Social Cognition in Disorders of the Basal Ganglia

By

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ABSTRACT

Patients with disorders of the basal ganglia, such as Parkinson's disease, Huntington's disease and Tourette's Syndrome, exhibit characteristic motor symptoms and less obvious cognitive deficits. These deficits can be understood with reference to the model of cortico-striato-thalamo-cortical circuitry proposed by Alexander et al. (1986) which highlights how the basal ganglia can affect the functioning of the whole of the frontal lobe. This thesis explored the possibility that patients with these disorders also have difficulties with social cognition.

Patients with Parkinson's exhibited deficits in reasoning about mental states. These deficits can largely be attributed to executive dysfunction which results from disordered activity in the circuitry linking the dorsolateral prefrontal cortex and the basal ganglia. Patients with Huntington's exhibited reduced fear responses which most likely results from abnormal amygdala activity. Patients with Tourette's exhibited deficits on a wide range of social cognitive tasks involving reasoning about mental states, non-literal language interpretation and economic decision making. These difficulties probably reflect dysfunction in circuitry linking the anterior cingulate and insula with the basal ganglia.

These studies offer insight into the neuroanatomical basis of the behavioural symptoms associated with these conditions whilst highlighting the necessity to develop more precise and inclusive models of frontostriatal circuitry.

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LIST OF ABBREVIATIONS

ACC	anterior cingulate cortex
ADHD	attention deficit hyperactivity disorder
BG	basal ganglia
CSTCC	cortico-striato-thalamic-circuit (as defined by Alexander et al., 1986)
CN	caudate nucleus
DA	dopamine
DBS	deep brain stimulation
DCCST	dimensional change card sorting task
DLPFC	dorsolateral prefrontal cortex
DOT-A	Digit Ordering Test-Adapted
GABA	gamma-amino-butyric-acid
GP	globus pallidus
GPe	globus pallidus external (lateral)
GPi	globus pallidus internal (medial)
HD	Huntington's disease
IAPS	International Affective Picture System
IFG	inferior frontal gyrus
MNS	Mirror Neuron System
MWU	Mann Whitney U-test
NA	nucleus accumbens
NOSIS	non-obscene socially inappropriate symptoms
OCD	obsessive compulsive disorder
OFC	orbitofrontal cortex
PD	Parkinson's disease
$\mathbf{r_P}$	Pearson's correlation co-efficient
SCRs	skin conductance responses
S.D.	standard deviation
SN	substantia nigra
SNc	substantia nigra pars compacta
SNr	substantia nigra pars reticulata
$\mathbf{r_s}$	Spearman's Rho correlation co-efficient
STN	subthalamic nucleus
ToM	Theory of Mind
TS	Tourette's syndrome
UG	Ultimatum Game
VMPFC	ventromedial prefrontal cortex
VTA	ventral tegmental area
WM	working memory

CHAPTER 1. GENERAL INTRODUCTION

Section 1.5 contains edited parts of an article in press:

Eddy, C.M., Rizzo, R. & Cavanna, A.E. Neuropsychological aspects of Tourette Syndrome: a review. *Journal of Psychosomatic Research*.

1.1: The Basal Ganglia and Movement Disorders

The first documented example of a movement disorder associated with basal ganglia (BG) dysfunction was written by James Parkinson in 1817 and entitled “the shaking palsy” (Parkinson, 2002). Many years later during that century the BG were recognized as having a major role in motor function, but it was only as recently as the 1950s that Arvid Carlsson (see Carlsson, 1987) identified the critical neurochemical changes affecting the BG that result in Parkinson’s disease (PD). Dysfunction of the BG also leads to the disordered movement that characterizes Huntington’s disease (HD) and Tourette’s Syndrome (TS).

The major components of the BG (for a review see Parent, 1990) are the striatum, globus pallidus (GP), subthalamic nucleus (STN), substantia nigra (SN) and the nearby ventral tegmental area (VTA). The striatum is so called due to its striped appearance (particularly apparent in the rodent brain), which is created by radiating bundles of cortico-fugal axons. In primates, the striatum consists of the caudate nucleus (CN) and putamen, along with the ventrally lying nucleus accumbens (NA). This latter striatal component is considered part of the limbic sector of the BG along with the VTA (Parent, 1990). The striatum is the main input structure of the BG, and receives excitatory (glutamatergic) inputs from all cortical regions, the thalamus and limbic structures such as the amygdala (Nauta, 1979; Parent, 1990). Outputs from the BG influence cortical regions in the frontal lobe, as well as midbrain targets such as the SN and pedunculopontine nucleus (McHaffie, Stanford, Stein, Coizet & Redgrave, 2005; Nauta, 1979; Parent, 1990).

The characteristic motor symptoms of movement disorders such as PD result from disturbances in the output of striatal neurons, which affect the functioning of the

supplementary motor area via the motor thalamus (Alexander, Delong & Strick, 1986; Alexander & Crutcher, 1990). More recently, attention has been drawn towards evidence of significant non-motor symptoms in patients with BG disorders. For example, during the 1980s, patients with PD were shown to exhibit changes in cognitive functioning. Delis, Direnfield, Alexander & Kaplan (1982) reported cognitive difficulties during medication 'off' periods (when motor symptoms return because dopamine levels are low). Research conducted since has revealed evidence of a range of cognitive and behavioural changes indicating that BG dysfunction can exert profound effects on many non-motor functions reliant on the frontal cortex. The work contained in this thesis extended research in this area by investigating social cognition in patients with disorders of the BG.

1.2: Disorders of the Basal Ganglia: Parkinson's Disease, Huntington's Disease and Tourette's Syndrome

The cardinal motor signs of PD are tremor, rigidity, bradykinesia (slowness of movement) and progressive loss of voluntary movement (Jankovic, 2008). The symptoms of this hypokinetic movement disorder are in contrast to the hyperkinetic, graceful involuntary writhing movements (termed 'chorea') exhibited by patients with HD (Walker, 2007). Involuntary movements are also present in TS, which is characterized by tics: compulsive and repetitive movements or vocalisations that may be simple or complex in nature, and vary in number, frequency and severity over time (Leckman, 2002; Robertson, 2000).

The varying motor symptoms of PD, HD and TS, are assumed to result from different forms of dysfunction within the neural pathways through which the BG exerts movement control (Figure 1). There is clear evidence that the symptoms of PD and HD result from striatal dysfunction, with PD resulting from loss of striatal dopamine and HD from striatal degeneration. Patients with TS have also been shown to exhibit abnormalities of the BG (e.g. Singer et al., 1993) and these neural structures are likely to be involved in tic generation (Salloway & Cummings, 1996). In PD and HD, degenerative processes result in structural changes to motor circuits, while the efficacy of dopaminergic pharmacotherapy in treating both TS and PD indicates an important role for neurochemical dysregulation in these disorders.

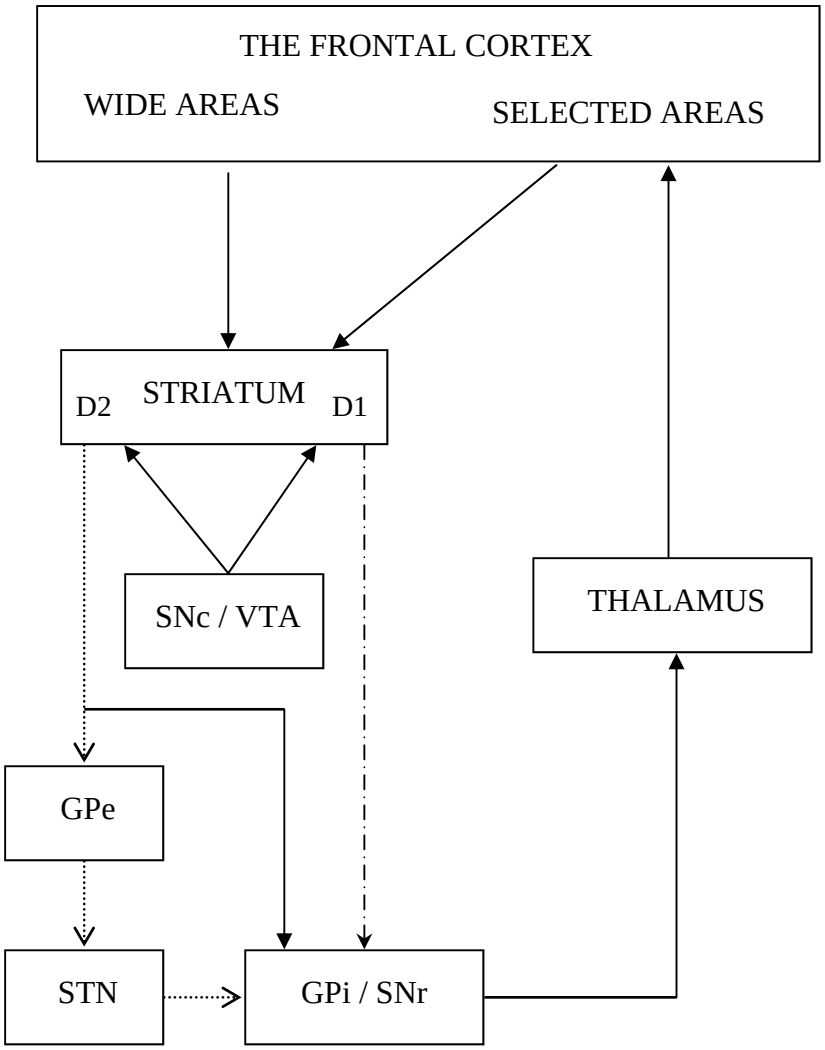


Figure 1. The direct and indirect pathways through the basal ganglia.
Dashed arrows show the direct route
Dotted arrows show the indirect route

ABBREVIATIONS:

SNc	Substantia nigra pars compacta
SNr	Substantia nigra pars reticulata
GPe	Globus pallidus external
GPi	Globus pallidus internal
STN	Subthalamic nucleus
D1	Projections with type 1 dopamine receptors
D2	Projections with type 2 dopamine receptors

The BG can affect motor control via a direct and an indirect route (Penney & Young, 1986). The direct route originates from medium spiny striatal GABAergic projection neurons which also contain dynorphin/substance P and express high levels of D1 receptors (Gerfen et al., 1990). These neurons project directly to the medial segment of the globus pallidus (GPi) and the substantia nigra pars reticulata (SNr). The indirect route begins with GABAergic neurons which use the peptide transmitter enkephalin and express high densities of D2 receptors (Gerfen et al., 1990). These neurons project to lateral segment of the globus pallidus (GPe). This in turn sends GABAergic projections to the STN. Glutamatergic efferents travel from the STN to the BG output nuclei (GPi and SNr) (Albin, Aldridge, Young & Gilman, 1989; Mitchell, 1990; Smith & Parent, 1988). Both routes end via inhibitory GABAergic efferents leading from the BG output nuclei to motor nuclei in the thalamus. Glutamatergic projections travel from the thalamus to the supplementary motor cortex (McCormick, 1992).

The activation of these two different pathways leads to opposite net effects on the output of BG circuitry (see Blandini, Nappi, Tassorelli & Martignoni, 2000). Activation of GABAergic neurons at the start of the direct pathway leads to inhibition of GABAergic neurons affecting the BG output nuclei, leading to disinhibition of thalamic motor nuclei. In contrast, activation of striatal neurons at the start of the indirect pathway leads to inhibition of GPe, resulting in disinhibition of the STN. The resulting increase in STN activity leads to increased excitation of glutamatergic projections, increased excitation of output nuclei, and so inhibition of motor thalamic nuclei. The final output of the BG circuit is therefore under direct control of the STN (Mitchell, Jackson, Sambrook & Crossman, 1989; Mitchell, 1990; Mitchell, Boyce, Sambrook & Crossman, 1992).

PD and HD are progressive neurodegenerative conditions. In PD, neuronal degeneration begins in those parts of the substantia nigra pars compacta (SNc) that innervate the dorsal striatum. Degeneration progresses to eventually encompass the nigral inputs to more ventral regions of the CN. Dopaminergic degeneration of the SNc leads to overactivity or disinhibition of the BG output structures through the indirect pathway, leading to increased inhibition of the motor thalamus, and reduced glutamatergic output to the motor cortex. This hypoactivity is enhanced by sustained glutamatergic inputs to the BG output nucei received via the STN. This may be due to decreased inhibitory control exerted by the GPe. However, changes in dopamine (DA) may also affect the STN directly (Blandini et al., 2000). Pharmacological treatments include DA precursors (Levodopa) and direct agonists (e.g. Bromocriptine, Pramipexole), which temporarily reinstate normal neurochemical functioning within the motor circuits (Hagan, Middlemiss, Sharpe & Poste, 1997). Surgical interventions have included deep brain stimulation (DBS) of the STN. This procedure involves the insertion of a stimulator into a brain region which when activated at a high frequency paradoxically leads to reduced activity in that region (Wichmann & DeLong, 2006). Although the resulting reduction in activity offers symptomatic relief, concerns have been raised that some patients with DBS exhibit changes in mood and behaviour (e.g. Okun et al., 2009).

In HD cell death progresses ventrally, at first affecting the CN, then putamen, leaving the NA relatively intact (Vonsattel et al., 1985; Vonsattel & DiFiglia, 1998). Chorea is likely to result from death of enkephalinergic medium spiny projection neurons that project to GPe, in the indirect pathway (Mitchell, 1990; Penney & Young, 1986). The injection of bicuculine (a GABA antagonist) directly into GPe can result in choreiform movements (as shown in monkeys by Crossman, Mitchell,

Sambrook & Jackson, 1988). This chorea is seen in association with reduced 2-deoxyglucose uptake by the STN, indicating reduced activity of this structure (Mitchell et al., 1989; Mitchell, 1990; Mitchell et al., 1992). The motor symptoms of HD are therefore likely to result from abnormal outputs in the indirect pathway. That is, reduced excitation of glutamatergic projections which travel from the STN to the BG output nuclei, which leading to decreased inhibitory output from these structures and resultant disinhibition of motor thalamic nuclei.

Disinhibition of excitatory neurons in the thalamus may lead to tics in TS (Ackermans, Temel & Visser-Vanderwalle, 2008). Mink (2001) described how movement initiating pattern generators in the cerebral cortex and brainstem are controlled by the striatum, which acts as a braking mechanism. Healthy striatal functioning ensures that only a chosen motor pattern generator is disinhibited by BG output nuclei. The rest of the BG inhibits potentially interfering motor patterns, ensuring that only selected voluntary movements are performed. Mink suggested that tics occur from abnormal activity in the striatum leading to a loss of inhibitory control over striatal output. Mink further suggested that each tic is related to a separate set of striatal neurons, and that the repetitive, stereotyped, involuntary movements associated with TS result from a focal population of striatal neurons becoming overactive in discrete, repetitive episodes. This overactivity may occur due to excessive input from the cortex or thalamus to the striatum, poor intrastriatal inhibition, altered DA transmission or changes in membrane excitability.

Support for the role of DA in TS is provided by the clinical efficacy of pharmacological agents that antagonize this transmitter (e.g. Risperidone, Haloperidol). These agents may counteract the increased DA transporter binding that has been reported in TS (Singer, 1992), or the influence of DA on corticostriatal

transmission via long term depression or potentiation (Mink, 2001). Mink suggests that abnormalities in the regulation of the resting potential of striatal neurons in TS may alter responses to DA and DA transmission. More specifically, tics could occur due to striatal cells spending an excessive time in a hypopolarised resting state, leading to a facilitatory effect of DA on D1 receptors and the firing of cells to weak cortical output. Changes in the probability of the membrane potential being hypopolarised over time may also explain the waxing and waning of tics (Ackermans et al., 2008).

Recent successful surgical therapeutic interventions for TS have included DBS of the centromedian nucleus, substantia periventricularis and nucleus ventrooralis internus of thalamus (Temel & Visser-Vanderwalle, 2004) and bilateral lesion of median, intralaminar and inner ventral oral thalamic nuclei (Visser-Vanderwalle, Temel & Boon, 2003). These are thalamic intralaminar nuclei which project to the striatum and receive projections from striatal output nuclei.

Although alterations in motor functions play a prominent role in PD, HD and TS, other features of these disorders cannot be explained by dysfunction within frontostriatal motor circuits. Patients with PD often suffer from depression, while patients with HD can experience obsessive or psychotic episodes (Shoulson, 1990). Patients in the later stages of PD and HD may develop ‘subcortical dementia’, a condition associated with changes in arousal, motivation and personality rather than difficulties with language and memory (Cummings, 1986). Attention deficit hyperactivity disorder (ADHD) and obsessive compulsive disorder (OCD) are common comorbidities in TS. Patients may exhibit tics specifically relating to socially inappropriate behaviour involving offensive language (coprolalia) or gestures (copropraxia) (Cavanna, Servo, Monaco & Robertson, 2009). Some patients with TS

also exhibit non-obscene socially inappropriate symptoms (NOSIS: see Kurlan et al., 1996) and/or a tendency to self-injurious behaviour (Robertson, 2000). These symptoms may involve dysfunction within other frontostriatal circuits involving the BG.

1.3: The Model of Frontostriatal Circuitry

Investigation of the non-motor symptoms of BG disorders emerged as a product of growing awareness that the influence of the BG on cortical functioning was not limited to the supplementary motor cortex. This new understanding of the critical underlying functional neuroanatomy was expounded in the seminal paper by Alexander, Delong and Strick (1986), that described the involvement of the BG in five parallel cortico-striato-thalamo-cortical circuits (CSTCC)s. These circuits are formed by neurons originating in different regions of the cortex, which project to the striatum, the GP and SN, before returning to the frontal cortex via the thalamus (Figure 2). Two of these frontal regions (the supplementary motor and oculomotor cortex) perform motor functions. Three other cortical regions that form part of different CSTCCs subserve non-motor functions (Figure 3). These are the dorsolateral prefrontal cortex (DLPFC), lateral orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC).

Evidence supporting this model rests on the finding that dysfunction of the subcortical components within a CSTCC can result in deficits that resemble those that would be observed if the cortical area involved in the circuit was damaged directly (Middleton & Strick, 2000). Although tremendously influential, it should be noted that the model was developed before the role of the STN in movement disorders was understood and prior to the conceptualization of the direct and indirect pathways through the BG (as explained in section 1.2). The description of circuitry involving different regions of the OFC (i.e. medial and lateral) is also problematic, as existing literature reflects limited consensus in relation to the precise anatomical interactions and functional specifications that may apply to these different sectors.

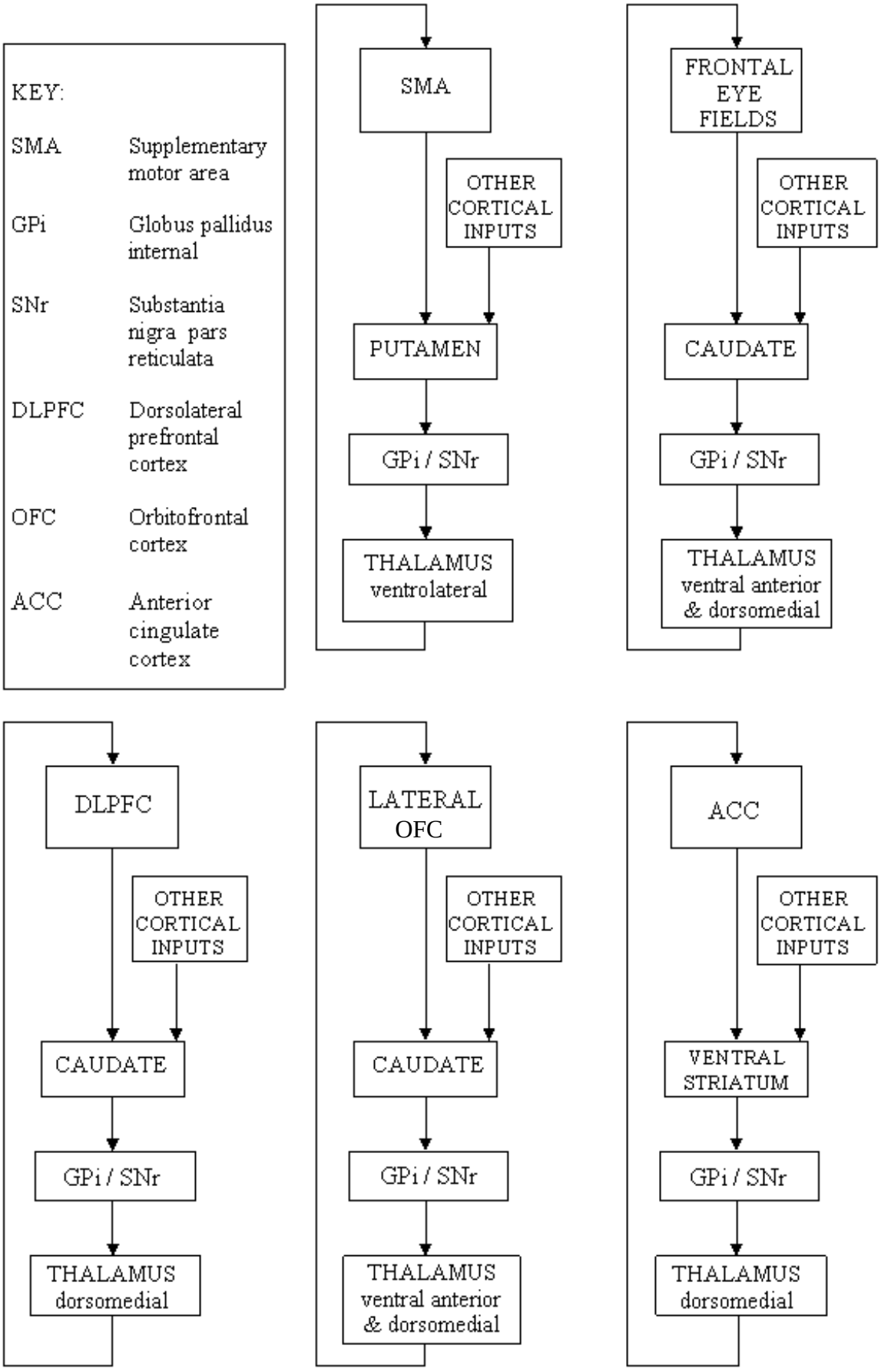
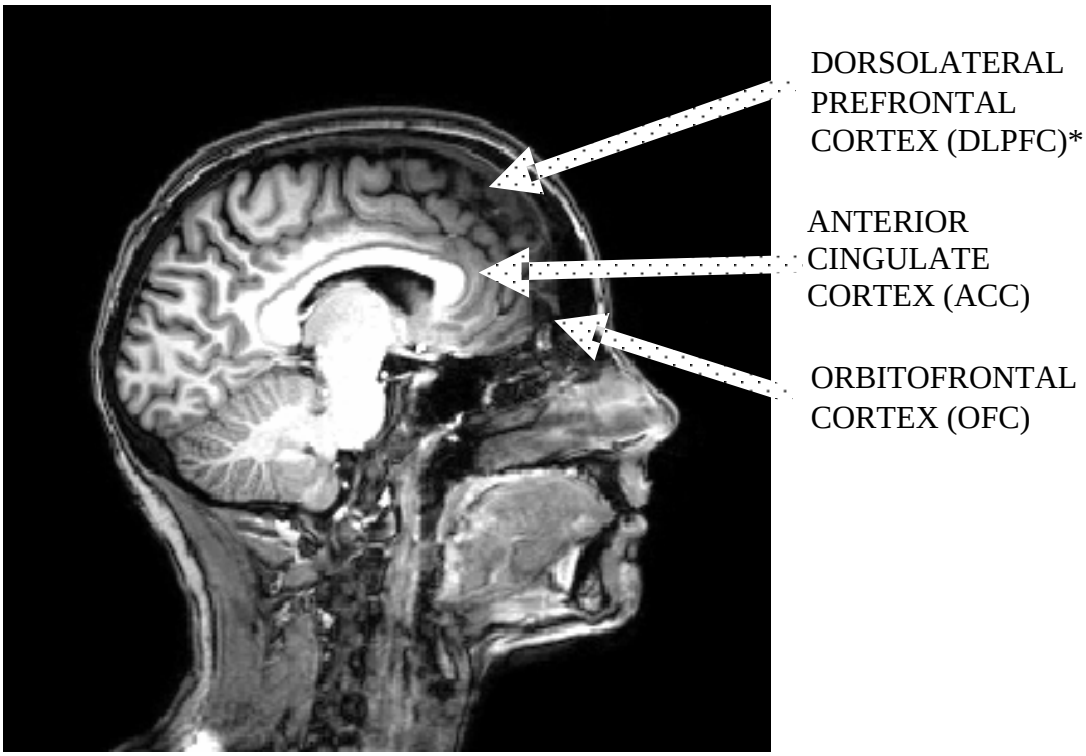


Figure 2. The cortico-striato-thalamo-cortical circuits (Alexander et al., 1986)



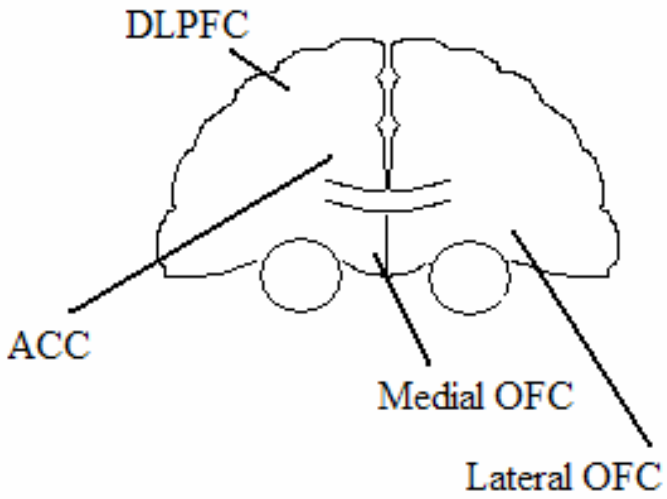


Figure 3. Diagram showing different regions of the frontal cortex involved in cognitive functions (scan courtesy of Birmingham University Imaging Centre).

* Arrow shows the approximate position of DLPFC on a medial scan. This region is actually located more laterally

The motor circuit begins in the supplementary motor cortex and passes through the putamen, then through the ventrolateral GPi and caudolateral SNr, and next through the ventrolateral nucleus of the thalamus, before returning (primarily) to the supplementary motor cortex. This circuit is involved in the preparation, execution, control and sequencing of movement. The other motor circuit (oculomotor) originates in the frontal and supplementary eye fields and has a striatal component within the CN. It travels through the dorsomedial GPi and the ventral anterior and dorsomedial thalamic nuclei before passing back to the frontal eye fields. Dysfunction within this circuit affects the control of voluntary visual fixation.

The dorsolateral prefrontal circuit begins in the DLPFC, and passes through the dorsolateral head of the CN, and then through the lateral dorsomedial GPi and rostrolateral SNr to the ventral anterior and dorsomedial thalamic nuclei, before returning to the DLPFC. The DLPFC is important for executive functions such as working memory (WM) (Aleman & van't Wout, 2008), cognitive flexibility or set-shifting (Smith, Taylor, Brammer & Rubia, 2004), attentional processes (Johnson, Strafella & Zatorre, 2007) and verbal fluency (Gallard et al., 2000).

The lateral orbitofrontal circuit begins in inferolateral frontal cortex and passes through the ventromedial CN, dorsomedial GPi and rostromedial SNr, before passing through the ventral anterior and dorsal thalamic nuclei and returning to the lateral OFC. The lateral OFC is important for learning involving negative reinforcement (O'Doherty et al., 2001) and recognizing negative facial expressions (Liang, Zebrowitz & Aharon, 2009). Damage to the OFC may lead to irritability, poor empathy and impulse control, and changes to personality and social functioning (Blair & Cipolotti, 2000).

The anterior cingulate circuit originates in the ACC and projects to the ventral striatum (NA), olfactory tubercle and regions of the ventromedial CN and putamen. There are other multiple inputs to the ventral striatum. The circuit returns via rostrolateral GPi and rostrodorsal SNr through the dorsomedial thalamic nucleus to the ACC. The ACC is implicated in drive and motivation (Devinsky, Morrell & Vogt, 1995) and cognitive functions related to conflict monitoring and resolution (Carter, Braver, Barch, Noll & Cohen, 1998) and response inhibition (Barch et al., 2001), which is needed during tasks such as the Stroop. The CSTCC involving this region (described by Alexander et al., 1986) may also involve connections to medial OFC (Nauta, 1962; Yeterian & VanHoesen, 1978), which appears to play a role in social cognition (Fletcher et al., 1995). Note that some clinical studies use the term ventromedial prefrontal cortex (VMPFC), a region that includes medial OFC.

1.4: The Neural Basis of Striato-cortical Influences

Patients with BG disorders experience motor symptoms as a result of striatal dysfunction. However, striatal dysfunction may have the potential to affect cognitive, social and emotional functioning in these disorders. This is due to connections between striatal output structures and the prefrontal cortex, which result in the CSTCCs (described by Alexander et al. 1986).

In PD, neural loss is greatest in regions of the SN that project to the CN (Rinee, Rummikainen, Paljarvi & Rinne, 1989). The greatest DA decline is seen in the anterodorsal head of the CN (Kish et al., 1986), which receives projections from the DLPFC (Rosvold, 1972). Changes in DA receptor levels have also been reported in the DLPFC (Kaasinen et al., 2003). There is less evidence for the involvement of other non-motor frontostriatal circuits in PD. More ventral regions of the CN, that have greater connectivity with the OFC, are relatively preserved in early PD. Furthermore, the ventral striatum (NA, olfactory tubercle and ventral pallidum), which forms part of the ACC circuit, receives DA from the VTA, so may be expected to be less disrupted by neurochemical alterations in PD.

Early degeneration of the dorsal striatum in HD is also likely to lead to dysfunction within the DLPFC CSTCC (described by Alexander et al., 1986). The ventral striatum appears relatively intact in comparison to the dorsal striatum (at least until later disease stages: Vonsattel & DiFiglia, 1998). The involvement of ACC circuitry may therefore appear unlikely. However, it is possible that as degeneration progresses to encompass more ventral regions of the CN, the CSTCC involving lateral OFC may be affected. Loss of inhibitory striatal output neurons to the medial segment

of the GP later in HD (Bradshaw, 2001) could further implicate the involvement of this circuit.

A range of findings implicate alterations in the functioning of the CSTCC involving the ventral striatum and ACC (described by Alexander et al., 1986) in TS. Imaging studies have highlighted abnormalities in the ACC (Muller-Vahl et al., 2009; Peterson et al., 2001; Watkins et al., 2005) and differences in the functional connectivity of the ventral striatum in patients with TS and controls (Jeffries et al., 2002). Reports of structural changes to the CN in TS (e.g. Peterson et al., 2003) may implicate the involvement of many frontostriatal pathways. However, such alterations may be more closely associated with comorbidities. Compensatory changes may lead to increased DLPFC volumes in children with TS (Peterson et al., 2001), and abnormalities of the DLPFC have also been reported in ADHD (Seidman et al., 2006). Studies implicate the OFC in association with obsessive symptoms in TS (Braun et al., 1995) and increased lateral OFC activity is apparent in patients with OCD (Ursu & Carter, 2009). Jeffries et al. (2002) report that activity in motor circuitry and the lateral OFC circuit is positively coupled in patients with TS, whereas a negative relationship exists in controls. A more recent study (Muller-Vahl et al., 2009) reported changes in the volume of regions including the ACC and medial OFC in TS.

In summary, many anatomical and pathological findings indicate that dysfunction of the BG in PD, HD and TS could affect the functioning of prefrontal regions that subserve social, cognitive and emotional functions.

1.5: Behavioural Evidence for Frontostriatal Circuit Dysfunction in Disorders of the Basal Ganglia

Behavioural studies support the possibility that BG disorders are associated with dysfunction within CSTCCs (Alexander et al., 1986) that subserve cognitive, social and emotional functions. Key findings include both the psychiatric symptoms and difficulties with higher cognitive functions that are exhibited by patients with PD, HD, and TS. This section discusses the behavioural evidence for frontostriatal dysfunction in each of these patient groups in turn.

Changes in the functioning of DLPFC circuitry may be associated with deficits in executive functions: higher cognitive abilities which include WM, inhibition, verbal fluency and attentional set-shifting. Zgaljardic et al. (2006) showed that the most significant executive impairments demonstrated by patients with PD are evident on tasks linked to the DLPFC. Patients exhibit impairment in WM (Gabrieli, Singh, Stebbins & Goetz., 1996), verbal fluency (Akinyemi et al., 2008), cognitive flexibility or set-shifting (Lees & Smith, 1983) and planning (Owen et al., 1995), as well as more general attentional impairments (Brown & Marsden, 1988; Drago et al., 2008; Poliakoff & Smith-Spark, 2008; Price & Shin, 2009). Patients with PD also exhibit other evidence of memory dysfunction, including deficits in temporal ordering and poor recency discrimination (Sagar, Sullivan, Gabrieli, Corkin & Growdon 1988; Vriezen & Moscovitch, 1990). The WM deficits exhibited by patients with PD have the potential to contribute to other difficulties, such as poor sentence comprehension (Grossman et al., 2002; Hochstadt, Nakano, Lieberman & Friedman, 2006), inference generation (Monetta, Grindrod & Pell, 2008) and deductive and inductive reasoning (Natsopoulos et al., 1997).

Executive deficits resulting from dysfunction of DLPFC in PD are likely to reflect the early degeneration of dopaminergic neurons in the dorsal region of the CN that project to this region (Lewis et al., 2003). These deficits may be alleviated by the action of medications such as Levodopa on the DLPFC (Lange et al., 1992). However, due to the uneven pattern of degeneration of DA neurons, systemically administered agents are likely to exert a differential effect on DA systems. Activity in the dorsal striatum will be normalised through such methods. However, the relatively intact ventral systems, which may be involved in more basic mnemonic functions, such as encoding and retrieval, or other executive tasks, may be overtreated (Cools, Barker, Sahakian & Robbins 2001a; Lange et al., 1992).

Patients with HD exhibit deficits in a range of cognitive abilities, including executive functions. Deficits have been reported in WM, planning, cognitive flexibility (Phillips, Shannon & Barker, 2008); attention (Butters, Wolfe, Granholm & Martone, 1986); response control and pattern recognition memory (Blackwell, Parterson, Barker, Robbins & Sahakian, 2008). Many of these deficits could result from DLPFC dysfunction. Studies by Wolf and colleagues revealed poor performance during high-load WM tasks that was associated with reduced activation in the DLPFC in patients with HD (e.g. Wolf et al., 2009). Even asymptomatic gene carriers (who express the mutant gene but do not yet exhibit frank clinical symptoms) can exhibit executive deficits. For example, impairments have been found in attentional set shifting (Lawrence et al., 1998) and verbal fluency (Larsson, Almkvist, Luszcz & Wahlen, 2008; Lawrence et al., 1998). Some aspects of cognitive functioning also decline with disease progression. For example, Ho et al. (2003) reported deteriorations in performance on attentional and inhibitory executive measures (e.g.

Stroop test, Trail Making Test) over a period of three to six years, in early to moderate HD.

Other behavioural changes in HD may result from dysfunction within OFC circuitry. Patients can exhibit increased irritability and aggression (Calder, Keane, Lawrence & Manes, 2004) and difficulties with social relationships which may reflect reduced empathy (Snowden et al., 2003). Similar changes have been seen in association with OFC dysfunction (Blair & Cipolotti, 2000). Some patients with HD exhibit comorbid obsessive compulsive symptoms (Baxter et al., 1987) and deficits in the recognition of facial expressions expressing negative emotions (Henley et al., 2008). These findings implicate dysfunction of frontostriatal pathways involving lateral OFC, which is dysfunctional in OCD (Ursu & Carter, 2009) and is activated during the recognition of facial expressions of negative emotion (Liang et al., 2009) in HD.

The investigation of higher cognitive functioning in TS is complicated by the high prevalence of comorbidities such as ADHD. Some reports of deficits in WM (Channon, Flynn & Robertson, 1992; Watkins et al., 2005) may reflect an influence of comorbid ADHD on performance. While some studies that have controlled for ADHD have reported deficits in WM (Chang, McCracken & Piacentini, 2006) and strategic and procedural memory (Stebbins et al., 1995), other investigations have yielded no evidence of impairment (e.g. Goudriaan, Oosterlaan, de Beurs & van den Brink, 2006; Ozonoff & Strayer, 2001). Reports of poor verbal fluency (Bornstein, 1990; Bornstein, 1991; Sutherland et al., 1982) may also have been influenced by comorbidities, although Schuerholz (1998) provided evidence of deficits in a sample without ADHD. Other studies report no such difficulties (Channon, Pratt & Robertson, 2003; Goudriaan et al., 2006; Stebbins et al., 1995; Watkins et al., 2005).

Comorbid ADHD may also have contributed to attentional difficulties reported during the Trail Making Test (Bornstein & Yang, 2001; Channon et al., 1992) and on continuous performance tasks (Harris et al. 1995; Shucard, Benedict, Tekokkilich & Licter, 1997). However, one study (Chang et al., 2006) reported deficits in spatial attention after controlling for comorbid ADHD. A number of studies found that patients with TS exhibited little difficulty on tasks involving planning (Goudriaan et al, 2006; Ozonoff & Jensen, 1999; Verte, Geurts, Roeyers, Oosterlaan & Sergeant, 2005; Watkins et al., 2005), multitasking (Channon, Pratt & Robertson, 2003; Channon, Sinclair, Waller, Healey & Robertson, 2004) or shifting (Bornstein, 1990; Bornstein and Yang, 2001; Brand et al., 2002; Channon, Pratt & Robertson, 2003; Channon, Gunning, Frankl & Robertson, 2006; Chang et al., 2006; Cirino, Chapieski & Massmans, 2000; Ozonoff & Jensen, 1999; Sutherland et al., 1982). In summary, there is little evidence overall that patients with TS exhibit deficits on tasks involving fluency, planning, WM and cognitive flexibility, which have been linked to the DLPFC (Alexander et al., 1986; Gallard et al., 2000; Milner, 1963; Rassner et al., 2005).

Inhibitory ability has received most attention in TS, which is likely to be due to the involuntary nature of the tics exhibited by patients. These investigations are complicated by the fact that inhibition is not a unitary construct but is composed of separable facets with different underlying neural substrates (Aron, 2007). The results of studies that have assessed patients' ability to inhibit a motor response have been mixed (Baron-Cohen, Cross, Crowson & Robertson, 1994; Goudriaan et al., 2006; Hershey et al., 2004; Muller et al., 2003; Ozonoff, Strayer, MacMahon & Filloux, 1994; Roessner, Albrecht, Dechent, Baudewig & Rothenberger, 2008), and comorbidities may have influenced some of these findings. One study of patients with

uncomplicated TS reported impaired performance during a flanker test that involved inhibition of a prepotent motor response (Crawford, Channon & Robertson, 2005). However, a later study failed to replicate these findings (Channon et al., 2006). Patients with TS can successfully inhibit verbal responses during the Stroop test (Brand et al., 2002; Channon et al., 1992; Chang et al., 2006; Goudriaan et al., 2006; Ozonoff & Jensen, 1999) even when comorbidities are present. However, reports of impairment during the Hayling test, which requires the inhibition of a prepotent verbal response, are persuasive. A number of studies by Channon and colleagues (Channon, Crawford, Vakili & Robertson 2003; Channon et al., 2006; Crawford et al., 2005) have revealed deficits in 'uncomplicated' TS. The failure of many studies to control for comorbidity makes it unclear whether any evidence of cognitive or executive dysfunction is specifically attributable to TS. However, evidence of impairment on the Hayling test in uncomplicated samples may indicate dysfunction within the CSTCC involving the ACC (described by Alexander et al., 1986), which has been linked to this task (Nathaniel-James, Fletcher & Frith, 1997).

1.6: Social Cognition

Social cognition involves the medial prefrontal cortex (e.g. Fletcher et al., 1995; Gallagher et al., 2000), and has been described as "the sum of those processes that allow individuals of the same species (conspecifics) to interact with one another" (Frith & Frith, 2007, pp. R724). One facet of social cognition is Theory of Mind (ToM), which involves the understanding of mental states, and may require representation of the perspective of another person. An understanding of beliefs, desires, emotions and intentions can offer covert explanations for overt behaviour and enable the prediction of others' actions.

MEASURING THE DEVELOPMENT OF SOCIAL COGNITION IN CHILDREN

A number of test materials have been designed to measure the development of ToM in children. Many of these tasks are now also used with clinical populations, so could be used to investigate social cognition in patients with BG disorders. Some tasks involve reasoning about different kinds of mental states, such as cognitions (e.g. beliefs) or emotions, and certain tasks are passed later in development than others.

One well documented task that addresses the understanding of a story character's false belief is the 'unexpected transfer' task (Wimmer and Perner, 1983). The task is presented using puppets or as a story. In the story, an object that is in one location during the protagonist's presence is transferred to a new location in their absence. The child is required to identify where the protagonist will search for the object on returning. Solving this task requires an appreciation of the protagonist's false belief (the object is in the original location), which is contrary to both reality and

one's own perspective. Up until around age four children respond on the basis of their own knowledge (Wellman & Brandone, 2009), indicating that the protagonist will look in the true location of the object, rather than the location the protagonist last saw it in.

Another task used in developmental research is the deceptive box or 'unexpected contents' task (Gopnik & Astington, 1988). During this task, the experimenter shows the child a closed container with a familiar name or logo on it that indicates the likely content of the container (e.g. a Smarties tube). The experimenter asks the child what they think is inside the container before revealing unexpected contents (e.g. pencils). The child is then asked what another person (such as a schoolmate) would think was inside the container. Young children often respond incorrectly, and suggest the other person will think the container holds what they now know it contains (e.g. pencils). Gopnik and Astington (1988) suggest that children fail this task because they cannot understand how two people can have different representations of the same object. It has also been shown that children aged 3 often fail to report their own previous false belief correctly after learning the true state of affairs (Gopnik & Slaughter, 1991). Young children therefore find it difficult to appreciate another perspective or representation of an object or situation that contrasts with their own current knowledge.

Although many studies suggest children begin to pass these ToM tasks from around age four (e.g. Mitchell & Neal, 2005), some recent research indicates that infants may have some understanding of an actor's false belief during the unexpected transfer task. One anticipatory looking task reported that 25 month olds looked to where actor's false belief would lead them rather that the true location of the transferred object (Southgate, Senju & Csibra, 2007). Onishi and Baillargeon (2005)

showed that in addition to looking where the returning actor would expect the object to be, 15 month olds who witnessed an unexpected transfer also looked longer if the actor looked towards the other location, perhaps reflecting surprise. Perner and Ruffman (2005) suggest that these infants' behaviour does not indicate they understand an actor's mental state, but simply reflects the neuronal events associated with making actor-object associations. That is, the increased looking when the actor looks in the true location (as shown by Onishi & Baillargeon, 2005) may simply be the result of the greater mental effort needed to create a new object actor association (between the actor and the novel location) which is in contrast to the actor object association already made (between the actor and the original location). The exact age at which children may be considered to understand false belief remains a topic of debate. It is clear however, that children do not master more complex tasks, such as those involving second order ToM (eg. understanding one person's belief about another person's belief) until perhaps seven years of age (Perner & Wimmer, 1985).

A more complex task involving ToM that has been used with older children is the faux pas task, which children pass between 9 and 11 years of age (Baron-Cohen, O'Riodan, Stone, Jones & Plaisted, 1999). Faux pas occurs when someone says something that may be detrimental or offensive towards another person. The remark is not a deliberate insult because the protagonist making the inappropriate remark has no intention to cause harm to the person they are speaking about or to. The understanding of faux pas therefore requires ToM reasoning because it involves consideration of the protagonist's lack of intent to offend and their failure to realize that their remark is socially inappropriate. It also involves consideration of the victim's likely emotional response.

Faux pas tasks may be more complicated than simple false belief tasks because of a need to integrate information about cognitive and affective (emotional) mental states (Shamay-Tsoory, Tomer, Berger, Goldsher & Aharon-Peretz, 2005). Understanding faux pas also requires second-order ToM, in order to appreciate the perpetrator's belief about the victim's mental state (as a result of their remark). As tasks involving the understanding of faux pas may make more complex social reasoning demands, they may be more sensitive to subtle changes in ToM. Indeed, some clinical groups, such as patients with damage involving the VMPFC, have been found to exhibit deficits on a faux pas task alongside intact performance on first order false belief tasks (Shamay-Tsoory, Tomer, Berger, Goldsher & Aharon-Peretz, 2005; Stone, Baron-Cohen & Knight, 1998). The involvement of the different factors described above may make the faux pas task a particularly sensitive tool for assessing possible ToM impairment in patients with BG disorders.

One group that has been studied extensively with regard to ToM is children with autism. These children are thought to exhibit specific difficulties with ToM. Research with these children has led to the development of other tasks, which have been modified for use with normal adults and clinical populations. One task is the 'Eyes Test' developed by Baron-Cohen and colleagues (Baron-Cohen, Wheelwright & Joliffe, 1997; Baron-Cohen, Wheelwright, Hill, Raste & Plumb, 2001). This task requires participants to make judgments about the mental states of a person based on observation of expressions in the eyes alone. Another example is The Strange Stories test (Happé, 1994) which features persuasion, white lies and double bluff. This task highlights a role for ToM in the understanding of language that must be interpreted in a non-literal way.

Non-literal language relies on an understanding of the speaker's mental state to ensure accurate interpretation. In the case of sarcasm for example, the words used by the speaker typically communicate the literal opposite to what they think or feel. Happé (1994) showed that children with autism exhibit poor understanding of non-literal language that is likely to be linked to their difficulties with ToM. Support for a role for ToM in the interpretation of non-literal language comes from imaging studies that indicate regions commonly activated by ToM tasks such as the OFC and inferior frontal gyrus (IFG) are active in healthy adults during the processing of sarcasm (Uchiyama et al., 2006).

FACTORS THAT MAY CONTRIBUTE TO TOM: SIMULATION, ABSTRACT PERSPECTIVE TAKING AND EXECUTIVE FUNCTIONING

Patients with BG disorders could exhibit deficits on social cognitive tasks as a result of deficits in different factors that contribute to ToM. These factors include simulation and abstract perspective taking. Executive functions can also contribute to performance on ToM tasks, but may be more important for some kinds of tasks than others.

Hadjikhani, Joseph, Snyder and Tager-Flusberg (2006) showed that some of the deficits in ToM exhibited by children with autism could be linked to abnormalities of neural regions involved in the Mirror Neuron System (MNS). The MNS is a network of brain regions that allows the imitation of observed behaviour. This network involves frontoparietal neurons that are active when both observing, and performing the same action (Rizolatti & Craighero, 2004). Iacoboni et al. (1999) suggest that a visual representation of the observation of an action is formed in the

superior temporal sulcus and sent via the parietal cortex to inferior frontal regions, which convert the representation to a motor plan and allow imitation. The performance of an action influences the concurrent perception of an action. Recognition is facilitated if the actions that are performed and observed are compatible. If the two actions are incompatible, interference occurs (Oberman, Winkielman & Ramachandran, 2007). These findings suggest there is a common representational code and neural substrate for the perception of and performance of a particular action.

The MNS may be involved in processes related to ToM, as it can be described as a system in which one's own experience and the observable results of the same experience felt by another overlap. The MNS may therefore act as a mechanism to allow one to understand the perspective of another through simulation. This network provides a basis for the overt or covert mirroring of posture and gestures (Oberman et al., 2007) and emotional facial expressions (Adolphs, 2002; Wicker et al., 2003) thus facilitating recognition of others' mental states. Oberman et al. (2007) showed that the recognition of emotional facial expressions in others is associated with covert mimicry of the perceived facial expression, and that blocking this mimicry can interfere with recognition.

Automatic mimicry may be described as emotional contagion. This implies that the observation of an emotion in another may lead to activation of the neural substrate involved in that emotion in the perceiver, allowing them to relate to and understand the emotion observed. For example, patients with HD may exhibit deficits in the recognition of disgust expressed vocally or in facial expressions (Snowden et al., 2008; Sprengelmeyer et al., 1997), and the experience of disgust elicited through the olfactory and gustatory modalities (Mitchell, Heims, Neville & Rickards, 2005)

and in response to pictures (Hayes, Stevenson & Colheart, 2007) and written scenarios (Snowden et al., 2008). Deficits in one's own experience of an emotion could therefore be closely associated with difficulties understanding that emotion in another. Functional studies of the insula add further weight to this argument. Wicker et al (2003) showed that the insula, a region involved in one's own subjective feelings (Craig, 2009) is involved not only in one's own experience of disgust, but also the recognition of this emotion when expressed by another. Jabbi and Keysers (2008) showed that the insula may relate the bodily sensations associated with mimcry to an internal representation of an emotional state to allow emotional contagion.

Some of the processes involved in reasoning about a person's emotions may be quite different to those involved in understanding others' cognitive mental states. Beliefs and intentions, for example, may be considered to be more abstract, as they are often not accompanied by visual cues such as facial expressions. Reasoning about ToM in situations when there may be no observable behaviour indicates a necessary role for the application of abstract theoretical knowledge (Olsson & Ochsner, 2007) or perspective taking processes. Shamay-Tsoory, Aharon-Peretz and Perry (2009) propose two anatomically dissociable systems involved in understanding the mental states of others. The first is a basic emotional contagion system which involves the MNS and IFG. The second is a more advanced cognitive perspective taking system which recruits VMPFC. This second system could be involved in making judgments about a person's emotions (particularly when facial expressions are not observable) and cognitions (which are never directly observable). The recruitment of these systems may vary according to whether input stimuli favour reflective reasoning and semantic processing, or low level recognition.

Higher cognitive abilities such as executive functions may be involved when more abstract reasoning processes are required in order to understand a person's mental state. Saxe, Moran, Scholz and Gabrieli (2006) showed that domain general executive abilities play a role when adults reason about other's beliefs. Executive functions have also been linked to ToM performance in both children (Carlson, Moses & Breton, 2002) and patients with brain damage (Henry, Phillips, Crawford, Ietswaart & Summers, 2006). Although executive functions such as WM may have a more incidental role on task performance, some of these higher cognitive abilities may play a central role in ToM performance. For example, Samson, Apperly, Kathirgamanathan and Humphreys (2005) provided evidence that the executive function inhibition is particularly important for performance on ToM tasks. These authors showed that a patient with deficits in inhibition could pass modified ToM tasks that were specially designed to reduce inhibitory demands. It may be that inhibition is important for ToM because one must inhibit one's own perspective of the world in order to understand another person's viewpoint, and so their mental state. Executive deficits in patients with disorders of the BG may therefore have the potential to affect performance on ToM tasks.

Executive deficits could affect reasoning about cognitive mental states (e.g. beliefs) more than affective mental states. Cognitive mental states are more abstract, so may therefore make greater executive demands. In support of this proposal, Shamay-Tsoory and Aharon Peretz (2007) showed that difficulties in reasoning about cognitive mental states could result from lesions to DLPFC, a region involved in many executive tasks. These authors also showed that circumscribed VMPFC (including medial OFC) damage can lead to specific deficits in reasoning about affective mental states.

In summary, particular impairments in ToM may result from specific difficulties with simulation, abstract perspective taking, or in executive functions that contribute to ToM performance. Dysfunction of the MNS may be associated with poor simulation or emotional contagion processes, leading to impaired understanding of emotions expressed through facial expressions. However, poor understanding of another's emotions may arise in association with deficits in one's own emotional experience. This may be linked to specific neural substrates for different emotions (such as the amygdala, which is linked to fear: Calder et al., 1996; and the insula, which is implicated in disgust: Phillips et al., 1997). Abstract perspective taking is also involved in some ToM and may involve the OFC (Hynes, Baird & Grafton, 2006). ToM may also be impaired through executive deficits resulting from DLPFC dysfunction. Patients with PD, HD and TS may therefore exhibit different deficits in ToM as a result of specific difficulties with simulation, abstract perspective taking or executive functioning.

1.7: Social Cognition in Disorders of the Basal Ganglia

Prefrontal dysfunction may lead to changes in social cognition in PD, HD and TS. In each of these disorders, changes in the functioning of the frontal cortex can occur as a result of dysfunction within frontostriatal pathways. In PD, prefrontal dysfunction may also arise due to the loss of direct DA input into this region. As the pattern of dysfunction within frontostriatal pathways varies in these movement disorders, it is likely that these patient groups will exhibit different deficits on social cognitive tasks.

Evidence of DLPFC dysfunction in PD suggests that executive impairments could affect patients' performance on ToM tasks. However, deficits on most executive tasks may be more closely associated with poor reasoning about abstract cognitive mental states (e.g. beliefs or intentions) in particular. Zelazo, Qu and Müller (2005) discuss a controversial, yet potentially useful distinction between executive and ToM tasks which can be classified as 'hot' or 'cool' according to whether the task involves an emotional element. 'Hot' ToM involves reasoning in relation to affect and motivation, while 'cool' ToM involves reasoning about more abstract mental states. The majority of executive tasks assess 'cool' executive functions (planning on the Tower of London, or set-shifting on the Wisconsin Card Sort Task). However, 'hot' executive functioning may be assessed through the use of affective decision making tasks, such as the Iowa Gambling Task. Furthermore, these authors suggest that 'hot' executive and ToM tasks are linked to OFC, while 'cool' aspects of these abilities rely on DLPFC. Dysfunction of circuitry involving the DLPFC in PD may therefore be more likely to affect patients' performance on 'cool' aspects of ToM.

The mesolimbic and mesocortical systems originate from the VTA and provide dopamine input to the medial prefrontal cortex (Marchese & Pani, 2002). It is likely that these inputs remain largely intact in PD (Evans & Lees, 2004). Widespread deficits in association with OFC dysfunction may therefore appear unlikely. However, some studies (e.g. Ouchi et al., 1999) have provided contrasting evidence that indicates the mesocortical dopaminergic input may be dysfunctional in PD. It is also possible that if the OFC is intact, dopaminergic medication may over-stimulate these regions (Cools et al., 2001a). Dysfunction of OFC could implicate the involvement of other CSTCCs (described by Alexander et al., 1986) in PD, such as the anterior cingulate and\or lateral OFC CSTCCs.

In HD, deficits in domain general executive functions could arise through DLPFC dysfunction and lead to impairment on ToM tasks. Although the current anatomical models and pathological data would not implicate changes within the ACC CSTCC (which includes connections to medial OFC) in HD, a study by Snowden et al. (2003) found that patients with HD exhibited reduced empathy and offered abnormal interpretations of social behaviour. These findings could reflect dysfunction within the ACC circuit. The possible dysfunction of both OFC and DLPFC in HD could lead to impairments in both 'hot' and 'cool' aspects of ToM.

Other difficulties with ToM may occur as a result of dysfunction within the lateral OFC CSTCC (as described by Alexander et al., 1986), which could be affected by degeneration within ventral regions of the CN. Studies showing that patients with HD exhibit difficulties in the recognition of emotional expressions (e.g. Henley et al., 2008) could implicate dysfunction in the lateral OFC CSTCC (as described by Alexander et al., 1986) that includes the IFG (part of the MNS). The neural substrates involved in the recognition of an emotion in another could also be involved in one's

own emotional experience (e.g.Wicker et al., 2003). Therefore, patients may also experience changes in their own subjective experience of certain emotions.

In TS, possible dysfunction within the CSTCC involving ventral striatum and ACC (outlined by Alexander et al., 1986) could lead to changes in inhibition and associated impairments on ToM tasks. As DLPFC dysfunction appears unlikely, patients without comorbidities would not be expected to exhibit widespread deficits on ToM tasks in association with executive deficits. Dysfunction of the ACC may implicate involvement of the amygdala and connections to medial OFC, which could result in more fundamental deficits on many tasks involving ToM perspective taking processes. The NOSIS exhibited by some patients with TS (Kurlan et al., 1996) could be linked to deficits in ToM, as poor consideration of others' mental states in response to one's own actions could contribute to these symptoms. As patients with TS are more likely to exhibit dysfunction within circuitry involving medial OFC than DLPFC, this should lead to greater difficulty with aspects of 'hot' rather than 'cool' ToM.

The following chapters of this thesis describe a series of experiments that investigated the performance of patients with BG disorders on a range of social cognitive tasks. Throughout chapter 1, HD is discussed directly after PD because these two disorders are both neurodegenerative and TS is a neurodevelopmental disorder. However, the order of the chapters in this thesis first covers work carried out with patients with PD, then TS and then HD, reflecting the chronological order that experimental work was carried out.

CHAPTER 2: SOCIAL COGNITION IN PARKINSON’S DISEASE

2.1: Social Cognition in PD: Introduction

In PD, degeneration of DA neurons in the SN leads to dysfunction within frontostriatal pathways. The CSTCCs (Alexander et al., 1986) are formed from connections that pass through the thalamus and join the striatum with different regions of the frontal cortex. While characteristic motor symptoms arise due to dysfunction of motor circuits, cognitive difficulties may result from the dysfunction of circuits with non-motor functions. Patients exhibit executive deficits on tasks such as the Tower of London test (e.g. Weintraub et al., 2005), Wisconsin Card Sorting Test (e.g. Lees & Smith, 1983) and on WM tasks (e.g. Gabrieli et al., 1996). Zgaljardic et al. (2006) showed that patients' greatest deficits were apparent on tasks linked to DLPFC functioning.

Frontal dysfunction can lead to deficits in ToM (see section 1.6). Changes in frontal functioning in PD (due to dysfunction within frontostriatal circuitry) could therefore lead to deficits in ToM. Studies have therefore investigated ToM ability in adults with other neurological conditions. Deficits have been demonstrated by patients with schizophrenia (Shamay-Tsoory et al., 2007), fronto-temporal dementia (Gregory et al., 2002; Lough et al., 2006) and traumatic brain injury (Bibby & McDonald, 2005). Many clinical studies indicate that the medial OFC is important for ToM (Blakemore, den Ouden, Choudhury & Frith, 2007; Fletcher et al., 1995; Gallagher et al., 2000; Stone et al., 1998). If striatal dysfunction was to extend so far as to affect circuitry involving medial OFC, patients with PD could exhibit deficits on ToM tasks.

Clinical and developmental studies have highlighted relationships between ToM and executive functions. Studies of patients with brain injury have shown that impairments in ToM can be linked to deficits in inhibition (Samson et al., 2005) or

WM (Bibby & McDonald, 2005; Stone et al., 1998). Developmental research has highlighted similar associations. For example, Flynn (2007) suggests that the development of inhibitory control may underpin the understanding of false belief. Similarly, Gordon and Olson (1998) reported correlations between 3-5 year olds' performance on ToM and WM tasks. Although research indicates a link between executive functioning and ToM ability, the exact nature of this relationship remains unclear. Inhibitory ability could be important for ToM because it may be necessary to inhibit one's own point of view in order to see the world from another person's perspective. In the case of WM it is possible that this executive function provides a general contribution to task performance through the maintenance and manipulation of task relevant information. WM could therefore have an incidental role in performance on ToM tasks. Alternatively, ToM reasoning itself could be carried out in a generic WM system, so poor WM could also lead to a ToM deficit through loss of competence (see Apperly, Samson & Humphreys, 2005, pp 573). This possibility is open to discussion.

Relationships could be seen between poor performance on ToM tasks and executive tasks assessing WM because domain general WM is likely to contribute to ToM performance (see McKinnon and Moscovitch, 2007). Difficulties with WM as a result of DLPFC dysfunction are common in PD (e.g. Gilbert, Belleville, Bherer & Chouinard, 2005) and could lead to deficits on reasoning tasks. Patients exhibit impairments on tasks involving deductive and inductive reasoning (Natsopoulos et al., 1997), and Monetta, Grindrod and Pell (2008) showed that patients with PD can exhibit deficits in inference generation as a result of WM dysfunction. One specific link between WM impairment in PD and ToM deficits could therefore be through impaired inferential reasoning.

A few studies have reported evidence of ToM difficulties in patients with PD. Saltzman, Strauss, Hunter and Archibald (2000) showed that PD patients can perform more poorly on some ToM tasks in comparison to controls. These impairments were related to executive deficits. Another study (Peron et al., 2009) revealed limited evidence for ToM impairment in PD. Advanced but non-demented PD patients performed poorly on questions relating to a faux pas task, although patients at an earlier stage of the disease performed similarly to controls. Patients with PD also did not differ from controls on the 'Eyes Test' (developed by Baron-Cohen et al., 2001: see section 1.6). Patients' deficits were still apparent when they were taking DA medication.

Peron et al. (2009) suggest that the understanding of cognitive mental states (cognitive ToM) such as intentions or beliefs could be more vulnerable in PD than the understanding of emotions (affective ToM). Specific difficulties with cognitive ToM could occur because PD is associated with executive dysfunction and cognitive ToM relies more on executive functioning than affective ToM. One study of patients with frontal lesions (Shamay-Tsoory & Aharon Peretz, 2007) provided evidence for largely separate neuroanatomical substrates for affective and cognitive ToM, and impairments in cognitive ToM were more often associated with lesions to the DLPFC.

Though research investigating ToM in PD is rather scarce, studies have indicated that patients with PD demonstrate difficulties on tasks involving related aspects of social cognition. For example, patients can exhibit deficits in the recognition of emotional facial expressions (Clark, Neargarder & Cronin-Golomb, 2008; Suzuki, Hoshino, Shigemasu & Kawamura, 2006). Patients with PD can also exhibit poor understanding of pragmatic communication (McNamara & Durso, 2003), including poor comprehension of metaphor (Monetta & Pell, 2007) and sarcasm

(Monetta, Grindrod & Pell, 2009). ToM deficits could underlie impaired comprehension of pragmatic language such as metaphors and sarcasm, because the accurate interpretation of non-literal language involves appreciation of the speaker's mental state. This proposal is supported by findings reported by Monetta et al. (2009), who found that patients with PD performed poorly on first and second-order belief questions during a pragmatic comprehension task. These difficulties were related to poor performance on measures of WM and verbal fluency, so executive deficits are likely to have resulted in the ToM difficulties which in turn led to poor interpretation of non-literal language.

Another ability shown to be impaired in PD that could involve similar processes to ToM is counterfactual thinking. Counterfactual reasoning occurs after an event when one imagines how things could have turned out differently. McNamara, Durso, Brown and Lynch (2003) reported deficits in counterfactual reasoning in PD. Riggs, Peterson, Robinson & Mitchell (1998) found evidence of a relationship between children's performance on ToM and counterfactual reasoning tasks. Both counterfactual thinking and ToM involve looking at the world from different perspectives. To think counterfactually one must set aside current reality and imagine an alternative reality. However, to reason about another person's mental state, one sets aside one's own personal reality and then attempts to see the world from another person's perspective. Deficits in counterfactual reasoning could indicate that patients with PD exhibit general difficulties with perspective taking which could lead to impaired performance on ToM tasks.

Chapter 2 of this thesis describes three experiments that were conducted to investigate whether the frontostriatal dysfunction in PD could result in ToM deficits and whether any such deficits were related to executive dysfunction. The tasks used

involved cognitive ToM because the understanding of cognitive mental states could be more vulnerable to PD (Peron et al., 2009). Unlike other studies carried out with patients with PD, these experiments used a standard first order false belief task involving 'unexpected transfer' (see section 1.6). Some tasks were modified to reduce WM demands, and tests of non-inferential ToM were included.

2.2: PD Experiment 1

INTRODUCTION

In experiment 1, the performance of PD patients and neurologically intact controls was compared on two ToM tasks. One ToM task consisted of standard 'unexpected transfer style' vignettes (devised by Apperly, Samson, Chiavarino & Humphreys, 2004). These vignettes featured the movement of a person or object from its original location to a new location, during a story character's absence. ToM ability was assessed by asking participants to identify the absent character's false belief about the object's location (the object is in the original location). Another question assessed counterfactual reasoning, and two questions ('memory' and 'reality') were included to check memory.

The other ToM task was a faux pas task (Baron-Cohen et al., 1999), which involved understanding that one story character's remark could have hurt or offended another character. The ability to recognise faux pas develops later than the understanding of false belief and involves the attribution of cognitive and affective mental states: the false belief of the protagonist (what they say or do will not offend) and the victim's feelings of hurt or offence. Peron et al. (2009) found that some patients with PD exhibit impairment on a version of this faux pas task. Kawamura and Koyama (2007) reported research (Oeda, 2003) indicating that although PD patients could recognise faux pas, they performed poorly on related false belief questions. These errors were despite intact recall of factual information.

The FAS test was administered to assess verbal fluency, an aspect of executive functioning. Patients were expected to perform more poorly than controls on this

word generation task, which has been linked to activity in the DLPFC (Gallard et al, 2000). Shamay-Tsoory & Aharon Peretz (2007) found that ToM ability correlated with performance on verbal fluency tasks in patients with frontal lesions, so a correlation between performance on the FAS and ToM vignette task was expected.

METHOD

This study and all other experiments contained in this thesis were granted ethical approval by South Birmingham NHS Ethics Committee.

PARTICIPANTS

Thirty outpatients with PD from the Neurosciences Department at the Queen Elizabeth Hospital, Birmingham, volunteered to take part in this experiment. They were invited to participate through their consultant neurologist. This senior clinician ensured that all patients selected neither showed frank symptoms of dementia nor exhibited motor symptoms rated at greater than stage 3 on the Hoehn and Yahr (1967) scale. The Hoehn and Yahr scale is a standard measure of the severity of motor symptoms in PD. Stage 3 characterises patients who have mild to moderate disease with impaired balance, but are physically independent.

All patients were taking standardly prescribed DA medications. There were 19 males and 11 females, of mean age 64.27 years (S.D. 8.80, range 52-82), with mean 13.30 years (S.D. 2.56, range 9-18) of education. 15 controls (9 males and 6 females) were also recruited and matched as closely as possible for age (mean 61.80, S.D.

13.14, range 50-87 years) and education (mean 13.87, S.D. 2.59, range 10-18 years). A subset of 15 patients (10 males and 5 females) with mean age 65.60 years (S.D. 9.63, range 54-82) and mean education 13.67 years (S.D. 2.82, range 10-19) and another group of 10 controls consisting of 6 males and 4 females, of mean age 60.70 years (S.D. 9.60, range 50-81), with mean education 13.98 years (S.D. 2.22, range 11-16) completed the faux pas task. Fewer controls than patients were tested as controls performed at or close to ceiling on the social cognitive tasks.

PROCEDURE

All patients and some control participants were tested in a consultation room at the Queen Elizabeth Hospital. Occasionally a friend or relative was present, who sat silently and did not assist the patient with the tasks. Some control participants were tested in a quiet room in their own home. All participants read information sheets about the study and gave informed consent. Before the tasks, patients completed a short interview about their experience of the disease and the medication they took. Testing took approximately thirty minutes and was followed by a full debriefing.

The order of administration of the tasks was counterbalanced across participants, though the vignettes within the faux pas and ToM vignette tasks remained in a fixed order. Each vignette was read to the participant twice before they were asked the corresponding questions.

TOM TASKS

ToM vignette test

This test was taken from Apperly et al. (2004). It comprised four 'unexpected transfer' style vignettes, describing the actions of story characters, and a change in the location of a person or object. For example: "Andrew and Susie live in a rural cottage outside of the tiny village of Ely. Andrew is in bed suffering with the flu. Susie decides to drive into the nearest town to get him some medicine. While she's away, the phone in the cottage rings. The burglar alarm is sounding in the village school where Andrew works. Reluctantly, Andrew walks to the school in the village."

Each vignette was read twice and then four questions were asked. One assessed counterfactual reasoning: "Where would Andrew be if he hadn't gone to the school?" Another tested the understanding of a character's false-belief: "Where does Susie think Andrew is?" Two questions were included to check recall: "Where was Andrew at the start?" (memory) and "Where is Andrew now?" (reality: the final outcome of the story). There were two forced choice responses, the target's original and current locations. Each question was followed by two forced choice options; the original, and final location of the object. The original location was the correct answer to all but the reality question. The false belief and counterfactual questions came first and second, with the false belief question appearing first in the first and third vignettes, and second in the second and fourth vignettes. The memory and reality questions were asked third and fourth. They were counterbalanced so memory appeared as the third question in the first two vignettes and in fourth position in the last two vignettes.

Faux Pas test

This task contained eight vignettes that were developed by Baron-Cohen et al. (1999) and were originally used to test children with autism. Four control vignettes described exchanges between characters involving no faux pas and four test vignettes described a character saying something inappropriate to another character without realising it is likely to offend them. For example: "Jill had just moved into a new apartment. Jill went shopping and bought some new curtains for her bedroom. When she had just finished decorating the apartment her best friend Lisa came over. Jill gave her a tour of the apartment and asked "How do you like my bedroom?" "Those curtains are horrible," Lisa said, "I hope you're going to get some new ones."

The first question assessed recognition of faux pas: "Did someone say something they shouldn't have?" If participants responded yes, they were then asked "Who was it and what did they say?" Participants' reasoning was questioned through the use of two further probes: "Why shouldn't they have said that?", and "Why do you think they did say it?" Another question checked story recall, "What had Jill just bought?" Two other questions were asked about test vignettes. One was a question that asked about a characters desire or belief: "Did Lisa like the curtains?" The final question always asked about the protagonist's false belief which contributed to the faux pas: "Did Lisa know that Jill had chosen the curtains?" These questions were always presented in this fixed order.

EXECUTIVE TASKS

FAS verbal fluency test

Participants were requested to say as many words as they could think of beginning with a letter of the alphabet until asked to stop. They were instructed that they could say any words apart from peoples' proper names. One minute was given for each of the letters F, A and S. Scores were calculated by summing the number of the words generated across these three trials. Repeats were noted and not counted. If participants stopped responding and said they could not think of any more words they were asked to continue trying until the minute given for that letter ended.

RESULTS

Analysis indicated that patients (n=30) and controls (n=15) did not significantly differ for age, $t(21.30)=0.77$, $p=.499$, or years of education, $t(43)=-0.70$, $p=.489$ overall. There was also no difference in age and education when the subgroup of 15 patients who completed the faux pas task were compared to the group of 10 controls who completed this task (age: $t(23)=1.25$, $p=.225$; education: $t(21.65)=-0.63$, $p=.538$).

Non-parametric tests were used for the analysis of task performance as data were not normally distributed and included outliers. Between comparisons were conducted using Mann Whitney U (MWU) tests and Kruskal Wallis tests. Within comparisons employed Friedman tests and Wilcoxon signed ranks tests. Relationships

were examined using Spearman's rho (r_s) correlation coefficients. These tests were used for the majority of analysis reported in results sections throughout this thesis. Any exceptions are indicated where they arise.

TOM TASKS

ToM Vignette Test

While controls performed at ceiling, patients answered 9.38% of questions on the vignette test incorrectly, a mean of 1.5 errors per patient (S.D. 2.13, median 0, range 0-9). This difference was highly significant, MWU=120, p=.002. Patient errors were spread across all four question types and there was no significant difference in performance according to question type, $\chi^2(3)=5.54$, p=.136. Patients who made false belief errors also tended to make errors on memory or reality questions. As can be seen from Table 1, patients made fewest errors on the counterfactual question.

Table 1. Errors made by patients (n=30) on ToM vignette questions

Question type	False belief	Counter-factual	Memory	Reality	Total
Total errors/total possible	13/120	6/120	10/120	16/120	45/480
Percentage incorrect	10.83	5	8.33	13.33	9.38
Number of patients making errors	11	6	9	10	14/30

When between comparisons were conducted for errors made on each of the four question types, patients with PD performed significantly more poorly than controls on false belief, MWU=142.5, p=.008, and reality, MWU=150, p=.013, questions. The difference for memory questions just reached significance, MWU=172.5, p=.045. There was a trend for poor performance on the counterfactual questions, MWU=180, p=.066.

Faux pas test

Although about half of the patients made at least one error when required to recognize whether faux pas had occurred, there was no significant difference between patients and controls in the recognition of faux pas, MWU=59, p=.313. Patients (n=15) made 14 errors in total (mean 0.93, S.D. 1.28, median 0, range 0-4), and controls (n=10) made 4 errors (mean 0.4, S.D. 0.70, median 0, range 0-2). As can be seen from Table 2, errors were made on both test and control vignettes.

Table 2. Percentage of faux pas recognition errors made by patients and controls

Group	Total errors	Test scenarios	Control scenarios
Patients (n=15)	11.67	11.67	11.67
Controls (n=10)	5.00	7.50	2.50

Patients performed significantly more poorly than controls on check questions, MWU=36.5, p=.029. Both test and control scenarios were followed by a question

checking recall of factual information contained in the story. Patients performed significantly more poorly than controls on these fact check questions, MWU=37.5, *p*=.027. This finding suggests that patients' comprehension or memory for the story details was poor, though this did not seem to lead to a decline in faux pas recognition.

Table 3. Percentage of incorrect responses for patients and controls for faux pas check questions

Question type	Patients (n=15)	Controls (n=10)
Total fact check	18.33	6.25
Test scenario fact check	8.33	2.50
Control scenario fact check	28.33	10.00
Desire\belief check	13.33	2.50
False belief check	28.33	12.50

Test scenarios were followed by two more check questions. The first asked about the protagonist's desire or belief, and the second concerned the protagonist's false belief. When these question types were considered separately, patients exhibited a trend for poorer performance on the first question (see Table 3), MWU=47, *p*=.057, but didn't perform significantly more poorly on the false belief check, MWU=53.5, *p*=.186.

EXECUTIVE TASKS

FAS test

On average patients generated 43.37 words (S.D. 17.69, median 40.5, range 15-74) over the FAS test. Controls generated mean 54.4 words (S.D. 16, median 47, range 30-95). Some patients exhibited very low scores on this test, and the difference between patients and controls approached signficance, MWU=144.5, p=.052.

CORRELATIONS

Correlations were conducted to look for relationships between patients' performance on the tasks administered and assess the influence of time since medication. A significant negative correlation was found between patient performance on the FAS and ToM vignette test (Table 4). Better executive performance as measured by high scores on the FAS was associated with fewer errors on ToM vignettes. No other significant relationships were found.

Due to the problems associated with multiple comparisons, a more stringent level of significance (such as 0.01) is often used when analysing correlations. However, for this experiment, and throughout this thesis, correlations with a p-value less than 0.05 were considered. This was for two reasons. Firstly, both non-parametric tests and small sample size led to an increased probability of making a type II error. Secondly, as some of the research contained in this thesis was exploratory, weaker correlations were still of use in indicating areas of further investigation.

Table 4. Correlations for patient performance on tasks and time since medication

Measure:	FAS (total words generated)	ToM (all errors)	Faux pas (recognition errors)	Time since Medication (minutes)
FAS (total words generated)	x	-.529 .043*	-.448 .094	.164 .576
ToM (all errors)		x	.446 .096	-.375 .186
Faux pas (recognition errors)			x	.229 .431

KEY:
Upper value = Spearman's r correlation coefficient, lower value = *p*-value
* Significant at the 0.05 level

DISCUSSION

Patients made more errors on the ToM vignette test than controls. The fact that the control group performed at ceiling makes the number of errors made by patients striking. It should be noted that the forced choice style of questioning used on the vignette test could mean that patients answered correctly by chance on many occasions. However, another difficulty with interpretation is that on the occasions when patients performed well on false belief questions but also made errors on the

memory questions (confusing the start and end location of the transferred object), a correct false belief response may not reflect the accurate inference of a false belief but rather the incorrect inference of a true belief.

Although most errors made by patients were on false belief and reality questions, errors were also made on memory and counterfactual questions, providing no evidence for a selective deficit in the understanding of false-belief. There was evidence of a weak relationship between performance on the ToM vignettes and the FAS test, which provided some evidence of mild executive impairment in the patient group. This link between executive and ToM performance could be explained by an executive component directly involved in ToM, or the presence of incidental executive demands made by the ToM vignette task.

Experiment 1 revealed little evidence in support of a counterfactual deficit as patients made fewest errors on counterfactual questions. However, one should be cautious in interpreting the counterfactual data as patients made a number of errors on memory and reality questions. The small number of counterfactual errors that were made by patients is in contrast to the finding of McNamara et al. (2003). This discrepancy can be explained by task differences. One of the tasks used by McNamara et al. was designed to elicit spontaneous generation of counterfactual thoughts: patients were required to generate counterfactual thoughts when prompted to think about their own previous life experiences. In contrast, the ToM vignette task used in the present experiment questioned patients' counterfactual reasoning more directly. It may be that patients can reason counterfactually when explicitly directed to but are less likely to do so spontaneously because of the cognitive demands made by the inferential reasoning and perspective taking processes involved in counterfactual reasoning.

Patient performance on the faux pas test provided little evidence for deficits in ToM. Although patients performed more poorly on questions assessing recall of factual information, they did not perform significantly more poorly on false belief questions relating to this measure. This is in contrast to findings reported by another Oeda (2003) and Peron et al. (2009). The patients tested by Peron et al. may have exhibited deficits on the faux pas task because they were in later stages of the disease. This study included patients with symptoms rated at stage 4 on the Hoehn and Yahr scale whereas patients tested in the present experiment were judged to be at most stage 3. Stage 4 patients are still able to walk or stand unassisted but are more severely physically disabled than stage 3 patients, reflecting a greater degree of neurodegeneration.

Recognition of faux pas was not associated with performance on the ToM vignette task. This could reflect the fact that performance on the vignette task involved counterfactual, reality and memory questions as well as false belief. However, it is also the case that the faux pas task involved reasoning about emotions, in addition to false belief. This difference could further explain why performance on the FAS task was related to performance on the standard false belief vignettes but not the faux pas task. The executive skills assessed by the FAS test were perhaps less relevant to the understanding of affective mental states (understanding the negative emotions experienced by the victim in the faux pas scenario) than cognitive mental states (attributing false belief).

Differences were apparent between patients and controls when they were asked to justify their responses to the faux pas identification questions. After indicating that faux pas had occurred, participants were asked to explain why the protagonist made the remark and why they should not have said what they did.

Patients were more likely to mention character's desires or emotions, or simply restate the basic facts of the story, rather than focus on the character's false belief. In fact, some patients failed to mention beliefs at all during the test. These findings could suggest that patients were more readily able to reason about the emotional response of the victim in the faux pas scenarios than the protagonist's false belief, providing possible evidence of a differentiation in performing reasoning about affective and cognitive mental states (or 'hot' and 'cool' ToM: Zelazo, Qu and Müller, 2005). It can be speculated that such a differentiation could occur due to a greater reliance on cognitive or executive functions when reasoning about more abstract mental states. If the executive deficits exhibited by patients with PD make them more likely to exhibit impaired reasoning about cognitive rather than affective mental states it would explain why executive performance was more closely tied to errors made on the false belief vignette task than the faux pas test.

The false belief errors made by patients on the ToM vignettes are insufficient to provide evidence of impairments in ToM *per se*, due to an association with errors on memory and reality questions. The number of errors made on these memory check questions was surprising as the vignettes were fairly short and control performance was at ceiling. It is quite possible that WM impairments affected basic comprehension and recall leading to errors on all question types. False belief errors are perhaps more likely to reflect a deficit in WM processes contributing to performance on the ToM vignettes, rather than a deficit in ToM *per se*. Experiment 2 therefore investigated patients' performance on ToM tasks with reduced WM demands.

2.3: PD Experiment 2

INTRODUCTION

In experiment 1, PD patients performed poorly on a ToM vignette task. Errors were not limited to performance on false belief questions as they were also apparent on questions involving memory and counterfactual reasoning. This pattern of errors could reflect poor WM. WM deficits are commonly reported in PD (e.g. Gabrieli et al., 1996) and may result from DLPFC dysfunction (Aleman & van't Wout, 2008). The deficits in verbal fluency exhibited by patients in experiment 1 would be in keeping with this suggestion as fluency tasks have been linked to the DLPFC (Gallard et al., 2000). Experiment 2 was designed to investigate whether the errors made by patients could indeed be attributed to deficits in WM. New ToM tasks were included that were designed to reduce WM demands. Evidence of false belief errors on these new tasks would provide stronger evidence for a deficit in ToM *per se*.

One way in which WM demands were reduced was by decreasing the amount of information contained in the vignettes. The shortest new vignettes were two lines long and were of the 'unexpected transfer' style used in previous experiments. A direct comparison could be made between patients' performance on longer vignettes (6-7 lines long: Apperly et al., 2004 vignettes) and these shorter 'unexpected transfer' vignettes which involved similar reasoning processes.

Another way that the potential impact of WM impairment was reduced was through the inclusion of non-inferential ToM vignettes. Inferential reasoning involves using available information to deduce a likelihood that is not explicitly stated. Inferential reasoning deficits have been reported in PD, and were linked to deficits in

WM (Monetta et al., 2008). Furthermore, research carried out with patients with traumatic brain injury led Dennis and Barnes (1990) to suggest that inference ability may be predicted from WM, perhaps because inferential reasoning involves considering multiple pieces of information (perspectives) simultaneously. WM ability is likely to affect inferential reasoning processes that are relevant to performance on some ToM tasks. The ToM vignette task used in PD experiment 1 required good comprehension, retention and manipulation of the information given, in order to move beyond explicitly stated facts and infer mental states.

The non-inferential ToM vignettes used in this experiment were 'deceptive box' style vignettes. These vignettes described one character being deceived by another about the true identity of an object. The fact that a mistaken belief was held by the deceived character was explicitly stated; participants were told that the character in question believed the lie the other character told them. Another advantage relating to the inclusion of these deceptive style vignettes was that they assessed ToM (false belief) using tasks of an alternative format to 'unexpected transfer' style tasks. It was hypothesized that patients would exhibit better performance on both types of new shorter vignettes in comparison to the longer 'unexpected transfer' style vignettes (used in experiment 1).

During experiment 1, PD patients made errors on many question types, perhaps indicating they have a general cognitive impairment which could affect performance on many different reasoning tasks. To address this possibility, a deductive reasoning task which involved counterfactual syllogisms was used in experiment 2. These syllogisms described facts that were contrary to reality and made few demands on WM as they consisted of a few very short sentences.

The patients tested in this experiment also completed the FAS test and a WM test (Digit Ordering Test Adapted; Werheid et al., 2002; adapted from Cooper, Sagar, Jordan, Harvey & Sullivan, 1991) which provided a meaure of verbal WM manipulation span. Patients were expected to exhibit deficits on these executive tests and it was predicted that WM scores would be related to performance on the longer ToM vignette task. WM was not expected to be as closely related to performance on the shorter 'unexpected transfer' and 'deceptive box' style tasks as these were designed to make fewer WM demands, and the 'deceptive box' task was non-inferential. Any false belief errors made on the 'unexpected transfer' and 'deceptive box' style vignettes would provide stronger evidence of deficits in ToM.

METHOD

PARTICIPANTS

Twenty-four volunteers with PD (18 males) participated in this experiment. They were selected based on the criteria described in experiment 1 method. Their mean age was 66.63 years (S.D. 9.82, range 49-86) and they had mean 12.83 years (S.D. 2.01, range 11-19) of education. None of the patients tested took part in experiment 1.

Control data was collected for the WM measure (DOT-A). Twelve controls (6 males and 6 females) were matched to the patients as closely as possible for age (mean 65.33 years, S.D.12.37, range 43-79 years) and education (mean 13.17, S.D. 2.28, range 11-17 years). Control data was not collected for the ToM tasks or

counterfactual syllogisms. This was because controls' performance on the longer ToM vignette task was at ceiling in experiment 1, and the new ToM vignettes were shorter and some were non-inferential so should elicit fewer errors. Children between 2 and 3 years of age can pass counterfactual syllogism tasks (Richards & Sanderson, 1999) so there was no reason to expect neurologically intact controls would perform below ceiling on the deductive reasoning task.

PROCEDURE

Testing was conducted as described in the procedure of Experiment 1. Patients first undertook one executive task, then the ToM vignettes as a combined set, then the other executive task and finally the counterfactual syllogisms. The position of the two executive tasks alternated across participants so as to form two counterbalanced fixed orders.

TOM VIGNETTES

These were three types of ToM vignettes presented as a block in a fixed order. The order of presentation was counterbalanced by type, so that vignettes of the three types were distributed as evenly as possible throughout the fixed order.

A 'physical people' vignette was included at the end of the ToM block as a control for basic comprehension, which involved reasoning about people but not ToM. The vignette described a change in the physical state of a person, in the style of those used by Saxe and Kanwisher (2003): "Rebecca has very long hair that reaches past her shoulders. Today she goes to the hairdressers and asks for a new style. Rebecca is

really pleased when the hairdresser cuts her hair very short." Participants were asked memory (e.g. What was Rebecca's hair like before?) and reality (e.g. What is Rebecca's hair like now?) questions.

Short 'deceptive box' style vignettes

These vignettes were four sentences long. Each described one character telling another character a lie to deceive them about the identity of an item they themselves had purchased. In half of the vignettes the deception was for a positive reason (e.g. a white lie about surprise present) and in others for a negative reason (e.g. to avoid disapproval or cover up mischievousness). For example: "It is Arthur and Beryl's Anniversary. Beryl tells Arthur that she has bought him a CD. In fact, she has bought him tickets to a concert. Arthur doesn't know that Beryl is going to surprise him so he believes Beryl". Unlike both sets of transfer vignettes, these vignettes were non-inferential, because they explained that one character was unaware of the deception so believed the other character's lie. These vignettes were followed by false belief (e.g. What does Arthur think Beryl has bought him for his birthday?) and reality (What has Beryl really bought for Arthur?) questions, with two forced choice options. The order of presentation of positive and negative vignettes was counterbalanced.

Short 'unexpected transfer' vignettes

The 'unexpected transfer' vignettes were of the same style as the vignettes devised by Apperly et al. (2004), but were shorter, consisting of two sentences containing only the necessary information to answer the questions that followed. For

example: "Judy leaves some cigarettes on the coffee table. While she is in bed asleep, her son takes the cigarettes and puts them in his schoolbag". Participants were asked false belief (e.g. where does Judy think the cigarettes are?) and reality (e.g. where are the cigarettes really?) questions, with the correct answer being the object's original and current location, respectively. These two forced choice options were given with each question.

Longer ToM vignettes

These vignettes were devised by Apperly et al. (2004) and administered as described in experiment 1.

COUNTERFACTUAL SYLLOGISMS

This deductive reasoning task contained four items that were read to patients involving counter-to-fact statements, such as "all sheep are green" (see Beck, Riggs & Gorniak, in press). Participants were told that they would hear some facts that sounded strange, and were instructed to pretend that the statement was true. They were asked a question that required acceptance of this counterfactual information in order to generate a correct answer e.g. "Sally is a sheep. What colour is Sally?" Responses were simply scored correct or incorrect.

EXECUTIVE TASKS

FAS test

As described in experiment 1.

Digit Ordering Test-Adapted

The Digit Ordering Test was originally developed by Cooper et al. (1991) and adapted by Werheid et al (2002), resulting in the DOT-A. Participants were asked to listen to individual streams of digits, with the length of the stream increasing from 3 to 8 digits as testing progressed. A pair of streams was presented of each length. Participants were asked to remember the digits and say them back in ascending order immediately after presentation. They were told that the streams would get longer as the test continued and to make sure they recalled a digit twice if it was featured twice within a stream. A participant's maximum span was the longest stream they could respond to correctly. When a participant answered two streams of a single length incorrectly, the test ended. Participants who only responded correctly to one stream of a single length had 0.5 points deducted from their maximum span. To help prevent strategy use, the streams sometimes contained one repeated digit.

RESULTS

Patients' age did not differ from that of controls tested in the present experiment, $t(34)=0.34$, $p=.735$, or experiment 1, $t(37)=1.35$, $p=.186$. Patients' years of education also did not to differ from controls tested in the present experiment, $t(34)=-0.45$, $p=.657$, or experiment 1, $t(37)=-1.40$, $p=.171$.

THEORY OF MIND VIGNETTES

'Deceptive box' style vignettes

A total of 18 errors were made on the 'deceptive box' vignettes, with a mean of 0.75 per patient (S.D. 1.07, median 0, range 0-4). As can be seen from Table 5, an equal number of false belief and reality errors were evident. A Friedman test showed no significant difference in the number of errors made on individual deceptive box vignettes, $\chi^2(5)=83.64$, $p=.124$.

Table 5. Errors made by patients (n=24) on short unexpected transfer and deceptive box vignettes

Vignette type:	'Unexpected transfer'	'Deceptive box'
False belief errors	6	9
Reality errors	6	9
Number of patients making errors	4	10

'Unexpected transfer' vignettes

Patients made fewest errors (12) on 'unexpected transfer' vignettes, leading to a mean of 0.5 errors per patient (S.D. 1.25, median 0, range 0-5). As can be seen from Table 5, patients made an equal number of false belief and reality errors on these vignettes. Though more errors were made on certain vignettes, Friedman tests showed no significant difference in the number of errors made on individual 'unexpected transfer' vignettes, $\chi^2(5)=9.41$, $p=.094$.

Longer ToM vignettes (devised by Apperly et al., 2004)

Overall, patients made 47 errors on this test, and each patient made an average of 1.96 errors (S.D. 2.07, median 1.5, range 0-7), out of a possible 16. The 15 controls tested in experiment 1 exhibited scores at ceiling. Table 6 shows that errors made on the longer ToM vignettes were spread across question type. The number of counterfactual errors was of interest. This differed from Experiment 1, where patients made very few. However, a Friedman test indicated no significant difference in performance on false belief, counterfactual, memory and reality questions, $\chi^2(3)=1.41$, $p=.703$, indicating general impairment on this task. Patients made significantly more errors on certain vignettes, $\chi^2(3)=8.85$, $p=.031$. The same number of errors (7) was made on each of the first two vignettes. More errors were made by patients on the third (13) and final (20) vignettes. This finding is probably more likely to reflect the the effects of fatigue than an item effect, as the vignettes were very similar in content and format.

Table 6. Errors made by patients (n=24) on longer ToM vignettes

Question type	False belief	Counter-factual	Memory	Reality	Total
Errors/ total possible	9/96	14/96	11/96	13/96	47/384
Percentage incorrect	9.38	14.58	11.46	13.54	12.24
Number of patients making errors	8	7	11	12	15

COMPARISON BETWEEN TOM VIGNETTE TYPES

Because the longer ToM vignettes were followed by a total of 16 questions, and the 'deceptive box' and 'unexpected transfer' vignettes by 12, it was necessary to convert error counts into percentages for comparisons. Wilcoxon signed ranks tests indicated significant differences between the number of errors made on the longer ToM vignettes compared to both the short 'unexpected transfer', z=-3.42, p=.001, and 'deceptive box' vignettes, z=-2.16, p=.031. Patients made fewer errors on 'deceptive box' and 'unexpected transfer' vignettes compared to the longer ToM vignettes (Table 7). In contrast, the number of errors made on the 'deceptive box' and 'unexpected transfer' vignettes did not differ significantly, z=-0.998, p=.318.

Table 7. Patients' errors made on longer ToM vignettes, deceptive box vignettes and unexpected transfer vignettes

ToM vignette type:	Longer ToM vignettes	'Deceptive box' vignettes	'Unexpected transfer' vignettes
Total errors/total possible	47/384	18/288	12/288
Percentage	12.24	6.25	4.17

COUNTERFACTUAL SYLLOGISMS

The patient group made just one error on this task.

EXECUTIVE TESTS

FAS Test

The mean number of words generated by patients over the test was 38.83 (S.D. 17.28, median 40.5, range 14-95), which was significantly lower than the controls tested in experiment 1, who achieved a mean score of 54.40 words (S.D. 16, median 47, range 30-95), MWU=102.5, p=.025. Some patients performed particularly poorly on this test, with four patients generating 20 words or fewer, and only 5 patients achieved or surpassed the experiment 1 control mean.

Digit Ordering Test – Adapted

Patients achieved a mean WM manipulation span of 4.58 digits (S.D. 0.99, median 4.5, range 2.5-6.5) on this test. This score was significantly different to that obtained by controls who achieved a mean span of 5.58 digits (S.D. 0.733, median 5.5, range 4.5-7), MWU: 55.5, p=.002. Only a quarter of patients reached or surpassed this control mean.

CORRELATIONS

Correlations were conducted to look for relationships between patients' performance on tasks (Table 8).

A Pearson correlation (r_p) was appropriate for analyzing the relationship between patients' performance on the FAS and DOT-A as scores on these measures were normally distributed. Performance on the FAS test correlated significantly with performance on the DOT-A, indicating that higher verbal fluency scores were associated with better WM ability. Non-parametric correlations indicatd that DOT-A WM scores correlated significantly with performance on the longer ToM vignettes at the 0.05 level, indicating that more errors were made by patients with poorer WM. Errors made on the longer ToM vignettes were also positively related to errors made on the short 'unexpected transfer' vignettes. No other significant correlations were evident.

Table 8: Correlations between patients' performance on executive and ToM measures

Measure:	FAS (total words generated)	DOT-A (max WM span)	Longer ToM vignette errors	'Deceptive box' vignette errors	'Unexpected transfer' vignette errors
FAS (total words generated)	x	.428† .037*	-.207 .331	-.345 .099	-.245 .248
DOT-A (max WM span)		x	-.413 .045*	-.368 .077	-.309 .142
Longer ToM vignette errors			x	.320 .128	.569 .004**
'Deceptive box' vignette errors				x	.373 .072

KEY:
Upper value = Spearman's r correlation coefficient, † Pearson's correlation coefficient
lower value = *p*-value
* significant at 0.05 level
** significant at 0.01 level

DISCUSSION

Once again, patients exhibited frontal executive dysfunction as evidenced through poorer performance on both executive tasks. In contrast to experiment 1

however, performance on the FAS test was not related to performance on the longer ToM vignettes from Apperly et al (2004). It may be that the relationship between ToM and verbal fluency is generally weak, and the executive functions such as WM could be more relevant to performance on the vignette tasks used in the current experiment.

FAS performance was found to correlate positively with scores on the other executive measure, the DOT-A. This finding is likely to reflect the involvement of the DLPFC in both of these tasks (Aleman & van't Wout, 2008; Gallard et al., 2000). Patients with PD also exhibited WM impairment, further implicating dysfunction of the DLPFC (e.g. Owen et al., 1999).

WM deficits were associated with increased errors on the longer ToM vignettes. Because WM scores only correlated with performance on longer vignettes it is likely that it was the amount of information, rather than the reasoning processes involved in the tasks, that led to errors. This conclusion is further supported by the increase in errors made on questions relating to the longer ToM vignettes in comparison to the short 'unexpected transfer' vignettes. Patients made fewest errors on the 'unexpected transfer' vignettes, the group of vignettes which contained the fewest sentences. As both of these types of vignettes were inferential and involved unexpected transfer, this difference is unlikely to be due to the style of ToM reasoning involved. The similar content of these two types of vignette is also likely to explain the significant correlation found in performance on these two tasks.

Patients made errors on the non-inferential 'deceptive box' vignettes. This finding could be considered to provide stronger evidence for a deficit in ToM than the errors made on longer ToM vignettes. However, ToM deficits provide a less parsimonious explanation for the deficits observed on these tasks than difficulties in

WM. WM dysfunction may have led to impairment on ToM tasks in an incidental manner, through comprehension difficulties. Studies such as Apperly, Samson, Carroll, Hussain and Humphreys (2006) have shown that grammatical difficulties, which can lead to poor comprehension, can directly affect ToM performance on a false belief task. It could be that poor WM compromised patients' comprehension in experiment 2 leading to the errors made on the ToM vignettes. An alternative explanation however, is that executive abilities like WM could have a more direct role in ToM processes. For example, Apperly, Samson and Humphreys (2005) suggest that ToM reasoning could be carried out in a 'generic working memory system' (pp. 573).

A further point of discussion relating to patients' performance on the longer ToM vignettes is the number of errors made in response to questions assessing counterfactual reasoning. McNamara et al. (2003) reported a counterfactual impairment in PD. This task required spontaneous generation of counterfactual thoughts, and so tested counterfactual reasoning in a less direct way. The counterfactual errors made by the patients in experiments 1 and 2 are could be more likely to reflect WM impairment rather than a counterfactual deficit. Patients made very few counterfactual errors in experiment 1, and overall performance on the Apperly et al. (2004) vignettes correlated with WM in the present experiment. The possibility that counterfactual errors on the ToM vignette task reflect a true counterfactual deficit is further weakened by the finding that patients performed almost at ceiling on the counterfactual syllogism task. This task required participants to answer a question with a logical answer based on the information contained in two short clauses, each consisting of just a few words. Accordingly, performance may have been less affected by general executive impairments such as deficits in WM. However, it is possible that patients with PD do have difficulties with counterfactual

reasoning and the inhibitory demands made by the counterfactual tasks used in this experiment were not great enough to elicit evidence of impairment.

Experiment 2 illustrated that reducing the amount of information contained in ToM vignettes (and presumably WM demands) improved performance. However, patients still made errors on false belief and memory questions in response to shorter vignettes. In experiments 1 and 2, vignettes were read twice to patients before questioning, and the information was not represented in a visual form. The WM deficits exhibited by patients with PD could have less of an impact on ToM performance when information is also presented in the visual modality and is left available throughout questioning. This possibility was investigated in Experiment 3.

2.4: PD Experiment 3

INTRODUCTION

Experiment 3 involved the investigation of patients' performance on tasks with minimal incidental WM demands. The set of ToM vignettes used were the standard (longer) unexpected transfer vignettes (Apperly et al., 2004), as WM was found to be related to performance on a selection of these vignettes in experiment 2. These vignettes were presented to patients in three different formats with different WM demands. Bibby and McDonald (2005) suggest there is evidence that as well as reducing WM load, presenting information in written as well as verbal form increases participants' attention and engages them with the task more. Visual presentation could aid patients' encoding and comprehension through the presence of pictures accompanying the story, so could lead to enhanced performance.

Experiment 3 involved 3 conditions. For condition A, false belief vignettes were simply read to participants, as in previous studies. For condition B, vignettes were also presented in the visual modality, in the form of a flip-book of cartoons, with accompanying story text. For condition C, the same cartoons and story text were used again, but were presented in the form of a comic strip, which was present throughout questioning. This condition was intended to reduce memory demands as much as possible. It was hypothesized that patients' performance would be best in condition three. Intact performance on false belief questions in this condition could indicate intact ToM.

Possible associations between performance on the ToM vignette test and three different executive tasks was investigated. Once again the FAS phonological fluency

test was used along with the DOT-A (Werheid et al., 2002) which was included to assess WM. The third executive task was a black and white Stroop test (Beck et al., in press). The Stroop tests inhibition, an executive function that has been linked to ToM reasoning in studies with children (e.g. Carlson & Moses, 2001) and patients with brain damage (e.g. Samson et al., 2005). This task was included in order to assess whether difficulties with inhibition, in addition to WM deficits, may contribute to impaired ToM performance in PD.

METHOD

PARTICIPANTS

Twenty-four outpatients with PD from the Neurosciences Department at the Queen Elizabeth Hospital, Birmingham, took part in this experiment. They were selected based on the criteria described in the procedure of experiment 1. There were 15 males and 9 females, of mean age 62.45 years (S.D. 9.81, range 41-75), with mean 13.25 years of education (S.D. 2.23, range 11-17). 10 neurologically intact controls (5 females) also completed the Stroop test. Their mean age was 56.70 years (S.D. 9.29, range 41-71), and mean years of education was 14 years (S.D. 2.22, range 11-16). Control data was needed for this new executive test but was not collected for the social cognition measures. The controls tested in experiment 1 performed at ceiling on a subset of the ToM vignettes used in this experiment.

PROCEDURE

Testing was conducted as in Experiment 1. Participants completed three executive tasks and undertook three different conditions involving ToM vignettes. These three conditions were divided by two executive tasks; the FAS Test and DOT-A. The order of administration of these two executive tasks was alternated. The black and white Stroop task was always given last. The order of the three ToM conditions (aural only, with accompanying flip-book and with accompanying cartoon strip) was counterbalanced across participants. Counterbalancing produced twelve different procedure orders, each undertaken by two participants.

TOM VIGNETTES

A larger set of twelve ToM vignettes was used (taken from Apperly et al., 2004), as described in experiment 1. These vignettes were presented in the same order to all participants. Each participant received four of the twelve vignettes in conditions A, B and C. The order of conditions was counterbalanced across participants, and each vignette appeared equally often in each condition overall.

In condition A, the vignettes were read out loud twice to each participant, with no accompanying visual representation.

In condition B, the vignettes were read twice with an accompanying flip-book. Each flip-book had four pages and featured a cartoon with corresponding story text underneath it. The first cartoon illustrated the original state (e.g. object's starting position). The second illustrated the absence of the character holding the false belief. The third picture showed an event occurring that lead to the change in location of the

object, and the final picture showed the outcome of the transfer (object's new location). The accompanying story text was in Times New Roman font size 18. The appropriate flip-book page was displayed as the story was read to the participant, and the flip-book was removed before questioning.

For condition C, a cartoon strip was displayed as the vignette was read twice to the participant, and was present throughout questioning. The same pictures and text used for flip-books were presented, but this time in the form of a comic strip. Figure 4 shows an example of a false belief comic strip used in PD experiment 3 (although in the experiment the pictures were shown in single row).

EXECUTIVE TASKS

FAS test

As described in experiment 1 (section 2.2)

DOT-A

As described in experiment 2 (section 2.3)

Figure 4. Example of a false belief vignette comic strip used in PD experiment 3. Vignette text from Apperly et al. (2004)

Black and white Stroop test

The black and white Stroop (Beck et al., in press) involved responding to two visual stimuli using "reverse rules" and is similar to other inhibitory tasks used in research with children (see Simpson & Riggs, 2009). Stimuli consisted of a page of 40 equally sized squares coloured black or white and arranged in a pseudorandom order, to form eight rows of five squares. There were two conditions; baseline and test. The baseline condition was always presented first. Participants were asked to say the colour of each square, going across each row from left to right, and not to correct any incorrect answers. The stimuli sheet was covered by a blank sheet of paper and the next row of stimuli was revealed by the experimenter on completion of the row above. For the test condition, the same stimuli sheet was turned upside-down, and participants were told to say black if they saw a white square, and say white for a black square. The rest of the procedure was identical to the baseline condition. The time taken (in seconds) to say the colour of all of squares on the sheet, and the number of errors made was recorded for each participant, for both conditions.

RESULTS

Patients did not significantly differ in age or years of education, to controls tested in experiment 1 (age: $t(37)=0.070$, $p=.944$, education: $t(37)=-0.790$, $p=.435$) experiment 2 (age: $t(34)=-0.760$ $p=.453$; education: $t(34)=105$, $p=.907$) or experiment 3 (age: $t(32)=1.583$, $p=.123$; education: $t(32)=-0.417$, $p=.679$).

TOM VIGNETTES

ToM false belief vignettes

Nine of the twenty-four patients made at least one error during the vignette test. Seven made errors on the verbal condition, while five made errors during the flip-book condition, and four made errors when responding to comic strip questions. A Friedman test, $\chi^2(2)=1.27$, $p=.529$, indicated no significant difference in the number of errors made by patients across presentation conditions. A mean of 0.38 errors were made by each patient during the flip-book (S.D. 0.9, median 0, range 0-3) and comic strip (S.D. 0.9, median 0, range 0-3) conditions. Slightly more (mean 0.54, S.D. 1.1, median 0, range 0-4) errors were made in response to verbal-only presentation, though Wilcoxon tests revealed this result was not significantly different to the number of errors produced for the flip-book, $z=-0.81$, $p=.417$, or comic strip, $z=-0.64$, $p=.522$, conditions.

As can be seen from Table 9, there was little difference in the number of false belief, counterfactual, memory and reality errors made within each condition. The number of errors made in response to each question type was also similar across conditions. When the total number of false belief, counterfactual, memory and reality errors were compared after being collapsed across conditions, a Friedman test failed to reveal any significant differences, $\chi^2(3)=5.59$, $p=.134$.

Table 9. Errors made by patients (n=24) on the ToM vignette task across presentation conditions

Presentation condition:	Verbal	Flip-book	Comic strip
False belief errors	3	1	0
Counterfactual errors	2	1	4
Memory errors	3	3	2
Reality errors	5	4	3
Total	13	9	9

Order of conditions

The influence of order of conditions (verbal, flip-book and comic strip) on performance was analysed by separating participants into independent groups using two different methods. The first method split patients according to which condition they undertook first and the second method split the group according to which condition they received last. These analyses allow the investigation of interactions between fatigue and condition type during testing, as the first condition is least likely to be affected by fatigue, whereas the last condition is more likely to be affected by fatigue. Overall however, 35.48% of errors were made in the first condition undertaken, 16.13% in the second condition, and 48.39% in the last condition (regardless of presentation condition type).

The first method divided patients into three groups of eight based on the condition they underwent first. The number of errors made in the first condition

undertaken was compared. A Kruskal Wallis test indicated no significant difference in the number of errors made in the first condition according to type (i.e. verbal, flip-book and comic strip), $\chi^2(2)=3.146$, $p=.207$.

The second method divided patients into three groups of eight based on the condition they underwent last. The number of errors made in the last condition undertaken was compared. A Kruskal Wallis test indicated a marginally significant difference in the number of errors made in the last condition according to type (i.e. verbal, flip-book and comic strip), $\chi^2(2)=6.193$, $p=.045$. As can be seen from Table 10, many more errors were made during the verbal condition when verbal presentation occurred last.

Table 10. Number of errors made in each condition of the ToM vignette task according to conditions undertaken first and last

Condition order		Verbal errors	Flip-book errors	Comic strip errors
First condition	Verbal	**0**	1	0
	Flip-book	10	**5**	3
	Comic strip	3	3	**6**
Last condition	Verbal	**10**	6	4
	Flip-book	1	**1**	3
	Comic strip	2	2	**2**

EXECUTIVE TASKS

Patient performance on the two executive tasks was compared to the performance of controls tested in experiments 1 and 2.

FAS test

Patients generated a mean of 46.29 (S.D. 15, median 49, range 20-78) words on this task. This value was not found to differ significantly from the mean 54.4 words (S.D. 16, median 47, range 30-95) produced by controls in experiment 1 , MWU=146, p=.326.

DOT-A

The mean WM manipulation span for the current patient group was 5.60 digits (S.D. 1.2, median 5.5, range 4-8). This did not differ significantly from the control mean of 5.58 digits (S.D. 0.73, median 5.5, range 4.58-7) reported in experiment 2, MWU=140.5, p=.905. As a group, the patients in the current experiment exhibited superior performance on this task to that which was expected; however, some patients did only achieve low scores on this task. Due to variation in patient performance, and as WM performance was particularly relevant to the current investigation, more detailed analysis was conducted on this measure.

As WM span ranged from 4 to 8 digits across the patient group, the group was divided according to scores on this measure. Patients were divided into two groups based on comparison of each participant's span with the group median of 5.5. Two

patients had scores equal to this median value, so these patients were excluded.The WM+ group and WM- group each contained 11 patients.

The WM+ and WM- groups differed significantly in mean words generated on the FAS test, MWU=28, p=.033. Patients in the WM- group exhibited lower scores on the FAS. The mean number of errors made by patients on the Stroop test condition also differed significantly according to group, MWU=24, p=.013. Patients in the WM+ group exhibited a lower mean number of errors on the black and white Stroop. However, there was no significant difference for Stroop times (i.e. the extra time needed to complete the inhibition versus baseline condition), MWU=45, p=.309.

Although the WM- group made more errors on the vignette test overall (Table 11), this difference was not significant, MWU=41.5, p=.171. When the two groups were examined separately to see if more errors occurred in certain conditions (i.e. verbal, flip-book or comic strip), there were no significant differences apparent for the WM+, $\chi^2(2)=1.4$, p=.497, or WM-, $\chi^2(2)=4.52$, p=.104, groups.

Table 11. Errors made on the ToM vignette test by patients with higher (WM+) and lower (WM-) working memory scores

Condition type	Group	Verbal	Flip-book	Comic strip	Total
Number of errors	WM+	2	4	6	12
	WM-	11	5	3	19
Number of patients making errors	WM+	2	2	2	3
	WM-	5	3	2	7

It was not possible to carry out within group comparisons relating to order of conditions after either of the two group splits. This was because of uneven distribution of condition orders undertaken by patients in the WM + and – groups. All of the patients that underwent the verbal condition first achieved high WM scores, and all who undertook the flip-book condition first exhibited low WM scores. These findings were due to chance.

Black and white Stroop test

Patients with PD made significantly more errors on the black and white Stroop in comparison to controls, MWU=60, *p*=.014. Patients (n=24) made a total of 44 errors (mean 1.83 per patient, S.D. 2.35, median 1, range 0-8) and the control group performed almost at ceiling (n=10) made just three errors in total (mean 0.3 per control, S.D. 0.95, median 0, range 0-3). However, patients did not show a greater effect of condition (inhibition versus baseline) during the Stroop in comparison to controls in terms of time taken, MWU=85, *p*=.186. Patients' mean time difference of 10.74 seconds (S.D. 8.37, median 9.00, range 0.86-36.29) was not significantly greater than controls' mean time difference of 6.92 seconds (S.D. 3.36, median 6.75, range 2.34-13.1).

CORRELATIONS

Analyses were conducted to identify possible relationships between patient performance on executive tasks, executive and ToM vignette performance, and time since disease onset and task performance (Table 12). Time since disease onset could be related to task performance because PD involves progressive neurodegeration.

Relationships were found between FAS score and DOT-A span, and between the number of errors made on the Stroop test condition and DOT-A score. These findings show that patients who performed poorly on one executive measure exhibited deficits on other executive tasks.

No significant correlation between WM performance and vignette errors was observed. This was surprising as this relationship was seen in previous experiments. Therefore, a further correlation was carried out between DOT-A score and vignette errors made only in the verbal condition. This was not significant, r_s=-.303, p=.150.

Table 12. Correlations for patient performance on executive and ToM tasks and time since onset of PD

Measure:	FAS Test	DOT-A	Stroop errors	Stroop times	ToM vignette errors	Time since disease onset
FAS Test	X	.598 .002**	-.030 .888	-.143 .504	-.004 .984	.008 .972
DOT-A		X	-.531 .008**	-.258 .224	-.286 .175	-.158 .460
Stroop errors			X	.352 .092	.301 .153	.358 .086
Stroop times				X	.364 .081	-.135 .529
ToM vignette errors					X	.073 . 736

KEY:
Upper value = Spearman's r correlation coefficient, lower value = *p*-value
* Significant at the 0.05 level ** Significant at the 0.01 level

DISCUSSION

Some of the findings in experiment 3 suggest that patients with PD are unlikely to exhibit deficits in ToM *per se* and that errors on the ToM vignette task are more likely to reflect executive or cognitive difficulties. For example, throughout the whole of experiment 3 patients usually made fewer errors on false belief and counterfactual questions than on memory and reality questions. Patients also made most errors on the ToM vignettes in the condition involving most WM demands (the verbal condition) and no false belief errors were made when WM demands were minimal (the comic strip condition). It is also the case that many of the patients tested in experiment 3 exhibited less evidence of executive dysfunction than patients tested in previous experiments. No overall group deficits in verbal fluency or WM were evident, and WM scores appeared higher than the PD patients tested in experiment 2. Patients with PD may only exhibit ToM deficits in association with executive dysfunction, which would explain why fewer errors were made on the ToM vignettes test by the patients tested in experiment 3 in comparison to patients tested in earlier experiments.

One finding that could weaken the above proposal is that performance on the ToM vignette task did not appear closely related to executive performance on tasks assessing WM, fluency or inhibition. The finding that there was no relationship between ToM vignette errors and WM scores was particularly surprising. This could have arisen due to the format of presentation of the ToM vignette task used in this experiment. It may be that during experiment 3, WM mechanisms were less engaged by the ToM vignette task overall due to the presence of the flip-book and comic strip during the testing session. The task as a whole should have made fewer demands on

WM resources, and patients were perhaps therefore less likely to consider that the task was a difficult memory test. This possibility was most likely when the verbal condition was given last. Interestingly, and perhaps in support of this idea, an increase in errors in the verbal condition was seen when it was given last. It could therefore be speculated that patients were less prepared for this more demanding condition when it came last, or perhaps expected the task to make fewer cognitive demands, leading to reduced activation of WM mechanisms.

An alternative explanation for the lack of a relationship between WM and vignette performance is that not all of the errors made by patients are due to deficits in WM. This proposal is supported by the observation that errors were made on ToM vignettes in experiment 3 despite the finding that the patient group did not exhibit significant deficits in WM. Furthermore, no significant difference was seen in performance on the ToM vignette test when patients were divided into two groups containing patients with high or low WM scores. Therefore, the deficits exhibited by patients with PD on ToM vignettes cannot completely be explained by the incidental WM demands made by the task. However, reducing incidental task demands (e.g. making the vignettes shorter) would not affect any WM demands that were integral to ToM.

It could be that patients with PD made errors on the ToM vignettes because they were easily cognitively fatigued. That is, they found it more difficult to attend or concentrate for shorter periods of time than neurologically intact individuals. Fluctuations in attention over time could explain why patients made errors on many tasks throughout the testing session, such as the black and white Stroop.

Counterbalancing for order was implemented. However, it is possible that the effects of fatigue could have contributed to impairment on the vignette task. Although

patients did not show a consistent pattern of producing more errors as they progressed through the testing session, the effect of fatigue may have interacted with condition. Significantly more errors were made in the verbal condition when this was given last. No such difference was apparent for the flip-book and comic-strip conditions. The verbal condition was most likely to be affected by fatigue because it made greater WM demands. The effects of fatigue may be increased in patients with PD, and particularly under conditions that demand greater attention, concentration and memory.

2.5: Social Cognition in PD: Discussion

This series of experiments showed that PD patients exhibit deficits on standard false belief vignette tasks. These errors could reflect a deficit in ToM *per se*, the impact of WM limitations on task performance, or less specific cognitive difficulties. The possibility that deficits were due to difficulties in ToM *per se* is weakened by the fact that errors were not specific to false belief and were also apparent on counterfactual and memory check questions. Errors could have resulted from WM dysfunction leading to difficulties with inferential reasoning. However, further experiments indicated these factors did not fully explain patients' poor performance. For example, in PD experiment 2 patients were shown to make errors on non-inferential vignettes and when dealing with just two sentences of aurally presented information. Similarly, errors continued to be made even when the story text and accompanying illustrations were present throughout questioning in PD experiment 3.

WM deficits are apparent in some patients with PD and could contribute to deficits in ToM. One reason why ToM deficits may result from WM dysfunction is because information in the story must be remembered in order to infer a character's perspective and make judgments about their mental state. It could also be considered that WM plays a more integral role in ToM, by providing the basis for the consideration of more than one perspective at the same time (i.e. one's own knowledge about reality and the perspective of the character that holds a false belief). This series of experiments could not determine whether false belief errors may have occurred due to an incidental role of WM in task performance, or through an integral role in ToM. Whatever the case, WM deficits cannot explain all of the errors exhibited by patients with PD on these vignettes, as patients made memory errors

when the information needed to answer the questions was in front of them and WM scores were not related to performance (experiment 3).

Another explanation for deficits on the ToM vignette test is that patients' cognitive resources are more easily fatigued than neurologically intact participants, so patients are more vulnerable to 'cognitive overload'. These effects may lead to more severe impairments under conditions that demand a certain degree of attention and concentration. Patients did however make some errors early in testing. Dysfunction of the DLPFC has been associated with poor attention and arousal, and may result in 'non specific global cognitive impairment' in PD (Berry, Nicolson, Foster, Behrmann & Sagar, 1999). At times when cognitive resources are insufficient, patients show blanking and mind wandering (Watts, McLeod & Morris, 1988). Such difficulties could affect patients' performance on both WM and ToM tasks.

Poor attention and concentration could have 'knock-on' effects on memory processes. Faglioni, Botti, Scarpa, Ferrari and Saetti (1997) studied learning and forgetting of a prose passage in PD and controls. They found patients to be 'grossly' impaired at story recall, exhibiting poor gist extraction and a peculiar pattern of forgetting indicating that retaining processes may be abnormal. These authors suggest there is evidence for widespread deficits in PD, affecting acquisition, retention and possibly retrieval. More general memory impairments are likely to lead to unspecified errors.

Despite significant deficits in performance on the false belief vignette task that required reasoning about cognitive mental states, no differences were found between patients and controls on a faux pas task that involved reasoning about both cognitive and affective mental states. One reason this was surprising is because this task is passed by older children than simpler false belief tasks (e.g. Baron-Cohen et al.,

1999). Patients demonstrated good understanding of the victim's emotional response to the protagonist's offensive remark during this task, although made less reference to the protagonist's mental state (e.g. belief that the remark would not cause) than control participants. These findings could imply that patients with PD exhibit specific difficulties with 'cool' aspects of ToM (reasoning about cognitive mental states). However, despite these differences in spontaneous responses during the task, no significant deficit was evident on the false belief check question, suggesting that it is unlikely that the patients tested exhibited fundamental deficits in reasoning about cognitive mental states. The finding that patients with PD performed poorly on the false belief vignette task but not on the faux pas task may also be in keeping with the proposal that errors reflect executive impairments, rather than a deficit in ToM *per se*. Cognitive ToM could be more vulnerable to executive dysfunction, so patients' executive difficulties could impair reasoning about false belief. However, the key question asked during the faux pas task ("did someone say something they shouldn't have?") involves affective ToM (reasoning about the victim's feelings of offence), which may not rest so heavily on executive functioning (see section 1.6).

The number of errors made by patients on these ToM vignette tasks was surprising as controls performed at ceiling on even the most difficult of the tasks. PD patients however, have exhibited impairment on seemingly straightforward tasks in other studies, making what appear to be obvious errors. For example, in a study by Zalla et al. (1998), PD patients had to order cards relating to predetermined events belonging to examples of everyday activity scripts such as making coffee and buying a newspaper. Patients made errors involving mixing up the cards for separate activities and ordered cards in a way that resulted in physical violations (the sequence did not make sense physically e.g. arriving at the destination before getting on the

plane). The authors report that in a previous experiment patients could order the components of the activity script correctly provided they were self generated. They suggest therefore, that script knowledge was intact, and that errors occurred due to poor on-line comparison with memory. It is possible that reduced cognitive resources in PD leads to poorer self monitoring. Patients seem to lack the automatic feedback needed to correct their errors but could realize their mistakes when cued appropriately. In relation to the errors made on the vignettes in the current experiment, it would be interesting to investigate whether patients would identify their mistakes if they were encouraged to evaluate their responses, perhaps after a delay to allow more time for memory consolidation.

Patients in the current experiment were always questioned immediately after the vignette was read to them. Some studies suggest that while patients perform poorly on memory tasks if tested immediately after presentation, performance can be better after a delay. Sagar et al. (1988) administered a recency discrimination task and found that non-demented, medicated PD patients exhibited a disproportionately severe deficit for shorter delays. These authors further suggest that patients with PD are often poor at any memory task soon after registration of information. Such findings could be linked to bradyphrenia (i.e. slowing of thought processes) in PD. Resource deficits may lead patients to need more time for encoding or consolidation processes. Knoke, Taylor and Saint-Cyr (1998) showed that PD patients' recall of items on the California Verbal Learning Test was worse when tested immediately as opposed to after a delay. They suggest their findings provide evidence of incomplete encoding of items for recall. However, these authors also consider that patients can also show poor use of strategies to aid encoding, poor organization of material, and impaired implicit organizational strategies. Attentional and organizational strategies for encoding and

recollection have been linked to activity in the DLPFC (Vingerhoets, Vermeule & Santens, 2005).

The use of pictures and text could improve performance related to specific WM deficits, but would not necessarily aid performance in the face of general cognitive resource deficits leading to poor attention and concentration. Maylor, Moulson, Muncer & Taylor (2002) used Happé's Strange Stories Task (1993) with groups of healthy young and old participants. The oldest participants were slower and performed more poorly on the mental state tasks, and the presence of the story failed to enhance their performance. It is possible that patients were distracted by the presence of irrelevant details in the pictures during the tasks in the current experiment. Attentional deficits could have diverted their attention to inappropriate visual stimuli while the story was being read, so performance was not enhanced. Limitations in cognitive resources may mean that patients experience greater attentional difficulties than neurologically intact individuals if distracted.

Possible inhibitory deficits are likely to have made it more difficult for patients to focus on information only relevant to the task at hand. Other studies have found evidence for impaired inhibitory processes in PD. Mari-Betta, Hayes, Machado & Hindle (2005) found increased priming effects in PD and suggested these provided evidence for poor inhibitory processes when controlling word activation while reading. However, this series of experiments found little evidence that the observed deficits were related to inhibitory difficulties. The patients tested in experiment 3 perfomed poorly on the Stroop, providing possible evidence of inhibitory dysfunction, but these deficits were not found to be related performance on the ToM vignettes. Activity in the DLPFC during the traditional Stroop task has been linked to attentional demands (Schroeter, Zysset, Wahl & von Cramon, 2004; Vanderhasselt et al., 2006a).

Deficits on the Stroop could therefore be linked to attentional rather than inhibitory problems.

Another possible explanation for the errors observed on false belief vignette tasks could be related to attentional set shifting deficits often seen in PD. Some studies have shown that poor set-shifting can be related to impairments on reasoning and problem solving tasks. For instance, Cronin-Golomb, Corkin and Growdon (1994) reported that despite intact logical reasoning, patients exhibited deficits on deductive reasoning tasks (intrusive errors and perseveration). Errors correlated with poor performance on the Wisconsin Card Sort Test leading these authors to suggest a role for set-shifting in reasoning performance. Developmental research has highlighted a link between ToM and performance on card sorting tasks. Perner, Lang and Kloo (2002) found a robust correlation between 3-6 year olds performance on a card task involving switching and ToM ability. It may be that processes involved on shifting tasks are linked to ToM because of a role for switching between perspectives in order to adopt another person's point of view and so understand their mental state.

In summary, this series of experiments has shown that the cognitive limitations associated with PD clearly have the potential to affect the ability of some patients to reason about false belief. However, the impairments observed on ToM tasks in experiments 1 to 3 probably do not reflect deficits in ToM *per se*. Instead, these deficits could arise from an inability to meet the attentional demands associated with these tasks. The evidence of possible ToM deficits as reported by other studies (Peron et al., 2009; Monetta, Grindrod & Pell, 2009) encourages further research into possible social and emotional changes in PD. The findings of experiments 1 to 3 compel the design of future investigations to take into account the significant cognitive restrictions exhibited by even some medicated, early stage patients.

CHAPTER 3. SOCIAL COGNITION IN TOURETTE'S SYNDROME

Parts of section 1, 2, 3 and 5 have been submitted as scientific articles for publication. TS experiment 1 is an edited version of an article currently in press:

Eddy, C.M., Mitchell, I.J., Beck, S.R., Cavanna, A.E. & Rickards, H. Altered Attribution of Intention in Tourette's Syndrome. *Journal of Neuropsychiatry and Clinical Neurosciences.*

3.1: Social Cognition in TS: Introduction

TS is a chronic neurodevelopmental disorder characterized by the presence of multiple motor tics and one or more phonic tics, which can be defined as sudden, semi-voluntary, repetitive, stereotyped movements and vocalizations (DSM-IV^{TR}: American Psychiatric Association, 2000). While little is known about the pathophysiology of tic expression, converging lines of evidence suggest that tics are likely to be associated with striatal dysfunction (Albin & Mink, 2006; Singer, 2005). Changes in striatal functioning could affect abilities reliant on the functioning of the frontal cortex, such as social cognition, through dysfunction within frontostriatal pathways (Alexander et al., 1986; Middleton and Strick, 2000).

Involuntary tic-related symptoms include uttering offensive language (coprolalia) and comorbid psychiatric disorders including OCD and ADHD are common (Cavanna et al., 2009; Leckman, 2002; Robertson, 2000). Many patients also exhibit non-obscene socially inappropriate symptoms (NOSIS). A study carried out by Kurlan et al. (1996) found that some patients with TS experienced urges to act in a socially inappropriate way (22%) or make socially inappropriate remarks including insults (30%). Failure to suppress these urges sometimes results in major social difficulties, including physical confrontation and arrest.

A number of clinical studies involving other patient groups (Lough et al., 2006; Shamay-Tsoory, Tomer, Berger & Aharon-Peretz, 2003) have shown that individuals who exhibit problematic social interaction also demonstrate impairment on tasks involving ToM. For example, socially inappropriate remarks can be made due to a failure to consider the likely emotional response of the listener to such

remarks. Therefore, given the social problems associated with TS, it is possible that patients have deficits in ToM.

Impairments in ToM have been linked to deficits in the understanding of non-literal language such as sarcasm or metaphor (Channon, Pellijeff & Rule, 2005; Channon et al., 2007; Dennis, Lazenby & Lockyer, 2001; Happé, 1993; Shamay-Tsoory, Tomer & Aharon-Peretz, 2002; Winner, Brownell, Happé, Blum & Pincus, 1998). There is also evidence that brain regions linked to ToM, such as the temporal poles, superior temporal sulcus, medial prefrontal cortex and IFG, are active in neurologically intact participants during sarcasm comprehension (Uchiyama et al., 2006). These findings are likely to indicate that accurate interpretation of a non-literal remark requires an appreciation of the speaker's mental state. The speaker of a sarcastic remark for example, often means the opposite of what they say, and this is not directly conveyed through their use of language. One study (Channon et al., 2004) involving patients with uncomplicated TS (i.e. motor and phonic tics only, with no associated behavioural problems or comorbidities) assessed patients' performance on two tasks involving ToM that contained examples of non-literal language. No deficits were evident on these tasks. However, this could reflect either a small sample size or lack of sensitivity in the measures used.

Patients with TS could exhibit poor performance on tasks involving ToM due to inhibitory dysfunction. Patients with uncomplicated TS exhibit inhibitory deficits on the Hayling task (Burgess & Shallice, 1996), as shown by a number of studies (Channon, Pratt & Robertson, 2003; Channon et al., 2004; Channon et al., 2006). Evidence of inhibitory dysfunction in TS prompts the investigation of ToM because appreciating another's mental state often requires inhibition of one's own perspective. Developmental and clinical studies have found links between performance on ToM

tasks and inhibitory tasks (see section 1.6). There is also evidence that the same inhibitory processes recruited during executive tasks contribute to performance on ToM tasks (Saxe et al., 2006).

Taken together, the evidence of inhibitory deficits and social difficulties exhibited by patients with TS suggest that patients may exhibit deficits in ToM. The experiments contained in this chapter investigated ToM in patients with TS. The findings of experiments 1 and 2 led to the administration of a range of reasoning tasks in experiment 3 that were linked to a common neurological substrate. Patients with TS appear to exhibit changes in ToM processes that lead to performance deficits on a variety of tasks, and which could indicate dysfunction within specific CSTCCs (described by Alexander et al., 1986).

Section 2. TS Experiment 1

INTRODUCTION

Experiment 1 involved the investigation of ToM in patients with TS using two tasks. One of these was a false belief vignette task which involved 'unexpected transfer' (section 1.6). This task contained a false belief question, memory questions, and a counterfactual question, which required reasoning about where an object would be if it had not been moved (see section 2.2, PD experiment 1). This false belief task assessed cognitive (or 'cool') ToM. The other ToM task administered involved the understanding of faux pas (see section 1.6). Understanding faux pas is likely to make more complex reasoning demands than a first order false belief task and involves both reasoning about cognitive ('cool' ToM) and affective ('hot' ToM) mental states. In addition to understanding the perpetrator's false belief (the remark is inoffensive), understanding faux pas may require an appreciation of the victim's negative emotional response (offence), and comprehension of the perpetrator's belief about the victim's mental state, which involves second-order ToM. Reasoning about faux pas could also involve knowledge about conventionally acceptable social behaviour. This kind of task may be particularly sensitive to any changes in ToM in patients with TS in light of NOSIS, which often involve the uttering of contextually specific socially inappropriate remarks.

As performance on ToM tasks can be related to executive functioning (e.g. Carlson et al., 2002) two executive tasks were administered. These tasks assessed WM (Digit Ordering Test-Adapted: Werheid et al., 2002) and inhibition (Hayling test: Burgess & Shallice, 1996), as these executive functions are often related to

performance on ToM tasks (Gordon & Olson, 1998; Samson et al., 2005). The Hayling test may be sensitive to TS because it involves inhibition of a prepotent verbal response, and Channon et al. (2004) have suggested that deficits on this task could be linked to some patients' failure to suppress the urge to utter socially inappropriate language.

METHOD

PARTICIPANTS

Sixteen outpatients with TS (3 females) of mean age 32.06 years (S.D. 13.52, range 17-61) and mean education 12.94 (S.D. 3.19, range 10-17) years were recruited from the TS clinic, Queen Elizabeth Psychiatric Hospital, Birmingham. Each subject was diagnosed with TS according to DSMIV^{TR} criteria. Four exhibited comorbid OCD, two of whom had ADHD, and one an anxiety disorder. Seven patients were taking medication for tics (3 Risperidone, 2 Ariprazole, 1 Sulpiride & 1 Pimozide). Eight healthy controls (3 females) of mean age 34.25 years (S.D. 10.15, range 24-47) with mean education 14.63 years (S.D. 1.85, range 12-17) also participated.

PROCEDURE

All patients were tested in a consultation room after neuropsychiatric consultation at the Tourette clinic, Queen Elizabeth Psychiatric Hospital, while controls were tested at the University of Birmingham or in their own home.

Participants gave informed consent after reading information leaflets about the study. They were fully debriefed after testing which usually took between 30 and 40 minutes.

Tasks were separated into two blocks containing the executive and ToM tasks. The order of tasks was alternated within these two blocks. Executive tasks were always presented first. This resulted in four procedure orders.

TOM TASKS

ToM vignettes

Participants were read four 'unexpected transfer' style vignettes (see section 2.2, PD experiment 1 method) devised by Apperly et al. (2004).

Faux Pas task

This task was taken from Baron-Cohen et al. (1999) and is described in PD experiment 1 method.

EXECUTIVE TASKS

Hayling Sentence Completion Task (adapted)

This test comprised two parts. For each part of the test, ten sentences were read one by one to the participant. They were told to complete each sentence with a

single word. Some sentences were taken from Burgess and Shallice's (1996) study and some were developed for this experiment. For part A, initiation, participants were instructed to complete the sentences with obvious words that fitted the sentence. Part B, inhibition, required the suppression of a more obvious word strongly primed by the cue sentence (suitable answers to part A). However, for part B, participants were told the word should still make sense, but it must not be the most obvious word and something more unusual. These modified task instructions prevented participants from using a simple strategy (e.g. responding with the names of objects in the test room), because their responses needed to remain contextually appropriate, and were intended to result in a more sensitive test of inhibitory ability.

Participants completed two practice sentences before each set of ten test sentences to check their understanding of the instructions. The sentences used in each part were constant across participants. The time taken to respond to each sentence in part B was measured with a stopwatch. Incorrect responses for part A were words that did not make sense. Incorrect words for part B were words that made sense but were too obvious or conventional (ie. words that would be correct for part A) or words that made no sense in relation to the sentence.

DOT-A

This WM task was taken from Werheid et al., 2002, and was administered as described in PD experiment 2 (section 2.3). Scores reflected the number of digits presented in pseudorandom order that could be correctly recalled in ascending order.

RESULTS

Patients and controls did not differ signifcantly for age, $t(22)=-0.40$, $p=.691$, or years of education, $t(22)=-1.38$, $p=.183$.

TOM TASKS

ToM vignettes

Patients with TS made an average of 0.56 errors (S.D. 0.89, median 0, range 0-2) on the standard false belief vignettes (Table 13). Although controls performed at ceiling, this difference was not statistically significant, MWU=44, $p=.083$. Patients only made errors on counterfactual (2), memory (1) and reality (6) questions, providing no evidence for a deficit in false-belief.

Faux pas task

Patients were significantly poorer than controls at recognizing faux pas, MWU=58, $p=.017$. Patients made an average of 1.19 (S.D. 1.11, median 1, range 0-4) errors in comparison to controls, who made an average of 0.25 (S.D. 0.46, median 0, range 0-1) errors on the faux pas recognition question. Patients made nine recognition errors on test scenarios (omissions) and ten errors on control scenarios (false alarms). However, patients' recall of factual information contained in the vignettes was not significantly different, MWU=61, $p=.843$. Patients made a mean of 0.88 errors on fact

recall checks (S.D. 0.81, median 1, range 0-2) in comparison to controls, who made a mean of 0.75 (S.D. 0.71, median 1, range 0-2) errors.

Patients with TS performed at ceiling on the desire\belief check during the faux pas test, and controls made just one error overall. In contrast, significantly more errors (see Table 13) were made by patients than controls on faux pas false belief questions, MWU=30, p=.021. Patients made mean 1.06 errors (S.D. 1.00, median 1, range 0-3) in comparison to controls, who made mean 0.125 (S.D. 0.35, median 0, range 0-1) errors. These errors were even made by patients on occasions when they identified faux pas. When failing to attribute a false belief to the perpetrator, patients often inferred the offensive remark was intentional. In such cases, explanations for the faux pas remark included anger or jealousy. Patients also attributed negative personality traits to the protagonist and described them as 'nasty', 'mean', 'a bitch', or 'sarcastic'.

Table 13. Patient and Control Performance on the ToM measures

ToM measure	Patients with TS (n=16)		Controls (n=8)	
	% incorrect	Errors / total possible	% incorrect	Errors / total possible
ToM vignettes (all errors)	7.03	9/256	0	0/128
Faux pas task:				
Recognition errors	14.84	19/128	3.13	2/64
False belief errors	26.56	17/64	3.13	1/32
Fact recall errors	10.94	14/128	9.34	6/64

EXECUTIVE TASKS

Hayling task

Controls performed at ceiling on the Hayling task while 6 patients made a total of 9 errors (mean 0.56, S.D. 0.89, median 0, range 0-3), but this difference did not quite reach statistical significance, MWU=40, *p*=.052. However, patients took significantly longer than controls to respond to inhibitory items, MWU=13, *p*=.005, indicating possible inhibitory dysfunction. Patients took a mean of 4.40 seconds per item (S.D. 2.60, median 3.93, range 1.9-10.52) whereas controls took mean 2.14 second (S.D. 0.57, median 1.94, range 1.48-3.15).

DOT-A

There was no significant difference between patients' and controls' performance on the DOT-A, MWU=54.5, *p*=.548. Patients' mean manipulation digit span was 6.22 (S.D. 1.02, median 6, range 4.5-8) and controls' mean span was 6.31 (S.D. 0.26, median 6.5, range 6-6.5).

COMORBIDITY ANALYSIS

Patients with TS often exhibit comorbid conditions such as ADHD and OCD which could be related to impairments in task performance. To investigate whether the deficits with TS were associated with comorbid disorders, 4 patients who exhibited OCD or OCD and ADHD were removed and analysis of task performance

was reconducted. This smaller group of patients performed significantly more poorly than controls on the faux pas test, MWU=20, p=0.020, and for times on the Hayling task, MWU=10, p=0.012. The difference for Hayling errors, MWU=24, p=0.022, and errors on the ToM vignette test also became significant, MWU=28, p=0.041.

CORRELATIONS

No significant correlations were evident for patients' performance on the executive and ToM measures (Table 14).

Table 14. Correlations for patient performance on the executive and ToM measures

Measure	Faux pas recognition errors	ToM vignette errors (all)	DOT-A scores	Hayling task part B errors	Hayling task part B times
Faux pas recognition errors	X	.324 .222	-.132 .626	.279 .356	.279 .356
ToM vignette errors (all)		X	-.117 .667	.260 .331	-.156 .612
DOT-A scores			X	.253 .345	-.126 .681
Hayling task part B errors				X	-.028 .927

KEY:
Upper value = Spearman's r correlation coefficient, lower value = *p*-value
* Significant at the 0.05 level ** Significant at the 0.01 level

It may be noted that some of these differences would not be considered significant if adjustments for multiple comparisons were applied to the results. However, such corrections were considered too stringent, as small sample sizes and the use of non-parametric tests would have increased the likelihood of making a Type II error. Therefore, throughout this thesis, any findings with a p-value below 0.05 were considered to be significant.

DISCUSSION

Patients with TS made errors on ToM tasks despite unimpaired WM and accurate recall of factual information contained in the vignettes. Therefore, the errors made by patients on ToM questions were not due to poor memory or comprehension difficulties (unlike those made by patients with PD reported in chapter 2). Significant deficits were apparent during the faux pas task. Patients often failed to recognize the protagonist's false belief (the remark was not offensive) and so inappropriately assumed the faux pas was intentional. Similar deficits are exhibited by patients with frontal-variant frontotemporal dementia (Gregory et al., 2002). This pattern of deficits was not associated with the presence of OCD or inhibitory problems as shown by the Hayling task. The latter finding could indicate that patients with TS exhibit deficits in ToM that are independent of executive difficulties. However, further research should investigate this possibility using different inhibitory tasks.

Patients performed more normally on the false belief task that involved cognitive ('cool') ToM, despite deficits on the faux pas task which involved affective ('hot') and cognitive ToM. However, patients did not exhibit a straightforward

specific deficit with affective ToM. For example, belief (cognitive ToM) errors were apparent on the faux pas task. It may be that patients failed to understand the false belief of the protagonist on the faux pas task because it involved the attribution of intentions to the protagonist. Thus, patients' difficulties may not reflect a deficit in ToM competence, but rather a difference in application, whereby patients are capable of understanding other's beliefs but apply ToM reasoning differently in certain social situations. Developmental research shows that when belief and outcome information conflict adults' judgments are determined primarily by the belief. By contrast, young children often fail to integrate beliefs and intentions and make judgments based on outcome alone (Young & Saxe, 2008). Negative consequences therefore lead to negative attributions about the actor, regardless of whether the outcome was intended. Patients with TS could therefore have reasoned differently about the protagonist's belief during the faux pas task because it was in conflict with the consequences of the inappropriate remark. Reasoning about beliefs may be more cognitively demanding in comparison to reasoning based on consequences, as the former involves inferential reasoning. As discussed in chapter 2, inferential reasoning appears to draw on cognitive resources including executive functions (e.g. Monetta, Grindrod & Pell, 2008). It could be that frontostriatal dysfunction in TS reduces patients' cognitive resources, leading to difficulties with the cognitively demanding task of reasoning about beliefs relative to reasoning based on consequences.

Future research should aim to further specify the nature and basis of patients' differences in social reasoning. Orbitofrontal, medial prefrontal and anterior paracingulate activity has been linked to reasoning about other's intentions during social interactions (Blakemore et al., 2007; Rushworth, Behrens, Rudebeck & Walton, 2007). These regions are also active when processing first/third person perspective

and transgressions of social norms, along with the ACC,temporal poles and precuneus (Cavanna & Trimble, 2006). Activity in these regions varies depending on whether transgressions are considered intentional or unintentional (Berthoz, Armony, Blair & Dolan, 2002). Changes in these brain regions could be associated with alterations in the attribution of intentions in TS.

Overall, these findings suggest that social difficulties could arise in TS from a lack of understanding of the intentionality of social actions. The possibility that patients with TS may exhibit poor performance on other tasks involving ToM and reasoning about social intentions was investigated in experiment 2.

3.3: TS Experiment 2

INTRODUCTION

In experiment 1, patients with TS performed poorly on a faux pas task. This task required the identification of a remark made by one story character that could cause offense to another character. Errors made by patients included failure to recognize faux pas, mistakenly inferring faux pas had occurred when this was not the case and incorrect inferences that an offensive remark was made intentionally. These deficits are likely to reflect changes in ToM.

It is possible that patients with TS find other aspects of ToM difficult. For example, difficulty reasoning about social intentions could be related to poor comprehension of non-literal language, because understanding a speaker's communicative intention may be important for the interpretation of their non-literal remark. Deficits in ToM have been associated with poor comprehension of non-literal language in patients with brain damage (e.g. Channon et al., 2005) and the brain regions activated during ToM tasks are also active during the processing of sarcasm (Uchiyama et al., 2006).

Accurate interpretation of the meaning of non-literal language requires consideration of the speaker's belief or emotion, or intent to communicate in a non-literal way. These factors are not directly expressed by the words contained in their remark. ToM can aid the comprehension of sarcasm through an understanding of the negative affective state of the speaker, as this kind of non-literal utterance often expresses criticism or disapproval. Consideration of this affective state should aid rejection of the literal interpretation of the utterance which is the opposite of that

which the speaker believes or intends to convey. The interpretation of metaphor could be aided by appreciation of the speaker's intent to use language in a symbolic manner to represent a belief or emotion, while the understanding the meaning of an indirect request also requires the listener to infer the speaker's true desire or intention. Non-literal remarks occur frequently during everyday social interaction, so poor comprehension of non-literal language could have a significant impact on patients' social functioning.

Only one previous study of patients with TS included tasks featuring non-literal language. Channon and colleagues (2004) assessed the performance of fifteen patients with uncomplicated TS on tasks that included some stories containing examples of sarcasm and lies. No impairments were reported on these two short tasks, though it may be premature to conclude that patients have no difficulties in processing non-literal language in light of other evidence indicating changes in ToM in TS (experiment 1).

Evidence of possible inhibitory dysfunction in TS in experiment 1 (and in other studies: Channon et al., 2004; Channon et al., 2006; Crawford et al., 2005) further prompts the investigation of the comprehension of non-literal language in TS. Inhibitory dysfunction can impair the understanding of non-literal language either directly, through a failure to inhibit automatically activated literal meanings (see Grice, 1975; 1978), or indirectly, through deficits in ToM, because appreciation of another's mental state may involve the inhibition of one's own perspective of the world (Samson et al., 2005). Other patient groups who exhibit executive impairment as a result of frontostriatal dysfunction (patients with HD or PD) perform poorly on tasks involving non-literal language (Chenery, Copland & Murdoch, 2002; Monnetta & Pell, 2007).

In experiment 2, the comprehension of non-literal language was investigated in patients with TS using tasks featuring sarcastic and metaphorical remarks (Langdon and Coltheart, 2004) and indirect requests (Cocoron, Mercer and Frith, 1995). Patients also completed the faux pas test (Baron-Cohen et al., 1999) that had previously indicated impairment in TS (experiment 1) in order to investigate possible relationships between the understanding of non-literal language and ToM. Two inhibitory measures were administered: a black and white Stroop (Beck et al., in press) and the Hayling task (Burgess and Shallice, 1996). The inclusion of these tasks allowed relationships between inhibition and ToM to be investigated.

METHOD

PARTICIPANTS

15 participants (8 females) with TS were recruited as described in experiment 1. Patients with TS were of mean age 25.67 (S.D. 11.71, range 17-54) years, and they had an average of 13 (S.D. 1, range 12-15) years of education. Six exhibited comorbid OCD, and one of these also had ADHD. Another patient exhibited TS and comorbid ADHD without OCD. 5 patients were taking medication for tics (4 Risperidone, 1 Haloperidol). 10 healthy controls (3 females), matched as a group for age (mean 24.70, S.D. 7.60, range 17-41) and years of education (mean 13.4, S.D. 1.78, range 11-16) also took part. None of the participants tested took part in experiment 1.

PROCEDURE

Testing was conducted as described in the procedure of TS experiment 1. All participants undertook 5 tasks in the following order; Hayling task, faux pas task, black and white Stroop and then alternating vignettes from the Hinting task (which featured indirect requests) and Pragmatic Story Comprehension Task (which included sarcastic and metaphorical remarks). These tasks were administered in a set order because this experiment investigated differences in performance between the patient groups rather than across the tasks.

NON-LITERAL LANGUAGE TASKS

All vignettes were presented on paper in black ink, font Size 18. Participants were asked to read each vignette carefully and indicate when they had done so. They were then questioned by the experimenter who recorded their responses. The appropriate vignette remained in view during questioning. The order of presentation of vignettes within each task was in a fixed order.

The Hinting Task

This task consisted of four vignettes which described short social scenarios involving two characters (developed by Corcoran, Mercer & Frith, 1995). Each vignette ended with a remark made by one of the two characters, which should be correctly interpreted as an indirect request. For example: "Melissa goes to the bathroom for a shower. Anne has just had a bath. Melissa notices the bath is dirty. She

calls downstairs to Anne "Couldn't you find the bleach Anne?" Participants were first asked what the character meant by his or her remark, and then what that character wanted the other character to do. Correct responses required an inferential and appropriate non-literal interpretation identifying the speaker's hint (e.g. Melissa wanted Anne to clean the bath).

The Pragmatic Story Comprehension Task

This task contained four vignettes taken from Langdon and Coltheart (2004). They describe social scenarios involving two characters, and end with a list of four possible remarks that could be spoken by one of the characters in response to a behaviour exhibited by the other character. The questions used in this experiment asked the participant to decide which of these remarks would make sense; what the character would mean if they said them, and if there were any remarks that did not make sense. Three of the remarks made sense relating to the story context: one was literally appropriate, one was appropriate if interpreted as sarcasm and another was an appropriate use of figurative language (metaphorical). The remaining statement did not make sense. For example: "Mr. Jones is a very generous man. He has donated $10,000 to the local hospital. When he tells his friend Peter what he had done, Peter says... 1. "How generous!" [literal] 2. "What a miser!" [sarcastic] 3. "You've got big pockets!" [metaphorical] 4. "You keep pulling the shutters down" [nonsense].

The four remarks were presented in a counterbalanced order across the stories. The vignettes consisted of two pairs. Within these two pairs two of the four possible remarks were the same; however, depending on the story they could be interpreted appropriately as literal or sarcastic (i.e. the appropriate literal and sarcastic remarks

were reversed). The vignettes appeared in a fixed order for each participant. Presentation of these vignettes alternated with presentation of the four vignettes from the Hinting task.

TOM: FAUX PAS TASK

As described in section 2.2 (PD experiment 1 method).

INHIBITORY MEASURES

Hayling Sentence Completion Test - adapted

As described in TS experiment 1.

Black and white Stroop test

As described in section 2.4 (PD experiment 3).

RESULTS

Patients with TS and controls did not differ in age, $t(23)=0.23$, $p=.820$, or years of education, $t(23)=-0.72$, $p=.478$. One patient with TS did not complete the faux pas and Hayling tasks.

NON-LITERAL LANGUAGE TASKS

Controls performed at ceiling on the Hinting task while the patient group made three errors (mean 0.2, S.D. 4.14, median 0, range 0-1), a difference that was not significant, MWU=60, p=.140. Patients appeared to exhibit little difficulty in the understanding of indirect requests.

In contrast, patients (n=15) demonstrated a significant impairment on the Pragmatic Story Comprehension Task, MWU=12.5, p<.001. Patients made a total of thirty-six errors (mean 2.4, S.D. 1.72, median 2, range 0-6) while controls (n=10) made just one error (mean 0.1, S.D. 0.32, median 0, range 0-1) overall. Errors were made by patients for all trial types, indicating errors in judging the appropriateness of sarcastic, metaphorical, literal and nonsense remarks. When comparing the number of errors made by patients in response to the four remark types, pair-wise comparisons indicated that patients exhibited a significant deficit in the detection of appropriate use of sarcasm, MWU=20, p=.001. Patients also made considerably more errors than controls in detecting the appropriate use of metaphor (Table 15), and this difference reached borderline significance, MWU=46, p=.051. Patients were not significantly poorer at detecting appropriate literal remarks, MWU=55, p=.082, or rejecting inappropriate nonsense statements, MWU=55, p=.082. It was also noted that while control participants always correctly described the speaker's intended meaning in their own words, when patients with TS had correctly identified a contextually appropriate remark they sometimes gave a poor explanation of its meaning. Misinterpretations included the classification of literal and metaphorical remarks as sarcastic, as well as literal interpretations of non-literal language.

Table 15. Errors made by patients (n=15) on different trial types during the Pragmatic Story Comprehension Task

Trial type:	Sarcasm detection	Metaphor detection	Literal detection	Inappropriate rejection
Total errors	15	11	5	5
Number of patients who made errors	11	7	4	4
% incorrect responses	25	18.33	8.33	8.33

TOM: FAUX PAS TASK

As can be seen from Table 16, the control group made only one error when detecting whether faux pas had occurred (mean 0.1, S.D. 0, median 0, range 0-1). Patients' total of 16 errors, a mean of 1.07 (S.D. 1.17, median 1, range 0-4), was significantly greater, MWU=29.5, p=.008. When test and control scenarios were considered separately, patients made mean 0.6 errors (S.D. 1.08, median 0, range 0-4) and were found to perform significantly more poorly than controls on test vignettes, MWU=40, p=.020. Patients made more errors (mean 0.47, S.D. 0.65, median 0, range 0-2) on control vignettes than control participants (mean 0.1, S.D. 0.32, median 0, range 0-1 errors), but this difference was not significant, MWU=46.5, p=.083.

Controls performed at ceiling and patients (mean 0.13, S.D. 0.35, median 0, range 0-1 errors) almost performed at ceiling for story recall checks. No difference in performance was evident, MWU=58, p=.265. Patients made four errors (mean 0.27, S.D. 0.70, median 0, range 0-2) in total on desire\belief checks, while controls

performed at ceiling. This difference was not significant, MWU=65, p=.238). Patients (mean 0.33, S.D. 0.62, median 0, range 0-2 errors) did not perform more poorly than controls (mean 0.6, S.D. 0.699, median 0, range 0-2 errors) on belief check questions, MWU=65, *p*=.238.

Table 16. Errors made by patients and controls on the faux pas task

Error type	Patients with TS (n=15)		Controls (n=10)	
	% incorrect	Errors / total possible	% incorrect	Errors / total possible
Recognition errors:				
All	14.55	16/110	1.25	1/80
Test vignettes (omissions)	15	9/60	0	0/40
Control vignettes (false alarms)	11.67	7/60	2.5	1/40
False belief errors:	8.33	5/60	15	6/40
Fact recall errors:	1.82	2/110	0	0/80

INHIBITORY MEASURES

Hayling task

The control group performed at ceiling on the Hayling task while patients made a total of three errors (mean 0.2, S.D. 0.43, median 0, range 0-1), a difference

that was not significant, MWU=55, *p*=.126. On average, patients (mean 1.84 seconds, S.D. 3.57, median 1.64, range 0.79-3.91), exhibited a greater increase in response latency for each inhibition trial in relation to baseline when compared to controls (mean 1.13 seconds, S.D. 0.5, median 1.07, range 0.53-2.10). This marginally significant difference, MWU=36, *p*=.046, may indicate evidence of mild inhibitory dysfunction.

Black and white Stroop

Patients with TS made 30 errors (mean 2, S.D. 2.67, median 0, range 1-8) on the black and white Stroop interference condition in comparison to controls who made 6 (mean 0.6, S.D. 0.84, median 0, range 0-2). This difference was not significant MWU=55, *p*=.229. Patients showed a greater increase in response latency (mean 7.33 seconds, S.D. 0.92, median 6.84, range 1.2-16.03) from baseline to the interference condition in comparison to controls (mean 5.13 seconds, S.D. 1.05, median 5.36, range 3.2-6.7). This difference only approached significance, MWU=40.5, *p*=.056.

COMORBIDITY ANALYSIS

It is possible that deficits in task performance exhibited by patients with TS reflect the influence of comorbid disorders. Because six of the patients tested in this study exhibited comorbid OCD, further analysis addressed this possibility by separately comparing the performance of patients with TS and OCD, and TS without OCD, to that of controls. These comparisons were carried out for the measures that elicited evidence of impairment in the patient group as a whole.

When patients with TS and no OCD (n=9) were compared to controls, the differences in performance found for the patient group as a whole remained significant. Patients without OCD made significantly more errors than controls on the Pragmatic Story Comprehension Task, MWU=6.5, *p*=.001, and the faux pas task, MWU=12, *p*=.004, and showed an increased effect of inhibition in comparison to baseline as reflected in time differences on the Hayling task, MWU=p=12, *p*=.013.

The performance of patients with TS and comorbid OCD (n=6) was also compared to the control group. Despite the fact that power was low due to the small number of patients exhibiting comorbid OCD, this group performed significantly more poorly on the Pragmatic Story Comprehension Task in comparison to controls, MWU=6, *p*=.003. These patients did not perform more poorly on the faux pas task, MWU=17.5, *p*=.073, but no significant difference for Hayling times, MWU=24, *p*=.515.

CORRELATIONS

Correlations were conducted to identify relationships between patients' performance on the tasks administered (Table 17). Calculations did not include errors made on the Hayling task or Hinting task as there were so few. A significant positive relationship was seen between errors and time differences on the black and white Stroop, indicating that patients who made more errors took more additional time to complete the inhibition condition (in comparison to baseline). A significant negative relationship was also present between time differences on the Hayling test and black and white Stroop. Patients who responded more slowly to inhibitory items on the Hayling test (i.e. showed a greater increase in time for the inhibitory condition to

baseline) took less time to complete the inhibitory condition of the black and white Stroop. This unexpected negative relationship may reflect differences between the tasks. The Stroop involved two possible responses, whereas the Hayling involved generation of a contextually appropriate word that was not the obvious word cued by the sentence. Therefore, patients with inhibitory difficulties appear to respond more quickly on the Stroop (and give inaccurate prepotent responses) and more slowly on the Hayling test because they found it difficult to inhibit the word cued by the sentence.

Table 17. Correlations for patient performance on executive and ToM measures

Measure:	Faux pas recognition errors	Pragmatic story comprehension task errors	Stroop errors	Stroop time difference	Hayling task time difference
Faux pas recognition errors	X	.182 .533	.221 .447	-.041 .888	.228 .433
Pragmatic story comprehension task errors		X	.169 .547	-.102 .718	.117 .691
Stroop errors			X	.537 .039*	-.251 .388
Stroop time difference				X	-.657 .011*

KEY:
Upper value = Spearman's r correlation coefficient, lower value = *p*-value
* Significant at the 0.05 level
** Significant at the 0.01 level

DISCUSSION

Performance on the Pragmatic Story Comprehension Task indicated a profound deficit in the comprehension of non-literal language in patients with TS. On many occasions when patients read non-literal remarks they decided that the statements did not make sense. Patients failed to detect the use of appropriate metaphorical remarks on quite a few occasions. Their greatest impairment, however, was in the detection of the contextually appropriate use of sarcasm. This deficit was despite accurate comprehension of indirect requests, as revealed by intact performance on the Hinting test. The Pragmatic Story Comprehension Task may have been a more sensitive test than the Hinting test, which simply required patients to interpret non-literal utterances. During the Pragmatic Story Comprehension Task, patients had to first recognize and select sarcastic and metaphorical remarks that would make sense based on the story context before justifying their selection. The difference in performance on these two tasks could reflect the questioning procedure. That is, there is likely to have been a greater margin for error on the Pragmatic Comprehension Story Task where patients were free to decide that the remarks did not make sense.

Changes in ToM are exhibited by patients with TS as indicated by impaired performance on the faux pas task (as seen in experiment 1). Errors included both failures to detect faux pas and occasions where patients suggested that an inappropriate remark had been made in control vignettes containing no faux pas. This pattern of impairment has been previously reported in patients with frontal-variant frontotemporal dementia (Gregory et al., 2002) in addition to experiment 1. While failure to detect faux pas could indicate reduced sensitivity to socially inappropriate

behavior in TS, such impairments do not adequately explain instances where patients thought an offensive remark had been made when this was not the case. This kind of error suggests that while patients are mindful of the fact that inappropriate social behaviour can occur, their judgment of what is socially appropriate differs to that of controls. Other changes in reasoning about social exchanges may have contributed to patients' unconventional interpretations of characters behaviour in control scenarios. For example, patients could have a tendency to assume that behaviours that result in negative consequences are always made with negative intent.

Patients with TS exhibited a mild deficit in the inhibition of prepotent verbal responses during the Hayling task (as found by Channon et al., 2004; Channon et al., 2006) which could indicate dysfunction of the ACC (Nathaniel-James et al., 1997; Rubia et al., 2001). Difficulties in inhibition could lead to poor performance on the Pragmatic Story Comprehension Task, through poor inhibition of the literal meaning of non-literal remarks. It is also possible that inhibitory deficits led to impairments on both the Pragmatic Story Comprehension Task and faux pas task through difficulties with ToM. Failure to inhibit one's own perspective may impair ToM (Samson et al., 2005), which in turn could have led to difficulties understanding the speaker's intent to use non-literal language during the Pragmatic Story Comprehension Task and the victim's feelings of offense during the faux pas task. However, the present study found no evidence that inhibitory performance was related to patients' impairments on these tasks. Although some of the patients' errors on the Pragmatic Story Comprehension Task were associated with literal interpretations which could be related to a failure to inhibit literal meanings, other errors were not, such as instances when patients described metaphorical remarks as sarcastic.

One possible explanation for patients' deficits on the Pragmatic Story Comprehension Task and faux pas task could be the involvement of both cognitive and affective mental states (i.e. 'hot' and 'cool' ToM). Difficulties dealing with conflicting cognitive (e.g. beliefs) and affective (e.g. emotions) mental states could also contribute to poor comprehension of non-literal language. For example, a speaker can make a remark which has a literal meaning that is in direct conflict with their feeling, as often in the case of sarcasm. The faux pas task involves consideration of both the victim's emotional reaction (affective mental state) and the protagonist's belief and lack of intent to offend (cognitive mental states). Shamay-Tsoory, Tomer, Yaniv and Aharon-Peretz (2002) reported deficits on a faux pas task in people with Asperger syndrome and suggested these impairments reflected poor integration of cognitive and affective mental states. This is likely to reflect dysfunction of right VMPFC (Shamay-Tsoory et al., 2003). Some errors made by patients with TS, such as failure to recognize faux pas, may simply reflect poor consideration of the victim's likely emotional response to the protagonist's remark. However, reasoning about both cognitive and affective mental states, particularly when these are in conflict (i.e. the protagonist's lack of intent to offend versus the victim's feeling of offence) should make greater cognitive demands and so is more likely to have elicited impairment.

Despite the possibility that changes in ToM in TS could contribute to patients' poor comprehension of non-literal language, no correlation was apparent between patients' performance on the faux pas task and Pragmatic Story Comprehension Task. Relationships between performance on ToM and non-literal language measures could be stronger if the non-literal language task administered is richer in ToM cues. For example, auditory cues such as vocal tone may aid the understanding of the affective mental state of the speaker. The task used in the present study did not involve such

cues and interpretation of the speaker's mental state relied upon situational context. However, while these cues tend to enhance appreciation of speaker attitude, they may not be sufficient to lead to the successful comprehension of non-literal language. Demorest, Meyer, Phelps, Gardner and Winner (1984) suggest that an understanding of the speaker's desire or intent to play with language is most critical. McDonald (1999) however, suggests processes such as counterfactual reasoning are needed in order to reconcile the facts about the situation with the mental state of the speaker, as sarcasm involves an appreciation that the speaker's remark can be counter to what they actually feel or think. Future research could investigate patients' performance on standard counterfactual reasoning tasks (e.g. Mandel, 2003).

Some of the errors made by patients with TS on the faux pas task indicated changes in ToM, whereby patients reasoned about mental states differently to controls. Therefore, some errors did not demonstrate a deficit in terms of an inability to consider a character's mental state. However, other errors on the faux pas task and Pragmatic Story Comprehension Task did reflect poor consideration of mental states. On some occasions when patients failed to infer a character's mental state they based their interpretation of a character's communicative intentions on the literal outcome of that character's behaviour. Although poor consideration of mental states could indicate specific changes to ToM, it is possible that the superficial literal interpretations made by patients reflect a more general impairment in inferential reasoning. Further research should investigate whether patients with TS only exhibit deficits on tasks that require drawing inferences that involve mental states.

The observed difficulties in understanding faux pas and non-literal language in TS are likely to result from frontostriatal dysfunction. Deficits in ToM and the comprehension of non-literal language have been seen in schizophrenia (Corcoran et

al., 1995; Drury, Robinson & Birchwood, 1998), bipolar disorder (Bora et al., 2005), and autism (Happé, 1993; Wang, Lee, Signman & Dapretto, 2006). These changes could be associated with hypo or hyperactivity within the prefrontal cortex (Hadjikhani et al., 2007; Kanahara et al., 2009; Robinson et al., 2008; Taylor, Welsh, Chen, Velander & Liberzon, 2007; Wang et al., 2006). Damage to the VMPFC can lead to poor performance on tasks involving sarcasm and faux pas (Shamay-Tsoory et al., 2003; Shamay-Tsoory, Tomer, & Aharon-Peretz, 2005), so dysfunction of the CSTCC involving this region (the ACC CSTCC described by Alexander et al., 1986) could contribute to the deficits in the understanding of both faux pas and non-literal language exhibited by the TS patients in the current study. However, other brain regions are also implicated. Amygdala dysfunction can impair performance on the faux pas task (Stone, Baron-Cohen, Calder, Keane & Young, 2003) and studies have also indicated volumetric abnormalities of the amygdala in TS (Ludolph et al., 2008; Peterson et al. 2007). Patients may also exhibit dysfunction of the IFG (Baym, Corbett, Wright & Bunge, 2008), which is involved in the comprehension of non-literal language (Kircher, Leube, Erb, Wolfgang & Rapp, 2007; Uchiyama et al., 2006).

There is evidence that TS in association with obsessive compulsive symptoms is associated with altered activity in corticolimbic pathways involving orbitofrontal and amygdala regions (Braun et al., 1995; Kurlan, Kersun, Ballantine & Caine, 1990; Nordstrom & Burton, 2002), raising the important issue of comorbidity. Although the present study included just two patients with ADHD, six of the fifteen patients exhibited comorbid OCD, and this latter factor could have contributed to impairments in task performance. However, when the performance of patients and controls was compared after patients with comorbid OCD were removed from analysis, significant

group differences in performance on the faux pas task and Pragmatic Story Comprehension Task were still evident. This finding indicated that deficits in ToM and the comprehension of non-literal language appeared to result from TS rather than comorbid OCD.

In summary, patients with TS exhibited a highly significant deficit in the comprehension of non-literal language. Furthermore, the present study replicates findings of poor understanding of faux pas in TS (experiment 1). These deficits were apparent despite evidence of only mild inhibitory dysfunction. Patients' difficulties indicate changes in ToM in TS. Further research should seek to determine whether the observed impairments reflect changes in specific aspects of ToM and specify the precise neural substrates and functional changes involved.

3.4: TS Experiment 3

INTRODUCTION

Patients with TS have been shown to exhibit deficits on two tasks involving social cognition (TS experiment 1 & 2), indicating changes in ToM. Similar tasks involving ToM are problematic for patients with VMPFC damage (Lough, Gregory & Hodges, 2001; Shamay et al., 2003; Shamay-Tsoory, Tomer & Aharon-Peretz, 2005), so dysfunction of frontostriatal pathways involving this region is likely to be implicated in TS. This study aimed to investigate whether patients with TS exhibit impairment on other tasks linked to the VMPFC. These additional tasks involved reasoning about mental states, humour, and economic decision making.

Research by Shamay-Tsoory and colleagues suggests that the recognition of certain emotions may be vulnerable to VMPFC dysfunction. Patients with damage to this region performed poorly on a task featuring faces with emotional expressions, which required the understanding of envy and gloating (Shamay-Tsoory, Tibi-Elhanany & Aharon-Peretz, 2007). Poor performance on items involving recognition of these 'socially competitive emotions' contrasted with good performance on items that required patients to judge which character the central character felt the same as or identified with. The recognition of 'socially competitive emotions' involves reasoning about conflicting mental states. In the case of gloating, the subject experiences pleasure in light of another's displeasure. Envy involves feeling displeased in light of someone else's pleasure. Shamay-Tsoory (2008) gave a version of the 'socially competitive emotions' task to people with Asperger's syndrome and high-functioning autism. This mixed group of patients performed poorly on this task in comparison to

controls, while exhibiting intact performance on matched tasks that involved reasoning about characters' cognitive and affective mental states e.g. what a character was thinking about or what a character loved. A short version of the 'socially competitive emotions' task used by Shamay-Tsoory et al. (2007) was used in experiment 3. Reasoning that requires the understanding of conflicting emotional mental states could pose a particularly complex task, so tasks assessing the understanding of 'socially competitive emotions' may reveal more subtle deficits, and could therefore be more sensitive to changes in ToM in patients with TS.

Torralva et al. (2007) found that patients with frontal-variant frontotemporal dementia (which involves degeneration of VMPFC including OFC) performed poorly on the 'Eyes Test' (Baron-Cohen, Joliffe, Mortimore & Robertson, 1997). This task involves making judgments about the emotional state of a person based on a picture of the eyes alone. Poor performance on the 'Eyes Test' was related to poor performance on a faux pas task, which has also been shown to elicit impairment in patients with TS (TS experiments 1 & 2). The amygdala, which has inputs to the VMPFC, is also likely to be involved in the 'Eyes Test' (Adolphs, Baron-Cohen & Tranel, 2002). One study assessed the performance of ten patients with TS on a version of this task and failed to find a deficit (Baron-Cohen, Joliffe, Mortimore & Robertson, 1997). However, the study used an early version of the test which may not have been as sensitive enough to detect a deficit, particularly in a small sample of patients. Experiment 3 included a more recent version of the 'Eyes Test' (Baron-Cohen et al., 2001) which contained more items, more forced choice options and involved complex mental state terms. Performance on this task could be impaired if patients with TS exhibit dysfunction within circuitry involving the ACC and medial OFC as hypothesized.

Activation in the VMPFC and amygdala has been linked to humour appreciation and funniness ratings (Goel & Dolan, 2001). For this reason, experiment 3 investigated the comprehension and appreciation of humour in TS.

Samson, Zysset and Huber (2008) reported more activity in VMPFC (as well as the IFG, temporo-parietal junction and supramarginal gyrus) in response to funny cartoons in comparison to baseline materials. The amygdala was implicated in humour appreciation by Bartolo, Benuzzi, Nocetti, Baraldi & Nicelli (2006), who presented humourous cartoons to healthy adult participants and found that activity in the amygdala correlated with reported ratings of amusement.

Humour is thought to rely on the detection and then resolution of incongruity, such as that between an expectation and reality, or when a prediction is not confirmed (Bartolo et al., 2006). Moran, Wig, Adams, Janata & Kelley (2004) suggest that detecting incongruity in humour activates left inferior frontal and posterior middle temporal regions, while solving the incongruity involves activity in bilateral insula and amygdala. Bartolo et al. (2006) showed that regions activated by humourous cartoons included left superior temporal gyrus, left middle temporal gyrus and cerebellum. They also note that these regions were activated by a non-verbal task involving the attribution of intentions in a study by Brunet, Sarfati, Hardy-Bayle & Decety (2000). This led them to suggest that ToM is one mechanism that can be used to resolve a detected incongruity in order to understand a joke. Some studies (e.g. Gallagher et al., 2000) have shown that cartoons involving ToM activates regions such as VMPFC, temporo-parietal junction and temporal poles more than cartoons not involving ToM related humour (e.g. slapstick). However, other evidence suggests that there is no qualitative difference in the network of brain regions activated by semantic

cartoons that do not involve reasoning about mental states and those that do (Samson et al., 2008).

Humourous materials involving sarcasm could be poorly understood by TS patients due to impairments in ToM. Deficits in ToM may lead to poor resolution of the incongruity present in a joke involving sarcasm because the humour in sarcasm derives from an incongruity between the speaker's remark and their mental state. Nonetheless, there are other kinds of humour that do not rely on ToM. For example, humour involving irony perhaps simply requires the appreciation of an incongruity between what is expected and what has occurred. Similarly, jokes that rely on simple visual 'slapstick' style humour (e.g. violence) are also unlikely to be affected by deficits in ToM. 'Slapstick' style humour tends to be understood by children as young as 3 years of age (e.g. Schultz, 1972) and may be based on simply detecting an incongruity (an unexpected physical event) without resolving why it occurred (Samson et al., 2008). It is therefore less likely to make considerable cognitive demands reliant on frontal functioning.

In experiment 3, participants' understanding and appreciation of humour was assessed using cartoons involving sarcasm or irony, in comparison to cartoons involving other kinds of humour such as 'slapstick' style comedy. Patients were expected to show difficulties understanding humour based on sarcasm because previous experiments revealed impairments in ToM (experiments 1 & 2) and the understanding of sarcasm in TS (experiment 2). Cartoons featuring irony were included because this kind of humour involves understanding an indirect communication but does not necessarily require ToM. It was expected that patients would be less likely to exhibit poor understanding of a selection of humourous cartoons that included 'slapstick' style humour.

The hypothesized dysfunction of frontostriatal pathways involving VMPFC in TS could cause the patients to show deficits in economic reasoning. Koenigs and Tranel (2007) showed that patients with VMPFC damage exhibit poor economic decision making during the Ultimatum Game (UG). During this task, a sum of money must be split between two players who act as proposer and responder. The proposer offers a proportion of the money to the responder and will keep the remainder. If the responder accepts this single offer, the money is split as proposed. If the responder rejects the offer, both players receive nothing. The conventional response is to accept any offer, as any personal gain should be preferable to no gain. However, if the proposer's offer is low, the responder may reject it due to feelings of unfairness or anger (Pilutla & Murnighan, 1996). Some estimates suggest neurologically intact individuals acting as responders reject about half of offers below twenty percent of the total (Nowak, Page & Sigmund, 2000). Koenigs and Tranel (2007), found that rejection rates for very unfair offers (eg. the proposer keeps $8 or $9 from $10) were significantly greater in patients with VMPFC damage in comparison to healthy controls and patients with damage outside VMPFC (such as lateral temporal or dorsolateral damage). Koenigs and Tranel (2007) suggest that one explanation for "irrational" rejections is poor regulation of negative emotional responses which leads to impulsive rejections.

Increased acceptance of unfair UG offers has been reported in patients with autism (Sally & Hill, 2006). This could reflect the well established deficits in ToM in autism as decision making during the UG often involves reasoning about the mental state of the proposer (Polezzi et al., 2008). For example, some rejections may be associated with feelings of envy, due to feelings of negative emotion which contrast with attributions of positive emotion to the proposer. Previous research indicating

possible changes in ToM in TS (experiments 1 & 2) therefore further prompted the assessment of patients' performance on the UG.

During experiment 3, participants played a short version of the UG where they always acted as the responder. Participants also completed other tasks that were sensitive to the functioning of the VMPFC. These were the 'Eyes Test' (Baron-Cohen et al., 2001), a task involving reasoning about 'socially competitive emotions' (including stimuli from Shamay-Tsoory et al., 2007) and tasks assessing appreciation and comprehension of humour in cartoons. Executive functioning was also assessed through the use of two tasks that provided measures of verbal fluency, and inhibition, which is most likely to be impaired in TS (see Channon, Crawford, Vakili & Robertson, 2003; Channon et al., 2006) and could be related to ToM performance (Samson et al., 2005).

METHOD

PARTICIPANTS

Sixteen patients with TS (6 females) were recruited as outlined in TS experiment 1. The mean age of the sample was 26.31 years (S.D. 9.80, range 16-47), with an average of 13.25 (S.D. 2.27, range 11-18) years of education. Five exhibited comorbid OCD, and one had comorbid ADHD. Four were taking medication for tics (2 Clonidine, 1 Risperidone & 1 Aripriprazole). Three patients were taking Fluoxetine, and two Sertraline. 20 healthy controls (11 females) of mean age 21.50 years (S.D. 4.43, range 18-37) with mean 13.80 years (S.D. 1.20, range 11-16) of

education also participated. Patients who had participated in earlier experiments were not excluded from participation as the tasks used in this experiment were not used in earlier experiments. The only exception was the black and white Stroop, but previous exposure to this task would not lead to a long term practice effect.

PROCEDURE

Testing was conducted as described in the procedure of TS experiment 1. All participants undertook two executive tasks, the Ultimatum Game (UG), the recognition of 'socially competitive emotions' task, the humourous cartoons task and the 'Eyes Test'. The order of administration of the tasks was counterbalanced. Half of the participants received the tasks in the following order: black and white Stroop, cartoons, 'socially competitive emotions' task, UG, 'Eyes Test', FAS. The other half of the two groups received the tasks in reverse of order: FAS, 'Eyes Test', UG, 'socially competitive emotions' task, cartoons, black and white Stroop.

THE 'SOCIALLY COMPETITIVE EMOTIONS' TASK

The stimuli used in this task were taken from Shamay-Tsoory et al. (2007). There were sixteen items (see Figure 5 for an example). Each item featured a cartoon face (that was originally called 'Yoni' and was re-named 'Harry'), surrounded by four other faces, which were arranged above and below 'Harry', on the left and right sides. For half of the items these other faces were also cartoon style, for the other eight items they were photographs of male and female faces taken from Ekman and Friesen (1976). Both 'Harry' and the other four faces exhibited emotional expressions.

'Harry' had either a happy or sad face, while the other faces depicted a range of expressions that included happiness, sadness, surprise, fear, anger, disgust or a neutral expression. There were four conditions. Participants had to select the face that 'Harry' either 1. felt the same as, 2. identified with, 3. was gloating over or 4. was envious of. Condition 1 required a simple match from the expression on Harry's cartoon face to another character. For condition 2 participants were told that when you identify with someone you have things in common with them. This condition also required participants to select the character with the same expression as 'Harry'. Conditions 3 and 4 involved the understanding of 'socially competitive emotions'. For condition 3, gloating was defined as a "positive experience in the face of another's misfortune" and envy as a "negative experience in the face of another's fortune" (as Shamay-Tsoory et al., 2007). For condition 3, 'Harry' showed a happy expression, and the correct response was to pick the character with a sad expression. For condition 4, 'Harry' had a sad face, and the correct response was to select the character with a happy expression. The definitions were given to all participants and avoided any explicit reference to emotions. Responses were simply scored as correct or incorrect for each item.

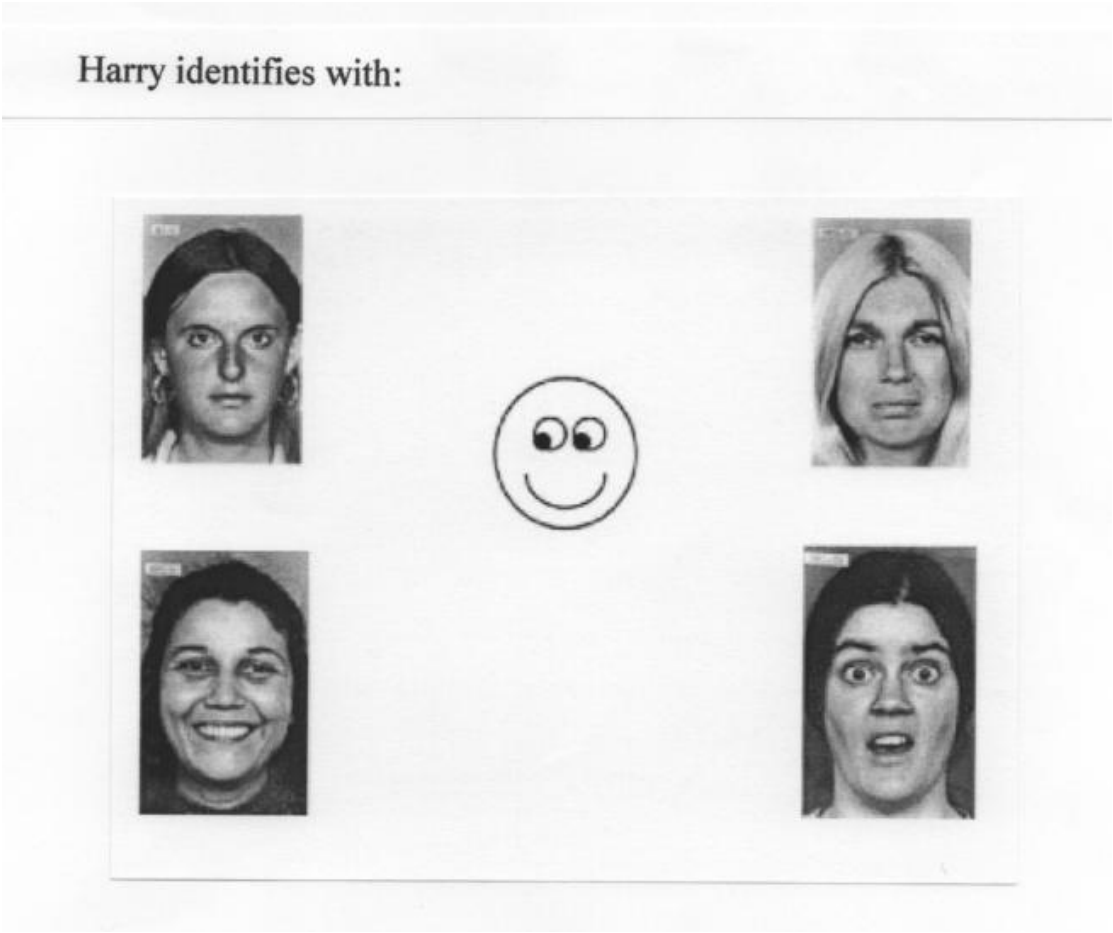


Figure 5. Example of stimuli used in the 'socially competitive emotions' task modified from Shamay-Tsoory et al. (2007). The facial photographs are from Ekman & Friesen (1974)

ULTIMATUM GAME

The experimenter told participants they had to imagine a hypothetical situation, but respond as if the circumstances were real life. In the version of the UG used in this experiment participants were always responders, and a story character 'Sam' was the proposer. Participants were told to imagine that a banker had given 'Sam' money on the condition that 'Sam' gave some of this money to them. 'Sam' would make a single offer of how much money they could have. If they accepted

'Sam's offer, the money would be split between the two of them as 'Sam' proposed. If they did not accept the offer, neither they nor 'Sam' would get any money. Three individual trials were presented. In each case the banker gave 'Sam' ten pounds. All participants received the trials in the same order. The first trial featured an offer to the participant of four pounds, the second offer was one pound, and the final offer was two pounds fifty. For each trial, participants were asked whether they would accept or reject the offer. The 'logical' response in every case would be to accept the offer, no matter how small, because any gain is better than nothing.

HUMOUROUS CARTOONS

This task involved 16 cartoons, printed in black and white, taken from an online database (www.CartoonStock.com). There were four conditions, each containing four items. The baseline condition featured cartoons that had been modified to obscure the intended joke (e.g. the punchline had been removed). Test cartoons all contained jokes that could be understood through the picture and language presented either as a caption or within the picture itself.

Test cartoons formed three conditions, which involved sarcasm, irony, or other kinds of simple humour such as 'slapstick' style comedy (comparison condition). There were four cartoons in each of these three conditions. The sarcastic condition included a cartoon of a man sitting at an office desk making paper aeroplanes, who was being asked by a man in a suit if he could "have a moment of his precious time". In one cartoon from the ironic condition, the first picture featured a man saying he would like to come back (to earth) as a bird, and be free as a bird. The second picture was of a caged bird. The comparison cartoons did not involve sarcasm or irony, and

included 'slapstick style' comedy. Such cartoons contained a visual representation of an unfortunate incident, for example, one cartoon featured a lady whose knickers had fallen down.

The first part of the task required participants to rate each item based on how amusing they felt them to be, on a scale from 0 to 9. They were told to use a rating of 0 if they could not see that any joke was present in the cartoon, and that higher scores should be given to more amusing jokes, so that a rating of 9 indicated the joke was hilarious. Participants were told that they should find some of the cartoons amusing, but there should be some stimuli that they did not find funny. Participants were also told that in order to rate a cartoon as amusing, they should have a particular reason or justification for why it was funny.

The second part of the task involved a multiple choice test for the test stimuli. Participants were shown the test items again, and asked to select the main reason why they thought the cartoon was meant to be funny, or how it was designed to be funny, from four options. One option for each item represented the most appropriate answer, involving appreciation of the sarcasm, irony, or slapstick element of humour. A correct answer therefore constituted selection of this option. Another option provided a concrete literal interpretation of the cartoon elements. This option could be selected if a participant could not infer beyond the material presented. A further option simply concerned a possible contradiction to the cartoon picture or statement. This option comprised a plausible answer if participants understood the incongruity or surprise\unexpected element of humour, but incorrectly inferred the cartoonist's intention. The last option was based on a random inference that could be made relating to a feature of the cartoon. All of the forced choice options contained

explanations that were contextually appropriate at face value. They were presented in a fixed pseudorandom order for each cartoon.

THE 'EYES TEST'

This task was taken from Baron-Cohen et al. (2001). It contained 36 photographs of pairs of eyes. The expression associated with each set of eyes was considered to reflect a particular complex mental state. Each photograph was surrounded by four complex mental state terms that appeared above and below on the left and right sides of the photograph. A glossary of these terms was provided. Participants were given standardised instructions as laid out by Baron-Cohen et al. (2001). They were told to look carefully at each picture and select the word they felt best expressed what the person in the picture was thinking or feeling. They were encouraged to refer to the glossary definitions if any of the words required clarification. Participants were given as long as they wanted to complete the test. Responses were scored according to Baron-Cohen et al. (2001).

EXECUTIVE TASKS

FAS word fluency test

As described in PD experiment 1 (section 2.2).

Black and White Stroop Test

As described in PD experiment 3 (section 2.4).

RESULTS

Patients and controls did not differ significantly for years of age, $t(19.88)=1.82$, $p=.084$, or education, $t(21.59)=-0.88$, $p=.390$.

'SOCIALLY COMPETITIVE EMOTIONS' TASK

One of the patients did not complete this task. Controls performed almost at ceiling (mean 0.05 errors, S.D. 0.31, median 0, range 0-1). Patients however, made a total of 12 errors (mean 0.8, S.D. 1.01, median 0, range 0-3). This difference was significant, MWU=91, $p=.01$. Seven of the patients made at least one error on this task. The majority of errors (8) were made in the condition where participants had to pick the face that Harry was gloating over. The two errors made by controls were also made during this condition. Patients also made a few errors over the other three conditions (same = 1, identify = 2, envy = 1) but the number of errors made in different conditions were considered too small for comparing conditions. Errors were made for both cartoon and photograph stimuli.

ULTIMATUM GAME

Patients with TS made many more rejections (mean 1.56 overall, S.D. 1.21, median 2, range 0-3) than controls (mean 0.5, S.D. 0.61, median 0, range 0-2) during the UG, and this difference was significant, MWU=80.5, p=.007. As can be seen from Table 18, patients made more rejections than controls on each of the three trials. Eleven of the sixteen patients rejected the lowest offer of £1 from £10, and nine of the twenty controls rejected this amount. Ten patients rejected the offer of £2.50, while just one control did so. Four patients rejected the highest offer of £4, which was unanimously accepted across control group.

Table 18. Rejections made by patients and controls during the Ultimatum Game

Group:	Measure:	£1 from £10	£2.50 from £10	£4 from £10
Patients with TS (n=16)	Total number of rejections	11	10	4
	% of group rejecting	69	63	25
Controls (n=20)	Total number of rejections	9	1	0
	% of group rejecting	45	5	0

HUMOUROUS CARTOONS

One of the cartoons from the comparison condition (including 'slapstick' style comedy) was removed from analysis because half of the control group made an error on this item in the comprehension task.

Subjective amusement ratings

Amusement ratings are shown below in Table 19. There was no difference in mean subjective amusement ratings given by patients and controls overall for test (humourous) cartoons, MWU=128, *p*=.308, and baseline cartoons (that were not humourous), MWU=116.5, *p*=.159. There was also no significant difference in ratings for cartoons featuring irony, MWU=148, *p*=.701, sarcasm, MWU=151.5, *p*=.786, or for the comparison cartoons, MWU=104.5, *p*=.076, when these were analysed separately.

Table 19. Amusement ratings given by patients and controls in response to stimuli to baseline (non-humourous) and test (humourous) cartoons (rating scale from 0-9)

Cartoon type:		Baseline	Sarcastic	Ironic	Comparison	All test
Patients	Mean	1.41	4.45	5.20	5.04	4.89
	SD	1.56	1.73	1.86	1.45	1.41
	Median	0.75	4.88	5.38	5.33	5.14
	Range	0-7	0-9	0-9	0-9	0-9
Controls	Mean	0.53	4.63	5.48	5.77	5.29
	SD	0.51	1.67	1.50	1.50	1.51
	Median	0.5	5	5.75	5.75	5.68
	Range	0-4	0-9	0-9	1-9	0-9

Patients with TS (n=16) gave thirteen zero ratings in total in response to test jokes, while only four zero ratings were given by controls (n=20). Most zero ratings (7) were given by patients for cartoons in the sarcasm condition. This suggests that patients were more likely to fail to recognize when humour was present in a cartoon, especially if the cartoon involved sarcasm. However, patients were also more likely than controls to provide ratings of nine (maximum) when considering their amusement level. It was also noted that some of these high ratings were given by patients who provided zero ratings.

Humourous cartoons comprehension task

Error totals for each group in each condition are shown in Table 20. When asked to identify the main reason why the humourous (test) cartoons were meant to be funny, a significant difference was apparent between patients and controls, MWU=41.5, $p<.001$. Patients made a mean of 2.75 errors (S.D. 2.66, median 1, range 0-9) on this task, in comparison to controls, who made mean 0.9 errors (S.D. 0.91, median 1, range 0-3).

Errors for the three test conditions were analysed separately. Patients gave fourteen unconventional responses for sarcastic cartoons, while controls gave four. This difference was significant, MWU=74, $p=.004$. Patients also made more selections (11) of less appropriate explanations for cartoons involving irony than controls (2), MWU=92, $p=.012$. Patients made 9 unconventional selections in response to comparison cartoons in comparison to the control group, who made 2. This difference did not reach significance, MWU=93.5, $p=.088$.

Table 20. Unconventional responses given by patients and controls during the humourous cartoons comprehension task

Unconventional response type	Group	Literal	Random	Contradiction
Sarcasm	Patients	8	2	4
	Controls	2	1	1
Irony	Patients	9	2	0
	Controls	2	0	0
Comparison (inc. 'slapstick')	Patients	4	2	3
	Controls	2	0	0

Performance was also analysed according to the response selected. Over all conditions, patients with TS selected more erroneous literal interpretations, MWU=66, $p<.001$, than controls. Patients were also significantly more likely to select unconventional explanations based on a contradiction than controls, MWU=107.5, $p=.015$, which led to the opposite interpretation to that which should be inferred. However, patients were not significantly more likely than controls to select incorrect answers from the random category, MWU=127.5, $p=.085$, which contained explanations based on simple observations or inferences that were not prompted by the information provided in the cartoon.

THE 'EYES TEST'

The patient group (n=16) made a total of 155 errors on this task (mean 9.68 per patient, S.D. 4.64, median 10, range 2-21), while controls (n=20) made 117 errors (mean 5.85 per control, S.D. 2.96, median 5.5, range 0-14). A significant difference between the groups indicated that patients selected more unconventional answers when asked to describe the mental state of the person in the photograph, MWU=79.5, *p*=.01.

EXECUTIVE TASKS

FAS test

Patients with TS (mean 42.63, S.D. 14.72, median 41, range 24-70) tended to generate fewer words than controls (mean 49.95, S.D. 11.4, median 50, range 32-79) during the FAS test, although this difference was not significant, MWU=103.5, *p*=.072.

Black and white Stroop

Patients' performance on the black and white Stroop yielded no evidence of inhibitory dysfunction. Patients (n=16) made 11 errors (mean 0.69, SD. 1.01, median 0, range 0-3) on the inhibitory condition, while the control group (n=20) made a total of 20 (mean 1, S.D. 1.08, median 0.5, range 0-3), a difference that was not significant, MWU=127, *p*=.256. On average, each patient took an additional 6.18 (S.D. 2.93,

median 6.09, range 0.1-13.71) seconds to complete the inhibition condition in comparison to baseline, which was very similar to the extra 6.05 (S.D. 2.44, median 5.83, range 1.93-10.84) seconds taken by each control, MWU=159, *p*=.975.

COMORBIDITY ANALYSIS

Because comorbid OCD could lead to impaired task performance, the four patients with this diagnosis were removed from the patient group and analysis compared the performance of the remaining patients with TS who had no OCD (n=11) to the control group. Analysis was re-conducted for overall error totals on tasks that elicited evidence of impairment in the patient group as a whole. All significant differences in errors on the 'socially competitive emotions' task, MWU=57, *p*=.011, rejections on the UG, MWU=59.5, *p*=.025, errors on the 'Eyes Test', MWU=43.5, *p*=.006, and errors on the humourous cartoons comprehension task, MWU=34.5, *p*=.001, were still evident.

CORRELATIONS

Correlations were conducted to investigate relationships in patients' performance on executive measures, total errors made on the 'socially competitive emotions task', the 'Eyes test' and the humourous cartoons comprehension task, and total rejections made during the UG (Table 21). Significant correlations were found between the number of errors made on the humourous cartoon comprehension task and errors made on the 'Eyes Test' and the socially competitive emotions task. The

relationship between number of errors made on the humourous cartoons comprehension test and number of UG rejections approached significance.

Table 21. Correlations for patient performance on executive measures, the socially competitive emotions task, the UG, the 'Eyes Test' and the humourous cartoons comprehension task

	1. FAS scores	2. Stroop errors	3. Stroop time difference	4. UG rejections	5. 'Socially competitive emotions' task errors	6. 'Eyes Test' errors	7. Humourous cartoons comprehen-sion test errors
1.	X	-.074 .669	-.090 .600	-.217 .203	-.105 .550	-.303 .073	-.262 .123
2.		X	.220 .196	-.025 .884	.162 .352	.005 .977	-.137 .427
3.			X	.096 .576	.136 .471	.002 .990	.069 .689
4.				X	.243 .168	.229 .178	.315 .061
5.					X	.293 .087	.445 .007**
6.						X	.662 <.001***

KEY:

Upper value = Spearman's r correlation coefficient, lower value = *p*-value
* Significant at the 0.05 level
** Significant at the 0.01 level

DISCUSSION

Patients with TS exhibited significant deficits on a range of tasks involving social and economic reasoning that are linked to VMPFC. These deficits were apparent despite little evidence of executive impairment on tasks assessing fluency or inhibition. Many studies have failed to reveal evidence of significant deficits in verbal fluency in TS (Channon, Pratt & Robertson, 2003; Goudriaan et al., 2006; Stebbins et al., 1995; Watkins et al., 2005). However, inhibitory impairments are commonly reported on the Hayling task (Channon et al., 2006; Crawford et al., 2005). Inhibitory deficits were also observed on the Hayling task during TS experiments 1 and 2. This implies that the Hayling task is more sensitive than the Stroop used in the present study. The higher sensitivity of the Hayling task may be related to its reliance on the functioning of the ACC (Nathaniel-James et al., 1997). The ACC forms part of a CSTCC described by Alexander et al. (1986). This circuit involves projections from ventromedial prefrontal regions (such as medial OFC) and from the amygdala to the ventral striatum. The deficits reported on the Hayling task (e.g. TS experiment 1) are therefore likely to have resulted from dysfunction within the same CSTCC linked to the impairments noted on the social and economic reasoning tasks administered in experiment 3.

Patients made significantly more errors than controls on the 'socially competitive emotions' task, which required the participant to judge which face the central character felt the same as, identified with, was envious of, or was gloating over. Patients found the gloating condition most difficult, which required the selection of a face showing the opposite emotion to the central character. All participants were given definitions of the above terms, and understood the task before testing

commenced. Errors should therefore indicate that patients found it difficult to reason about interactions involving the contrasting emotions of two characters (i.e. when one character was happy and the other sad). Previous research (TS experiments 1 & 2) has highlighted difficulties on a faux pas task that also involved contrasts between the mental state of two characters (the protagonist's lack of awareness of the effect of their offensive remark, and the protagonist's feeling of offence). Perhaps this element of conflict is particularly related to the demonstrated role of VMPFC in understanding 'socially competitive emotions' (e.g. Shamay-Tsoory et al., 2007).

The conflicting interests of two people are also present in the UG, during which, patients with TS rejected significantly more offers overall in comparison to controls. Some patients even rejected the fairest split offered (four pounds out of ten) while no controls rejected this split. Koenigs and Tranel (2007) reported a similar increase in 'irrational' rejections during the UG by patients with VMPFC damage. They suggested that one explanation for this phenomenon is poor emotional regulation. It could be that patients with TS were less able than controls to suppress the emotional frustration felt in response to unfair UG offers, in order to reason in an economically advantageous manner. Reports of increased aggression (Cavanna et al., 2009) and explosive disorder (Budman, Rockmore, Stokes & Sossin, 2003) in some patients with TS could also be related to emotional dysregulation. If increased rejections during the UG reflect poor impulse control, it may be expected that rejecting behaviour could be related to inhibitory performance on executive tasks. The present study provided no evidence for such a link. However, it can be speculated that patients with TS experience greater difficulty inhibiting behaviour that is associated with an affective component. This could explain why many studies involving standard

inhibitory tasks have failed to elicit evidence of impairment (e.g. Brand et al., 2002; Ozonoff & Jensen, 1999).

Increased rejections on the UG are likely to implicate a role for the insula in the pathophysiology of TS. Rejection of unfair offers has been associated with increased activation of the anterior insula (Sanfey, Rilling, Aronson, Nystrom & Cohen, 2003), a brain region associated with the experience of disgust (e.g. Wicker et al., 2003). Sanfey, Loewenstein, McClure and Cohen (2006) also reported higher anterior insula activity for unfair offers that were rejected, but showed that when unfair offers were accepted, insula activity was always below that of the DLPFC. It may be that the neural basis of competition between higher level reasoning over emotional responses during the UG involves
top-down control exerted by the DLPFC over limbic activity. Increased rejecting behaviour in TS could imply reduced DLPFC input during decision making. However, there is little evidence to support DLPFC dysfunction in TS, as studies provide limited evidence of deficits in executive abilities that are linked to this region. For example, experiment 1 showed that patients with TS do not exhibit deficits in WM, an executive function linked to the DLPFC (Curtis, Zald & Pardo, 2000). Future research could investigate the possibility of increased autonomic responsiveness during the UG in patients with TS, as neurologically intact participants exhibit higher skin conductance responses (SCRs) for unfair UG offers (van't Wout, Kahn, Sanfey, & Aleman, 2006).

More reasoned rejections could be motivated by a desire to punish the proposer for being selfish or greedy, and deferring from the social norms of fairness and cooperation. In this way, a norm can substitute for mentalising (Pillutla & Murnighan, 1996). Rejections can therefore be seen as a form of altruistic

punishment, because the proposer is punished for their own bad behaviour at the responder's own cost. Such behaviour encourages the maintenance of social norms, and though it does not benefit the individual at the time, altruistic punishment does benefit a social group or society in the long term and consequently leads to evolutionary adaptiveness (Fehr & Fischbacker, 2003). In support of the fact that altruistic punishment motivated some of the observed rejections, patients sometimes stated that the responder should have offered an even split because that was the fair or right thing to do. A strong desire to punish a proposer is associated with increased activity in the thalamus, VMPFC and OFC (de Quervain et al., 2004). Further research could investigate whether patients with TS do exhibit a strong desire for fairness and the upholding of social norms through the use of tasks involving moral judgement.

ToM can play a role in decision making during the UG. Pillutla and Murnighan (1996) showed that participants in their study who knew that an offer was low and that the proposer knew it was low were far angrier than those who understood the proposer was unaware of the fairness of their offer. This anger resulted in a greater frequency of rejection and was more predictive of the likelihood of rejection than was the actual degree of unfairness alone. These authors suggest that a responder might reject a small offer because they imagine that the proposer believes them to be unworthy, gullible, or dim-witted. Children with autism, who exhibit deficits in the understanding of mental states, are more likely to accept small offers (Sally & Hill, 2006), perhaps because they are less likely to make negative inferences about the proposer's intentions. This pattern of increased acceptance of more unfair UG offers is the opposite of that exhibited by patients with TS in the present study, who rejected these offers more often than controls. However, changes in reasoning about mental

states could still have influenced patients' performance. TS experiments 1 and 2 highlighted errors on ToM tasks that were associated with a negative bias when drawing inferences about a story character's communicative intentions, rather than a simple failure to consider mental states. Negative inferences about mental states were evident during the faux pas task used in experiments 1 and 2, when some patients thought that the protagonist's offensive remark was deliberate. It may be that in experiment 3, patients were more likely than controls to reject UG offers because they were more likely to make negative inferences about the mental state of the proposer.

Performance on the 'Eyes Test' provided further evidence for changes in social cognition in TS. This task included making judgments about epistemic mental states (e.g. interested), cognitive mental states (e.g. thoughtful) and affective mental states (e.g. worried) based on a photograph of a person's eyes. Although one study reported intact performance on an earlier, less complex version of the task (Baron-Cohen Joliffe, Mortimore & Robertson, 1997), this experiment may be the first to test patients with TS using the more recent and arguably more sensitive version. Other patient groups including those with Huntington's disease (Havet-Thomassin, Verny, Bonneau, Dubas & Le Gall, 2008) and traumatic brain injury involving prefrontal regions such as OFC (Havet-Thomassin et al., 2006) have been shown to perform poorly on this task. One brain region likely to be particularly crucial for performance is the amygdala, which is important for tasks involving eye gaze, facial expressions and reasoning about social emotions (Adolphs, 2002; Adolphs et al., 2002). There is some, albeit limited, evidence for amygdala involvement in TS (Ludolph et al., 2008; Peterson et al., 2007), so further research should investigate the possible involvement of this structure. The amygdala has inputs into the VMPFC (including medial OFC and ACC), and both the amygdala and VMPFC project to the ventral striatum

(Alexander et al., 1986). Possible amygdala dysfunction could therefore implicate the ACC CSTCC.

ToM difficulties could be linked to the problems understanding jokes based on sarcasm exhibited by patients in experiment 3. Patients may have failed to infer the mental state of the relevant character in the cartoon or had difficulty inferring the cartoonist's intentions. However, patients' difficulties understanding ironic cartoons may not have resulted from poor consideration of mental states. Sarcasm and irony are indirect forms of communication. However, irony involves a kind of exaggerated appropriateness or connectivity and requires inferences to be drawn about what is commonly expected in contrast to what is depicted in the cartoon.

Patients with TS performed comparatively well on cartoons that relied less on inferential reasoning. These included cartoons in the comparison condition featuring 'slapstick style' humour that was conveyed through obvious visual elements. For example, patients performed almost at ceiling on one cartoon that showed a character with a custard pie splattered in their face. Children from the age of three who do not yet have a fully mature frontal cortex often find this kind of humour amusing (Schultz, 1972). It could be that patients made fewer errors on these items because these jokes could be understood on a more superficial level. Deficits in inferential reasoning were particularly apparent in patients' tendency towards more obvious misinterpretations of the cartoons across all test conditions. Poor inferential reasoning led patients to select more unconventional explanations in the form of literal interpretations and 'contradiction' explanations that described the opposite to what should be inferred based on the information contained within the cartoon. Further research should investigate whether patients' difficulties in understanding irony reflect more general underlying difficulties with inferential reasoning.

The patient group responded differently to controls when asked to explain why the cartoons were meant to be humourous. However, the overall mean ratings of subjective amusement for the patients on both baseline and test cartoons were not significantly different to those given by controls. This could suggest that while patients could detect an incongruity in the humourous cartoons (stage one of humour comprehension) and so appreciated a joke was present, they failed to accurately resolve this incongruity (stage two), so were drawn towards erroneous explanations for their subjective amusement. Studies implicate the right frontal regions in humour comprehension (Shammi & Stuss, 1999). Moran et al. (2004) specify that detecting incongruity in humour activates left inferior frontal and posterior middle temporal regions, while solving the incongruity involves activity in bilateral insula and amygdala.

If deficits on the humourous cartoons comprehension task were related to dysfunction of pathways involving VMPFC in TS, it would also help to explain correlations in patients' performance on the humour comprehension task and other measures. Performance on the 'Eyes Test' and 'socially competitive emotions' task may have been strongly related to performance on the humourous cartoon comprehension task because humour comprehension required ToM related inferences about the mental state or intention of the cartoonist and\or the characters featured in some of the cartoons. Performance on the UG is likely to have been less strongly related to performance on the humourous cartoons comprehension task because factors other than ToM (such as financial considerations) also contributed to performance.

In conclusion, patients with TS exhibited significant deficits on a range of tasks linked to the VMPFC. These tasks involved ToM, humour and economic

decision making. The findings of this experiment provide evidence of changes in social and emotion related reasoning processes in TS, which are likely to be linked to dysfunction within frontostriatal pathways involving VMPFC and the amygdala.

3.5: Social Cognition in TS: Discussion

Patients with TS exhibited changes in reasoning processes leading to deficits on a range of social cognitive tasks. These deficits were apparent despite limited evidence of executive dysfunction. Although patients exhibited evidence of inhibitory impairment on the Hayling task (experiments 1 and 2), significant deficits were not evident on the Stroop (experiments 2 and 3) or on verbal fluency or WM measures (experiment 1). Furthermore, there was no evidence that difficulties with inhibition were linked to the changes in performance exhibited by patients on tasks involving social cognition.

Patients with TS were impaired on tasks involving ToM, such as the faux pas task, 'socially competitive emotions' test, and the 'Eyes Test'. Deficits that could at least partly depend on ToM were also apparent on reasoning tasks that involved the understanding of non-literal language. However, the difficulties exhibited by patients on one of these tasks (that featured humourous cartoons involving irony) indicated deficits in inferential reasoning that could be less closely related to ToM. Reasoning deficits were also apparent on an economic decision making task. While changes to ToM may have influenced patients' unconventional behaviour during this task, further research is necessary to rule out the contribution other factors, such as alterations in emotional regulation.

The changes in reasoning exhibited by patients with TS on these tasks can be classified into two categories. The first category includes instances when patients failed to draw inferences about mental states. The second category includes errors that were not characterised by a failure to infer mental states, but rather unconventional

interpretations of social interactions that could be linked to increased sensitivity to negative affect.

The first category of errors was associated with a superficial level of reasoning and an acceptance of information at face value resulting in a 'literal bias'. This kind of error would account for patients' difficulties in inferring mental states on many of the tasks administered, including failure to recognise faux pas and poor understanding of non-literal language. Patients' errors in reasoning beyond the information initially available appeared similar to errors that would be seen as a result of inhibitory dysfunction, which prevented the consideration of an alternative perspective. Deficits of this nature could reflect a reduction in cognitive resources, which may lead to poor inferential reasoning in general, leading to difficulties on tasks not so closely linked to ToM (e.g. in reasoning about irony). Inferential reasoning is likely to rely heavily on cognitive resources such as executive functions. Although these experiments have shown that patients with TS only exhibit mild inhibitory dysfunction, patients could have a tendency to adopt reasoning strategies that are less cognitively demanding due to the effort involved in tic suppression.

The second category of errors made by patients on these tasks was associated with a tendency towards unconventional, negative interpretations of social interactions, and perhaps increased sensitivity to negative emotion. Errors that reflect this difference in reasoning include errors on the faux pas task, where patients signalled faux pas had occurred when it had not, or inferred that the protagonist's offensive remark was deliberate. This kind of reasoning may also have contributed to increased rejections during the UG, due to attributions of negative intention to the proposer and overwhelming feelings of offense or anger on the part of the patient acting as responder. It could be that patients with TS exhibit increased emotional

reactivity which is most evident on tasks that highlight conflict within social interaction, such as situations where one person may be negatively affected by another person's actions. These kind of situations were evident during the faux pas task (where the protagonist's remark could offend another person), the 'socially competitive emotions' task (where the gloating of a central character may lead to upset for the subject of the gloating) and the UG (where the proposer would profit more when a responder accepted a lower offer despite feelings of unfairness). Increased emotional reactivity in response to stimuli associated with negative emotion could lead to reduced 'logical' control over decision making, with significant implications for patients' social and emotional functioning.

Although patients with TS exhibit differences on tasks involving social cognition, many of these changes do not reflect a simple failure to reason about mental states. Differences are apparent in the way that patients reason about social interaction and make attributions about the motives and intentions behind social behaviour. Although comorbid OCD was not related to the observed deficits, it would be useful to investigate whether the two different kinds of changes in reasoning outlined above could be exhibited by different subgroups of patients (e.g. patients with or without NOSIS). Further research should investigate larger samples of patients to identify whether any relationship between these two differences in reasoning style may be associated with other disease characteristics.

These experiments show that patients with TS exhibit deficits on a range of tasks linked to VMPFC, implicating a role for frontostriatal circuitry involving this region in TS. This ACC CSTCC (as described by Alexander et al., 1986) originates from the medial OFC (VMPFC) and amygdala, which project to the ventral striatum. VMPFC appears to be important for both reasoning tasks that involve empathy

(Young & Koenigs, 2007) and decision making that involves an affective component (Tranel, Bechara & Denberg, 2002). The medial OFC in particular has been linked to ToM abilities based on abstract perspective taking (Hynes et al., 2006). However, the lateral OFC, which forms part of a separate CSTCC, is involved in processing affect related negative feedback. The amount of activity in lateral OFC correlates with amount of money just lost during a gambling game (O'Doherty, Kringelbach, Rolls, Hornak & Andrews, 2001) which is likely to be related to the finding that this region is specifically active during the effortful control of negative emotions (Ochsner, Bunge, Gross & Gabrieli, 2002).

The pattern of impairment demonstrated by patients with TS can also be discussed in terms of 'hot' and 'cool' aspects of ToM and executive functioning. Although the use of these terms is controversial they could help highlight a useful distinction in the performance of patients with TS. 'Hot' aspects of these abilities relate to affect, whereas 'cool' aspects are more abstract (Zelazo et al., 2005). The majority of difficulties exhibited by patients with TS involved aspects of 'hot' ToM. Patients with TS exhibited less difficulty on tasks involving purely 'cool' ToM (the false belief vignette task used in experiment 1), although 'cool' ToM was more impaired when the task also included elements of 'hot' ToM (e.g. the faux pas task: experiment 1). Patients also exhibited deficits on the UG, which involves affect related decision making, so may involve 'hot' aspects of executive functioning. Patients with TS did not exhibit deficits on certain executive tasks that involved 'cool' executive functions (the FAS test, DOT-A test). One possible discrepancy is that patients exhibited deficits on the Hayling task which may involve 'cool' executive functioning. However, this task activates the ACC (Nathaniel-James et al, 1997) which is part of the same CSTCC circuit (Alexander et al., 1986) as medial OFC.

Medial OFC is implicated in 'hot' ToM and executive functions, while 'cool' ToM and executive functions (used for the FAS test and DOT-A) are linked to the DLPFC (Zelazo et al., 2005). In summary, patients with TS are more likely to exhibit deficits on tasks involving 'hot' aspects of ToM or executive functioning, due to greater involvement of the ACC CSTCC in TS than the DLPFC CSTCC.

CHAPTER 4. SOCIAL COGNITION IN HUNTINGTON’S DISEASE

4.1: HD Experiment

INTRODUCTION

HD is an inherited neurodegenerative disorder associated with a selective pattern of degeneration that begins in the CN, and progresses from dorsal to ventral regions of the striatum. The characteristic involuntary choreiform movements of HD occur as a result of frontostriatal dysfunction. HD is often accompanied by obsessive compulsive or psychotic behaviour and dementia in later stages of the disease (Lauterbach et al., 1998). Executive dysfunction is common, and patients exhibit deficits in memory, attention, cognitive flexibility, fluency, inhibition and decision making (Campbell, Stout & Finn, 2004; Butters et al., 1986; Snowden et al., 2008). These deficits implicate dysfunction within frontostriatal pathways involving ACC and DLPFC (Aleman & van't Wout, 2008; Peterson et al., 1999; Vanderhasselt et al., 2006a,b).

Patients can also show increased irritability and aggression (Calder et al., 2004) and reduced empathy for others (Snowden et al., 2003). These changes could contribute to the breakdown of interpersonal relationships (Snowden et al., 2003), and increases in criminal behaviour. Jensen, Fenger, Bolwig and Sorensen (1998) reported that patients with HD were almost three times as likely as controls to be listed on the Danish National Central Criminal Register for crimes such as drink driving, assault, molestation and robbery. A lack of empathy for others could contribute to such instances of poor social conduct. Changes in emotional and social behaviour in HD are likely to reflect dysfunction of frontostriatal pathways involving the OFC, as

damage to this region can lead to loss of empathy and sociopathic behaviour (Blair & Cipolotti, 2000).

Some studies have also indicated that HD can be associated with deficits in ToM. Patients have been found to display abnormal interpretations of real-life social situations (Naarding, Kremer & Titman, 2001) and Snowden et al. (2003) showed that patients made faulty inferences in response to tasks involving social interactions. Patients can also exhibit deficits on tasks of social cognition that involve faux pas, and judging mental states based on photographs of people's eyes on the 'Eyes Test' (Havet-Thomassin et al., 2008). Similar tasks elicit impairment in patients with damage to VMPFC (Shamay-Tsoory et al., 2003) and the amygdala (Stone et al., 2003), respectively. These findings could indicate dysfunction within the CSTCC involving the ventral striatum (described by Alexander et al., 1986) in HD.

There is evidence that the understanding of emotions in others appears to be impaired in HD, as many studies have revealed deficits in the recognition of emotional facial expressions. While patients could exhibit significant difficulty with a range of negative emotions (e.g. Henley et al., 2008), some authors have provided evidence for greater deficits in the recognition of disgust. Sprengelmeyer et al. (1997) found mild impairments in the recognition of a number of emotional expressions in HD, but patients exhibited a more severe deficit for disgusted faces. Gray, Young, Barker, Curtis & Gibson (1997) found that this specific deficit extended to huntingtin gene carriers. Further support was provided by Wang, Hoosain, Yang, Meng & Wang (2003), who reported a similar 'differentially severe impairment' for disgust expressions in both Chinese patients with HD and patients with Wilson's disease (another disorder associated with BG dysfunction). However, other reports have indicated that patients sometimes exhibit most impairment in the recognition of facial

expressions of fear (Milders, Crawford, Lamb & Simpson, 2003) or anger (Henley et al., 2008; Snowden et al., 2008). The expression recognition deficits exhibited by gene carriers can also extend to anger, fear and sadness (Johnson et al., 2007).

It is possible that patients with HD exhibit a general impairment in facial emotion recognition and greater impairments are found for certain emotions because they are more difficult to recognize. This suggestion is supported by evidence of mild deficits on more general face perception measures in HD (e.g. Wang et al., 2003). However, another study that used a wide range of tasks reported no effect of item difficulty (Snowden et al., 2008).

The inconsistency of impairments reported across studies could reflect the involvement of different subsets of patients, with greater degeneration in neural substrates involved in recognising particular negative emotions. There is evidence that the ventral striatum could play a central role in the recognition of angry faces (Calder, et al., 2004). The amygdala however, is activated during the recognition of fearful expressions (Adolphs et al., 2002). Selective deficits with disgust in HD patients and gene carriers have been linked to a reduced response in left dorsal anterior insula (Hennenlotter et al., 2004). However, Henley et al. (2008) found that impaired recognition of angry, disgusted, surprised and fearful faces were all associated with striatal volume loss. These authors also reported that deficits in the recognition of fear, but not disgust, were also related to right insula degeneration.

Reports indicate that brain regions associated with recognizing a particular emotion in another are likely to be involved in the direct experience of that emotion (Adolphs, 2002). Despite these findings, research investigating patients' own emotional responses to emotion-provoking stimuli is limited in HD. One study (Snowden et al., 2008) showed that deficits in the recognition of emotional facial

expressions in HD could indeed be associated with changes in emotional responses to affect provoking stimuli. In addition to poor recognition of disgust and other negative emotions from face and voice, HD patients exhibited a reduced disgust response to written scenarios that elicited this emotion in control participants. A few other studies have indicated disgust deficits in HD can also be observed in response to pictures, olfactory and gustatory stimuli (Hayes et al., 2007; Mitchell et al., 2005). This experiment aimed to extend research in this area, by assessing HD patients' subjective emotional responses to stimuli selected to elicit emotions including core and moral disgust.

Core disgust may be best defined through its common elicitors, which include body products, death and corpses, threat of contamination (or infection) and violation of the body exterior (Rozin, Haidt & McCauley, 2000). Core disgust can serve an adaptive function, by helping one to avoid contact with potentially harmful stimuli. Disgust can also be elicited by some moral offences (Rozin, Haidt & McCauley, 2000). It may be speculated that moral disgust may serve a more social function, through discouraging uncivilized behaviour, and so be more vulnerable to individual differences and cultural values. Perhaps these differences explain why core and moral disgust have been shown to activate different neural substrates. Moll et al. (2002) investigated the brain activity of healthy adults in response to unpleasant pictures linked to core disgust (e.g. dirty toilet, mangled face) and emotionally charged moral pictures (e.g. war, abandoned children). The amygdala, thalamus and upper midbrain were active when viewing both sets of images. However, stimuli likely to be most closely associated with core disgust elicited specific activity in right middle frontal gyrus and right anterior insula, while moral stimuli led to additional increased activation in the OFC, medial prefrontal cortex and superior temporal sulcus.

The brain regions that Moll et al. (2002) showed were more activated in response to moral stimuli (e.g. OFC) have been linked to ToM (Lough et al., 2006; Moriguchi, Ohnishi, Mori, Matsuda & Komaki, 2007) which as noted earlier, could be compromised in HD (see Havet-Thomassin et al., 2008; Snowden et al., 2003). Moral disgust may occur in association with empathy for victims of an act judged to be immoral, so ToM deficits in HD could impair feelings of moral disgust through poor consideration of mental states.

This experiment involved the assessment of subjective emotional responses in HD using pictures from the International Affective Picture System database (IAPS: Lang, Bradley & Cuthbert, 1995) and written scenarios. Participants provided fear, happiness, sadness, surprise, anger and disgust ratings in response to four sets of pictures and four sets of scenarios selected to primarily elicit either happiness, fear, core disgust or moral disgust. It was expected that patients would respond normally to the stimuli selected to elicit happiness, but would exhibit deficits in response to fear and core disgust stimuli due to reports of poor recognition of these emotions in facial expressions in HD (e.g. Henley et al., 2008). It was also expected that patients could differ in their response to moral disgust items in light of the evidence of possible ToM impairment in HD. Executive tasks were included to determine whether any differences in performance on the emotive stimuli tasks were associated with executive dysfunction.

METHOD

PARTICIPANTS

Thirteen outpatients (8 males) with HD were recruited from the Queen Elizabeth Psychiatric Hospital, Birmingham. They were selected by their senior clinical consultant who ensured participants exhibited no frank signs of dementia nor suffered from overt cognitive difficulties. Patients mean age was 53.07 years (S.D. 10.3, range 37-73) and mean years of education was 13.31 (S.D. 2.39, range 11-17) years. Twelve neurologically intact controls (6 males) were also enrolled. Their mean age was 53.08 (S.D. 12.1, range 30-71) years and mean years of education was 14.00 (S.D. 2.22, range 11-16) years. Two patients were taking Risperidone, one Carbermazepine and one Citalopram. No patients were formally diagnosed with OCD but three patients self-reported sub-threshold symptoms. One patient did not complete the emotive scenarios task.

PROCEDURE

Patients were approached through their consultant, and received information leaflets about the study before they decided whether to take part. Participants were advised that they may find some of the stimuli they would see and read about during the study emotionally striking, and that the emotional responses they had may at times be negative. All participants gave informed consent and were fully debriefed after participation.

The five tasks were ordered so that the three executive tasks were administered separately and the emotive stimuli tasks were completed independently in between. Each executive task was featured in the first, third and fifth position equally often and the emotive stimuli tasks came in the second and fourth position equally often, resulting in 12 different task orders.

EMOTIVE STIMULI TASKS

The emotional categorization of the stimuli (fear, happiness, core disgust and moral disgust) was validated using the emotional ratings provided by control participants (see Tables 22 and 23 in the results section). Moral disgust stimuli were carefully selected so that they did not directly or explicitly feature stimuli that were likely to elicit core disgust, such as injury or mutilation.

Emotive Pictures

These twenty pictures were taken from the IAPS database (Lang, Bradley & Cuthbert, 1995). There were four sets of five, each set selected to elicit predominantly emotional responses of happiness, fear, core disgust or moral disgust. The pictures intended to elicit fear (numbers 1525, 1932, 6300, 8179, 8485) featured threatening stimuli such as dangerous animals and fire. The pictures selected for the happiness category (numbers 2303, 2345, 2530, 4626, 8380) included scenes of a couple on their wedding day and some Olympic athletes celebrating winning medals. The pictures chosen for core disgust (numbers 1111, 3250, 7380, 9042, 9300) included a dirty toilet and an open chest cavity. Moral disgust stimuli (numbers 2710, 2745.2,

2751, 3500, 6312) included an image of a drug addict and a shoplifter in action. The pictures in this category did not feature stimuli overtly associated with core disgust, such as blood as a result of violence.

Participants were instructed to look at each picture and rate their emotional response to the events described in terms of six basic emotions; anger, sadness, surprise, fear, happiness and disgust. Ratings were on a scale of 0-9, where a score of 0 indicated the participant felt the emotion was not relevant to their response to the vignette and a score of 9 indicated that emotion was completely relevant.

Emotive Scenarios

This task featured twenty short vignettes. Each vignette consisted of two sentences that were intended to elicit an emotional response. There were five scenarios designed to predominantly elicit each of the following four emotions; happiness, fear, core disgust and moral disgust. The fear, happiness and core disgust scenarios were written so that the reader was the subject of the experience. The scenarios designed to elicit fear responses described threatening experiences such as hearing an intruder while home alone and coming face to face with a ferocious dog. The vignettes involving situations that should result in happiness included experiencing a lottery win and getting a short story published. Core disgust scenarios included descriptions of finding a slug in a salad while eating at a café and being vomited on by a drunk. For the moral disgust scenarios, the reader was a witness to the experience of another. This was done for three reasons. Firstly, had the participant been the subject of vignettes featuring violence or assault, fear was likely to have

been the primary emotion elicited. Secondly, moral disgust stimuli included examples of shop-lifting and drug taking, and it was felt that participants could find it difficult to think about themselves in these situations. Thirdly, the use of other people as victims in some stimuli allowed for the potential influence of empathy on emotional ratings, which may comprise an important aspect of reasoning about moral disgust stimuli. Moral disgust scenarios included witnessing violence against a frail old woman and being aware of a toddler being left home alone while his father went out drinking. These vignettes were adapted from scenarios used in an imaging study carried out by Moll et al. (2007).

Participants were told to read each vignette and think about their emotional response to it. They received the same instructions and used exactly the same rating system and scale as described above for the emotive pictures.

EXECUTIVE TASKS

FAS test

As described in PD experiment 1(section 2.2).

Digit Ordering Test-Adapted (Werheid et al, 2002; Cooper et al, 1991)

As described in PD experiment 2 (section 2.3).

Black and White Stroop Task

As described in PD experiment 3 (section 2.4).

RESULTS

One patient did not complete the emotive scenarios task, so comparisons involving this task were between the remaining twelve patients and twelve controls. There was no significant difference between patients and controls for age, $t(23)=-0.001$, $p=.999$, or education, $t(23)=-0.75$, $p=.462$.

EMOTIVE STIMULI TASKS

Emotive pictures

Table 22 shows the mean and standard deviation of the six emotions (anger, sadness, surprise, fear, happiness and disgust) rated by patients and controls for stimuli within each emotional category (fear, happiness, core disgust and moral disgust). Although differences were not tested statistically (due to concerns about multiple comparisons), the target emotion for each of the four categories (fear, happiness, core disgust, moral disgust) was the emotion given the highest mean rating by control participants. Patients with HD showed more variation in emotional ratings for fear, core disgust and moral disgust stimuli than the control group, as reflected in higher standard deviations. Ratings of zero were most commonly given by patients

when rating fear in response to pictures and stimuli selected to elicit this emotion, and such ratings were given by the majority of patients. Only one zero rating for fear in response to fear stimuli was provided by the control group, while 29 ratings of zero were provided by patients.

Table 22. Mean and standard deviation of emotional ratings given by patients and controls in response to pictures within the four emotional categories

Category (pictures chosen to elicit):	Fear		Happiness		Core disgust		Moral disgust	
	P	C	P	C	P	C	P	C
Happiness	1.49 (1.11)	0.35 (0.53)	**8.62** **(0.88)**	**8.17** **(1.14)**	0.51 (0.80)	0.05 (1.73)	0.14 (0.24)	0.00 (0.00)
Sadness	1.00 (1.57)	1.45 (1.13)	0.32 (0.64)	0.12 (0.28)	1.62 (2.25)	1.15 (0.96)	3.69 (2.67)	4.67 (2.54)
Surprise	4.26 (2.71)	4.08 (3.00)	1.43 (2.35)	0.50 (1.01)	4.18 (2.96)	4.55 (2.78)	3.95 (2.92)	3.72 (2.41)
Fear	**5.51** **(3.06)**	**8.00** **(0.84)**	0.46 (0.89)	0.13 (0.46)	4.85 (5.67)	2.98 (1.53)	3.95 (2.73)	3.77 (1.72)
Disgust	2.69 (2.32)	1.62 (1.10)	0.28 (0.83)	0.00 (0.00)	**5.51** **(2.44)**	**6.52** **(1.13)**	**6.11** **(2.31)**	**7.07** **(1.42)**
Anger	3.77 (2.94)	1.00 (1.14)	0.26 (0.68)	0.00 (0.00)	2.95 (3.54)	1.48 (1.16)	5.48 (2.71)	5.83 (1.73)

KEY:
Upper value = mean, lower value = S.D.
Target emotions for each category are shown in bold
P = patients
C = controls

Split plot ANOVAs were conducted for each of the four emotional categories that contained pictures selected to elicit fear, happiness, core disgust and moral disgust. Group was the between participants variable and emotion was the within participants variable. Emotion had six levels. These were the six emotions that participants gave ratings for in response to each picture (anger, sadness, surprise, fear, happiness, disgust). Analysis involved Greenhouse-Geiser correction to control for the possibility of breaking the assumption of sphericity.

For pictures chosen to elicit fear, there was a main effect of emotion, $F(3.52, 23)=40.65$, $p<.001$, with fear being the emotion rated most highly on average by both patients and controls. There was no main effect of group on emotional ratings, $F(1, 23)=0.80$, $p=.381$, but there was a significant interaction, $F(3.52, 23)=6.64$, $p<.001$, suggesting that emotional ratings differed according to group in relation to certain target emotions. Pairwise comparisons indicated that patients and controls differed in their ratings for fear and anger. Patients' fear ratings were significantly lower for fear pictures than controls', $t(13.95=-2.82$, $p=.014$, while their anger ratings were significantly higher than controls', $t(15.78)=3.15$, $p=.006$. No other comparisons were significant.

For pictures selected to elicit happiness, there was a significant effect of emotion, $F(1.49, 23)=324.00$, $p<.001$. Overall, happiness ratings were the highest ratings given by patients and controls. There was no significant effect of group, $F(1, 23)=2.65$, $p=.117$, or interaction, $F(1.49, 23)=0.68$, $p=.472$.

For pictures chosen to elicit core disgust, there was a significant main effect of emotion, $F(2.91, 23)=25.18$, $p<.001$. Overall, disgust was the emotion rated most highly by both patients and controls. There was no significant main effect of group, $F(1, 23)=0.47$, $p=.498$, or interaction, $F(2.91, 23)=1.64$, $p=.191$.

For pictures selected to elicit moral disgust, there was a significant main effect of emotion, $F(3.49, 23)=59.42$, $p<.001$. Disgust was the emotion rated most highly overall by both patients and controls, although mean ratings for anger were also high for both groups. There was no significant effect of group, $F(1, 23)=0.08$, $p=.78$, or interaction, $F(3.49, 23)=0.59$, $p=.649$.

Emotive scenarios

Table 23 shows the mean and standard deviation of the six emotions (anger, sadness, surprise, fear, happiness and disgust) rated by patients and controls for stimuli within each emotional category (fear, happiness, core disgust, moral disgust).

Although differences were not tested statistically, the target emotion for stimuli selected to elicit fear, happiness and core disgust was the emotion given the highest mean rating by control participants. For moral disgust scenarios, the emotion rated most highly on average by patients and controls was anger, but this value was only very slightly higher than the mean rating for the target emotion disgust.

Table 23. Mean and standard deviation of emotional ratings given by patients and controls in response to scenarios within the four emotional categories

Category (scenarios chosen to elicit):	Fear		Happiness		Core disgust		Moral disgust	
	P	C	P	C	P	C	P	C
Happiness	0.12 (0.35)	0.00 (0.00)	**8.25 (1.25)**	**8.60 (0.52)**	0.05 (0.17)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
Sadness	1.47 (2.27)	1.17 (1.56)	0.10 (0.35)	0.05 (0.17)	1.93 (2.40)	1.67 (2.27)	2.85 (2.90)	4.80 (2.55)
Surprise	4.75 (2.43)	6.45 (2.40)	4.45 (2.37)	6.72 (1.33)	4.03 (2.94)	4.38 (2.84)	3.75 (2.77)	4.63 (2.69)
Fear	**6.50 (2.70)**	**8.57 (0.64)**	1.17 (0.42)	0.70 (1.71)	2.33 (2.98)	1.22 (1.42)	3.12 (3.87)	3.00 (2.29)
Disgust	2.75 (3.17)	1.13 (1.65)	0.07 (0.23)	0.00 (0.00)	**6.80 (2.12)**	**7.63 (1.05)**	**6.42 (2.15)**	**7.87 (1.04)**
Anger	4.43 (3.41)	2.25 (2.33)	0.05 (0.17)	0.08 (0.29)	5.00 (2.27)	4.38 (2.05)	7.23 (2.00)	7.95 (1.23)

KEY:
Upper value = mean, lower value = S.D.
Target emotions for each category are shown in bold
P = patients
C = controls

For scenarios selected to elicit fear, there was a significant main effect of emotion, $F(3.03, 22)=64.08$, $p<.001$. Fear was the emotion rated highest on average, by both patients and controls. There was not a significant main effect of group, $F(1,22)=0.02$, $p=.904$, but there was a significant interaction, $F(3.03, 22)=5.93$, $p=.001$. Pair-wise comparisons indicated that patients' ratings for fear were

significantly lower than controls', $t(12.22)=-2.58$, $p=.024$. No other comparisons were significant.

For scenarios chosen to elicit happiness, there was a significant main effect of emotion, $F(2.17, 22)=330.27$, $p<.001$. Mean ratings for happiness were highest for both groups. A significant effect of group was evident, $F(1, 22)=6.34$, $p=.020$, showing that controls gave higher ratings overall. A significant interaction, $F(2.174, 22)=4.93$, $p=.010$ was also evident. Pair-wise comparisons indicated a significant difference for surprise ratings, $t(22)=-2.89$, $p=.009$. Patients gave lower surprise ratings (mean 4.45) in comparison to controls (mean 6.72). No other comparisons were significant.

For scenarios selected to elicit core disgust, there was a significant main effect of emotion, $F(3.23, 22)=56.44$, $p<.001$. Disgust was the emotion rated most highly by both patients and controls. There was no significant main effect of group, $F(1, 22)=0.06$, $p=.809$ and no significant interaction, $F(3.23, 22)=1.01$, $p=.397$.

For scenarios selected to elicit moral disgust, there was a significant main effect of emotion, $F(3.50, 22)=49.15$, $p<.001$. The highest ratings given by patients and controls were for anger, and mean disgust ratings were next highest (Table 22). This finding indicates that the stimuli associated with moral disgust are likely to elicit other strong negative emotions, as also indicated by mean emotional ratings given by controls for moral disgust pictures. There was no significant main effect of group, $F(1, 22)=2.16$, $p=.155$ or interaction, $F(3.50, 22)=0.96$, $p=.425$.

EXECUTIVE TASKS

FAS test

Patients exhibited a highly significant deficit in verbal fluency, MWU=15.5, *p*=.001, generating just 25.31 words on average (S.D.16.47, median 18, range 10-66) over the FAS test, in comparison to controls' mean of 55.33 words (S.D. 18.72, median 51, range 31-92).

DOT-A

Performance on the DOT-A indicated profound impairments in WM in the patient group, MWU=1.5, *p*<.001. Patients exhibited a mean manipulation span of just 4.04 digits (S.D. 0.75, median 4, range 3.5-6) in comparison to controls, who demonstrated intact recall for mean 6.67 digits (S.D. 0.72, median 6.5, range 5.5-8).

Black and white Stroop test

Patients with HD made significantly more errors than controls on the black and white Stroop test, MWU=38.5, *p*=.020. On average, patients made 3.15 (S.D. 3.08, median 2, range 0-9) errors on the inhibition condition of the Stroop, in comparison to controls' 0.67 (S.D. 0.23, median 0, range 0-3) errors. However, patients did not show a significantly greater difference in time taken to complete the inhibition condition to the baseline condition, when compared to controls, MWU=49, *p*=.115. Patients took a mean extra 15.70 (S.D. 16.82, median 10.97, range 3.31-55.6)

seconds to complete the inhibition condition in comparison to baseline, in comparison to mean extra 7.42 (S.D. 3.28, median 7.49, range 2.34-13.1) seconds for controls.

CORRELATIONS

Correlational analysis examined relationships between patients' target emotion ratings and executive performance (Table 24). Relationships were found between executive measures and target emotional ratings. The number of errors made on the Stroop was negatively related to FAS and DOT-A scores. This suggests that patients who performed poorly on the Stroop performed poorly on other executive measures, as would be expected. Happiness ratings on happy scenarios were negatively correlated with FAS scores, suggesting that patients who were less cognitively intact exhibited greater happiness in response to happy scenarios. Fear ratings on fear scenarios were positively related to FAS scores and negatively related to errors made on the Stroop. This suggests that patients who performed more poorly on the executive tests linked to the DLPFC and ACC gave lower fear ratings in response to fear stimuli. However, similar relationships were not apparent between executive performance and emotional ratings for other emotion stimuli, including fear pictures.

There were also correlations between target emotional ratings for stimuli selected to elicit different target emotions. There was a positive relationship between disgust ratings in response to moral disgust scenarios and fear ratings for fear scenarios. This is likely to indicate that patients who felt more fear in response to fear scenarios also felt more disgust in response to moral disgust scenarios. Disgust ratings for core disgust pictures were positively related to disgust ratings for moral disgust scenarios, perhaps indicating that disgust felt in response to moral stimuli could

indeed be related to core disgust. Happiness ratings on happy scenarios were positively related to fear ratings on fear scenarios. There is no obvious interpretation for this unexpected correlation.

The correlations reported in this results section are not discussed further. They were intended to be exploratory, but are often not easy to interpret.

Table 24. Correlations between patients' performance on executive tasks and target emotional ratings for picture and scenarios selected to elicit fear, happiness, core disgust and moral disgust

	1. FAS	2. DOT-A	3. Stroop errors	4. Stroop times	5. Fear P	6. Fear S	7. Happy P	8. Happy S	9. Core disgust P	10. Core disgust S	11. Moral disgust P	12. Moral disgust S
1.	X	.696 <.001	-.293 .155	-.437 .029*	.067 .750	.323 .124	-.144 .491	-.450 .027*	.309 .133	.095 .659	-.062 .770	.295 .162
2.		X	-.47 .021*	-.244 .240	.178 .396	.413 .045*	-.161 .443	-.247 .245	.162 .439	.058 .789	.068 .747	.237 .266
3.			X	.162 .440	- .363 .074	-.574 .003**	-.323 .115	-.353 .091	-.215 .301	-.154 .473	.006 .976	-.061 .777
4.				X	- .110 .601	-.259 .222	-.128 .541	.317 .131	.053 .802	.117 .585	.173 .408	-.139 .516
5.					X	.410 .052	.022 .918	.423 .039*	.253 .223	.300 .154	-.002 .994	.391 .059
6.						X	.307 .145	.251 .237	.530 .008	.464 .023	.196 .360	.556 .005**
7.							X	.383 .065	-.120 .566	.162 .449	-.234 .260	-.059 .783
8.								X	.242 .255	.467 .021	.196 .358	.289 .171
9.									X	.714 <.001	.248 .231	.511 .011*
10.										X	.037 .863	.457 .025*
11.											X	.490 .015

Key: upper value = Spearman's correlation coefficient, lower = *p*-value
P = picture stimuli S = scenarios
* = significant at the 0.05 level ** = significant at the 0.01 level

DISCUSSION

Patients' mean fear ratings were significantly lower than controls' across pictures and stories selected to elicit this emotion. Patients' highest ratings in response to these stimuli were for fear, but these responses were muted in comparison to controls'. Similar findings were reported by Sprengelmeyer, Schroeder, Young and Epplem (2006), who showed that patients with HD can exhibit a steady decline in fear ratings in response to fear eliciting scenarios (Wolpe & Lang, 1964).

Changes in patients' emotional responses to fear eliciting stimuli also included increased anger in comparison to controls. This finding was significant for the pictures but not significant for the scenarios. This may be because the picture task elicited a more automatic response as it required less conscious perspective taking or semantic reasoning than the scenario task. The reasoning processes associated with scenarios perhaps prompt greater access to semantic information about what emotions are relevant to particular situations.

It may be speculated that at times, patients confuse feelings of fear and anger. Sprengelmeyer et al. (1997) showed that patients with HD can confuse negative emotions. The two patients in Sprengelmeyer et al.'s study misreported disgusted facial expressions as depicting anger, and sometimes transposed the correct reponses for faces showing fear and disgust. These patients also completed self assessment scales of emotional experience. Both patients rated their fear experience below that of controls, although Sprengelmeyer et al. caution that these scales do not directly measure patient's current real life experience and can be influenced by past events or world knowledge. It is possible that patients exhibit a "devil may care" attitude, and are less concerned about danger due to knowledge of the fact that they have a terminal

illness. However, evidence of other emotional changes in HD support the idea that patients are likely to exhibit a genuine deficit in emotional experience with a neurological rather than psychological basis.

Changes in fear response in HD could have the potential to lead to subtle alterations in emotional responses to stimuli that elicit a range of negative emotions. For example, the experience of fear could be linked to disgust, as many core disgust elicitors also tend to signal potential threat in the form of contamination. However, this experiment found no evidence of reduced disgust responses towards stimuli chosen to elicit core disgust. The lack of a difference in core disgust responses between patients and controls was unexpected. It is possible that the patients tested in the present study exhibited no disgust differences due to limited dysfunction of brain regions linked to disgust, such as the anterior insula (Wicker et al., 2003).

The patients tested in the current study exhibited no deficits in moral disgust. However, it is possible that this is related to the finding that patients did not exhibit significant deficits in core disgust. In other words, deficits in moral disgust may be more likely in patients with HD who exhibit deficits in core disgust. The possibility of changes in moral disgust in HD has so far received little attention. This is despite evidence of altered social conduct, including increased criminal behaviour (Jensen et al., 1998), and possible changes to social cognition in HD (Havet-Thomassin et al., 2008; Snowden et al., 2003) which could be related to deficits in moral disgust. In the present study, stimuli selected to elicit moral disgust elicited strong feelings of anger in both controls and patients with HD. The investigation of moral disgust is therefore likely to prove complex, due to the fact that stimuli associated with this emotion tend to provoke other negative emotions.

The present study found no evidence that patients with HD show changes in target emotional responses to stimuli selected to elicit happiness. However, patients with HD did exhibit reduced surprise in comparison to controls in response to happiness eliciting scenarios, although not in response to the happiness eliciting pictures. The greatest differences between patients and controls were for scenarios that described lucky events that they had no influence over (a lottery win and a surprise holiday), indicating that patients were less surprised by fortunate events that occurred by chance. This unexpected difference is particularly difficult to explain because decreased surprise was not evident in response to other kinds of stimuli. It could be that patients with HD are more fatalistic. However, this seems unlikely as patients only exhibited this difference on happiness eliciting scenarios.

Patients with HD exhibited significant difficulty on all three executive tasks. The most striking executive deficits were evident in verbal fluency and in WM. Errors on the Stroop provided some evidence of inhibitory difficulty. These findings are in agreement with those reported by other studies of executive functioning in HD (see Montoya et al., 2006). Executive tasks involving fluency, WM and inhibition have been linked to activation within DLPFC and ACC (Aleman & van't Wout, 2008; Peterson et al., 1999; Schroeter et al., 2004; Szatkowska, Grabowska & Szymanska, 2000), so executive deficits in HD probably reflect dysfunction within frontostriatal pathways involving these regions.

The neural basis for reduced fear responses in HD could lie in amygdala dysfunction. Reports have indicated structural changes to the amygdala in HD (Mann, Oliver & Snowden, 1993; Rosas et al., 2001) although alterations in functioning could occur as a result of dysfunction within frontostriatal pathways. This region has been shown to be involved in many fear related processes. These include the experience of

fear and fear conditioning (Le Doux, 1995). Lesions to the amygdala reduce fear in primates (Kalin, Shelton, Davidson & Kelley, 2001) and even cognitive representations (e.g. imagined fear eliciting stimuli) that elicit changes in SCRs are associated with amygdala activity (Adolphs, Russell & Tranel, 1999). Damage to amygdala affects generation of SCRs in response to pictures from IAPS selected to elicit fear (Gläscher & Adolphs, 2003), so further research could measure SCRs in response to these stimuli in patients with HD.

Amygdala dysfunction can also impair the recognition of fear expressed by others vocally (Phillips et al., 1997) and through facial expressions (Calder et al., 1996). One limitation of this experiment was that tasks assessing the recognition of fear in others were not included. Imaging studies have shown an increased amygdala response to fearful faces in comparison to facial expressions of anger (Whalen et al., 2001) and disgust (Phillips et al., 1997). The intensity of fear in facial expressions has also been found to be positively coupled with regional cerebral blood flow changes in the left amygdala (Morris et al., 1996; Morris et al., 1998). Schienle et al. (2002) suggest that the insula can also be activated by fear eliciting stimuli. However, this insula activation may reflect its strong interconnections with the amygdala. It is also true that a number of studies (e.g. Phillips et al., 2004) report a dissociation between regions involved in the recognition of disgusted (insula) and fearful expressions (amygdala), and the present study found no evidence of reduced disgust in response to core and moral disgust eliciting stimuli.

Dysfunction within frontostriatal pathways could implicate a role for the STN in alterations in fear response in HD. Vicente et al. (2009) found that patients with PD who had undergone deep brain stimulation of the STN exhibited reduced fear and lower differentiation between fear and other emotions, in response to films selected to

elicit fear. Other studies involving patients with PD who have undergone DBS of the STN have reported deficits in the recognition of emotional facial expressions, including fearful expressions. Le Jeune et al. (2008) showed that these deficits were linked to decreased glucose metabolism in orbitofrontal regions and suggest that the STN can modulate amygdala activity, via the OFC. There is also some evidence for mood changes and increased anger after DBS of STN in patients with PD (Okun et al., 2009). It is likely that dysfunction of frontostriatal circuitry involving the STN and\or OFC (Haegelen, Rouaud, Darnault & Morandi, 2009) and the amygdala could contribute to the observed fear deficits in patients with HD. The emotional scenarios task used in the present study is likely to be associated with cortical activation due to the use of perspective taking processes that would allow participants to judge their likely emotional responses to the scenarios described.

If amygdala dysfunction is present in patients with HD it could lead to significant personal and social consequences. Reduced fear in response to a range of stimuli or situations could lead to poor decision making and increased risk-taking behaviour in HD. Dysfunction within a frontostriatal circuit involving the amygdala could be related to a range of behavioural changes, ranging from poor decision making on gambling tasks (Campbell et al., 2004; Stout, Rodawalt & Siemens, 2001) to the increased prevalence of drink driving in HD (Jensen et al., 1998). Amygdala dysfunction has also been associated with deficits in ToM. Stone et al. (2003) reported that patients with bilateral amygdala damage exhibited significant deficits on two ToM tasks (a version of the 'Eyes test' and a faux pas task) that were very similar to those shown to elicit impairment in patients with HD (Havet-Thomassin et al., 2008). Changes in reasoning about other's mental states could account for reports of reduced empathy in HD (Snowden et al., 2003) and some of the social consequences

of amygdala dysfunction may result from failure to appreciate fear expressed by others. When Preston et al. (2007) asked participants to imagine fear provoking situations they found no difference in the brain regions activated for personal and non-personal (other centred) imagery. In addition, Sprengelmeyer et al. (2006) found that reduced fear in response to fear eliciting scenarios was correlated with a decline in the recognition of fearful facial expressions in patients with HD. Reduced feelings of fear, and poor appreciation of fear expressed by others could affect social conduct. This could help explain the increased incidence of aggression, anti-social or criminal behaviour in HD (Fenger, Bolwig & Sorensen, 1998).

CHAPTER 5: GENERAL DISCUSSION

5.1: Social Cognition in Disorders of the Basal ganglia

The series of experiments described in this thesis indicated that patients with movement disorders resulting from BG dysfunction exhibit deficits on tasks involving social cognition. Different patterns of impairment were exhibited by patients with PD, HD and TS, as summarised in Table 25. Patients with PD and HD exhibited significant deficits on executive tasks assessing verbal fluency and WM. In contrast, patients with TS only exhibited mild inhibitory deficits. The social cognitive difficulties exhibited by patients with PD were likely to be related to executive dysfunction, whereas the deficits exhibited by patients with HD and TS appeared more independent of such difficulties. The executive and social cognitive deficits reported in this thesis are likely to reflect aberrant processing within cortical regions that result from striatal dysfunction. The precise nature of striatal dysfunction within these BG disorders varies and will result in specific patterns of cortical dysfunction. That is, patients with PD, HD and TS are likely to exhibit different patterns of dysfunction within the ACC, lateral OFC and DLPFC CSTCCs described by Alexander et al. (1986).

Table 25. The deficits on social cognitive and executive tasks exhibited by patients with basal ganglia disorders documented in this thesis

	Patient group		
	PD (mild to moderate: up to Hoehn & Yahr (1967) stage 3).	TS	HD (early stage patients)
Known pathology	SNc degeneration Primary effect: dorsal striatum Secondary effect: DLPFC CSTCC	Assumed ventral striatum (NA) dysfunction which implicates ACC CSTCC	Dorsal caudate degeneration implicates 1. DLPFC CSTCC 2. Lateral OFC CSTCC?
Significant deficits not apparent:	1. Faux pas task 2. Counterfactual syllogisms	1. WM manipulation span task (DOT-A) 2. FAS verbal fluency 3. Standard false belief vignettes	Target emotion ratings for stimuli selected to elicit 1. Happiness 2. Core disgust 3. Moral disgust
Significant executive deficits	1. FAS verbal fluency 2. WM manipulation span task (DOT-A) manipulation span 3. Stroop (inhibition\attention)	The Hayling task (inhibition)	1. FAS verbal fluency 2. WM manipulation span task (DOT-A) 3. Stroop (inhibition\attention)
Significant social cognitive deficits	Standard false belief vignettes	1. Faux pas task 2. Non-literal language task 3. Humourous cartoons comprehension task (cartoons involving sarcasm and irony) 4. UG decisions 5. Socially competitive emotions task 6. The ‘Eyes Task’	1. Target emotion ratings for stimuli selected to elicit fear 2. Anger ratings (increased) for pictures selected to elicit fear
Neural regions likely to be intact	ACC CSTCC	DLPFC CSTCC	ACC CSTCC?
Neural regions likely to be dysfunctional based on behavioural findings	DLPFC CSTCC	ACC CSTCC Amygdala Insula Lateral OFC CSTCC?	DLPFC CSTCC Lateral OFC CSTCC? Amygdala

Three experiments demonstrated that patients with PD can perform poorly on tasks involving false belief. These impairments were not always due to poor inferential reasoning, as errors were even apparent on non-inferential ToM vignettes (PD experiment 2). However, poor performance could have arisen as a result of deficits in executive function rather than deficits in ToM *per se*. For example, the WM deficits exhibited by patients with PD in experiments 1 and 2 could have made it difficult for them to remember the story information in order to make inferences about mental states. In experiment 3 a group of PD patients who exhibited less significant WM deficits made fewer ToM errors, particularly during conditions where WM demands were reduced. In fact, no false belief errors were made in the condition with least WM demands (when vignettes were presented as a comic strip and left in view throughout testing). Evidence of deficits in ToM *per se* in PD was further weakened by the finding that patients performed normally on the faux pas task during PD experiment 1. However, clinicians and carers should be made aware that patients' executive deficits could lead to difficulties in reasoning about mental states. Patients with PD could exhibit difficulties with social cognition in everyday life, perhaps leading to social communication difficulties and relationship problems.

Patients with PD made more errors on the false belief task than faux pas task. This is perhaps surprising, as the latter is thought to be a more difficult test of ToM and is mastered later in development (Baron-Cohen et al., 1999). This unexpected finding may have occurred because understanding faux pas involves both affective ToM (consideration of the victim's offence in response to the inappropriate remark) and cognitive ToM (the protagonist's belief that the remark is offensive). Patients with PD could have greater difficulties with cognitive ToM, which would affect performance on the false belief questions asked during the standard false belief

vignette task. However, performance on the key question asked during the faux pas task ("did someone say something they shouldn't have?") would not have been affected, as this question could be answered correctly by reasoning about the victim's affective mental state without recourse to reasoning about cognitive mental states. One difficulty with this explanation is that patients did not make significantly more errors than controls on the belief check (that assessed the understanding of a cognitive mental state) during the faux pas task.

Perhaps a more parsimonious explanation for the discrepancy between performance on the standard false belief vignettes and faux pas task is that the faux pas task illustrates a fairly common occurrence in social interaction which can be understood through recognition of the violation of a social norm. That is, a decision that the remark is inappropriate could arise from a judgment that the remark is negative and therefore does not sound like something that would commonly be said in that social context. Such reasoning does not involve true consideration of the characters' mental states and this task may therefore not always test ToM. The false belief tasks used in this series of experiments tended to involve descriptions of more arbitrary associations and the questions could not be answered through an understanding of social norms. Patients' performance could have suffered more on the standard false belief vignette task because it relied more heavily on memory and attentional processes that are necessary for ToM rather than semantic knowledge about socially acceptable behaviour.

Patients with TS showed a pattern of performance on the faux pas task and false belief vignettes that contrasted with the performance of PD patients. That is, patients with PD performed normally on the faux pas task and exhibited deficits on the false belief vignettes, whereas patients with TS exhibited the converse pattern of

performance. One way of describing this difference is that patients with PD can exhibit difficulty on tasks that require just cognitive ('cool') ToM, whereas patients with TS exhibit deficits on tasks that involve aspects of affective ('hot') ToM. This complementary pattern of deficits could be related to executive function. Patients with PD did not exhibit fundamental changes in ToM *per se*. Their deficits on the standard false belief vignette tasks, which consisted of arbitrary associations, rather reflected executive problems including compromised WM. The poor performance exhibited by patients with TS on a range of social cognitive tasks implies that they exhibit changes in ToM *per se*. These deficits, however, are likely to apply to certain aspects of ToM which do not encompass deficits in reasoning about first order cognitive mental states, as patients performed well on standard false belief vignettes in TS experiment 1.

Patients with TS exhibited deficits on a range of social cognitive tasks. On some occasions, deficits in ToM appeared to result from poor (or a lack of) inferential reasoning. For example, failures to infer mental states could have led to the errors observed on the faux pas and non-literal language task. The inferential reasoning processes involved in ToM are likely to make considerable cognitive demands. This is illustrated by the finding that cognitive limitations such as executive deficits can impair inferential reasoning (Monetta, Grindrod & Pell, 2008). Although patients with TS exhibited limited evidence of executive dysfunction, the inhibitory deficits observed on the Hayling task suggest that patients' executive functioning is impaired in the context of certain demands. Patients with TS may allocate a considerable amount of cognitive resources (e.g. attention or concentration) to the effort involved in suppressing tics. This could lead to cognitive resource saving strategies that are biased against voluntary higher level reasoning. The use of such strategies could result in superficial interpretations of social interaction and deficits in understanding

indirect communication and mental states (as reported in chapter 3). It may be that greater cognitive resources (e.g. increased attention) are available at a cost (i.e. poorer tic suppression). This could further explain why patients perform better on questions that explicitly demand higher level reasoning (e.g. the Hinting Task: what does this indirect request really mean?) in comparison to tasks that do not force this level of reasoning directly (e.g. the Pragmatic Story Comprehension Task: which of these remarks would make sense?). That is, patients could be more likely to engage the cognitive resources required by a ToM task when questioned more explicitly.

Other unconventional responses given by patients with TS on social cognitive tasks were associated with a tendency towards negative or cynical interpretations of social situations. This kind of error indicated that while some patients are clearly capable of reasoning about mental states, they nonetheless demonstrate a tendency to unconventional interpretations about communicative intention and social interaction. These unconventional interpretations could reflect poor emotional regulation in response to stimuli containing negative affect, which could consequently affect patients' reasoning. Increased sensitivity to stimuli associated with negative affect in TS would contrast with the decreased sensitivity to negative emotions exhibited by patients with HD (i.e. the reduced fear ratings reported in chapter 4).

The pictures selected to elicit fear resulted in reduced fear ratings in HD patients but higher anger ratings. This finding is in keeping with the problems with anger that are associated with HD patients including irritability, aggression and explosive disorder (Folstein, 1989). The current findings offer greater insights into the possible basis of some of the behavioural problems associated with HD. Changes in the subjective experience of fear and anger may be linked to difficulties understanding fear in others, which could contribute to the anti-social symptoms noted above.

Reduced fear responses also have the potential to contribute to risk taking behaviour and could therefore pose a threat to patients' safety.

THE NEURAL BASES OF SOCIAL COGNITIVE DEFICITS IN DISORDERS OF THE BASAL GANGLIA

The basal ganglia are able to affect both motor control and cognition by virtue of its extensive influence over the whole of the frontal lobe. The neural bases of the motor deficits associated with PD, HD and TS are well described (chapter 1). Many patients with these disorders take medication that is specifically prescribed to affect the functioning of motor circuitry. These pharmacological treatments have the potential to also alter the functioning of parallel neural circuits that subserve cognitive or emotional functions. The possibility that some of the deficits reported in this thesis could have been influenced by patients' medications is therefore worthy of consideration. A medication related factor (time since medication had been taken) was investigated in patients with PD in experiment 1 (although not in further experiments) and was not found to have a significant influence. Although some of the patients with TS tested were taking medications, many patients who exhibited deficits on tasks were not under pharmacological treatment. Few of the patients with HD were taking any medication. In conclusion, it may be considered that there is no convincing evidence to suggest that the influence of medication made a considerable contribution to the social cognitive (or executive) deficits recorded in this series of experiments, so the observed deficits reflect neuropathological changes. However, the possibility that the presence or absence of medication could have affected certain patients' task performance cannot be entirely ruled out.

In PD, degeneration of dopaminergic cells in the SNc initially results in dopaminergic denervation within the dorsal striatum (e.g. Tedroff, Ekesbo, Rydin, Longstrom & Hagberg, 1999). The resultant dysfunction of the dorsal striatum could lead to changes in the functioning of the DLPFC as well as the supplementary motor area. The findings reported in section 2 are in accordance with these pathophysiological events. Dyfunction within the DLPFC CSTCC (as described by Alexander et al., 1986) would explain why the early stage patients tested demonstrated significant executive deficits in both this series of PD experiments and in other studies (e.g. Gabrieli et al., 1996; Lees & Smith, 1983; Zgaljardic et al., 2006). These executive deficits included deficits in verbal fluency, WM and perhaps more general attentional dysfunction (which is likely to have contributed to poor performance on the Stroop). Dysfunction of the DLPFC CSTCC is also likely to have led to the executive deficits exhibited by patients with HD reported in chapter 4. This circuitry was not implicated in the abnormal responses made by patients with TS, who did not exhibit significant deficits on fluency and WM measures (chapter 3).

PD experiments 1-3 provide no evidence of ToM deficits that are clearly independent of executive impairment. Dysfunction within medial OFC (that is, part of the ACC CSTCC as described by Alexander et al., 1986) is likely to lead to more general and consistent difficulties on ToM tasks than those reported in chapter 2. The suggestion that the neuropsychological functioning of the ACC CSTCC (which includes the ventral striatum) is intact in PD would be in accordance with the assumption that dopamine inputs into the ventral striatum from the VTA are intact. However, Peron et al. (2009) reported impairments on the faux pas task in patients with later stage PD. Faux pas deficits could implicate medial OFC (e.g. Stone et al.,

1998). This implies that the ACC circuit may be affected in patients in a more advanced stage of the disease than those tested in this series of experiments.

There was greater evidence that the ACC CSTCC (as described by Alexander et al., 1986) is dysfunctional in TS and HD than PD. Patients with TS or HD exhibited deficits on social cognitive tasks that appeared less related to executive dysfunction. Patients with TS exhibited impairment on a range of tasks that have been linked to the functioning of regions such as the VMPFC, which forms part of the ACC CSTCC. Patients with HD exhibited deficits in subjective fear in response to verbal and visual stimuli (similar emotional deficits were reported by Sprengelmeyer et al., 2006) that could specifically implicate the amygdala. This structure has connections to many parts of the OFC (Barbas, 1995). Dysfunction of the amygdala could therefore be related to changes in the functioning of the ACC (which includes medial OFC) and/or lateral OFC CSTCCs (as described by Alexander et al., 1986).

In HD, alterations in fear response could reflect a reduction in fear *per se*, as a result of amygdala dysfunction. Alternatively, these changes could result from a reduced awareness of patients' understanding of their own emotional responses, which could implicate cortical regions. Personal experience of fear is likely to be closely related to activity in the amygdala. Activity in this structure increases in response to fear eliciting stimuli presented in visual (Anderson & Phelps, 2001) and auditory modalities (Scott et al., 1997). It has also been shown that electrical stimulation of the amygdala in humans elicits autonomic reactions associated with feelings of fear (Gloor, 1992). Difficulties in understanding one's own emotions could involve dysfunction of the paracingulate gyrus. This structure, which borders rostral ACC and the medial prefrontal cortex, is active during self-reflective thought (Johnson et al. 2002) and more specifically, when representing one's own mental

states (Frith & Frith, 1999). However, dysfunction in cortical regions could be expected to lead to general deficits in the understanding of emotions whereas patients exhibited a selective deficit with fear. Reduced subjective fear ratings in HD could result from dysfunction within connections between the amygdala and ACC or medial OFC within the ACC CSTCC.

Dysfunction within the ACC CSTCC, which involves the medial OFC and ventral striatum (described by Alexander et al., 1986) is likely to have led to the differences in performance on ToM tasks that were demonstrated by patients with TS. The suggestion that the ACC is likely to be dysfunctional in TS is supported by imaging and behavioural evidence. Patient exhibit mild deficits on the Hayling task (as seen in chapter 3 and as reported by other studies e.g. Channon et al., 2006), a test which is sensitive to ACC function (Nathaniel-James et al., 1997). Imaging studies have revealed abnormalities in this region in TS, including evidence of decreased grey and white matter (Muller-Vahl et al., 2009).

Patients with TS exhibit some characteristics that are similar to those displayed by patients with medial OFC dysfunction. For example, patients with TS exhibit NOSIS whilst inappropriate social behaviour is exhibited by patients with sustained orbitofrontal damage (e.g. Beer, John, Scabini & Knight, 2006). Dysfunction of this region has also been linked to poor prioritization of solutions to interpersonal problems (Saver & Damasio, 1991). In keeping with this view, one study reported that patients with TS produced fewer solutions and selected poorer final solutions than controls in response to problematic social scenarios (Channon, Crawford, Vakili & Robertson, 2003). These findings add support to the conclusion that the social cognitive deficits seen in TS result from dysfunction of the ACC CSTCC (as described by Alexander et al., 1986).

The difficulties with drawing inferences about mental states that were exhibited by some patients with TS are likely to reflect dysfunction within ACC rather than DLPFC circuitry. This tentative conclusion is based on the finding that patients with TS performed well on a WM task linked to DLPFC functioning. There is evidence that the ACC is also involved in tic suppression and, as suggested above, this factor could be related to some of the observed deficits. Thus, increased ACC activity occurs during tic suppression (Peterson et al., 1998) and there is a positive correlation between activity in this region and tic severity (Stern et al., 2000). Engagement of the ACC CSTCC in tic suppression may result in fewer resources being available for social cognitive tasks. It is perhaps likely that one of the processes involved in tic suppression is a form of inhibition. However, there was no evidence that performance on measures involving this executive function was linked to the observed social cognitive deficit.

Other deficits on social cognitive tasks exhibited by patients with TS that could also be related to dysfunction within the ACC circuit included poor reasoning in relation to social stimuli associated with negative emotions. The VMPFC (which includes medial OFC, part of the ACC CSTCC) has a role in the automatic regulation of emotional behaviour (Philips et al., 2003). The ACC is activated in situations that require the control of negative emotional responses (Ochsner et al., 2006). Furthermore, the resolution of conflict associated with negative emotion activates ventral ACC and the amygdala (Etkin, Egner, Peraza, Kandel & Hirsch, 2006). Poor regulation of or control over negative emotion provides one explanation for the finding that patients with TS exhibit an increased tendency to reject offers during the UG. The conventional response to unfair offers could involve the suppression of an urge to reject that derives from negative affect due to the realisation of unfairness.

Dysfunction of the ACC CSTCC (as described by Alexander et al., 1986) could be associated with poor control over this urge leading to an increased number of rejections.

One region that may fulfill a particularly important role during the UG is the insula. The insula has connections to the ACC and amygdala (Shelley & Trimble, 2004) and is active when subjects decide to reject an unfair offer (Sanfey et al., 2003). The insula is also active during tic release (Stern et al., 2000; Lerner et al., 2007) and when neurologically intact participants suppress the natural urge to blink (Lerner et al., 2009). This region contains a somatotopic representation of the subjective feelings associated with one's movements of the body (Craig, 2009) and could sense the premonitory sensations linked to motor tics (Kwak, Dat Vuong & Jankovic, 2003). Lerner et al. (2009) see the insula as a "sensor and executor of physiological urges" (pp. 220) whereas the ACC is seen as providing motivational input to suppress an urge. Failure of the ACC to suppress an urge may result in a tic.

The OFC has medial and lateral regions. The lateral OFC is connected to the insula (Shelley & Trimble, 2004). Consequently, the lateral OFC CSTCC could be implicated in the deficits exhibited by patients on the UG. Changes in the functioning of the lateral OFC CSTCC were found by Jeffries et al. (2002), who showed that patients with TS exhibit abnormal activity in frontostriatal pathways involving the lateral OFC and insula.

Dysfunction within the lateral OFC CSTCC could also be implicated in patients' deficits on tasks involving non-literal language. The IFG, which can be considered part of the lateral OFC CSTCC, is active during the processing of sarcasm (Uchiyama et al., 2006). Studies have reported abnormalities of the IFG in patients with TS. For example, one imaging study reported decreased white matter in this

region (Muller-Vahl et al., 2009). The IFG is also active during the Hayling task (Nathaniel-James et al., 1997) and some studies implicate this structure in inhibitory control (Aron, Robbins & Poldrack, 2004). It may therefore be speculated that dysfunction of the IFG in TS could lead to difficulties in the comprehension of non-literal language.

The social cognitive deficits described in this thesis could be related to the incidence of NOSIS in TS. One way is through poor inferential reasoning about people's mental states in response to their behaviour. For example, some patients could make socially inappropriate remarks because they fail to consider other people's feelings. However, it may be speculated that NOSIS could occur in patients who are aware of the negative affective consequences of socially inappropriate behaviour, in association with emotional dysregulation.

NOSIS are dependent on the stimuli in the patient's immediate environment. In patients who exhibit these symptoms, an intial evaluation of reinforcement contingencies signalled by the environment could be associated with a greater awareness of potential behaviours linked to negative affective consequences (e.g. shouting "fatty" on seeing a person who is overweight). This process is likely to involve the OFC which is involved in the appraisal of stimuli in relation to associated reinforcement contingencies (e.g. Rolls, 2004). An awareness of the negative connotations associated with a particular behaviour may be associated with a change in autonomic arousal. Changes in autonomic arousal could act as a deterrent to warn against behaviour linked to negative reinforcement. Autonomic arousal is regulated by the heavily interconnected amygdala and insula. These neural structures process negative affective experiences and contribute to social judgments (Shah, Klumpp, Angstadt, Nathan & Phan, 2009). The anticipatory autonomic arousal associated with

the awareness of potential socially inappropriate behaviours could be heightened in patients with TS. Increased arousal in TS could lead to greater psychological and physical discomfort. This increased discomfort could lead to an urge to release the behaviour in order to reduce the anticipatory arousal. Feeling an urge to act and feeling discomfort as a result of the increased arousal are likely to involve the insula and ACC. The insula both senses interoceptive information and is involved in the generation of subjective feelings and urges (Craig, 2009). The ACC is also activated by autonomic arousal (Critchley, 2005). In healthy individuals, ventromedial prefrontal regions help regulate arousal and somatic state through the amygdala (Williams et al., 2004). In TS, failure of VMPFC and\or ACC to control or regulate this arousal could lead to NOSIS, and other symptoms of emotional dysregulation (such as the social cognitive deficits described in chapter 3).

One interesting consequence of this model is that efficacious treatments for TS could regulate the functioning within these neural regions by either: reducing emotional arousal, encouraging the attenuation of autonomic responses associated with the arousal or enhancing cortical control over the arousal. Future research should investigate the possibility of increased autonomic reactivity in patients with TS.

5.2: Implications for Social Cognition

The experimental findings described in this thesis demonstrate that striatal dysfunction may lead to a range of deficits in abilities related to social cognition. The different social cognitive difficulties exhibited by each patient group can offer insight into issues related to the study of social cognition in general. These include the impact of executive functioning, semantic knowledge and personal experience on ToM performance.

THEORY OF MIND AND EXECUTIVE FUNCTIONING

As discussed in section 1.6, developmental (e.g. Carlson et al., 2002), clinical (Henry et al., 2006) and imaging (Saxe et al., 2006) studies have explored the relationship between performance on ToM and executive tasks. Executive functions could make different contributions to ToM performance. WM could allow one to hold different perspectives of the world in mind. Other executive functions, such as attentional set-shifting and\or inhibition may be needed to switch away from one's own to another's perspective in order to understand their mental state.

The social cognitive tasks administered are likely to vary in their demands on executive function. Accordingly, one reason for the differing social cognitive deficits exhibited by patients with BG disorders is likely to be the degree of executive dysfunction exhibited by patients with these disorders. Greater executive deficits were exhibited by patients with PD than patients with TS. Patients with PD also performed poorly on the standard false belief task which did not elicit significant impairment in patients with TS. It could be that reasoning about beliefs involves greater cognitive

demands because beliefs are abstract. Accordingly, patients with PD would be expected to perform more poorly on the false belief task as a result of WM deficits and attentional difficulties. These findings appear to be in accordance with those reported by Shamay-Tsoory and Aharon Peretz (2007) who showed that difficulties in reasoning about cognitive mental states (i.e. 'cool' ToM) could arise in association with lesions to DLPFC.

Patients with PD exhibited little difficulty in understanding faux pas which involved reasoning about affective mental states. In contrast patients with TS performed poorly on this task. The poor performance exhibited by patients with TS on the faux pas task was not correlated with executive dysfunction. Shamay-Tsoory & Aharon-Peretz (2007) showed that damage to VMPFC (which includes medial OFC) could lead to deficits in affective ToM. The findings reported in chapter 3 appear to support the suggestion that dysfunction within medial OFC can lead to particular impairments in ToM involving affective mental states (i.e. 'hot' ToM) which appear to be independent of executive dysfunction.

The findings reported in this thesis indicate that certain executive functions are likely to be important for ToM performance. Relationships were observed between ToM performance and WM and verbal fluency scores in the experiments reported in chapter 2. However, these relationships were not found consistently. This could be because it is necessary to have an executive deficit at a certain threshold before it leads to a decrement in ToM performance. This possibility was supported by the finding that mainly patients with WM scores below the group median performed poorly on the ToM vignette task in experiment 3.

WM could be critically important for ToM reasoning as indicated by developmental studies (e.g. Gordon & Olson, 1998) and the findings in chapter 2.

WM ability reflects the capacity to hold and manipulate information in one's mind. In order to understand a person's false belief, one must hold in mind the situational context (or series of events) so as to allow the adoption of the perspective of the person holding the false belief. In this way, WM could make an incidental contribution to ToM performance, that is, it is not considered part of the perspective taking process itself.

Some authors suggest that WM may be considered to make a more fundamental contribution to ToM. Apperly, Samson and Humphreys (2005) suggest that although participants with deficits in WM can perform poorly on false belief tasks due to performance demands, it is also possible that belief reasoning is carried out in a generic WM system (pp.573). For example, the WM system could provide a basis for holding in mind one's own perspective and the perspective of another, and be involved in the 'decoupling' of those perspectives (Gallagher & Frith, 2003). This would mean that even controlling performance demands will not necessarily lead to an improvement in performance as patients would continue to demonstrate difficulties in competence. The experiments with patients with PD in chapter 2 can be considered to provide some evidence for this proposal, as patients continued to make false belief errors in some conditions involving reduced WM demands (PD experiments 2 and 3).

There are also difficulties investigating the contribution that inhibition makes to ToM performance. The ToM deficits exhibited by patients with TS (chapter 3) were not related to the mild inhibitory difficulties observed on the Hayling task. However, inhibition could still have contributed to patients' difficulties in some way. Patients' performance on other tasks provided evidence of poor reasoning in association with stimuli related to negative affect. It could be that patients exhibit most inhibitory difficulties when reasoning is influenced by negative emotions. This

would explain the deficits on social cognitive tasks linked to negative emotion (the faux pas task, UG, 'socially competitive emotions' task etc.), in contrast to the lack of prominent difficulties on the Stroop (experiments 2 & 3) and the standard false belief vignette task (experiment 1), which did not involve emotion. Perhaps broader types of executive function should be considered slightly different abilities depending on the context in which they are used or measured (see Aron, 2007). Inhibition for example, would be better conceptualised as a collection of abilities that can be applied to cognition, emotion or behaviour. It could therefore follow that particular types of inhibition are more relevant to performance on different ToM tasks. For example, performance on tasks that involve inhibition of one's own emotion could be more closely related to reasoning about another's emotion.

In summary, it is hard to determine the exact contribution made by different executive functions to ToM. It could be that the roles of certain executive functions overlap or are interdependent. For example, understanding another person's mental state could involve first ignoring one's own mental state through a process of inhibition. The perspective taking process that involves imagining another person's point of view could be seen as involving a shift of attention, but this shift of attention may further be conceptualized as involving inhibitory ability. As shifting away from one's own perspective could be considered to require inhibition and/or attentional set-shifting there are even problems with knowing whether the executive functions are themselves truly independent.

THE ROLE OF SEMANTIC KNOWLEDGE AND PERSONAL EXPERIENCE ON TOM PERFORMANCE

ToM performance on tasks such as the faux pas task could be influenced by semantic knowledge about social norms and convention. Reasoning about socially (or morally) acceptable behaviour should provide a greater opportunity for factors such as social learning or even moral reasoning to influence performance. Children can acquire an understanding of what constitutes socially unacceptable behaviour through a process of classical or operant conditioning, whereby the child learns to associate certain behaviour with negative consequences (Aronfeed, 1968). These consequences may not always require an understanding of another's mental state. During the faux pas task, the participant could recognize a socially inappropriate remark simply because past experience or learning informed them that making that kind of remark is out of place rather than because they truly reasoned about the implications of such behaviour, such as the negative emotion felt by the subject of an insulting remark. It is possible that patients with PD in experiment 1 performed well on the faux pas task simply by recognizing the violation of a social norm rather than reasoning about mental states. Task performance does not provide such a pure measure of ToM ability (as discussed in section 5.1) in cases where performance is not contingent on on-line reasoning about mental states.

Reasoning about an emotion in another and one's own emotional experience appear to be related and perhaps involve the same neural substrate (e.g. Wicker et al., 2003). The reduction in fear response in HD could therefore be associated with poor appreciation of this emotion when expressed by others. This possibility is supported by the observation that HD patients exhibit poor recognition of fearful facial

expressions (e.g. Henley et al., 2008). As HD involves neural degeneration later in life, this may imply that the neural substrates involved in understanding an emotion in another ('hot' ToM) are necessary for on-line performance and not just for learning. As one's own emotional experience changes, one's ability to reason about other's emotional experience could also change. The findings reported in this thesis suggest that structures thought to play a key role in one's own emotional experience (such as the amygdala and insula) appear to subserve processes that have a greater impact on ToM performance than previously appreciated.

THE ASSESSMENT OF TOM: DEFINING DIFFERENT TYPES OF IMPAIRMENT

Careful task design should allow the type or level of deficit exhibited by a participant to be specified. The extended questioning associated with the faux pas task provided qualitative data that led to an enhanced appreciation of the nature of changes in ToM exhibited by participants with TS (chapter 3). The subtle differences in reasoning exhibited by patients with TS were most apparent on later questions on the faux pas task that addressed the content of characters' minds more explicitly. The social cognitive deficits demonstrated by patients with TS raise an important issue relating to the assessment of ToM ability. These patients made significantly more errors on many social cognitive tasks in comparison to controls. However, on many occasions, patients did demonstrate evidence of the ability to reason about mental states. The findings relating to the performance of patients with TS indicate poor scores on ToM tasks do not necessarily indicate a deficit in terms of a lack of ability. Perhaps patients' unconventional responses should not be referred to as 'deficits'.

There appeared to be a difference between patients' performance on tasks that required more spontaneous reasoning about mental states and those that directed participants to think about ToM more explicitly. In TS experiment 2, deficits were evident on a non-literal language task that asked participants to select appropriate non-literal remarks from a short list before discussing their meaning. However, the same group of patients performed well on another non-literal language task when the remarks had to be accepted as appropriate because the patients were simply asked to explain them. This task is likely to have directed reasoning about mental states more explicitly, as the participant was asked to think about what the character meant by their remark, rather than whether the remark made sense at face value. These discrepancies in performance indicate that certain tasks can reveal deficits in a certain level of ToM. Consequently, reasoning about mental states spontaneously and reasoning about them when explicitly directed or cued to do so could be viewed as separate abilities.

5.3: Implications for Models of Frontostriatal Circuitry

The anatomical model of basal ganglia-cortical interactions most frequently used to account for the deficits seen in patients with BG disorders is the CSTCC model developed by Alexander et al., (1986). Although more than 20 years old, this model can still provide an initial framework for attempting to identify the neurological bases underlying the cognitive and emotional deficits reported in this thesis. However, many of the social cognitive difficulties exhibited by patients with HD and TS in the current series of experiments cannot be accommodated by the Alexander et al. model. The current findings therefore highlight the need to develop a more detailed and inclusive model of frontostriatal interactions.

FINDINGS THAT CAN BE UNDERSTOOD THROUGH REFERENCE TO THE MODEL DESCRIBED BY ALEXANDER ET AL. (1986)

Some of the findings of this series of experiments fit well with existing model of CSTCCs (Alexander et al., 1986). These include the observed executive dysfunction in patients with PD and HD. Such difficulties are likely to occur due to dysfunction with the dorsolateral prefrontal CSTCC as a result of dysfunction of the dorsal striatum. The model could also account for the changes to ToM in TS which are likely to be related to pathological changes in ACC circuitry. Imaging studies of TS patients (e.g. Muller-Vahl et al., 2009) have reported abnormalities within regions that form part of the ACC CSTCC.

The experiments in this thesis provide evidence that the CSTCCs conceptualised by Alexander et al. (1986) are likely to make different contributions to performance on social cognitive tasks. Patients with PD (chapter 2) predominantly exhibit deficits associated with dysfunction of the DLPFC CCSTC. The executive deficits that result from this can lead to poor reasoning about false belief (impairments in 'cool' ToM). Patients with TS and HD appear to exhibit slightly different impairments which are in keeping with dysfunction of circuitry involving the OFC. The patterns of deficits exhibited by patients across the different tasks suggest that reasoning about affective mental states ('hot' ToM) and social norms utilizes the ACC CSTCC. These findings therefore provide further support for the existence of different frontostriatal circuits which can make different contributions to performance on cognitive and social cognitive tasks.

FINDINGS THAT ARE NOT ACCOMMODATED BY ALEXANDER ET AL.'S (1986) MODEL

Some of the findings reported in this thesis are difficult to accommodate in the CSTCC models as originally described by Alexander et al. (1986). The social cognitive deficits described in experiments carried out with patients with HD and TS implicate the involvement of structures that are not described in terms of frontostriatal circuitry. Fear deficits in HD and poor performance on the 'Eyes test' as exhibited by patients with TS are likely to implicate the amygdala. The performance of patients with TS on the UG (experiment 3) implicates changes in neural functioning involving the insula. This structure is also implicated in disgust deficits in HD (as reported in other studies, e.g. Henley et al., 2008). In relation to Alexander et al's model, it is not

clear why the amygdala or insula should be dysfunctional in HD or TS, as these regions are not suggested to be directly influenced by the outputs of any of the CSTCCs. However, the amygdala and insula do have connections to the regions of the OFC that are considered part of the ACC and lateral OFC CSTCCs. Anatomical models of basal ganglia-cortical interactions should be extended to encompass a stronger role for temporal structures in the functioning within frontostriatal circuits. . There could be changes in functioning within the amygdala and insula, in the connections between these structures and other neural regions, and\or within other neural regions that influence these structures.

A further limitation of the model described by Alexander et al. (1986) is that the roles of certain parts of the BG, in particular the STN, were not outlined. The model refers to the direct pathway through the BG but does not consider the indirect pathway that passes through the STN. The STN, which is now known to have an important role in affect, could contribute to the deficits exhibited by patients with HD in Chapter 4. Dysfunction of the STN (Le Jeune et al., 2008) has been linked with changes in fear responses and patients with PD undergoing DBS of STN can show changes in mood including increased anger (Okun et al., 2009). Although this nucleus is clearly implicated in motor function, it has more recently begun to be recognized as subserving a key role in limbic functions (Haegelen et al., 2009). An updated model of frontostriatal circuitry could specify how particular parts of the STN are involved in different frontostriatal pathways and associated functions. Joel and Weiner (1997) suggest that the STN can be separated into sensorimotor (dorsolateral), cognitive-associative (ventromedial) and limbic (medial) regions. For example, the ventromedial tip of the STN receives afferents from cortical regions including medial prefrontal and ACC (Canteras, Shammah-Lagnado, Silva & Ricardo, 1990). Different

parts of the STN could therefore be involved in different frontostriatal circuits. An improved model would include a description of the roles of these subdivisions of the STN.

DIFFICULTIES CONCEPTUALISING THE FUNCTIONAL ANATOMY OF THE MEDIAL AND LATERAL ORBITOFRONTAL CORTEX

One particular difficulty with using Alexander et al.'s model (1986) to interpret clinical findings results from the division of the OFC into medial and lateral regions. The medial and lateral OFC form critical parts of separate frontostriatal circuits: the ACC CSTCC and lateral OFC CSTCC respectively. Although such a subdivision could allow for greater specificity, it is difficult to identify particular functions that are associated with these subregions. There is currently limited literature available to aid the distinction between medial and lateral OFC as many studies refer simply to 'orbitofrontal cortex'.

A further difficulty concerns the problem of specifying which of the CSTCCs the amygdala forms part of. The amygdala receives many projections from the OFC but relatively few from BA 10 (Ghashghaei, Hilgetag & Barbas, 2007) which can be considered part of lateral OFC CSTCC (as described by Alexander et al., 1986). It may therefore be that the amygdala has a greater influence on the ACC CSTCC than the lateral OFC CSTCC.

Similar problems apply to the insula. The insula has connections with many parts of the OFC (Shelley & Trimble, 2004) and activity in the anterior insula is often mirrored in changes in the the IFG (Craig, 2009). However, the anterior insula is also strongly connected to the amygdala (Holstad & Barbas, 2008) so could influence the functioning of both the ACC and lateral OFC CSTCC.

The STN could also play an important role in both the lateral OFC and ACC circuits. DBS of the STN can affect activity in the insula and orbitofrontal regions including the IFG (Schroeder et al., 2003). Connections via the OFC (Canteras et al., 1990), may also allow the STN to modulate the activity of the amygdala (Le Jeune et al., 2008), although there is currently no evidence for direct connections between the STN and OFC.

5.4: Future Research and Conclusion

The experiments presented in this thesis have revealed that deficits in social cognition are exhibited by patients with BG disorders. Further work is essential in order to address specific issues that have been raised in relation to the nature of the impairments exhibited by these patient groups and to determine the neural basis for these difficulties. The findings discussed in previous chapters also motivate the design of investigations that will enhance our understanding of social cognition and the neuroanatomical circuits involved in different cognitive functions.

STUDIES INVESTIGATING SOCIAL COGNITION

One area of social cognition that merits further research is the relationship between ToM and executive functioning. For example, the experiments conducted with patients with PD have shown that executive limitations such as deficits in WM can contribute to difficulties with ToM. Different facets of ToM could make differing executive demands. For example, there may be a varying executive contribution whether reasoning about cognitive or affective mental states. Zelazo et al. (2005) suggest that like ToM, executive functions can be categorised as 'hot' if they involve affect or 'cool' if not. Although many studies have investigated the relationship between 'cool' executive functions on fluency, WM and shifting tasks, fewer have investigated links between ToM and performance on tasks involving 'hot' executive functions, such as affective decision making tasks. Future studies could investigate relationships between performance on tasks involving 'hot' or 'cool' aspects of ToM, and both 'hot' and 'cool' executive tasks.

A potential limitation of the research described here is the lack of inclusion of an attentional set-shifting task. Patients with PD exhibit deficits in set-shifting (e.g. Cools et al., 2001b; Lees & Smith, 1983) and Natsopoulos et al., (1997) showed that reasoning impairments can be linked to poor set-shifting performance. Frye, Zelazo and Palfai (1995) showed that children's ToM performance can also be related to mental shifting ability. Kloo and Perner (2003) reported correlations between children's set shifting performance on the Dimensional Change Card Sorting Task (DCCST) and false belief tasks. They further showed that training children on one of these tasks led to improved performance on the other kind of task. These authors suggest their findings indicate that a common ability is needed for the DCCST and false belief task, to be precise, the ability to understand that an object or entity can be viewed in more than one way (i.e. possess more than one description) at the same time. Understanding false belief necessitates an appreciation that two people can have different views or descriptions for the same world. The DCCST requires a shift from sorting cards based on one descriptive dimension (e.g. colour) to another dimension (e.g. shape). As set shifting deficits can be related to impairments in ToM it would be useful to assess set-shifting alongside performance on the ToM tasks in patients with BG disorders.

Our understanding of the relationship between ToM and executive functioning may be enhanced through studies that can relate specific processes involved in ToM to particular executive functions. The perspective taking process involved in ToM could require an initial inhibition of one's own mental state state prior to the expression of the ability to shift attention in order to appreciate another's point of view. Studies could identify specific deficits with inhibition or attentional set-shifting

that were related to ToM impairment. This would enable ToM deficits to be accounted for in terms of precise underlying executive processes. However, there are clear difficulties with such investigations, as the contribution of some executive functions could overlap, or be interdependent.

One way executive functioning is likely to affect ToM performance is through inferential reasoning. Some of the ToM deficits reported in this thesis could be linked to general difficulties with inferential reasoning. This limitation should be addressed in future research by investigating patients' performance on tasks that involve inferential reasoning but not ToM. Studies have indicated links between executive deficits and impairments in inferential reasoning (e.g. Monetta et al., 2008). Perhaps non-inferential ToM tasks are easier than inferential ToM tasks because they are associated with fewer executive demands. The ToM deficits exhibited by patients with PD could have resulted from poor inferential reasoning due to executive dysfunction. However, PD experiment 2 provided little evidence that ToM deficits were a result of inferential reasoning deficits because patients made many errors on non-inferential ToM vignettes. It is possible that ToM may depend on inferential reasoning and executive functions in neurologically intact individuals. Further research could investigate relationships between executive performance and matched inferential and non-inferential ToM tasks.

Another factor related to task design that could be addressed by future work concerns the style of questioning. This factor could explain why some findings reported in this series of experiments are not always in agreement with the existing literature. For example, tasks that assess the spontaneous use of ToM may yield different results to those which question the ability more directly or explicitly. Differences in the style of questioning could also have played a role in the pattern of

impairments exhibited by patients with TS in experiment 2. Deficits could also have been apparent on one measure of non-literal language (the Pragmatic Story Comprehension Task) but not another (the Hinting Task) because the former measure questioned patients' understanding in a less direct way than the latter. Future research should compare the performance of patients on a range of tasks so that the skill assessed is sometimes implicit to the task while on other occasions the skill is more explicitly questioned. This could also help to specify whether the participants tested exhibit specific deficits at a particular level.

A further issue that may be elucidated by future research is the relationship between one's own emotional experience and the understanding of emotion as expressed by others. More specifically, it would be useful to know whether the HD patients who exhibited reduced feelings of fear in response to fear-eliciting stimuli also exhibited difficulty in recognising this emotion in others. One limitation of the HD experiment described in this thesis is that the patients tested did not complete tasks that involved understanding others' emotions. The concurrent inclusion of tasks involving both the evaluation of one's own emotion and the identification of that emotion in another would provide a better evaluation of whether dysfunction within the same system could impair both of these abilities.

The experiments carried out with patients with TS have raised another important issue, that is, the consequences of an actor's behaviour appear to have an important influence on reasoning about that actor's intentions. Patients with TS showed a tendency to think that the unintentional offensive remarks described in the faux pas task were intentional. This could have been due to increased focus on the negative consequences associated with that action (i.e. the victim's feelings of offence). Other studies have indicated that there may be a particularly important role

for the influence of consequences when reasoning about intentions (Young & Saxe, 2008). Further research should investigate the contribution of outcome information in reasoning about intentions as such factors are likely to have important implications in areas such as moral judgment and jury decision making.

STUDIES TO FURTHER INVESTIGATE SOCIAL COGNITION AND RELATED REASONING PROCESSES IN PATIENTS WITH BG DISORDERS

The social cognitive difficulties identified in patients with PD, HD and TS could have significant impact on patients' social functioning. For example, in HD, changes in the emotional processing of fear could impact on quality of life by leading to poor decision making due to a lack of consideration for negative consequences. It would therefore be useful for further experiments to collect data from structured questionnaires that assess everyday behaviour and quality of life. Documenting the incidence of NOSIS in the TS patients tested on the social cognitive tasks used in the experiments described in chapter 3 would offer insight into whether NOSIS were related to the social cognitive deficits observed, and could arise in association with emotional dysregulation.

The evidence of possible emotional dysregulation in patients with TS was present despite the finding that patients exhibited limited inhibitory difficulties on executive measures. The increased number of rejections made by patients with TS during the UG could indicate that patients act more impulsively specifically in response to stimuli associated with negative affect. This increased impulsivity may resemble disinhibition. Future research could directly compare patients' performance on tasks requiring inhibition that did, or did not, involve affective information or cue affective states. For example, performance on a standard Stroop or Go-no go task

could be compared to performance on an emotional Stroop or Go-no go task. The emotional version of these inhibitory tasks is likely to involve 'hot' executive functioning, which could be more sensitive to TS (see section 3.5). Relationships between performance on 'hot' executive tasks and tasks involving 'hot' ToM could also be investigated.

Changes in the ACC CSTCC (as described by Alexander et al., 1986) in TS (and possibly HD) could affect moral reasoning. Moral reasoning could rely on the function in this circuit along with its connections to medial OFC (e.g. Moll et al., 2002). Some of the erroneous responses given by TS patients appeared to involve blame or anger in response to a social behaviour associated with negative consequences. This occurred on the faux pas task when patients saw the faux pas as intentional and suggested that the protagonist was 'nasty' or 'mean'. A similar response was seen during the UG when patients who showed increased levels of rejections appeared to feel more frustration in response to unfair offers. Some patients with TS appear particularly sensitive to the negative affect that can accompany violations of socially appropriate behaviour. On many occasions patients remarked that the proposer 'should be fair'. However, further research should better clarify patients' reasons for rejection during the UG. Future studies could also investigate patients' performance on tasks involving moral judgment by manipulating the affective information contained about a victim. In addition, whether an actor's intentions or the consequences that result from the actor's actions are positive, negative or neutral could be varied.

Another area worthy of investigation in TS is counterfactual thinking, a kind of reasoning that is related to social cognition. Counterfactual thinking does not necessarily require reasoning about mental states, but does involve looking at the

world from an alternative perspective, as does ToM. Counterfactual thoughts are generated after an event, when a person thinks about how things could have turned out differently. Although counterfactual thinking can happen after a positive event in association with a positive emotion (such as relief), counterfactual thoughts occur most often after a negative event which results in negative affect (Roese, 1994). It may be speculated that if patients with TS are more sensitive to stimuli related to negative affect, they could display an increased tendency to reason counterfactually.

Some of the errors made by patients with TS on the faux pas task support the idea that these patients pay more attention to counterfactual type thoughts. During the faux pas task, patients often exhibited a tendency to assume that the protagonist's offensive remark was made intentionally. Patients could have engaged in counterfactual reasoning, identified the fact that offending the victim was avoidable, and then decided that the protagonist should have had greater insight into the possible consequences of their behaviour. A study by Goldinger, Kleider, Azuma and Beike, (2003) showed that more attention to counterfactual information is associated with greater attribution of responsibility. Patients with TS may have seen the protagonist as more responsible for their insulting remark if counterfactual thoughts were particularly salient.

Goldinger et al. (2003) showed that limiting cognitive resources makes it more difficult for neurologically intact subjects to ignore a counterfactual thought. Participants in this study were given counterfactual information that should have been discounted in order to make a logical judgment. This information had a much greater influence on participants' judgments when they were holding a concurrent memory load during reasoning. It may be speculated that the inhibitory difficulties exhibited by patients with TS could contribute to a similar effect. Difficulty in ignoring a

counterfactual thought (that offense could have been avoided) after generating it could have further contributed to patients' tendency to blame the protagonist and not appreciate their false belief (the remark is not offensive).

Further research should also investigate counterfactual reasoning in HD. As patients with HD appear to be less subjectively 'fearful' this could be associated with poor consideration of the negative consequences of behaviour and so a reduction in the spontaneous generation of counterfactual thoughts.

STUDIES TO FURTHER INVESTIGATE THE NEURAL BASES OF DEFICITS IN SOCIAL COGNITION IN PATIENTS WITH BG DISORDERS

The deficits in social cognition revealed by the experiments in this thesis have been linked to possible dysfunction in specific CSTCCs (as described by Alexander et al., 1986). However, the extensive connectivity within these circuits makes it difficult to specify whether the impairments can be linked to dysfunction of particular structures within those circuits. For example, the deficits exhibited by patients with HD in the subjective experience of fear are likely to reflect amygdala dysfunction. However, the lateral OFC also appears to be involved in the evaluation of some stimuli that are linked to this emotion, such as fearful facial expressions (e.g. Liang et al., 2009). Both carefully designed behavioural studies and the use of functional imaging during task performance would allow better specification of the neural substrates that are implicated in the observed deficits.

Future investigations should seek to specify whether HD involves dysfunction of the ACC. The deficits exhibited by patients with HD (chapter 4) implicate the amygdala, which could affect the functioning of the ACC CSTCC (as described by

Alexander et al., 1986). It would also be constructive to investigate the performance of patients with HD on the tasks used with patients with TS (chapter 3). One study provided possible evidence for deficits on some of these tasks (Havet-Thomassin et al., 2008).

Other behavioural studies should assess the performance of all three patient groups on tasks linked specifically to lateral OFC. Studies have indicated that patients with PD can exhibit difficulty in the recognition of negative emotion expressed by others through facial expressions (e.g. Suzuki, Hoshino, Shigemasu & Kawamura, 2006) or vocally (Dara, Monetta & Pell, 2008). Studies could compare the performance of patients on tasks involving these abilities (which may be more closely linked to lateral OFC functioning) and other ToM tasks linked to medial OFC functioning. Little research, if any, has addressed the performance of patients with TS on tasks linked to the lateral OFC. However, overactivity in this region has been associated with OCD (Ursu & Carter, 2009). Future research should therefore compare the performance of patients with and without this comorbidity on such tasks. The deficits in non-literal language in TS reported in experiment 2 could implicate the IFG. This structure can be considered part of the lateral OFC CSTCC (as described by Alexander et al., 1986). The non-literal language task used in TS experiment 2 did not involve affective or acoustic cues. Further research should, therefore, investigate whether patients' deficits are still apparent when these cues are present.

It is possible that the social cognitive deficits exhibited by patients with BG disorders result more from poor connectivity between structures within a circuit rather than changes in functioning within a particular structure. For example, amygdala dysfunction could occur in disorders of the BG in a number of ways. The amygdala projects to the OFC directly, but could also influence this region indirectly, through

projections to the ventral striatum within the ACC CSTCC. Dysfunction of the striatum could also affect the amygdala indirectly via the action of frontostriatal pathways that terminate in OFC, which in turn sends projections to the amygdala. The striatum also has the potential to affect the functioning of the amygdala more directly, via the intramlaminar nucleus of the thalamus. It would therefore be useful to use imagining techniques that can provide a measure of the integrity of the connections between regions.

Recent imaging studies have also used a technique termed functional connectivity. This technique involves the identification of correlated changes in activity in different brain regions and can be employed to identify neural networks that are involved in particular cognitive tasks. For example, it is likely that patients with TS exhibit dysfunction with the emotional salience network described be Seeley et al. (2007). This network involves the anterior insula, ACC, amygdala, hypothalamus, and ventral striatum, so includes structures that are part of the ACC CSTCC (described by Alexander et al., 1986). The salience system integrates sensory data with visceral, autonomic and hedonic “markers” that allow the organism to make decisions about what to do next. Other studies have provided evidence of changes in the functioning of neural networks in patients with clinical conditions, such as TS (Church et al., 2009). Future research could identify the neural networks involved in the social cognitive tasks that have elicited deficits in this series of experiments and identify whether particular pathways involved in these networks are dysfunctional in patients with movement disorders.

CONCLUDING REMARKS

BG disorders are primarily seen as disorders of movement though recently patients with these diseases have been recognised as having a number of cognitive difficulties. This series of experiments has demonstrated that three patient groups with disorders of the BG exhibit changes in social cognition. Changes in social and emotional functions therefore appear to represent an integral component of these neuropsychiatric conditions.

Chapter 3 reported particularly striking social cognitive deficits in patients with TS. This disorder has not previously been considered to involve difficulties with social reasoning. The deficits on a range of tasks involving ToM indicated that some patients with TS exhibit deficits in inferring mental states. Difficulties are also apparent when patients with TS reason about social situations involving negative emotion, perhaps as a result of emotional dysregulation. These changes in social cognition suggest that TS is associated with dysfunction of structures including the amygdala, insula, and other regions involved in the ACC and lateral OFC CSTCCs. The social reasoning difficulties exhibited by patients with TS extend beyond reasoning about mental states so as to affect their understanding of non-literal language and humour, as well as impairing economic decision making. Changes in social cognition in TS could also be related to the occurrence of NOSIS, as explained in section 1 of this chapter. These findings can therefore encourage greater insight into some of the symptoms associated with this disorder, the basis for which has so far remained unexplained.

Other BG disorders are associated with social and emotional deficits. Patients with HD exhibit unexpectedly reduced fear reactions when confronted by stimuli that

elicit this emotion strongly and reliably in neurologically intact individuals. This finding makes a vital contribution to the existing literature by implicating the involvement of the amygdala, a temporal structure, in this disorder. Many of the neural substrates commonly linked to social cognition (e.g. medial OFC) appear to function normally in PD. Nevertheless, the experiments reported in chapter 2 indicate that at least under certain conditions, patients with PD exhibit deficits in ToM. These changes are likely to have a considerable impact on patients' everyday functioning and may pose important treatment implications.

The findings reported in this thesis have highlighted critical limitations in the current conceptualisation of frontostriatal circuitry as defined in the classic paper of Alexander et al. (1986). This model of frontostriatal interactions was revolutionary at the time it was developed. Critically, it challenged the widely held assumption that the BG's sole role was in motor control. Although more than two decades have now passed, Alexander et al.'s model is still extremely influential. The findings reported in this thesis clearly indicate that the description of CSTCCs outlined by these authors do not provide an adequate explanation for the range of symptoms exhibited by patients with disorders of the BG. This is because the existing descriptions of CSTCCs do not specify how striatal dysfunction can affect the amygdala and insula. The social cognitive deficits exhibited by patients with HD and TS in particular can therefore only be accounted for through the development of a more precise and comprehensive model of frontostriatal circuitry.

Parkinson's disease, Huntington's disease and Tourette's syndrome have long been classified as disorders of movement. The experiments reported in this thesis have demonstrated that patients suffering from these conditions also show profound alterations in affect and social cognition. The social cognitive deficits observed

compel us to consider these disease states in a new light and encourage the advancement of plausible neurobiological accounts for the behavioural changes associated with these disorders. These findings further challenge contemporary conceptualisations of how the striatum, which is the major site of pathology in these conditions, affects the functioning of the prefrontal cortex and associated limbic structures. A greater understanding of the functional interactions between the basal ganglia, amygdala and insula, and the development of more refined psychological tests will play a critical role in further elucidating the neural and psychological processes underlying social cognition.

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