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Cosgrove, Jeremy, Hinder, Mark, St George, Rebecca et al. (5 more authors) (2021) Significant cognitive decline in Parkinson's disease exacerbates the reliance on visual feedback during upper limb reaches. Neuropsychologia. 107885. ISSN 0028-3932

https://doi.org/10.1016/j.neuropsychologia.2021.107885

Significant cognitive decline in Parkinson's disease exacerbates the reliance on visual feedback during upper limb reaches

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Keywords:

Parkinson's disease, dementia, reaction time, visual feedback, reach execution

Abstract:

While upper limb reaches are often made in a feed-forward manner, visual feedback during the movement can be used to guide the reaching hand towards a target. In Parkinson's disease (PD), there is evidence that the utilisation of this visual feedback is increased. However, it is unclear if this is due solely to the characteristic slowness of movements in PD providing more opportunity for incorporating visual feedback to modify reach trajectories, or whether it is due to cognitive decline impacting (feed-forward) movement planning ability. To investigate this, we compared reaction times and movement times of reaches to a target in groups of PD patients with normal cognition (PD-NC), mild cognitive impairment (PD-MCI) or dementia (PD-D), to that of controls with normal cognition (CON-NC) or mild cognitive impairment (CON-MCI). Reaches were undertaken with full visual feedback (at a 'natural' and 'fast-as-possible' pace); with reduced visual feedback of the reaching limb to an illuminated target; and without any visual feedback to a remembered target with eyes closed.

PD-D exhibited slower reaction times than all other groups across conditions, indicative of less efficient movement planning. When reaching to a remembered target with eyes closed, all PD groups exhibited slower movement times relative to their natural pace with full visual feedback. Crucially, this relative slowing was most pronounced for the PD-D group, compared to the PD-MCI and PD-NC groups, suggesting that substantial cognitive decline in PD exacerbates dependence on visual feedback during upper limb reaches.

1. Introduction:

Reaching to targets with the upper limb is an essential action for independent living. Such tasks are often undertaken in situations of reduced visual feedback, for example grabbing a tin from the back of a dark cupboard or reaching to turn on a bedside lamp in the middle of the night. How we integrate the available visual feedback to permit modification of the ongoing motor commands – thus allowing smooth and accurate reach execution – is a fundamental motor control issue in both healthy and clinical populations.

Parkinson's disease (PD) is a neurodegenerative disorder resulting in progressive motor dysfunction. One of the defining features is a characteristic slowing of movements, termed bradykinesia, which is attributed to reduced levels of dopamine within the basal ganglia (Dickson, et al., 2009). As well as the motor deficits, it is important to consider that cognitive decline – a core non-motor feature of PD – may also affect movement planning and execution. Cognitive impairment within a PD population can be subdivided into mild cognitive impairment (PD-MCI) and dementia (PD-D); while both of these groups perform abnormally on tests of cognitive function, activities of daily living (ADLs) are significantly impacted in PD-D, but not in PD-MCI (Emre, et al., 2007; Litvan, et al., 2012). Studies suggest that at the time of PD diagnosis approximately 20% of patients have MCI (Lawson, et al., 2016). At 10 years post diagnosis, 50% of those with PD have developed dementia (Auyeung, et al., 2012; Perez, et al., 2012; Williams-Gray, et al., 2013) and after 20 years this figure is 80% (Hely, Reid, Adena, Halliday, & Morris, 2008).

Previous studies have shown that reaching is impaired in PD. In PD patients with normal cognition (PD-NC), reaching with the upper limb towards a target is slower compared to healthy controls. Specifically, reaction time (RT), defined as the time between a 'go' stimulus and onset of voluntary movement (or muscle activation), is prolonged, and continues to increase as the disease advances (Kwon, et al., 2014). Movement time (MT), defined as the time from movement onset until reach completion, is also prolonged in both the *on* (after dopaminergic medications) and *off* (without dopaminergic medication) states (Castiello & Bennett, 1994; Castiello,

Stelmach, & Lieberman, 1993). When perceptual and decision requirements of the task are increased, such as when there is a choice between two or more alternative responses, some studies show more pronounced slowing in RT in PD patients compared to controls (Gauntlett-Gilbert & Brown, 1998). However, without considering PD-related cognitive deficits, it is difficult to discern the likely cause of prolonged reaction and movement times in PD.

Additional evidence suggests PD patients have a greater reliance on visual feedback to guide the reaching arm towards a target; PD patients are less accurate than controls when pointing (Adamovich, Berkinblit, Hening, Sage, & Poizner, 2001), or reaching and grasping towards a target in the dark, or when a target is illuminated but the pointing finger/reaching arm is not (Schettino, et al., 2006). It has been proposed that patients with PD are less able than healthy controls to integrate proprioceptive information from the arm with visual information, or information stored as a visual memory (Adamovich, et al., 2001). While patients with dementia were excluded from these particular studies, patients known to have MCI were not explicitly excluded, nor was a cognitive screening test undertaken.

It therefore remains unclear to what extent these motor planning and sensory integration deficits may be associated, at least to some extent, with PD-related cognitive decline. While there is some evidence to suggest links between RT and cognition in PD (Berry, Nicolson, Foster, Behrmann, & Sagar, 1999; Jordan, Sagar, & Cooper, 1992) – possibly related to executive dysfunction (Kwon, et al., 2014) – investigations into how cognitive ability affects movement duration in PD, and how movements are affected by manipulations of visual feedback, have not been systematically undertaken. For PD patients, such questions are highly relevant to their everyday activities, because cognitive impairment is common, and reaching is often required in situations of reduced visual feedback.

Here we investigated initiation and execution of upper limb reaches towards a stationary target in various visual feedback conditions, conducted at a natural, or fast-as-possible pace. We compared the time to initiate the reach (RT) and the time to

execute the reach (MT) in groups with PD and normal (PD-NC), mildly impaired (PD-MCI), or significantly impaired (PD-D) cognitive function, to healthy controls with normal (CON-NC) or impaired (CON-MCI) cognition. Based on prior research (Castiello & Bennett, 1994; Castiello, et al., 1993), we expected PD to significantly increase RT and MT, and that this prolongation would be exacerbated when less visual feedback of the moving limb was presented (Adamovich, et al., 2001; Schettino, et al., 2006), particularly in PD patients with reduced cognitive abilities.

2. Materials and methods:

2.1 Ethical approval

This study received UK National Regional Ethics Service approval and local Research and Development approval from Leeds Teaching Hospitals NHS Trust and was conducted in accordance with the principles stated in the Declaration of Helsinki. All participants provided written informed consent prior to participation.

2.2 Subjects

Fifty-five PD patients and 29 control participants (spouses, partners or friends of PD patients) were recruited from the regional neurosciences centre outpatient clinics of two neurologists who are movement disorder specialists (JA, SJ). Demographic data (age/gender) was recorded for patients and controls, and clinical data (LEDD does, disease duration) was collected for patients. Classification of PD patients into cognitive groups was made (by JC) in accordance with 'level 1' MDS diagnostic criteria (Emre, et al., 2007; Litvan, et al., 2012) using total Montreal Cognitive Assessment (MoCA) score (Nasreddine, et al., 2005) – a well-validated global cognitive screening tool in PD (Dalrymple-Alford, et al., 2010; Hoops, et al., 2009) – and global score on Clinical Dementia Rating scale (CDR) (Morris, 1993), based on an informant interview within one month of the initial assessment in order to ascertain ability to perform ADLs. The PD-NC group was defined by a normal MoCA score (≥26/30); PD-MCI by an abnormal MoCA score (<26/30) and score of 0 or 0.5 on the CDR; PD-D by an abnormal MoCA score and CDR score of ≥1 (Wyman-Chick & Scott 2015). MoCA score was used to categorise control participants into CON-NC (≥26/30) and CON-MCI (<26/30). On the basis of these assessments, the 55 PD patients were classified into PD-NC (n=22),

PD-MCI (n=23) and PD-D (n=10). The 29 control participants were classified into CON-NC (n=19) and CON-MCI (n=10).

2.3 Apparatus and Materials

Participants sat in a non-swivel high-backed chair facing a table at an adequate distance so that they could place their hands in the correct starting position whilst maintaining 90 degrees of flexion at the elbow. The required starting position for each hand was semi-pronated, such that the ulnar border of each hand was resting on the table. The little finger metacarpophalangeal (MCP) joint of each hand was placed on the relevant 'marker', five cm from the table edge and 20cm from the midline; see Figure 1. Participants were asked to hold their hands in a lightly closed position with the wrist in a neutral position, in line with the forearm. The participant's sternum was aligned with the centre of the cylindrical target object. The reaching distance from markers 1 and 2 (left and right hands, respectively) to nearest edge of the target cylinder was 32cm.

Figure 1 – Schematic drawing of the apparatus set-up:

SEU; Systems electronic unit: MCP; Metacarpal-phalangeal.

The target object was a cylindrical Philips Imageo rechargeable candle made of Perspex, eight cm diameter and 11.5cm height (Koninklijke Philips N.V., Amsterdam, Netherlands), modified to incorporate Bluetooth connectivity so that the light could be turned on and off by a remote tablet computer. Recordings of movement were made using a Polhemus Patriot (Polhemus Inc., Vermont, U.S.A) electromagnetic (EM) tracking device composed of a systems electronic unit (SEU), two EM sensors with six degrees of freedom and a magnetic transmitter. The position and orientation of the sensors, relative to the magnetic transmitter, were recorded at a frequency of 60Hz by the SEU for offline analysis. In this study the positional co-ordinates (*x, y* and *z*) of the wrist of each hand of the participant were analysed by attaching a sensor at the palmar aspect of the wrist.

2.4 Assessment protocol

All PD patients were tested whilst *on* (i.e., following dopaminergic medication), and their regular regimen of dopaminergic medications was not altered. All participants initially provided demographic data and completed the MoCA. PD patients were also assessed using the Movement Disorders Society revision of Unified Parkinson's Disease Rating Scale part III (MDS-UPDRS III). This validated scale, with a maximum score of 132, assesses the severity of motor dysfunction in PD with higher scores denoting greater severity (Goetz, et al., 2008).

Before commencement of each trial, a Research Assistant (JC) reminded participants of the relevant instructions for each visual condition (see below) and ensured that the participant and the cylinder were at the correct starting positions. Participants were instructed to reach and grasp the cylinder target "as though grasping a cup", lift it vertically and then place back on the table. The 'go' signal to start this reaching movement was a computer-generated beep sound. A demonstration was provided prior to commencement of the experiment. Trials alternated between hands until five reaches per hand, per condition, had been completed. There was a random, variable delay (range three to seven seconds) between the start of each trial and the auditory 'go' tone.

Reaches were conducted under four different task conditions, resulting in each participant performing a total of 40 reaches. Each condition was completed before moving to the next, and the conditions were completed in the following order: **FULL-NAT:** In normal lighting, participants were asked to reach to the target at a natural speed; **LESS-NAT:** The room was darkened as much as possible for this task so participants had reduced visual feedback of their reaching arm; full darkness was not achieved and thus participants were still able to see their reaching arm to some degree. Participants were asked to reach at a natural speed to the target, which in this instance was illuminated (such that vision of the target was not degraded) when the auditory go tone sounded; **FULL-FAST:** In normal lighting, participants were asked to reach as quickly as possible to the target; **NONE-NAT:** Participants closed their eyes (in readiness for the upcoming trial) and then reached for the cylinder at a natural speed. Once the cylinder had been lifted and placed back on the table the subject was

instructed to open their eyes. Eyes remained open whilst preparing for the next trial with the alternate hand. The Research Assistant (JC) observed participants and if the eyes opened during the reach the trial was repeated.

2.5 Data processing

The *x, y* and *z* coordinates from the wrist sensors were used to calculate the Euclidean distance (positional separation), D, between the wrist sensor and the magnetic transmitter (in the target) every 1/60th second using the following formula: $D = \sqrt{(x^2 + y^2 + z^2)}$ where *x, y* and *z* are the coordinate distances of the wrist sensor relative to magnetic transmitter. The position of the wrist sensor relative to the target for each time point during the reach was generated. Reach onset was defined as the first point after the auditory tone that the wrist sensor began to move towards the target, enabling RT to be calculated. The time point at which D reached the minimum value was defined as reach completion, enabling MT to be calculated. An average value was taken from the ten reaches per condition per participant.

2.6 Statistical Analysis

Demographic and clinical data were tested for normality using the Shapiro–Wilk test. When normality was met, variables (age, disease duration and MDS-UPDRS III scores) were compared with one-way ANOVA with GROUP as a between-subjects factor (five levels: PD-D, PD-MCI, PD-NC, CON-NC, CON-MCI). Non-parametric Kruskal-Wallis tests compared group differences when assumptions of normality were violated (levodopa equivalent daily dose (LEDD) (Tomlinson, et al., 2010) and MoCA). The categorical variable of gender was compared between groups using a Chi-squared test.

To determine how movement planning and execution varied according to PD diagnosis and cognitive ability, as well as a result of manipulations on the available visual feedback and reaching instructions, we conducted two-way ANOVA on RT and MT independently. GROUP was a between-subjects factor (five levels: PD-D, PD-MCI, PD-NC, CON-NC, CON-MCI) and reach CONDITION was a repeated-measures factor

(four levels: FULL-NAT, LESS-NAT, FULL-FAST and NONE-NAT). Because age varied between groups (see Results 3.1), we included age as a covariate.

For all analyses, the a-priori alpha level was set at 0.05, with violations of the assumption of sphericity ($\varepsilon < 0.7$) corrected by way of the Greenhouse-Geisser correction. Statistically significant ($p < 0.05$) main effects and interaction terms were further explored using post-hoc pairwise comparisons with false discovery rate (FDR) corrections for multiple comparisons. Partial eta-squared (η_ρ^2) are presented as a measure of effect size to assist in interpreting main effects and interactions. All statistics were undertaken using IBM SPSS Statistics 27 (Armonk, NY, USA).

3. Results:

3.1 Demographic and clinical data

Demographic and clinical data are shown in Table 1. There was a statistically significant effect of group on age ($F_{(4,80)}=3.0$, $p=0.024$, $\eta_\rho^2=0.13$), with post-hoc analyses indicating this effect was driven by CON-NC being younger than the CON-MCI ($p=0.032$), PD-MCI ($p=0.015$) and PD-D ($p=0.005$) groups. In addition, PD-NC were significantly younger than PD-D ($p=0.045$). A chi-squared test indicated gender differed between the groups ($\chi^2=18.3$, $p=0.001$), with a greater proportion of females in the control groups compared to the PD groups. ~~Although PD is more common in males, the gender difference here has been exaggerated by recruiting controls from the spouses, partners or friends of the PD patients.~~

There was a difference in disease duration across the PD groups ($F_{(2,53)}=5.9$, $p=0.005$, $\eta_\rho^2=0.18$). Post-hoc tests indicated this effect was driven by a longer disease duration in PD-D than both PD-NC ($p=0.005$) and PD-MCI ($p=0.014$) groups. Total MDS-UPDRS III score and LEDD were not significantly different between the three PD groups ($F_{(2,53)}=1.9$,$p=0.154$, $\eta_\rho^2= 0.07$; $H_{(2)}=1.2$, $p=0.537$ respectively. Finally, as expected, cognitive ability recorded via MoCA scores varied between the three PD groups $H_{(2)}=43.4$, $p<0.001$.

Table 1 – Demographic and Clinical details:

*Age, years (SD, range)	63.8 (7.9, 50-75)	70.5 (4.8, 62-79)	66.6 (9.4, 44-84)	69.8 (7.9, 47-85)	72.6 (5.3, 64-83)
*Gender (%F)	79%	90%	27%	42%	40%
*Disease duration, years	-	-	5.3 (3.7, 1-15)	5.9 (3.9, 1-15)	10.7 (6.3, 1-20)
MDS-UPDRS III	-	-	25.9 (11.0, 3-49)	28.6 (11.4, 7-52)	34.4 (12.7, 12-56)
LEDD, mg/day	-	-	656.0 (621, 0-2836)	606.2 (499, 0-2047)	835.8 (636, 0-2210)
*MoCA score	28.0(1.5, 26-30)	23.0(2.2, 18-25)	26.9 (1.1, 26-29)	22.2 (2.3, 17-25)	17.6 (4.0, 12-23)

* p<0.05 (main effect of GROUP).

MDS-UPDRS III; Movement Disorders Society revision of Unified Parkinson's Disease Rating Scale total score of section III: LEDD; Levodopa Equivalent Daily Dose: MoCA; Montreal Cognitive Assessment.

3.2 Reach Data

3.2.1 Reaction Time (RT)

Two-way ANOVA revealed statistically significant main effects of GROUP (F=7.956, $p < 0.001$, $\eta_\rho^2 = 0.290$) and CONDITION (F = 3.651, $p = 0.013$, $\eta_\rho^2 = 0.045$); however, the interaction between the two factors was not statistically significant (F = 1.624, $p = 0.086$, $\eta_\rho^2 = 0.077$). The covariate of age did not have a statistically significant effect on RT (F = 0.890, $p = 0.348$, $\eta_\rho^2 = 0.011$). Post-hoc pairwise comparisons revealed that, averaged across all reach CONDITIONS, the PD-D group exhibited slower RT than the other four groups (all $p < 0.001$). There were no statistically significant differences in RT between the other four groups. Averaged across all participant groups, RT was slower in FULL-NAT, compared to all the other conditions (all $p < 0.001$). RT was significantly faster in the FULL-FAST condition compared to all other conditions (all *p*

< 0.001). RT in the LESS-NAT and NONE-NAT conditions did not vary significantly (p = 0.612). See Figure 2A.

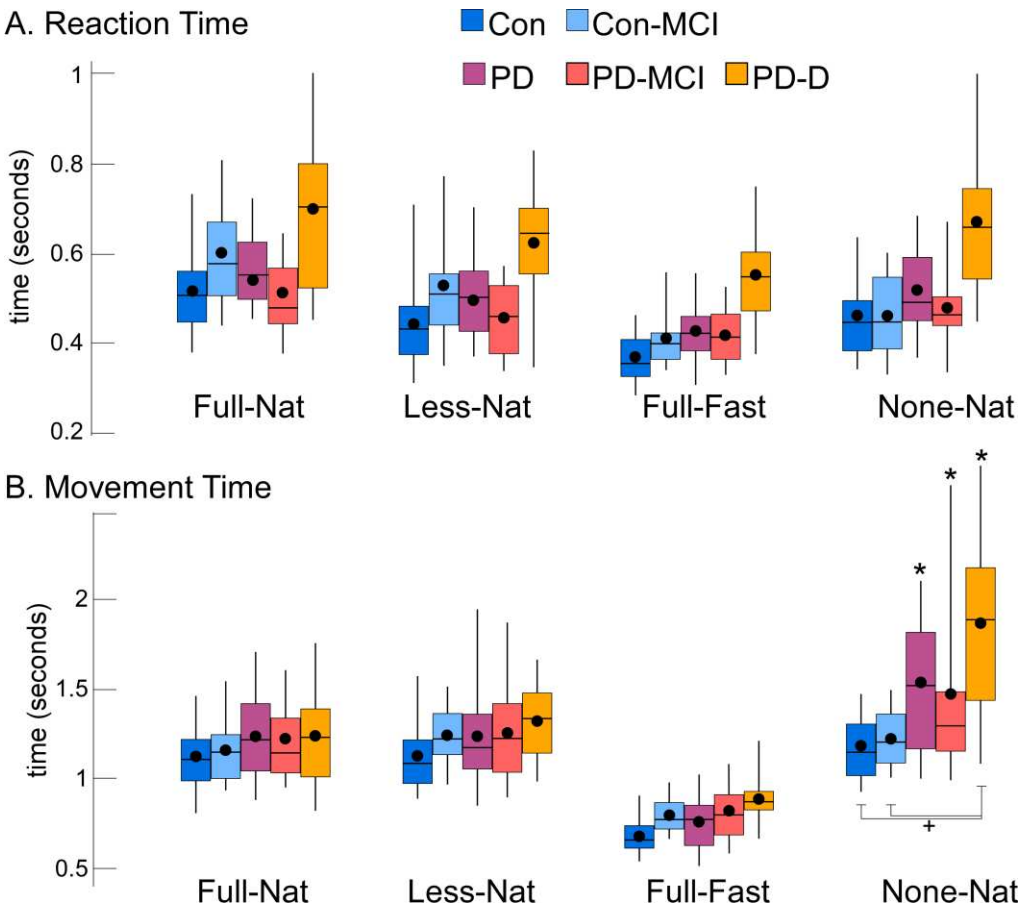

Figure 2 – Reaction Time (A) and Movement Time (B) in each of the four reach CONDITIONS and five participant groups. For all plots the Estimated Marginal Means are shown by the solid black dots and the horizontal black bands indicate the group median. The vertical spread of the boxes depicts the 25th and 75th quartiles for each group. The vertical lines, or 'whiskers' indicate 5th and 95th percentiles. See legend for group information. Significant key findings related to movement times are shown: '+' indicates significantly slower MT than both CON-NC and CON-MCI in the same visual condition, p<0.05, and '*' indicates slowing relative to this groups' performance in the other natural visual conditions, p<0.05.

3.2.2 Movement Time (MT)

Two-way ANOVA on MT revealed ~~statistically significant~~ the main effects of GROUP (F=1.886, p = 0.121, η_ρ^2 = 0.088) and CONDITION (Greenhouse-Geisser correction applied; F = 0.738, p = 0.530, η_ρ^2 = 0.009) were not statistically significant. However,

the GROUP x CONDITION interaction was statistically significant (F = 2.607, p = 0.003, η_ρ^2 = 0.118); accordingly, pairwise post-hoc comparisons were conducted on this interaction (see below). The age covariate did not significantly affect MT (F = 2.551, p = 0.114, η_ρ^2 = 0.032).

MT did not vary significantly between any of the groups in either the FULL-NAT and LESS-NAT conditions (all p > 0.223). In the FULL-FAST condition, the PD-D and PD-MCI groups exhibited longer MT than the CON-NC group (p = 0.008, p = 0.033, respectively). The most pronounced differences in MT between groups were observed in the NONE-NAT condition (see Figure 2B); in this condition the PD-D group exhibited significantly longer MT than both control groups (CON-NC: p = 0.004; CON-MCI: p=0.007). The difference in MT between PD-D and both PD-NC (p = 0.155) and PD-MCI (p = 0.063) did not reach statistical significance. These between-group differences observed at the specific conditions can be further explored by considering the differences in MT for each group between visual feedback conditions.

For each of the five groups, there was no statistical difference in MT between the FULL-NAT and LESS-NAT conditions (all p > 0.146). All groups exhibited a significantly shorter MT in the FULL-FAST condition relative to their respective MT in both FULL-NAT and LESS-NAT (all p < 0.001), indicating the ability of all groups to move substantially quicker towards the target in this condition. Critically, however, differences are apparent in how MT was affected in the NONE-NAT condition for each group. For both CON-NC and CON-MCI, MT in this condition *was not* statistically different from MT in either FULL-NAT or LESS-NAT conditions (all p > 0.323). For all PD groups, MT in the NONE-NAT condition was significantly longer than their respective MT in the FULL-NAT or LESS-NAT conditions (all p < 0.001). The respective effect sizes (PD-D: η_ρ^2 = 0.371 and 0.281; PD-MCI: η_ρ^2 = 0.106 and 0.059 PD-NC: η_ρ^2 = 0.153 and 0.118; for comparisons with FULL-NAT and LESS-NAT conditions, respectively) suggest the slowing in this NONE-NAT condition was particularly evident for the PD-D group.

4. Discussion:

This study compared upper limb reaching in PD patients with normal cognition, MCI or dementia, to control participants with or without MCI. Visual feedback and reach instructions were manipulated to ascertain how reach planning and execution are impacted by PD and associated cognitive decline. Across all reaching conditions, the PD patients with dementia (PD-D group) had significantly longer RT than all other groups, indicative of deficits in movement planning and initiation. When full vision or reduced vision of the limb was available, and reaches were made at a natural pace (FULL-NAT, LESS-NAT), all patient and control groups exhibited similar MT. When asked to reach more quickly, those PD groups with concomitant cognitive decline (PD-D, PD-MCI) exhibited slower MT than the CON-NC group. Finally, when reaching was assessed *without* visual feedback (NONE-NAT condition) MT was disproportionately prolonged in the PD-D group compared to PD patients with normal cognition or MCI (PD-NC, PD-MCI; Figure 2B). Overall, the results indicate a combined effect of PD and cognition on movement planning (i.e., the time to react to initiate a movement - RT). Furthermore, the results show for the first time that cognitive decline has a substantial influence on reach kinematics in PD when visual feedback is precluded, and feedforward planning of reach is thus emphasised.

4.1 Reaction time and movement time effects in PD with normal cognition

When visual feedback of the reaching limb was available, PD patients with normal cognition (PD-NC) exhibited RT and MT that did not differ statistically from the control group with normal cognition (CON-NC) (Figure 2A, B). These results are consistent with previous findings in similar patient groups during pointing (Adamovich, et al., 2001) and reach and grasp (Schettino, et al., 2006) tasks.

Reducing the richness of visual feedback of the limb by substantially darkening the room (LESS-NAT), while ensuring that the target remained distinct by way of illumination, did not cause a marked change in kinematic parameters compared to full vision (FULL-NAT) for PD-NC. Previous studies have reported that movement times are *prolonged* when vision of the reaching limb is completely precluded while illuminating the target (Adamovich, et al., 2001; Schettino, et al., 2006). The current findings thus extend upon previous research and indicate that partial feedback of reaching limb is

still sufficient to maintain similar reaching characteristics to those observed with full vision of the limb.

When visual feedback (of the limb *and* target) was completely precluded during the reach (NONE-NAT) by having participants close their eyes and reach to a remembered target, PD-NC but not CON-NC exhibited a significant prolongation of their MT. Previous studies comparing reaching in PD *on* and *off* states have shown that dopaminergic medication speeds up MT (Castiello, Bennett, Bonfiglioli, & Peppard, 2000; Negrotti, Secchi, & Gentilucci, 2005). The current finding indicates that movement slowing in the absence of visual feedback is not mitigated by being *on* medication and is thus unlikely to be a result of bradykinesia. It may be that PD patients have more difficulty rapidly integrating *proprioceptive* feedback in real-time to 'guide' their reaches in the absence of visual feedback, and thus slow down their movements to compensate. Indeed, proprioceptive afferents, both joint position sense (Maschke, Gomez, Tuite, & Konczak, 2003) and passive motion detection (Konczak, Krawczewski, Tuite, & Maschke, 2007) are disrupted in PD, increasing reliance on visual feedback during the reach. Consequently, when internal forward models (that prepare motor commands based on sensory input) only have access to proprioceptive cues, movement is compromised, manifested as slower reaches.

4.2 Accentuation of movement slowing in PD with cognitive decline

In addition to the slowing of movements described above for PD with normal cognition, the current study demonstrated – for the first time – that when cognitive decline occurs in conjunction with PD, movement slowing in the absence of visual feedback is exacerbated. Despite the relatively low number of participants in the PD-D group, a greater degree of slowing in PD-D compared to PD-MCI and PD-NC in the NONE-NAT condition was observed, such that *only* the PD-D exhibited MT that was significantly slower than the control groups in the absence of visual feedback (figure 2B) . It could be argued that movement slowing in the NONE-NAT condition occurred as a result of fatigue in PD given that – because of the study design- this condition was always undertaken at the end of the experiment. However, we feel that any fatigue effects are unlikely to drive the disproportionate slowing in the PD-D group. All

patients and participants were given adequate opportunity to rest between conditions, and between reaches within a condition, limiting fatigue effects. Moreover, the fact that only PD-D (and not PD-CON or PD-MCI) exhibited slower MT than controls in the NONE-NAT condition suggests that the movement slowing is not a generic fatigue effect, but rather an interaction of PD and cognitive impairment. The fact that no statistical differences in MT were observed between the three PD groups when full (FULL-NAT) or reduced vision of the limbs (LESS-NAT) was available is further evidence that bradykinesia is unlikely to be the influencing factor. Indeed, total MDS-UPDRS III score and LEDD were not significantly different between the three PD groups, and patients were tested in the *on* state, after taking their usual medications. The data are thus consistent with the notion that cognitive decline (e.g. less efficient processing in the higher-level association regions of the brain) may degrade how sensory input from the limbs (via proprioceptive afferents) is interpreted and used to modify ongoing motor commands. As described above, it is known that these afferents themselves are also degraded in PD (relative to healthy controls). Accordingly, when visual feedback is precluded, there ~~is~~ appears to be a combined effect of reduced 'quality' in sensory afferent signals, and a reduced capability to *process* those signals. Because of the low numbers of patients in the PD-D group, we acknowledge that these results and postulation needs to be interpreted tentatively, and confirmed in future larger cohort studies.

4.3 Declines in sensory and motor processing may underlie movement slowing

As well as the impaired processing of *somatosensory* afferents during the reach as proposed above, basal ganglia dysfunction in PD may result in abnormal processing of *motor* commands. The supplementary motor area (SMA) is thought to play a key role in the initiation and integration of multiple motor subroutines that make up a motor action (Goldberg, 1985), and motor subroutines are context dependent and 'anticipatory' (Goldberg, 1985; Schettino, et al., 2006). As part of a 'medial-circuit', the SMA and basal ganglia use an internal forward model system based on past-experience to predict the required motor action for a situation. Conversely, a 'lateral circuit', connecting the pre-motor and parietal cortices, is proposed to be responsive rather than anticipatory, driven by external stimuli rather than an internal forward

model (Conte, Khan, Defazio, Rothwell, & Berardelli, 2013; Goldberg, 1985). Damage to the basal ganglia in PD may cause the medial circuit to malfunction, and there is also good evidence that the SMA is underactive in PD (Berardelli, Rothwell, Thompson, & Hallett, 2001; Jahanshahi, et al., 1995). Accordingly, movements may become more dependent on the lateral circuit (Berardelli, et al., 2001), i.e. result in a greater dependence on external stimuli to generate and modify movements. This could translate into a greater reliance on visual feedback, in this case to guide reaching (Goldberg, 1985; Schettino, et al., 2006).

4.4 Spatial Working memory effects

An alternate explanation for the increased reliance on visual feedback to guide reaching in PD is decline in visual memory, specifically spatial working memory (SWM). SWM is critical in situations where participants reach without vision to a remembered location in space (the target) such as the NONE-NAT condition, where there was a three to seven second delay between trial commencement (and eye closure) and the go tone, compared to a one second delay in previous work (Schettino, et al., 2006). This delay potentially placed increased demand on SWM in our study, although the impact of elapsed time on SWM is debated (Cuthbert & Standage, 2018).

A number of studies have identified deficits in SWM in PD and have shown that these are more severe in moderate versus mild disease (Owen, et al., 1992) and when *off* versus *on* medication (Lange, et al., 1992). The caudate nucleus (within the basal ganglia) has strong connections with the dorsolateral prefrontal cortex as part of the dopaminergic cognitive neural network (Alexander, DeLong, & Strick, 1986; Lewis & Barker, 2009), and dopaminergic depletion of the caudate nucleus, a pathological feature of PD (Piggott, et al., 1999), is therefore a candidate region for impaired SWM (Possin, Filoteo, Song, & Salmon, 2008). Moreover, the fact that effective cognitive strategies are needed to both encode and maintain mental representations of spatial information during short-term memory tasks (Fisk et al. 2003) may account for the significant reach delays observed in the PD-D group.

Using total MoCA score as a global screening tool for cognition allowed categorisation of the Parkinson's patients in line with Level 1 Movement Disorders Society diagnostic

criteria for PD-MCI and PDD (Emre et al. 2007 & Litvan et al. 2012). Looking at specific MoCA subset scores could help better understand the underlying cognitive processes, but in the present study the small number of patients and limited spread of MoCA scores would impact the usefulness of correlation analysis. A larger study, with two dedicated tests of each of the different cognitive domains affected in Parkinson's (and therefore enabling categorisation of Parkinson's patients based on Level 2 MDS diagnostic criteria) could explore this idea in more detail.

4.5 Summary

- PD patients with dementia had significantly prolonged reaction times when reaching (at a natural pace, as fast as possible and with and without visual feedback) compared to healthy controls, PD patients with normal cognition and PD patients with mild cognitive impairment.
- In contrast to controls with and without mild cognitive impairment, patients with PD had a significantly longer movement times when reaching without visual feedback, when compared to reaching in full or reduced visual conditions, and the prolongation in movement time was greatest in the PD group with dementia.

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Conflict of interest:

"On behalf of all authors, the corresponding author states that there is no conflict of interest."

Acknowledgements:

"There are no funders to mention"