group effect.

Measures		Descriptive (Mean ± SD)		t-test *(p-value)*
Measure	Scale	OCD	Controls	Overall group effect
OCI Frequency	Washing	13.31 ± 7.26	2.00 ± 2.75	.000 **
	Checking	13.84 ± 7.92	1.85 ± 2.68	.000 **
	Doubting	5.61 ± 2.97	1.15 ± 1.60-	.000 **
	Ordering	8.72 ± 5.59	2.38 ± 2.73	.000**
	Obsessing	13.44 ± 8.40	1.99 ± 2.29	.000**
	Hoarding	3.22 ± 3.42	1.70 ± 2.03	.083
	Mental Neutralising	9.61 ± 5.01	2.25 ± 2.73	.000**
	Total Frequency	67.87 ± 25.66	13.31 ± 12.48	.000**
OCI Distress	Washing	14.69 ± 10.38	0.71 ± 1.46	.000**
	Checking	12.90 ± 7.65	0.60 ± 1.19	.000**
	Doubting	5.50 ± 3.05	0.60 ± 1.14	.000**
	Ordering	7.39 ± 5.35	1.10 ± 1.41	.000**
	Obsessing	13.62 ± 8.73	1.44 ± 2.04	.000**
	Hoarding	2.39 ± 3.03	0.40 ± 0.83	.008*
	Mental Neutralising	8.28 ± 4.92	1.50 ± 2.07	.000**
	Total Distress	64.76 ± 22.71	6.35 ± 7.73	.000**
DASS	Depression	15.56 ± 13.79	3.15 ± 4.34	.002*
	Anxiety	10.72 ± 9.92	2.50 ± 2.74	.003*
	Stress	19.94 ± 12.53	6.00 ± 5.10	.000**

*p<0.05 **p<0.001

A series of multiple univariate ANOVAs were conducted in order to explore between group differences on all cognitive ability variables. Multiple ANOVAs, as opposed to Multivariate ANOVA, was considered appropriate for two reasons: (i) the research was exploratory; and (ii) the design allowed all major cognitive domains to be explored (from memory, IQ, speed of information processing, visuospatial ability, executive function etc.), thus many of the variables were seen to be "conceptually independent" (Biskin, 1980, p.70), with no interest in seeking any underlying factor

(Huberty & Morris, 1989). However, in using multiple ANOVAs rather than multivariate ANOVA, adjustments for multiple comparisons are not made to the alpha level. That is, alpha remains at α=0.05 for each individual statistical comparison in order to avoid missing potential effects. It is clear that there is also an increased chance of a false positive result, especially where significance levels are very near 0.05. These results would be interpreted with caution.

Further, the analysis controlled for variables thought to be possible confounds of neuropsychological test results; the covariates were age, years of education, psychotropic medication status and DASS depression scores. The analysis did not control for differences in IQ because the differences observed in WASI FSIQ disappeared when Matrix Reasoning subscores were excluded from a composite FSIQ. It was considered that a deficit in visual reasoning was illustrative of the difficulties upon testing that was observed in the OCD group. Table 5.3 shows a summary of results of cognitive assessment.

Table 5.3. Cognitive test results in OCD and healthy controls with descriptive and ANOVA overall group effect.

Measures		Descriptive (Mean ± SD)		ANOVA (*p*-value)
Cognitive domain	Test	OCD	Controls	Overall group effect / (controlling for VIQ)
Current intellectual ability	WASI FSIQ	102.44 ± 14.47	114.86 ± 11.36	.035*
	WASI VIQ	104.89 ± 14.14	114.35 ± 11.7	.229
	WASI PIQ	99.00 ± 15.99	111.95 ± 12.57	.017* (.043*)
	WASI Vocabulary	53.50 ± 10.45	60.40 ± 7.23	.507
	WASI Similarities	54.83 ± 7.30	57.20 ± 6.92	.895
	WASI Block Design	51.00 ± 9.73	55.65 ± 10.02	.273
	WASI Matrix Reasoning	49.17 ± 10.91	57.85 ± 6.7	.027* (.061)
Speed of information processing	WAIS-III Digit-Symbol Coding	68.11 ± 16.71	72.00 ± 17.39	.363
Attention & working memory	Digit Span Forward	9.50 ± 2.31	10.75 ± 2.4	.133

Table 5.3 continued.

	Digit Span Backward	6.44 ± 2.20	8.15 ± 2.18	.059
Verbal Memory	WAIS-III Logical Memory II	22.44 ± 7.66	26.4 ± 6.89	.392
Visual Memory	RCFT Recall	13.19 ± 6.85	18.45 ± 7.61	.009* (.016*)
	RCFT Recognition	16/19	18/20	.589 (Cramer's V)
Language	Boston Naming Test	52.00 ± 5.18	56.15 ± 3.73	.275
Visuospatial ability	RCFT Copy	32.83 ± 3.32	34.35 ± 1.43	.076
Executive Function	BADS Rule Shift Cards Test II errors	1.67 ± 2.06	1.15 ± 1.04	.507
	BADS Zoo Map I errors	1.00 ± 1.14	0.60 ± 1.05	.916
	WCST trials to complete 1st category	20.28 ± 24.96	12.35 ± 3.57	.049* (.061)
	WCST number of categories	5.17 ± 1.58	5.60 ± 0.99	.447
	WCST perseverative responses	19.89 ± 19.55	14.2 ± 13.26	.288
	WCST perseverative errors	16.56 ± 14.56	12.5 ± 10.81	.240
	WCST failure to maintain set	1.22 ± 1.56	0.35 ± 0.59	.269
Theory of Mind vs. Non-Theory of Mind	Theory of Mind Stories	6.78 ± 1.00	6.85 ± 1.39	.942
	Non-Theory of Mind Stories	6.33 ± 1.85	6.95 ± 1.15	.774
	Theory of Mind Cartoons	10.11 ± 1.97	9.75 ± 1.74	.552
	Non-Theory of Mind Cartoons	7.78 ± 2.37	8.90 ± 2.05	.965

*p<0.05 **p<0.001 For Visuospatial ability, see also results of WASI Matrix Reasoning and Block Design. For Executive Function, see also WASI Similarities, WASI Matrix Reasoning and RCFT and Non-ToM Stories/Cartoons.

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No between-group differences were found on measures of speed of information processing, attention, working memory, verbal memory, language, visuospatial ability and almost all measures of EF. The only tests on which the OCD group performed significantly worse than the controls was WASI Matrix Reasoning (F= 5.35, df= 1, p= .027), RCFT Recall (F= 7.67, df= 1, p= .009), and one measure of EF- the number of trials taken to complete the first category on the WCST (F=4.18, df= 1, p= .049). See Figures 5.1, 5.2 and 5.3 respectively. Performance of the WASI-III Digit Span Backward subtest approached significance (F= 3.82, df=1, p= .059) with the OCD group reciting less numbers backwards (correctly) than the control group.

While there was a significant difference between the OCD and control group on WASI FSIQ and PIQ, these scores are composite scores that include performance on Matrix Reasoning. A difference in FSIQ and PIQ here is an artefact of a specific deficit in Matrix Reasoning in the OCD group. There is no difference in VIQ between the OCD and control group.

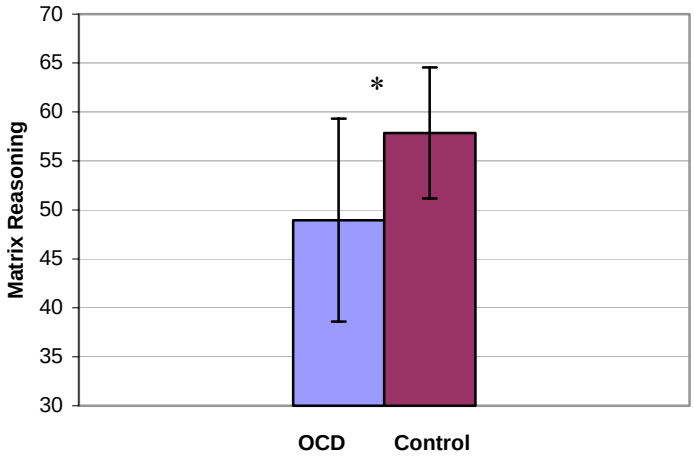

Figure 5.1. OCD and control performance on Matrix Reasoning. OCD participants scored significantly lower than controls on Matrix Reasoning.

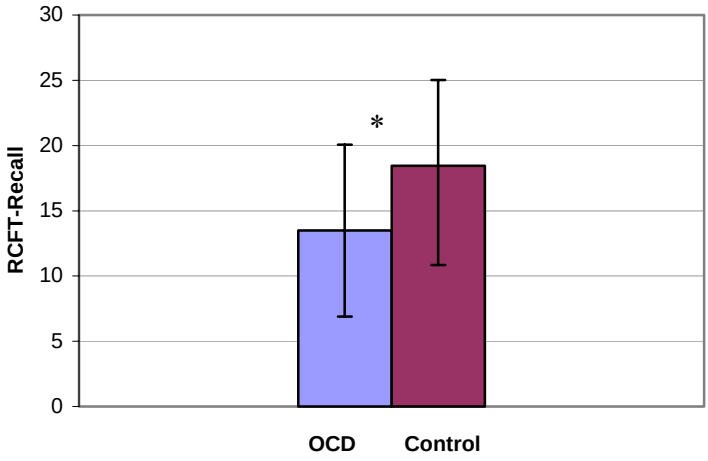

Figure 5.2. OCD and control performance on RCFT-Recall. OCD participants recalled significantly less than controls after a 3-minute delay on the RCFT.

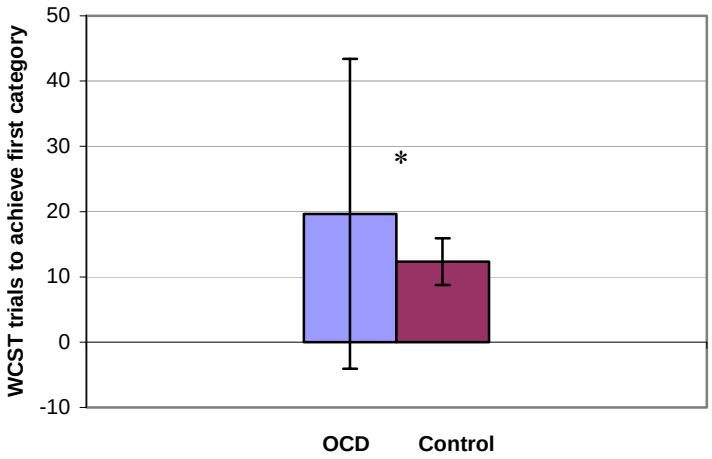

Figure 5.3. OCD and control performance on WCST trials taken to achieve first category. OCD participants required significantly more cards to complete the first category on the WCST.

There was no significant difference between the OCD group and controls on both ToM measures (stories and cartoons). Paired samples t-tests were performed to investigate the difference between ToM and non-ToM performance. There was no significant difference between ToM and non-ToM story performance in the OCD group. The OCD group performed significantly better on the ToM cartoons than the non-ToM cartoons (t= 4.42, df= 18, p= .000). The control group also performed better on ToM cartoons than non-ToM cartoons, though this was not significant (p= .077).

Statistically significant results were further analysed by including WASI VIQ as a covariate (results indicated in Table 5.3 in brackets). Statistically significant results persisted on WASI PIQ score and RCFT-Recall.

To examine whether differences in cognitive performance within the OCD group were related to symptoms subtypes, a series of exploratory parametric (Pearson), nonparametric (Spearman R) and partial correlational analyses were performed on selected cognitive variables and scores on the OCI. The selected variables were neuropsychological tests scores measuring cognitive domains where deficits have been reported in the literature and where group differences were found in the present study. These were: all measures of EF (see Table 5.3), visual memory (RCFT Recall), working memory (Digit Span backwards), speed of information processing (Digit-

Symbol Coding) and WASI Matrix Reasoning. WASI FSIQ, VIQ and PIQ scores were also included to explore any possible relationships with general intellectual function. In total, 14 neuropsychological test scores were chosen and correlations were run against all 16 OCI (subscale and total) scores.

The paucity of literature examining the relationships between OCD symptom measure scores and neuropsychological performance rendered this study exploratory, and cognitive variables were seen to be conceptually independent. Therefore, all correlational permutations were performed between the 14 selected cognitive variables and the 16 OCI scores, in an attempt to avoid missing potentially significant and clinically interesting relationships between cognition and OC symptoms. Given the large number of possible permutations, 11 significant correlations could be expected by chance. The present study found only 4, suggesting that the results are essentially negative. Clinical significance was also not apparent where statistically significant results were obtained. Further correlational analyses were therefore not pursued.

4.2 Frontotemporal dementia results

Results were based on 10 demographically similar control participants (friends or spouses of the FTD group). Nine FTD participants (8 frontal variant FTD and 1 temporal variant FTD) were included in the analysis.

Pearson's goodness of fit chi-square analyses was conducted to investigate frequencies in categorical demographic variables between the FTD and control groups. Fisher's exact test was used for a 2 x 2 design analysis and Cramer's V test was employed when any cell had a count less than 5.

The groups did not differ in handedness (1 control was left-handed, 0 FTD), retirement status (5 controls were retired, 8 FTD), ESL (1 subject in each group), history of alcohol use, presence of mood/anxiety disorder, or use of psychotropic medication. As expected, the groups did differ significantly in present alcohol intake, with all 9 FTD participants drinking either no alcohol or less than 3 glasses per week (usually reduced intake since time of diagnosis), and 6 control participants drinking

moderate amounts of alcohol (having at least 1 drink most days) (Cramer's V= .702, df= 2, p< .05).

To ensure the groups were indeed matched, independent samples t-tests were conducted to investigate the between group differences in age, years of education, and estimated premorbid IQ. There were no significant differences (α=0.05) in age, education and estimated premorbid IQ between the groups. Table 5.4 shows a summary of results.

Table 5.4. Means, standard deviations and p-value of age, years of education and estimated premorbid IQ for FTD and healthy controls.

Group	FTD	Controls	T-test (*p*-value)
Age (years)	62.4 (±11.2)	63.6 (±9.3)	.809
Education (years)	11.9 (±2.3)	13.3 (±2.5)	.225
NART FSIQ	100.6 (±13.2)	109.5 (±5.8)	.073

To investigate the presence of OC symptoms in the FTD group, significant scores on the OCI and prevalence rates on aspects of the NPI (namely, the SRB and Aberrant Motor Behaviour subscale) can be seen in Tables 5.5 & 5.6 respectively.

The number of FTD participants who scored 1-2 s.d. above control group scores on the OCI total and subtype scales does not exceed 2 (see Table 5.5). In total, 4 participants scored above controls on at least one OCI frequency subscale. No FTD participants scored 2+ s.d. above controls on the OCI. More prevalent compulsive behaviours were reported on the NPI, where 7 of the FTD participant carer's reported at least one stereotypic and ritualistic behaviour (see Appendix E for individual FTD profiles).

Table 5.5. Number and percentage of FTD patients with clinically significant Obsessive-Compulsive Inventory scores. Patient scores were considered significant if they fell >1s.d. above the range of controls' scores. Participant case numbers indicate which participants endorsed OCI subscale items.

Obsessive-Compulsive Inventory		No. significant (%)	[participant case no.]
Frequency scores			
	Washing	2 (22%)	[4,5]
	Checking	2 (22%)	[5,7]
	Doubting	0	
	Ordering	1 (11%)	[5]
	Obsessing	1 (11%)	[5]
	Hoarding	2 (22%)	[5,8]
	Mental Neutralising	0	
	Total	1 (11%)	[5]
Distress scores			
	Washing	0 (1+)	
	Checking	1 (1+)	[9]
	Doubting	2 (1+)	[1,9]
	Ordering	1 (1+)	[8]
	Obsessing	0 (1+)	
	Hoarding	0 (1+)	
	Mental Neutralising	0 (1+)	
	Total	0 (1+)	

+ missing values- [Participant 5] see Appendix E for individual profiles

Table 5.6. Number and percentage of FTD patients with informant-reported Psychiatric Change: Stereotypic & Ritualistic behaviours (detailed); Aberrant Motor behaviours (detailed). Clinically significant scores on a subscale were obtained using the Cummings et al. (1997) interpretation of assessment notes.

Measure	No. significant (%)
Neuropsychiatric Inventory (patient informant reports)	
Stereotypic & Ritualistic Behaviours (at least one SRB)	7 (78%)
Has developed repetitive phrase	2 (22%)
Repeats questions & answers	4 (44%)
Has developed a routine around home/garden	4 (44%)
Is preoccupied with counting things	2 (22%)
Clock watches & is preoccupied with time	3 (33%)
Consistently choses same leisure activity	3 (33%)
Collects or hoards obsessively	2 (22%)
Wants to eat the same food repeatedly	0
Aberrant Motor Behaviours	6 (67%)
Paces around house without purpose	3 (33%)
Rummages, opens & unpacks drawers & closets	4 (44%)

Multivariate analysis of variance (MANOVA) was conducted to explore between group differences on obsessive-compulsive symptoms. Table 5.7 shows a summary of results of OC symptom assessment.

There were no significant group differences between FTD participants and controls on OC symptoms, as measured by the OCI. A significant difference was found on all three DASS scales, with FTD participants reporting higher levels of symptoms consistent with depression, anxiety and stress. However, only 3 FTD participants fell in the clinical range on these scales: 1 participant fell in the clinical range on depression, anxiety and stress, 1 fell in the clinical range on anxiety and 1 fell in the clinical range on depression and stress (see Appendix E for individual FTD neuropsychological and psychiatric profiles).

Table 5.7. Obsessive-compulsive symptoms, depression, anxiety & stress in FTD and healthy controls with descriptive and MANOVA overall group effect.

Measures		Descriptive (Mean ± SD)		MANOVA *(p-value)*
Measure	Scale	FTD	Controls	Overall group effect
OCI Frequency	Washing	2.00 ± 2.89	2.30 ± 2.54	.824
	Checking	2.00 ± 2.00	1.40 ± 2.80	.634
	Doubting	0.86 ± 1.46	1.10 ± 1.66	.760
	Ordering	3.71 ± 3.30	2.50 ± 3.34	.470
	Obsessing	1.76 ± 2.07	1.77 ± 2.09	.988
	Hoarding	3.00 ± 2.77	2.10 ± 2.42	.488
	Mental Neutralising	1.29 ± 1.70	1.70 ± 2.41	.702
	Total	14.61 ± 9.37	12.87 ± 12.18	.756
OCI Distress	Washing	0.43 ± 0.79	0.51 ± 0.87	.877
	Checking	0.71 ± 1.11	0.20 ± 0.42	.199
	Doubting	0.57 ± 0.98	0.30 ± 0.68	.506
	Ordering	1.71 ± 2.43	0.70 ± 1.06	.256
	Obsessing	0.86 ± 1.07	1.29 ± 2.22	.645
	Hoarding	0.43 ± 0.54	0.40 ± 0.97	.945
	Mental Neutralising	0.45 ± 0.81	0.80 ± 1.62	.610
	Total	5.17 ± 3.81	4.20 ± 6.30	.724
DASS	Depression	11.57 ± 11.82	1.70 ± 2.41	.020*
	Anxiety	6.43 ± 4.67	0.50 ± 0.71	.001**
	Stress	11.00 ± 10.02	3.20 ± 1.81	.028*

*p < 0.05 **p < 0.001

Multivariate analysis of variance (MANOVA) was conducted to explore between group differences on cognitive variables. Table 5.8 shows a summary of results of cognitive assessment. Results reflect those of the entire FTD sample, including the temporal variant FTD case (WP). WP's performance on the WCST was not impaired.

FTD participants performed significantly worse than controls on almost all measures of cognition. The only cognitive domain in which FTD participants were not impaired in comparison to controls was visual memory (RCFT-Recall).

Table 5.8. Cognitive test results in FTD and healthy controls with descriptive and MANOVA overall group effect.

Measures		Descriptive (Mean ± SD)		MANOVA (*p*-value)
Cognitive domain	Test	FTD	Controls	Overall group effect
Current intellectual ability	MMSE	24.44 ± 4.56	29.60 ± 0.70	.003*
	WASI FSIQ	80.89 ± 17.28	116.70 ± 9.06	.000**
	WASI VIQ	81.78 ± 27.11	116.00 ± 9.33	.002*
	WASI PIQ	84.33 ± 15.10	113.70 ± 10.50	.000**
	WASI Vocabulary	35.89 ± 20.25	61.40 ± 5.44	.001*
	WASI Similarities	39.89 ± 18.10	58.20 ± 5.51	.007*
	WASI Block Design	37.67 ± 8.76	54.0 ± 10.25	.002*
	WASI Matrix Reasoning	39.44 ± 11.84	61.20 ± 2.82	.000**
Speed of information processing	WAIS-III Digit-Symbol Coding	31.22 ± 20.89	58.80 ± 11.11	.002*
Attention & Working Memory	Digit Span Forward	7.33 ± 2.12	9.70 ± 2.50	.041*
	Digit Span Backward	3.78 ± 2.33	7.10 ± 1.45	.002*
Verbal Memory	WAIS-III Logical Memory II	12.67 ± 9.73	24.50 ± 6.57	.006*
Visual Memory	RCFT Recall	11.39 ± 9.39	16.00± 6.54	.227
	RCFT Recognition	8/9	8/10	.596 (Cramer's V)
Language	Boston Naming Test	39.33 ± 18.39	56.30 ± 4.88	.012*
Visuospatial ability	RCFT Copy	28.50 ±9.20	34.05 ± 1.34	.076
Executive Function	BADS Rule Shift Cards Test II errors	4.00 ± 4.42	1.10 ± 0.88	.057
	BADS Zoo Map I errors	3.33 ± 2.55	0.90 ± 1.37	.018*
	WCST trials to complete 1st category	78.22 ± 60.43	13.80 ± 4.67	.004*
	WCST number of categories	1.22 ± 2.05	5.40 ± 1.27	.000**
	WCST % perseverative responses	60.78 ± 32.78	15.30 ± 12.37	.001*
	WCST failure to maintain set	0.89 ± 1.17	0.40 ± 0.52	.245

Table 5.8 continued

Theory of Mind vs. Non -Theory of Mind	Theory of Mind Stories	3.71 ± 2.63	6.70 ± 1.06	.005*
	Theory of Mind Cartoons	5.71 ± 3.45	9.90 ± 1.60	.004*
	Non -Theory of Mind Stories	3.43 ± 3.26	7.00 ± 1.16	.006*
	Non-Theory of Mind Cartoons	5.71 ± 3.73	8.40 ± 1.65	.060

*p<0.05 **p<0.001 For Visuospatial ability, see also results of WASI Matrix Reasoning and Block Design. For Executive Function, see also WASI Similarities, WASI Matrix Reasoning, RCFT Copy and Non-ToM Stories/Cartoons.

The FTD group performed significantly worse than controls on both verbal and visual ToM tasks (stories and cartoons). Paired samples t-tests were performed to investigate the difference between ToM and non-ToM performance in the FTD group, and no significant difference between ToM and non-ToM story or cartoon performance was found.

Pearson correlational analysis was conducted to investigate the relationship between aspects of cognitive impairment and presence of OC symptoms as measured by the OCI, as well as the presence of stereotypic, ritualistic and aberrant motor behaviours as measured by the NPI. The relationship between age, education and length of illness and the presence/absence of OC symptoms was also explored in this analysis. No significant correlations were found between performance on cognitive tasks and OC, stereotypic, ritualistic and aberrant motor behaviours.

Chapter 6

Discussion I: Obsessive-Compulsive Disorder findings

Motivated by findings that implicate common neuroanatomical substrates, as well as neuropsychological studies that point to impaired executive function in both OCD and FTD, the current study investigated neuropsychological variables associated with OC symptoms in idiopathic OCD and in FTD, a degenerative neurological condition in which compulsive behaviours are often a feature. The first phase of the study investigated cognitive deficits, and their association with OC symptoms, in a group of patients with OCD. Three significant differences in cognitive function were found between the OCD and control groups: Visual reasoning (Matrix Reasoning), visual memory (RCFT-Recall), and one measure of EF (WCST trials to complete first category).

The view that EF deficits are the most significant neuropsychological deficits in OCD has been fuelled not only by the clinical presentation of the disorder (difficulties with cognitive control and being "stuck in set," preventing the patient from terminating the obsessional thought or repetitive behaviour) but also the bulk of neuropsychological studies that have reported deficits in EF measured by the WCST, aspects of the CANTAB, the TMT, the Money Roads Test, as well as verbal fluency (Airaksinin, Larsson & Forsell, 2005; Cox, 1997; Christensen et al., 1992; Cox, Fedio & Rapoport, 1989; Fontenelle et al., 2001; Head, Bolton & Hymas, 1989; Lacerda et al., 2003; Moritz et al., 2001; Purcell et al., 1998; Veale et al., 1996). That view was not supported in this study, which employed several tests of EF, including two that have not previously been used in this population.

The WCST has been widely used in many but not all studies reporting deficits in EF. Here the OCD group required significantly more cards to complete the first category (colour) of the card-sorting task than controls (the mean was almost twice as many in the OCD group, see Table 5.3). It must be noted that this overall group effect was only slightly below the significance level ($p=0.49$, with $\alpha=0.05$) and after further controlling for VIQ, no longer significant ($p=0.061$). Therefore, the strength of this finding is weak. Utilising fewer cards required a good organisational and problem

solving strategy, as well as the ability to inhibit incorrect responses (it was noted that some participants would say, "I know this is wrong… I know it's not shape…" but proceeded to match the cards by shape). It was expected that the OCD group would also perform poorly on total errors and perseveration (the extent to which participants revert to a previous solution after the card sorting rules has changed), however this was not the case. Christensen et al. (1992) and Boone et al. (1991) did not find deficits on any WCST outcome measure.

Tallis (1997) points out that poor performance on the WCST might be attributed to a range of deficits, and that the test may not be differentially sensitive to EF per se in OCD. That is, failures in planning, fluency and set shifting ability (thought to be subserved by regions of the dorsolateral prefrontal cortex) does not target the executive dysfunction produced by a disruption in the frontal-basal ganglia connections purported in OCD.

In the present study no significant deficits were found on planning (Zoo Map) or response inhibition (Rule Shift Cards). It is possible that the tests were not sensitive enough to detect deficits in EF in an OCD sample, with ceiling effects potentially masking significant differences between the groups. The question remains, however, that if deficits in EF are a subtle phenomenon, can they explain the dramatic and disruptive symptoms seen in OCD? While it was hypothesised that deficits in EF would be found in the OCD group, this study provided little support for that hypothesis. Instead, more significant deficits in tasks ascribed to right hemisphere function were detected.

OCD participants performed significantly worse than controls on a measure of visual reasoning and visuospatial ability (Matrix Reasoning). This was the most sensitive measure in discriminating between the OCD and control group. It is plausible that poor performance on Matrix Reasoning could arise from difficulties with problem solving and abstraction, but deficits in these aspects of EF were not found on other tasks. Other studies have supported this result, pointing towards right-hemisphere dysfunction, despite imaging studies that consistently implicate the frontal-striatal-thalamic circuits. Boone et al. (1991), Insel et al. (1983) and Head, Bolton and Hymas (1989) have also reported reduced PIQ in comparison to VIQ in OCD samples. Some

authors have suggested that where a visuospatial deficit is apparent, it can be related to the clinical presentation of OCD, arguing that checking compulsions might be related to visuospatial deficits in processing visual information ("I can see that the stove is off, but can I really trust what I'm seeing?") (Insel et al., 1983; Rapoport, 1989).

Tallis (1997) argued that where VIQ-PIQ discrepancies have been identified, this may result from slowness on timed tasks related to meticulousness and task-irrelevant processing (such as intruding obsessional thoughts) rather than a primary impairment in visual processing per se. Matrix Reasoning, however, is not a timed task and participants were explicitly instructed to "take their time." At the same time Block Design, a test of visuoconstructional ability was not impaired in the OCD group, in spite of its being a timed task. Head, Bolton and Hymas (1989) and Moritz et al. (2005) found deficits in Block Design, while other studies have not (Beers, Rosenberg & Dick, 1999; Christensen et al., 1992). In all, results in this domain have been inconsistent from study to study.

These inconsistencies are not amenable to simple interpretation. Tallis' (1997) claim that they arise from other aspects of OC symptomatology offers one possible account. Another possibility is difficulty working with abstract material, complex reasoning and planning specifically in the visual arena. Some evidence for this lay in the RCFT Copy on which OCD participants scored in the normal range but qualitative observation found that approximately two-thirds of the OCD group produced a copy that was either piecemeal, included superfluous components or elements that were perseverative. These details are not reflected in the score but observably quite different from normal controls. Boldrini et al. (2004) also found that OCD patients used poorer organisational strategies on the RCFT Copy, noting that OCD patients tended to start the copy from particular elements compared with controls' more holistic strategies. Abstract problem solving and reasoning are also required for Similarities and no difficulties were detected here. Together these findings suggest that insofar as there is either an EF or right hemisphere deficit, the problem seems to lie in the performance of complex visuospatial tasks.

The OCD group performed significantly worse than controls at recall of the Rey complex figure, a measure of visual memory. This was found in previous studies (Christensen et al., 1992; Cox, Fedio & Rapoport, 1989). Unique to the present study was a recognition memory component of this task on which no significant difference between the groups, when asked to recognise the figure from amongst distractors, was found. Again, these results suggest that it was effortful retrieval of complex visual information that was compromised in the OCD sample.

Frampton (2003) argues that neuropsychological models that are based on deficits in memory functioning are potentially "strong candidates to account for the phenomenology of obsessions and compulsions (doubting whether an action has been completed; being compelled to check)" (Frampton, 2003, p.44-45). Other studies have corroborated the present finding with deficits reported in visual memory using the RCFT (Christensen et al., 1992; Cox, Fedio & Rapoport, 1989, Roh et al., 2005) and the Benton Visual Retention Test (Aranowitz, Hollander & DeCaria, 1994; Cohen Hollander & DeCaria, 1996; Simpson et al., 2006). Because deficits in visual but not verbal memory have been reported, it has further fuelled the right hemisphere dysfunction hypothesis.

Between-group analysis neared, but did not reach significance on a test of working memory (Digit Span backwards). This result is consistent with that of Moritz et al. (2001) study that demonstrated that poorer results on Digit Span backwards were associated with higher depression ratings. In the present study, when depression was not controlled for, results reached significance. It seems likely then, that it is a mood disturbance, not OCD alone that best accounts for any deficits in working memory in an OCD sample. Despite arguments linking OCD to a "general slowness" (Purcell et al. 1998a; 1998b, Tallis, 1997) on cognitive tasks, no deficit in speed of information processing was found in the present study.

This study is the first to employ a ToM measure, thought to be sensitive to orbitofrontal function, in an OCD population. No deficit in ToM was in fact found in the OCD group. Unexpectedly, controls and OCD participants performed better on the ToM cartoons than the non-ToM cartoons, though no such difference was found between ToM and non-ToM stories, suggesting that task difficulty may be significant

here. It is also possible that hypermetabolism in the orbitofrontal cortex, as reported in OCD, could improve orbitofrontal function though no such effect would be expected for controls.

It has been suggested that any neuropsychological deficits in OCD should correlate with symptom severity (Frampton, 2003). Further, the heterogeneous nature of OCD requires attentions to both total symptom severity and also symptom subtypes. For instance, a relationship between high scores on checking may exist with measures of visual memory, but high scores on mental neutralising may not. Likewise, it has been suggested that washing may have more to do with aspects of EF than with memory (Mataix-Cols et al., 1999). It was expected that there would be a negative correlation between aspects of cognitive performance and OC symptoms and that symptom subtypes would correlate differentially with the selected cognitive performance scores.

On the whole, this study did not support evidence for a relationship between measures of cognition and clinical symptoms. In the present study at least, where significant cognitive deficits were found (visual reasoning and visual memory), no significant correlations were found between these deficits and OCD symptoms, both total frequency and symptom subtypes.

Previous studies have also failed to find correlations between other aspects of cognition and OCD symptoms or severity (Purcell et al., 1998; Schmidtke et al. , 1998; Singh & Mukandan, 2003). It has been argued that cognitive deficits are not OCD-specific, rather can be attributed to other psychiatric processes that effect cognition (high trait anxiety and depression). However, studies that have implemented clinical controls refute this claim, finding cognitive deficits among OCD patients that are not found in other psychiatric conditions (Panic Disorder, PTSD, major depression, schizophrenia). While the present study did not implement a clinical control group, OCD was either the only or the primary diagnosis in each case, and using a depression inventory score as a covariate in the analysis controlled for the impact of mood.

There has recently been some debate regarding differences related to age of onset in OCD. It has been suggested that from developmental and neurobiological

perspectives, early onset (child and adolescent), and late onset (adult) OCD are two distinct categories of OCD (Fontenelle, Mendlowicz, Marques & Versiani, 2003). Roth, Milovan, Baribeau and O'Connor (2005) found that late onset OCD participants performed worse than early onset OCD participants on measures of EF and that late onset OCD was associated with poorer visual memory relative to healthy controls. Post-hoc analysis of the subjects in this study divided the OCD group, with 8 participants falling in the child/adolescent-onset group (significant symptoms beginning before the age of 16) and 11 participants falling in the adult-onset group. No significant differences were found between the child/adolescent-onset and adult-onset OCD participants on any cognitive measures, nor on any subscale or total score on the OCI. There was also no significant difference in depression, anxiety and stress levels as measured by the DASS. Hence, while sample sizes were quite small, the cognitive and psychiatric profiles were similar no matter the age of OCD onset.

It has been argued that the variability in results of cognitive performance in OCD can be explained by differences in medication status and the inclusion of patients with comorbid diagnoses (Frampton, 2003). Though not all the present participants were medication naive, the use of SSRIs and TCAs was controlled for in all between group analyses, while use of stronger psychotropic medication was a criterion for exclusion. There is other evidence that cognitive impairments in OCD are not secondary to antidepressant use. Nielen and Den Boer (2003) and Roh et al. (2005) found that while clinical symptoms improved with antidepressant medications, cognitive deficits remained, suggesting that impaired cognitive performance may form part of the core pathology of OCD.

The possible impact of comorbid conditions such as depression, social anxiety and Panic Disorder was minimised in the present study. Comorbid psychosis and a history of drug or alcohol abuse were exclusion criteria, while depression was controlled for in the analysis. Crucially, OCD was the primary diagnosis having the greatest impact on the participant's life. Comorbid anxiety disorders are especially common in OCD but this was not addressed in the analysis because it was assumed that if OCD was the primary diagnosis, any OCD-specific neuropsychological deficit would also emerge in those OCD participants who met diagnostic criteria for a secondary anxiety disorder.

In summary, this study found deficits in visual reasoning and visual memory in OCD, supporting a right hemisphere disturbance previously suggested in neuropsychological studies although not corroborated on neuroimaging. There was, in addition, little evidence of executive dysfunction in OCD, and no deficits were seen on tests thought to sensitive to basal ganglia and orbitofrontal function, the areas purported to be implicated in OCD. The deficits observed did not correlate with any OC symptom measure, rendering their impact on the clinical presentation of OCD doubtful. In general, this study revealed little to strongly implicate cognition in OCD symptoms. However, such a negative finding is also a useful one as it can highlight a parsimonious explanation for the inconsistent findings in this area of research. That is, relationships are likely tenuous and are certainly not reliably replicated. Future research may need to go beyond the scope of neuropsychology when attempting to account for the phenomena of obsessions and compulsions.

Chapter 7

Discussion II: Frontotemporal dementia findings

Stereotypic and ritualistic behaviours stand amongst the core clinical features of FTD. It is, then, not surprising that such behaviours are described as "OCD-like" with some researchers claiming that a proportion of FTD patients meet diagnostic criteria for OCD (Ames et al., 1994; Brun & Gustafson, 1999; Tonkonogy, Smith & Barreira, 1994). Obsessions are less likely in FTD (highlighted only in a few case examples e.g., Lough & Hodges, 2002; Tonkonogy, Smith & Barreira, 1994), and while the behaviour may be performed as if to relieve some form of uncertainty (Mendez et al., 1997), unlike OCD, anxiety is not generally attributed to the condition.

The relationship between OC symptoms in OCD and those in FTD is not well understood. It has been argued that OC symptoms lie on a spectrum, with repetitive stereotypies (often seen, for instance, in developmental and tic disorders) falling at one end of the spectrum, and complex and time consuming, ritualistic behaviours falling at another (Menzies & de Silva, 2003). The degree of insight and distress associated with OC symptoms may also form a continuum. Complex compulsive behaviours in FTD can look very much like compulsions seen in OCD, often being high on a "complexity continuum," but low on a "continuum of insight or distress." It is also clear, that as in OCD, OC symptoms in FTD are heterogeneous. In this study, no two FTD participants displayed the same pattern of OC behaviour. The two cases described in Chapter 4 exemplify the idiosyncratic nature of compulsive behaviours in FTD. With DE in particular, singing and praying had always formed part of her life: these compulsions appeared to be ego-syntonic. This is rarely the case in OCD.

Attempting to interrogate this issue, and unique to this study, a measure of OC symptoms frequently used in OCD was administered to participants with FTD. It was hoped thereby directly to compare compulsive behaviours in the two disorders. Somewhat surprisingly, there was no difference between the FTD and control groups on the OCI frequency scores clearly indicating that the OCI frequency scales are not a sensitive measure of compulsive symptoms in FTD.

Conversely, the incidence of compulsive behaviour, as measured by the NPI SRB revealed 78% (7/9) of FTD participant carers/informants endorsed at least one stereotypic and ritualistic behaviour, a result that is concordant with previous research (Ames et al. 1994; Miller et al., 1995; Nyatsanza et al., 2003). The most commonly endorsed items at 44% were "Repeats questions and answers" and "Has developed a repetitive routine around the home and garden." A "preoccupation with time and clockwatching" and "consistently choosing the same leisure activity" were the second most common items endorsed (33%). A number of aberrant motor behaviour findings e.g., 44% endorsed "rummages, opens and unpacks drawers and closets" were also reported (see Table 5.6). Results from the NPI also indicate that the majority FTD group carers reported significant levels of apathy, indifference, agitation and eating changes, behavioural and personality changes common in FTD (Nyatsanza et al., 2002).

The inability of the OCI to discriminate between FTD participants and controls raises the notion that compulsive behaviours in FTD may look somewhat like the compulsions of OCD but yet not be "OCD-like," particularly when not associated with obsessions or the distress felt at the senselessness of the behaviour, that is usual in OCD. One difference may lie in the distinction between complex compulsions and other simpler, repetitive behaviours. The FTD group reported a high incidence of aberrant motor behaviours, such as simple repetitive behaviours that are also reported in Alzheimer's disease (Miller et al., 1995; Nyatsanza et al., 2003), as well as developmental disorders such as autism and Asperger's disorder (Russell, 2005). These are not typically seen in OCD and are likely to be indicative of more significant neuroanatomical disruption than is seen in OCD.

The incidence of obsessions in FTD is much more tricky to ascertain. Reported absence of obsessions in this population has been associated with the lack of insight, preventing the patient from reporting obsessional experiences (Perry & Miller, 2001). Further, responses here relied on the second-hand report of carers, who likely have no access to whether the patients experience obsessions, an internal mental state, or not. WP's overt need for symmetry does resemble the obsession for order, symmetry and potentially safety common in OCD. However, with the exception of a few items that measure obsessions with observable behaviours (e.g., "I get upset if objects are not

arranged properly"), the presence and nature of any obsessions could not be measured.

In keeping with other studies (Bozeat et al., 2000b; Hodges et al., 1999; Mendez, 1996; Pasquier et al., 2001), FTD participants performed significantly worse than matched controls on all measures of cognition, apart- remarkably - from visual memory (RCFT-Recall). Thus, in this neurological condition in which OC symptoms are commonly reported, the results of neuropsychological investigation are almost exactly the converse of those for OCD (in whom there was little cognitive dysfunction, with the exception of visual memory).

Some researchers have argued that the cognitive profile in FTD is quite focal, with orbitofrontal function especially affected (Eslinger, 1999). In keeping with this view, previous studies have demonstrated specific impairment in ToM in FTD (Gregory et al., 2002; Lough et al., 2006; Lough & Hodges, 2002; Lough, Gregory & Hodges, 2001). In contrast, in the present study FTD patients were impaired on all tasks including both ToM and non-ToM control tasks. It is possible that "pragmatic language ability," described as the interaction between linguistic and non-linguistic cognitive systems, (Perkins, 1998) affected results here: that is, deficits were not specific to ToM stimuli because formulating a response and verbally conveying the answer requires significant demands on EF for both ToM and non-ToM stimuli. Participants in the FTD group, with the exception of the temporal variant case, were severely impaired on all measures of both EF and ToM so that obtaining a pure measure of orbitofrontal function is problematic in this group.

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No significant correlations between OC symptoms and cognition were found in the FTD group. Lack of statistical power due to small sample size may be a contributing factor, although the sparsity of significant correlations between cognition and symptoms in the OCD group, a larger sample, points to the likelihood of relative independence of cognitive deficits and psychiatric variables.

While neuropathological changes are undeniably responsible for the cognitive and behavioural changes characteristic of FTD, it is plausible that compulsive phenomena

may also serve a functional purpose. Perhaps the production of more repetitive, stereotyped and ritualistic behaviour in FTD is an attempt to maintain some degree of control and routine in a world that is increasingly bewildering. This would account for the heterogeneous nature of OC symptoms in FTD, for what would work in this way for one person may not for another. This account would also differentiate between OC symptoms in OCD in comparison those in FTD. Common to both OCD and FTD however, would be the need for homeostasis: for the OCD sufferer, a relief from the guilt, responsibility or fear of death caused by the obsession. For the FTD sufferer, a relief from disorientation, confusion or boredom.

Previous research has suggested that compulsive behaviours are most common in the early stages of the disease (Bathgate et al., 2001; Tonkonogy, Smith & Barreira, 1994). The present study did not support this claim. In fact, the two case examples presented in Chapter 4, both of whom demonstrated high OC symptomatology, were two of the most impaired FTD patients from a cognitive point of view, indicative of a later stage of the disease. Ames et al. (1994) similarly found no relationship between disease duration and those FTD patients who did and did not exhibit OC symptoms.

Snowden et al. (2001) and Nyatsanza et al. (2002) have argued that complex compulsive behaviours are more prevalent in the temporal variant of the disease, despite previous studies linking compulsive phenomena more closely with frontal variant FTD (Ames et al. 1994; Bathgate et al., 2001). One temporal variant FTD participant was included in this study (WP). He was perhaps the most "OCD-like" of all the participants, with clinical levels of depression and stress, and demonstrating distress if his compulsions were disrupted. This observation, as well as the findings of Snowden et al. (2001) and Nyatsanza et al. (2002) indicates that more attention to OC symptoms in temporal variant FTD may be warranted. Importantly, WP was also the only FTD participant without EF deficits. In the OCD group, EF was also generally intact. These findings suggest that the relationship between EF and OC symptoms is tenuous, accounting for the lack of significant correlations between EF and OC symptoms in both groups.

In this study, only a limited amount of prototypical OC symptomatology was present in the FTD group: Two FTD patients reported washing and cleaning behaviours on

the OCI, two reported checking and hoarding behaviours and one reported ordering behaviours. In general however, the present results revealed little concordance between the OC symptomatology in OCD and FTD as measured by the OCI.

While it was hypothesised that aspects of cognition would correlate with OC symptoms, neuropsychological investigation did not provide any support for an association between aspects of cognition and OC symptoms in either FTD or OCD. There were, however, qualitative similarities between OC symptoms in both groups, highlighted by the two FTD illustrative case examples.

Chapter 8

Discussion III: General discussion

8.1 Summary & conclusions

This neuropsychological investigation of OCD revealed deficits in visual reasoning and visual memory, providing support for the right hemisphere dysfunction hypothesis in OCD. The notion that OCD patients suffer from deficits in executive was generally not supported in the present study. No deficits in ToM, a measure of orbitofrontal function, were detected. Where cognitive deficits were present, there was no correlation between these and OC symptoms.

Likewise, no relationship between cognitive function and OC symptoms in the FTD group was revealed. A diffusely impaired neuropsychological profile (including severe executive dysfunction) was found in the FTD group, with the exception of intact visual memory, one of the few cognitive domains impaired in OCD. The neuropsychological profiles in these two clinical populations with OC symptoms are therefore diametrically opposed. Further, the nature of OC symptoms in OCD were found to be both quantitatively and qualitatively different from the OC behaviours seen in FTD, evidenced by the relative difference in OC symptoms recorded on the OCI in both groups. In neither population did neuropsychological deficits correlate with OC symptoms.

It has been postulated that in OCD the frontal-basal-striatal dysfunction may cause secondary cortical disinhibition with increased metabolism, whilst in FTD the primary pathology is known to be cortical (cell atrophy) although subcortical structures such as the basal ganglia are also compromised. Interruption of this fronto-subcortical circuit at different levels is likely to cause superficially similar behavioural disturbances (Cummings, 1993). In this study, the similarity in OC symptomatology between FTD and OCD patients was found to be extremely superficial, not least in the the lack of insight and anxiety and the rarity of obsessional thoughts in these patients (Lawrence, Ronca, Tyrrell & Rossor, 1994) compared with OCD patients. It is perhaps in the relationship between anxiety and OC symptomatology that the greatest disparity lies.

Cognitive-behavioural and other functional models of OCD place great emphasis on the obsessional thought and it's role in increasing anxiety, as the precursor to compulsive behaviour. The model, indicated below, shows the relationship between obsessions, anxiety and compulsions in OCD (adapted from Frampton, 2003, p.40).

The primary role of the obsessional thought and anxiety as precursors to compulsive behaviours in OCD sets it apart from other psychiatric disorders where OC symptoms are reported (e.g., tic and impulse control disorders) as well as in conditions where OC symptoms are acquired, such as following head injury and in neurological conditions including FTD. This is not to suggest that we cannot learn about idiopathic OCD from studying OC symptoms when they are acquired, or from studying compulsive behaviours when they occur in the absence of anxiety and obsessions, however from a neuropsychological standpoint it is clear that the relationship between OC symptoms in OCD and those in FTD cannot be accounted for by any similarities in cognitive deficits.

Models of OC symptoms should attempt to account for both their cause *and* role. For instance, anxiety reduction models provide an explanation of the role of compulsions in people with OCD. However, the underlying cause of what prompts a person to reduce anxiety in this way is less well understood. The present study has attempted to investigate a possible basis for OC symptoms in neuropsychological status but found no relationship between performance on neuropsychological tests and OC symptomatology. While the neuroanatomical basis of cognitive deficits in FTD is better understood than in OCD, there remains the possibility that compulsive behaviours may also have a functional role in FTD.

8.2 Limitations & strengths

This study, like many other neuropsychological studies, was limited in scope due to small sample size (Kirkby, 2003). While correlational analysis allowed for the exploration of the relationship between aspects of cognition and OC symptoms, both total scores and subscale scores, the OCD group was not divided into discrete

subtypes (e.g. predominantly washing, predominantly obsessing, predominantly hoarding). The OCI as a measure, would have allowed for this, however with groups as small as n=1, no meaningful between-group comparisons could have been undertaken within the OCD sample.

While the OCI provided a good measure of symptom frequency and distress, it is a criticism of any OCD self-report scale that an accurate measure severity is less easily derived. Total frequency and distress scores on the OCI are not necessarily reflective of overall symptom severity: a participant may score very highly on one subscale, however because their OC symptoms lie only on that subscale and no other, total OC symptom frequency scores would be low. On the other hand, a participant who has less frequent and distressing symptoms on a number of subscales may score higher on a total score. The YBOCS (Goodman et al., 1989), a clinician administered structured interview, is a valid measure of severity in OCD, however due to the length of the interview combined with the length of neuropsychological testing, using the YBOCS in this study was not considered practicable. This meant that the relationship between the severity of OCD and cognitive deficits could not be reliably ascertained.

While a deficit in visual memory was detected in the OCD group, only one measure- the RCFT- was employed in this study. Future studies that wish to fully investigate the nature of a possible right hemisphere disturbance in OCD would benefit from the inclusion of a range of visuospatial ability and visual memory measures, perhaps with emphasis on tests of effortful visual recall.

There is a dearth of studies that have attempted to relate cognitive deficits in OCD to OC symptoms. This study is the first to attempt this in both an idiopathic OCD sample and in a sample where OC symptoms are acquired, as well as the first to investigate compulsive phenomena in FTD from a neuropsychological standpoint. Methodological shortcomings of previous research in the neuropsychology of OCD were avoided by statistically controlling for depression and medication status, and ensuring groups were matched.

8.3 Future directions

There are several questions that remain beyond the scope of this study: Do neuropsychological deficits contribute to metacognitive processes that underlie functional impairment? If so, can treatment strategies benefit from the use of cognitive remediation? For instance, where deficits in visual memory are found, would strategies that aim to improve visual memory have any effect on OC symptoms? Present psychotherapy treatment strategies for OCD such as Exposure and Response Prevention and Cognitive Therapy aimed at reducing threat expectancy and perceived responsibility focus on reducing the role, most commonly of compulsions, in the maintenance of OCD. However, with treatment response rates for OCD as they stand, more attention towards functional models that account for the contributing underlying cause(s) of the disorder is warranted. Novel treatment strategies based on a new evidence-based working model of OCD may come into view.

The relationship between acquired psychiatric symptoms and cognitive decline in patients with neurodegenerative conditions is a new and exciting field of research. Future research may provide an increased understanding of the similarities and differences in psychiatric symptoms in both psychiatric and neurodegenerative conditions, potentially unravelling the question of contributing factors in the pathogenesis of psychiatric symptoms, idiopathic and acquired.

References

Aalten, P. de Vugt, M. E., Lousberg, R. Korten, E., Jaspers, N., Senden, B. et al. (2003). Behavioral problems in dementia: A factor analysis of the neuropsychiatric inventory. *Dementia and Geriatric Cognitive Disorders, 15*(2), 99-106.

Abramowitz, J. S., Brigidi, B. D. & Roche, K. R. (2000). Cognitive-behavioral therapy for obsessive-compulsive disorder: A review of the treatment literature. *Research on Social Work Practice, 11*(3), 357-352.

Airaksinen, E., Larsson, M. & Forsell, Y. (2005). Neuropsychological functions in anxiety disorders in population-based samples: Evidence of episodic memory dysfunction. *Journal of Psychiatric Research, 39,* 207-214.

Alegret, M., Junque, C., Vakkedoriola, F., Vendrell, P., Marti, M.J. & Tolosa, E. (2001). Obsessive-compulsive symptoms in Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry, 70,* 394-396.

American Psychiatric Association (2000). *Diagnostic and Statistical Manual of Mental Disorders (4th Edition).* Washington, DC: American Psychiatric Association.

Ames, D., Cummings, J. L, Wirshing, W. C., Quinn, B. & Mahler, M. (1994). Repetitive and compulsive behavior in frontal lobe degenerations. *The Journal of Neuropsychiatry and Clinical Neurosciences, 6,* 100-113.

Anderson, K. E., Louis, E. D., Stern, Y. & Marder, K. S. (2001). Cognitive correlates of obsessive and compulsive symptoms in Huntington's disease. *The American Journal of Psychiatry, 158*(5), 799-801.

Aranowitz, G. E., Hollander, E. & DeCaria, C. (1994). Neuropsychology of obsessive-compulsive disorder: preliminary findings. *Neuropsychiatry, Neuropsychology and Behavioral Neurology, 7,* 81-86.

Baron-Cohen, S., Ring, H., Moriarty, J., Schmitz, B., Costa, D. & Ell, P. (1994). The brain basis of theory of mind: the role of the orbitofrontal region. *British Journal of Psychiatry, 165,* 640-649.

Bathgate, D., Snowden, J. S., Varma, A., Blackshaw, A. & Neary, D. (2001). Behavior in frontotemporal dementia, Alzheimer's disease and vascular dementia. *Acta Neurologica Scandinavica, 103*(6), 367-378.

Baxter, L. R., Phelps, M. E. & Mazziotta, J. C. (1987). Local cerebral glucose metabolic rates in obsessive-compulsive disorder: A comparison with unipolar

depression and in normal controls. *Archives of General Psychiatry, 44,* 211-218.

Beers, S. R., Rosenberg, D. R. & Dick, E. L. (1999). Neuropsychological study of frontal lobe functioning in psychotropic-naïve children with obsessive-compulsive disorder. *American Journal of Psychiatry, 15,* 777-779.

Benkelfat**,** C., Nordahl, T. E., Semple, W. E., King, C., Murphy, D. L. & Cohen, R. M. (1990). Local cerebral glucose metabolic rates in obsessive-compulsive disorder: Patients treated with clomipramine. *Archives of General Psychiatry. Vol 47*(9), 840-848.

Berthier, M. L., Kuliesevsky, J., Gironell, A. & Heras, J. A. (1996). Obsessive-compulsive disorder associated with brain lesions: Clinical phenomenology, cognitive function, and anatomic correlates. *Neurology, 47,* 353-361.

Berthier, M. L., Kuliesevsky, J., J., Gironell, A. & Lopez, O. L. (2001). Obsessive-compulsive disorder and traumatic brain injury: behavioral, cognitive, and Neuroimaging findings. *Neuropsychiatry, Neuropsychology and Behavioral Neurology, 14*(1), 23-31.

Biskin, B. H. (1980). Multivariate analysis in experimental counseling research. *The Counseling Psychologist, 8,* 69-72.

Boldrini, M., Del Pace, L., Placidi, G. P. A., Keilp, J., Ellis, S. P., Signori, S. et al. (2004). Selective cognitive deficits in obsessive-compulsive disorder compared to Panic Disorder with agoraphobia. *Acta* Psychiatrica Scandinavica*, 111*(2), 150.

Boone, K. B., Ananth, J., Philpott, L., Kaur, A. & Djenderedjian, A. (1991). Neuropsychological characteristics of nondepressed adults with obsessive-compulsive disorder. *Neuropsychiatry, Neuropsychology and Behavioral Neurology, 4,* 96-109.

Bozeat, S., Gregory C. A., Ralph, M. A. & Hodges J. R. (2000a). Which neuropsychiatric and behavioural features distinguish frontal and temporal variants of frontotemporal dementia from Alzheimer's disease? *Journal of Neurology, Neurosurgery & Psychiatry, 69,* 178–86.

Bozeat, S., Ralph, M. A., Patterson, K., Garrard, P. & Hodges, J. R. (2000b). Non-verbal semantic impairment in semantic dementia. *Neuropsychologia, 38,* 1207-1215.

Brambilla, P. Barale, F., Caverzasi, E. & Soares, J. E. (2003). Anatomical MRI findings in mood and anxiety disorders. *Epidemiologia e Psychiatria Sociale, 11*(2), 88-98.

Breiter, H. C., Rauch, S.L., Kwong, K. K., Baker, J. R., Weisskoff, R. M., Kennedy, D. N. et al. (1996). Functional magnetic resonance imaging of symptom provocation in obsessive-compulsive disorder. *Archives of General Psychiatry, 53*(7), 595-606.

Brun, A.& Gustafson, L. (1999) Clinical and pathological aspects of Frontotemporal dementia. In Miller, B. L. & Cummings, J. L. (Eds.) *The Human Frontal Lobes.* (349-369). New York: The Guildford Press.

Calamari, J. E., Wiegartz, P. S. & Janeck, A. S. (1999). Obsessive-compulsive disorder subgroups: A symptom-based clustering approach. Behaviour *Research and Therapy, 37*(2), 113-125.

Carlson, N. R. (1999). *Foundations of Physiological Psychology (4th Edition).* Allyn and Bacon: Boston.

Castelli, F., Frith, C., Fappe, F. & Frith, U. (2002). Autism, Asperger syndrome and brain mechanisms for the attribution of mental states of animated shapes. *Brain, 125,* 1839-1849.

Channon, S., Sinclair, E., Waller, D., Healey. L. & Robertson, M. M. (2004). Social cognition in Tourette's syndrome: Intact Theory of Mind and impaired inhibitory functioning. *Journal of Autism and Developmental Disorders, 34*(6), 669-677.

Christensen, K. J., Kim, S. W., Dysken, M. W. & Hoover, K. M. (1992). Neuropsychological performance in obsessive-compulsive disorder. *Biological Psychiatry, 31,* 4-18.

Cohen, L., Hollander, E. & DeCaria, C. M. (1996). Specificity of neuropsychological impairment in obsessive-compulsive disorder: A comparison with social phobic and normal control subjects. *Journal of Neuropsychiatry, 8,* 82-85.

Cottraux, J., Gerard, D., Cinotti, L., Froment, J. C., Deiber, M. P., Le Bars, D. et al. (1996). A controlled positron emission tomography study of obsessive and neutral auditory stimulation in obsessive-compulsive disorder with checking rituals. *Psychiatry Research, 60,* 101-112.

Cox, C. S. (1997). Neuropsychological abnormalities in obsessive-compulsive disorder and their assessments. *International Review of Psychiatry, 9,* 45-60.

Cox C.S., Fedio P. & Rapoport, J. (1989). Neuropsychological testing of obsessive-compulsive adolescents: In Rapoport J. L. (Ed.). *Obsessive-Compulsive Disorder in Children and Adolescents.* Washington, D.C.: American Psychiatric Press, Inc., pp.73-85.

Crino, R. D. & Andrews, G. (1996). Obsessive-Compulsive Disorder and Axis I Comorbidity. *Journal of Anxiety Disorders, 10*(1), 37-46.

Cummings, J. L. (1993). Frontal-subcortical circuits and human behavior. *American Journal of Psychiatry, 50,* 873-880.

Cummings, J. L. (1997). The Neuropsychiatric Inventory: Assessing psychopathology in dementia patients. *Neurology, 48(5),* S10-15.

Cummings, J. L. & Cunningham, K. (1992). Obsessive-Compulsive Disorder in Huntington's Disease. *Biological Psychiatry, 31,* 263-270.

Daniele, A., Bartolomeo, P. & Cassetta, E. (1997). Obsessive-compulsive behaviour and cognitive impairment in a parkinsonian patient after a left putaminal lesion. *Journal of Neurology, Neurosurgery and Psychiatry, 62,* 288-289.

De Marchi, N. & Mennella, R. (2000). Huntington's Disease and its association with psychopathology. *Harvard Rev Psychiatry, 7*(5), 278-289.

Devinsky, O. & D'Esposito, M. (2004). *Neurology of Cognitive and Behavioral Disorders.* New York: Oxford University Press, Inc.

Diamond, A. (1990). Developmental time course in human infants and infant monkeys, and the neural basis of inhibitory control in reaching. *Annals of the New York Academy of Sciences, 608, i637-676.*

Eaton, W. W., Kramer, M., Anthony, J. C., Dryman, A., Shapiro, S. & Locke, B. Z. (1989). The incidence of specific DIS/SSM-III mental disorders: Data from the NIMH Epidemiological Catchment Area program. *Acta Psychiatrica Scandinavica, 79*(2), 163-178.

Edwards-Lee, T., Miller, B. L., Benson, D. F., Cummings, J. L., Russell, G. L., Boone, K. & Mena, I. (1997). The temporal variant of frontotemporal dementia. *Brain, 120,* 1027-1040.

Eslinger, P. J. (1999). Orbital frontal cortex: Historical and contemporary views about its behavioral and psychological significance. An introduction to special topics papers. *Neurocase, 5*(3), 225-229.

Evans, D. W., Lewis, M. D. & Iobst, E. (2004). The role of orbitofrontal cortex in normally developing compulsive-like behaviors and obsessive-compulsive disorder. *Brain and Cognition, 55,* 220-234.

Foa, E. B., Huppert, J. D., Leiberg, S., Langner, R., Kichic, R., Hajcak, G. & Salkovskis, P. M. (2002). The Obsessive-Compulsive Inventory: Development and validation of a short version. *Psychological Assessment, 14*(4), 485-496

Foa, E. B., Kozak, M. J., Salkovskis, P. M., Coles, M. E. & Amir, N. (1998). The validation of a new obsessive-compulsive disorder scale: The Obsessive Compulsive Inventory (OCI). *Psychological Assessment, 10*(3), 206-214.

Folstein, M. F., Folstein, S. E. & McHugh, P.R. (1975). "Mini-mental state": A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research, 12*(3), 189-198.

Fontenelle, L. F., Mendlowicz, M. V., Marques, C. & Versiani, M. (2003). Early- and late-onset Obsessive-Compulsive Disorder in adult patients: An exploratory clinical and therapeutic study. *Journal of Psychiatric Research, 37,* 127-133.

Fontenelle, L., Marques, C., Engelhardt, E. & Versiani, M. (2001). Impaired set-shifting ability and therapeutic response in Obsessive-Compulsive Disorder. *The Journal of Neuropsychiatry & Clinical Neurosciences, 13,* 508-510.

Frampton, I. (2003). Neuropsychological models of OCD. In R. G. Menzies & P. de Silva (Eds.), *Obsessive-Compulsive Disorder: Theory, Research and Treatment.* Chichester: John Wiley & Sons.

Freud, S. (1913). The predisposition to obsessional neurosis. In *Collected Papers,* vol. 2. London: Hogarth Press.

Gallagher, H. L., Happe, F., Brunswick, N., Fletcher, P. C., Frith, U. & Frith, C. D. (2000). Reading the mind in cartoons and stories: An fMRI study of 'theory of mind' in verbal and nonverbal tasks. *Neuropsychologia*, *38*(1), 11–21.

Gedanke, S. R., Bravo, M. C., Belotto, C. & Miguel, E. (2001). Predictive factors of treatment response in OCD. *Behavior Therapist, 24*(3), 57-60, 70.

Goodman, W. K., Price, L. H., Rasmussen, S. A., Mazure, C., Delgado, P., Henninger, G. R. & Charney, D. S. (1989). The Yale-Brown Obsessive-Compulsive Scale: I. Development, use and reliability. *Archives of General Psychiatry, 46,* 1006-1011.

Green, J. D. W. & Hodges, J. R. (2000). The dementias. In Berrios, G. E. & Hodges, J. R. (Eds.) *Memory disorders in psychiatric practice.* (122-163). Cambridge: Cambridge University Press.

Gregory, C. A. & Hodges, J. R. (1996). Frontotemporal dementia: Use of consensus criteria and prevalence of psychiatric features. *Neuropsychiatry, Neuropsychology, and Behavioral Neurology, 9*(3), 145-153.

Gregory, C., Lough, S., Stone, V., Erzinclioglu, S., Martin, L., Baron-Cohen, S. & Hodges, J. R. (2002). Theory of Mind in patients with frontal variant frontotemporal dementia and Alzheimer's disease: Theoretical and practical implications. *Brain, 125,* 752-764.

Greisberg, S. & McKay, D. (2003). Neuropsychology of obsessive-compulsive disorder: A review and treatment implications. *Clinical Psychology Review, 23*(1), 95-117.

Grimmer, T., Diehl, J., Drzezga, A., Foerstl, H. & Kurz, A. (2004). Region-specific decline of cerebral glucose metabolism of patients with Frontotemporal dementia: A prospective 18-FDG-PET study. *Neurology, 62* (7), 297.

Gross-Isseroff, R., Sasson, Y., Voet, H., Hendler, T., Luca-Haimovici, K., Kandel-Sussman, H. & Zohar, H. (1996). Alternation learning in obsessive-compulsive disorder. *Biological Psychiatry, 39,* 733-738.

Happaney, K. Zelazo, P. D. & Stuss, D. T. (2004). Development of orbitofrontal function: Current themes and future directions. *Brian and Cognition, 55,* 1-10.

Harvey, R. J. (2001). Epidemiology of presenile dementia. In Hodges, J. R. (Ed.) *Early-onset dementia: a multidisciplinary approach.* (pp.1-23) Oxford: Oxford University Press.

Head, D., Bolton, D. & Hymas, N. (1989). Deficit in cognitive shifting ability in patients with obsessive-compulsive disorder. *Biological Psychiatry, 25*(7), 929-937.

Heaton, R. K., Chelune, G. J., Talley, J. L., Kay, G. C. & Curtis, G. (1993). *Wisconsin Card Sorting Test- Manual, Revised and Expanded*. Odessa, FL: Psychological Assessment Resources Inc

Hodges, J. R. & Miller, B. (2001). The neuropsychology of frontal variant Frontotemporal dementia and Semantic dementia. Introduction to the Special Topic Papers: Part II. *Neurocase, 7,* 113-121.

Hodges, J. R., Patterson, K., Ward, R., Garrard, P., Bak, T., Perry, R. & Gregory, C. (1999). The differentiation of semantic dementia and frontal lobe dementia (temporal and frontal variants of Frontotemporal dementia) from early Alzheimer's disease: A comparative neuropsychological study. *Neuropsychology, 13*(1), 31-40.

Hollander, E., DeCaria, C. M., Nitescu, A. Gully, R., Suckow, R. F., Cooper, T. B. et al. (1992). Serotonergic function in obsessive-compulsive disorder: Behavioral and neuroendocrine responses to oral m-chlorphenylpiperazine and fenfluramine in patients and healthy volunteers. *Archives of General Psychiatry, 49*(1), 21-28.

Honig, L. S., Bell, K. & Chin, S. S. (2003). Frontotemporal dementia. *Science of Aging Knowledge Environment, 13,* 112-115.

Huberty, C. J. & Morris, J. D. (1989). Multivariate analysis versus multiple univariate analysis. *Psychological Bulletin, 105*(2), 302-308.

Insel, T. R. & Winslow, J. T. (1992). Neurobiology of Obsessive-Compulsive Disorder. *Psychiatric Clinics of North America, 15*(4), 813-824.

Insel, T. R., Donelly, E. F., Lalakea, M. L., Alterman, I. S. & Murphy, D. L. (1983). Neurological and neuropsychological studies of patients with obsessive-compulsive disorder. *Biological Psychiatry, 18,* 741-751.

Isaacs, K. L. (2004). The neuropsychological deficits associated with obsessive-compulsive symptoms in patients with epilepsy. *Dissertation Abstracts International: Section B: The Sciences and Engineering, 64*(7-B), 3526.

Janet, P. (1903). *Les Obsessions et la Psychaesthenie.* Paris: Alcan.

Kaplan, E., Goodglass, H. & Weintraub, S. (1983). *Boston Naming Test*. Philadelphia: Lea & Febiger.

Karno, M., Golding, J., Sorenson, S. & Burnam, A. (1988). The epidemiology of obsessive-compulsive disorder in five U.S. communities. *Archives of General Psychiatry, 45,* 1094-1099.

Kirkby, K. C. (2003). Obsessive-Compulsive Disorder: Towards better understanding and outcomes. *Current Opinions in Psychiatry, 16,* 49-55.

Kwon, J. S., J. Kim, Lee, D. W., Lee, J. S., Lee, D. S., Kim, M. S. et al. (2003). Neural correlates of clinical symptoms and cognitive dysfunctions in obsessive-compulsive disorder. *Psychiatry Research: Neuroimaging, 122,* 37-47.

Lacerda, A. L., Dalgalarrondo, P., Caetano, D., Hass, G. L., Camargo, E. E. & Kesahvan, M. S. (2003). Neuropsychological performance and regional blood flow in obsessive-compulsive disorder. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 27*(4), 657-665.

Lawrence, R. M., Ronca, M. A., Tyrell, P. & Rossor, M. N. (1994). Psychiatric symptoms in patients with focal cortical degeneration. *Behavioral Neurology, 7,* 153-158.

Leckman, J. F., Grice, D. E., Boardman, J., Zhang, H., Vitale, A., Bondi, C. et al. (1997). Symptoms of obsessive-compulsive disorder. *American Journal of Psychiatry, 154*(7), 911-917.

Lezak, M. D. (1995). *Neuropsychological Assessment* (3rd ed.). New York: Oxford University Press.

Liu, W., Miller, B. L., Kramer, J. H., Rankin, K., Wyss-Coray, C., Gearhart, R. et al. (2004). Behavioral disorders in the frontal and temporal variants of frontotemporal dementia. *Neurology, 62,* 742-748.

Lough, S. & Hodges, J. R. (2002). Measuring and modifying abnormal social cognition in frontal variant frontotemporal dementia. *Journal of Psychosomatic Research, 53,* 639-646.

Lough, S. Gregory, C. & Hodges, J. R. (2001). Dissociation of social cognition and executive function in frontal variant Frontotemporal dementia. *Neurocase, 7,* 123-130.

Lough, S., Kipps, C. M., Treise, C., Watson, P., Blair, J. R. & Hodges, J. R. (2006). Social reasoning, emotion and empathy in frontotemporal dementia. *Neuropsychologia, 44,* 950-958.

Lovibond, P. F. & Lovibond, S. H. (1995). The structure of the negative emotional states: Comparison of the Depression Anxiety Stress Scales (DASS) with the Beck depression and anxiety inventories. *Behaviour Research and Therapy, 33*(3), 335-343.

March, J. S. & Mulle, K. (1998). *OCD in Children and Adolescents: A Cognitive-Behavioral Treatment Manual.* New York: Guilford.

Martin, A., Pigott, T. A., LaLonde, F. M., Dalton, I., Dubbert, B. & Murphy, D. L. (1993). Lack of evidence for Huntington's disease-like cognitive dysfunction in Obsessive-Compulsive Disorder. *Biological Psychiatry, 33,* 345-353.

Martin, A., Wiggs, C. L., Altemus, M., Rubenstein, C. & Murphy, D. L. (1995). Working memory as assessed by subject-ordered tasks in patients with obsessive-compulsive disorder. *Journal of Clinical and Experimental Neuropsychology, 17*(5), 786-792.

Martin, I. & McDonald, S. (2003). Weak coherence, no theory of mind, or executive dysfunction? Solving the puzzle of pragmatic language disorders. *Brain and Language, 85,* 451-466.

Mataix-Cols, D., Junque, C., Sanchez-Turet, M., Vallejo, J., Verger, K. & Barrios, M. (1999). Neuropsychological functioning in a subclinical obsessive-compulsive sample. *Biological Psychiatry, 45*(7), 898-904.

Mataix-Cols, D., Rosario-Campos, M. & Leckman, J. F. (2005). A multidimensional model of Obsessive-Compulsive Disorder. *American Journal of Psychiatry, 162*(2), 228-238.

Mathuranath, P. S., Nestor, P. J., Berrios, P. E., Rakowicz, W. & Hodges, J. R. (2000). A brief cognitive test battery to differentiate Alzheimer's disease and frontotemporal dementia. *Neurology, 55*(11), 1613-20.

Mendez, M. F., Cherrier, M., Perryman, K., Pachan, N., Miller, B. L. & Cummings, J. L. (1996). Frontotemporal dementia versus Alzheimer's disease: Differential cognitive features. *Neurology, 47*(5), 1189-1194.

Mendez, M. F., Perryman, K. M., Miller, B. L., Swartz, J. R. & Cummings, J. L., (1997). Compulsive behaviors as presenting symptoms of frontotemporal dementia. *Journal of Geriatric Psychiatry & Neurology, 10*(4), 154-157.

Menzies, R. G. & de Silva, P. (Eds). (2003). *Obsessive-Compulsive Disorder: Theory, Research and Treatment.* Chichester: John Wiley & Sons.

Meyers, J. & Meyers, K. (1995). *The Meyers Scoring System for the Rey Complex Figure and Recognition Trial: Professional Manual*. Odessa, FL: Psychological Assessment Resources.

Miller, B. L., Darby, A. L., Swartz, J. R., Yener, G. G. & Mena, I. (1995). Dietary changes, compulsions and sexual behavior in frontotemporal degeneration. *Dementia, 6,* 195-199.

Miller, B. L., Ikonte, C., Ponton, M., Levy, M., Boone, K., Darby, A. et al. (1997). A study of the Lund-Manchester research criteria for frontotemporal dementia: Clinical and single-photon emission CT correlations. *Neurology, 48*(4), 937-942.

Modell, J., Mountz, J., Curtis, G. & Greden, J. (1989). Neurophysiological dysfunction in basal ganglia/limbic striatal and thalamocortical circuits as a pathogenetic mechanism of obsessive-compulsive disorder. *Journal of Neuropsychiatry & Clinical Neuroscience, 9,* 27-36.

Moritz, S., Birkner, C., Loss, M., Jacobsen, D., Fricke, S., Bothern, A. & Hand, I. (2001). Impact of comorbid depressive symptoms on neuropsychological performance in obsessive-compulsive disorder. *Journal of Abnormal Psychology, 110*(4), 653-657.

Moritz, S., Kloss, M., Jacobsen, D., Kellner, M., Andresen, B., Fricke, S. et al. (2005). Extent, profile and specificity of visuospatial impairment in Obsessive-Compulsive Disorder. *Journal of Clinical and Experimental Neuropsychology, 27,* 795-814.

Neary, D., Snowden, J. S. & Mann, D. M. (2000). Classification and description of frontotemporal dementias. *Annals of New York Academy of Sciences, 920,* 46-51.

Neary, D., Snowden, J. S., Gustafson, L., Passant, U., Stuss, D., Black, S. et al. (1998). Frontotemporal lobar degeneration: A consensus on clinical diagnostic criteria. *Neurology, 51*(6), 1546-1554.

Nelson, H. E. (1991). *The National Adult Reading Test (NART; Second Ed.): Test Manual.* Windsor: NFER-Nelson.

Nielen, M. M. A. & den Boer, J. A. (2003). Neuropsychological performance of OCD patients before and after treatment with fluoxetine: Evidence for persistent cognitive deficits. *Psychological Medicine, 33,* 917-925.

Nordahl, T. E., Benkelfat, C., Semple, W. E., Gross, M., King, A. C. & Cohen, R. M. (1989). Cerebral glucose metabolic rates in obsessive-compulsive disorder, *Neuropsychopharmacology, 2*(1), 23-28.

Nyatsanza, S., Shetty, T., Lough, S., Dawson, K. & Hodges, J. R. (2002). A study of stereotypic behaviours in Alzheimer's disease and frontal and temporal variant frontotemporal dementia. *Journal of Neurology, Neurosurgery & Psychiatry, 74,* 1398-1402.

Otto, M. W. (1992). Normal and abnormal information processing: A neuropsychological perspective on Obsessive-Compulsive Disorder. *Psychiatric Clinics of North America, 4,* 825-827.

Pasquier, F., Grymonprez, L., Lebert, F. & Van der Linden, M. (2001). Memory impairment differs in Frontotemporal dementia and Alzheimer's disease. *Neurocase, 7,* 161-171.

Perani, D., Colombo, C. Bressi, S., Bonfanti, A., Grassi, F., Scarone, S. et al. (1995). [18F]FDG PET study in obsessive-compulsive disorder. A clinical/metabolic correlation study after treatment. *British Journal of Psychiatry, 66,* 244-250.

Perkins, M. R. (1998). Is pragmatics epiphenomenal? Evidence from communication disorders. *Journal of Pragmatics, 29,* 291-311.

Perry, R. J. & Miller, B. L. (2001). Behavior and treatment in Frontotemporal dementia. *Neurology, 56* (S4), S46-S51.

Philpot, M. P. & Banerjee, S. (1998). Obsessive-Compulsive Disorder in the elderly. *Behavioural Neurology, 11,* 117-121.

Pigott, T. A. (1998). Obsessive-compulsive disorder: Symptom overview and epidemiology. *Bulletin of the Menninger Clinic, 62,* A4-A32.

Psychological Corporation (Ed.). (1999). *WASI: Technical Manual*. San Antonio: Harcourt Bruce and Co.

Psychological Corporation (Ed.). (1997a). *WAIS-III: Technical Manual*. San Antonio: Harcourt Bruce and Co.

Psychological Corporation (Ed.). (1997b). *WMS-III: Technical Manual*. San Antonio: Harcourt Bruce and Co.

Purcell, R., Maruff, P., Kirrios, M. & Pantelis, C. (1998b). Cognitive deficits in Obsessive-Compulsive Disorder on tests of frontal-striatal function. *Society of Biological Psychiatry, 43,* 348-357.

Purcell, R., Maruff, P., Kirrios, M. & Pantelis, C. (1998a). Neuropsychological deficits in Obsessive-Compulsive Disorder: A comparison with unipolar depression, Panic Disorder, and normal controls. *Archives of General Psychiatry, 55*(5), 415-423.

Rapoport, J. L. (1989). *The Boy Who Couldn't Stop Washing- The Experience and Treatment of OCD.* New York: Dutton.

Ratnavalli, E., Brayne, C., Dawson, K. & Hodges, J. R. (2002). The prevalence of Frontotemporal dementia. *Neurology, 58,* 1615-1621.

Reed, G. F. (1968). Some formal qualities of obsessional thinking. *Psychiatria Clinica, 1,* 382-392.

Robinson, D. H., Wu, H. & Munne, R. A. (1995). Reduced caudate nucleus volume in obsessive-compulsive disorder. *Archives of General Psychiatry, 52,* 393-398.

Roh, K. S., Shin, M., Kim, M., Ha, T., Shin, Y., Lee, K. & Kwon, J. S. (2005). Persistent cognitive dysfunction in patients with Obsessive-Compulsive Disorder: A naturalistic study. *Psychiatry and Clinical Neurosciences, 59,* 539-545.

Rosenberg, D. R., Dick, E. L., O'Hearn, K. M. & Sweeney, J. A. (1996). Response-inhibition deficits in Obsessive-Compulsive Disorder: An indicator of dysfunction in frontostriatal circuits. *Journal of Psychiatry Neuroscience, 22*(1), 29-38.

Rosenblatt, A. & Leroi, I. (2000). Neuropsychiatry of Huntington's Disease and other basal ganglia disorders. *Psychosomatics, 41*(1), 24-30.

Rosso, S. M., Roks, G., Stevens, M., de Koning, I., Tanghe, H. L. J., Kamphorst, W. et al. (2001). Complex compulsive behavior in the temporal variant of frontotemporal dementia. *Journal of Neurology, 248,* 965-970.

Roth, R. M., Milovan, D., Baribeau, J. & O'Connor, K. (2005). Neuropsychological functioning in early- and late-onset Obsessive-Compulsive Disorder. *The Journal of Neuropsychiatry & Clinical Neurosciences, 17*(2), 208-213.

Rubin, T. R. & Harris, G. J. (1999). Obsessive-Compulsive Disorder and the Frontal Lobes. In Miller, B. L. & Cummings, J. L. (Eds). *The Human Frontal Lobes.* (522-536). New York: The Guildford Press.

Russell, A. J., Mataix-Cols, D., Anson, M. & Murphy, D. G. M. (2005). Obsessions and compulsions in Asperger syndrome and high-functioning autism. *British Journal of Psychiatry June, 186,* 525-528.

Saint-Cyr, J. A., Taylor, A. E. & Nicholson, K. (1995). Behavior and the basal ganglia. *Behavioral Neurology of Movement Disorders, 65,* 1-28.

Sano, M., Marder, K. S., Dooneief, G. H., Robertson, M. M. & Yakeley, J. (2000). Basal ganglia disorders. (Chapter). In Fogel, B. S & Schiffer, R. B (Eds) et al. *Synopsis of Neuropsychiatry*. (pp. 405-424). Philadelphia, PA, US: Lippincott Williams & Wilkins Publishers.

Savage, C. R. & Rauch, S. L. (2000). Cognitive deficits in obsessive-compulsive disorder. *The American Journal of Psychiatry, 157*(7), 1182.

Saxena, S. & Rauch, S. L. (2000). Functional neuroimaging and the neuroanatomy of Obsessive-Compulsive Disorder. *Psychiatric Clinics of North America, 23*(3), 563-586.

Saxena, S., Brody, A. L., Schartz, J. M. & Baxter, L. R. (1998). Neuroimaging and fronto-subcortical circuitry in obsessive-compulsive disorder. *British Journal of Psychiatry, 173*(35S), 26-37.

Schmidtke, K., Schorb, A., Winkelmann, G. & Hahage, F. (1998). Cognitive frontal lobe dysfunction in obsessive-compulsive disorder. *Biological Psychiatry, 43*(9), 666-673.

Sharma, P. & Gupta, N. (2002). Obsessive-compulsive phenomenon and Parkinson's disease. *Journal of Neurology, Neurosurgery and Psychiatry, 72*(3), 420.

Simpson, H. B., Rosen, W., Huppert, J. D., Lin, S., Foa, E. B. & Liebowitz, M. R. (2006). Are there reliable neuropsychological deficits in Obsessive-Compulsive Disorder? *Journal of Psychiatric Research, 40,* 247-257.

Singh, S. & Mukandan, C. R. (2003). Symptom severity, comorbid depression anxiety associated with the neuropsychological performance of OC patients. *Journal of the Indian Academy of Applied Psychology, 29*(1-2), 25-30.

Snowden, J. S., Neary, D. & Mann, D, M. (1996). *Frontotemporal lobar degeneration: frontotemporal dementia, progressive aphasia, semantic dementia.* In Gardner, L., Singleton, P. (Eds). New York: Churchill Livingstone.

Snowden, J. S., Bathgate, D., Varma, A., Blackshaw, A., Gibbons, Z. C. & Neary, D. (2001). Distinct behavioural profiles in frontotemporal dementia and semantic dementia. *Journal of Neurology, Neurosurgery & Psychiatry, 70*(3), 323-332.

Snowden, J. S., Neary, D. & Mann, D. M. (2001). Frontotemporal dementia. *The British Journal of Psychiatry, 180,* 140-143.

Spreen, O. & Strauss, E. (1998). *A Compendium of Neuropsychological Tests: Administration, Norms & Commentary (2nd ed.).* New York: Oxford University Press.

Stein, R. A. & Strickland, T. L. (1998). A review of the neuropsychological effects of commonly used prescription medications. *Archives of Clinical Neuropsychology, 13*(3), 259-284.

Stone, V. E., Baron-Cohen, S. & Knight, R. T. (1998). Frontal lobe contributions to theory of mind. *Journal of Cognitive Neuroscience, 10,* 640-656.

Swartz, J. R., Miller, B. L., Lesser, I. M. & Darby, A. L. (1997). Frontotemporal dementia: Treatment response to serotonin selective reuptake inhibitors**.** *Journal of Clinical Psychiatry, 58*(5), 212-216.

Swedo, S. E., Schapiro, M. B., Grady C. L., Cheslow, D. L., Leonard, H. L., Kumar, A. et al. (1989). Cerebral glucose metabolism in childhood-onset obsessive-compulsive disorder. *Archives of General Psychiatry, 46,* 518-523.

Tallis, F. (1997). The neuropsychology of obsessive-compulsive disorder: A review and consideration of clinical implications. *British Journal of Clinical Psychology, 36,* 3-20.

The Lund and Manchester Groups. (1994). Clinical and neuropathological criteria for frontotemporal dementia (Review). *Journal of Neurology, Neurosurgery and Psychiatry, 57,* 416-418.

Tonkonogy, J. M., Smith, T. W. & Barreira, P. J. (1994). Obsessive-compulsive disorders in Pick's disease. *Journal of Neuropsychiatry and Clinical Neurosciences, 6*(2), 176-180.Veale, D. M., Sahakian, B. J., Owen, A, M. & Marks, I. M. (1996). Specific cognitive deficits in tests sensitive to frontal lobe dysfunction in obsessive-compulsive disorder. *Psychological Medicine, 26*(6), 1261-1269.

Ward, C. D. (1988). Transient feelings of compulsion caused by hemispheric lesions: Three cases. *Journal of Neurology, Neurosurgery & Psychiatry, 51,* 266-268.

Whitney, K. A., Fastenau, P. S., Evans, J. D. & Lysaker, P. H. (2004). Comparative neuropsychological function in Obsessive-Compulsive Disorder and schizophrenia with and without obsessive-compulsive symptoms. *Schizophrenia Research, 69,* 75-83.

Wilson, B.A., Alderman, N., Burgess, P., Emslie, H. & Evans, J. (1996). *Behavioural Assessment of the Dysexecutive Syndrome.* Suffolk: Thames Valley Test Company.

Wilson, B.A., Evans J. J., Emslie, H., Alderman, N. & Burgess, P. (1998). The development of an ecologically valid test for assessing patients with a dysexecutive syndrome. *Neuropsychological Rehabilitation, 8,* 213-228.

Woods, C. M., Vevea, J. L., Chambless, D. L. & Bayen, U. J. (2002). Are compulsive checkers impaired in memory? A meta-analytic review. *Clinical Psychology: Science and Practice, 9*(4), 353-366.

World Health Organisation. (1994). *International statistical classification of diseases and related health problems (10th Revision).* Geneva: World Health Organisation.

World Health Organisation. (1996). *The Global Burden of Disease.* Geneva: World Health Organisation.

Zald, D. H. & Kim, S. W. (2001). The orbitofrontal cortex. In Salloway, S, P. & Malloy, P. F. (Eds.). *The Frontal Lobes and Neuropsychiatric Illness*. New York: New York Raven Press.

Zielinski, C. M., Taylor, M. A. & Jurzwin, K. R. (1991). Neuropsychological deficits in obsessive-compulsive disorder. *Neuropsychiatry, Neuropsychology & Behavioral Neurology, 4,* 110-126.

Zohar, J. & Kindler, S. (1992). Serotonergic probes in obsessive compulsive disorder. *International Clinical Psychopharmacology, 7*(1), 39-40.