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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