Is step initiation during improbable events affected in PD with or without FOG? An explorative study.

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Main objectiveTo investigate whether dopamine affects the ability to initiate the correct step in response to a sudden change (improbable picture in a predictable context) in PD with and without FOG. Secondary objectiveTo investigate whether...

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

Summary

ID

NL-OMON42242

Source
ToetsingOnline

Brief title
Step initiation in Parkinson's disease

Condition

- Movement disorders (incl parkinsonism)

Synonym
Parkinson's disease

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud
Source(s) of monetary or material Support: This research is funded by a European Community□s Seventh Framework Programme FP7/2012 to C Stummer and E Mallia under

grant agreement No. 316639

Intervention

Keyword: Action selection, Dopamine, Freezing of gait, Parkinson's disease

Outcome measures

Primary outcome

Average Reaction Time: defined as the average time from appearance of the visual stimulus to first unloading of any leg (Creath et al., 2013).

Secondary outcome

- Step Length: defined as the distance from step onset to end of step.

- Step Duration: defined as the time from step onset to end of step.

- Anticipatory Postural Adjustments: defined as the maximum increase in vertical force directed towards the stepping leg, normalized for body weight and corrected for the amount of loading (Mensink et al., 2014).

- Learning Rate: The time taken to reach 95% errorless performance. This will be measured only during training.

Study description

Background summary

Introduction
Parkinson*s disease (PD) is a progressive neurological condition that affects movement as well as behavior. It is typically characterized by slowness in initiating movement, muscular rigidity, and tremor (Rodriguez-Oroz et al., 2009). It is more common in the elderly (over 65) (Ma et al., 2014), and with an ageing population in Europe (EuropeanCommission, 2012) an increasing number of people will become affected by the condition.
The nature of their condition causes people with PD to make short shuffling steps when walking, making them more likely to experience a fall (Latt et al., 2009). Additionally, they take longer to perform everyday activities, and

eventually are unable to care for themselves. Around a third of people with PD experience *freezing* when trying to initiate a forward stepping movement (Nutt et al., 2011, Schaafsma et al., 2003, Chee et al., 2009) - known as freezing of gait (FOG). They describe this transient phenomenon (typically lasting <1 minute) as *being glued to the floor* (Schaafsma et al., 2003).
The difficulties in initiating a movement, such as a step, that people with PD face means that they have difficulty navigating their environment. For people with PD who also have FOG, initiating a step is even more of a challenge (Tard et al., 2014), as they experience *freezing* when they turn, go through doors or encounter obstacles (Schaafsma et al., 2003). The mechanisms underlying the movement difficulties observed in PD, with and without FOG, when initiating a step are still not well understood.

Rationale
To navigate an environment, we must be able to continually adapt to it. When faced with an improbable obstacle we have to suddenly adapt to it to, for example, prevent falling. To adapt, the brain selects the *best-at-the-time* action from a set of possible actions within a given environment - a process known as Action Selection (Cisek, 2007). Dopamine, a neurotransmitter in the brain, is thought to be critically involved in this process (Galea et al., 2012, Friston et al., 2012).
There is a severe loss of the brain cells that produce dopamine in people with PD (Lees et al., 2009). Their symptoms, including slowness in initiating movement and FOG episodes, worsen when off their dopaminergic medication (Giladi, 2008, Schaafsma et al., 2003). We propose that their ability to select the *best-at-the-time-action* is affected, and contributes to the difficulties observed, in PD, in initiating a step.
The importance of dopamine in Action Selection has already been shown for initiating finger movements in PD (Galea et al., 2012). During the task people with PD on and off dopaminergic medication, and controls, were asked to press four different buttons each of which corresponded to a picture on the screen. In a predictable context pictures appeared in sequence, however the sequence was at times interrupted, when a picture out of sequence appeared - an improbable picture. Participants had to suddenly adapt to this. In an unpredictable context pictures appeared in a random order. People with PD, off their dopaminergic medication, were unable to react (press the correct button) fast enough to the improbable pictures in a predictable context.
The improbability of an event has also been shown to precipitate *freezing* episodes in people with PD and FOG. When confronted with an improbable obstacle while walking on a treadmill people with PD and FOG, off their dopaminergic medication, are unable to initiate a forward stepping movement (Snijders et al., 2010).
To explore how initiating a step is affected in PD, action selection during step initiation will be investigated in PD and PD with FOG. The work on finger movements in people with PD will be translated to a stepping task. Participants, including age-matched controls, will be asked to make four different steps each of which corresponds to a picture on the screen, in both a

predictable and unpredictable context (as explained above).
Measuring participants with PD, and PD with FOG off their dopaminergic medication will allow us to investigate whether there is an action selection deficit, i.e. whether they are able to initiate the correct step in response to a sudden change (improbable picture in a predictable context). By measuring them also on their dopaminergic medication we can compare performance in *on* and *off* to investigate whether it is indeed dopamine that is contributing to the action selection deficit observed.
Our aim is to understand whether action selection contributes to the difficulties in stepping seen in PD with and without FOG.

Hypothesis
We hypothesize that action selection is affected in PD both with and without FOG, when off their dopaminergic medication. This means that they will be unable to make the right step fast enough in response to the improbable pictures in a predictable context, when compared to healthy age-matched controls. Additionally, we expect that action selection is more severely affected in PD with FOG, off their dopaminergic medication, when compared to PD without FOG in *off*. As dopamine is critical for action selection we do not expect the deficit to be present when subjects are tested *on* their dopaminergic medication.

Study objective

Main objective
To investigate whether dopamine affects the ability to initiate the correct step in response to a sudden change (improbable picture in a predictable context) in PD with and without FOG.

Secondary objective
To investigate whether dopamine affects step length and step duration, and anticipatory postural adjustments, in PD with and without FOG, when they attempt to make the correct step in response to a sudden change (improbable picture in a predictable context).

Study design

An experimental study analysing three parallel groups (PD-NFOG, PD-FOG, controls), for their movement performance to probable and improbable environmental cues (stimuli). More importantly this study does not involve any intervention.
Participants will be allocated to either of three groups: Controls, PD without FOG (PD-NFOG), PD with FOG (PD-FOG). PD participants will be tested in ON and OFF states (dopaminergic medication), preferably one week apart. Days for ON and OFF dopaminergic medication will be randomly assigned. After training, participants will undergo the Main Experiment Task. This will consist of 2

Unpredictable blocks, and 2 Predictable blocks. The order of the blocks will be randomised.

Study burden and risks

As this is not an interventional study, no immediate benefits are expected. Benefit comes from the impact that the results from this study will have on therapeutic strategies for people with Parkinson*s disease.
There are no expected risks during this study. Note however that some discomfort is expected from resurgence of the parkinsonian symptoms following withdrawal of antiparkinsonian medication during the OFF measurement.

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

• Men/women of age > 60 years
• Can provide written informed consent
• For participants with Parkinson*s disease: Idiopathic Parkinson*s disease, according to the UK Brain Bank Criteria (Hughes et al., 1992)
• For participants with PD and FOG: Presence of FOG (Subjectively: defined as a score of 1 on question *Have you experienced FOG in the past month* from the NFOGQ, and, objectively: objectively measured observed at any time by a neurologist or during previous experiments)
• For both PD groups: Clinically worsened (as measured by UPDRS) during OFF state (Galea et al., 2012)
• Able to walk without an aid, even when off dopaminergic medication

Exclusion criteria

- Presence of any other neurological disorders such as stroke or epilepsy or psychiatric disease
- Pain, and or major outstanding musculoskeletal/ orthopaedic conditions in their lower limbs or back (pain that prevents independent performance of an activity of daily living)
- Dyslexia (or unable to read and write)
- Visual impairments which would affect seeing the screen in the balance lab
- Uncontrolled diabetes or thyroid problems
- History of severe, frequent headaches
- Dementia (cognitive impairment): TICs-m score of <=27 (Knopman et al., 2010, de Jager et al., 2003, Markopoulou et al., 2014)
- ON-freezing (freezing when on dopaminergic medication) (Espay et al., 2012)
- Depression: GDS-5/15 score of > 4 (Weintraub et al., 2006, D'Ath et al., 1994)
- Patients with deep brain stimulation
- Polineuropathy

Study design

Design

Study type:	Observational non invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active

Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	26-02-2015
Enrollment:	45
Type:	Actual

Ethics review

Approved WMO

Date:	10-03-2015
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	NL51313.091.14