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Failure of stop and go in de novo Parkinson's disease—a functional magnetic resonance imaging study

Chris Vriend [a,b,c,*], Niels J.H.M. Gerrits [b,c], Henk W. Berendse [c,d], Dick J. Veltman [a,c], Odile A. van den Heuvel [a,b,c,1], Ysbrand D. van der Werf [b,c,e,1]

[a] Department of Psychiatry, VU University Medical Center, Amsterdam, the Netherlands
[b] Department of Anatomy & Neurosciences, VU University Medical Center, Amsterdam, the Netherlands
[c] Neuroscience Campus Amsterdam, VU/VUmc, Amsterdam, the Netherlands
[d] Department of Neurology, VU University Medical Center, Amsterdam, the Netherlands
[e] Netherlands Institute for Neuroscience, Royal Netherlands Academy of Arts and Sciences, Amsterdam, the Netherlands

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ABSTRACT

Behavioral impairments in response inhibition and initiation are common in Parkinson's disease (PD) and are associated with reduced impulse control. No prior study, however, has investigated the functional correlates of response inhibition in de novo PD. Twenty-one de novo PD patients and 37 matched healthy controls performed a stop-signal task during functional magnetic resonance imaging. The results showed that PD patients, compared with healthy controls, were slower on response initiation but not inhibition. Task-related activation of the response inhibition network, including the inferior frontal gyrus, was reduced in PD patients, and the activity in the inferior frontal gyrus correlated negatively with motor symptom severity. These findings show that de novo PD patients exhibit functional deficits in the response inhibition network, which are partly related to disease pathology and already evident before commencing dopamine replacement therapy. This study provides insights into the neural underpinnings of impulse control deficits, relevant for the study of the neural vulnerability factors involved in the development of impulse control disorders in PD.

1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder that affects, among others, dopaminergic afferents toward the striatum (Braak et al., 2004; Kish et al., 1988). This striatal dopaminergic denervation lies at the root of the PD-related motor disturbances, but there is growing evidence that it is also involved in the development of nonmotor symptoms, such as depression (Hesse et al., 2009; Vriend et al., 2014c) and impulse control disorders (ICD) (Voon et al., 2013; Vriend et al., 2014a). ICD are characterized by an inability to suppress certain (potentially dangerous) impulses (American Psychiatric Association, 2013). It is hypothesized that ICD in PD arise after commencing dopamine replacement therapy in patients with a certain neurobiological susceptibility (Vriend et al., 2014b). Nevertheless, nonclinically significant deficits in impulse control have also been described in PD patients without ICD (Aarts et al., 2012; van der Vegt et al., 2013; Ye et al., 2014). Response inhibition is a frequently used measure of the ability to control one's impulses in an experimental setting (Aron, 2011). Response inhibition tasks require subjects to inhibit inappropriate responses when certain cues are provided. Previous behavioral studies have shown deficits in response inhibition in patients with PD compared with healthy controls (Gauggel et al., 2004; Nombela et al., 2014; Obeso et al., 2011a). Furthermore, these deficits in response inhibition in PD correlated with alterations in neurophysiological markers (Beste et al., 2009, 2010; Bokura et al., 2005) and were associated with altered brain activity patterns (Baglio et al., 2011; Farid et al., 2009) and reductions in frontal-striatal brain volume (O'Callaghan et al., 2013). However, all previous studies were carried out in PD patients that were on dopamine replacement therapy, making it impossible to disambiguate the consequences of (chronic) medication from the pathophysiological alterations associated with the disease itself. Nevertheless, 2 previous studies using an ON/OFF paradigm showed that levodopa is unable to fully restore deficits in response

* Corresponding author at: Department of Psychiatry, VUmc, Medical Faculty Building, room G102-b, van der Boechorststraat 7, 1081 BT, Amsterdam, the Netherlands. Tel.: +31 20 4449683; fax: +31 20 4448054.
E-mail address: c.vriend@vumc.nl (C. Vriend).
[1] These authors contributed equally to this work.

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inhibition (Farid et al., 2009; Obeso et al., 2011b), suggesting that the deficits are primarily because of pathophysiological changes.

The stop-signal task exerts higher demands on subjects compared with the Go/no-Go task that was used in almost all previous neuroimaging studies in PD (Sebastian et al., 2013). Therefore, the stop-signal task puts higher strain on the compensational resources of the inhibition network and is thus more likely to reveal subtle between-group differences in brain activation. This was also observed in a very recent article that showed decreased activation of the right inferior frontal gyrus in medicated PD patients compared with healthy controls during performance of a stop-signal task (Ye et al., 2014). Based on this and other previous studies, we hypothesized that, compared with healthy controls, de novo PD patients would show impairments in response initiation and inhibition concomitant with hypoactivation of inhibition-related brain areas.

2. Methods

2.1. Participants

PD patients were recently diagnosed by a movement disorder specialist according to the UK Parkinson's disease Brain Bank criteria (Daniel and Lees, 1993), for idiopathic PD. All patients were naive for dopamine replacement therapy (de novo). We used the Unified Parkinson's Disease Rating Scale motor section (UPDRS-III) (Fahn et al., 1987) and Hoehn and Yahr stage (Hoehn and Yahr, 1967) to assess disease severity and disease stage, respectively. Healthy controls were recruited through advertisements. Exclusion criteria in healthy controls were current or previous severe traumatic head injuries, other neurologic or psychiatric disorders, including alcohol or drug dependence. Exclusion criteria in PD were a current or previous psychiatric or neurologic disorder other than PD itself. Participants were screened for the presence of psychiatric disorders using the Structured Clinical Interview for DSM-IV Axis-I Disorders (First et al., 2002) and for signs of dementia using the Mini Mental State Examination (MMSE) (Folstein et al., 1975). All participants with excessive movement during functional magnetic resonance imaging (fMRI) scanning (>3 mm) or use of centrally active drugs were excluded. We administered the Dutch version of the national adult reading test (Schmand et al., 1991) to provide a measure of premorbid intelligence. All participants provided written informed consent according to the declaration of Helsinki, and the study was approved by the local research ethics committee.

2.2. Stop-signal task

Participants performed a visual stop-signal task during fMRI scanning (de Wit et al., 2012) in which they responded to the direction of an arrow (left or right) by pressing a button with the index finger of the concordant hand (go-trials). Go-trials were interspersed pseudo-randomly with stop-trials, in which a cross was superimposed on the arrow with some delay after the initial presentation of the arrow. On these trials, participants had to refrain from responding. The delay of the stop-signal (stop-signal delay) was continuously adapted by a staircase tracking mechanism to approximate a 50% inhibition on all stop-trials. Participants were instructed to respond quickly but accurately. They were also told that the design of the task would prevent them from accurately inhibiting their responses on all stop-trials. Further details on the task are provided in the Supplementary Methods. Behaviorally, we measured the mean reaction time on successful go-trials (speed of go process), the stop-signal reaction time (speed of stop process), and the error percentage on go-trials and stop-trials. Participants with a go-trial error percentage >40% were excluded (Congdon et al., 2012). Stop-signal reaction time (SSRT) was estimated with the integration method, which according to simulations gives the most reliable estimate of SSRT (Verbruggen et al., 2013). Because response latencies gradually increased during the task, SSRTs were estimated separately in 4 smaller blocks (each block consisting of at least 50 trials) and subsequently averaged. Blocks from subjects with stop-trial error percentages <25% or >75% were excluded (Congdon et al., 2012).

2.3. Image acquisition

Imaging data were collected using a GE Signa HDxT 3T MRI scanner (General Electric, Milwaukee, WI, USA) at the VU University Medical Center (Amsterdam, The Netherlands). Task stimuli were projected on a screen behind the participant's head at the end of the scanner table, visible through a mirror mounted on the head coil. The participant's head was immobilized using foam pads to reduce motion artifacts.

T2*-weighted echo-planar images with blood oxygenation level dependent (BOLD) contrast were acquired in each session; slice order: sequential and ascending, repetition time = 2100 ms, echo time = 30 ms, flip angle = 80°, 40 slices (3.75 × 3.75 mm in-plane resolution; 2.8 mm slice thickness; matrix size 64 × 64) per echo-planar image volume. Structural images were acquired using a 3D sagittal T_1-weighted sequence (inversion time = 450 ms, echo time = 3 ms, voxel size 1 × 0.977 × 0.977 mm, 172 slices). In addition, we acquired [^{123}I]FP-CIT ([^{123}I]*N*-ω-Fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)nortropane) Single Photon Emission Computed Tomography (SPECT) scans from a subgroup of PD patients to measure presynaptic striatal dopamine transporter availability as a measure for striatal dopamine integrity. Dopamine transporter availability was measured in the ventral striatum, anterior-dorsal striatum, and posterior putamen. See the Supplementary Material for a full description of the [^{123}I]FP-CIT SPECT acquisition and delineation of the region's of interest.

2.4. Data preprocessing and analyses

Behavioral analyses were conducted in IBM SPSS 20 (Armonk, NY, USA). Between-group differences were analyzed with 2-sample t tests or Mann-Whitney U tests, depending on the variable's distribution. Correlations between behavior and clinical measures were analyzed with Pearson *r* correlation coefficient.

Imaging preprocessing and analyses were performed with SPM8 (Wellcome Trust Center for Neuroimaging, London, UK). Functional brain images were manually reoriented, slice-time corrected, and realigned to the first volume. The resulting mean image was then coregistered to the structural T1 image, and images were normalized to Montreal Neurological Institute (MNI) space and spatially smoothed using an 8 mm Full-Width-at-Half-Maximum Gaussian kernel. All imaging analyses were performed in the context of the general linear model. Onsets of successful go-trials, successful stop-trials, and unsuccessful stop-trials were modeled per participant (first level) using delta functions convolved with the hemodynamic response function. Participants' movement parameters (3 translation and 3 rotation parameters) were added as additional regressors of no interest. A 128-second high-pass filter was used to remove noise associated with low-frequency confounds. Inhibition-related BOLD activity was modeled by contrasting successful stop-trials with successful go-trials (successful stop > successful go). Error-related activity was probed by contrasting unsuccessful stop-trials with successful stop-trials. These contrasts were brought into second-level random effects analyses.