Fronto-striatal contributions to cognition and behaviour: Investigations in neurodegeneration

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ORIGINALITY STATEMENT

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I herby certify that all co-authors of the published or submitted papers agree to Claire O'Callaghan submitting those papers as part of her Doctoral Thesis.

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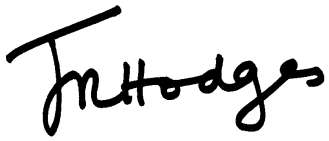

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CHAPTER 1 – INTRODUCTION

Recent years have seen an increasing push toward refining our understanding of cognitive and behavioural symptoms in neurodegenerative diseases of ageing. Combining sensitive and specific neuropsychological tests with *in vivo* biomarkers, such a structural neuroimaging, has provided a wealth of insight into these complex symptoms. Such insights are crucial to facilitate prompt and accurate diagnoses, and to establish robust brain-behavioural relationships that can inform the pattern and progression of disease pathology. Improving disease-modifying and symptom-based therapeutics also hinges upon a better understanding of these symptoms, and their neural signatures.

This thesis explores cognitive and behavioural symptoms in two neurodegenerative conditions, Parkinson's disease (PD) and behavioural variant frontotemporal dementia (bvFTD). To investigate these symptoms, both novel and established neuropsychological measures are utilised, in combination with voxel-based morphometry – a structural neuroimaging technique to assess regional grey matter loss. In particular, the focus is on delineating fronto-striatal contributions to the clinical symptoms seen in PD and bvFTD. These neurodegenerative conditions are important models for examining fronto-striatal contributions to cognition and behaviour. PD is hallmarked by a cascading striatal dysfunction, resulting in various motor and non-motor symptoms, however a role for more diffuse cortical pathology is increasingly recognised. Importantly, such cortical changes are apparent in PD without dementia, and our understanding of the pathophysiology of early cognitive-behavioural symptoms in PD continues to be refined. Such refinement is necessary, to both improve the

efficacy of possible early intervention strategies and to facilitate more accurate prognosis as to who may develop dementia over time. In contrast, cortical changes in bvFTD are well described, with early mesial and orbital atrophy often heralding the disease. Nevertheless, pervasive and early striatal pathological change has more recently been documented in bvFTD, and the impact this has on the characteristic cognitive-behavioural symptoms, in terms of their nature, extent and trajectory, is not fully appreciated.

In this introduction, a brief overview of fronto-striatal circuitry and its relationship to cognition and behaviour is provided. The majority of the introduction will then outline the two neurodegenerative conditions in more detail, with particular attention paid to fronto-striatal changes and related insights into cognitive-behavioural symptoms. This is followed by a brief overview of the voxel-based morphometry technique. The experimental chapters then discuss empirical findings characterising neuropsychiatric changes in PD and bvFTD, learning in PD, and complex social dysfunction in bvFTD. Papers included in these chapters are either published in peer-reviewed journals or in submission. Together, the studies offer novel insights into the fronto-striatal structural changes that underpin cognitive and behavioural symptoms in PD and bvFTD. Broader conclusions and implications are then discussed in the conclusions chapter.

1.1 Fronto-striatal circuitry and its relationship to cognition and behaviour

The latter half of the 20th century saw exciting developments in our understanding of basal ganglia – thalamocortical pathways. Convergence across anatomical and physiological studies corroborated the concept of segregated pathways, each following a discrete functional and anatomical topography, projecting from prefrontal areas to specific striatal regions, via the indirect and direct routes of the basal ganglia to the thalamus, and feeding back to the initial frontal territories (Alexander *et al.*, 1986; see Figure 1). Far from its original conceptualisation as a mere "funnel" integrating cortio-cortico transmissions, these developments led to the recognition of the basal ganglia as a critical component in the orchestration of a multitude of motor, cognitive and emotional behaviours (Haber, 2003).

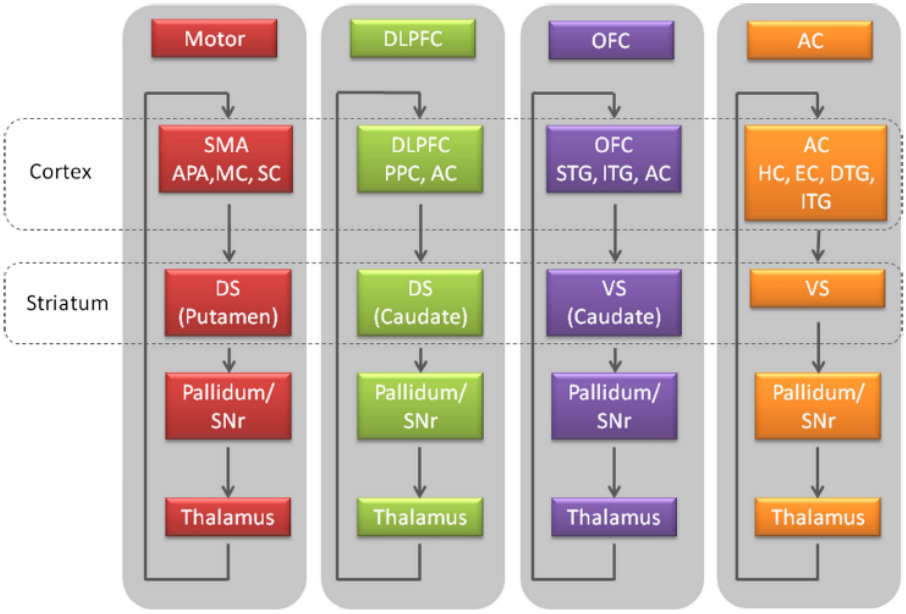

Figure 1. Simplified representation of basal ganglia-thalamocortical circuits. AC, anterior cingulate area; APA, arcuate premotor area; DS, dorsal striatum; DLPFC, dorsolateral prefrontal cortex; EC, entorhinal cortex; HC, hippocampal cortex; ITG, inferior temporal gyrus; OFC, orbitofrontal cortex; MC, motor cortex; PPC, posterior parietal cortex; SC, somatosensory cortex; SMA, supplementary motor area; SNr, substantia nigra; STG, superior temporal gyrus; VS, ventral striatum. From O'Callaghan *et al.* (2014; Appendix B, Publication B1).

As illustrated in Figure 1, the striatum is a central hub in the cortico-subcortical loops, projecting to, and receiving input from, many cortical areas. There is a high degree of spatial topography in striatal organisation, corresponding to functional divisions that follow a dorsal-ventral gradient whereby the dorsolateral striatum (i.e., putamen) is engaged in sensorimotor functions, the dorsomedial striatum (i.e., caudate) in associative functions, and the ventral striatum (i.e., nucleus accumbens and ventral portions of the caudate and putamen) in motivational and emotional function (Voorn *et al.*, 2004, Redgrave *et al.*, 2010). The putamen is primarily connected to sensory and motor cortices, the caudate with frontal and parietal association cortices, and the nucleus accumbens connects with limbic structures (amygdala, hippocampus) as well as the ventromedial prefrontal cortex. It must be noted, however, that in addition to these segregated, parallel pathways, non-reciprocal connections exist between the loops, which allow for transmission of information between motor, cognitive and limbic processing (Haber, 2003).

Fronto-striatal circuitry is implicated across all levels of cognition and behaviour. Whilst aspects of this circuitry are critically involved in motor and oculomotor function, the current thesis is focused on the prefrontal cortex, and its reciprocal connections with specific striatal territories. The prefrontal cortex has long been known to play a role in complex cognition and behaviour, critical to high-level, adaptive human function (Bianchi and Macdonald, 1922, Luria, 1969). Broadly, the prefrontal cortex is characterised by its role in 'top-down' processes. This aspect of behavioural control is especially apparent when flexible, goal-directed behaviour is required. The prefrontal cortex has a fundamental role in actively maintaining desired goals, and in integrating and evaluating information in the service of achieving those goals (Miller and Cohen,

2001). This is in contrast to less flexible, automatised behaviours driven primarily by sensory stimuli, which are considered a form of 'bottom-up' processing. Due to its position as a key node in fronto-striatal circuitry, the prefrontal cortex is ideally placed to integrate information involving emotion, memory, motor planning and environmental stimuli. This is further facilitated by its abundance of reciprocal connections with limbic regions (amygdala; hippocampus), higher-order sensory association areas in the temporal and parietal cortices, and premotor and supplementary motor regions (Wood and Grafman, 2003).

Functional topography of the prefrontal cortex can be categorised by those regions that subserve classical executive function (dorsolateral prefrontal cortices), motivation and outcome evaluation (ventromedial cortex), and reward- or emotion-based behaviour (orbitofrontal cortex) (Alvarez and Emory, 2006). Much effort has been dedicated to breaking down functions of the prefrontal cortex into component processes, in order to determine their neural correlates. Functions associated with the dorsolateral regions include response selection and working memory (Rowe *et al.*, 2000, Rottschy *et al.*, 2012), and aspects of cognitive control (which also recruit the more ventrolateral aspect of the prefrontal cortex, specifically the inferior frontal gyrus) such as task-set switching (MacDonald *et al.*, 2000, Aron *et al.*, 2004a) and response inhibition (Aron *et al.*, 2004b). The ventromedial region, which includes the dorsal portion of the anterior cingulate, is involved in other aspects of cognitive control, namely conflict detection and performance monitoring, also action selection, value encoding and motivation (Shackman *et al.*, 2011, Shenhav *et al.*, 2013).

A primary function of the orbitofrontal cortex is its role in processing emotion and encoding the affective and reward values of reinforcers, both negative and positive (Kringelbach, 2005, Etkin *et al.*, 2011). Therefore, this region is involved in regulating aspects of decision-making and social-emotional behaviours (Schultz *et al.*, 2000, Hornak *et al.*, 2003, Mar *et al.*, 2011), and is engaged during reinforcement and probabilistic learning (O'Doherty *et al.*, 2003, Rushworth *et al.*, 2011).

The role of the striatum in cognition and behaviour continues to be uncovered, and the extent to which striatal function plays primarily a causal or modulatory role in high-level cognitive and emotional functions, and by what mechanisms, is still debated. Functional brain imaging in healthy subjects provides evidence of a direct role for the striatum in many executive functions, including working memory, abstract rule learning and attention (Cools, 2011). Combined insights from human and rodent studies specify that the dorsal striatum has a role in forming action-outcome associations and in action selection (Balleine and O'Doherty, 2009). Damage to the dorsolateral striatum impairs the ability to form habits, resulting in a over-reliance on goal-directed modes of behavioural control (Yin and Knowlton, 2006). Distinct striatal modes of behavioural control are evident with prolonged overtraining on a motor task, which will initially activate the associative striatum, but over time will recruit the sensorimotor region (Lehéricy *et al.*, 2005). Transference to automaticity appears to be a critical role of the striatum, and this mechanism is essential in facilitating multi-tasking and enabling the performance of a concurrent goal-directed actions.

The striatum has also been implicated in reward-based cognition, with functional imaging suggesting that activity in the ventral striatum codes subjective value, reward

expectation and reward magnitude (Kable and Glimcher, 2009, Diekhof *et al.*, 2012). Animal lesion and neuronal recording studies indicate that key processes underpinning reward-related cognition, namely prediction error, incentive salience and valence coding, are directly associated with the ventral striatum, and are critical for reward learning, attaching motivational values to stimuli and processing its hedonic value. In these animal models, ventral striatal lesions have been associated with various forms impulsivity (Basar *et al.*, 2010), motivational deficits and anxiety (Phillips *et al.*, 2003).

Dense anatomical, and functional, connectivity between the prefrontal cortex and striatum highlights that precise orchestration across this entire circuitry is essential, in order to successfully generate cognition and behaviour. Function of the fronto-striatal circuitry is strongly regulated by ascending neuromodulatory neurotransmitter systems, most notably catecholaminergic (dopamine and noradrenaline), serotonergic and acetylcholinergic (Robbins, 2000). An important principle guiding modulation of this circuitry is the dissemination of 'prediction error signals' via these neurotransmitter systems. Prediction error signalling is an integral component of the complex behaviours that are initiated, maintained and learnt via cortico-basal ganglia circuitry (Schultz and Dickinson, 2000). From a computational perspective, understanding the mechanisms by which cognition and behaviour is implemented by fronto-striatal pathways remains a challenge to modern neuroscience. Broadly, computational models of complex abilities, including reasoning, working memory, learning and inhibition (O'Reilly and Frank, 2006, Wiecki and Frank, 2013, Donoso *et al.*, 2014), hold that that basal ganglia serves as a selection and gating mechanism, whereby signals transmitted via the "go" or "no-go" pathways regulate prefrontal cortex excitation. In this way, reward- and value-based signals, and previously learnt information, can be flexibly integrated in cortical regions,

which in turn feedback to update basal ganglia responses. Essentially, the neurobiological and computational parameters of frontal cortex and striatal regions are intimately linked, and successful, adaptive behaviour relies on the integrity of these regions and their inter-connections.

From this brief review, it is clear that fronto-striatal circuitry is involved in an abundance of cognitive and behavioural functions. It follows that neurodegenerative processes with a predilection for this circuitry can have significant consequences for all aspects of motor, cognitive and limbic function.

1.2 Parkinson's disease

1.2.1 Fronto-striatal changes

Parkinson's Disease (PD), which is characterised by hallmark motor disturbances (bradykinesia, tremor, rigidity and postural instability), has its neurobiological basis in degeneration of nigrostriatal dopamine neurons and the pathological spread of α-synuclein Lewy body formations (Dickson *et al.*, 2009). Earliest pathological changes are evident in olfactory and brainstem nuclei, followed by tegmentum and basal forebrain nuclei and the pars compacta of the substantia nigra. Following a rostro-caudal progression, the spread of pathology is then noted in striatal and subcortical structures, mesocortex, and finally higher-order neocortical association areas (Goedert *et al.*, 2012). Ultimately, the pathologic process is associated with cell death in vulnerable neuron populations (Halliday and McCann, 2010, Obeso *et al.*, 2010).

Considering the impact of striatal dysfunction on symptoms, the early prominence of nigrostriatal pathology results in severe dopamine depletion in the dorsal striatum,

whilst the ventral striatum is comparatively preserved (Jellinger, 2001). In accordance with striatal functional topography, this causes the greatest depletion of dopamine in the sensorimotor territory, followed by the associative and limbic territories. Very early degeneration of dopamine neurons in the ventrolateral substania nigra, projecting to the putamen, is associated with characteristic motor impairments that evolve with disease progression (Greffard *et al.*, 2006). Later involvement of dopaminergic cells in the medial substania nigra and ventral tegmental area, with their projections to the caudate and ventral striatum, are implicated in neuropsychiatric and cognitive features of PD (Halliday *et al.*, 2014).

A similar pattern of striatal pathologic change is seen with dopamine transporter neuroimaging, where reductions in presynaptic dopamine function follow a caudal to rostral gradient, with the most reduction evident in the posterior putamen (Stoessl *et al.*, 2014). Intra-striatal functional connectivity is compromised, though this is largely normalised after dopamine administration, further highlighting the dopaminergic basis of striatal dysfunction in PD (Bell *et al.*, 2014). Brainstem nuclei providing major sources of serotonin and noradrenaline, as well as the nucleus basalis and pedunculopontine nucleus sources of acetylcholine, are affected in PD. These regions have direct or indirect striatal projection targets, however the modulatory role these neurotransmitter systems play on striatal dysfunction in PD is less clear (Halliday *et al.*, 2014).

On a macroscopic level, using voxel-based morphometry (VBM), striatal atrophy is not reliably apparent in *de novo* PD (Menke *et al.*, 2014, Tessa *et al.*, 2014). However, in the study by Tessa *et al*., the same patients showed higher rates of atrophy in the head of

the caudate at follow-up after three years. In keeping with this, volumetry and shape analysis of the striatum in early stage, untreated PD, has demonstrated volume reductions in the putamen and nucleus accumbens, and also deformation of the putamen (Lee *et al.*, 2014). VBM studies have shown atrophy of the caudate head in early-stage, non-demented PD (Brenneis *et al.*, 2003), with additional volumetric techniques also revealing reductions in the caudate, and more variably the putamen (Lisanby *et al.*, 1993, Geng *et al.*, 2006, Lee *et al.*, 2011, Tinaz *et al.*, 2011). Nevertheless, other studies using either VBM or volumetric mapping suggest that striatal atrophy is absent in cognitively intact PD, and emerges only in the mild cognitive impairment stage (PD-MCI) (Apostolova *et al.*, 2010, Melzer *et al.*, 2012, Hanganu *et al.*, 2014) and dementia states (Almeida *et al.*, 2003, Burton *et al.*, 2004, Nagano-Saito *et al.*, 2005, Summerfield *et al.*, 2005). These striatal changes documented with cognitive decline most consistently involve the caudate, but also putamen and nucleus accumbens.

Frontal dysfunction in PD manifests as both functional changes in the cortical projection targets of the cortico-striatal loops (due primarily to dopamine depletion), or as a direct product of cortical Lewy body deposition and cell degeneration. The progressive rostro-caudal gradient of dopamine depletion is mirrored in impairments across the motor, cognitive and limbic cortico-striatal loops, fitting with the diverse range of symptoms in PD (Owen, 2004, Lewis and Barker, 2009b, Redgrave *et al.*, 2010). Intrinsic functional connectivity studies in PD confirm disruption within, and between, the various cortio-striatal circuits (Helmich *et al.*, 2010), although some aspects of fronto-striatal connectivity are normalised after dopamine administration (Wu *et al.*, 2009).

Evaluating prefrontal atrophic change in PD exposes a similar state of affairs to the emergence of striatal atrophy, whereby the presence of atrophy is variably reported in cognitively intact PD, but robustly associated with cognitive change and the advent of dementia. VBM assessment of prefrontal atrophic change in early stage, *de novo* patients has not revealed differences compared to age-matched controls (Tessa *et al.*, 2014). However, from baseline, *de novo* patients can show higher rates of atrophy in the prefrontal cortex, relative to control subjects (Tessa *et al.*, 2014). Consistent with this, medial prefrontal cortex atrophy has been documented in early stage, non-demented PD (Nishio *et al.*, 2010), as well as more extensive cortical thinning in the orbitofrontal, rostral frontal, and ventrolateral prefrontal cortices (Lyoo *et al.*, 2010, Tinaz *et al.*, 2011). In contrast, others have found no significant cortical grey matter loss in early PD if the patients were specifically assessed as being cognitively intact (Weintraub *et al.*, 2011, Melzer *et al.*, 2012). It becomes clear that in the assessment of early cortical changes, the presence of cognitive impairment must be considered. In studies that have more carefully identified mild cognitive impairment status in their cohorts, prefrontal atrophy is documented with more consistency, via VBM and cortical thickness analysis, when compared to either age-matched controls or PD with normal cognition (Beyer *et al.*, 2007, Song *et al.*, 2011, Melzer *et al.*, 2012, Mak *et al.*, 2013, Pereira *et al.*, 2014), though see (Dalaker *et al.*, 2010, Yarnall *et al.*, 2014). In PD with dementia, a more severe and widespread pattern of atrophic change is noted, via *in vivo* methods, in the prefrontal and anterior cingulate cortices (Burton *et al.*, 2004, Summerfield *et al.*, 2005, Song *et al.*, 2011). Overall, the spread of neurodegeneration in the prefrontal cortex, as a marker for cognitive decline over time, is in keeping with clinico-pathological correlations that define cortical pathology as the most significant predictor of cognitive impairment (Mattila *et al.*, 2000). In addition, the impact of Alzheimer-type pathology

is also increasingly recognised in PD. *In vivo* measures suggest that amyloid accumulation contributes to cognitive decline over time in PD-MCI (Gomperts *et al.*, 2013), although a synergistic role for Alzheimer-type pathology in PD cognitive symptoms is yet to be fully established (Halliday *et al.*, 2014).

The evidence described above highlights the co-occurrence of both prefrontal and striatal atrophic change in PD. On balance, prefrontal atrophy seems to be more robustly reported in comparison to striatal atrophy. This may reflect that VBM and volumetry techniques, used to assess atrophy and morphology, are more sensitive to the cell loss and neurodegeneration that mostly drives cortical changes, in contrast to the striatal dysfunction that can be primarily mediated by dopaminergic denervation. Nevertheless, atrophic change is common to both prefrontal and striatal regions, and exploring them in tandem seems particularly important. Evidence from other imaging modalities emphasises an important inter-relationship between frontal and striatal regions. Functional neuroimaging reveals that co-activation of frontal and striatal regions – which is apparent when controls successfully perform cognitive or motor tasks – is lost or disrupted in PD (Monchi *et al.*, 2004, Jubault *et al.*, 2009). More recently, specific reductions in the associative fronto-striatal loop, while performing a set-shifting task, were documented in PD-MCI but not in cognitively intact PD (Nagano-Saito *et al.*, 2014). This inter-relationship between striatal and cortical changes is also seen using *in vivo* assessment of dopamine function. Slowed cognitive speed in newly diagnosed, unmedicated patients has been linked to reduced flurodopa uptake across the caudate-anterior cingulate circuitry (Jokinen *et al.*, 2013). Further, in PD patients with MCI, severe dopamine depletion measured in the associative striatum was predictive of reduced D2 receptor availability in the insula (Christopher *et al.*, 2014).

Taken together, fronto-striatal pathological changes in PD manifest as the combined effects of dopaminergic depletion and neurodegeneration, with the likely contributions of additional neurotransmitter abnormalities and additional pathologies. There is much scope to continue to delineate the relative contributions of these mechanisms to cognition and behaviour in PD. Studies reported in the current thesis have sought to more directly establish the role of fronto-striatal atrophy in the genesis of cognitive and neuropsychiatric dysfunction in PD.

1.2.2 Cognition and Behaviour

Cognitive decline is common in early PD, with mild impairments evident in 15-20% of *de novo*, untreated patients (Aarsland *et al.*, 2009b). The importance of identifying initial cognitive dysfunction is evident in recent efforts to formalise and refine the concept of a mild cognitive impairment status specific to PD, i.e., PD-MCI (Litvan *et al.*, 2012, Goldman *et al.*, 2013). A "fronto-striatal" pattern of cognitive impairment is the most prominent initial profile in PD. More specifically, this profile includes a range of executive deficits in planning, working memory, attention, verbal fluency, reinforcement learning, inhibition and memory recall (Robbins and Cools, 2014). Dysfunction in the dorsal striatum (particularly the dorsolateral caudate head) is directly linked to this dysexecutive profile, given its strong connectivity with the dorsolateral prefrontal cortex (Poston and Eidelberg, 2012). Imaging studies in very early PD suggest a dopaminergic basis to these deficits, with under-recruitment of the dorsal striatum apparent during aspects of working memory (Ekman *et al.*, 2012), set-shifting (Monchi *et al.*, 2007) and planning (Dagher *et al.*, 2001). It follows that dopamine

replacement therapy can alleviate certain executive deficits arising from dysfunction in the associative loop (Cools *et al.*, 2001, Lewis *et al.*, 2005b).

In addition to a fronto-striatal pattern of impairments, some patients also manifest early deficits in memory and visuo-spatial function (Dalrymple-Alford *et al.*, 2011). Early presence of these posterior-cortical deficits is a strong predictor of transition to dementia (Williams-Gray *et al.*, 2009). A dual syndrome hypothesis has been proposed (Kehagia *et al.*, 2010), to characterise those fronto-striatal impairments as having a primarily dopaminergic basis due to dysfunction of the ascending cortico-striatal loops, versus the widespread cortical deficits signalling involvement of other neurotransmitter systems and extra-striatal pathology. Evidence for this is bolstered by findings that not all cognitive deficits present in the "off" state are remediated by dopamine therapy (Lewis *et al.*, 2005b). As described earlier, the role of other neurotransmitter systems, and other pathological processes, in PD cognitive decline is not clearly defined, but they likely have an impact on non-dopamine mediated cognitive change. Certainly the extra burden of Alzheimer-type pathology is also a candidate mechanism for understanding these more widespread deficits, given its link to cognitive decline.

Damage to the dorsal striatum also impairs the ability to form and execute habits in PD (Redgrave *et al.*, 2010). PD patients have difficulty expressing automatic actions from the early stages of the disease (Hoshiyama *et al.*, 1994), affecting habitual movements such as gait, arm-swing and facial expression. These clinical observations are echoed in experimental evidence of impaired habit learning in PD (Knowlton *et al.*, 1996). Additional impairment in patients' automatic processes ensues when they are required to simultaneously perform a concurrent cognitive or motor task (Brown and Marsden,

1991, Shine *et al.*, 2011). Increased cognitive load due to over-reliance on the goal-oriented system impedes multitasking and interferes with an individual's ability to carry out everyday cognitive and motor tasks. To a certain degree this is likely exacerbated by dopaminergic depletion across the motor, cognitive and limbic loops all converging on the same basal ganglia output nuclei, which are therefore comprised in their ability to segregate and co-ordinate competing inputs (Lewis and Barker, 2009a).

Different processes are mediated by the ventral striatum, including reward processing, response inhibition and value-based decision-making. Given the relative preservation of dopamine levels in the earliest stages of PD, it is unsurprising to find that *de novo* patients perform similarly to controls on reward-based decision-making tasks (Poletti *et al.*, 2010) and show intact probabilistic reversal learning (Swainson *et al.*, 2000). Impairment in ventrally mediated functions can arise, however, with the progression of the disease and with dopamine replacement therapy. Experimentally, dopamine replacement therapy can cause impaired reversal learning and reward-based decision-making in PD patients (Cools *et al.*, 2001). Clinically, dopamine replacement therapy can lead to impulse control disorders (ICDs) in a portion of patients, including pathological gambling, hypersexuality, compulsive shopping and binge eating (Voon and Fox, 2007). Combined, these experimental and clinical findings support the notion of a dopamine overdose hypothesis, whereby dopamine therapy, which is titrated to replenish severely depleted dopamine levels in the dorsal striatum and address motor symptoms, results in abnormally elevated levels in the ventral striatum. The effect of this overdose can be to obscure learning signals or enhance reward processing in the ventral striatum (Cools *et al.*, 2007, Voon *et al.*, 2010), giving rise to the behavioural features. Interestingly, the contribution of fronto-striatal atrophic changes to inhibitory

deficits in PD has not been previously addressed. In the current thesis, Publication II, Chapter 2, uses VBM to provide the first description of fronto-striatal atrophy in relation to verbal and motoric inhibitory function in PD.

As reviewed above, both prefrontal and atrophic changes bear a robust relationship to cognitive status in PD. Of the relatively few studies that have attempted to establish relationships between grey matter loss/cortical thinning and decline in specific cognitive abilities, the results have been mixed. Some studies failed to find a direct association with cognitive variables (Dalaker *et al.*, 2010, Tessa *et al.*, 2014). Others have related prefrontal atrophy to impaired attention (Brück *et al.*, 2004) and decision-making impairments (Ibarretxe-Bilbao *et al.*, 2009). Domain specific impairments in PD-MCI, including executive, memory and visuo-spatial abilities, have been linked to prefrontal cortical thinning (Pereira *et al.*, 2014). The current thesis extends this literature, by providing a description of the fronto-striatal grey matter contributions to learning impairment in PD (Publication III, Chapter 3).

PD is associated with a range of behavioural, or neuropsychiatric disturbances, many of which intervene later in the disease as a result if the more distributed pathology and as complications of long-term dopaminergic treatment (Voon *et al.*, 2009). However, affective disturbances can be prevalent in the early stages (Khoo *et al.*, 2013) and in some cases can predate motor symptoms (Shiba *et al.*, 2000). Depression, apathy and anxiety are the most common affective complaints and clinically significant symptoms are present in over 25% of *de novo*, untreated PD patients (Aarsland *et al.*, 2009a). Prevalence rates of up to 70% of patients experiencing these symptoms during the course of the disease have been reported, with apathy having the highest incidence

(Aarsland *et al.*, 2009c). Early manifestation of these affective symptoms suggests a role for striatal dopamine dysfunction, and some improvement can result from dopaminergic therapy (Gallagher and Schrag, 2012). However, it is likely that early and preclinical affective disturbances result from a complex interaction of striatal dopamine and also serotonergic and noradrenergic neurotransmitters in the striatum and brainstem (Aarsland *et al.*, 2009c), and further studies with *de novo* patients may shed more light on this. There is some clearer evidence for dissociable roles of the striatum in mild and more advanced PD. Functional imaging of the striatum in mild PD has shown that apathy correlates with reduced binding of dopamine in the ventral striatum (Remy *et al.*, 2005), which is in keeping with the role of the limbic loop in driving appetitive and motivational behaviour (Levy and Dubois, 2006). Depression and anxiety in mild PD have been related to reduced dopamine uptake in the anterior putamen (Weintraub *et al.*, 2005) and the caudate (Vriend *et al.*, 2014b), and to more extensive dopaminergic dysfunction throughout the dorsal striatum in advanced PD (Koerts *et al.*, 2007). Only recently have affective and motivational disturbances been linked to prefrontal atrophy in PD (Feldmann *et al.*, 2008, Reijnders *et al.*, 2010). In Publication I, Chapter 1, of this thesis, the contribution of fronto-striatal atrophic change to neuropsychiatric symptoms is explored.

Clearly, in PD both the underlying pathological processes, and the manifest cognitive and behavioural impairments, represent a complex interaction between neurotransmitter changes and neurodegenerative processes. Classically, most efforts to characterise cognitive and behavioural deficits in PD have focussed on the contribution of fronto-striatal dopamine dysregulation. As mentioned above, the primary aim of the PD studies reported in this thesis is to better establish the contribution of fronto-striatal atrophy to

cognition and behaviour in PD. This is particularly important in the context of growing literature to implicate grey matter loss in the evolution of PD cognitive decline. Ultimately, improved understanding of the pathophysiology of cognitive and behavioural change in PD will have implications for management and therapeutics.

1.3 Behavioural variant frontotemporal dementia

1.3.1 Fronto-striatal changes

Frontotemporal dementia (FTD) refers to a spectrum of neurodegenerative diseases associated with predominant frontal and temporal atrophy, and underlying neuropathology characterised by intraneuronal protein inclusions (tau; 43 kDa TAR DNA-binding protein – TDP-43; and RNA-binding protein fused in sarcoma – FUS). Three clinical subtypes of FTD are recognised: two language variants (progressive nonfluent aphasia – PNFA, and semantic dementia – SD) and a behavioural variant (behavioural variant FTD – bvFTD). The diagnostic criteria for each FTD subtype were recently revised, to reflect advances in the clinical characterisation, genetics and biomarkers (Gorno-Tempini *et al.*, 2011, Rascovsky *et al.*, 2011), with recent pathological validation (Chare *et al.*, 2014).

On an anatomic level, the clinical distinctions are determined by the extent and location of pathology, rather than by the histologic subtype. PNFA is associated with a prevalence of pathology in the left anterior insular, the inferior frontal, and the perisylvian regions (Nestor *et al.*, 2003, Rohrer *et al.*, 2009). SD is characterised by pathology of the anterior and inferior temporal regions, usually more prominent on the left side (Chan *et al.*, 2001, Rosen *et al.*, 2002). In bvFTD, the mesial and orbitofrontal cortices are typically the initial and most consistent regions affected, with variable

involvement of the dorsolateral prefrontal cortices, and a distinctive pattern of atrophy in the ventromedial prefrontal cortex, anterior cingulate, insula, amygdalae and striatum, with a right-lateralised predilection often observed (Rosen *et al.*, 2002, Seeley *et al.*, 2008). However, these categorical distinctions underemphasise the overlap between the FTD subtypes in terms of both clinical features and the locus of pathology, particularly with the merging of behavioural and language features that can occur with disease progression.

The current thesis deals with bvFTD, which has classically been viewed as a prototypical example of frontal dysfunction, as these patients present with insidious and pervasive behavioural abnormalities. Hallmark features include disinhibition, apathy, emotional blunting, distractibility, motor and verbal stereotypies, disturbed satiety, and impaired insight, all of which contribute to a general decline in personal and social conduct (Neary *et al.*, 1998, McKhann *et al.*, 2001, Rascovsky *et al.*, 2011). In terms of cognition, executive dysfunction is considered a core diagnostic feature, however the ubiquity of executive deficits from the early stages is contentious (Piguet *et al.*, 2011). Increasingly, there is a move toward considering key cognitive deficits in bvFTD as comprising social-emotional, theory of mind, decision-making, inhibitory and memory impairments.

As mentioned, the clinical spectrum of FTD is underpinned by heterogeneous molecular pathologies, termed collectively the frontotemporal lobar degenerations (FTLDs). BvFTD is a prime example of this heterogeneity, as the clinical syndrome has a roughly equal probability of being associated with intra-cellular accumulations of either tau or TDP-43 pathology, with only a small proportion associated with FUS pathology

(Josephs *et al.*, 2011). A current challenge in bvFTD continues to be establishing a link between the clinical phenotype and underlying molecular pathology, which becomes increasingly important as disease-modifying agents are developed.

Accumulation of pathology in bvFTD is associated with severe regional brain atrophy at the macroscopic level, as well as neuronal loss. Post mortem disease staging in bvFTD reveals that the earliest disease stage is marked by mesial and orbitofrontal atrophy, followed by the hippocampus, temporal pole, dorsolateral prefrontal cortex and basal ganglia (Broe *et al.*, 2003). Importantly, the stages in the scheme correlate with clinical severity and disease duration, as well as underlying neuronal loss (Kersaitis *et al.*, 2004). Progression of atrophy is similar across the pathological subtypes, and does not necessarily reflect the burden of protein deposition (Kril and Halliday, 2011). Currently, pathologic staging methods based on specific FTLD subtypes are yet to be established (Brettschneider *et al.*, 2014). In this respect, making associations between *in vivo* biomarkers and underlying pathology proves difficult. Whilst there is suggestion that certain neuroimaging signatures may be more reliably associated with tau, TDP-43 or FUS pathology (Whitwell *et al.*, 2005, Josephs *et al.*, 2010, McMillan *et al.*, 2013), this is not reflected in the post mortem literature. Other biomarkers have been investigated, including plasma and CSF concentrations of TDP-43 and tau (Bian *et al.*, 2008, Foulds *et al.*, 2009, Hu *et al.*, 2013, Suárez-Calvet *et al.*, 2014), though their reliability and reproducibility is not confirmed.

Neuroimaging investigations in bvFTD are consistent with the progressive, and severe atrophy documented post mortem. From the early disease stages, volumetric magnetic resonance imaging (MRI) typically reveals fronto-insular atrophy (including

orbitofrontal, anterior cingulate, anterior portions of the insula, hippocampus/amygdala), and less prominently, in the dorsolateral cortices, basal ganglia and thalamus (Schroeter *et al.*, 2007, Seeley *et al.*, 2008). Volumetry and VBM studies demonstrate that atrophy in bvFTD progresses over time (Whitwell *et al.*, 2007, Frings *et al.*, 2012), and this progression is marked by continued spread of atrophy throughout the fronto-insular regions, basal ganglia, subcortical limbic structures and parietal cortex (Barnes *et al.*, 2006, Seeley *et al.*, 2008) Structural change is also evident in the white matter integrity, which is particularly affected in those tracts connecting fronto-temporal regions (Chao *et al.*, 2007, Whitwell *et al.*, 2010). Functional connectivity studies show widespread disruption in bvFTD with regards to the fronto-insular "salience" network (Seeley *et al.*, 2009, Zhou *et al.*, 2010). More specific investigations of the striatum in bvFTD show significant atrophy across the entire complex (i.e., nucleus accumbens, caudate and putamen), with putamen atrophy being more right lateralised and less severe than caudate atrophy (Garibotto *et al.*, 2011, Halabi *et al.*, 2013). Atrophic change in the striatum is significant, as bvFTD patients are reported to show a 25% caudate volume reduction compared to age-matched controls (Looi *et al.*, 2008).

Despite the severe structural abnormalities characteristically associated with bvFTD, it is important to note that a normal appearing MRI does not exclude the diagnosis (Piguet *et al.*, 2011). Early on, very minimal atrophy can still be associated with florid behavioural changes. This concern is particularly relevant with the recent identification of the *C9ORF72* mutation as a common cause for familial, and also sporadic, bvFTD (Renton *et al.*, 2011). The clinical phenotype associated with this mutation is characterised by a slower progression and less brain atrophy (Devenney *et al.*, 2014),

therefore early MRI is not like to be very informative. Together, given the variable utility of neuroimaging, and the primarily behavioural features, bvFTD continues to pose a particular diagnostic difficulty. Patients are often initially misdiagnosed as suffering a different dementia, such as Alzheimer's disease, or a psychiatric illness (Manes, 2012). The overlap between bvFTD and Alzheimer's disease becomes apparent in light of mounting evidence that these patient groups can present with equally profound amnestic memory deficits (Hornberger *et al.*, 2010, Hornberger *et al.*, 2012). This is further complicated by the fact that frontal presentations of Alzheimer's disease are not uncommon in a younger onset cohort (Alladi *et al.*, 2007, Warren *et al.*, 2012). It follows that ruling in a diagnosis of bvFTD based on a frontal presentation, or ruling it out based on memory impairment, is not a fail-safe strategy. A further complication is psychiatric illnesses, or "phenocopies", that can mimic bvFTD (Kipps *et al.*, 2010). Although a proportion of such cases are now accounted for by the discovery of the *C9ORF72* mutation, others remain difficult to distinguish from bvFTD and their aetiology is unknown. In this context, continued development of tools to assess early cognitive and behavioural change in bvFTD remains an important goal, in order to improve diagnostic accuracy.

1.3.2 Cognition and Behaviour

Behavioural dysfunction is the characteristic feature of bvFTD. The combination of ventromedial prefrontal, striatal and limbic pathology described above, forms the basis of the profound behavioural regulation, social and motivational dysfunction in bvFTD. Behavioural abnormalities in bvFTD have been thoroughly quantified via caregiver-based questionnaires and clinician-derived ratings, with several investigations relating these to prefrontal dysfunction. Convergent evidence across neuroimaging modalities

suggests that atrophy and hypometabolism in orbitofrontal/ventromedial prefrontal cortices (Franceschi *et al.*, 2005, McMurtray *et al.*, 2006, Peters *et al.*, 2006, Zamboni *et al.*, 2008, Hornberger *et al.*, 2011) is associated with both apathy and disinhibition as reported by caregivers. Loss of insight has been linked to right prefrontal hypoperfusion in bvFTD (McMurtray *et al.*, 2006), and ventromedial and frontopolar prefrontal atrophy across the FTD spectrum (Hornberger *et al.*, 2014). Studies in bvFTD and other dementias support the notion that behavioural dysfunction is most robustly related to right hemisphere dysfunction (Rosen *et al.*, 2005).

Despite well documented striatal pathological change in bvFTD, its impact on both behavioural and cognitive features has not been extensively investigated, in comparison to cortical changes. Striatal atrophy has been shown to covary with broad behavioural symptoms, including disinhibition (Rosen *et al.*, 2005, Halabi *et al.*, 2012) and binge eating (Woolley *et al.*, 2007). Interestingly, there is an apparent lateralisation of striatal contributions to behavioural disturbances in the FTD spectrum, with the right striatum more often linked to behavioural disturbances, including eating disorders, apathy, reduced empathy and aberrant motor behaviour (Rosen *et al.*, 2005, Rankin *et al.*, 2006, Eslinger *et al.*, 2012, Halabi *et al.*, 2012)**.** Informant rated disinhibition in bvFTD has also been linked hypometabolism (Franceschi *et al.*, 2005) and atrophy (Zamboni *et al.*, 2008) in the nucleus accumbens. More recently, abnormalities in reward seeking behaviour (including overeating, increased sweet preference, hypersexuality and new-onset substance use) was linked, via VBM, to reduced volume of the right ventral putamen specifically in bvFTD (Perry *et al.*, 2014). In terms of the few studies that have looked at functional or cognitive sequelae of striatal pathologic change, across the FTD spectrum striatal atrophy is found to covary with functional disability (Chow *et al.*,

2008) and poorer general cognition (Looi *et al.*, 2009). In contrast to the predominance of right striatum involvement in behavioural disturbance, the left striatum appears to have greater involvement in cognitive functions and its atrophy has been linked to executive, language and psychomotor dysfunction in FTD (Raczka *et al.*, 2010, Garibotto *et al.*, 2011). Publications II and IV in this thesis provide new insights into the striatal correlates with tasks assessing inhibition and social decision-making, specifically in bvFTD.

In terms of cognitive decline, as mentioned above, bvFTD has classically been associated with a dysexecutive profile (Neary *et al.*, 1998). Nevertheless, traditional executive tests examining working memory, attentional set-shifting, rule learning and planning have yielded inconsistent results in bvFTD. Many patients perform within normal limits in the early and middle stages of the disease (Hodges *et al.*, 1999, Kramer *et al.*, 2003, Hornberger *et al.*, 2008, Torralva *et al.*, 2009). However, those abilities assessed via traditional executive measures predominantly engage dorsolateral prefrontal areas, which are only variably affected in the early and mid stages of bvFTD. Efforts to detect bvFTD deficits more specifically have increasingly employed cognitive measures of social-emotional processing, theory of mind, decision-making and inhibition. To a degree, these processes can be gauged via caregiver questionnaires, some of which were outlined above, although such an approach is not always ideal. By nature, caregiver report relies on the presence of an involved, insightful carer, and therefore convergence with objective measures, where possible, is advisable. Such convergence may be critical to inform diagnosis, and further to that, measures that can accurately and objectively assess specific cognitive function are crucial for monitoring outcomes in pharmacological or clinical interventions.

Deficits on theory of mind tasks, and measures of complex social cognition involving empathy and moral judgements, are well described in bvFTD (Gregory *et al.*, 2002, Lough *et al.*, 2006, Torralva *et al.*, 2009, Gleichgerrcht *et al.*, 2011, Bertoux *et al.*, 2012). Applying VBM in bvFTD, deficits in resolving social dilemmas (Eslinger *et al.*, 2007) and impaired theory of mind (Couto *et al.*, 2013) have been related to orbitofrontal cortex atrophy. Expression of complex social-emotional behaviour, in the form of embarrassment, is reduced in bvFTD and related to smaller right pregenual anterior cingulate cortex grey matter volume (Sturm *et al.*, 2012).

Decision-making paradigms have left little doubt that bvFTD patients have difficulty maximising strategic choice via calculations of risk and rule-learning (Gleichgerrcht *et al.*, 2010), and impairment on a gambling task has been linked to prefrontal atrophy (Kloeters *et al.*, 2013). However, behavioural assessment of decision-making does not always appear to have good specificity in bvFTD patients, as it does not reliably discriminate them from Alzheimer's disease patients (Bertoux *et al.*, 2013, Kloeters *et al.*, 2013). Publication IV, Chapter 4 in this thesis, describes a novel cognitive task to assess decision-making in a social context, in bvFTD patients. The study therefore engages a more ecological measure of decision-making, combined with insights into social processing.

Assessment of inhibitory function in bvFTD represents another avenue for determining more disease-specific deficits. Despite the fact that disinhibited behaviour is seen in nearly 80% of patients at presentation (Piguet *et al.*, 2009), inhibitory processes have only more recently been investigated for their potential utility in early diagnosis (O'Callaghan *et al.*, 2013; Appendix B, Publication B2). As described above, caregiver-

based or clinician assessment of behavioural disinhibition has been linked to orbitofrontal/ventromedial prefrontal and nucleus accumbens dysfunction. However, less work has been done to substantiate caregiver report of behavioural disinhibition with objective neuropsychological tests. One study reporting convergence between objective measures and caregiver report of disinhibition confirmed shared neural correlates in the orbitofrontal cortex (Hornberger *et al.*, 2011). In Publication II, Chapter 2 of this thesis, objective measures of both verbal and motor disinhibition in bvFTD are related to fronto-striatal atrophy.

On balance, there is still much scope to better characterise the cognitive and behavioural symptoms in bvFTD that arise from fronto-striatal atrophic change, either separately or in concert. Along with continued identification of more disease-specific clinical measures, such characterisations will refine our understanding of bvFTD clinical phenotype and increase diagnostic accuracy.

1.4 Voxel-based morphometry

Voxel-based morphometry (VBM) is a method developed to provide *in vivo*, unbiased assessment of brain differences based on structural MRI images (Ashburner and Friston, 2000, Good *et al.*, 2001). Essentially, the technique allows regional differences in grey matter to be compared on a voxel-by-voxel basis. Such differences can be explored at the population level, for example via comparing local grey matter concentration between groups, or grey matter concentration can be correlated against given clinical variables. To achieve this, MRI images are spatially normalised and registered to the same stereotactic space and a pre-processing pipeline involving segmentation of grey and white matter, then grey matter smoothing, is applied. Voxel-wise parametric or non-parametric statistical tests, correcting for multiple comparisons, are then applied to the smoothed grey matter.

It is apparent from the studies reviewed above that the VBM technique has been employed extensively to study neurodegeneration. This application, however, has provoked some controversy. The procedure was designed to be sensitive to grey matter differences whilst cancelling out large-scale differences in macroscopic structure and spatial positioning (Ashburner and Friston, 2001). Therefore, questions have been raised as to the validity of co-registering images that have gross anatomical differences (Davatzikos, 2004), and whether artifactual differences may emerge as a result of "mis-registration" (Bookstein, 2001). Methods including additional statistical modulation algorithms, masking procedures and the use of disease-specific pre-processing pipelines to account for regional atrophy (Ashburner and Friston, 2000, Mechelli *et al.*, 2005, Ridgway *et al.*, 2009, Pereira *et al.*, 2010), have been suggested to counteract this potential limitation. It becomes clear that it is essential to consider the potential utility

of VBM pertaining to the disease under investigation. From the studies reviewed above, VBM has been widely applied in PD and bvFTD with a reasonable degree of consistency across studies. Perhaps most encouraging is VBM findings where features of disease progression, or correlates of cognition and behaviour, converge with those reported from other neuroimaging modalities. Further to this, convergence has also been reported between distribution of regional change in VBM and post mortem data (Hornberger *et al.*, 2012). The on going reconciliation between *in vivo* neuroimaging markers and neuropathologic investigations remains critical in bvFTD and PD. It follows that there remains much scope for the continued application of VBM in these diseases to continue to inform a variety of areas.

CHAPTER 2 – NEUROPSYCHIATRIC SYMPTOMS IN PARKINSON'S DISEASE AND FRONTOTEMPORAL DEMENTIA

2.1 Publication I – "Neuropsychiatric symptoms in Parkinson's disease: Fronto-striatal atrophy contributions"

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Neuropsychiatric symptoms in Parkinson's disease: Fronto-striatal atrophy contributions

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ABSTRACT

Background: Neuropsychiatric symptoms (NPS) in Parkinson's disease (PD) have been mostly attributed to neurotransmitter imbalances. However, recent findings suggest that gray matter atrophy also contributes to NPS in PD. We contrast PD patients with different levels of NPS, who are well-matched for dopaminergic medication levels and disease stage, to identify the fronto-striatal gray matter atrophy areas associated with NPS in PD.
Methods: Fifty mild, non-demented PD patients were included. We median-split the group via a neuropsychiatric screening tool (Cambridge Behavioural Inventory-Revised), which resulted in higher vs. lower NPS groups ($n = 25$ in each group). Using T1 brain scans acquired on a 3 Tesla MRI scanner, voxel-based morphometry analysis was applied to characterize the pattern of fronto-striatal gray matter atrophy associated with elevated NPS.
Results: We found that the higher NPS group was characterized by greater atrophy in the prefrontal cortex, but not striatal areas. This was further corroborated by a post-hoc analysis cross-correlating the severity of NPS with gray matter loss across the whole PD group, which revealed that atrophy in the orbitofrontal cortex and frontal pole was specifically associated with elevated NPS.
Conclusions: Prefrontal cortex atrophy in PD has an additional effect to dopamine replacement therapy on the generation of NPS in these patients. These findings are an important step towards the delineation of atrophy vs. neurochemical imbalance in PD, and the results emphasize the importance of considering interactions between prefrontal atrophy and neurochemical dysfunction in the genesis of neuropsychiatric symptoms in PD.

1. Introduction

Neuropsychiatric symptoms are prevalent, debilitating features of Parkinson's disease (PD) that have significant impact on patient quality of life [1], and yet the pathophysiology of these symptoms is still poorly understood and they remain difficult to treat. A range of neuropsychiatric features can emerge with PD, from psychosis and impulsivity to affective and motivational disturbances, of which apathy, depression and anxiety have the highest prevalence [2] and can manifest even in prodromal and *de novo*, untreated patients [3].

Neuropsychiatric symptoms in PD have been associated with imbalances in the catecholaminergic and serotonergic neurotransmitter systems, as well as additional up-regulatory affects in the dopaminergic system that can arise with medication. Throughout the limbic circuitry, conversely hyper-and hypo-dopaminergic levels are known to contribute to positive (i.e. impulsivity) and negative (i.e. depression, apathy) neuropsychiatric symptoms [4,5]. More specifically, apathy and impulsivity have been linked to dopaminergic imbalance in the ventral striatum [6,7] whereas, disruption to serotonergic, noradrenergic and dopaminergic activity in the midbrain nuclei, amygdala and cingulate regions has been implicated depression and anxiety [6,8]. Recent evidence, however, has also linked prefrontal atrophic changes in PD to affective and motivational disturbances [9,10]. This raises the possibility that prefrontal atrophy may be an additional risk factor for neuropsychiatric symptoms in PD, and that brain

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Table 1
Mean (standard deviation) of PD patient and control scores on demographics and clinical characteristics

Demographics and clinical characteristics	Control	PD − NPS	PD + NPS	*p* Value
N	30	25	25	–
Sex (M:F)	20:10	21:4	18:7	–
Age	65.4 (6.0)	65.0 (8.1)	66.9 (6.5)	n.s.
MMSE (max. 30)[a]	29.3 (.89)	28.8 (1.6)	28.5 (1.4)	n.s.
Duration (years)[a]	–	5.72 (4.0)	5.32 (3.1)	n.s.
LEDD (mg/day)	–	700.3 (418.5)	770.8 (619.6)	n.s.
DA-DDE (mg/day)	–	286.2 (204.6)	210.0 (177.7)	n.s.
Hoehn & Yahr stage[a]	–	2.0 (.58)	2.2 (.50)	n.s.
UPDRS III	–	23.8 (13.7)	30.5 (13.7)	n.s.
Tremor score	–	.40 (.35)	.50 (.47)	n.s.
Non-tremor score	–	.85 (.55)	1.2 (.47)	*

n.s. = non significant; * = $p < .05$.
MMSE = mini-mental state examination; LEDD = levodopa dopamine dose equivalent.
DA-DDE mg/day = dopamine agonist dose in LEDD; UPDRS III = motor score from the Unified Parkinson's Disease Rating Scale.
[a] F values indicate significant differences across groups, otherwise due to unequal variance χ^2 indicates differences across groups.

atrophy may make a distinct contribution to neuropsychiatric symptoms apart from the known neurotransmitter imbalances. Striatal atrophy has been directly linked to neuropsychiatric symptoms in a range of neurodegenerative conditions [11]. In PD, whilst striatal atrophy has been associated with disinhibition [12], the contribution of striatal atrophy to a broader range of neuropsychiatric symptoms has not yet been characterized.

In the current study, we compared mild, non-demented PD patients with higher vs. lower neuropsychiatric symptoms. We used voxel-based morphometry to characterize the pattern of fronto-striatal atrophy associated with elevated neuropsychiatric symptoms. The high vs. low groups were matched for disease severity and, crucially, were equivalent for levels of dopamine replacement medication. We hypothesized that prefrontal and ventral striatal atrophy would be more prevalent in PD patients with global neuropsychiatric features, and that atrophy in these regions would make a direct contribution to symptoms.

2. Methods

2.1. Case selection

A total of 50 PD patients who were routinely evaluated in the Brain and Mind Institute Parkinson's Disease Research Clinic were invited to participate in this study, with 25 forming a PD control group without globally elevated neuropsychiatric symptoms (PD-NPS) and 25 forming a group with elevated symptoms (PD + NPS). Patients were recruited consecutively over six months, selected on the basis that a close informant was available for completion of the Cambridge Behavioural Inventory-Revised and that there if there were no contraindications for MRI scanning. Exclusion criteria included dementia or history of other significant neurological or psychiatric diagnosis. All patients satisfied the United Kingdom Parkinson's Disease Society Brain Bank criteria and were between Hoehn and Yahr stages I and III. Patients were assessed by an experienced movement disorders neurologist (SJGL) to rule out atypical parkinsonism presentations. Global cognitive function was assessed via the Mini Mental State Examination (MMSE) and patients scoring below the cut-off for dementia (i.e. MMSE < 24/30) were excluded, and none of the included patients met Movement Disorder Society-Parkinson's disease dementia (MDS-PDD) criteria. Patients were assessed on the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) and the motor score (UPDRS-III) is reported. To compare relative burden of tremor vs. non-tremor symptoms we derived an average "tremor score" (i.e. average of items 23 and 50–59) and "non-tremor score" (i.e. average of items 14, 16, 22 and 25–49) using a method previously described elsewhere [13]. With respect to antiparkinsonian medications, one patient was untreated; forty three patients were taking levodopa (fourteen of whom were also on entacapone) and twenty-six of those were also taking a dopamine agonist; one patient was on agonist monotherapy, two were taking an agonist plus an adjuvant and one was taking an agonist plus a monoamine oxidase inhibitor; finally, two patients were taking monoamine oxidase inhibitor monotherapy. For treated patients, L-dopa daily dose equivalents (DDE mg/day) were calculated and for those on a dopamine agonist, total dopamine agonist dose in DDE (DA-DDE mg/day) was also calculated. All motor and cognitive assessments were completed with patients in their ON state, having taken their usual medications. In addition, 30 age-matched healthy controls, selected from a volunteer panel, provided the normative data set for the Cambridge Behavioural Inventory-Revised.

The study was approved by the Human Ethics Committees of the Central and South Eastern Sydney Area Health Services and the Universities of Sydney and New South Wales, and complies with the statement on human experimentation issued by the National Health and Medical Research Council of Australia. All participants provided informed consent in accordance with the Declaration of Helsinki.

2.2. Assessment of neuropsychiatric symptoms

Neuropsychiatric symptoms were assessed with a validated informant-rated questionnaire, the Cambridge Behavioural Inventory-Revised (CBI-R), previously shown to be sensitive to behavioral dysfunction in PD [14]. The CBI-R incorporates sub-scores probing a variety of neuropsychiatric, cognitive and functional symptoms and requires informants to rate the frequency of dysfunctional behaviors on a scale ranging from 0 (*never*) to 4 (*constantly*). We collected informant-rated CBI-R data for both controls and PD patients and converted the ratings for each sub-section and for the overall total into percentage values, with higher percentages endorsed indicating greater behavioral disturbance. Finally, we extracted the sub-scales that most directly reflect neuropsychiatric features, namely "Abnormal behavior", "Mood", "Beliefs", "Stereotypic motor behavior" and "Motivation", then combined the percentages endorsed on these sub-scales to create a composite Neuropsychiatric Sub-score (NPS score). Elevated neuropsychiatric symptoms were defined as scoring greater than 1.5 standard deviations above the mean NPS score of control subjects (see Table 2), forming the PD + NPS and PD − NPS groups.

2.3. Statistical analyses

Data were analyzed using SPSS19.0 (SPSS Inc., Chicago, IL, USA). Parametric demographic and clinical variables were compared across the groups via one-way ANOVAs followed by Tukey post-hoc tests. A priori, variables were plotted and checked for normality of distribution by Kolmogorov–Smirnov tests and variables showing non-parametric distribution were analyzed via Chi-square, Kruskal–Wallis and Mann–Whitney *U* tests. Spearman's rank order correlations were used to explore inter-correlations between NPS sub-scores.

2.4. Imaging acquisition

All subjects underwent the same imaging protocol with whole-brain T1 images acquired using 3T Philips MRI scanners with standard quadrature head coil (8 channels). The 3D T1-weighted sequences were acquired as follows: coronal orientation, matrix 256 × 256, 200 slices, 1 × 1 mm^2 in-plane resolution, slice thickness 1 mm, TE/TR = 2.6/5.8 ms.

Table 2
Mean percentage endorsed on the CBI-R and selected sub-scales, with higher percentage endorsed scores indicating greater behavioral dysfunction.

	Control	PD − NPS	PD + NPS	*p* Values	PD + NPS vs. control	PD-NPS vs. control	PD + NPS vs. PD − NPS
CBI-R total (% endorsed)	2.6 (2.6)	6.4 (3.8)	20.3 (9.7)	***	***	*	***
NPS total (% endorsed)	2.2 (3.0)	2.7 (1.9)	16.9 (7.2)	***	***	n.s.	***
Abnormal behavior	1.5 (3.2)	2.3 (3.2)	12.8 (10.5)	***	***	n.s.	***
Mood	2.7 (5.6)	5.0 (4.4)	21.8 (9.7)	***	***	n.s.	***
Beliefs	.28 (1.5)	.67 (2.3)	2.3 (5.7)	n.s.	–	–	–
Stereotypic motor behavior	4.4 (7.4)	2.3 (4.4)	17.5 (12.6)	***	***	n.s.	***
Motivation	2.2 (5.4)	2.8 (5.4)	26.0 (16.2)	***	***	n.s.	***

n.s. = non significant; *** = $p < .001$; ** = $p < .01$; * = $p < .05$.
CBI = Cambridge Behavioural Inventory-Revised; NPS = Neuropsychiatric Sub-score.
Standard deviations shown in brackets.

Table 3
Fronto-striatal region of interest voxel-based morphometry results showing areas of gray matter intensity decrease for PD patients with elevated neuropsychiatric features (PD + NPS), relative to patients without neuropsychiatric symptoms (PD − NPS). All results corrected for multiple comparisons using the family-wise error at a threshold of $p < .05$.

Regions included within cluster	Hemisphere (L/R/B)	MNI coordinates at peak voxel			Number of voxels	*T* score
		X	*Y*	*Z*		
PD + NPS vs. PD − NPS						
Frontal pole/frontal orbital and subcallosal cortices/anterior cingulate[a]	B	−4	46	−26	1153	2.01
Frontal orbital cortex/inferior frontal gyrus[b]	L	−48	28	−16	973	
Frontal orbital cortex/inferior frontal gyrus[c]	R	52	28	−16	641	

Hemisphere: L = left; R = right; B = bilateral; [a]Brodmann areas BA 10/BA 11, 47, 25/BA 32; [b]Brodmann areas BA 11, 47/BA 44, 45; [c]Brodmann areas BA 11, 47/BA 44, 45.

2.5. Voxel-based morphometry (VBM) analysis

3D T1-weighted sequences were analyzed with FSL-VBM, a voxel-based morphometry analysis which is part of the FSL software package [15]. First, tissue segmentation was carried out using FMRIB's Automatic Segmentation Tool (FAST) [16] from brain extracted images. The resulting gray matter partial volume maps were then aligned to the Montreal Neurological Institute standard space (MNI152) using the nonlinear registration approach using FNIRT, which uses a b-spline representation of the registration warp field [17]. The registered partial volume maps were then modulated (to correct for local expansion or contraction) by dividing them by the Jacobian of the warp field. The modulated images were then smoothed with an isotropic Gaussian kernel with a standard deviation of 3 mm (FWHM: 8 mm). A region-of-interest mask for prefrontal and striatal brain regions was created by using the Harvard–Oxford cortical and subcortical structural atlas. The following regions were included in the mask: frontal pole, superior frontal gyrus, middle frontal gyrus, inferior frontal gyrus, frontal medial cortex, subcallosal cortex, paracingulate gyrus, cingulate gyrus (anterior division), frontal orbital cortex, caudate, putamen and nucleus accumbens. Finally, a voxelwise general linear model (GLM) was applied and permutation-based non-parametric testing was used to form clusters with the Threshold-Free Cluster Enhancement (TFCE) method, tested for significance at $p < .05$, corrected for multiple comparisons via family-wise error correction across space, unless otherwise stated.

3. Results

3.1. Demographics and clinical characteristics

Comparisons of demographics and clinical characteristics are shown in Table 1. Control and PD groups did not differ in terms of age or general cognition as assessed by the MMSE (p values >.1). The PD + NPS and PD − NPS groups did not differ on clinical characteristics including disease duration, levodopa dose equivalent, dopamine agonist dose and Hoehn and Yahr stage (p values >.1); there was a trend for greater overall motor impairment (i.e. higher UPDRS III score) in the PD + NPS group, but this did not reach significance ($p = .095$). Tremor scores were equivalent between the two PD groups ($p > .5$), however the non-tremor score was significantly higher in the PD + NPS group ($p = .05$).

3.2. Neuropsychiatric symptoms

Results from neuropsychiatric assessment scales are shown in Table 2. The overall score of the CBI-R was significantly different across the control and patient groups, with the PD − NPS group endorsing a higher percentage relative to controls ($p < .05$) and the PD + NPS group endorsing significantly more items than both the PD − NPS and the control groups (p values <.001). As predicted, given that the PD groups were defined based on the level of NPS symptoms endorsed relative to controls, the PD + NPS group had a higher percentage of NPS symptoms overall, compared to both controls and PD − NPS patients (p values < .001). Regarding individual NPS sub-scores, this significant difference was apparent for scores on the Abnormal behavior, Mood, Stereotypic motor behavior and Motivation sub-scales, however there was no group difference for items endorsed on the Belief sub-scale ($p > .1$) for which both patient groups were similar to controls. Importantly, the PD − NPS group was equivalent to controls for overall percentage of NPS symptoms endorsed and for all individual NPS sub-scores (p values >.1).

In the PD patients, correlation analyses revealed moderate to strong positive relationships between those NPS sub-scales that were associated with significant group differences (i.e. Abnormal behavior, Mood, Stereotypic motor behavior and Motivation). Spearman's rho correlation coefficients were all significant at p values <.001 (See Supplementary Table 1).

3.3. VBM: PD vs. controls

The PD patient group as a whole (i.e. PD + NPS combined with PD − NPS) was initially contrasted with controls to reveal overall pattern of brain atrophy in the fronto-striatal mask. PD patients showed gray matter atrophy in the medial frontal/subcallosal cortex, bilateral orbitofrontal cortex, anterior cingulate and insular cortex, left inferior frontal gyrus, and extending back into the bilateral caudate, putamen and nucleus accumbens (see Supplementary Table 2 and Supplementary Fig. 1).

3.4. VBM: PD + NPS vs. PD − NPS

We contrasted the PD groups to explore the differences in frontal and striatal atrophy associated with the PD + NPS group. Given the significant difference in non-tremor motor scores between the groups, non-tremor scores were included as a nuisance variable in the analysis. The PD + NPS group showed reduced gray matter intensity in prefrontal regions, including frontal pole, subcallosal cortex, anterior cingulate, and bilateral orbitofrontal cortex and inferior frontal gyri. See Table 3 and Fig. 1, panel (a).

3.5. VBM: post-hoc covariance analysis of gray matter density and NPS symptoms

To explore the direct contribution of regional brain atrophy to the global neuropsychiatric score, a post-hoc covariance analysis was conducted to corroborate whether NPS scores directly co-varied with gray matter atrophy. Results across the combined PD group showed that higher NPS scores co-varied with gray matter atrophy in the medial orbitofrontal cortex/frontal pole (peak voxels: $x = 8$, $y = 48$, $z = -18$). See Fig. 1, panel (b).

4. Discussion

We demonstrate that PD patients with elevated neuropsychiatric symptoms have greater atrophy in the prefrontal cortex, when compared to PD patients without neuropsychiatric symptoms, despite equivalent disease severity stages and dopamine

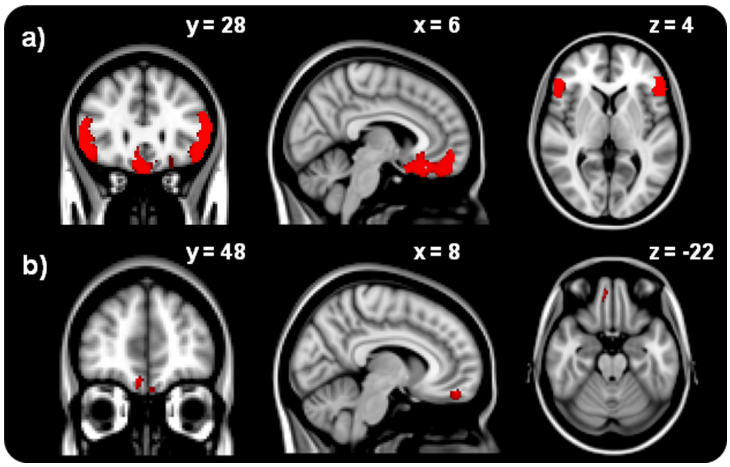

Fig. 1. Panel a) shows voxel-based morphometry results for regions of gray matter atrophy in PD patients with high levels of neuropsychiatric symptoms (PD + NPS), compared to the patient group without neuropsychiatric symptoms (PD − NPS). Results corrected for multiple comparisons using the family-wise error at a threshold of $p < .05$. Panel b) Voxel-based morphometry results showing regions of gray matter atrophy that co-varied with higher scores on the global Neuropsychiatric score across the whole PD cohort. Results significant at $p < .001$ uncorrected. All clusters are overlaid on the Montreal Neurological Institute standard brain ($t > 2.41$), using a cluster threshold of 40 contiguous voxels.

medication levels. These findings were corroborated by a covariance analysis across the whole PD cohort, confirming that higher levels of neuropsychiatric symptoms specifically related to the degree of gray matter atrophy in the medial orbitofrontal cortex/frontal pole. Our results confirm that in mild, non-demented PD, prefrontal atrophy makes a distinct contribution to neuropsychiatric symptoms, which is additional to the effects of dopamine medication. Contrary to our predictions, we did not observe atrophy in ventral striatal regions that related to neuropsychiatric presentation, suggesting that previously documented neurotransmitter imbalances in ventral striatal and brainstem nuclei may act in combination with prefrontal atrophy in the generation of neuropsychiatric symptoms in PD.

Our behavioral results corroborate previous studies demonstrating neuropsychiatric symptoms in non-demented PD patients without advanced cognitive or motor impairment [3]. Importantly, we show this using an informant-rated questionnaire, which allowed us to circumvent the reporting bias that can occur if patients have reduced insight into their psychiatric and behavioral changes. Individual sub-scores within the neuropsychiatric score we report were strongly correlated, highlighting that the range of symptoms represented in the global score are related and co-occurring within patients.

Previous efforts to characterize the pattern of gray matter atrophy in PD patients with affective and behavioral disturbances have focused on specific symptoms, namely depression and apathy. Consistent with our results, Feldmann et al. [9] found increased gray matter loss in orbitofrontal and right temporal regions of depressed vs. non-depressed PD patients (though see Kostić et al. [18]). Convergent evidence comes from other imaging modalities showing prefrontal metabolic dysfunction [19] and white matter changes [18] in PD with depression. Defining their PD groups on the basis of high and low apathy scores, Isella and colleagues [20] found no gray matter differences; however, looking specifically at regions of gray matter atrophy that co-vary with level of apathy symptomatology, Reijnders et al. [10] showed that higher apathy scores correlated with reduced gray matter density in prefrontal regions (inferior frontal gyrus and insula), with similar prefrontal regions also implicated in an FDG-PET exploration of apathy correlates in PD [21]. Our results are the first to implicate prefrontal atrophy in relation to globally elevated neuropsychiatric symptoms.

The global neuropsychiatric score we report incorporates a range of features, including depression, apathy, anxiety, impulsivity and rigid behavior. Our covariance analysis confirmed that elevated neuropsychiatric symptoms specifically correlated with atrophy in the orbitofrontal cortex/frontal pole – a region implicated in broad aspects of emotional regulation and goal-directed behavior. To our knowledge this is the first study to demonstrate a common neural correlate for diverse behavioral disturbances in PD, a finding supported by converging evidence across other neurodegenerative conditions and psychiatric disorders, where common regions of prefrontal pathology have been implicated in a range of mood, affective and behavioral symptoms [22]. Considering the positioning of the orbitofrontal cortex as an important hub in the fronto-striatal limbic circuitry, it is unsurprising that vulnerability in this region may be associated with a constellation of neuropsychiatric symptoms. This further elucidates why seemingly opposing 'positive' and 'negative' neuropsychiatric symptoms, such as apathy/depression and impulsivity, can co-exist in the same patient [4]. Conversely though, behavioral studies in PD have also demonstrated clear distinctions between neuropsychiatric symptoms [23] and there is considerable heterogeneity in the symptoms that can emerge. Therefore, whilst prefrontal atrophy may be a common risk factor for a range of neuropsychiatric symptoms, the combined influence of neurochemical dysfunction, disease stage, premorbid personality traits and reactive/psychosocial complications all likely contribute to their ultimate clinical manifestation.

We did not find an association between neuropsychiatric symptoms and ventral striatum atrophy, despite finding clear evidence of atrophy across the entire striatum in the PD cohort. Notwithstanding this result, receptor binding studies assessing apathy, depression, anxiety [6] and impulsivity [24,25] have consistently linked these symptoms to dopaminergic and noradrenergic dysregulation in the ventral striatum. Taken together with our findings, this suggests that neurotransmitter imbalance in the ventral striatum, as opposed to atrophy in the region, may be a

more significant determinant of neuropsychiatric symptoms. Nevertheless, the extent to which our PD groups were matched for dopamine medication levels confirms that prefrontal atrophy makes an additional contribution to neuropsychiatric symptoms, which is not determined by medication effects or striatal gray matter loss.

Patients with elevated neuropsychiatric symptoms also had a higher burden of non-tremor motor features, consistent with the non-tremor dominant phenotype that has been previously described [13]. Previous studies have linked depression and apathy to non-tremor dominant [26] and postural instability gait difficulty (PIGD) motor phenotypes – a further sub-classification within the non-tremor dominant phenotype [27]. Also, a recent VBM study found that prefrontal atrophy is amongst the distinctive features that differentiate the PIGD from the tremor dominant subtype [28]. Combined with our findings, this suggests that prefrontal atrophy may be a shared risk factor for both neuropsychiatric symptoms and a non-tremor dominant motor phenotype, which may contribute their high rates of co-occurrence. Whilst there is currently limited neuropathological data to verify these recent VBM findings, a higher burden of frontal cortical Lewy bodies (which are associated with neuronal cell loss) has been shown in the non-tremor phenotype and in patients with more severe cognitive and behavioral symptoms [29,30].

Cleary, the interaction between prefrontal atrophy (particularly ventromedial prefrontal cortex) and neurochemical dysfunction in the generation of neuropsychiatric symptoms in PD remains an important target for future research. PD is associated with pathological destruction of ascending brainstem modulatory systems, as well as direct pathology in subcortical limbic projection targets (e.g. basolateral amygdala, hippocampus, ventral striatum) [31,32] and dysfunction in these regions has been linked to neuropsychiatric symptoms [6,8]. However, many of these regions also have either direct or indirect connections with cortical limbic regions, including the orbitofrontal cortex. Indeed, it is possible that the elevated neuropsychiatric symptoms observed in a subset of PD patients are due to a combination of impairments across these three different levels of affective neural circuitry, which may even contribute to an increased predilection for ventromedial prefrontal atrophy given the substantial connectivity among these regions. Together, this would imply that neurotransmitter imbalances act in concert with prefrontal atrophy to produce neuropsychiatric disturbances in PD, which may partly explain why responsiveness to pharmacotherapy aimed to treat these symptoms by restoring neurotransmitter activity is often suboptimal [1]. The relative contributions of neurochemical imbalances in the brainstem nuclei and limbic projections vs. direct prefrontal atrophy should be further explored in *de novo* patients and longitudinal studies, as a more precise delineation will be important in better clarifying the pathophysiology of these symptoms and in informing future therapeutic targets.

Our findings, along with other recent evidence of atrophic change in PD, have important clinical implications as they highlight a need to assess the burden of prefrontal atrophy when evaluating a patient's risk of developing neuropsychiatric symptoms. As such, follow-up cognitive assessments and adjunctive imaging investigations should be designed to tap possible dysfunction or abnormalities in this region. From a theoretical perspective, just as data-driven approaches have linked neuropsychiatric features to a particular PD phenotype, the current findings speak to mounting evidence that patients with neuropsychiatric features also have distinctive patterns of functional and structural brain changes. Consideration of these underlying differences will be vital for research design, especially in clinical trials, where group-level treatment effects may be diluted if success of the therapeutic intervention is highly dependent on pre-existing structural or functional alterations. The results reported here converge with an accumulating body of literature confirming that volumetric change in PD is an important biomarker for non-motor symptoms [33].

It is important to note that the VBM technique utilized in this study is not without limitations, including registration and normalization issues and imperfect gray-white matter segmentation, particularly in relation to already atypical brains, and the possibility of false positives [34]. We applied a conservative cluster threshold and multiple comparisons corrections to reduce false positives, and despite the potential limitations, VBM is emerging as a useful tool to explore the contribution of gray matter loss to non-motor symptoms in PD [33]. Furthermore, the lack of striatal atrophy in the PD + NPS group may have been influenced by the relatively small sample size, and it would be valuable to replicate these findings in a larger cohort to further verify a possible role for striatal atrophy in the genesis of neuropsychiatric symptoms. Finally, corroborating the findings reported here with neuropathological data would be an important future direction, to confirm the clinical diagnoses of idiopathic PD and explore the relationship between regional pathology and neuropsychiatric symptoms.

In conclusion, this study has several important and novel findings. We have identified prefrontal atrophy as a characteristic feature of PD patients with elevated global neuropsychiatric symptoms, which is independent of medication levels. Our results highlight that neuropsychiatric disturbance in PD is not exclusively driven by neurotransmitter abnormalities, but that ventromedial prefrontal gray matter loss is an important factor in the pathophysiology of a range of neuropsychiatric symptoms. The interaction of those functional and structural changes in the generation of neuropsychiatric symptoms seems crucial to address in future studies, which in turn will have a significant impact on the development of targeted therapeutic approaches for these disabling symptoms in PD.

Conflict of interest disclosure

The authors report no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.parkreldis.2014.04.027.

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2.2 Publication II – "Fronto-striatal atrophy correlates of inhibitory dysfunction in Parkinson's disease versus behavioural variant frontotemporal dementia"

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Research report

Fronto-striatal atrophy correlates of inhibitory dysfunction in Parkinson's disease versus behavioural variant frontotemporal dementia

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ABSTRACT

Introduction: Impulsive behaviours commonly manifest in treated Parkinson's disease (PD) patients, and, are typically viewed as sequelae of dopaminergic therapy. However, recent evidence shows that impulsivity in those patients may not only depend on medication status. Instead, there is the suggestion that dopaminergic therapy interacts with existing neuroanatomical and/or neurochemical abnormalities, to produce impulsive behaviour in certain vulnerable patients.

Methods: In this study, we investigated whether grey matter atrophy in fronto-striatal brain regions contributes to inhibitory dysfunction – a key feature of impulsive behaviour – in PD. Importantly, we contrasted 25 PD patients with 11 behavioural variant frontotemporal dementia (bvFTD) patients, who have well-established inhibitory dysfunction and related grey matter atrophy. We employed a questionnaire to assess impulsive behaviours (Barrett Impulsiveness Scale), and measures of verbal inhibitory function (Hayling Test) and response inhibitory function (a go/no-go task). Behavioural analyses were conducted to examine performance in the PD and bvFTD patients and in 15 healthy controls. Scores on the verbal and response inhibition tasks were also entered as covariates in a region of interest voxel-based morphometry analysis, to determine the grey matter correlates.

Results: PD patients showed impairments in inhibitory function, though to a milder degree than bvFTD patients. In the Parkinson's sample, frontal atrophy (namely, orbitofrontal and right inferior frontal cortex) was shown to correlate with verbal disinhibition, and striatal atrophy (right nucleus accumbens) was associated with response disinhibition, whereas a more distributed pattern of fronto-striatal atrophy was associated with the bvFTD patients' performance on inhibitory measures.

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Conclusions: These results provide the first evidence that disinhibition in PD is related to fronto-striatal grey matter atrophy. Our study adds support to the hypothesis that impulsivity in PD is not solely mediated by dopaminergic medication effects, but that fronto-striatal structural abnormalities contribute to impulsive behaviours in these patients.

1. Introduction

Parkinson's disease (PD) is characterised by its hallmark motor features: bradykinesia, tremor, rigidity and postural instability (Litvan et al., 2003). A range of cognitive and neuropsychiatric disturbances have also been recognised with the disease (Aarsland et al., 2003), including impulsivity, which reportedly occurs in 13.6% of treated patients (Weintraub et al., 2010). Impulsivity in these patients may manifest as pathological gambling, hypersexuality, compulsive shopping and binge eating, with significant implications for patients and their families (Potenza et al., 2007; Voon and Fox, 2007). Cognitive tasks corroborate these clinical impressions by showing that PD patients make riskier choices in response to monetary rewards (Voon et al., 2011) and have impaired tolerance for delayed gratification (Voon et al., 2010). PD patients also show impulsivity on both verbal and action–response measures of inhibitory functioning, such as the Hayling Test and go/no-go tasks (Cooper et al., 1994; Obeso et al., 2011).

The cause of impulsive behaviours in PD – or impulse-control disorders (ICDs) as they are collectively termed – is not yet known. However, they most frequently manifest in patients with the advent of dopaminergic therapy (Weintraub et al., 2010). One hypothesis is that such therapy ameliorates motor symptoms arising from dopaminergic depletion in the dorsal striatum, while at the same time causing a dopamine "overdose" in the less depleted ventral striatum-orbitofrontal circuitry (Cools, 2006). More explicitly, increased *tonic* dopamine in the ventral striatum and prefrontal regions, prevents the *phasic* dopamine activity that is crucial for stimulus-outcome evaluation (Schultz, 2002). Associative-learning, which occurs when there is discrepancy between the expected and actual outcomes of a reinforcer, has been directly shown to covary with phasic activation of dopamine neurons in monkey neuronal-recording studies (Fiorillo et al., 2003), and disruption to this learning mechanism is thought to contribute to impulsive behaviours.

Nevertheless, findings from pharmacological manipulation studies have been mixed in their support for the dopamine hypothesis of impulsivity in PD. Consistent with the hypothesis, Cools et al. (2003) showed that dopamine medication induced impulsive betting behaviours in a non-demented PD sample. Furthermore, van Eimeren et al. (2009) found that dopamine agonists in PD patients diminished reward processing in the orbitofrontal cortex (OFC), causing impaired learning from negative outcomes. However, this desensitisation to reward was not associated with increased impulsivity on a risk-taking task. In a subsequent study with a probabilistic feedback task, dopamine agonists induced a reduction in cerebral blood flow in a fronto-striatal network, which correlated positively with gambling severity (van Eimeren et al., 2010). Importantly, this only occurred in PD patients with ICDs and not in those patients without such symptoms. Similarly, Voon et al. (2010) found that dopamine agonists were associated with increased impulsive choice, but only in those PD patients with ICDs. However, testing only PD patients without ICDs, Milenkova et al. (2011) demonstrated considerably greater impulsive choice on a delay discounting task, both ON and OFF medication.

Whilst undoubtedly both the clinical observations and the evidence from cognitive investigations suggest dopaminergic therapy to be a risk factor for impulsivity, the study by Milenkova and colleagues was the first to show that impulsive decision making in PD may not simply be dependent on medication status. This raises the possibility that impulsivity in PD may reflect a specific behavioural endophenotype of the disease (Voon and Dalley, 2011), whereby dopaminergic therapy interacts with existing neuroanatomical and/or neurochemical abnormalities, to produce impulsive behaviour in certain vulnerable individuals. One potential neuroanatomical change influencing impulsivity in PD could be atrophy or dysfunction in certain neural regions that normally exert control on impulsive behaviour.

Impulsivity may not be a unitary construct and there is considerable evidence that different forms of impulsivity may depend on different neural systems (Sonuga-Barke, 2003; Winstanley et al., 2006). Thus, it has been proposed that there are distinct systems mediating 'stopping' versus 'waiting' forms of impulsivity, the former implicating inferior frontal regions and the dorsal striatum, and the latter, including discounting and reward anticipation, depending on the ventromedial prefrontal cortex and ventral striatal regions (the nucleus accumbens) (Dalley et al., 2011). Within the ventral striatal 'loop' it could be postulated that the nucleus accumbens exerts motivational processes that drive impulsive behaviours, whereas a prefrontal component (possibly portions of the OFC) exerts inhibitory control (Cools, 2008; Fineberg et al., 2009). Human and animal lesion models have associated the nucleus accumbens with impulsive behaviour (Basar et al., 2010; Cardinal, 2006; Cardinal et al., 2001). In the case of the OFC the picture is a little more mixed in the pre-clinical literature, however Mar et al. (2011) showed that lesions of the lateral OFC in rodents induced impulsivity in a delayed discounting paradigm (whereas medial orbital lesions had the opposite effect). Findings from Rolls et al. (1994), Berlin et al. (2004) and Hornak et al. (2004) have tended to show that large lesions of the prefrontal cortex, that include the OFC, enhance impulsive responding. This is further substantiated by studies investigating the neural correlates of behavioural

dysfunction in neurodegenerative diseases, which show strong correlations between OFC atrophy and the level of response disinhibition (Franceschi et al., 2005; Hornberger et al., 2011; Peters et al., 2006).

Despite the substantial number of studies examining medication effects in PD, to our knowledge, no study to date has investigated the grey matter atrophy correlates of impulsivity in PD. The current study employed a region of interest (ROI) voxel-based morphometry (VBM) approach, by correlating verbal and non-verbal disinhibition measures with grey matter atrophy in frontal and striatal brain regions. Importantly, we compared the findings in PD to a group of behavioural variant frontotemporal dementia (bvFTD) patients, with known disinhibition deficits and associated grey matter atrophy (Hornberger et al., 2011). Our predictions were that PD patients would show inhibitory dysfunction in comparison to controls on verbal and non-verbal measures, however, that these deficits would be milder than in bvFTD. We further predicted that striatal atrophy would correlate with the disinhibition measures in PD, while bvFTD would show more prefrontal atrophy correlates for failure to inhibit.

2. Methods

2.1. Case selection

Twenty five non-demented PD patients were recruited from the Brain and Mind Institute Parkinson's Disease Research Clinic; all satisfied UKPDS Brain Bank criteria for diagnosis of PD (Gibb and Lees, 1988) and were between Hoehn and Yahr stages I and III (Hoehn and Yahr, 1967). Motor score from the Unified Parkinson's Disease Rating Scale (UPDRS-III) (Fahn et al., 1987) is also reported. One patient was untreated. Twenty one patients were taking levodopa (two of whom were also on entacapone), and fourteen of these were also taking a dopamine agonist. One patient was on agonist monotherapy and two were on an agonist plus rasagiline. Additionally, one of those patients on levodopa was also taking a serotonin-norepinephrine reuptake inhibitor. Patients performed behavioural testing in the ON state, having taken their usual medications. L-dopa daily dose equivalents (DDE mg/day) were calculated for treated patients and for those on a dopamine agonist, total dopamine agonist dose in DDE (DA-DDE mg/day) was also calculated. Eleven bvFTD patients were recruited from the FRONTIER dementia clinic; all met current consensus criteria for FTD (Neary et al., 1998; Rascovsky et al., 2011), with insidious onset, decline in social behaviour and personal conduct, emotional blunting and loss of insight. Fifteen age- and education-matched healthy controls were selected from a volunteer panel or were spouses/carers of patients. The research study was approved by the Human Ethics Committees of the Central and South Eastern Sydney Area Health Services and the Universities of Sydney and New South Wales, and complies with the statement on human experimentation issued by the National Health and Medical Research Council of Australia. See Table 1 for demographic details and clinical characteristics.

2.2. Behavioural testing

As a verbal inhibition measure, we employed the Hayling Test (Burgess and Shallice, 1997), which evaluates inhibition of a prepotent verbal response via a sentence completion task. The first section of the test consists of 15 open-ended sentences and subjects provide a word to complete the sentence plausibly (e.g., "He posted a letter without a…" Potentially correct answer: "stamp"). The second section contains 15 open-ended sentences the subject completes with a word that is unconnected to the sentence, which requires inhibition of the automatic response (e.g., "London is a very busy …" Potentially correct answer: "banana"). For this section, errors are recorded for words that are connected with the sentence ("A" errors are those that are *strongly* connected and "B" errors are those only *partially* connected). For both sections, the time taken to respond is recorded, which together with the error scores results in an overall score. In the current study, we report behavioural performance for the scaled score B (response time for section two), total errors (termed AB score, i.e., "A" errors plus "B" errors in section two) and the overall

Table 1 – Mean (SD) scores for Controls, FTD and PD patients for demographics and clinical characteristics. *F* values indicate significant differences across groups; Tukey post-hoc tests compare differences between group pairs.

Demographics and clinical characteristics	Controls	bvFTD	PD	*F* values	bvFTD versus Controls	PD versus Controls	bvFTD versus PD
N	15	11	25	–	–	–	–
Sex (M:F)	12:3	10:1	16:9				
Age	64.2 (4.9)	63.1 (7.2)	64.5 (7.3)	N.s.			
Education	14.2 (2.6)	12.2 (3.2)	13.3 (2.9)	N.s.			
MMSE (max. 30)	29.3 (.98)	23.9 (3.9)	28.0 (2.1)	***	***	N.s.	***
Carer BIS		72.4 (11.2)	53.2 (11.1)				**
Duration (years from diagnosis)		1.0 (.52)	7.3 (4.9)				***
Levodopa dopamine dose equivalent (LEDD mg/day)	–	–	896.5 (546.8)	–	–	–	–
Dopamine agonist dose in LEDD (DA-LEDD mg/day)	–	–	230.6 (145.3)	–	–	–	–
Hoehn & Yahr stage	–	–	2.0 (.59)	–	–	–	–
UPDRS-III	–	–	12.9 (7.3)	–	–	–	–

N.s. = non significant; *** = $p < .001$; ** = $p < .01$.

scaled score. We conduct further imaging analysis using the AB error score, as this is the most direct measure of response inhibition.

For the non-verbal disinhibition measure, we developed a go/no-go task to assess inhibition of a prepotent motor response. The task involved black and white photographs of faces displayed on a computer screen. Each face was preceded by a fixation cross (1500 msec) and then presented for 1000 msec during which the participants had to respond or not. The response required for 'go' trials was to press the spacebar as quickly as possible, for 'no-go' trials that response had to be withheld. Subjects were asked to respond to some faces but not others, based on either colour (normal photograph *vs* negative of a photograph) or emotional expression differences (sad *vs* happy), which differed across blocks. There were six blocks, each with 48 trials (32 'go' and 16 'no-go' trials randomly intermixed). A majority of 'go' trials ensures that the subject becomes increasingly habituated to responding, making suppression of the response more difficult on 'no-go' trials (Bruin and Wijers, 2002). Blocks were administered in a randomised order across participants to reduce any condition order confounds. For the go/no-go task we report a percent-correct score for 'no-go' trials, this was a measure of how efficiently subjects inhibited the motor response. Only valid 'no-go' trials contribute to the score, which were defined by a correct response on the preceding 'go' trial. This ensured that subjects who responded less frequently regardless of the trial were not awarded an inordinately high score for 'no-go' trials.

All patients underwent general cognitive screening with the Mini Mental State Examination (MMSE; Folstein et al., 1975) to determine their overall cognitive functioning. We administered a carer version of the Barrett Impulsiveness Scale [11th revision; BIS-11; (Patton et al., 1995)] designed to assess the prevalence of impulsive behaviours and personality traits. The original BIS-11 is a 30 item self-report questionnaire where items are given scores from 1 to 4 based on their frequency of occurrence (i.e., Rarely/Never; Occasionally; Often; Almost Always/Always) and higher scores indicate increased impulsivity. As a guide, the mean score on the BIS-11 for a sample of college undergraduates reported by Patton et al. (1995) was 63.82 [Standard Deviation (SD = 10.17)] and Stanford et al. (2009) suggest that a score of 72 or above should be used to classify an individual as highly impulsive. In a PD population of 21 patients with pathological gambling and 42 PD patients without compulsive behaviours, Voon et al. (2007) report total means (SDs) on the BIS-11 as 65.2 (12.2) and 54.1 (10.1), respectively ($p = .006$). This suggests that this measure of impulsivity, which is one of the most widely used (Cools, 2008), may be useful in detecting impulsive behaviour in PD. For the present study, we designed a carer-report version of the BIS-11 (for each question "I" was replaced with "He/She"); this was to accommodate for impaired insight, which is a prominent feature in bvFTD. Three items that related to employment and changing residences were removed. These items were deemed inappropriate for use in a bvFTD dementia population, as carers were encouraged to reflect upon current circumstances and patients would most often have retired and/or may not be in a position to make independent decisions regarding living arrangements.

We also included background neuropsychological data on executive functioning tasks. Verbal fluency was measured by the number of words produced in 60 sec, beginning with F, A and S (Benton et al., 1994). Repetitions were scored as perseverations; words beginning with a different letter, proper nouns and derivations of the same word stem were scored as rule breaks. The Trail-Making test was administered to assess visuomotor speed (Part A) and speeded set-shifting (Part B) (Partington and Leiter, 1949). Attention span and working memory were assessed via a digit span task, with digits repeated in their original order (forwards) and in reverse order (backwards) (Wechsler, 1997).

2.3. *Behavioural analyses*

Data were analysed using SPSS18.0 (SPSS Inc., Chicago, Ill., USA). Parametric demographic and neuropsychological data were compared across the groups via one-way ANOVAs followed by Tukey post-hoc tests. A priori, neuropsychological and disinhibition variables were plotted and checked for normality of distribution by Kolmogorov–Smirnov tests. Variables showing non-parametric distribution were analysed via Chi-square, Kruskal–Wallis and Mann–Whitney *U* tests.

2.4. *Imaging acquisition*

Due to patient scan eligibility, availability and technical reasons, only 12 PD patients were scanned and included in the VBM analysis. The subset of 12 PD patients, the bvFTD patients and controls underwent the same imaging protocol with whole-brain T1 images acquired using 3T Philips MRI scanners with standard quadrature head coil (8 channels). The 3D T1-weighted sequences were acquired as follows: coronal orientation, matrix 256 × 256, 200 slices, 1 × 1 mm^2 in-plane resolution, slice thickness 1 mm, TE/TR = 2.6/5.8 msec.

2.5. *VBM analysis*

3D T1-weighted sequences were analysed with FSL-VBM, a VBM analysis (Ashburner and Friston, 2000; Good et al., 2001) which is part of the FSL software package http://www.fmrib.ox.ac.uk/fsl/fslvbm/index.html (Smith et al., 2004). First, tissue segmentation was carried out using FMRIB's Automatic Segmentation Tool (FAST) (Zhang et al., 2001) from brain extracted images. The resulting grey matter partial volume maps were then aligned to the Montreal Neurological Institute standard space (MNI152) using the nonlinear registration approach using FNIRT (Andersson et al., 2007a, 2007b), which uses a b-spline representation of the registration warp field (Rueckert et al., 1999). The registered partial volume maps were then modulated (to correct for local expansion or contraction) by dividing them by the Jacobian of the warp field. The modulated images were then smoothed with an isotropic Gaussian kernel with a SD of 3 mm (FWHM: 8 mm). A ROI mask for prefrontal and striatal brain regions was created by using the Harvard-Oxford cortical and subcortical structural atlas. The following atlas regions were included in the mask: frontal pole, superior frontal gyrus, middle frontal gyrus, inferior frontal gyrus, frontal medial cortex, subcallosal cortex, paracingulate gyrus, cingulate gyrus (anterior

division), frontal orbital cortex, caudate, putamen and nucleus accumbens. Finally, a voxelwise general linear model (GLM) was applied and permutation-based non-parametric testing was used to form clusters with the Threshold-Free Cluster Enhancement (TFCE) method (Smith and Nichols, 2009), tested for significance at $p < .05$, corrected for multiple comparisons via Family-wise Error (FWE) correction across space, unless otherwise stated.

3. Results

3.1. Demographics, cognitive and behavioural screening measures

Demographics and general cognitive scores can be seen in Table 1. Participant groups did not differ in terms of age and education (p's $> .1$). As may be expected, the PD group had a significantly longer disease duration compared to the bvFTD group. PD and control groups did not differ on their MMSE scores, but the bvFTD group was significantly below both of these groups (p's $< .000$). The bvFTD patients showed more impulsivity on the BIS compared to PD patients ($p < .01$). Independent t-tests revealed no significant differences for demographics and screening measures between the sample of 25 PD patients and the subset of 12 with imaging data (p's $> .1$).

3.2. Background neuropsychology

Background neuropsychological performance is summarised in Supplementary Table 1. For total correct score on verbal fluency, the PD and control groups did not differ, and both groups obtained significantly more words than the bvFTD group ($p < .01$). In contrast, both the PD and bvFTD patient groups made more rule breaks than controls (p's $< .01$). There were no group differences in repetitions. For Trail-Making parts A and B, the bvFTD patients were slower than both PDs and controls ($p < .05$) and the PD and control groups did not differ. There were no group differences in errors for Trail-Making parts A or B. The PD and bvFTD patient groups performed significantly worse than controls for Digit Span forwards and backwards (p's $< .05$), with the bvFTD group significantly below the PD group for Digit Span forward ($p < .05$), but equal to the PD group for Digit Span backward. Independent t-tests did not reveal any significant differences on background neuropsychology measures between overall the PD sample and those with imaging (p's $> .1$).

3.3. Inhibition tasks

Results of inhibition tasks are shown in Table 2. On the Hayling Test, PD patients were equivalent to controls with respect to response latencies (scaled score B), but were impaired with regards to the amount of errors (AB score) ($p < .000$) and the overall scaled score ($p < .01$). The PD group performed better than the bvFTD group on all measures (p's $< .01$). The bvFTD patients were impaired on all measures derived from the Hayling Test: scaled score B, AB error score and overall scaled score (p's $< .001$). There were no significant differences for performance on the Hayling Test between the overall PD sample and the subset with imaging data (p's $> .1$) and importantly, the difference between the PD patients' and controls AB error score remained highly significant ($p < .01$) when only the 12 scanned patients were included in the analysis.

For the go/no-go task, the PD group's accuracy on 'no-go' trials was significantly below control levels ($p < .05$). The bvFTD patients made more errors on 'no-go' trials compared to controls ($p < .01$). The patient groups did not differ significantly from each other. Independent t-tests did not reveal significant differences between the overall PD sample and the 12 with imaging data (p's $> .1$), however, although the subset of 12 still had lower 'no-go' accuracy than the controls, this did not reach significance ($p = .08$). Results of the Hayling error score and 'no-go' accuracy are represented in Fig. 1.

Analyses using t-tests to compare the PD patients taking levodopa only/levodopa and an adjunct ($n = 7$) with those patients also taking a dopamine agonist/agonist monotherapy ($n = 17$) did not reveal any significant differences with regard to performance on measures of inhibitory function or behavioural impulsivity (p's $> .5$).

3.4. Correlation analysis of disinhibition measures

A correlation analysis conducted with the PD patients revealed that scores on the Hayling and go/no-go disinhibition measures, as well as the BIS, did not correlate significantly with age, dopamine medication (DDE, DA-DDE) or disease stage (Hoehn and Yahr score) (p's $> .1$). Furthermore, for the PD group there was no correlation between disease duration and 'no-go' accuracy ($p > .7$). However, there was a significant positive correlation between the overall scaled score on the

Table 2 – Mean (SD) scores for Controls, FTD and PD patients on disinhibition measures. Due to unequal variance χ^2 indicates differences across groups and Mann–Whitney U tests compare differences between group pairs.

	Controls	bvFTD	PD	χ^2 values	bvFTD versus Controls	PD versus Controls	bvFTD versus PD
Hayling test**							
Scaled score B (time)	6.0 (.37)	3.5 (2.3)	5.7 (.68)	***	**	N.s.	**
AB score (errors)	1.4 (2.2)	37.5 (19.7)	11.1 (13.0)	***	***	***	***
Scaled score Overall	6.7 (.72)	2 (1.8)	5.7 (1.1)	***	***	**	***
Go No-go task							
% Correct no-go trials	95.7 (4.0)	76.1 (24.0)	90.1 (6.0)	*	**	*	N.s.

N.s. = non significant; *** = $p < .001$; ** = $p < .01$; * = $p < .05$.

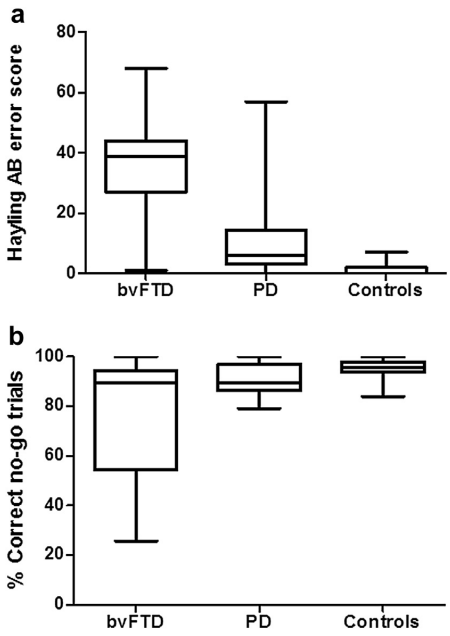

Fig. 1 – Box plot for a) Hayling AB error score, and b) percentage of correct 'no-go' trials across all three groups (bvFTD, PD and Controls). Whiskers indicate minimum and maximum values.

Hayling and disease duration ($p < .05$) and a strong negative correlation between Hayling AB error score and disease duration ($p = .59$), together suggesting that patients earlier in the course of their disease were more likely to display verbal disinhibition.

3.5. *VBM – group analysis*

Patient groups were initially contrasted with controls to reveal patterns of brain atrophy in the fronto-striatal mask. PD patients showed grey matter atrophy in medial OFC, extending back to the right nucleus accumbens. There was also more lateralised, bilateral OFC atrophy including the border to the inferior frontal cortex (IFC). The bvFTD patients showed distributed grey matter atrophy in medial OFC, with more lateralised OFC and IFC atrophy bilaterally, as well as atrophy involving both dorsal and ventral striatum (caudate/putamen and nucleus accumbens) (see Supplementary Table 2 and Supplementary Fig. 1).

3.6. *VBM – correlations with inhibition scores*

We entered the AB error score of the Hayling Test and the go/no-go percent-correct score as covariates in the design matrix of the VBM analysis. For PD patients, AB error scores covaried with medial OFC, and lateral right-sided OFC, insular and IFC. For bvFTD patients, AB error score covaried with medial and bilateral OFC, also left-sided IFC and putamen. On the go/no-go task, PD patients' 'no-go' accuracy scores covaried with atrophy in the right nucleus accumbens only, while bvFTD patients' scores for percentage of correct 'no-go' trials correlated with

Table 3 – ROI VBM results showing areas of significant grey matter intensity decrease that covary with disinhibition performance. All results uncorrected at $p < .001$; only clusters with at least 40 contiguous voxels included.

Regions	Hemisphere (L/R/B)	MNI coordinates			Number of voxels	T score
		X	Y	Z		
Hayling Test: AB error score						
bvFTD versus Controls						
Medial orbital frontal cortex, frontal pole	B	4	42	−30	1233	3.20
Lateral orbital frontal cortex, subcallosal cortex	R	16	10	−16	520	3.20
Putamen	L	−30	2	6	513	3.20
Lateral orbital frontal cortex	R	36	20	−22	505	3.20
Lateral orbital frontal cortex, insular cortex, inferior frontal gyrus	L	−28	28	−2	469	3.20
PD versus Controls						
Medial orbital frontal cortex, subcallosal cortex	B	2	26	−28	642	3.20
Inferior frontal gyrus, lateral orbital frontal cortex, insular cortex	R	50	20	−6	143	3.20
Lateral orbital frontal cortex, insular cortex	R	28	24	−6	41	3.20
Go No-go Task: % correct 'No-go' trials						
bvFTD versus Controls						
Putamen, nucleus accumbens	L	−16	14	−8	694	3.20
Frontal pole, inferior frontal gyrus, lateral orbital frontal cortex	L	−52	34	−8	549	3.20
Putamen, pallidum	R	24	0	−2	303	3.20
Lateral orbital frontal cortex, frontal pole	L	−34	26	−16	92	3.20
PD versus Controls						
Nucleus accumbens	R	10	10	−8	40	3.20

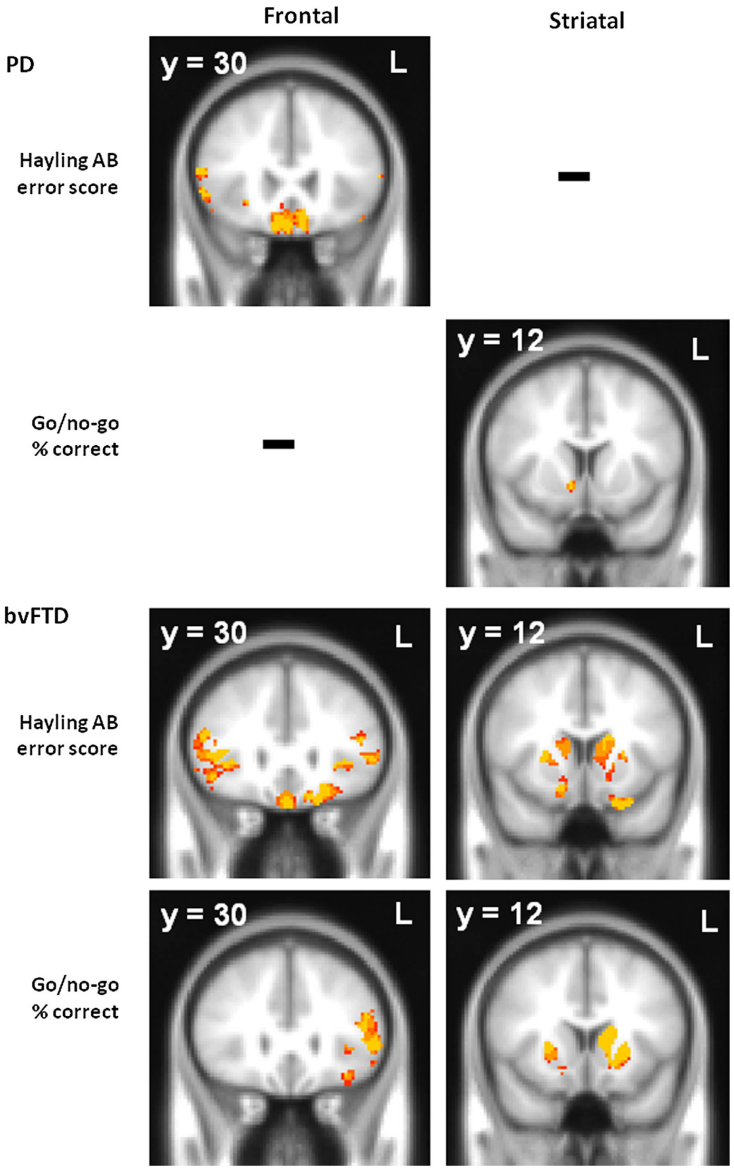

Fig. 2 – VBM analysis showing the frontal and striatal regions that correlate with Hayling AB errors and 'no-go' accuracy, for PD and bvFTD patients. Clusters are overlaid on the MNI standard brain ($t > 3.20$). Coloured voxels show regions which were significant in the analyses for $p < .001$ uncorrected and a cluster threshold of 40 contiguous voxels.

bilateral putamen and left nucleus accumbens, left-sided frontal areas including OFC and IFC (see Table 3 and Fig. 2).

A partial correlation analysis further explored whether common damage to the medial OFC and other regions (in particular IFC) could have explained the significantly correlations with the Hayling AB error score. Indeed, medial OFC still correlated significantly ($p < .05$) with the AB score when IFC atrophy was taken into account. By contrast, IFC atrophy did not correlate anymore significantly ($p > .1$) with the AB score once medial OFC atrophy was taken into account.

As a final step, we created an inclusive mask showing shared atrophy correlating with disinhibition for both patient groups. There was no atrophy overlap for the go/no-go task, but for the AB error score, there was atrophy overlap in the medial OFC region (peak voxel: $x = 2$, $y = 26$, $z = -28$; *voxels* $= 93$) (see Fig. 3).

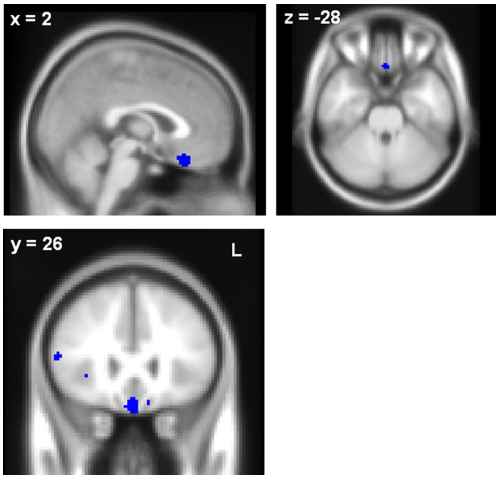

Fig. 3 – Region of overlap of grey matter atrophy in PD and bvFTD patients for Hayling AB error score. Clusters are overlaid on the MNI standard brain ($t > 2.50$). Coloured voxels show regions which were significant in the analyses for $p < .001$ uncorrected and a cluster threshold of 70 contiguous voxels.

4. Discussion

To our knowledge, this is the first study investigating the grey matter atrophy correlates of disinhibition in PD. Our results unequivocally show that grey matter atrophy in PD is related to inhibitory functioning across verbal and non-verbal measures of response disinhibition. Behavioural disinhibition effects were less severe in PD than in bvFTD, even though there were commonalities in the frontal and striatal areas that correlated with inhibitory dysfunction in both patient groups.

Behaviourally, PD patients showed less impulsivity/disinhibition than bvFTD patients on questionnaire and cognitive measures. The behavioural questionnaire (carer BIS-11) revealed that bvFTD patients were considerably more impulsive than the PD group. PD patients' scores were similar to those reported by Voon et al. (2007) in a non-ICD PD group, and below the recommended cut-off for designating high impulsivity (Stanford et al., 2009). Similarly, PD patients were less impaired than bvFTD group on the error measures of the Hayling Test; however, they showed significant difficulties in suppressing prepotent verbal responses compared to controls, which replicates previous findings (Obeso et al., 2011; Uekermann et al., 2004). On the go/no-go task, the PD group showed inhibitory deficits, which is consistent with previous studies identifying response inhibitory dysfunction in PD without dementia (Cooper et al., 1994; Gauggel et al., 2004). The bvFTD patients were markedly impaired across both inhibitory measures. This should be not surprising as disinhibition is one of the hallmarks in bvFTD and has been consistently reported in this patient group (Hornberger et al., 2011, 2008). Although, previous go/no-go studies have found only mild deficits in bvFTD (Collette et al., 2007), whereas bvFTD patients in the current study were comprehensively impaired on this measure.

On a neuroimaging level, VBM covariate analyses revealed that PD patients' performance on inhibitory tasks correlated with grey matter atrophy – with verbal disinhibition corresponding to frontal regions (medial OFC and right-sided lateral OFC/IFC) and response disinhibition corresponding to the right ventral striatal region (nucleus accumbens). To our knowledge this is the first time such a relationship has been shown in PD. Importantly, these regions correspond to the fronto-striatal network purportedly affected by dopaminergic "overdose", which has also been implicated in impulsivity in PD via functional imaging and pharmacological manipulation studies (Cools et al., 2007; Rao et al., 2010; van Eimeren et al., 2009; van Eimeren et al., 2010; Voon et al., 2011). Therefore, our results suggest a structural component to impulsivity in PD, with atrophy in the OFC, right-IFC and right nucleus accumbens contributing to verbal and non-verbal response disinhibition.

Our findings in the PD patients were further corroborated via comparison to the bvFTD group. The bvFTD patients' scores covaried with a more extensive distribution of fronto-striatal atrophy than PD patients, which can potentially explain the higher degree of disinhibition in this group. More importantly, both groups shared a common set of orbitofrontal regions which correlated with lack of inhibitory control. The orbitofrontal findings in bvFTD replicate previous results (Hornberger et al., 2011), however to date no study has shown striatal involvement to inhibitory dysfunction in bvFTD.

The OFC is known to represent subjective value of reinforcers and integrate this information to enable flexible, adaptive behaviour (Kringelbach, 2005). Long-standing theories propose that such regulation of behaviour is achieved by means of inhibitory processes (Ferrier, 1876). More recent theories have tended to downplay the role of OFC in inhibitory processes, and focus on its role in behavioural regulation via associative-learning or signalling outcome expectancies (Schoenbaum et al., 2009). The Hayling test provides a relatively unadulterated measure of verbal-response inhibition, without any reward contingencies or learning requirements. Therefore, our findings that OFC atrophy correlated with Hayling errors in both patient groups reaffirms that this region is indeed crucial for inhibitory functioning. Likewise, the IFC was associated with Hayling errors for both patient groups, suggesting that this region is also crucial for inhibitory function in the absence of learning and feedback. The IFC is well recognised as a site for action–response inhibition (Aron et al., 2004; Levy and Wagner, 2011). However, other studies have also identified IFC activation during learning and feedback tasks that require inhibition (i.e., cognitive set-shifting and reversal learning) (Cools et al., 2002; Konishi et al., 1999). Our partial correlation findings are of particular interest in this context, as they show that IFC atrophy only correlated with the verbal inhibitory scores due to the concomitant atrophy in the medial OFC region. After medial OFC atrophy was partialled out from the analysis, the IFC no longer correlated with the Hayling AB score. Thus, the disinhibition effects on the verbal measure appear to have been mainly driven by medial

OFC atrophy, with the IFC playing more of a supportive role. The precise nature of the relationship between the OFC and IFC in verbal disinhibition clearly warrants further investigation.

The nucleus accumbens atrophy that covaried with go/no-go commission errors in the PD patients is broadly consistent with current theories of response-inhibition networks (Aron et al., 2007; Dalley et al., 2011). That is, the stopping process is generated by the IFC, leading to activation in the striatum, thereby inhibiting thalamo-cortical output and ultimately reducing motor cortex activity. Indeed, the pronounced response disinhibition in our bvFTD sample did correlate with an extensive fronto-subcortical network, including OFC, left IFC and bilateral dorsal and ventral striatum. The precise role of the striatum in response inhibition is still debated (Aron, 2011). In human studies, lesions to the basal ganglia have been associated with response inhibition deficits (Rieger et al., 2003) and functional MRI has shown striatal activation during inhibitory control tasks (Chevrier et al., 2007; Vink et al., 2005). More specifically, animal models suggest that the nucleus accumbens is crucial for response inhibition (Ambroggi et al., 2011), although the evidence to date is mixed and it is suggested that the role of the nucleus accumbens in action–response inhibition is highly task dependent (Basar et al., 2010). Our findings highlight that the ventral striatum is implicated in failures of response inhibitory control. Furthermore, we show that this crucial area, thought to be mainly functionally compromised in PD without dementia, is in fact atrophic and associated with response disinhibition.

Taken together, our findings support Milenkova and colleagues' suggestion that factors other than dopaminergic therapy may mediate impulsivity in PD. Our study provides evidence that structural abnormalities in the OFC, right-sided IFC and right nucleus accumbens, are associated with failures in inhibitory control in PD, and thus may contribute to impulsive behaviours. Differences in grey matter atrophy may explain why some individuals are more vulnerable to effects of treatment and go on to develop ICDs. Clinically, this would indicate that clinicians may need to take such atrophy into account, particularly OFC, when assessing risk factors for the development of impulsivity in PD.

A potential limitation of our study is that we were not able to control fully for medication effects. All of our PD sample were assessed on their regular dopaminergic therapy, with the majority taking a dopamine agonist. Therefore, dopaminergic stimulation may well have played a role in the disinhibition we observed on the Hayling test and go/no-go task. However, none of our measures of impulsivity or inhibitory function correlated with dopaminergic dosages, and crucially, we demonstrated a structural underpinning to the inhibitory deficits, with the critical anatomical regions converging with another condition characterised by severe disinhibition effects (i.e., bvFTD). Future studies should explore the interaction between dopaminergic therapy and atrophy, with regard to inhibitory function in PD, in order to test the hypothesis that patients with atrophy in impulse-control sensitive regions are more susceptible to medication effects and, therefore, more likely to develop ICDs. The current study took a convenience sample, in order to define inhibitory processes in a typical PD population. Future studies should explore inhibitory dysfunction in PD patients with clinically defined ICDs versus those without prominent behavioural impulsivity. Replicating our findings in a larger sample of PD patients and studying longitudinal changes in inhibitory function in PD is also a consideration for future studies.

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Supplementary data

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2.3 Summary and future directions

The studies reported in this chapter demonstrate the impact of frontal and striatal atrophic change on both everyday neuropsychiatric symptoms (in PD) and cognitive manifestations of inhibitory dysfunction (in PD and bvFTD). These findings are particularly critical for informing our understanding of neuropsychiatric symptoms in PD. In Publication I, ventromedial prefrontal atrophy emerges as a neural signature associated with patients manifesting elevated neuropsychiatric symptoms. Further, a common region in the orbitofrontal cortex covaried with global levels of neuropsychiatric symptoms, suggesting that compromised function in this region may predispose patients to a range of symptoms. This is important considering more recent models of neuropsychiatric symptoms in PD, which postulate that seemingly opposite symptoms (such as impulsivity versus apathy or depression) reflect disruption in common neural circuits (Sinha *et al.*, 2013, Vriend *et al.*, 2014a). Whilst opposing symptoms have been related to up- versus down-regulated dopamine function within the same fronto-limbic-striatal circuitry, findings from Publication I highlight the possibility of a shared structural vulnerability contributing to various neuropsychiatric symptoms. Clearly the interaction between prefrontal atrophic change and dopamine function remains a crucial area of future exploration. Nowhere is this more apparent than with respect to the development of impulse control disorders (ICDs) in PD, as highlighted in Publication II. Results of this study suggest that at least some aspects of inhibitory function are impaired in PD and directly related to fronto-striatal atrophy. A more recent study further confirms that although inhibitory function is not uniformly impaired in PD, those aspects that are impaired are not necessarily mediated by levels of dopamine medication (Nombela *et al.*, 2014). Importantly, these findings have occurred in patients without florid ICDs. Together the findings confirm that deficits in inhibitory

control are likely to be an integral part of the cognitive changes in PD, which is often overlooked in routine clinical assessment and not typically considered in patient management. These findings further raise the important question of how underlying alterations in fronto-striatal inhibitory control circuitry may interact with dopaminergic medications or subthalamic nucleus deep brain stimulation, both of which can give rise to ICDs. Understanding this link may help identify patients who are more vulnerable to developing ICDs with these interventions. Implications for bvFTD arising from Publication II are that both frontal and striatal atrophy impact upon inhibitory function. Although previous studies have related the striatum to everyday behavioural inhibitory dysfunction, the findings presented here are the first to relate striatal atrophy to specific cognitive aspects of disinhibition, both verbal and motor. These results suggest that cognitive measures of inhibitory control are a sensitive means of tapping striatal dysfunction in bvFTD, which could potentially be employed as a disease-specific biomarker.

CHAPTER 3 – LEARNING IN PARKINSON'S DISEASE

3.1 Publication III – "Fronto-striatal grey matter contributions to discrimination learning in Parkinson's disease"

frontiers in
COMPUTATIONAL NEUROSCIENCE

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Fronto-striatal gray matter contributions to discrimination learning in Parkinson's disease

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Discrimination learning deficits in Parkinson's disease (PD) have been well-established. Using both behavioral patient studies and computational approaches, these deficits have typically been attributed to dopamine imbalance across the basal ganglia. However, this explanation of impaired learning in PD does not account for the possible contribution of other pathological changes that occur in the disease process, importantly including gray matter loss. To address this gap in the literature, the current study explored the relationship between fronto-striatal gray matter atrophy and learning in PD. We employed a discrimination learning task and computational modeling in order to assess learning rates in non-demented PD patients. Behaviorally, we confirmed that learning rates were reduced in patients relative to controls. Furthermore, voxel-based morphometry imaging analysis demonstrated that this learning impairment was directly related to gray matter loss in discrete fronto-striatal regions (specifically, the ventromedial prefrontal cortex, inferior frontal gyrus and nucleus accumbens). These findings suggest that dopaminergic imbalance may not be the sole determinant of discrimination learning deficits in PD, and highlight the importance of factoring in the broader pathological changes when constructing models of learning in PD.

Keywords: Parkinson's disease, discrimination learning, goal-directed learning, computational modeling, voxel-based morphometry, fronto-striatal

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative condition characterized by hallmark motor disturbances, with its primary neuropathology in the nigrostriatal pathway. This leads to severe dopamine depletion in the dorsal striatum, while the ventral striatum is relatively preserved in the earlier disease stages (Jellinger, 2001). In PD, both the progressive dopamine depletion in the basal ganglia and the concurrent beneficial and deleterious effects of dopamine replacement medications, have been associated with a range of distinct learning impairments (for reviews, see Price et al., 2009; Foerde and Shohamy, 2011b). These dopamine dependent learning deficits in PD have been informative in the development of theoretical accounts of learning function and have provided important advances and testable predictions for computational explanations of learning (Frank, 2005). In particular, PD has been associated with acquisition deficits in feedback-based discrimination learning (Myers et al., 2003; de Wit et al., 2011), which have also been described via computational approaches (Moustafa et al., 2010).

Feedback-based and trial-and-error learning is presumed to be mediated by relative patterns of tonic vs. phasic dopamine activity occurring in response to environmental reinforcers (Schultz, 2002; Bromberg-Martin et al., 2010). Indeed, current accounts of discrimination learning in PD have been derived through ON- vs. OFF-medication patient studies and through computational models, which have established a role for basal ganglia dopamine imbalance as a crucial factor underpinning the feedback-based learning deficits (Frank et al., 2004; Shohamy et al., 2006). Whilst such explanations of learning deficits based on dopaminergic imbalance do accord with the biological characteristics of PD, these theories have not addressed the potential contributions of other prevalent pathological effects in PD. For example, in addition to the characteristic dopamine depletion PD is also associated with gray matter loss and reduced white matter integrity (Duncan et al., 2013). Significantly, regions of gray matter loss in PD involve systems that are implicated in a range of higher level cognitive functions (including learning), and it is only more recently that direct associations between volumetric reductions and specific cognitive deficits have been confirmed in early stage, non-demented PD (Filoteo et al., 2013; O'Callaghan et al., 2013).

Given the known volumetric brain changes in PD and the possibility that they may directly affect learning processes, exploring

this relationship to inform future learning theories and computational approaches that rely on PD as a model is now vital. In the current study, we directly examined this issue by combining voxel-based morphometry analysis with a computational modeling technique in order to determine how fronto-striatal gray matter reductions relate to acquisition efficiency on a discrimination learning task. We hypothesized PD patients would show impaired learning acquisition rates and that these impairments would be associated with volumetric reductions in fronto-striatal regions that are crucial for feedback-based learning and reward processing.

MATERIALS AND METHODS

CASE SELECTION

Seventeen non-demented PD patients were recruited from the Brain and Mind Institute Parkinson's Disease Research Clinic; all satisfied UKPDS Brain Bank criteria for diagnosis of PD (Gibb and Lees, 1988) and were between Hoehn and Yahr stages I and III (Hoehn and Yahr, 1967). Motor score from the Unified Parkinson's Disease Rating Scale (UPDRS-III) (Goetz et al., 2008) is also reported. One patient was untreated; three were on levodopa monotherapy and two were taking levodopa plus an adjuvant; nine patients were on levodopa plus a dopamine agonist, and in this group four were also taking an adjuvant and one was taking a monoamine oxidase inhibitor; one patient was on a dopamine agonist plus a monoamine oxidase inhibitor and one was taking a monoamine oxidase inhibitor only. Treated patients performed behavioral testing in the ON state, having taken their usual medications. L-dopa daily dose equivalents (DDE mg/day) were calculated for treated patients. Patients with overt clinical depression were not included in the study and a measure of affective disturbance was obtained (Beck Depression Inventory-II; BDI-II, Beck et al., 1996). Eleven age- and education-matched healthy controls were selected from a volunteer panel. See **Table 1** for demographic details and clinical characteristics.

The research study was approved by the Human Ethics Committees of the Central and South Eastern Sydney Area Health Services and the Universities of Sydney and New South Wales, and complies with the statement on human experimentation issued by the National Health and Medical Research Council of Australia.

Table 1 | Mean (SD) values for Controls and PD patients on demographics, clinical characteristics and discrimination learning measures.

Demographics, clinical characteristics and executive function	Controls	PD	*F*/χ2-values
N	11	17	–
Sex (M:F)	3:8	13:4	–
Age (years)	66.3 (7.2)	66.4 (8.4)	n.s.
Education (years)[a]	14.9 (2.0)	14.1 (3.6)	n.s.
MMSE (max. 30)[a]	29.6 (0.71)	28.6 (1.6)	n.s.
Disease duration (years since diagnosis)	–	5.6 (5.4)	–
Hoehn and Yahr stage	–	2.1 (0.52)	–
UPDRS III	–	29.2 (12.8)	–
Dopamine dose equivalent (mg/day)	–	616.1 (453.1)	–
BDI-II	–	10.6 (6.9)	–
EXECUTIVE FUNCTION			
Digit span forwards	11.4 (1.8)	10.9 (2.3)	n.s.
Digit span backwards	9.1 (2.1)	7.4 (1.8)	*
Letter fluency	49.0 (15.9)	41.2 (13.5)	n.s.
Trail making test B-A	24.5 (19.4)	41.8 (25.0)	n.s.
DISCRIMINATION LEARNING			
Overall accuracy (%)	82.3 (10.6)	71.9 (19.6)	n.s.
Learning rate	0.217 (0.036)	0.163 (0.041)	**
Exploration[a]	0.70 (0.26)	0.85 (0.30)	n.s.

*n.s., non significant, *$p < 0.05$, **$p < 0.001$; F-values indicate significant differences across groups, otherwise due to unequal variance $\chi 2$ indicates differences across groups[a]. MMSE, Mini-Mental State Examination; UPDRS III, Motor score from the Unified Parkinson's Disease Rating Scale; BDI-II, Beck Depression Inventory II.*

NEUROPSYCHOLOGICAL ASSESSMENT

All patients and controls were administered the Mini Mental State Examination (MMSE; Folstein et al., 1975) to determine their overall cognitive functioning. For detailed measurement of executive function, patients and controls underwent a battery of tests including Verbal Fluency [measured by the number of words produced in 60 s, beginning with F, A, and S (Benton et al., 1994)]; the Trail-Making test (time B-A) to assess speeded set-shifting (Reitan and Wolfson, 1985); and a Digit Span task, with digits repeated in their original order (forwards) and in reverse order (backwards) (Wechsler, 1997) to assess attention span and working memory.

DISCRIMINATION LEARNING TASK

We administered a discrimination learning task developed by de Wit and colleagues, which was an abbreviated version of a more extensive instrumental learning measure described by de Wit et al. (2007). The task was computer based and programmed using Visual Basic 6.0, with keyboard response keys *z* and *m* programmed to register a *left* or *right* response.

Discrimination learning tasks involve a discriminative stimulus that signals whether or not a certain response will lead to a particular outcome; stimuli are presumed to have acquired discriminative control over instrumental performance when correct responding occurs in the presence of a given stimulus (i.e., when the stimulus: response-outcome contingency is acquired) (Bouton, 2007). In the current discrimination learning task, for each trial the discriminative stimulus consisted of a colored icon depicting a piece of a fruit on the front of a box. There were six possible fruits that could be pictured on the outside of the box (i.e., strawberry, lemon, grape, kiwi, melon, and orange). Subjects were required to make either a *left* or *right* response in order to "open" the box and obtain the outcome/reward inside (the outcome being a different fruit, i.e., coconut, pear, pineapple, cherry, banana, and apple). Each of the six stimulus fruits were associated with a particular correct response (i.e., *left* or *right*) that would result in obtaining the reward/outcome. These contingencies were kept constant, for example a *left* response to

the strawberry stimulus would always result in the box opening to reveal an outcome/reward, whereas if a *right* response was made to the strawberry stimulus, the box would open to reveal nothing inside. Additional feedback was provided as the opened box revealing the reward was paired with a positive sound and points displayed on the screen, whereas the opened box with nothing inside was paired with a negative sound effect. The initial fruit stimulus remained on the screen until subjects made a response and faster correct responses earned more points (in the range from 1 to 5). The outcome fruit was presented for 1 s, and inter-trial intervals were fixed at 1.5 s.

Subjects were instructed at the outset of the task that they would need to determine the correct response for each stimulus fruit via a trial and error process. It was emphasized that these contingencies would not change throughout the trials, so that it would be possible for them to learn these stimulus-response associations. They were also encouraged to memorise the stimulus: response-outcome associations, as they would be questioned on them at the end.

Each subject completed 96 trials, comprising of eight 12-trial blocks during which each of the six possible stimulus-response pairs was presented twice in a randomized order; three of the stimulus fruits were associated with a correct *left* response and the other three were associated with a correct *right* response. Across subjects, the particular fruits that served as the stimulus and those that served as the outcome were counterbalanced. From the discrimination learning task, we derived a binary outcome measure of either 1 or 0 for each trial (1 indicating a correct response for that trial, 0 an incorrect response). Finally, after completing the trials, patients were asked to fill in pencil and paper questionnaires that probed explicit knowledge of the stimulus: response-outcome contingencies. These questionnaires were divided into three parts (each with six items), assessing knowledge of: (1) stimulus-response knowledge; (2) response-outcome; and (3) stimulus-outcome. In part (1), subjects were shown pictures of each stimulus fruit one at a time and they were asked to verbally indicate whether a *left* or *right* response was associated with obtaining a reward for each stimulus. A similar procedure was followed in part (2), as subjects were shown each reward/outcome and asked to indicate whether a *left* or *right* response had been necessary to successfully achieve that reward. In part (3), subjects were shown each stimulus fruit alongside an array of all possible reward fruits and they selected the reward that had been paired with each particular stimulus.

COMPUTATIONAL MODEL

Given the insufficiency of classical statistical methods in extracting learning rates and trial-by-trial responses, we applied the reinforcement Q-learning model to the outcome measures generated from the discrimination learning task, for each subject's pattern of correct and incorrect responses across the 96 trials (Sutton and Barto, 1998). The input of this model is a trial-by-trial sequence of responses for each subject, while the output is the learning rate and exploration parameter values, which cannot be obtained from regular statistical analysis of behavioral data. Previous research has used similar computational models to fit model parameter values for each subject in genetic (Frank et al., 2007) and patient studies (Gold et al., 2012). The rationale for applying the Q-learning model to the behavioral data is to disentangle each subject's performance to different components, and also to determine which model parameters can better account for variations in behavioral performance across different groups. Here, we attempt to understand the observed behavioral results using the computational reinforcement Q-learning model (Watkins and Dayan, 1992; Sutton and Barto, 1998; Frank et al., 2007) and specifically, we have fitted our behavioral data using a Q-learning model (Frank et al., 2007).

By using the reinforcement Q-learning model, we fit individual subject's trial-by-trial data, which culminates in two parameter values that correspond to the subject's learning rate and exploration/exploitation bias. The learning rate parameter modulates the degree to which feedback on the current trial is used to adjust expectations for future trials. The exploration parameter indicates whether the subject is more likely to choose the same or a different response as on previous trials with the same stimulus. A small exploration/exploitation parameter indicates exploitation (i.e., increased likelihood that subjects will choose the same response as previously made, when presented with the same stimulus), and a large value indicates exploration (i.e., increased likelihood they will choose a different response when presented with the same stimulus). In principle, impaired feedback learning can occur because of small learning rate or decreased likelihood to explore alternative responses at the expense of exploiting previously erroneous response strategies.

Specifically, we compute a weight (*W*) value for selecting each stimulus *i* during trial *t*, such that the value of the chosen stimulus is modified by reinforcement feedback:

$$PE(t) = US(t) - W(t)$$

where $PE(t)$ is the prediction error at time t; $US(t)$ is feedback presented at time t, and is equal to 1 for positive and 0 for negative feedback. W-values are computed using the following equation.

$$W_i(t+1) = W_i(t) + \alpha PE(t)$$

where α is learning rate (for more details, see Frank et al., 2007).

We have modeled choice by using a softmax logistic function, with inverse gain (exploration) parameter β, such that the probability of choosing A over B was computed as:

$$P_A(t) = \frac{e^{W_A(t)/\beta}}{e^{W_A(t)/\beta} + e^{W_B(t)/\beta}}$$

Each participant's trial-by-trial choices were fitted with two free parameters, α and β, which were selected to maximize fit to participant's sequence of choices in the task. β is an inverse gain parameter and reflects the participant's tendency to either exploit (i.e., to choose the response with the currently highest W-value) or explore (i.e., to randomly choose a category).

We then fitted the model to each participant's data, by searching through the space of each of these two parameters from 0 to

1 with a step size of 0.01. We then optimized the log likelihood estimate (LLE) at trial t:

$$\text{LLE} = \text{Log}\,(\Pi_t P(t))$$

where t is trial number (for a total of 96 trials). For each participant, the best fitting parameter values are those associated with maximum LLE. Equivalently, maximum LLE is the most predictive of the participant's responses in the task. In this model, the best fitting parameter values to each participant's behavioral data accommodate trial-by-trial adaptations in response to feedback given based on participants' choices. In addition, we predict that these values will explain differences in learning efficiency between patients and controls.

Finally, to validate our model we compared our results with a random responder model. Specifically, we calculated the pseudo-R^2 measure, which is (LLE-r)/r, where r is the log likelihood of the data under a model of purely random choices, in which $p = 0.5$ for all trials (Camerer and Ho, 1999; Daw et al., 2006). The resulting pseudo-R^2 statistic reveals how well the model fits the data compared to a model predicting chance performance and is independent of the number of trials to be fit in each set (see Frank et al., 2007, for discussion).

BEHAVIORAL ANALYSES

Data were analyzed using SPSS19.0 (SPSS Inc., Chicago, Ill., USA). Parametric demographic and neuropsychological data were compared across the groups via One-Way ANOVAs followed by Tukey *post-hoc* tests. A priori, demographic and learning variables were plotted and checked for normality of distribution by Kolmogorov-Smirnov tests. Variables showing non-parametric distribution were analyzed via Chi-square, Kruskal-Wallis and Mann-Whitney *U*-tests. A repeated measures ANOVA with Bonferroni *post hoc* tests was used to explore group differences in learning accuracy across the eight blocks, with group (control vs. patient) as the between-subjects variable and block (blocks 1–8) as the within-subjects variable.

IMAGING ACQUISITION

All patients and controls underwent the same imaging protocol with whole-brain T1 images acquired using 3T Philips MRI scanners with standard quadrature head coil (8 channels). The 3D T1-weighted sequences were acquired as follows: coronal orientation, matrix 256 × 256, 200 slices, 1 × 1 mm^2 in-plane resolution, slice thickness 1 mm, TE/TR = 2.6/5.8 ms.

VOXEL-BASED MORPHOMETRY (VBM) ANALYSIS

3D T1-weighted sequences were analyzed with FSL-VBM, a voxel-based morphometry analysis (Ashburner and Friston, 2000; Good et al., 2001) which is part of the FSL software package http://www.fmrib.ox.ac.uk/fsl/fslvbm/index.html (Smith et al., 2004). First, tissue segmentation was carried out using FMRIB's Automatic Segmentation Tool (FAST) (Zhang et al., 2001) from brain extracted images. The resulting gray matter partial volume maps were then aligned to the Montreal Neurological Institute standard space (MNI152) using the non-linear registration approach using FNIRT (Andersson et al., 2007a,b), which uses a b-spline representation of the registration warp field (Rueckert et al., 1999). The registered partial volume maps were then modulated (to correct for local expansion or contraction) by dividing them by the Jacobian of the warp field. The modulated images were then smoothed with an isotropic Gaussian kernel with a standard deviation of 3 mm (FWHM: 8 mm). A region-of-interest (ROI) mask for prefrontal and striatal brain regions was created by using the Harvard-Oxford cortical and subcortical structural atlas. The atlas regions that comprise the entire prefrontal cortex and striatum were included in the mask, these included frontal pole, superior frontal gyrus, middle frontal gyrus, inferior frontal gyrus, frontal medial cortex, subcallosal cortex, paracingulate gyrus, cingulate gyrus (anterior division), frontal orbital cortex, caudate, putamen, and nucleus accumbens. Finally, a voxelwise general linear model (GLM) was applied and permutation-based non-parametric testing was used to form clusters with the Threshold-Free Cluster Enhancement (TFCE) method (Smith and Nichols, 2009), tested for significance at $p < 0.05$, corrected for multiple comparisons via Family-wise Error (FWE) correction across space, unless otherwise stated.

RESULTS

DEMOGRAPHICS, CLINICAL CHARACTERISTICS AND NEUROPSYCHOLOGICAL ASSESSMENT

Demographics and general cognitive scores can be seen in **Table 1**. Participant groups did not differ in terms of age, education or MMSE score (p's > 0.1). Patients and controls did not differ in their Digit Span forwards score ($p > 0.6$), but patients were impaired relative to Controls for Digit Span backwards ($p < 0.05$). Groups were equivalent for Letter Fluency scores ($p > 0.2$) and although groups did not differ significantly on Trail Making B-A scores, there was a strong trend toward worse performance in the patients ($p = 0.06$). See **Table 1**.

LEARNING MEASURES

Overall accuracy scores on the discrimination learning task are shown in **Table 1** and learning accuracy across the eight blocks is shown in **Figure 1**. Overall accuracy across the 96 trials was not significantly different between the groups ($p > 0.1$). Results of the repeated measures ANOVA showed that there was no significant main effect of group [$F_{(1,\ 26)} = 2.6$, $p > 0.1$]. Mauchly's test indicated that the assumption of sphericity had been violated [$\chi^2_{(27)} = 71.0$, $p < 0.001$] therefore degrees of freedom were corrected using Huynh-Feldt estimates of sphericity ($\varepsilon = 0.550$). The results show a significant main effect for block [$F_{(4.8,\ 124.2)} = 20.3$, $p < 0.001$], which reflected that, irrespective of group, accuracy in blocks 6, 7, and 8 was significantly higher than in blocks 1, 2, and 3 (p-values < 0.05), accuracy in block 5 was significantly higher than in blocks 1 and 2 ($p < 0.05$), and accuracy in block 4 was higher than accuracy in block 1 ($p < 0.002$). There was no significant group by block interaction [$F_{(4.8,\ 124.2)} = 1.6$, $p > 0.1$]. *Post-hoc* between-group comparisons revealed that controls and PD patients only differed significantly on their accuracy in block 7 with controls having a higher accuracy score ($p < 0.05$), no significant difference were observed in other blocks ($p > 0.05$). Within-group *post-hoc* analysis showed that controls had consistent significant differences in accuracy between early

and late blocks, with blocks 4, 5, 6, 7, and 8 all having higher accuracy than both blocks 1 and 2 (p-values < 0.05). PD patients showed a slightly less consistent pattern, with accuracy in blocks 5, 6, 7, and 8 higher than in block 1 (but not block 2) (p-values < 0.05); with all other block accuracies were equivalent, expect for blocks 7 and 8 being significantly higher than block 3 (p-values < 0.05).

Results of the learning rate and exploration parameters for the discrimination learning task, as derived from the computational model, are also shown in **Table 1**. Exploration parameters did not differ significantly between the groups ($p > 0.3$) and the small value of the parameter in both patients and controls suggested minimal exploration, which would be predicted based on the nature of the task. Learning Rate for the PD patients was significantly reduced relative to controls ($p = 0.001$) and these Learning Rate values were further analyzed in the VBM analysis. Results from the random responder model revealed the mean and standard deviation of pseudo-R^2 were 0.2901 and 0.173, respectively. This was significantly larger than zero, indicating our model performs better than chance at fitting individuals' data.

Participant groups did not differ in terms of explicit knowledge of Stimulus-Response-Outcome contingencies. The following mean (standard deviation) results on the three questionnaire sections were achieved, each section with a possible maximum score of 6 (i.e., 1 point per item). Stimulus-Response accuracy for controls was 5.6 (0.05) and for PD patients 5.3 (1.6); Response-Outcome accuracy for controls was 5.0 (1.2) and PD patients 4.6 (1.7); Stimulus-Outcome for controls was 3.5 (1.7) and PD patients 3.0 (2.2), with all p-values > 0.5. In a correlation analysis, none of the PD clinical variables (i.e., disease duration, Hoehn and Yahr stage, UPDRS III, DDE mg/day, BDI score) or the digits backward score, showed a significant relationship with the Learning Rate measure (p's > 0.1).

VBM ANALYSIS

The PD group was initially contrasted with controls to reveal overall patterns of brain atrophy in the fronto-striatal mask. PD patients showed gray matter atrophy bilaterally in the frontal orbital cortex and subcallosal cortex, extending back to the left ventral striatal (nucleus accumbens) territory; as well as in the inferior frontal gyri bilaterally (see Supplementary Table 1).

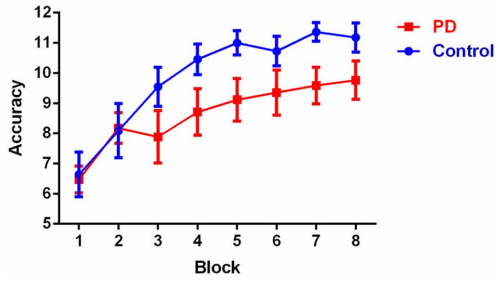

FIGURE 1 | Mean accuracy scores (with standard error bars) across the eight 12-trial blocks.

Learning rate was then entered as a covariate in the design matrix of the VBM analysis. For PD patients, Learning Rate score covaried with gray matter atrophy in the frontal medial cortex/frontal pole, the right inferior frontal gyrus and the left subcallosal cortex/left nucleus accumbens (see **Table 2** and **Figure 2**).

Finally, a partial correlation analysis was used to explore whether common damage to the ventromedial prefrontal cortex, right inferior frontal gyrus and left subcallosal cortex/nucleus

Table 2 | Region of interest Voxel-based morphometry (VBM) results showing areas of significant gray matter intensity decrease that covary with learning measures.

Regions	Hemisphere (L/R/B)	MNI coordinates			Number of voxels	*T*-score
		X	*Y*	*Z*		
LEARNING RATE						
Frontal medial cortex; Frontal pole	B	−6	46	−26	422	2.70
Inferior frontal gyrus	R	54	26	8	54	
Subcallosal/ extending back to L NAcc	L	−4	12	−14	46	

All results uncorrected at $p < 0.01$; only clusters with at least 40 contiguous voxels included.

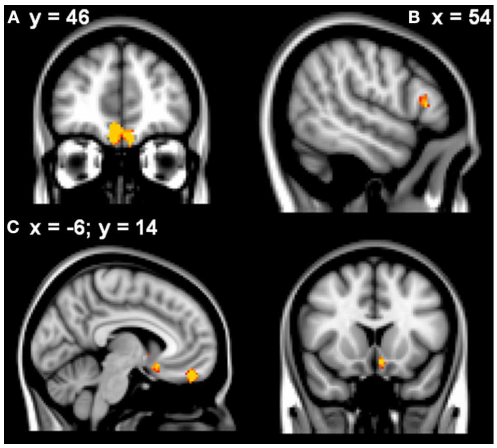

FIGURE 2 | VBM analysis showing the frontal and striatal regions that correlated with elevated learning rates in the patients in (A) frontal medial cortex (B) right inferior frontal gyrus (C) subcallosal/left nucleus accumbens. Clusters are overlaid on the MNI standard brain ($t > 2.50$). Cultured voxels show regions which were significant in the analyses for $p < 0.01$ uncorrected and a cluster threshold of 40 contiguous voxels.

accumbens explained the significant correlations with Learning Rate. The ventromedial prefrontal region still correlated significantly with Learning Rate ($p < 0.05$) when right inferior frontal gyrus and left subcallosal cortex/nucleus accumbens were taken into account. In contrast, neither right inferior frontal gyrus nor left subcallosal cortex/nucleus accumbens regions correlated significantly with Learning Rate when atrophy in the other regions was partialled out (p-values ≥ 0.2).

DISCUSSION

By employing a combined approach of computational modeling and VBM analysis, we show that PD patients have a learning acquisition deficit that is associated with volumetric reductions in discrete fronto-striatal regions. This is the first time that such learning deficits in PD have been probed via structural imaging techniques and our findings fit well with the broader learning literature, whilst highlighting a novel approach in order to further characterize discrimination learning in PD.

The nature of learning assessed in the current study reflects the formation of stimulus-response associations, which are learnt through incorporating feedback via a trial-and-error approach. Impaired learning acquisition rates on discrimination tasks have been demonstrated behaviorally in PD patients (Czernecki et al., 2002; Myers et al., 2003; de Wit et al., 2011; Shiner et al., 2012) and also in neurocomputational models of PD (Moustafa et al., 2010). Furthermore, Shohamy and colleagues (2004, 2006) have shown that in PD the feedback learning deficit is relatively specific, as patients are impaired when required to learn associations on the basis of feedback, but equivalent to controls when observational learning of the same associations was required.

Our results further confirm a feedback-based learning acquisition deficit in mild, non-demented PD. Patients and controls were equivalent in their exploration parameters, with both showing a minimal amount of exploration. This would be expected given the nature of the task wherein subjects are not encouraged to modify their responses as the stimulus-response-outcome contingencies do not change. Nevertheless, it further validates the utility of our model that it was able to identify this effect. Results from the analysis of learning accuracy across blocks indicated that deficient learning in the PD patients was mostly driven by poorer performance later in the task. We did not find a difference in explicit knowledge of stimulus: response-outcome contingencies, suggesting that despite a deficient learning rate the PD patients were ultimately able to attain a good level of knowledge of these contingencies (see also de Wit et al., 2011). The acquisition impairment did not correlate with any clinical disease variables; nor was a correlational relationship evident between learning rate and working memory (as assessed via the digit span backwards task), which was found to be mildly impaired. Importantly, on other executive domains assessed in the current study, the PD patients' performance was equivalent to controls, which supports the notion of a discrete discrimination learning deficit in this patient group.

The previous findings relating deficient feedback-based learning in PD to dopamine dysfunction have been somewhat equivocal, as comparisons between patients ON vs. OFF medication have found that performance on a variety of learning tasks is impaired in both scenarios (Czernecki et al., 2002; Ell et al., 2010; Moustafa and Gluck, 2011), or that performance differs based on task demands (Shohamy et al., 2006) or valence of feedback signals (Frank et al., 2004). A number of studies using feedback-based category learning in PD have suggested that respective demands on selective attention vs. working memory, which are differentially affected by dopamine therapy, may determine learning performance (Filoteo et al., 2005, 2007). Given that in the OFF state patients suffer severe depletion in dorsal striatum and its projection targets, whilst the ON state is associated with restoration of those levels and the possibility of dopaminergic "overdose" in ventral striatum and limbic regions (Cools et al., 2001), differential effects on discrimination learning would be expected. Nonetheless, the finding of similar effects arising from two ostensibly disparate conditions has been explained with respect to the "relative" rather than "absolute" levels of dopamine, as a reduced dynamic range of phasic dopamine activity can result from both the ON and OFF states (Frank, 2005).

In contrast to previous studies that have characterized discrimination learning deficits in PD with respect to dopaminergic dysfunction, our current results define these deficits with respect to the possible structural abnormalities that may be contributory. In addition to dopamine depletion, PD is also associated with gray matter loss and synaptic denervation in fronto-striatal regions essential to broad aspects of learning and feedback processing, including the striatum (Rosenberg-Katz et al., 2013), medial temporal regions (Filoteo et al., 2013) and ventromedial prefrontal cortex (O'Callaghan et al., 2013). More specifically, prefrontal volume loss has been identified in non-demented PD, in comparison to healthy controls (Song et al., 2011; Melzer et al., 2012). Our findings reveal that discrete fronto-striatal regions, namely ventromedial prefrontal cortex, right inferior frontal gyrus and nucleus accumbens, are directly associated with acquisition deficits during feedback-based discrimination learning. The presence of underlying gray matter loss contributing to learning deficits may to some degree explain why discrimination learning can be affected both ON and OFF medication, and thus indicate that dopamine imbalance may not be the sole explanation for learning deficits in PD.

Our findings potentially shed light on previous reports that disease severity in PD is associated with specific learning impairments (Owen et al., 1993; Swainson et al., 2006). In particular, Swainson et al. (2006) found that early-stage, unmedicated patients were not impaired on a complex discrimination learning task; whilst early-stage, medicated patients *were* impaired on the task, their performance was mediated by deficient perceptual categorization of the complex stimuli, rather than a learning deficit *per se*. In contrast, only patients with severe, medicated PD showed impaired learning in the absence of perceptual categorization deficits. This raises the possibility that some factor other than inappropriate dopamine levels may intervene in later-stage PD to produce learning impairments on the task. Interestingly, the comparison groups of Huntington's disease and frontal lobe lesion patients included in the study showed the same pattern of intact perceptual categorization, but impaired

learning, suggesting that more extensive fronto-striatal dysfunction may underpin the learning impairments. Taken together with our findings, it may be that fronto-striatal atrophy is a contributing factor to those learning impairments seen in PD with disease progression.

The possibility that fronto-striatal atrophy can mediate learning performance is also relevant to previous studies that have identified considerable variation within their PD cohorts. For example, using a rule-based category learning task, Ashby et al. (2003) found that PD patients were impaired at the group level, however, this effect was driven by impaired performance in only half of the patients, with the remainder performing equivalent to controls. The authors interpreted this as evidence of distinctive PD sub-groups. Indeed, differences in the clinical phenotypes of PD are well recognized (Lewis et al., 2005) and evidence is accumulating that the presence of more widespread fronto-subcortical atrophy may be characteristic of certain sub-groups (Feldmann et al., 2008; Melzer et al., 2012; Rosenberg-Katz et al., 2013). An admixture of PD patients with and without prefrontal volume loss may contribute to within-group variation in learning performance.

Results from our partial correlation analysis suggest that atrophy in the ventromedial prefrontal region may be driving the association with acquisition deficits. Although previous research using functional MRI in healthy controls has identified striatal activity as crucial during the acquisition phase of learning tasks (Pessiglione et al., 2006; Foerde and Shohamy, 2011a), others have shown ventromedial prefrontal cortex activity during learning acquisition (de Wit et al., 2009). Whereas the gradual learning of stimulus-response associations is presumed to reflect "habit" learning that is mediated by basal ganglia dopamine signals (Shohamy et al., 2008), "goal-directed" learning, which involves a focus on stimulus-response-outcome associations, has been linked to medial prefrontal regions (Balleine and O'Doherty, 2009). The interplay between the habitual and goal-directed modes can be explained by the "dual-systems" account, whereby instrumental learning can be supported by either modality (Dickinson and Balleine, 1994; de Wit and Dickinson, 2009). In line with the possibility that acquisition of instrumental discriminations is partly supported by goal-directed learning, de Wit et al. (2009) showed that engagement of the ventromedial prefrontal cortex during discrimination learning was predictive of goal-directed performance during a subsequent test phase. During that "instructed outcome-devaluation" test phase, participants were told that some of the fruit outcomes were no longer worth points. Participants with relatively strong engagement of the ventromedial prefrontal cortex during learning were better able to direct their responses toward the still-valuable outcomes and away from the devalued ones. More recently, individual differences in the strength of the white-matter pathway between the ventromedial prefrontal cortex and caudate have also been implicated in goal-directed control, whilst connectivity between the posterior putamen and premotor cortex has been related to habit learning (de Wit et al., 2012). Given these previous investigations of the role of the ventromedial prefrontal cortex in action control, our results are in keeping with a deficit in goal-directed learning.

In the category learning literature, the Competition between Verbal and Implicit Systems model (COVIS; Ashby et al., 1998) has been proposed to explain the neural systems that mediate rule-based learning vs. procedural (information-integration) learning. Whilst both are inherently feedback-based, these learning mechanisms necessitate different strategies and depend on divergent systems. The former comprising of an explicit hypothesis-testing system underpinned by a broad network including prefrontal cortex, anterior cingulate, hippocampus and caudate head; and the latter, requiring perceptual information to be integrated at a pre-decisional level, is mediated by cortical-striatal synapses within the putamen and premotor cortex circuitry (Ashby and Maddox, 2011). However, there is growing consensus that prefrontal regions, in particular ventromedial prefrontal cortex, may play a role in both types of learning (Seger, 2008). Schnyer et al. (2009) explored this directly by contrasting ventromedial prefrontal cortex lesion patients on rule-based vs. information-integration learning and found that patients were impaired in both types of learning. Work by Seger and colleagues (Seger and Cincotta, 2005; Seger et al., 2010) has also highlighted the role of the ventral striatum in encoding feedback during unstructured category learning tasks. These findings suggest that the ventromedial prefrontal cortex and ventral striatum—important hubs in the cortico-striatal motivational loop—are critical for monitoring and integrating feedback, regardless of the learning strategy.

Ventromedial prefrontal regions and ventral striatum (particularly nucleus accumbens) are also more generally associated with reward processing (Kringelbach, 2005), which may further explain why these regions were implicated in acquisition learning deficits in our patients, as the feedback involved in the task was reward-oriented. Specific reward-learning deficits have previously been demonstrated in PD (Swainson et al., 2000; Housden et al., 2010), and based on the volumetric reductions we found in regions crucial to reward processing in our patient cohort, it is likely that deficient reward processing may have contributed to the acquisition deficits. Our finding that the right inferior frontal gyrus was also associated with the acquisition deficit may reflect the demands of more general cognitive control that is required in such a learning task. The right inferior frontal gyrus is well known to be implicated in inhibitory control of behavior (Aron et al., 2004), however, a broader interpretation of its action is that it is involved in the detection/monitoring of task-relevant cues (Hampshire et al., 2010) and in terms of learning processes, the region is recruited during reversal learning (Cools et al., 2002).

From a mechanistic account, the involvement of prefrontal regions in learning from trial-by-trial feedback is also emphasized in computational models that seek to integrate basal ganglia and prefrontal function with respect to higher level executive processes. In the computational accounts proposed by O'Reilly and Frank (2006), the prefrontal cortex is active in maintaining information, whereby task-relevant information is determined via basal ganglia-prefrontal interactions that serve as a gating mechanism (see also Hazy et al., 2007). In these models, basal ganglia dopamine-dependant learning systems are presumed to trigger updates of working memory representations in the prefrontal cortex, whilst simultaneously inhibiting task-irrelevant

information—thus allowing intrinsic prefrontal cortical mechanisms to actively maintain the contents of working memory. Our results suggest that direct atrophy in prefrontal regions may interfere with the updating and maintenance of task-relevant information in these models, which may therefore contribute to deficient acquisition on learning tasks.

The VBM technique utilized in this study is not without limitations, including registration and normalization issues and imperfect gray-white matter segmentation, particularly in relation to already atypical brains (Mechelli et al., 2005). In addition, the analysis we conducted does not measure the particular morphological changes brain structures undergo in PD and in interpreting findings of reduced gray matter density, it must be borne in mind that the precise mechanisms of cell degeneration in PD are still a matter of debate (Obeso et al., 2010). Nevertheless, VBM provides an important tool to further characterize learning systems in PD.

Together, our findings suggest that discrete fronto-striatal regions contribute to the feedback-based learning deficits in PD. It is likely that gray matter loss in these regions interacts with dopaminergic dysfunction to produce these deficits, and that the ultimate behavioral manifestation reflects an interplay between neurotransmitter imbalance and underlying structural changes. Our findings have important implications for the development of learning theories based on PD as a model of dopaminergic dysfunction. Whereby current theories and computational approaches have tended to focus on dopamine imbalance in intra-basal ganglia circuitry, a broader appreciation of the more distributed brain changes, such as gray matter loss, and how these may also affect learning processes is crucial in order to continue to refine these theoretical models. These results highlight that dysfunction in dopaminergic systems may not be the sole explanation for feedback-based learning deficits in PD, but that gray matter loss may also contribute to these deficits.

AUTHOR CONTRIBUTIONS

Claire O'Callaghan contributed to the design and conceptualization of the study, data collection, analysis and interpretation of data, drafting and revision of the manuscript. Ahmed A. Moustafa carried out the computational modeling and contributed to interpretation of the data and revision of the manuscript. Sanne de Wit contributed to study conceptualization and manuscript revision. James M. Shine contributed to data collection and manuscript revision. Trevor W. Robbins was involved in revision of the manuscript. Simon J. G. Lewis contributed to interpretation of the data and revision of the manuscript. Michael Hornberger contributed to design and conceptualization of the study, analysis and interpretation of data, and revision of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: http://www.frontiersin.org/journal/10.3389/fncom.2013.00180/abstract

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3.2 Summary and future directions

The findings reported here provide strong argument for advancing our conceptualisation of learning impairments in PD beyond that of dopamine dysregulation in the fronto-striatal circuitry. These results dovetail with studies that have reported equivalent learning deficits in the "on" and "off" medication states (e.g., Czernecki *et al.*, 2002, Moustafa and Gluck, 2011), together providing additional evidence that factors other than dopamine levels intervene to cause learning impairments in PD. So whilst the effects of dopamine are doubtless an important contributor to learning deficits, they are unlikely to account for the range of learning deficiencies that are observed with reasonable consistency in PD. As highlighted in a recent review, the current state of evidence surrounding learning in PD gives cause to look for other possible factors at play (Robbins and Cools, 2014). As outlined in the thesis introduction, a host of non-dopaminergic and extra-striatal pathologic changes occur in PD. Still very little is understood regarding the impact of non-dopaminergic neurotransmitter systems on learning in PD, or cognition more broadly. The study reported here indicates that fronto-striatal atrophy is an important candidate mechanism driving learning impairment in PD. The course for future studies is clear – identify the relative contributions to learning impairment across all levels of dopaminergic and non-dopaminergic neurotransmitter systems, and brain atrophy. From a theoretical standpoint, these results highlight that perhaps PD has been held up somewhat uncritically as an ideal model for understanding how learning is mediated by fronto-striatal dopamine activity. Whilst studying PD in this context has provided important insights into learning processes, it seems critical in the future to factor in other PD disease-related changes when constructing models of learning derived from patient studies.

CHAPTER 4 – SOCIAL NORM COMPLIANCE IN BEHAVIOURAL VARIANT FRONTOTEMPORAL DEMENTIA

4.1 Publication IV – "Fair play – Social norm compliance failures in behavioural variant frontotemporal dementia"

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Abstract

Background: Adherence to social norms is compromised in a variety of neuropsychiatric conditions. We developed a novel neuroeconomic task to investigate social norm compliance in a neurodegenerative lesion model: behavioural variant frontotemporal dementia (bvFTD), a condition characterised by gross social dysfunction.

Methods: We administered a novel version of the Ultimatum Game in 16 bvFTD patients and 16 controls, to assess how decision-making behaviour was modulated in response to 1) fairness of monetary offers, and 2) social context of monetary offers (positive versus negative conditions). Voxel-based morphometry was used to characterise patterns of grey matter atrophy associated with task performance.

Results: Acceptance rates between patients and controls were equivalent when only fairness was manipulated. However, bvFTD patients were impaired in modulating their decisions in response to social contextual information. Greater impairment was associated with reduced capacity for empathy. Performance in the positive condition was mediated by atrophy in a distinct fronto-subcortical network (including striatum, anterior cingulate, dorsolateral and medial prefrontal cortices), whereas the negative condition was associated with right-lateralised ventrolateral prefrontal cortex atrophy. Further, we contrasted the conditions to reveal a positive "social norm compliance" network, which overlapped with fronto-subcortical regions previously implicated in healthy individuals.

Conclusions: We demonstrate that atrophy in key fronto-subcortical regions underscores a selective deficit for utilising social information to guide norm-based decisions, in the context of preserved fairness judgments. This study provides the first evidence for a dissociation between fairness perception and social norm compliance in a neurodegenerative lesion model, and confirms the presence of a "social norm compliance" network.

Introduction

Decisions in social contexts are complex and often require compromise between self-interest and consideration of others. Ever implicit in such decision-making is a regard for social norms – that collective sentiment of what constitutes appropriate behaviour, which is so fundamental to adaptive human interaction (1). Despite recent advances (2-4), very little is known regarding the neurobiology of social norm compliance. Even more pressing is the need for a framework to account for dysfunctional social norm compliance, which underscores symptoms across a range of neuropsychiatric conditions.

Social norm compliance is unlikely to be a unitary phenomenon, as it relies upon numerous feats of social cognition, including empathy, theory of mind, emotional intelligence, and sensitivity to reward and punishment evaluation (5). Nevertheless, insights from the field of neuroeconomics implicate a distinct network of fronto-striatal-insular regions that underpin this complex ability (2-4). In turn, it becomes increasingly apparent that a neuroeconomic approach is valuable for unravelling the neurocognitive endophenotypes that underlie neuropsychiatric symptoms (6,7).

The behavioural variant of frontotemporal dementia (bvFTD), a neurodegenerative condition with insidious, progressive change in personality and social interactions, represents the prototypical example of disordered social norm compliance. Patients commonly exhibit behavioural changes considered under this rubric, including loss of empathy and insight, disinhibited remarks or behaviour, egocentricity, impulsive spending or gambling, and gullibility (8). Intriguingly, the earliest sites of pathology overlap with those regions implicated in social norm compliance, most notably in the

ventromedial prefrontal cortex, anterior cingulate, insula, amygdalae and striatum (9-11). Pure decision making paradigms are found to have limited utility in bvFTD (12-14). Convergent approaches incorporating measures of social processing and decision-making represent a promising avenue to better detect the complex social-contextual deficits that typify bvFTD (15).

The Ultimatum Game, a paradigm drawn from the neuroeconomics literature, offers a means of gauging normative decision-making behaviours in a social context. The task requires participants to either accept or reject monetary offers, varying in their degree of 'fairness'. A consistent observation is that healthy participants frequently reject unfair offers, in order to punish their opponent, even though this decision incurs a personal cost (16,17). Such unfair offers are considered a violation of 'fairness norms' and therefore deserve sanctioning (18). Functional imaging in healthy subjects has implicated a network of brain regions in processing unfair offers, which coincides with those regions involved in social norm compliance, including dorsolateral prefrontal cortex, anterior cingulate and insula (19).

Here, we sought to explicitly measure social norm compliance in bvFTD by introducing social contextual factors in the Ultimatum Game. In this novel manipulation, we included reappraisal conditions intended to either induce participants to accept more offers, or to incite the desire to punish via rejecting more offers. We predicted that bvFTD patients would i) perform similarly to healthy controls in the classic Ultimatum Game; ii) have difficulty adapting their behaviours to conform with the expected social norms in the reappraisal conditions, and iii) that their pattern of behaviour would

correlate with grey matter loss in specific fronto-insula-striatal regions previously implicated in both social norm compliance and social-contextual decision-making.

Methods and Materials

Case selection

Sixteen bvFTD patients were recruited from the FRONTIER dementia clinic, at Neuroscience Research Australia. All patients met current consensus criteria for bvFTD (20,21). Sixteen age- and education-matched healthy controls were selected from a volunteer panel. The study was approved by the local Ethics Committees and all participants provided informed consent in accordance with the Declaration of Helsinki. See Table 1 (below) for demographic details and clinical characteristics.

Table 1 – Mean (standard deviation) of bvFTD patient and control scores on demographics, emotion processing and empathy.

Demographics, clinical characteristics & empathy		**Control**	**bvFTD**	***p* values**
N		16	16	-
Sex (M:F)		5:11	13:3	-
Age		63.3 (12.2)	66.1 (10.2)	n.s.
Education		13.21 (1.8)	11.9 (1.6)	n.s.
MMSE (max. 30)		29.2 (1.2)	26.3 (1.7)	***
Duration (yrs diagnosed)		-	2.6 (2.2)	-
CBI-R	Total score (max. 180)	-	68.7 (22.8)	-
	Empathy item (max. 4)	-	2.8 (1.7)	-

n.s. = non significant; *** = p < .001. MMSE = Mini-Mental State Examination; CBI-R = Cambridge Behavioural Inventory-Revised

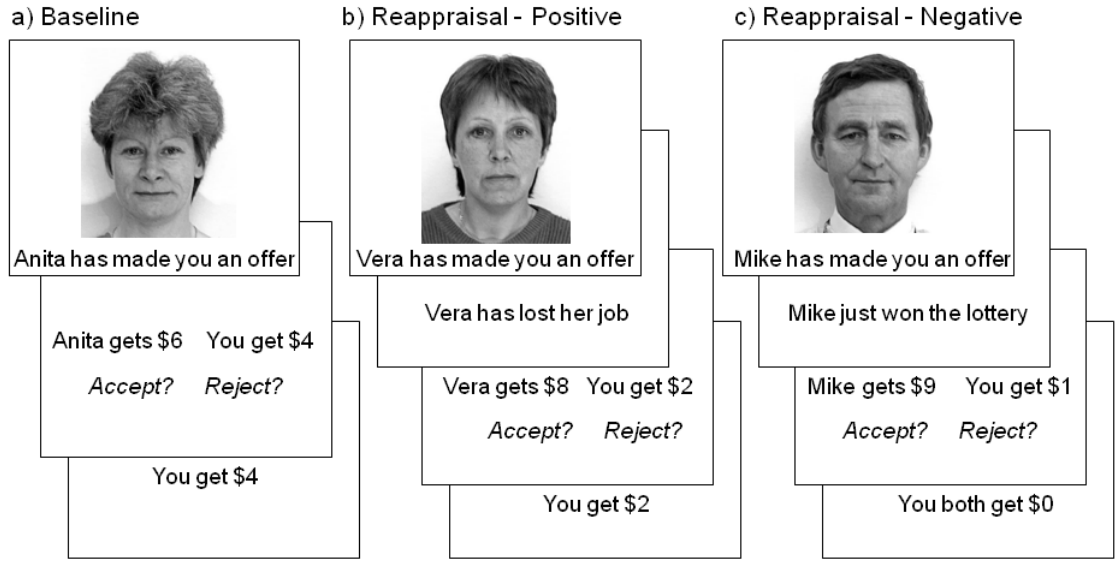
Behavioural assessments

Ultimatum Game

We created a modified Ultimatum Game with baseline and reappraisal versions, using the same monetary amounts and fair to unfair offer ratios that have been previously described (22). In both versions of our task, participants acted in response to different proposers who offered to split a hypothetical $10 with them. The proposer - responder offers ranged from fair ($5 - $5; $6 - $4), to unfair ($7 - $3; $8 - $2; $9 - $1). Based on previous findings (16), including those validated in neurological patients and in older adults (22), we operationalised 'fair' acceptance rates as the average of $5 - $5 or $6 - $4, and the 'unfair' as the average of $7 - $3, $8 - $2 and $9 - $1 acceptance rates.

In the baseline condition, participants were informed they would play against 22 different people, each of whom had been given $10 to divide. It was explained that proposers were free to decide how to split the money, but participants could choose whether to accept the offer (resulting in a payout for both players) or reject the offer (resulting in $0 for both). An example of baseline trials is shown in Figure 1 (a) (see over page). In each trial a neutral black and white photograph of a face, with the caption "[name] has made you an offer" was presented on a computer screen for 3.5 seconds. This was followed by a decision screen where the offer was stated, e.g., "[name] gets $7, you get $3", and a prompt to either "accept" or "reject". This decision screen was displayed until a response was made, followed by a feedback screen of "you get $3" or "you both get $0" (4 seconds) depending on the response made.

Figure 1 – Example of trials in the Ultimatum Game



Panel a) illustrates a trial in the baseline condition, where the participant has accepted the offer. Panels b) and c) illustrate trials from the positive and negative reappraisal conditions where the offers were accepted and rejected, respectively.

In the reappraisal version, participants were informed they would play against a set of 22 new people, each given $10 to divide, with the same contingences applying for accepting or rejecting offers. However, now they were provided information about the proposers' current circumstances. In the positive condition, proposers were framed as poor, or 'down on their luck', encouraging participants to view them in a positive light and to accept more offers. In the negative condition, information was designed to frame proposers as rich, so their offers (particularly the unfair ones) would be viewed as particularly unfavourable and would encourage higher rejection rates. Reappraisal trials are exemplified in Figure 1, (b) and (c). As in the baseline condition, in each trial a black and white neutral face was presented, followed by a description screen (4.5 seconds). Descriptions were restricted to brief and uncomplicated language. Examples of the *positive* condition included "[name] lost his/her house in a fire", "[name] is

saving for his/her son's operation", "[name] is homeless" and examples of the *negative* condition included "[name] owns an international company", "[name] just won the lottery", "[name] is a wealthy investment banker". A decision screen with the offer followed, then a feedback screen. To ensure patients understood the terminology (i.e., that winning the lottery or being a wealthy investment banker would be associated with being rich; or being homeless would be associated with being poor etc.), a checklist was administered at the end of the experiment. All patients included in the study demonstrated intact understanding of the reappraisal terminology.

In both the baseline and reappraisal conditions the 22 trials comprised two of each fair offer and six of each unfair offer. Offers were paired with proposers on a randomised cycle (50% male, 50% female). For the reappraisal condition, an equal mix of positive and negative descriptions made up the 22 trials, and these were presented in a randomised order. Each participant completed the baseline version first, followed by the reappraisal version.

Capacity for Empathy

The Cambridge Behavioural Inventory-Revised (CBI-R; 23) was used to assess behavioural disturbance in the patients. The CBI-R is a 45 item informant-rated questionnaire probing a variety of neuropsychiatric, cognitive and functional symptoms, rating their frequency of occurrence from 0 (*never*) to 4 (*constantly*). As such, higher CBI-R scores indicate greater behavioural dysfunction. To specifically assess empathy, we extracted scores from the item that best exemplifies deficits in this ability: "Appears indifferent to the worries and concerns of family members". Importantly, this question addresses empathic concern – an aspect of empathy primarily affected in bvFTD (24).

Behavioural analysis

We analysed our results by estimating a logistic model using the GEE (generalised estimating equations) technique, which accounts for subject heterogeneity by modelling the within-subjects correlation across decisions, generating a *chi-sq* statistic, 95% confidence interval and an associated *p*-value. The binary dependent variable is the decision to accept or reject an offer, and the independent variables are a three-way factorial of the fairness level (fair vs. unfair acceptance rates), group membership (control vs. bvFTD) and the reappraisal condition (baseline vs. negative vs. positive). All multiple comparisons are corrected using the Sidak correction. Analyses were conducted using the Stata 13 software package (Stata Corporation, College Station, Tx).

Imaging acquisition

Whole-brain T1 images were acquired using 3T Philips MRI scanners with standard quadrature head coil (8 channels). The 3D T1-weighted sequences were acquired as follows: coronal orientation, matrix 256 x 256, 200 slices, 1 x 1 mm^2 in-plane resolution, slice thickness 1 mm, TE/TR = 2.6/5.8 ms.

Voxel-based morphometry (VBM) analysis

3D T1-weighted sequences were analysed with FSL-VBM, a voxel-based morphometry analysis (25,26), part of the FSL software package http://www.fmrib.ox.ac.uk/fsl/fslvbm/index.html (27). First, tissue segmentation was carried out using FMRIB's Automatic Segmentation Tool (FAST) (28) from brain extracted images. The resulting grey matter partial volume maps were then aligned to the Montreal Neurological Institute standard space (MNI152) using the nonlinear

registration approach (FNIRT (29,30)), which uses a b-spline representation of the registration warp field (31). Registered partial volume maps were then modulated (to correct for local expansion or contraction) by dividing them by the Jacobian of the warp field. The modulated images were then smoothed with an isotropic Gaussian kernel with a standard deviation of 3 mm (FWHM: 8 mm). On the basis of previous studies that defined neural correlates of the Ultimatum Game (19) and social norm processing (3) across various prefrontal, striatal and limbic regions, we created a region-of-interest (ROI) mask using the Harvard-Oxford cortical and subcortical structural atlases. The following bilateral atlas regions were included in the mask: frontal pole, frontal orbital cortex, subcallosal cortex, frontal medial cortex, superior frontal gyrus, middle frontal gyrus, inferior frontal gyrus, cingulate gyrus (anterior division), paracingulate gyrus, caudate, putamen, nucleus accumbens, insula cortex and amygdala.

A voxelwise general linear model (GLM) was applied and permutation-based non-parametric testing (with 5000 permutations per contrast (32)) was used to form clusters with the Threshold-Free Cluster Enhancement (TFCE) method (33). Overall differences in grey matter intensity between patients and controls, within fronto-subcortical mask, were assessed via *t*-tests, tested for significance at $p < .05$, corrected for multiple comparisons via Family-wise Error (FWE) correction across space (Supplementary materials – Table 1 and Figure 1). Following this, correlations between Ultimatum Game performance and grey matter intensity were conducted. Acceptance rates for unfair offers in the negative and positive reappraisal conditions were entered as covariates in VBM design matrices, combining both patients and controls. Finally, to derive a contrast that reflected positive social norm compliance versus social punishment, unfair acceptance rates in the negative condition were subtracted from

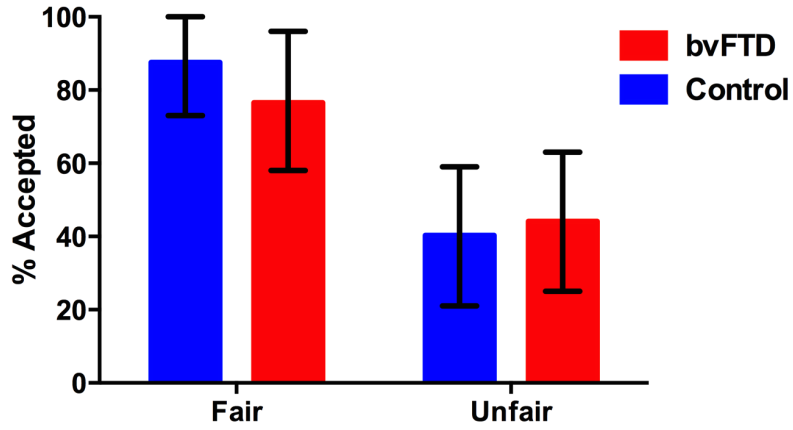
those in the positive condition. This contrast was also entered as a covariate in a VBM design matrix. Results of the three covariate analyses are reported at a significance level of $p < .01$ uncorrected and at a cluster threshold of greater than 15 contiguous voxels.

Results

Ultimatum Game baseline condition

In this section, we examine acceptance rates in the baseline condition, shown in Figure 2 (below). The group by fairness level interaction was significant (*chi-sq.(1)* = 4.65, p = 0.031). There was no main effect of group (*chi-sq.(1)* = 0.01, p = 0.912), but there was a significant main effect for fairness level (*chi-sq.(1)* = 148.28, $p < .0001$). Post-hoc tests revealed that both controls and bvFTD patients accepted significantly less offers in the unfair condition (*chi-sq.(2)=143.5, p*<0.0001), and that within both the fair and unfair conditions there was no difference in the acceptance rates of the two groups (*chi-sq.(2)=5.28, p*=0.071). Together, suggesting that acceptance rates for controls and patients were modulated to a similar degree by fairness levels.

Figure 2 – Baseline acceptance rates in the Ultimatum Game

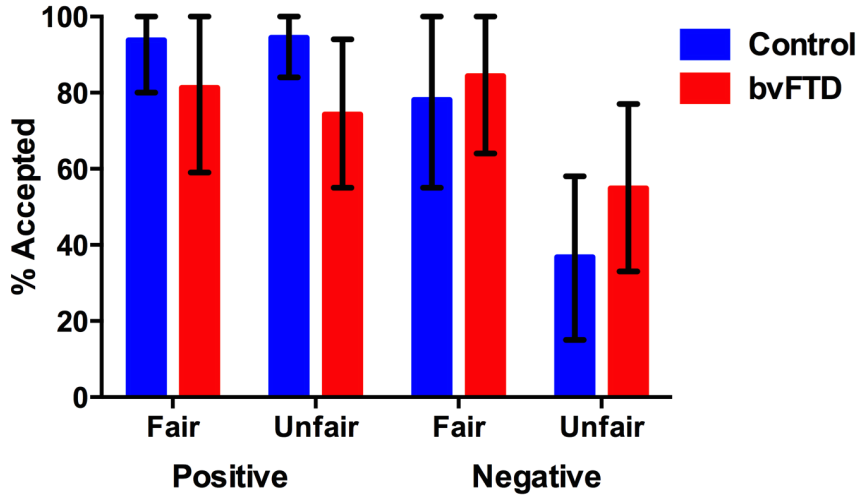


Percentage of offers accepted in the baseline condition for fair versus unfair offer amounts. Error bars represent 95% confidence intervals.

Reappraisal conditions

This section compares acceptance rates across the two reappraisal conditions (negative vs. positive), as illustrated in Figure 3 (below). The overall three-way interaction of fairness level, reappraisal and group was significant at the 10% level (*chi-sq.(1)=2.71, p*=0.0994). The fairness by group interaction was not significant (*chi-sq.(1)=0.12, p*=0.7285), indicating that response rates in both controls and patients were modulated to a similar degree by fairness level – a similar pattern to that seen in the baseline condition. By contrast, reappraisal interacted with fairness (*chi-sq.(2)=29.95, p*<0.0001), indicating that the reappraisal modulation had a significant effect on fairness of offers. More importantly, there was also a significant reappraisal by group interaction (*chi-sq.(2)=31.47, p*<0.0001), such that reappraisal condition modulated the responses of both groups differentially.

Figure 3 – Reappraisal acceptance rates in the Ultimatum Game



Percentage of fair versus unfair offers accepted in the positive and negative reappraisal conditions. Error bars represent 95% confidence intervals.

To further investigate the fairness by reappraisal interaction, post-hoc pairwise comparisons revealed there was no difference in fair and unfair acceptance rates in the positive condition, for both controls (*chi-sq.(1)=0.03, p*=0.999) and patients (*chi-sq.(1)=1.21, p*=0.717), whereas the pattern of accepting less unfair offers was apparent in the negative condition, for both controls (*chi-sq.(1)=37.15, p*<0.0001) and patients (*chi-sq.(1)=20.88, p*<0.0001). Together, suggesting that when interacting with poorer proposers the acceptance rates were not influenced by perception of fairness, yet, perceptions of fairness were relevant when interacting with rich proposers.

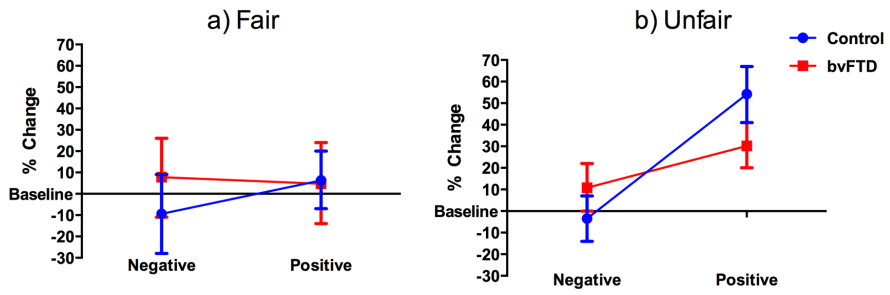
Furthermore, the acceptance rates for patients and controls did not differ in both the positive fair (*chi-sq.(1)=1.75, p*=0.56), and negative fair conditions (*chi-sq.(1)=0.3, p*=0.969). However, acceptance rates were significantly less for patients compared to controls in the positive unfair condition (*chi-sq.(1)=6.26, p*=0.0486), and were not significantly different for patients in the negative unfair condition (*chi-sq.(1)=2.55, p*=0.374).

Regarding the reappraisal by group interaction, post-hoc comparisons revealed that controls demonstrated significantly lower acceptance rates (a difference of 50% points) in the negative versus positive condition (*chi-sq.(1)=110.29, p*<0.0001). Patient acceptance rates were also significantly lower in the negative versus positive conditions (a difference of 15% points) (*chi-sq.(1)=315.18, p*=0.0002) Importantly, the effect size of the change in patients' acceptance rates (across conditions) is significantly less than that of the controls (*chi-sq.(1)=31.47, p*<0.0001). Hence, patients were significantly less influenced by condition than controls indicating a muted response to social context.

Comparisons with the baseline condition

Figure 4 (below) illustrates effects of the independent variables on changes in acceptance rates relative to the baseline rates. Post-hoc comparisons confirm that for fair offers, the effects of change from the baseline to positive or negative conditions across the groups (control vs. bvFTD) were not significant (*p*-values ranging from 0.778 to 0.9963), shown in Figure 4, panel a). However, highly significant effects were found for unfair offers in the positive condition for both control and bvFTD group (*chi-sq.(1)=128.24, p*<0.0001 and *chi-sq.(1)=61.036, p*<0.0001, respectively), shown in Figure 4, panel b). The effect size is significantly lower for the bvFTD group, 19.4%, compared to the control group, 57.63%, (*chi-sq.(1)=30.74, p*<0.0001). This is evidence that patients were significantly less influenced by social norms than the controls, pointing to a difficulty in integrating social cues into their decision-making processes. Furthermore, the change in acceptance rates from the baseline to the negative condition for unfair offers approached significance in the bvFTD group (*chi-sq.(1)=6.97, p*=0.0645) and was not significant for the control group (*chi-sq.(1)=0.76, p*=0.979). Importantly, this trend in the bvFTD patients reflected a tendency to accept more in the negative unfair condition, the opposite pattern to controls.

Figure 4 – Change from baseline acceptance rates in the reappraisal conditions



Panels show the change in acceptance rates from baseline in the reappraisal conditions, represented separately as fair (panel a) versus unfair (panel b) offer amounts. Error bars represent 95% confidence intervals.

Relationship to empathy

To investigate the effect of empathy on acceptance rates in the patients, we estimated a GEE logistic model using a three-way factorial design of the fairness level, reappraisal condition and the level of empathy impairment (minimal vs. severe). We categorised patients on the basis of their score on the CBI-R empathy item (ranging from 0 to 4, higher scores indicating more significant impairment). Minimal impairment was defined as values ranging from 0-3 and severe impairment as values of 4. Results showed that those with severely impaired empathy had significantly lower acceptance rates for positive unfair offers (62% vs. 90% accepted; (*chi-sq.(1)=4.06, p*=0.0439). The group with severely impaired empathy also accepted less unfair negative offers at a level that approached significance (73% vs. 41% , *chi-sq.(1)=3.59, p*=0.0582).

VBM analysis – Atrophy pattern in bvFTD group

The bvFTD group was initially contrasted with controls to reveal overall patterns of grey matter intensity decrease in the fronto-subcortical mask. Patients showed characteristic patterns of atrophy throughout the fronto-subcortical regions of interest. For details, see Supplementary Table 1 and Supplementary Figure 1.

VBM analysis – Ultimatum Game

Correlates of unfair acceptance rates across reappraisal conditions

Regions of decreased grey matter intensity that covaried with unfair acceptance rates in the negative reappraisal condition are shown in Table 2 and Figure 5, panel a) (over page). In the negative condition, unfair acceptance rates were associated with grey matter intensity in the right orbitofrontal cortex/frontal pole and bilateral superior frontal gyri. In the positive condition, unfair acceptance rates were associated with right

lateral-medial orbitofrontal cortex, bilateral regions of frontal pole, dorsolateral and ventrolateral prefrontal cortices, anterior and paracingulate cortices, left insula, right caudate, primarily dorsal, but also extending ventrally and incorporating nucleus accumbens, for details see Table 2 and Figure 5, panel b).

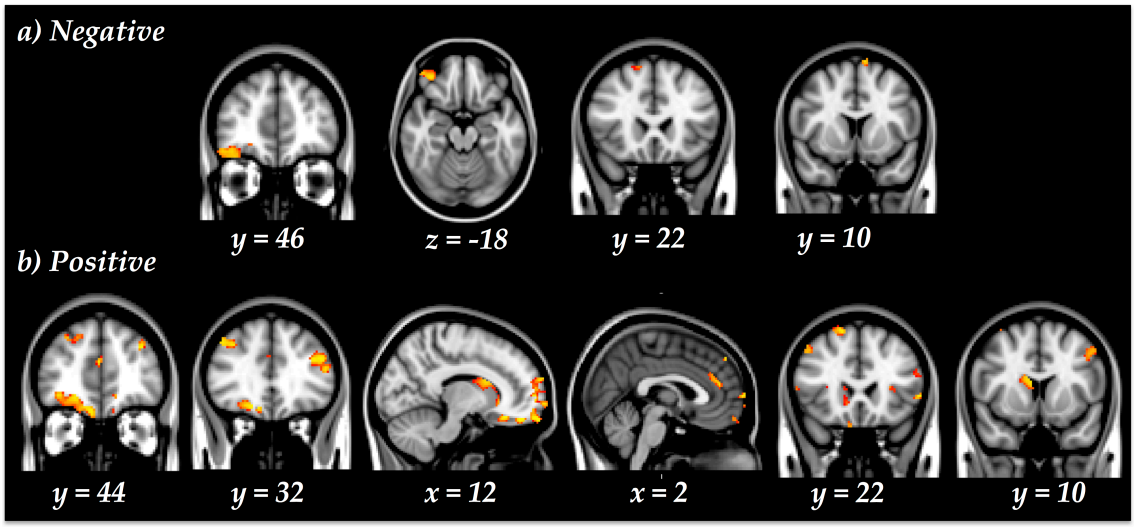
Table 2 – Region of interest Voxel-based morphometry (VBM) results showing areas of significant grey matter intensity decrease correlating with unfair acceptance rates in the reappraisal conditions.

Regions	*Hemisphere (L/R/B)*	*MNI coordinates for voxel of maximal intensity*			*Number of voxels*	*T value*
		X	*Y*	*Z*		
Negative						
Frontal pole; frontal orbital cortex	R	38	42	-22	170	2.83
Superior frontal gyrus	L	-8	10	72	37	
Superior frontal gyrus	R	16	20	58	28	
Positive						
Frontal pole; frontal orbital cortex	R	12	46	-22	714	
Middle frontal, inferior frontal gyri	L	-36	34	24	364	
Frontal pole	R	14	66	-22	352	
Middle frontal, precentral gyri	R	42	0	56	221	
Caudate, nucleus accumbens	R	10	6	16	207	
Middle frontal, inferior frontal gyri	L	-46	14	36	156	
Frontal pole	R	22	50	38	127	
Middle frontal gyrus; frontal pole	R	36	34	40	121	
Superior frontal gyrus	R	18	24	64	78	
Anterior cingulate, paracingulate gyri	B	2	44	18	78	
Anterior cingulate	B	-10	-4	38	75	
Precentral, Superior frontal gyri	L	-26	-8	60	64	

Frontal pole	R	32	52	22	64
Middle frontal gyrus	R	46	20	44	57
Frontal pole	R	42	48	10	39
Frontal pole	L	-30	66	2	35
Inferior frontal gyrus	R	52	26	18	28
Inferior frontal gyrus	L	-56	22	2	23
Precentral, Middle frontal gyri	R	42	4	40	21
Frontal pole	R	2	68	6	16
Insula	L	-28	22	10	16

Results uncorrected at $p < .01$ and at a cluster threshold of greater than 15 contiguous voxels.

Figure 5 – Voxel-based morphometry (VBM) showing regions of decreased grey matter in bvFTD patients associated with acceptance rates in the Ultimatum Game



Region of interest VBM results showing areas of significant grey matter intensity decrease in bvFTD patients relative to controls, which covaried with acceptance rates of unfair offers in the reappraisal conditions, negative (panel a) and positive (panel b). Results uncorrected at p < .01 and at a cluster threshold of greater than 15 contiguous voxels.

Correlates of positive norm compliance versus punishment

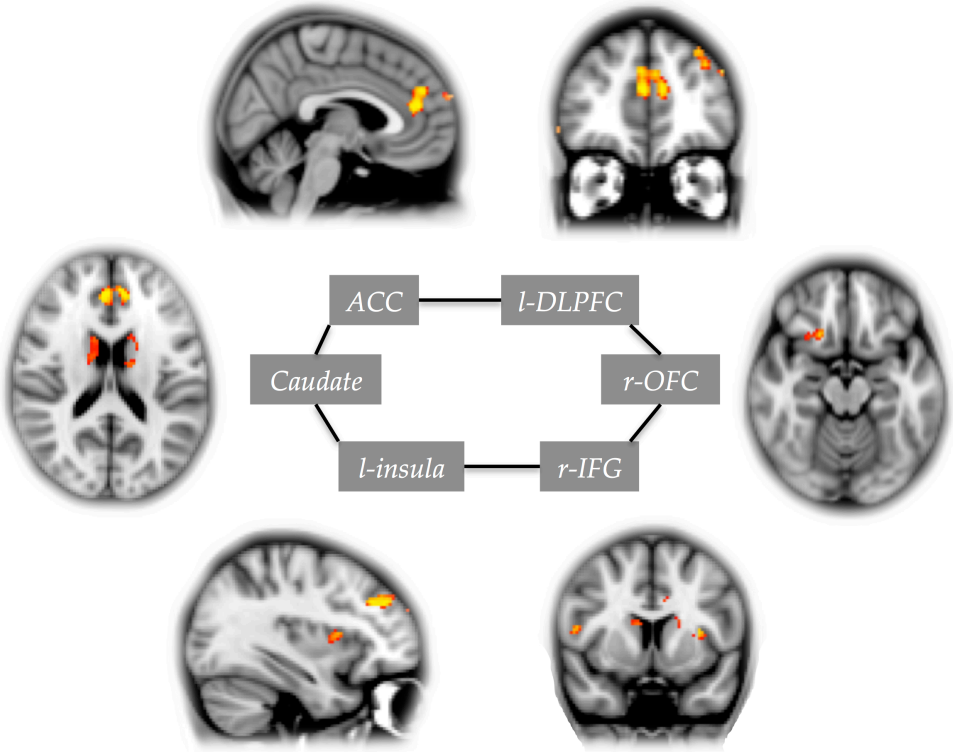
Regions of decreased grey matter intensity that correlated specifically with positive norm compliance, as contrasted against the negative condition, included the anterior and paracingulate cortices, left superior frontal gyrus, right orbitofrontal cortex, right frontal pole, right medial frontal gyrus, left anterior insula, and bilateral dorsal caudate (Table 3, Figure 6) (below).

Table 3 – Correlates of positive norm compliance versus punishment. Region of interest Voxel-based morphometry (VBM) results showing areas of significant grey matter intensity decrease that covaried with positive norm compliance.

Regions	*Hemisphere (L/R/B)*	*MNI coordinates for voxel of maximal intensity*			*Number of voxels*	*T value*
		X	*Y*	*Z*		
Anterior cingulate, paracingulate	B	4	40	16	367	2.83
Middle frontal gyrus, frontal pole	L	-32	34	30	162	
Caudate	R	18	22	8	155	
Insula	L	-32	8	10	80	
Frontal orbital cortex	R	20	22	-14	40	
Inferior frontal gyrus	R	52	6	12	24	
Caudate	L	-18	6	18	22	
Caudate	L	-12	6	16	21	
Superior frontal gyrus	L	-20	-4	66	20	
Frontal pole	R	14	60	36	19	
Frontal pole	R	24	64	-10	19	
Medial frontal gyrus	R	30	28	50	16	

Results uncorrected at $p < .01$ and at a cluster threshold of greater than 15 contiguous voxels

Figure 6 – Voxel-based morphometry (VBM) showing regions of decreased grey matter in bvFTD patients associated with social norm compliance



ACC, Anterior cingulate cortex (y = 46); l-DLPFC, left dorsolateral prefrontal cortex (y = 44); r-OFC, right orbitofrontal cortex (z = -16); r-IFG, right inferior frontal gyrus (y = 8); l-insula, left insula (x = -34); caudate (z = 18). Results uncorrected at p < .01 and at a cluster threshold of greater than 15 contiguous voxels.

Discussion

We present a novel neuroeconomic task to investigate social decision-making behaviour in a neurodegenerative lesion model characterised by gross social dysfunction (bvFTD). For the first time, we identify a dissociation of intact fairness perception and failure to integrate social contextual information into economic decisions, due to fronto-subcortical cell loss. From a wider theoretical standpoint, these findings speak to on going appeals that norm-based decision-making research be extended to clinical

populations (2,17), in an effort to determine causal mechanisms of social norm compliance, and its relevance to neuropsychiatric symptomatology.

Behaviourally, our most striking result was that despite intact fairness based decision-making, bvFTD patients showed impaired ability to modulate their behaviour in response to social contextual information. Perception of fairness norms and norm-compliant social behaviour have previously been found to dissociate in healthy individuals (2). Our results show the first such dissociation between fairness and social cues in a neurodegenerative lesion model.

Equivalent responses to fairness between patients and controls may, at first glance, seem difficult to reconcile, considering that core emotion processing regions known to underpin fairness behaviour are compromised in bvFTD. For example, activity in the anterior insula, a central hub for processing emotional and introceptive states, is strongly associated with processing unfair offers (19,34). Previous investigations in ventromedial PFC lesion patients, or during dietary serotonin depletion, indicate that emotion regulatory mechanisms interact with perceptions of unfairness. Accordingly, exaggerated emotional reactions lead to elevated rejection rates (22,35,36). In contrast, the well-described blunting of emotional reactivity in bvFTD (37), may temper the level of rejection rates in this group – resulting in reactions to unfairness that are similar to controls.

Our neuroimaging analysis of the reappraisal conditions demonstrated distinct neural correlates for positive and negative social decision-making. A network of regions involving the striatum, anterior cingulate, bilateral dorsolateral prefrontal cortices, and

medial/right PFC was implicated in decisions driven by positive social behaviours. Importantly, these positive-based correlates overlap with regions recruited during reward-guided decision making (38), with medial PFC and anterior cingulate cortices, in particular, being strongly associated with integrating social and emotional information to inform subsequent behaviour (39). For performance in the negative condition, the right-sided ventrolateral PFC was exclusively implicated, consistent with findings that lateralised regions of the orbitofrontal cortex are specialised for evaluating punishing stimuli (40).

In terms of behavioural responses to unfair offers, patients showed adaptation to positive social information, albeit to a significantly lesser extent than controls. However, those patients with more severely impaired everyday empathy had particularly low acceptance rates in the positive condition. A contingent relationship between social contextual factors and empathy has previously been demonstrated in the Ultimatum Game (41), indicating that empathic responses are modulated by evaluation of others' social behaviours. Our data does not allow us to establish a causal relationship between empathy and the ability to utilise positive social contextual information in bvFTD. Nevertheless, we revealed a distributed fronto-subcortical network involved in the integration of positive social contextual information with decision behaviour. This is consistent with the complex hierarchical brain regions known to be involved in the generation and expression of empathy (42). Most importantly, we have identified an objective social decision-making task that appears to discriminate between the capacity for empathy in an everyday setting. Future studies are needed to explore the directionality of this relationship. If addressing social contextual

impairments may directly influence empathy, this may have implications for behavioural and pharmacological management strategies in the future.

In response to negative social contextual information, bvFTD patients showed a distinctly different pattern to controls, accepting more than their baseline levels. Punishment of rich responders for unfair offers, albeit at a personal cost, is consistent with altruistic punishment. In essence, this describes a tendency to punish violators of social norms, when there is no material gain and even a loss to the punisher (43,44). Experimentally, altruistic punishment has been linked to activation of the dorsal caudate (45), fitting with a role for the dorsal striatum in reward-driven learning and subsequent action selection (46,47). We demonstrate a reduced tendency to engage in altruistic punishment in bvFTD patients. Our finding that right-lateralised orbitofrontal cortex covaried with performance in this negative condition, suggests that engaging in altruistic punishment may require intact processing of the initial negative stimulus (i.e., the norm violation committed against oneself). Thus, in the context of impaired processing of negative reinforcers, the ability to enact altruistic punishment may be compromised. As a further speculation, forgoing personal gain to punish another entails a more immediate inhibition of self-interest. Inhibitory dysfunction is well described in bvFTD (48) and linked to orbitofrontal abnormalities (49,50), with one study directly associating inhibitory dysfunction with right-sided ventrolateral PFC atrophy (51). This converging evidence from bvFTD highlights a role for the right-lateralised orbitofrontal cortex in successful engagement in altruistic punishment, which should be explored in future studies.

Together, our findings support a recent hypothesis proposing that a range of symptoms in bvFTD are underscored by a generalised deficit in the ability to effectively integrate social context and behaviour (15). Indeed, our results suggest that failure to integrate positive social contextual information may be particularly important in the expression of empathy. Further, we reveal a 'misuse' of negative social information, by highlighting a discrete deficit in exploiting negative contextual information to guide economic decisions. In doing so, this provides the first objective explanation for the commonly noticed financial gullibility of bvFTD patients. Maladaptive financial decision making in bvFTD is pervasive in both everyday life and experimental contexts (52-56). Extravagant spending, economic negligence and financial vulnerability can emerge long before a bvFTD diagnosis is achieved. As such, this deficit we describe in integrating negative social cues with economic decisions is clearly a critical area for early diagnostic assessment.

Finally, our contrast comparing positive versus negative conditions confirmed a distinct network of regions involved in positive social norm compliance. These regions overlap considerably with neural correlates identified for norm compliance in the face of apparent, or anticipated punishments (2-4,57). Our results provide compelling evidence that these regions, including anterior cingulate, lateral orbitofrontal and dorsolateral prefrontal cortices, insula and caudate, are causally involved in social norm compliance, irrespective of whether there is a punishment threat. This "social norm compliance" network represents an important target for future research into disordered norm compliance in bvFTD, as well as other neuropsychiatric conditions where social deficits have been related to analogous brain regions, including anti-social adolescents (58), borderline personality disorder (59) and autism (60). Further mechanistic insights into

this network will reveal how social norm compliance breaks down in acquired conditions, such as bvFTD. Uncovering processes by which social norms are established and consolidated within this fronto-subcortical network will also be of particular relevance to developmental conditions, where dysfunctional social normative interactions may become habitualised (61), contributing to the stability of maladaptive social engagement throughout the lifespan.

In conclusion, we have developed a novel neuroeconomic task to provide insights into complex social dysfunction in a neurodegenerative lesion model (bvFTD). In doing so, we have identified discrete deficits in patients' ability to integrate social contextual information to guide normative decision making behaviour, associated with abnormalities in key fronto-subcortical regions. Importantly, these findings provide further evidence that broad neuropsychiatric symptoms can be distilled to their component processes, in an effort to define discrete neural systems that are affected – an approach critical to extending current knowledge and therapeutics in neuropsychiatry (62).

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4.2 Summary and future directions

The findings described here, for the first time, show the relationship between fronto-limbic-striatal atrophy and complex social normative decision-making in bvFTD. The novelty of the task is particularly relevant, as it combines aspects of social norm compliance and social decision-making – two abilities known to be affected in bvFTD, but difficult to measure via objective, laboratory-based tasks. These results shed light on the particular component processes that likely underpin these compromised abilities in bvFTD, namely that patients can retain intact concepts of monetary value and fairness, but that difficulty utilising social information impinges upon their decision-making behaviour. Our results provide the first evidence of striatal involvement in such complex social decision-making processes.

The study describes a relationship between difficulty modulating behaviour in response to positive social information and reduced empathy. Whilst this relationship described is intriguing, and raises an interesting line of enquiry, more work is necessary to establish how perception of social context can influence both the generation of an empathic feeling and the expression of empathy. The complexities underlying empathy remain an extremely active area of research in modern neuroscience (Keysers and Gazzola, 2014, Melloni *et al.*, 2014), not only for its importance in fundamental human interactions, but also for its role in many neuropsychiatric conditions. In the study reported here, a further link is speculated between the social decision-making deficits described and everyday financial decision-making impairments in bvFTD, including gullibility and impulsive spending. Clarifying this link is an important future direction, as the exact cognitive and neural mechanisms underpinning this type of behavioural dysfunction, which is reasonably characteristic of bvFTD, are not well understood. Other possible

candidates contributing to those behaviours are altered reward processing, impulsivity and impaired future prospection, all of which are apparent in bvFTD. Distinguishing between the various influences on everyday financial decision-making in bvFTD will help establish a more accurate basis for its causal mechanisms and improve our ability to detect it and manage it. The current study demonstrates accurate fairness perception, suggesting that reward valuation is intact, at least to a degree. Although speculative, the implication is that difficulty integrating contextual information is the primary driving force for decision-making impairments in bvFTD, as opposed to reward processing deficits. Further studies contrasting the component processes that underpin complex social decision-making will help clarify this speculation.

CHAPTER 5 – CONCLUSION

The aim of this thesis has been to examine the contribution of fronto-striatal atrophic changes to cognition and behaviour, in two neurodegenerative disease populations (PD and bvFTD). From the studies presented, it is clear that both prefrontal and striatal changes contribute to aspects of cognition and behaviour in these conditions (See Figure 2).

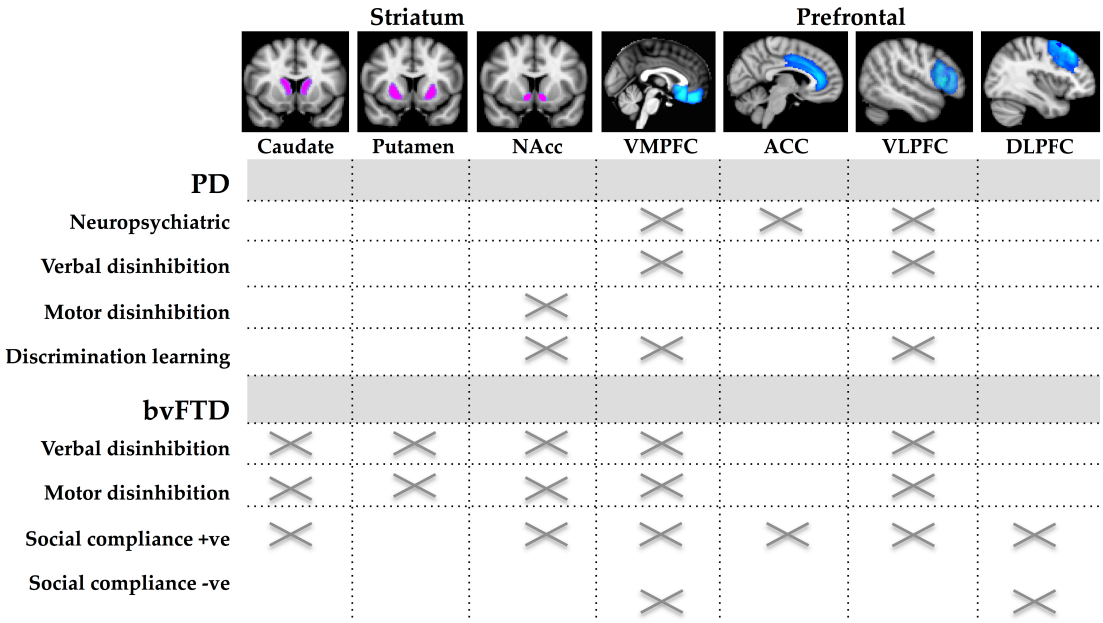

Figure 2. Summary of fronto-striatal regions where atrophy was correlated with cognitive or behavioural variables. NAcc, nucleus accumbens; VMPFC, ventromedial prefrontal cortex; ACC, anterior cingulate cortex; VLPFC, ventrolateral prefrontal cortex; DLPFC, dorsolateral prefrontal cortex; +ve, positive; -ve, negative.

Of particular importance, is that such deficits in PD have classically been related to a functional, dopamine-mediated disturbance. By highlighting the unique contributions of fronto-striatal atrophy in PD, the findings presented here further confirm that non-motor symptoms represent a complex interaction of functional and structural changes.

Continued insights, such as those described here, into the pathophysiology of cognitive and behavioural decline in PD remain critical if we are to develop better frameworks for approaching identification and treatment of these symptoms. In bvFTD, the results reported here are the first to describe striatal correlates of more specific cognitive and behavioural deficits. Furthering our understanding of the neural correlates of these symptoms in bvFTD will not only refine the potential to characterise and manage them, but will lead to increased diagnostic sensitivity. Detailed implications of the findings have been addressed in the discussion sections of each publication included in the thesis, and specific future directions have been suggested in the chapter summaries. The following section deals with the broader, clinically relevant implications of the included studies.

Regarding PD, findings in this thesis converge with mounting evidence that, from its earliest stages, the disease is truly a multisystem disorder (Khoo *et al.*, 2013, Halliday *et al.*, 2014). On the one hand this complexity poses its own set of challenges, trying to grasp the nature and trajectory of dysfunction across multiple systems, and how their interactions give rise to distinct phenotypic differences in PD. On the other hand, from a clinical perspective it emphasises the potential utility of a broad range of therapeutic targets.

In PD, decades of intensive investigation into the pathophysiology of its motor features have culminated in very effective therapies to address the symptoms and vastly improve patient quality of life. The same cannot be said for the cognitive and behavioural features of PD, for which effective treatment is not readily available. Continuing to delineate the relative contributions of dopaminergic and non-dopaminergic

neurotransmitter systems, brain atrophy, as well as the accumulation of both PD and Alzheimer's pathology, will ensure that an accurate framework is established to define these symptoms. Parallel investigations into drug therapies for these symptoms are still in their early stages, although they have uncovered several possible angles. The use of cholinesterase inhibitors such as rivastigmine has been investigated for some time, and can confer moderate benefits on broad aspects of cognition in PD dementia (Emre *et al.*, 2004). More recently, agents that target noradrenergic and serotonergic systems (i.e., the selective noradrenaline re-uptake inhibitor atomoxetine and the selective serotonin reuptake inhibitor citalopram) have been investigated for their potential remediating effects on impulsivity, and some other broad aspects of cognition in PD (Kehagia *et al.*, 2014, Ye *et al.*, 2014a, Ye *et al.*, 2014b). Across those studies, the behavioural effects were mixed, and the therapeutic agents were associated with either negligible or modest performance gains. However, of particular relevance to the arguments in this thesis, administration of both agents enhanced fronto-striatal activation, although the extent to which this occurred was dependent on integrity of the underlying fronto-striatal structural connections. These findings highlight the importance of characterising cognition and behaviour in PD with respect to changes across all levels of brain structure and function. Such a refined approach represents the clearest path toward developing effective treatments.

Refining our understanding of the emergence and trajectory of pathologic change across all levels of structure and function in PD also has important implications for offering prognoses. It is well recognised that distinct phenotypic categories exist in PD, and this has been verified both clinically (Lewis *et al.*, 2005a) and pathologically (Selikhova *et al.*, 2009). Early in the disease stages, however, identifying patients likely to follow a

relatively benign course, versus those who will progress more rapidly with a higher burden of non-motor complications, can be difficult. The ability to more accurately predict the disease course in individual patients has obvious benefits for planning on going disease management, but will also be crucial with the future development of disease-modifying therapies. The findings reported in this thesis demonstrate that the burden and distribution of fronto-striatal atrophy will be essential to consider in attempts to better characterise PD phenotypes and chart disease progression.

In stark contrast to PD, in bvFTD a prompt and accurate clinical diagnosis remains challenging and *in vivo* signatures of clinico-pathological relationships remain unsubstantiated. Furthermore, by comparison, effective treatments for cognition and behaviour in bvFTD seem even more elusive – which likely reflects the tenuous link between clinical symptoms and underlying pathology, and the unrelenting speed of the pathological process, making restorative interventions all the more challenging.

Nevertheless, as conceptualisation of bvFTD increasingly moves from its original standing as a dysexecutive syndrome, sensitive and specific clinical tools measuring social, emotional and inhibitory function promise to provide diagnostic insights and refine the clinical syndrome. The studies presented in this thesis employed laboratory-based tasks to assess inhibitory dysfunction and social processing in bvFTD. Distilling broad behavioural symptoms into their component processes is a challenge. However, this remains particularly important, firstly, in terms of diagnosis both inhibitory function and social processing deficits are amongst the earliest areas of decline in bvFTD. Secondly, the ability to quantify deficits that correspond to everyday behavioural dysregulation is likely to provide a more practical assessment of a patients'

ability. This is essential when advising family and caregivers on patient management, and assisting in future planning. The novel social decision-making task presented in Publication IV is an example of a laboratory-based test striving toward ecological validity, by assessing economic decision-making in a social context. An important future direction is to translate such ecological valid measures into standardised and streamlined tools that could form part of routine clinical assessment. This has been achieved in the development of clinical assessment batteries for certain social-emotion processes in bvFTD (Torralva *et al.*, 2009, Bertoux *et al.*, 2012). However, there remains scope to develop such tools for social contextual decision-making.

Findings detailed in this thesis provide important new insights into the contribution of striatal atrophy to cognitive and behavioural dysfunction in bvFTD. Clearly this is an important aspect in understanding the causal mechanisms of these symptoms. From a clinical standpoint, striatal pathologic change may represent an important disease-specific biomarker – particularly with respect to Alzheimer's disease. It has become increasingly apparent that an intact memory or ventromedial prefrontal dysfunction is not always a reliable marker for bvFTD. In this context, the profound striatal changes in bvFTD are likely to be important. As mentioned in the introductory chapter, bvFTD patients have a 25% caudate volume reduction compared to age-matched controls (Looi *et al.*, 2008). By comparison, studies quantifying caudate volume loss in Alzheimer's disease compared to age-matched control have found reductions of 6-7% (Madsen *et al.*, 2010). Only recently has fronto-striatal integrity been directly compared between bvFTD and Alzheimer's disease, and a combination of ventral fronto-striatal changes appears to be the most effective marker for bvFTD (Bertoux *et al.*, 2014). Taken together, striatal atrophy in bvFTD, and its cognitive behavioural sequelae, are likely to

be an effective diagnostic marker and potentially useful for tracking disease progression and monitoring intervention strategies.

Together, the findings described in this thesis offer new insight into the neural and clinical signatures for a range of complex cognitive and behavioural symptoms in neurodegenerative disease. It is hoped that continued exploration into the pathophysiology of these symptoms will in turn drive the development of more effective, disease-specific therapies.

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Appendix

APPENDIX A
Supplemental material for publications in Chapters

A1. Chapter 2 – Publication I

Supplementary Table 1. Spearman correlation values between the significant neuropsychiatric sub-scores (NPS) for PD patients.

	Abnormal behaviour	*Mood*	*Stereotypic motor behaviour*	*Motivation*
Abnormal behaviour	-	.595	.582	.467
Mood	.595	-	.662	.747
Stereotypic motor behaviour	.582	.662	-	.681
Motivation	.467	.747	.681	-

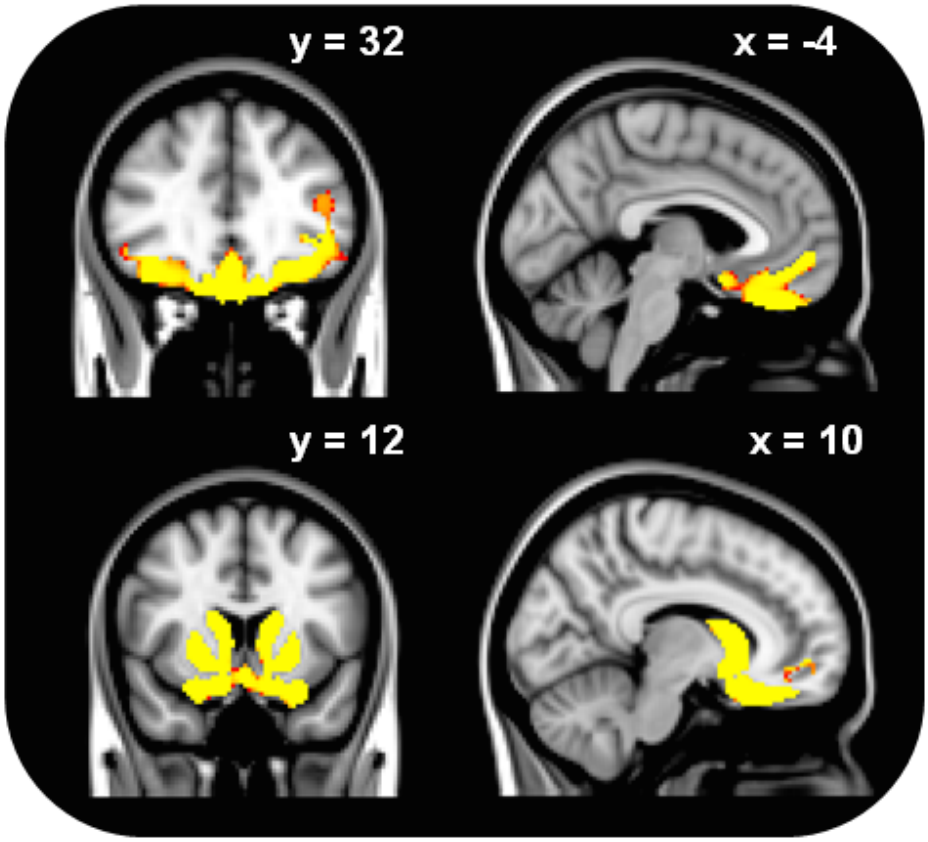
N.B. All Spearman's rho correlation coefficient significant at $p < .001$

Supplementary Table 2. Fronto-striatal region of interest voxel-based morphometry results showing areas of significant grey matter intensity decrease for PD patients (PD+NPS and PD-NPS combined) in comparison to Controls. All results corrected for multiple comparisons using the family-wise error at a threshold of $p < .05$.

Regions included within cluster	*Hemisphere (L/R/B)*	*MNI coordinates at peak voxel*			*Number of voxels*	*T score*
		X	*Y*	*Z*		
PD vs. Controls						
Frontal Medial and Subcallosal Cortex/ Orbital Frontal Cortex/Anterior Cingulate/ Left Inferior Frontal Gyrus/ Insular Cortex/* Caudate/Putamen/Nucleus Accumbens	B	-4	32	-30	7249	1.99

Hemisphere: L = left; R = right; B = bilateral.
*Brodmann areas: BA 11, 47, 25/ BA 10/ BA 32/ BA 44, 45/BA 13

Supplementary Figure 1. Voxel-based morphometry results showing regions of gray matter atrophy for all PD patients in comparison to Controls. Clusters are overlaid on the Montreal Neurological Institute standard brain ($t > 2.41$) and all results corrected for multiple comparisons using the family-wise error at a threshold of $p < .05$.



A2. Chapter 2 – Publication II

Supplementary Table 1. Mean (SD) scores for Controls, bvFTD and PD patients on executive function tasks. F values indicate significant differences across groups and Tukey post-hoc tests compare differences between group pairs[1]. Otherwise, due to unequal variance χ^2 indicates differences across groups and Mann-Whitney U tests compare differences between group pairs.

	Controls	bvFTD	PD	F / χ^2 values	bvFTD vs Controls	PD vs Controls	bvFTD vs PD
Verbal Fluency							
Total correct[1]	43.8 (10.0)	23.5 (15.2)	39.9 (12.4)	***	***	n.s.	**
Rule-breaks	.47 (1.1)	2.5 (2.7)	2.3 (2.4)	**	**	**	n.s.
Repetitions	1.2 (.94)	2.1 (1.6)	1.3 (1.1)	n.s.	-	-	-
Trails							
A Time	29.3 (9.8)	55 (21.9)	41.7 (23.6)	**	***	n.s.	*
A Errors	.20 (.41)	.45 (.69)	.12(.33)	n.s.	-	-	-
B Time	70.9 (23.7)	203.1 (159)	115 (92.2)	**	**	n.s.	*
B Errors	.33 (.82)	1.9 (2.2)	.63 (.88)	n.s.	-	-	-
Digit Span							
Forwards raw score	11.4 (2.0)	7.7 (1.4)	9.5 (2.5)	**	***	*	*
Backwards raw score[1]	8.3 (2.5)	4.6 (1.7)	6.0 (2.1)	***	***	**	n.s.

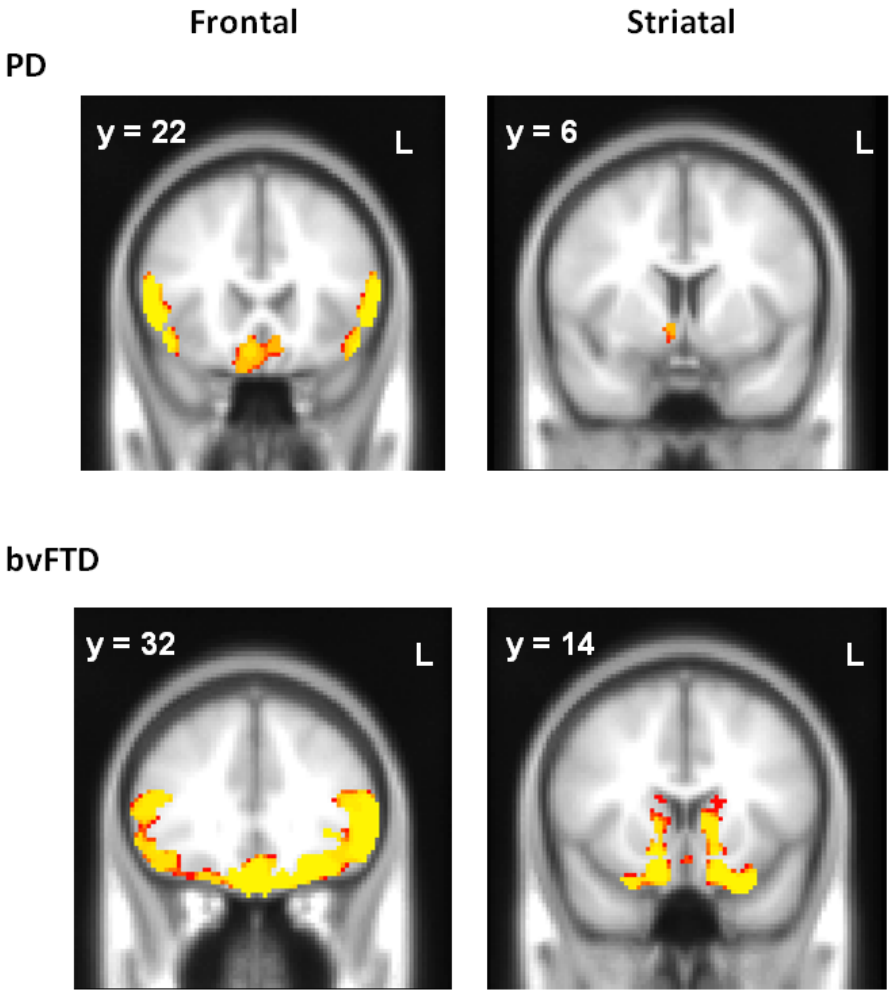
n.s. = non significant; *** = $p < .001$; ** = $p < .01$; * = $p < .05$.

Supplementary Table 2. Region of interest Voxel-based morphometry (VBM) results showing regions of significant grey matter intensity decrease for bvFTD and PD, in comparison to Controls. Results corrected for multiple comparisons (FWE) at $p < .05$.

Regions	*Hemisphere*	*MNI coordinates*			*Number of voxels*	*T score*
	(L/R/B)	*X*	*Y*	*Z*		
bvFTD vs. Controls						
Frontal Orbital Cortex, Subcallosal Cortex, Frontal Medial Cortex/Inferior Frontal Gyrus/Nucleus Accumbens, Caudate, Putamen	B	4	32	-30	5467	3.20
PD vs. Controls						
Subcallosal , Medial Orbital Frontal Cortex/Nucleus Accumbens	B/R	6	16	-18	876	2.70
Orbital Frontal Cortex	L	-44	24	-18	861	3.20
Orbital Frontal Cortex	R	46	22	-18	845	3.20

Supplementary Figure 1. ROI VBM analysis showing areas of significant grey matter intensity decrease for bvFTD and PD, in comparison to Controls. Results corrected for multiple comparisons (FWE) at $p < .05$, overlaid on the MNI standard brain ($t > 2.50$).

A3.



Chapter 3 – Publication III

Supplementary Table 1. Region of interest Voxel-based morphometry (VBM) results showing regions of significant grey matter intensity decrease for the PD group in comparison to Controls. Results corrected for multiple comparisons (FWE) at $p < .05$.

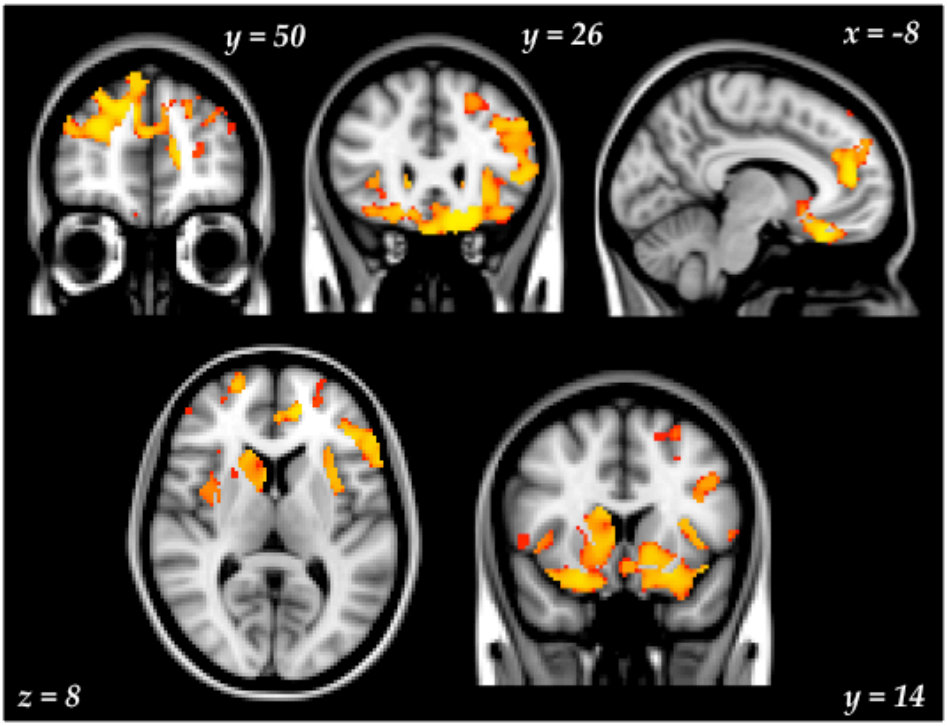
Regions	***Hemisphere***	***MNI coordinates***			***Number of voxels***	***T score***
	(L/R/B)	***X***	***Y***	***Z***		
PD vs. Controls						
Frontal orbital cortex; Inferior frontal gyrus	R	22	30	-22	939	2.05
Frontal medial/Subcallosal cortices; Left Nucleus accumbens	B	-6	26	-18	808	
Inferior frontal gyrus	L	-54	32	-2	322	

A4. Chapter 4 – Publication IV

Supplementary Table 1. Region of interest Voxel-based morphometry results showing significant grey matter intensity decrease within the fronto-subcortical mask, for the bvFTD group in comparison to controls. Results corrected for multiple comparisons (FWE) at $p < .05$, at a cluster threshold of greater than 20 contiguous voxels.

Regions	*Hemisphere (L/R/B)*	*MNI coordinates for voxel of maximal intensity*			*Number of voxels*	*T value*
		X	*Y*	*Z*		
Frontal pole; frontal orbital cortex; subcallosal cortex; extending to bilateral amygdalae; paracingulate and anterior cingulate cortices; left inferior frontal and middle frontal gyri; bilateral mid-anterior insula cortices; bilateral accumbens and putamen, right caudate, left ventral caudate.	B	-20	28	-16	9954	2.07
Superior frontal gyrus	L	-24	-6	56	174	
Posterior insula	R	38	-4	-14	29	
Inferior frontal gyrus	R	52	12	0	22	

Supplementary Figure 1. Region of interest VBM results showing areas of significant grey matter intensity decrease within the fronto-subcortical mask for bvFTD patients relative to controls. All results corrected for multiple comparisons (FWE) at $p < .05$ and at a cluster threshold of greater than 20 contiguous voxels.



APPENDIX B
Publications related to Thesis

B1. "Beyond and below the cortex: the contribution of striatal dysfunction to cognition and behaviour in neurodegeneration"

Cognitive neurology

REVIEW

Beyond and below the cortex: the contribution of striatal dysfunction to cognition and behaviour in neurodegeneration

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ABSTRACT
Investigations of cognitive and behavioural changes in neurodegeneration have been mostly focussed on how cortical changes can explain these symptoms. In the proposed review, we will argue that the striatum has been overlooked as a critical nexus in understanding the generation of such symptoms. Although the striatum is historically more associated with motor dysfunction, there is increasing evidence from functional neuroimaging studies in the healthy that striatal regions modulate behaviour and cognition. This should not be surprising, as the striatum has strong anatomical connections to many cortical regions including the frontal, temporal and insula lobes, as well as some subcortical regions (amygdala, hippocampus). To date, however, it is largely unclear to what extent striatal regions are affected in many neurodegenerative conditions—and if so, how striatal dysfunction can potentially influence cognition and behaviour. The proposed review will examine the existing evidence of striatal changes across selected neurodegenerative conditions (Parkinson's disease, progressive supranuclear palsy, Huntington's disease, motor neuron disease, frontotemporal dementia and Alzheimer's disease), and will document their link with the cognitive and behavioural impairments observed. Thus, by reviewing the varying degrees of cortical and striatal changes in these conditions, we can start outlining the contributions of the striatal nexus to cognitive and behavioural symptoms. In turn, this knowledge will inform future studies investigating corticostriatal networks and also diagnostic strategies, disease management and future therapeutics of neurodegenerative conditions.

INTRODUCTION

Impairment of the striatum (caudate, putamen, nucleus accumbens) in neurodegenerative conditions has long been recognised. Striatal dysfunction in motor disorders, including Parkinson's disease (PD) and Huntington's disease (HD), has uncovered the crucial role this region has in the organisation and production of voluntary movements. However, these same disorders can also present with substantial behavioural and cognitive symptoms, especially in volition, executive dysfunction and reward processing.

The role of the striatum in a diverse range of processes is supported by its anatomical positioning as a central hub in several cortico-subcortical loops, projecting to, and receiving input from many cortical areas. Figure 1, adapted from Alexander and colleagues,[1] shows a simplified version of the main corticostriatal connections (please note that interconnectivity between striatal regions is not taken into account in the figure). There is a high degree of spatial topography in the organisation of the striatum, which corresponds to functional divisions that follow a dorsal-ventral gradient whereby the dorsolateral region of the striatum (ie, putamen) is engaged in sensorimotor functions, the dorsomedial striatum (ie, caudate) in associative functions, and the ventral striatum (ie, nucleus accumbens) in motivational and emotional function.[2 3] In terms of connectivity, the putamen is primarily connected to sensory and motor cortices, the caudate with frontal and parietal association cortices, and the nucleus accumbens has substantial connections to limbic structures (amygdala, hippocampus) as well as the ventromedial prefrontal cortex[4] (figure 1). These extensive cortico-subcortical loops explain why a constellation of motor, cognitive and behavioural symptoms can result from striatal dysfunction.

Functional brain imaging in healthy subjects has highlighted the role of the striatum in complex cognitive functions, including working memory, abstract rule learning and attentional control.[5] Human and animal literature further confirm that the dorsal striatum has a role in forming action-outcome associations and in action selection, which contribute to high-level cognition and goal-directed behaviour.[6] The striatum has also been implicated in reward-related cognition, with human imaging studies associating the ventral striatum with representation of subjective value, reward expectation and reward magnitude.[7 8] Animal lesion and neuronal recording studies indicate that key processes underpinning reward-related cognition, namely prediction error, incentive salience and valence coding, are directly associated with the ventral striatum, and are critical for reward learning, attaching motivational values to stimuli and processing its hedonic value. Further, lesions in discrete ventral striatal regions have been associated with various forms of behavioural dysregulation (eg, impulsivity).[9] Animal models of anhedonia, motivational deficits and anxiety also confirm a crucial role for the striatum (particularly ventral striatum) in these processes.[10] Nevertheless, despite these robust associations between the striatum and a range of cognitive and psychiatric processes, the extent to which the striatum plays a causal or modulatory role, and by what mechanisms, is still debated.[5]

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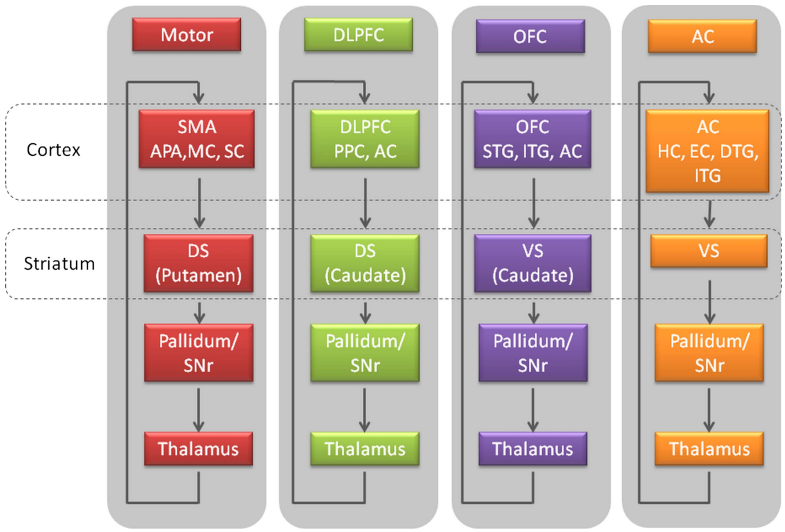

Figure 1 Simplified representation of basal ganglia-thalamocortical circuits, adapted from Alexander *et al*.[1] Each circuit engages specific regions of the cerebral cortex and striatum. Note, the figure does not take into account interconnectivity between striatal regions. AC, anterior cingulate area; APA, arcuate premotor area; DS, dorsal striatum; DLPFC, dorsolateral prefrontal cortex; EC, entorhinal cortex; HC, hippocampal cortex; ITG, inferior temporal gyrus; OFC, orbitofrontal cortex; MC, motor cortex; PPC, posterior parietal cortex; SC, somatosensory cortex; SMA, supplementary motor area; SNr, substantia nigra; STG, superior temporal gyrus; VS, ventral striatum.

The role of the striatum in non-motor symptoms has clear relevance for neurodegenerative conditions, with patients manifesting a variety of symptoms among which the diagnosis of behavioural/cognitive changes can be particularly challenging. Increased understanding of how striatal dysfunction gives rise to motor symptoms in neurodegenerative diseases has led to vast improvements in diagnostic techniques and in pharmacological and surgical therapies; however, the same cannot be said for the cognitive and behavioural symptoms in neurodegenerative disease where the focus has typically been on how cortical dysfunction modulates these impairments. Many neurodegenerative diseases present with both cortical and striatal changes, and thus a delineation of these regions and their contribution to the generation of behavioural/cognitive deficits would improve diagnostic procedures and also lead to disease-modifying therapies.

The current review aims to address this issue by reviewing striatal integrity and its relation to behavioural/cognitive symptoms in some of the most common neurodegenerative conditions. We start the review with conditions that have well described striatal damage: PD, progressive supranuclear palsy (PSP) and HD, before reviewing three other major neurodegenerative conditions: motor neurone disease, frontotemporal dementia (FTD) and Alzheimer's disease (AD), for which striatal damage has been less investigated to date. We have focussed on the early and even preclinical stages across the diseases to avoid findings being confounded by disease progression effects. Further, of the synucleinopathies with known cognitive/behavioural deficits, we have limited our discussion to PD as there has been the most extensive research into how these symptoms reflect striatal dysfunction (for these reasons we have not included sections on PD dementia, dementia with Lewy bodies or multiple-system atrophy). We deliberately excluded corticobasal degeneration (CBD) in the review, because of its current diagnostic uncertainty[11]; thus, any CBD studies are prone to the inclusion of an admixture of pathologies and behavioural syndromes, making it difficult to delineate specific striatal dysfunction in this condition.

DISORDERS WITH WELL DESCRIBED STRIATAL DYSFUNCTION

Parkinson's disease

PD, which is characterised by hallmark motor disturbances (bradykinesia, tremor, rigidity and postural instability), has its primary neuropathology within the nigrostriatal pathway. The resultant effect is severe dopamine depletion in the dorsal striatum, while the ventral striatum is relatively preserved in the early stages of the disease.[12] With disease progression, more extensive distribution of pathology (especially Lewy body pathology) is found throughout the brainstem and neocortex. On a macroscopic level, putaminal volumes have been shown to be significantly reduced in early PD,[13] and further atrophy of both caudate and putamen occurs with progression of the disease,[14] however, volumetric reductions in the striatum have not been consistently documented in de novo PD.[15]

Cognitive decline is common in early PD, with mild impairments evident in 15–20% of de novo, untreated patients.[16] Decline in executive abilities represents the dominant pattern of cognitive impairment in non-demented PD and dysfunction in the dorsal striatum (particularly the dorsolateral caudate head) has been directly linked to this dysexecutive profile, given its strong connectivity with the dorsolateral prefrontal cortex.[17] Imaging studies in very early PD suggest a dopaminergic basis to these deficits, with under-recruitment of the dorsal striatum apparent during aspects of working memory, set shifting and planning.[18] Dopamine replacement therapy can alleviate executive deficits arising from dysfunction in the associative loop[19] and normalise functional connectivity in these regions.[20] Nevertheless, cognitive impairment in non-demented PD is heterogeneous, and studies have identified other impairments, namely memory or visuospatial dysfunction, as being the most prominent initial deficits.[21] Widespread deficits may suggest more diffuse distribution of striatal and cortical Lewy bodies and an additional burden of non-PD pathology (eg, amyloid); indeed, striatal amyloid has been documented in PD dementia[15] and even more consistently in Lewy body dementia.[22 23] In their in vivo study Edison *et al*[23] found non-demented PD patients to have mildly increased amyloid load in the striatum

but not in the cortical regions, suggesting that the striatum may be an early site of amyloid deposition in synucleinopathies—with amyloid burden recently being linked to accelerated cognitive decline over time in non-demented PD.[24]

Damage to the dorsal striatum impairs the ability to form habits, resulting in an over-reliance on slower and more effortful goal-directed modes of action at the expense of the faster and less demanding parallel processing involved in automatic behaviours.[3] PD patients have difficulty expressing automatic actions from the early stages of the disease, affecting habitual movements such as gait, arm-swing and facial expression. Additional impairment in automatic processes ensues when patients are required to simultaneously perform a concurrent cognitive or motor task.[25] Difficulty managing cognitive load and an over-reliance on goal-directed behaviour impedes multitasking and interferes with patient's ability to carry out everyday cognitive and motor tasks. Improving this via cognitive training in mild patients represents an important avenue of non-pharmacological treatment in PD.

A different set of cognitive functions are mediated by the ventral striatum, including reward-related learning, response inhibition and value-based decision making. Given the relative preservation of ventral striatum integrity in the early stages of PD, it is unsurprising to find that de novo patients perform similarly to controls on reward-based decision making and reversal learning tasks.[26] However, impairment in these ventrally mediated functions can arise with the progression of the disease and with dopamine replacement therapy. In particular, dopamine replacement therapy—titrated to replenish severely depleted dopamine levels in the dorsal striatum and improve motor symptoms—can cause impaired reversal learning and reward-based decision making in PD patients.[27] Clinically, dopamine replacement therapy can lead to impulse control disorders (ICDs) in a portion of patients. ICDs include pathological gambling, hyper sexuality, compulsive shopping and binge eating, and can be considered to reflect deficient reward-valuation and impulse control due to dysfunction in the ventral striatum.

PD is associated with a range of behavioural/neuropsychiatric disturbances, which can even predate motor symptoms. Apathy, depression and anxiety are most common among these disturbances, and clinically significant symptoms are present in over 25% of de novo, untreated patients.[28] Prevalence rates of up to 70% of patients experiencing these symptoms during the course of the disease have been reported, with apathy having the highest incidence.[29] The early manifestation of these neuropsychiatric symptoms suggests a role for striatal dopamine dysfunction, and some improvement can result from dopamine therapy. However, it is likely that early and preclinical affective disturbances result from a complex interaction of dopaminergic, serotonergic and noradrenergic imbalances in the striatum and brain stem, and further studies with de novo patients may shed more light on this. There is some clearer evidence for dissociable roles of the striatum in mild and more advanced PD. In mild PD, apathy symptoms correlate with reduced binding of dopamine in the ventral striatum.[30] Depression and anxiety have been related to reduced anterior putamen dopamine uptake in mild PD,[31] and more extensive dopaminergic dysfunction throughout the dorsal striatum in advanced PD.[32]

Progressive supranuclear palsy

PSP shares some motor features with PD (eg, bradykinesia, rigidity), although PSP is associated with more pronounced postural instability, eye movement abnormalities and pseudobulbar features, with its pathological hallmark including accumulation of tau protein and neuropil threads throughout the basal ganglia and brainstem.[33 34] Motor abnormalities are usually the presenting feature in PSP, though cognitive impairment (most prominently executive dysfunction), cognitive slowing and behavioural change often emerge early in the disease course.[35] Frontal neuropsychiatric features are prevalent, in particular apathy and disinhibition which have a higher incidence and greater severity than in PD.[36] When present, such neuropsychiatric symptoms can be as severe as those seen in FTD.[37]

In vivo volumetric studies have consistently shown dorsal striatum atrophy, with significantly smaller striatal volumes found in PSP patients (ie, putaminal volumes 10% smaller and caudate volumes 17% smaller than in age-matched controls).[38] Striatal pathology occurs in concert with more significant atrophy of the thalamus and midbrain—regions that exert major regulatory effects on movement, cognition and behaviour process via projections through the caudate. Importantly, PSP patients also exhibit some degree of cortical atrophy, with a predilection for prefrontal areas.[39–41] Both cortical and subcortical grey matter atrophy, as well as degeneration of the connective white matter tracts, is already apparent in mild patients.[42] A recent resting state study complements these findings by showing significant connectivity disruptions within large-scale networks involving the brainstem, basal ganglia and cortex.[43]

Studies exploring regional atropy correlates of cognitive/behavioural dysfunction in PSP are comparatively limited and have been inconclusive with respect to whether subcortical or frontal pathology are driving these deficits. While evidence has linked basal ganglia dysfunction to executive deficits in this patient group,[44] there is also evidence implicating prefrontal atrophy.[40] More interestingly, some behavioural symptoms, in particular apathy, have been shown to correlate with volume loss in both frontal and striatal regions (primarily posterior frontal lobe and putamen).[45] Still, given the scarcity of these investigations these findings require future corroboration.

Huntington's disease

Similar to PD, research into HD has been strongly focussed on striatal damage. This is not surprising, as caudate and putamen changes are one of the hallmarks of HD,[46] with preferential involvement of the basal ganglia 'indirect' pathway causing the early prominence of choeric movements.[47] Nevertheless, other cortical and subcortical regions can also be affected in HD, leading to an overall brain weight loss of greater than 40% at the end of the disease. Microscopic pathology usually begins in the dorsal caudate head and progresses to the ventrolateral striatum, and is characterised by neuronal intranuclear inclusions and severe loss of projection spine neurons.[46]

In vivo neuroimaging reveals substantial macroscopic changes, with caudate and putamen both showing marked volume loss over time,[48–50] and volume loss being related to age of onset and length of trinucleotide (CAG) repeat.[51] Positron emission tomography (PET) and MRI findings indicate that caudate loss is already apparent in presymptomatic HD gene carriers[48] and is thus considered to be an excellent anatomical outcome measure for HD clinical trials. In terms of cortical changes, premotor and sensorimotor cortices are particularly affected and longer disease duration has been associated with more widespread cortical changes.[49 52] These findings suggest that corticostriatal circuits are systematically affected in HD.

Indeed, diffusion tensor imaging investigating white matter integrity in HD has identified widespread changes in the cortex and striatum, even in presymptomatic cases.[53] Recent white matter tractography investigation of specific corticostriatal

motor pathways corroborate this notion by showing that caudate and putamen white matter connections to motor and sensorimotor cortical regions are most severely affected.[54] Further functional neuroimaging findings have shown corticostriatal changes, with functional connectivity between caudate and motor cortex being particularly affected from the prodromal stages.[55]

The above findings suggest that the motor system is mostly affected in HD, however, cognitive and mood/behavioural changes are well recognised, and deficits across the three domains represent the classic triad of HD symptomatology. There is significant variability in the time course of when symptoms emerge, with some patients eluding mood/cognitive symptoms until well into the course of their motor dysfunction and others manifesting these symptoms at onset or preclinically.

Early and preclinical emergence of cognitive and behavioural disturbance in HD suggests striatal dysfunction plays a critical role, as this is the initial primary site of pathology. Executive function deficits have been consistently described in early and preclinical HD[56] and have been linked to striatal damage, in particular measures of planning, attention and rule learning have been strongly associated with caudate atrophy.[57] Still, cortical atrophy in combination with striatal atrophy has also been linked to cognitive symptoms in HD.[58] Similarly, corticosubcortical white matter tract changes have been associated with those deficits.[59] Finally, functional imaging studies of cognitive changes in HD have consistently found cortical and striatal activation alterations compared with healthy controls in relation to cognitive load, planning, attention[60] and more specifically, ventral striatal regions being related to reward processes.[61] Of particular relevance are studies that show alterations of cortical and striatal functional connectivity between HD patients and healthy controls,[60] indicating that cortical and striatal regions, and also their interaction, are explicitly affected during these cognitive processes.

HD is associated with an array of behavioural/neuropsychiatric disturbances. These include apathy, anxiety, irritability, aggression or disinhibition and are experienced, to varying degrees, by nearly all patients.[62] The natural progression of neuropsychiatric symptoms in HD is not well known and likely reflects interplay between disease-specific neurodegeneration, genetic and reactive factors. Subtle affective and behavioural disturbances are reported in presymptomatic individuals, even decades prior to diagnosis. Depression is common in this preclinical group[63] in addition to apathy and disinhibition which have been associated with smaller striatal volume in presymptomatic individuals.[64] Interestingly, although a variety of neuropsychiatric disturbances can emerge within the course of HD, they do not typically show stepwise evolution with disease severity (by contrast with cognitive symptoms, which tend to worsen with disease progression).[47] One exception is the progression of apathy, which is strongly related to disease stage and motor symptom severity[65]; this is presumed to reflect progressive impairment of the more ventral areas as neuronal loss in the striatum progresses along a dorsal-ventral gradient.

DISORDERS WITH LESS DESCRIBED STRIATAL DYSFUNCTION

Motor neuron disease

By contrast with PD, PSP and HD, motor neuron disease (MND), also referred to as amyotrophic lateral sclerosis (ALS), had been classically regarded as a progressive motor systems disorder causing muscle weakness.[66] It is now increasingly recognised that the central nervous system can be also affected in MND patients even at an early disease stage, and that those patients presenting with more pronounced cortical changes can exhibit cognitive impairments as well.[67] The combination of motor and cognitive symptoms in MND suggests that striatal regions might also be affected in this disorder, in particular in those patients with additional marked behavioural/cognitive impairment (MND with FTD symptoms: MND-FTD). Additionally, striatal dysfunction has been shown in a rare levodopa-responsive PD-ALS variant (Brait–Fahn–Schwartz disease),[68 69] and can be associated with a dementia syndrome, though not necessarily one that is characteristic of FTD,[70] suggesting that this PD-ALS variant may represent a distinct nosological entity.

Neuropathological investigations have commonly observed microscopic striatal changes in MND patients with extrapyramidal features.[71] In particular, MND-FTD patients have been regularly reported to have striatal pathologic changes.[72 73] Accordingly, those striatal changes consisted of ubiquitin inclusions in MND-FTD, and also moderate to severe cell loss and gliosis.[72] Interestingly, these pathological changes were much less severe or even absent in MND patients without extrapyramidal symptoms.[73]

Similarly, on a macroscopic level, there has been little evidence of striatal changes in MND without extrapyramidal changes,[74] but white matter intensity changes in the caudate have been identified in MND patients with cognitive FTD-like symptoms.[75] These convergent microscopic and macroscopic striatal findings in MND suggest that the striatum is intact in MND patients without extrapyramidal changes. By contrast, MND patients presenting with extrapyramidal features and FTD-like behavioural/cognitive symptoms show striatal changes, although it is currently unclear which parts of the striatum are affected. Still, few studies have investigated the striatum in MND and, thus, further investigations are needed, in particular those contrasting MND patients with and without behavioural/cognitive symptoms directly.

Frontotemporal dementia

FTD has the most significant behavioural and cognitive changes of all the reviewed neurodegenerative conditions. Three clinical syndromes of FTD exist: behavioural variant FTD (bvFTD), primary progressive aphasia—semantic variant (PPA-sem) and primary progressive aphasia—non-fluent variant (PPA-nfv), all with varying degrees of frontal, temporal and insula atrophy. This cortical atrophy has long been identified and associated with prototypical cognitive and behavioural symptoms in FTD. Specifically, prefrontal cortex atrophy in bvFTD has been consistently associated with severe behavioural changes, and the memory and language deficits in FTD have been mostly associated with frontotemporal-insula atrophy.[76]

Only recently has the focus in FTD shifted towards the striatum, which neuropathological and perfusion imaging studies have shown to be affected significantly and from the early disease stages, particularly in the bvFTD subtype.[77] This was further corroborated by structural neuroimaging studies that identified striatal atrophy in FTD, again with the most severe changes seen in bvFTD.[78 79] In both bvFTD and PPA-nfv, atrophy has been shown in the caudate and putamen, as well as nucleus accumbens, with putaminal atrophy in bvFTD being more right lateralised and less severe than caudate atrophy.[78 79] By contrast, in PPA-sem the caudate nucleus appears to be relatively spared, while there have been inconsistent results for putamen integrity.[78–80] These structural findings are

complimented by resting-state fMRI findings that show striatal dysfunction in FTD.[81]

Among studies that have directly investigated the subcortical correlates of cognitive and behavioural functions in FTD, striatal atrophy has been shown to covary with poorer general cognition,[80] disinhibition[82] and binge eating.[83] These findings are further supported by a case study of a patient with striatal infarcts who developed behavioural and cognitive changes mimicking bvFTD.[84] Interestingly, there is an apparent lateralisation of striatal contributions to behavioural/cognitive disturbances in FTD, with the right striatum being more often linked with behavioural disturbances, including eating disorders, apathy, reduced empathy and aberrant motor behaviour.[82 85] By contrast, the left striatum appears to have greater involvement in cognitive functions and has been linked to executive, language and psychomotor dysfunction in FTD.[79]

Overall, there is growing evidence that FTD behavioural and cognitive symptomatology is highly related to striatal impairments. Still, how the cortical and striatal dysfunctions interact to cause the symptoms remains to be explored.

Alzheimer's disease

Finally, AD is clinically characterised by a progressive decline of cognitive functions, among which episodic memory impairment is typically the earliest and most prominent. Structural cortical changes of the medial temporal lobe and hippocampus are characteristically observed, as well as hypoperfusion or hypometabolism in temporoparietal areas.[86]

Voxel-based morphometry studies investigating striatal integrity in AD patients reported either no change[80] or only subtle atrophy of the caudate in more severe cases,[87] which is taken to be proportional to the whole brain atrophy seen in the later stages of the disease. This is further confirmed by neuropathological findings that show a moderate to severe presence of amyloid deposition in the striatum at late-stage AD.[88] More importantly, recent neuropathological findings suggest that microstructural damage in the striatum can occur independently of macrostructural changes during the late stages of AD.[89] Studies quantifying caudate volume loss in AD compared with age-matched control have found reductions of 6–7%, with prodromal AD patients in the form of mild cognitive impairment only showing 3.5% reduction.[90] By comparison, bvFTD patients have been reported to show a 25% caudate volume reduction compared with age-matched controls.[91] Similarly, the nucleus accumbens and putamen appeared to be relatively spared in AD,[78 80] although some studies have reported putaminal volume loss, in particular for the left putamen.[92]

There have been few investigations into whether these relatively subtle striatal changes contribute to cognitive or behavioural symptoms in AD. Selected findings show that overall general cognitive functioning covaries with caudate[90] and putamen[92] volumes. An important direction for future research would be to explore striatal dysfunction in the atypically presenting frontal variant of AD. Given the overlap in cognitive/behavioural symptoms across frontal-variant AD and bvFTD, it may be the case that there is also more significant striatal dysfunction, which would provide further insight into the pathophysiology of this atypical AD variant.

SUMMARY

The above review clearly shows that striatal dysfunction is a crucial factor in the generation of cognitive and behavioural symptoms in neurodegenerative disease. In the reviewed conditions, striatal damage has been most strongly linked with executive dysfunction, impaired reward/punishment processing, and affective and motivational disturbances, with PD, PSP, HD and FTD showing structural and functional changes throughout the course of disease, while in MND and AD striatal involvement appears to depend on extrapyramidal signs and disease stage, respectively (table 1). Nevertheless, review of the literature to date highlights that there is still much scope to better delineate cortical versus striatal contributions to cognitive and behavioural symptoms via a more targeted assessment approach. In the following section, we propose future directions to address this issue and identify areas where further delineation of these contributions would have important implications for improving diagnostic and therapeutic strategies.

In terms of assessing striatal function, cognitive tests that tap executive abilities, such as attention, working memory and set shifting are already in routine clinical usage as part of brief screening tools (eg, The Montreal Cognitive Assessment[93]; Addenbroke's Cognitive Examination—Revised[94]), however, though the dorsal striatum is implicated in these processes, existing screening measures may lack the sensitivity to detect early striatal dysfunction. A possible candidate may be cognitive tests that include more demanding measures of working memory, as caudate activation has been uniquely found during the *manipulation* phase in working memory tasks[95]—a finding that fits well

Table 1 Striatal dysfunction and the associated cognitive and behavioural impairments across the neurodegenerative conditions at diagnosis

	Striatal dysfunction			
	DS	VS	Cognitive symptoms	Behavioural symptoms
PD	++	+	Working memory, planning, set-shifting, cognitive load	VS—apathy; DS—depression/anxiety
PSP	+	+	Executive dysfunction, cognitive slowing	Apathy, disinhibition
HD	+++	++	Planning, attention, rule learning, reward processing	VS—apathy; Depression, anxiety, disinhibition, irritability
MND				
+EPS	+	+	FTD-like cognitive syndrome	FTD-like behavioural syndrome
−EPS	–	–	–	–
FTD	++	++	Executive, language and psychomotor dysfunction	Apathy, binge eating, reduced empathy, aberrant motor behaviours
AD	–	–	–	–

Note: Striatal dysfunction incorporates both atrophic and functionally mediated changes; see text for further detail of the relative contributions of these across the different conditions.
– Not impaired + Mild ++ Moderate +++ Severe.
AD, Alzheimer's disease; DS, dorsal striatum; EPS, extrapyramidal symptoms; FTD, frontotemporal dementia; HD, Huntington's disease; PD, Parkinson's disease; PSP, progressive supranuclear palsy; VS, ventral striatum.

with computational models, whereby the balance of excitatory and inhibitory striatal activity triggers updates in working memory representations in the prefrontal cortex.[96]

By contrast, few clinical screening tools incorporate measures of ventromedial prefrontal cortex/ventral striatum cognitive functions, and mostly these are assessed by very involved gambling, probabilistic learning or reward-valuation tasks, which are not always feasible in a clinical setting. As such, assessment and monitoring of these functions does not often form part of routine clinical practice. A useful starting point would be to adapt these decision-making/reward-valuation tasks into briefer screening tools. A further strategy is to use established executive measures, and instead of focussing on overall achievement scores, focus on error scores, which have been found to be sensitive to inhibitory and self-monitoring processes that relate to ventral striatum function.[97]

Contrasting across diseases may be a valuable way of exploring the interaction between striatal and cortical contributions to symptoms. In this regard, contrasting PD and FTD patients could be of great interest, as early PD patients show mainly striatal dysfunction, while FTD patients, in particular bvFTD, show both cortical and striatal changes. Behavioural and cognitive symptoms in FTD have been mostly ascribed to cortical changes, but contrasts with PD patients 'on' and 'off' dopamine replacement would offer insight into dorsal and ventral striatal contributions to those symptoms. To our knowledge, only one study to date has taken such an approach and shown that FTD and PD share cortical and striatal contributions to inhibitory dysfunction, with FTD having more severe symptoms and significantly more ventromedial prefrontal cortex atrophy associated with these symptoms.[98] These findings suggest that ventral striatal regions make a contribution to inhibitory dysfunction in both diseases, but that the prefrontal cortex changes are predominant in causing the disinhibition. Delineation of those striatal and cortical contributions seems, therefore, very informative, as striatal damage might increase or even mimic cortical symptoms.

Regarding neuropsychiatric symptoms, apathy is consistently related to striatal dysfunction in the reviewed conditions. Although apathy is primarily associated with ventral striatum dysfunction, that is not always clear as it can be a prominent feature early in the disease courses of PD, HD and PSP when the dorsal striatum is typically more affected. Similarly, other symptoms, such as depression and anxiety, can emerge at varying time courses in the reviewed conditions and have been associated with both ventral and dorsal striatum dysfunction. In this respect, it might be useful if future studies incorporated the framework suggested by Levy and Dubois[99] to describe apathy. They suggest three distinct manifestations of apathy: (1) an emotional/affective type related to disruption of the ventral striatum-orbitofrontal cortex (limbic territory) causing deficits in the ability to link emotional and affective signals with the required ongoing behaviour; (2) a cognitive type, related to disruptions to dorsal striatum-dorsolateral prefrontal cortex (associative territory), whereby there is a deficit in elaboration/planning of actions necessary for ongoing or forthcoming behaviour and finally (3) an autoactivation deficit relating to more diffuse prefrontal and striatal dysfunction, causing marked difficulties in self-activating thoughts and actions. Such a framework may explain why apathy can originate from different regions of striatal dysfunction, and it offers testable predictions for possible qualitative differences in the types of apathy exhibited in neurodegenerative conditions. Such differences could be probed by more targeted measures, such as exploring other symptoms that correlate with the types of apathy (eg, would expect greater executive dysfunction to accompany cognitively driven apathy). By the same methods of validation, it could be further explored whether anxiety and depressive features are mediated by discrete emotion, affective, or cognitive processes.

There are several areas where diagnostic strategies could be improved by applying more sensitive striatal measures and by better delineating cortical versus striatal contributions to symptoms. Tasks that are sensitive and specific to dorsal striatum function could be extremely useful as outcome measures in clinical trials, for example, in HD where traditional measures employed have lacked the sensitivity to tap striatal dysfunction in those prodromal patients who are now identifiable by genetic testing and available for clinical trials.[56 97] Specific ventral striatum tools may have important utility in improving patient management in PD, where dopaminergic therapies can cause ventral striatal dysfunction with associated behavioural/cognitive changes. More sensitive screening tools that could detect ventral striatal pathology may better inform clinicians as to which patients may be more susceptible to dopaminergic overdose with the initiation of treatment.

By contrast with PD and HD, the initial diagnosis of FTD is still challenging, and to date only a neuropathological FTD diagnosis is seen as definite. Incorrect diagnosis in FTD is not uncommon, and sensitive and specific biomarkers are urgently needed. This is especially the case for bvFTD patients who can present with symptoms that overlap with AD, such as amnesia.[100] Recent research has endeavoured to find more specific atrophy and behavioural profiles for bvFTD, with particularly ventromedial prefrontal cortex dysfunction emerging as a prominent candidate,[101] although a small percentage of atypical AD patients can also show deficits in this brain region.[102] The above review highlights that the striatum is virtually intact in AD while it is impaired in FTD. Substantial striatal changes in FTD have only been recently described, which is likely due to prevailing cortical atrophy masking the subcortical changes seen in these patients, and this raises the question as to whether striatal integrity could be employed as a diagnostic marker in FTD. In combination with the well-known ventromedial prefrontal cortex atrophy, striatal changes could potentially distinguish bvFTD and AD to a very high degree. Similarly, tasks or screening tests tapping into striatal dysfunction in FTD would be important. One obvious task type would be probabilistic learning, and a recent study highlights that FTD patients are impaired on this measure, and that the performance is dependent on prefrontal and striatal integrity.[103]

Striatal integrity might also be an important diagnostic factor in the classification of MND-FTD patients. The reviewed studies suggest that MND patients with FTD symptoms can show significant striatal changes, while in MND patients without extrapyramidal symptoms, the striatum appears virtually intact. This finding is of great diagnostic potential, as currently a diagnosis of MND-FTD is based mostly on clinical and neuropsychological assessment, while the neural correlates of this group are still being established.[104] Thus, identification of striatal atrophy may be a promising avenue to identify MND-FTD patients even very early on in the disease course. Again, striatal screening tests would be vital for the diagnostic procedures of this patient group as well.

CONCLUSION

Taken together, there is increasing evidence that the striatum is affected across many neurodegenerative conditions, even if they do not present with motor symptoms. In concert with animal

and healthy neuroimaging findings, this supports that the striatum, in conjunction with the cortex, plays an important role in behavioural regulation and cognition. There is an urgent need to further delineate the functions of striatum and cortical regions to determine the genesis of behavioural and cognitive symptoms. In turn, this will allow the development of novel striatal screening tests, which will increase diagnostic accuracy, as well as informing disease modifying therapies in many neurodegenerative conditions.

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REVIEW ARTICLE

Inhibitory Dysfunction in Frontotemporal Dementia
A Review

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Abstract: Failure of inhibitory control is an early and consistent feature in patients suffering from frontotemporal dementia (FTD). This appears because of their pervasive ventromedial prefrontal atrophy—particularly in the orbitofrontal cortex—which has been linked to inhibitory dysfunction in studies on human and monkey lesions. However, the range of measures currently available to assess inhibitory processes in FTD is limited, and, as such, inhibitory dysfunction in FTD remains relatively underexplored. Subjective caregiver questionnaires are useful for defining disinhibition as it manifests behaviorally; however, endorsement of symptoms can vary largely across patients as it is contingent on the perceptiveness of the caregiver. The few objective neuropsychological tasks that tap directly into inhibitory functioning have potential, although they mostly rely on intact language and semantics, which can confound performance in FTD patients. An emergent possibility is to explore inhibitory functioning in FTD through nonverbal experimental tasks. Adaptation of such experimental tasks into clinical tools is a promising avenue for exploring one of the earliest behavioral features in FTD patients and concomitantly tap into their prevalent orbitofrontal cortex dysfunction. We suggest that improved characterization of early inhibitory dysfunction may facilitate more accurate diagnosis of FTD.

Key Words: inhibitory dysfunction, disinhibition, frontotemporal dementia, Alzheimer disease, orbitofrontal cortex

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FRONTOTEMPORAL DEMENTIA

Frontotemporal dementia (FTD) refers to a spectrum of neurodegenerative diseases with intraneuronal protein inclusions (tau, TDP43, or FUS) associated with focal frontal and temporal atrophy. The onset is insidious and the course is progressive, with the median survival from symptom onset being approximately 4 to 6 years.[1,2] Three clinical subtypes of FTD have been recognized: 2 language variants [progressive nonfluent aphasia (PNFA) and semantic dementia (SD)] and a behavioral variant [behavioral variant FTD (bvFTD)]. The diagnostic criteria for each FTD subtype were recently revised.[3,4]

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In this review, the above nomenclature is used preferentially, as the division of FTD into PNFA, SD, and bvFTD is now well recognized. However, many studies (particularly earlier in the literature) have either not differentiated between the FTD subtypes or reserved the label of FTD only for behavioral variant patients. For the purposes of this review, the term FTD is used when referring to the spectrum as a whole.

On an anatomic level, the clinical distinctions are determined by the extent and location of pathology rather than by the histologic subtype. PNFA is associated with a prevalence of pathology in the left anterior insular, the inferior frontal, and the perisylvian regions.[5,6] SD is characterized by pathology of the anterior and inferior temporal regions, which is usually more prominent on the left side.[7,8] In bvFTD, the mesial and orbitofrontal cortices appear to be the initial and most consistent regions affected, with variable and late involvement of the dorsolateral prefrontal cortices.[7,9,10] However, these categorical distinctions underemphasize the overlap between the FTD subtypes in terms of both clinical features and the locus of pathology.

Patients with PNFA manifest faltering, hesitant, and distorted speech output. Articulation is disturbed and speech is marked by word-finding pauses. Single-word comprehension is preserved, despite difficulty with more complex syntax.[11–13] By contrast, SD patients present with a loss of memory for words and show severe anomia, with impaired comprehension of word meaning and global loss of conceptual knowledge.[11,12] Behavioral changes, which mirror those found in bvFTD, are also common in SD.

Patients with bvFTD present with insidious and pervasive behavioral dysfunction, which poses particular difficulty for caregivers in terms of behavior management and in readjusting to the progressive erosion of the patient's personality. Hallmark features include disinhibition, apathy, emotional blunting, distractibility, motor and verbal stereotypies, disturbed satiety, and impaired insight, all of which contribute to a general decline in personal and social conduct.[4,12,14]

The linguistic deficits in SD and PNFA have been the topic of extensive investigation, resulting in the development of experimentally derived tasks that are in widespread usage.[3] The parallel development of tasks capable of detecting and quantifying cognitive dysfunction in the case of bvFTD has been much more challenging. We argue that this reflects an overreliance on traditional tests of executive function, which tap aspects of frontal lobe function that are not markedly affected early in the course of bvFTD.

Traditional executive tests such as digit span, trail making, Wisconsin card sort, and Tower of London have yielded inconsistent results in FTD. Many patients perform within normal limits in the early and middle stages of the

disease.[15–18] Given the fact that bvFTD patients have extensive damage in the prefrontal cortex—an area that executive function tests purportedly assess—this is somewhat surprising. One explanation is that the traditional tests of executive function recruit abilities such as planning, divided/sustained attention, and working memory, which depend more on the dorsolateral prefrontal cortex than on the mesial and orbital regions affected early in bvFTD. Further consideration relates to heterogeneity across patients. It has become apparent that a subgroup of patients with symptoms of bvFTD fail to progress, despite careful follow-up over many years. Such patients are characterized by normal performance on the tests of executive function and emotional processing[17,19] and by lack of structural and even functional imaging abnormalities.[9,20] Initially termed "nonprogressors," a case of phenocopy is now the preferred sobriquet. An admixture of true pathologic and phenocopy cases in earlier clinical studies may have contributed to some of the inconsistencies in previous reports of executive function in bvFTD, with only true bvFTD patients showing executive dysfunction.

As it stands, the search for more specific and objective diagnostic measures of behavioral dysfunction in FTD is vital in order to substantiate the clinical diagnosis and improve diagnostic accuracy. Despite the fact that disinhibited behavior is seen in nearly 80% of patients at presentation,[21] inhibitory processes have only recently been investigated as being potentially useful in early diagnosis. The orbitofrontal cortex, a key region for the modulation of inhibition, has been identified as one of the earliest locations of pathology in bvFTD.[10] Tasks that reliably assess inhibitory dysfunction may prove to be efficient diagnostic markers and important in the evolution of therapies.

INHIBITORY PROCESSES AND THEIR NEURAL CORRELATES

Humans and animals undoubtedly apply active inhibition to prevent unwanted stimuli, responses, or emotions from interfering with their optimal actions.[22] Inhibition has been conceptualized as the ability to resist both endogenous and exogenous interference, to curb previously activated cognitive contents, and to suppress inappropriate, or irrelevant, responses.[23] From these properties, a 2-fold distinction of inhibitory processes emerges: cognitive and behavioral inhibition.[22,24,25]

Cognitive inhibition has been postulated to account for our ability to suppress irrelevant stimuli so as to enable selective attention. This can occur at an initial perceptual stage of processing before conscious awareness. Termed "unintentional" inhibition by Wilson and Kipp,[26] this involves suppression of internal stimuli, such as unwanted thoughts or automatically activated information, which may interfere with current attentional and working memory operations.[24,27] During the selection of external stimuli and once this information has entered working memory, cognitive control processes prioritize relevant information and inhibit irrelevant information, which occurs at a conscious or "intentional" level.[25,26] Such cognitive control is subserved by a broad prefrontal network that mediates selective attention, performance monitoring, and set shifting[28]; imaging and lesion studies suggest that these functions are predominantly reliant on the dorsolateral prefrontal cortex.[29–31]

In contrast, behavioral inhibition refers to the regulation of social and emotional behaviors in a broad context. Processes fundamental to behavioral inhibition include the ability to adapt one's actions in response to changing environmental cues, to suppress impulses that may be in violation of social norms, and to delay immediate gratification in favor of a larger reward later.[23,27] Damage to the orbitofrontal cortex, particularly in the right hemisphere, disrupts processes fundamental to behavioral inhibition.[32–38] The orbitofrontal cortex contains afferents and efferents to many regions, including the amygdala, the cingulate cortex, the insula/operculum, the hypothalamus, the hippocampus, the striatum, the periaqueductal gray, and the dorsolateral prefrontal cortex.[39] With these extensive connections, the orbitofrontal cortex is ideally placed to integrate and monitor multiple cognitive, sensory, and emotional stimulus values. In monkeys, neurons in the orbitofrontal cortex encode the reward and punishment values of stimuli and respond to changes in these values.[32,40] Similarly, human functional imaging studies have demonstrated that the orbitofrontal cortex encodes positive and negative values for a wide range of reinforcers, including food taste,[41] pain,[42] music,[43] and facial attractiveness.[44] Damage to the orbitofrontal cortex causes impairments in learning stimulus values and in behavioral responses to changing reinforcement contingencies.[34,35] Discrete orbitofrontal damage has been associated with disinhibited, perseverative, and socially inappropriate behaviors,[36,37] reflecting an inability to evaluate cues or reinforcement and to adapt to behavior accordingly.

Turning back to FTD, the majority of bvFTD and many SD patients show orbitofrontal atrophy. Thus, measures that tap the orbitofrontal dysfunction hold great promise for the evaluation of patients with suspected FTD.

INHIBITORY DYSFUNCTION IN FTD

Questionnaire Inhibitory Measures

Deficient behavioral inhibition is a prominent feature in bvFTD and SD patients. Close family members of patients report a range of abnormal behaviors that can be considered to reflect failures of inhibitory control, including embarrassing social interactions, impulsivity with excessive spending, and a new onset of gambling.[45–47]

To capture these symptoms in a systematic and quantitative manner, a number of standardized caregiver questionnaires have been used. For example, the Neuropsychiatric Inventory (NPI),[48] the Cambridge Behavioral Inventory,[49] and the Frontal Systems Behavior Scale (FrSBe)[50] all contain subscales related to disinhibition. Studies using these questionnaires have found that endorsement of behaviors related to disinhibition (in particular, inappropriate social behavior, impulsive motor/verbal actions, and ritualistic routines) was significantly higher in FTD patients compared with Alzheimer disease (AD) patients.[45,46,49,51]

Recently, efforts were made to quantify disinhibited behaviors in FTD through questionnaires and correlate them with an anatomic locus. In a study on 41 bvFTD patients, Peters et al[52] obtained metabolic data using fluorodeoxyglucose positron emission tomography (FDG-PET) and levels of disinhibition based on the NPI. Scores on the NPI disinhibition subscale were significantly correlated with hypometabolism in the posterior orbitofrontal cortex. In another FDG-PET study, Franceschi et al[53] defined

bvFTD patients as either disinhibited or apathetic on the basis of the clinical interpretation of behavioral symptoms and the NPI. A pattern of predominant disinhibition was associated with selective hypometabolism in a network of limbic structures (the orbitofrontal cortex, the anterior cingulate cortex, the hippocampus/amygdala, and the nucleus accumbens) instrumental in the processing and interpretation of emotional stimuli.

Although FDG-PET shows higher sensitivity in detecting dysfunction, a voxel-based morphometry (VBM) of magnetic resonance imaging data has a higher spatial resolution and specificity. In a VBM study, Rosen et al[54] showed that, for bvFTD and SD patients, scores on the NPI disinhibition subscale were associated with atrophy in the right ventromedial prefrontal cortex. This is consistent with a recent VBM study by our group[55] using the NPI disinhibition score in a bvFTD sample, which found that the medial orbitofrontal atrophy (similar to the FDG-PET findings) correlated with the frequency of disinhibited behaviors in the patients. These studies contrast with a VBM study by Zamboni et al,[56] in which atrophy in the right mediotemporal structures (the amygdala and the hippocampus) and the right nucleus accumbens was related to disinhibition scores on the FrSBe in behavioral and language variant FTD patients. It is currently not clear why there is a discrepancy between these findings, but it may reflect differences in sensitivity between the NPI and FrSBe for measurement of disinhibition in FTD.

Behavioral questionnaires are an important adjunct to clinical interview and show good discrimination of FTD from other neurodegenerative conditions, notably AD. The use of questionnaires to explore the neural basis of disinhibition has suggested that, in the majority of studies, the orbitofrontal regions and the mesolimbic dopaminergic system are critical. Importantly, the contribution of orbitofrontal dysfunction to disinhibited behaviors in FTD converges with the lesion findings in both humans and monkeys.[32,35–37]

However, the subjective nature of caregiver questionnaires is somewhat problematic as the accurate depiction of behavioral symptoms requires an observant and insightful caregiver, and therefore results are likely to vary widely across patients. As such, clinicians should aim to substantiate caregiver report of disinhibited behavior with objective measures of inhibitory dysfunction.

Neuropsychological Inhibitory Measures

Traditional neuropsychological tests of executive function are mostly sensitive to those functions subserved by the dorsolateral prefrontal cortex that involve information processing, working memory, and planning rather than functions such as cognitive control and inhibitory regulation. This bias is evident in the executive component of one of the most commonly used cognitive screening tests—the Mini-Mental State Examination—[57]in which measurement of executive function is limited to attention and working memory. In contrast, the Frontal Assessment Battery[58] screening test is more specific for assessment of cognitive control and inhibitory processes, including motor response inhibition and resistance to interference. Slachevsky and colleagues[59] found that scores on the Frontal Assessment Battery successfully differentiated between patients with FTD and those with AD, whereas the Mini-Mental State Examination scores did not reveal a difference between the disease groups.

Nevertheless, classic executive function tests can be used as a proxy to estimate disinhibited behavior by focusing on error patterns rather than on overall achievement scores. Kramer et al[16] assessed mild bvFTD, SD, and AD patient groups on a brief neuropsychological screen that examined memory, executive function, naming, spatial ability, and abstract reasoning. A composite error score, which included errors on a trail-making test and rule violations on verbal fluency tasks, correctly classified 89.2% of AD and FTD cases. Similarly, Thompson et al[60] compared bvFTD patients with AD patients on an extensive battery of tests measuring language, perceptuospatial, memory and executive functions. Test scores correctly classified 93% of AD patients and 71% of bvFTD patients. When error scores and qualitative features indicative of deficient cognitive control (eg, poor performance monitoring or susceptibility to interference, as indicated by rule violations in verbal fluency, perseverations, and intrusions during memory recall) were taken into account, classification accuracy increased to 96% for bvFTD but did not change for AD patients. These studies suggest that, compared with overall scores on executive tests, error measures are more specific to FTD dysfunction. Possin et al[61] conducted imaging analysis for rule-violation errors on executive function tasks in a mixed sample of controls and patients with mild cognitive impairment and dementia. Controlling for impairments in global cognitive function, the study showed that error performance covaried with the right lateral prefrontal cortex, further confirming the role of this region in cognitive control processes.

Another classic executive function test, verbal fluency, is also sensitive to detecting dysfunction in cases of bvFTD by assessing both overall performance and errors. Impaired verbal fluency has been widely reported in bvFTD patients.[17,62] Verbal fluency measures are categorized as initial-letter fluency (the subject produces as many words beginning with a specified letter in a given time frame, usually 1 minute; words beginning with a different letter, proper nouns, and derivations of the same word stem are considered intrusions) or semantic fluency (the subject produces as many exemplars from a semantic category—for example "animals"—in a specified time frame; deviations from the specified category are considered intrusions). Libon et al[63] found that bvFTD patients were equally impaired on both initial-letter and semantic fluency measures, with VBM analysis showing the former to correlate with bilateral frontal atrophy and the latter with left frontotemporal atrophy. Comparisons on verbal fluency measures have been used to differentiate between FTD and AD. For instance, in our own study bvFTD patients had a significantly lower age-scaled score for initial-letter verbal fluency compared with AD patients.[64] Furthermore, Rascovsky et al[65] found that bvFTD patients made a higher proportion of intrusion errors on an initial-letter fluency task, but AD patients were more likely to make intrusions during semantic fluency, although the proportion of perseverative errors (repetitions) was highest for the FTD group across both categories.

Of the validated neuropsychological tests designed more specifically to tap cognitive control and inhibitory dysfunction, the Stroop and Hayling tests have been used most extensively in FTD. Both of these measures are reliant on suppression of prepotent verbal responses and withstanding interference.

In the Stroop task, subjects are asked to identify the color of the ink with which a word is printed and ignore the identity of the word, thereby suppressing the automatic response to read the word. BvFTD patients perform significantly poorer than controls on the Stroop, although the same is true for AD patients, and poor differentiation across these disease categories makes the diagnostic utility of the Stroop questionable.[62,66] This might be because of the multidimensional nature of the test that, in addition to inhibiting prepotent responses, places high demand on attention and working memory. This was highlighted by a recent study[67] that correlated performance on the Stroop task using FDG-PET imaging in early AD patients and a combined behavioral and semantic variant FTD group. Behaviorally, dementia patients showed impairment on the Stroop task relative to controls, but there was no difference between the patient groups. Imaging correlates of regional hypometabolism revealed significant overlap for both AD and FTD in the inferior frontal junction, which is slightly more posterior to the mid-dorsolateral region similarly associated with set-shifting and cognitive control.[68]

The Stroop does not appear to be sensitive to orbitofrontal dysfunction, which is further illustrated by findings that Stroop performance was not significantly associated with behavioral disinhibition as measured by the NPI in a large sample of patients with dementia and mild cognitive impairment.[69]

The most sensitive standard test of inhibitory function appears to be the Hayling test.[70] In this test, a series of sentences with the last word missing are read out to the subject. In the first section, the subject must provide a correct word to complete each sentence ("He posted a letter without a…" Correct answer: "stamp"). In the critical second section, they must provide a word that is unconnected to each sentence, necessitating inhibition of the prepotent verbal response ("London is a very busy …" Potentially correct answer: "banana"). BvFTD patients show impaired performance on the Hayling test, even from the early stages of the disease.[17,71] Impaired performance has also been demonstrated in AD patients.[72] Our recent study revealed that, although the performances of both bvFTD and AD groups were well below control levels, the bvFTD patients' performance was significantly poorer.[64] We have also shown that the error score on the Hayling test is directly linked to the degree of orbitofrontal cortex atrophy[64] and, importantly, taps into the same region as the NPI disinhibition score, with both scores being related to the orbitofrontal damage.[55] The Hayling is a useful means of classifying bvFTD by means of inhibitory deficits, although an obvious drawback is that performance is contingent upon intact verbal expression and comprehension, which limits its applicability to FTD language variants.

From the above, it is clear that neuropsychological tests have revealed deficits in cognitive inhibitory control in FTD, which can be useful in differential diagnosis. However, there certainly remains scope to develop new diagnostic tests that are more specific to orbitofrontal function, such as the Hayling. Tapping into the orbitofrontal function is crucial for improving diagnosis in FTD, as this is one of the earliest areas affected and as, at present, most measures that reflect orbitofrontal dysfunction are subjective behavioral questionnaires. The development of new objective inhibitory measures and their translation into usable clinical tests could have important implications for further improving diagnostic accuracy in FTD.

Experimental Inhibitory Measures and Future Directions

A potential way forward is to develop clinically applicable tasks modeled on those that have been used experimentally to explore inhibitory function. Experimental measures typically use large trial numbers, complex setups, and counterbalancing procedures, which are not feasible in a clinical assessment. Nevertheless, adapting such experimental tests for clinical purposes could have enormous potential, as seen in the Hayling test, which was based on the authors' experimental work. Experimental paradigms that assess inhibitory processes include inhibition of return (IOR), negative priming, stop-signal, and go/no-go tasks.

IOR and negative priming paradigms are presumed to reflect the inhibitory processes active during selective attention.[73] In IOR tasks, subjects make rapid responses to targets appearing at different spatial locations on a computer screen, which are preceded by a cue. Response times are typically slower when a target appears in a spatial location that was previously cued, relative to targets that appear in new locations.[74] It is suggested that the previously cued spatial location suffers inhibition, thus reflecting an attentional bias for novel events. Several studies have shown that this perceptual, preconscious inhibition remains intact in both normal aging and AD[75,76] but has so far not been investigated in FTD.

In negative priming tasks, slower response times are expected when the subject responds to a target stimulus that was previously primed to be ignored. This is thought to reflect residual effects of the inhibition that was initially directed at the stimulus in an effort to ignore it and focus on the target at that time.[77,78] Negative priming is considered to be a measure of how effectively an individual inhibits irrelevant information. Reduced, or absent, negative priming effect has been demonstrated in normal aging[79,80] and in AD patients.[81,82] In a small sample of FTD patients who were in a quite advanced duration of disease, Dimitrov et al[83] found moderate impairments on a negative priming task.

Stop-signal and go/no-go tasks were developed to measure motor response inhibition and assess the underlying process required to cancel an intended movement.[84] These tasks have 2 components: "go" trials and "stop" or "no-go" trials.[85,86] The "go" trials involve a motor response in a choice reaction time task (eg, pressing a button in response to the letter Q appearing on screen). The "stop" or "no-go" trials require inhibition of that response. "Stop" trials are associated with a signal (eg, an auditory tone), and the "no-go" trials are associated with an alternative stimulus (eg, the letter X). When these trials occur, they indicate for the motor response to be withheld. These inhibitory trials should be interspersed relatively infrequently among "go" trials, so that suppression of the response is rendered more difficult as subjects are increasingly habituated to making the response.[87] Functional neuroimaging studies have identified various areas of prefrontal activation during go/no-go tasks, including the orbitofrontal, inferior dorsolateral, and ventrolateral prefrontal cortices,[84,88–90] and lesions of the orbitofrontal cortex (in humans and primates) have been associated with poor suppression of responses on go/no-go tasks.[91,92]

For stop-signal and go/no-go tasks, the findings in AD patients have been mixed. Amieva et al[81] found that early-stage AD patients were slower than age-matched controls on both go/no-go and stop-signal tasks. After controlling for the effects of processing speed, the groups did not differ in their accuracy on the go/no-go task, but on the stop-signal task AD patients made slightly more errors compared with controls. Others have found clearer deficits on a go/no-go task in more advanced AD patients.[93] These tasks have not been thoroughly explored in FTD. Dimitrov et al[83] found advanced FTD patients to be impaired relative to controls on a stop-signal task. Only 1 study has compared mild AD and FTD patients on the basis of a go/no-go task, and surprisingly little impairment was found in the patient groups.[66] The lack of sensitivity may reflect test design, in that a higher proportion of "go" trials is necessary to strongly reinforce the motor response, making inhibition more difficult on "no-go" or "stop" trials. The 50:50 ratio used in studies to date creates less reinforcement and consequently less of a demand on inhibition.[94]

Little is known at present about which aspects of inhibitory processing may be differentially impaired in FTD and at what stage various inhibitory deficits may emerge. Experimental measures offer a promising avenue to explore the breakdown of inhibitory processes in FTD, and with adaptation of such measures into clinically applicable tests they may prove to be useful diagnostic tools. One clear benefit is their lack of reliance on verbal responses, which is especially relevant given the co-occurrence of language and behavioral changes in patients with FTD.

CONCLUSIONS

Failure of inhibitory control is clearly an early and discriminating feature in patients with FTD; yet, the nature of inhibitory dysfunction in the disease has not been thoroughly characterized. This is partly because of a lack of established measures available to reliably assess inhibitory dysfunction. A drawback of questionnaire measures is that they rely on subjective caregiver report. The arsenal of objective measures is limited and generally restricted to tasks that require verbal responses, which are not appropriate for many FTD patients. There is considerable scope for further development of objective measures to assess inhibitory processes in FTD, with the aim of tapping the predominant orbitofrontal dysfunction in these patients. In turn, FTD patients can be seen as human lesion models to study inhibitory functioning, which can add more generally to our understanding of the construct of inhibition.

On a clinical level, tests able to discriminate between FTD and other neurodegenerative conditions—especially AD—are of utmost importance, particularly considering that a frontal presentation of AD with disproportionate impairments in executive skills is well recognized and not uncommon.[95,96] There is also increasing evidence that poor episodic memory does not reliably distinguish between FTD and AD, as has been shown in a recent study in which bvFTD and AD patients were equally impaired on most memory measures.[97] This highlights a need to design tasks that capture dysfunction more specific to FTD, particularly in the early stages. Considerable progress has been made in the area of social cognition (a term encompassing theory of mind, emotion recognition, and reactivity), which has emerged as an important area for understanding the manifestation of FTD and has proven to be useful in differentiating FTD from AD.[18,19,71,98,99] However, most social cognition tasks are experimental and are not in routine clinical usage, and such tasks have limited clinical utility because of complexity, reliance on verbal responses, and cross-cultural differences. The tasks based on inhibitory control processes have, arguably, a more widespread applicability. Ultimately, establishing objective behavioral and anatomic inhibitory control correlates for FTD could have ramifications for improving diagnostic accuracy and enabling better patient management and prompt therapeutic intervention of this disease in the future.

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Short communication

A novel bedside task to tap inhibitory dysfunction and fronto-striatal atrophy in Parkinson's disease

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ABSTRACT

Background: Given the heterogeneity of mild cognitive deficits in non-demented Parkinson's disease (PD), sensitive and anatomically specific behavioural measures are crucial when evaluating cognition in this patient group. Inhibitory dysfunction is one such deficit increasingly being recognised in non-demented PD; however, few clinical measures exist to detect it and its associated fronto-striatal pathology.

Methods: In 50 non-demented PD patients and 27 controls we employ a novel measure, the Excluded Letter Fluency (ELF) test, to objectively assess inhibitory dysfunction. ELF results were also contrasted with an established inhibitory measure (Hayling Test) and covaried against grey matter atrophy via voxel-based morphometry analysis in a subset of patients.

Results: The findings show that patients made significantly more rule-break errors than controls on the ELF and this measure was more sensitive than the Hayling in detecting inhibitory dysfunction, classifying over 76% of patients in logistic regression analysis. Importantly, ELF rule-break errors correlated with grey matter atrophy in known inhibitory-control regions (orbitofrontal cortex, inferior frontal gyrus and ventral striatum).

Conclusions: The ELF is a brief bedside task that efficiently detects inhibitory dysfunction in non-demented PD. The utility of this novel behavioural measure is further substantiated by its anatomical specificity for fronto-striatal inhibitory control regions.

1. Introduction

Among the heterogeneous cognitive deficits that occur in non-demented Parkinson's disease (PD), there is mounting evidence to suggest inhibitory deficits in this patient group [1]. This is not surprising as both action-response inhibition and cognitive/behavioural inhibitory processes are mediated via fronto-striatal neural circuits known to be dysfunctional in PD. Studies using experimental measures of inhibition have revealed impairments in PD and linked these to dysfunction in inhibitory control brain regions [2–4]. Importantly, these regions, including orbitofrontal cortex and ventral striatum, differ from those regions implicated in working memory (i.e. dorsolateral/ventrolateral prefrontal cortex and dorsal striatum [5]), suggesting that inhibitory deficits are dissociable from the more general multi-tasking deficits seen in PD. However, the experimental paradigms employed to assess inhibitory processes typically require complex computerised set-ups and a large number of trials, which are not feasible in a clinical setting for routine assessment of cognitive function in PD patients.

In the current study, we introduce a novel, validated clinical measure—the Excluded Letter Fluency (ELF) task—to detect inhibition deficits in PD. We determine the concurrent validity of the ELF by contrasting it against the well-established Hayling Test of inhibitory function and cross-validate our behavioural findings by exploring whether the ELF is tapping into neuroanatomical abnormalities in fronto-striatal inhibitory control regions via voxel-based morphometry. We predict that the ELF, as a very demanding inhibitory measure, will detect inhibitory deficits in non-demented PD and emerge as an effective clinical tool to employ in the cognitive assessment of these patients.

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2. Methods

2.1. Case selection

Fifty non-demented PD patients were consecutively recruited from the Brain and Mind Institute Parkinson's Disease Research Clinic; all satisfied UKPDS Brain Bank criteria for diagnosis of PD; were between Hoehn and Yahr stages I and III and were assessed with the Mini Mental State Examination (MMSE). Patients performed behavioural testing in the ON state, having taken their usual medications. (For medication details, see Supplement). Twenty seven age- and education-matched controls were selected from a volunteer panel. The study was approved by the Human Ethics Committees of the Central and South Eastern Sydney Area Health Services and the Universities of Sydney and New South Wales.

2.2. Behavioural testing

Order of administration of the two behavioural tasks was randomised across participants and they were administered on the same day. For the ELF [6] subjects were given three trials of 90 s each to produce as many words as possible that did not contain a specified letter: "A", then "E" and "I". They were instructed that the words must be longer than three letters and they could not be proper nouns or derivations of the same word-stem (e.g. 'drive', 'driver', 'driving'). Subjects were provided with examples of inappropriate words and then asked to give words without the letter "S" as a practice. In between trials they were reminded of the rules. The ELF is represented by an overall correct score and two error scores: rule-violations (i.e. words containing the excluded letter, proper nouns, derivations of the same word stem and words with three letters or less) and repetitions. We further explored the rule-violations score in an imaging analysis.

The Hayling Test evaluates inhibitory control via a sentence completion task. The crucial second section contains 15 open-ended sentences that the subject must complete with a word unconnected in meaning, which requires inhibition of the prepotent response. We report response time for section two (Scaled score B), inhibition errors for section two (i.e. responses connected in meaning: AB Error Score) and overall scaled score. (For detailed explanation of the Hayling Test, see Supplement).

2.3. Behavioural analyses

Data were analysed using SPSS18.0 (SPSS Inc., Chicago, Ill., USA). Parametric demographic and clinical data were compared across groups via one-way ANOVAs followed by Tukey post-hoc tests. A priori, inhibitory control variables were checked for normality via Kolmogorov–Smirnov tests. Variables showing non-parametric distribution were analysed via Chi-square, Kruskal–Wallis and Mann–Whitney *U* tests. Pearson correlations were used to compare inhibitory control measures. We employed backwards Wald stepwise binary logistic regression analysis to determine the efficacy of inhibitory control variables in predicting group membership.

2.4. Imaging acquisition and voxel-based morphometry (VBM) analysis

A subset of 12 PD patients and 15 controls were scanned and included in a VBM analysis to determine the relationship between ELF rule-violations and grey matter atrophy. A region-of-interest mask for prefrontal and striatal brain regions was created and the relationship between ELF performance and grey matter intensity was considered significant at $p < 0.05$ False Discovery Rate (FDR) corrected for each voxel and a cluster extent threshold of at least 20 contiguous voxels. (For details, see Appendix).

3. Results

3.1. Demographics, clinical characteristics and screening measures

Participant groups did not differ in age or education (p values > 0.1). Patient MMSE scores were significantly lower than the controls ($p < 0.01$), although still well above the cut-off for dementia [7] (See Table 1).

Independent *t*-tests revealed no differences in demographics or clinical characteristics between the overall PD sample ($n = 50$) and the group that underwent further imaging analysis ($n = 12$) and there were no differences between the overall control group ($n = 27$) and the subset with imaging ($n = 15$) (p values > 0.1).

3.2. Inhibitory control measures

On the ELF, patients and controls did not differ with respect to total amount of words produced over the three trials or their repetition errors (p values > 0.1). However, PD patients made significantly more rule-violations than controls ($p < 0.000$). On the Hayling, there was no difference between the groups for inhibition time (Scaled Score B) or overall scaled score (p values > 0.1), but PD patients committed significantly more inhibition errors (AB Error Score) compared to controls ($p < 0.01$). (See Table 1).

Independent *t*-tests showed that the overall PD and control samples versus the subsets included in the imaging analysis did not differ on any inhibitory control measures (p values > 0.1).

3.3. Concurrent validity and classification sensitivity of the ELF measure

Pearson correlation analysis for PD patients and controls revealed a strong positive relationship between failures of inhibitory control on the ELF (rule-violation score) and inhibitory failures on the Hayling (AB score) ($r = 0.368$, $p < 0.01$).

Entering the ELF rule-violation and Hayling AB scores in backwards step-wise regression produced a significant model [$\chi^2 = 21.402$, $p < 0.000$, Nagelkerke's $R^2 = 0.390$] with only the ELF rule-violation score emerging as a significant predictor variable [$\beta = -0.299$, $p < 0.01$] and 76.6% of PD patients being distinguished from controls on this measure alone.

3.4. VBM − correlation with ELF inhibition score

We entered ELF rule-violation scores as covariates in the design matrix of the VBM analysis. PD patients' rule-violations covaried with grey matter atrophy in medial orbitofrontal cortex (OFC), left inferior frontal gyrus (IFG) and right nucleus accumbens (ventral striatum − VS). (See Supplementary Fig. 1 and Supplementary Table 1).

4. Discussion

Our results unequivocally show that the ELF is a sensitive measure to assess inhibitory dysfunction in non-demented PD patients, with good anatomical specificity for inhibitory-control brain regions.

On the ELF test PD patients made significantly more rule-violations than controls, indicating deficits in inhibitory control

Table 1
Mean (SD) values for controls and PD patients on demographics, clinical characteristics and measures of inhibitory control.

Demographics, clinical characteristics and behavioural results	Controls	PD	F/χ^2 values
N	27	50	–
Sex (M:F)	16:11	34:16	–
Age (years)	65.6 (6.7)	63.8 (7.7)	n.s.
Education (years)	14.0 (3.2)	13.4 (2.6)	n.s.
MMSE (max. 30)	29.4 (0.81)	28.0 (2.0)	**
Disease duration (years since diagnosis)	–	5.8 (4.4)	–
Hoehn & Yahr stage	–	2.1 (0.46)	–
Dopamine dose equivalent (mg/day)	–	775.6 (545.5)	–
Excluded letter fluency			
Total correct	46.5 (12.8)	47.7 (12.1)	n.s.
Rule-violations[a]	4.1 (3.1)	8.2 (5.3)	***
Repetitions[a]	0.70 (1.0)	0.96 (1.6)	n.s.
Hayling test			
Scaled score B (inhibition time)[a]	5.9 (1.0)	5.7 (0.8)	n.s.
AB score (inhibition errors)[a]	3.0 (5.5)	10.0 (12.0)	**
Scaled score overall[a]	6.4 (1.2)	5.8 (1.2)	n.s.

n.s. = non significant; *** = $p < 0.001$; ** = $p < 0.01$; * = $p < 0.05$.
MMSE = Mini-Mental State Examination.
[a] *F* values indicate significant differences across groups, otherwise due to unequal variance χ^2 indicates differences across groups.

processes (i.e. verbal response inhibition and self-monitoring). Patients were also impaired on the Hayling Test, consistent with previous findings [1], with logistic regression analysis confirming that the ELF had a higher sensitivity than the Hayling test to detect inhibitory dysfunction in PD.

PD patients' inhibition errors on the ELF were associated with grey matter atrophy in the OFC, IFG and VS. In PD, these regions have previously been implicated in adaptive and inhibitory control process, including reward sensitivity [2], action-response inhibition [4] and reversal learning [8]; with dopaminergic dysfunction in these regions directly related to gambling severity [9], riskier choices [3] and impaired reward processing [10] in PD patients with impulse-control disorders. Our results provide further evidence that the OFC, IFG and VS are critical for flexible inhibitory control processes, with the OFC and VS comprising important hubs of the mesolimbic fronto-striatal loop and the IFG a crucial component in the fronto-striatal network for reactive stopping. Interestingly, previous studies have typically associated the right-IFG with inhibitory function [11], our finding that left-sided IFG was implicated in inhibitory control on the ELF may reflect the verbal nature of the task.

The type of inhibitory control presumed to be measured by the ELF is goal-directed and selective, whereby prefrontal cortical regions modulate striatal activity on the basis of a "top-down inhibitory set" [12] (i.e. the set of rules that must be followed to successfully complete ELF trials). Measures of this kind of inhibitory control are thought to bear more resemblance to the inhibitory control we apply in daily life [12]. Furthermore, tasks such as the ELF that probe OFC dysfunction are likely to have good ecological validity, as it has been shown in other neurodegenerative diseases that the degree of OFC dysfunction is highly related to the degree of disinhibited behaviour reported by caregivers [13]. As such, a future direction would be to explore the relationship between inhibitory dysfunction on the ELF and behavioural manifestations of disinhibition in PD, such as impulse-control disorders.

Our findings further confirm the presence of inhibitory dysfunction in non-demented PD; therefore, sensitive and anatomically specific clinical measures to detect this are of great importance when monitoring PD patients' cognition over time, as well improving disease management and informing future disease modifying therapies. The ELF is brief, easy to administer and potentially more sensitive to mild impairments, making it an efficacious clinical tool to identify inhibitory dysfunction and associated fronto-striatal atrophy.

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Competing interests: The authors report no conflicts of interest or disclosures.

Appendix

1. Patient medication details

Of the sample of fifty Parkinson's disease patients, four patients were untreated, forty one patients were taking levodopa (five of whom were also on entacapone), and sixteen of these were also taking a dopamine agonist. Three patients were on agonist monotherapy and two were on an agonist plus rasagiline.

2. Behavioural testing—The Hayling Test

The Hayling Test [1] evaluates inhibition of a prepotent verbal response via a sentence completion task. The first section of the test consists of 15 open-ended sentences and subjects provide a word to complete the sentence plausibly (e.g. "He posted a letter without a…" Potentially correct answer: "stamp"). The second section contains 15 open-ended sentences the subject completes with a word that is unconnected to the sentence, which requires inhibition of the prepotent response (e.g. "London is a very busy …" Potentially correct answer: "banana"). For this section, errors are recorded for words that are connected with the sentence ("A" errors are those that are *strongly* connected and "B" errors are those only *partially* connected) and participants are not permitted to use the same answer for each item. For both sections, the time taken to respond is recorded, which together with the error scores results in an overall score. In the current study, we report behavioural performance for the scaled score B (response time for section two), total errors (termed AB score, i.e. "A" errors plus "B" errors in section two) and the overall scaled score. We conduct further imaging analysis using the AB error score, as this is the most direct measure of response inhibition.

3. Imaging acquisition

Patients and controls underwent the same imaging protocol with whole-brain T1 images acquired using 3T Philips MRI scanners with standard quadrature head coil (8 channels). The 3D T1-weighted sequences were acquired as follows: coronal orientation, matrix 256×256, 200 slices, 1×1 mm^2 in-plane resolution, slice thickness 1 mm, TE/TR = 2.6/5.8 ms.

4. Voxel-based morphometry (VBM) analysis

3D T1-weighted sequences were analysed with FSL-VBM, a voxel-based morphometry analysis [2,3] which is part of the FSL software package http://www.fmrib.ox.ac.uk/fsl/fslvbm/index.html [4]. First, tissue segmentation was carried out using FMRIB's Automatic Segmentation Tool (FAST) [5] from brain extracted images. The resulting gray matter partial volume maps were then aligned to the Montreal Neurological Institute standard space (MNI152) using the nonlinear registration approach using FNIRT [6,7], which uses a b-spline representation of the registration warp field [8]. The registered partial volume maps were then modulated (to correct for local expansion or contraction) by dividing them by the Jacobian of the warp field. The modulated images were then smoothed with an isotropic Gaussian kernel with a standard deviation of 3 mm (FWHM: 8 mm). A region-of-interest (ROI) mask for prefrontal and striatal brain regions was created by using the Harvard-Oxford cortical and subcortical structural atlas. The following atlas regions were included in the mask: frontal pole, superior frontal gyrus, middle frontal gyrus, inferior frontal gyrus, frontal medial cortex, subcallosal cortex, paracingulate gyrus, cingulate gyrus (anterior division), frontal orbital cortex, caudate, putamen and nucleus accumbens. Finally, the statistical analysis was performed by employing a voxel-wise general linear model. Significant clusters were formed by employing the threshold-free

cluster enhancement (TFCE) method [9]. The TFCE method is a cluster-based thresholding method which does not require the setting of an arbitrary cluster forming threshold (e.g. $t,z < 4$), instead it takes a raw statistics image and produces an output image in which the voxel-wise values represent the amount of cluster-like local spatial support. The TFCE image is then turned into voxel-wise p-values via permutation testing. We employed a permutation-based non-parametric testing with 5000 permutations [10]. We built a regression model with the performance on the ELF rule-violations as the explanatory variable of main interest and total intracranial volume (TIV) as a covariate. A covariate only statistical model with a [10] t-contrast was used, providing an index of association between decreasing grey matter volume and higher ELF error scores while taking TIV across patients into account. Relationship of ELF performance and grey matter intensity was considered significant at $p < 0.05$ False Discovery Rate (FDR) corrected for each voxel. In addition, we applied a cluster extent threshold of at least 20 contiguous voxels for each significant cluster to reduce the likelihood of false positive voxels.

5. Appendix reference list

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Appendix A. Supplementary data

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.parkreldis.2013.04.020.

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B4. “Screening for impulse control symptoms in patients with de novo Parkinson disease: A case-control study”

Section Editor
Robert C. Griggs, MD

WriteClick: *Editor's Choice*

Editors' Note: In this week's WriteClick, O'Callaghan and Hornberger point out that there are studies that contradict the findings of authors Weintraub et al. that dopaminergic therapy in Parkinson disease (PD) is the driver behind impulse control disorders rather than the disease itself. They suggest a compromise theory and more objective screening. The authors disagree on both points.

Megan Alcauskas, MD, and Robert C. Griggs, MD

SCREENING FOR IMPULSE CONTROL SYMPTOMS IN PATIENTS WITH DE NOVO PARKINSON DISEASE: A CASE-CONTROL STUDY

Claire O'Callaghan, Michael Hornberger, Sydney, Australia: Weintraub et al.[1] found that de novo PD itself does not confer an increased risk for impulse control disorders (ICDs). This implies that dopaminergic therapy is the critical factor driving ICDs in PD.

However, other studies have shown that patients with PD—even without ICDs—perform more impulsively than controls on laboratory-based tasks.[2,3] Similarly, gray matter atrophy in impulse-control regions (nucleus accumbens, orbitofrontal cortex) correlates with inhibitory-control failures in PD,[4] suggesting that increased impulsivity may not only be dependent on medication status but also on neuroanatomical abnormalities intrinsic to PD. It is possible that there is a clinical PD subgroup with an impulsivity endophenotype[5] due to neuroanatomical/neurochemical abnormalities in impulse-control brain regions, which could be further aggravated via dopamine therapy.

Identifying this potential clinical subgroup should be the target of future investigations of patients with de novo PD. In particular, targeted imaging of impulse-control brain regions and employment of more objective impulse-control measures should be investigated because these can be more sensitive than self-completed screening questionnaires. This would allow identification of patients who are more vulnerable to developing ICDs later in the disease course or with initiation of dopaminergic therapy.

Author Response: Daniel Weintraub, Andrew Siderowf, Kimberly Papay, Philadelphia: We thank Drs. O'Callaghan and Hornberger for their interest in our recent article, where we demonstrate that clinical impulse disorders are not more common in patients with untreated de novo PD than in controls.

We agree that identification of a biological substrate for ICDs is an important area for research and that structural changes on MRI are a potential biomarker for ICD risk. We also agree that some studies show abnormalities in laboratory-based tests of impulsiveness in patients with untreated PD. However, this finding is not consistent across all studies.[6] In addition, changes within laboratory-based tasks will not always predict the occurrence of ICD behaviors that are important to patients with PD.

Based on our study, and prior research,[7] we believe that treatment with dopamine agonist medications is the most important risk factor for development of ICDs in PD and that clinically meaningful ICDs occur in patients with untreated PD as frequently as they occur in the general public. Moreover, the results of validation studies support the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP) as a useful screening tool for clinically relevant ICDs. The QUIP is highly sensitive and brief enough to be administered in a busy office practice.[8]

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APPENDIX C

Declaration supporting inclusion of Publications in the Thesis

1) Publication I – **O'Callaghan, C**., Shine, J. M., Lewis, S. J. G., & Hornberger, M. (2014). Neuropsychiatric symptoms in Parkinson's disease: Fronto-striatal atrophy contributions. *Parkinsonism & Related Disorders*, 20(8), 867-872.

2) Publication II – **O'Callaghan, C**., Naismith, S. L., Hodges, J. R., Lewis, S. J. G., & Hornberger, M. (2013). Fronto-striatal atrophy correlates of inhibitory dysfunction in Parkinson's disease versus behavioural variant frontotemporal dementia. *Cortex*, 49(7), 1833-1843.

3) Publication III – **O'Callaghan, C.**, Moustafa, A. A., de Wit, S., Shine, J. M., Robbins, T. W., Lewis, S. J. G., & Hornberger, M. (2013). Fronto-striatal grey matter contributions to discrimination learning in Parkinson's disease. *Frontiers in Computational Neuroscience*, 7, 180.

4) Publication IV – **O'Callaghan, C.**, Bertoux, M., Irish, M., Shine, J. M., Spiliopoulos, L., Hodges, J. R., & Hornberger, M. Fair play – Social norm compliance failures in behavioural variant frontotemporal dementia, (prepared for submission).

5) Appendix B1 – **O'Callaghan, C.**, Bertoux, M., & Hornberger, M. (2014). Beyond and below the cortex: the contribution of striatal dysfunction to cognition and behaviour in neurodegeneration. *Journal of Neurology, Neurosurgery and Psychiatry*, 85(4), 371-378.

6) Appendix B2 – **O'Callaghan, C.**, Hodges, J. R., & Hornberger, M. (2013). Inhibitory Dysfunction in Frontotemporal Dementia: A Review. *Alzheimer Disease & Associated Disorders*, 27(2), 102-108.

7) Appendix B3 – **O'Callaghan, C.**, Naismith, S. L., Shine, J. M., Bertoux, M., Lewis, S. J. G., & Hornberger, M. (2013). A novel bedside task to tap inhibitory dysfunction and fronto-striatal atrophy in Parkinson's disease. *Parkinsonism & Related Disorders*, 19(9), 827-830.

8) Appendix B4 – **O'Callaghan, C.**, & Hornberger, M. (2013). WriteClick: Editor's Choice - Screening for impulse control symptoms in patients with de novo Parkinson disease: A case-control study. *Neurology*, 81(7), 694-695.

Declaration:

For each Publication listed above, I certify that this publication was a direct result of my research towards this PhD, and that reproduction in this thesis does not breach copyright regulations.

Claire O'Callaghan

Date: 18 December 2014