Functional magnetic resonance imaging of Parkinson*s disease patients to investigate the effects of dopamine on visual attention.

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We aim to extend our recent work on fundamental mechanisms that underlie automatic influences of reward on attention to clinical populations that suffer from reduced and excessive reward-driven behaviours. That is, we will investigate whether…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Movement disorders (incl parkinsonism)
Study type	Interventional

Summary

ID

NL-OMON44476

Source
ToetsingOnline

Brief title
PD and the role of dopamine in visual attention

Condition

- Movement disorders (incl parkinsonism)

Synonym
Parkinson's disease

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit

Source(s) of monetary or material Support: European Research Committee (ERC)

Intervention

Keyword: fMRI, Parkinson's, Reward, Visual attention

Outcome measures

Primary outcome

Using fMRI analysis, we will identify regions of interest for all patients (VTA, SNpc, basal ganglia, LOC, V1-V4). These are associated with our hypotheses regarding reward contingencies and visual processing of the stimuli displayed in the task. In these regions, the processed brain activation data will be subjected to the following group-level analyses:

1. Within-subjects analyses, in which patients are compared in the withdrawal and the medicated condition. This will be carried out with repeated-measures ANOVAs.
2. Between-subject analyses, in which controls are compared both to patients in the withdrawal state, and to patients in the medicated condition, to identify whether patients in one or the other state are closer to *normal* as represented by controls. Alpha levels will be corrected for multiple comparison (Bonferroni; family-wise error correction; cluster threshold; permutation analysis; as appropriate).

We will carry out whole brain analysis for the resting-state scans, using our regions of interest as seeds for independent component analysis (ICA).

All analyses will be done using Python, FSL, Freesurfer, and SPSS.

Secondary outcome

We will use results from the questionnaires and neuropsychological assessment

of patients and investigate if these correlate with fMRI task activity in the

identified regions of interest and with fMRI resting state activity.

Study description

Background summary

Parkinson *s disease (PD) is a disease of the central nervous system. Patients typically present with motor symptoms, and these remain the primary target of clinical interventions. Nevertheless, it has long been recognized that PD is also characterized by non-motor symptoms, such as autonomic dysregulations, cognitive dysfunctions and neuropsychiatric disorders, and these have increasingly become the focus of study (e.g. Bosboom et al., 2004). Such symptoms are often related to degeneration of the dopaminergic system, and to medication that works through this system, such as L-DOPA or DA-agonists. In particular, it has been suggested that decision-making is altered both in the state of relative dopamine deprivation that characterizes PD patients during withdrawal from medication, and also in the medicated state itself (e.g., Frank et al., 2004). Such alterations of decision-making have in turn been linked to changes in behaviour of PD patients on medication, in particular to a proneness to gamble, hypersexuality, and compulsive eating and buying (Seedat et al., 2000; Wolters et al., 2008; Van den Heuvel et al., 2010). These are collectively referred to as impulse control disorders (ICDs).
We recently showed that previously rewarded stimuli automatically capture attention, even when that stimulus is no longer rewarding (Hickey et al., 2010). Disruption of pathways from the dorsal part of the substantia nigra (SN) and the ventral tegmental area (VTA) to the nucleus accumbens (NAcc) and caudate nucleus (CN) in PD patients has been associated with impaired motivational functions (Middleton & Strick, 2000a,b). Some studies have suggested a role for dopaminergic reward processing in guiding attention by altering the priority given to certain features over others (Berridge & Robinson, 1998; Hickey et al., 2010; Anderson et al. ,2011a, b). These and other results have led to the suggestion that dopamine may be important to the assignment of priority to environmental stimuli. Abnormalities in dopaminergic neurotransmission in PD may lead to aberrant prioritization of stimuli which could potentially explain the reward-driven behaviours in PD patients with ICD (i.e., gambling, hypersexuality, binge eating). In other words, these

reward-driven behaviours may be explained by processes that automatically steer attention to valued objects.
The present study is premised on the idea that prioritization of sensory input will be negatively affected in PD patients. Patients will show decreased sensitivity of attention to reward contingencies in the environment (i.e. a decreased tendency to pay attention to rewarding stimuli). Dopaminergic drug treatments should restore normal processing, as compared to controls, or perhaps even enhanced processing of sensory input in the case of ICD patients, as a result of normal or enhanced sensitivity to reward contingencies respectively.
The primary goal of this study is thus to investigate the role of dopamine in reward-modulated attention and visual processing in PD patients with varying levels of ICD symptoms. For example, it may be that extra attention given to rewarded features leading to positive reinforcement is an important element in learning (Roelfsema et al., 2010; Frank et al., 2004; Jocham et al., 2011) which may contribute to the cognitive and neuropsychiatric symptomatology of PD. Greater understanding of learning mechanisms in PD patients may thus have practical implications, since dopaminergic medication likely underlies behavioural alterations such as ICD. If alterations in attention due to dopaminergic medication indeed underlie deficits in learning and decision making, the research may also guide the development of strategies to mitigate these behavioural abnormalities.

Study objective

We aim to extend our recent work on fundamental mechanisms that underlie automatic influences of reward on attention to clinical populations that suffer from reduced and excessive reward-driven behaviours. That is, we will investigate whether impaired reward processing in PD patients is caused by alterations in selective attention. We will examine this mechanism in PD patients with varying levels of ICD symptoms, as we expect individuals with more ICD symptoms to show greater sensitivity to reward value and a greater automaticity in the allocation of attention toward rewarding objects than patients with lower levels or with no ICD symptoms.
Firstly, we plan to establish that all PD patients in a state of overnight withdrawal from medication are less sensitive to reward in their attentive response than normal controls. We will investigate this by examining known fMRI correlates of reward processing. We are particularly interested in regions where activation is elicited by reward feedback; ventral tegmental area (VTA), substantia nigra pars compacta (SNpc), and the basal ganglia (BG), including the ventral striatum (VSr), and their relationship to other regions that indicate the deployment of selective attention (visual cortex; areas V1-V4, and lateral occipital cortex (LOC)). Our expectation is that patients who are off medication should be less sensitive to reward than controls, reflected in reduced visual attention for rewarded stimuli. When the same patients are on medication, they should be equally or more sensitive than controls. In the case of patients with greater ICD symptoms, they should be

more sensitive to rewarded stimuli when on medication (Frank et al., 2004) and should show enhanced patterns of visual attention toward stimuli, as compared to controls. Selective visual attention will be quantified using an fMRI data analysis technique called multivariate pattern analysis (MVPA).
Secondly, in addition to analysing task-related fMRI BOLD signal to investigate our hypotheses, we will also look at resting-state fMRI activity, in particular the default mode network (DMN) and visual attention networks. We intend to assess how reward-related regions are connected to occipital visual areas. In line with our hypotheses, we expect to see differences in the functional connectivity of the basal ganglia to visual areas between patients and controls, and also within patients when they are on and off their medication.
As a final objective, we aim to relate the amount of pain participants experience as a result of their disease to connectivity measures of resting-state fMRI activity. Alterations in the DMN have been associated with pain in individuals experiencing various forms of chronic pain, in particular decreased connectivity of the medial prefrontal cortex (MPFC) to posterior parts of the DMN, and increased connectivity to the insular cortex (Baliki et al., 2014; Otti et al., 2013). In this study, pain-related questionnaires will be included during the neuropsychological assessment phase, and patients will give a brief update before and at a particular point during fMRI scanning. Correlations between these measures and resting-state fMRI activity will then be investigated.

Study design

A schematic of the study design is provided in Fig. 1 (see Protocol). Patients will first undergo neuropsychological assessment. For the fMRI sessions, we will perform a counterbalanced repeated measures study in which patients are scanned once during a state of overnight withdrawal from L-DOPA or 24 hour withdrawal from DA agonists, and once in a medicated state. This means that every patient undergoes the task session twice. On one day, they will undergo our task experiment before they have taken their morning medication - this is the state of withdrawal. On an evening later that same weekend (for one half of patients), or on an evening earlier that weekend (for other half of patients), they are tested after ingestion of their standard doses of dopamine medication - this is the medicated state. Both fMRI sessions occur in the same weekend, but are not on the same day, so that effects of an un-medicated morning don*t spill into the second fMRI session. The main neurophysiological difference between the withdrawal and the medicated state is thus the level of dopamine available within the brain of the patient. The counterbalancing of the on/off session being first or second is used to control for the effects of repeated testing. Healthy controls will undergo one fMRI session, with one half of controls participating in the morning and the other half in the evening.

The experimental task is the same for the two sessions, however the trial sequence is randomized in each. Participants visit the Transitorium building of

the Vrije Universiteit (VU) on one occasion and are subsequently scanned at the out-patients building of the VU Medical Centre, VUmc (Polikliniekgebouw, De Boelelaan, Amsterdam) over two separate fMRI sessions.

Intervention

Cognitive performance measurements of PD patients when on L-DOPA medication and during a practically-defined off-medication state (i.e. following overnight withdrawal of dopamine medication).

Study burden and risks

There will be no direct benefit for the subjects to participate in the study. However, participation is expected to result in increased insight into the neurobiological background of the disorder, which will contribute subsequently to the development of treatment alternatives, and particularly the mitigation of the cognitive side effects associated with pharmacological treatment. Cognitive impairments and especially impairments in visual attention in PD have been relatively under-investigated, as compared to the motor deficits associated with the disease. This project aims to dissociate effects on visual selective attention as a result of the disease itself, the prescribed medication, and the level of ICD symptoms in these patients. Results of this project will also have important implications in other groups of people with disturbances in their reward system, such as patients with addiction or obsessive compulsive disorder.

The risks can be considered minimally above negligible. In fMRI a strong magnetic field and radio waves are used to generate radio signals in the body. These signals are picked up by an antenna (frame), which is placed over the participant*s head. Patients will hear various noises at varying volumes during scanning. Thus, ear protection is always provided to reduce noise levels. In addition, an emergency button is always available in case the patient experiences too much discomfort and wishes to be taken out of the scanner. Patients may also experience some discomfort during withdrawal from medication. To minimize the duration of this, patients will be provided either with accommodation close to the imaging centre the evening before their off-medication session, or a taxi to chauffer them directly to the VUmc so that they can partake in the session in the early morning. A medical doctor will be on-site at the VUmc in case any assistance is required. Moreover, patients will be encouraged to take their medication if they feel excessive discomfort.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

-Diagnosis of idiopathic PD following UK Brain Bank criteria in Hoehn and Yahr
-40-75 years old
-Informed consent
-Normal/corrected-to-normal vision

Exclusion criteria

-Psychotropic medication (controls) other than L-DOPA or DA agonists (patients). If using psychotropic medication in the past, they must be at least 4 weeks off that medication.
- Major somatic disorder or psychosis
- Dementia (MoCA <21)
- History of head injury, stroke or other neurological diseases

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Other

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	09-08-2015
Enrollment:	48
Type:	Actual

Ethics review

Approved WMO Date:	10-03-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-12-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-01-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-03-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL47760.029.14