How does cognition affect reaching in Parkinson's disease?

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Objective: To explore differences in kinematic parameters of reach in those with Parkinson's disease (PD) classified into normal cognition (PD-NC), mild cognitive impairment (PD-MCI) and dementia (PDD).

Background: A highly specialised neural pathway passing from the occipital cortex to the premotor cortex via the posterior parietal cortex controls reaching. In the macaque monkey it has been shown that the major parietal reaching node is visual area V6A within the parietal reach region of the posterior parietal cortex. A human homologue of this area has been identified using functional MRI and wide-field retinotopic stimulation[1]. Information from visual area V6A passes to the dorsal pre-motor cortex and then the primary motor cortex to generate a motor action (Figure 1).

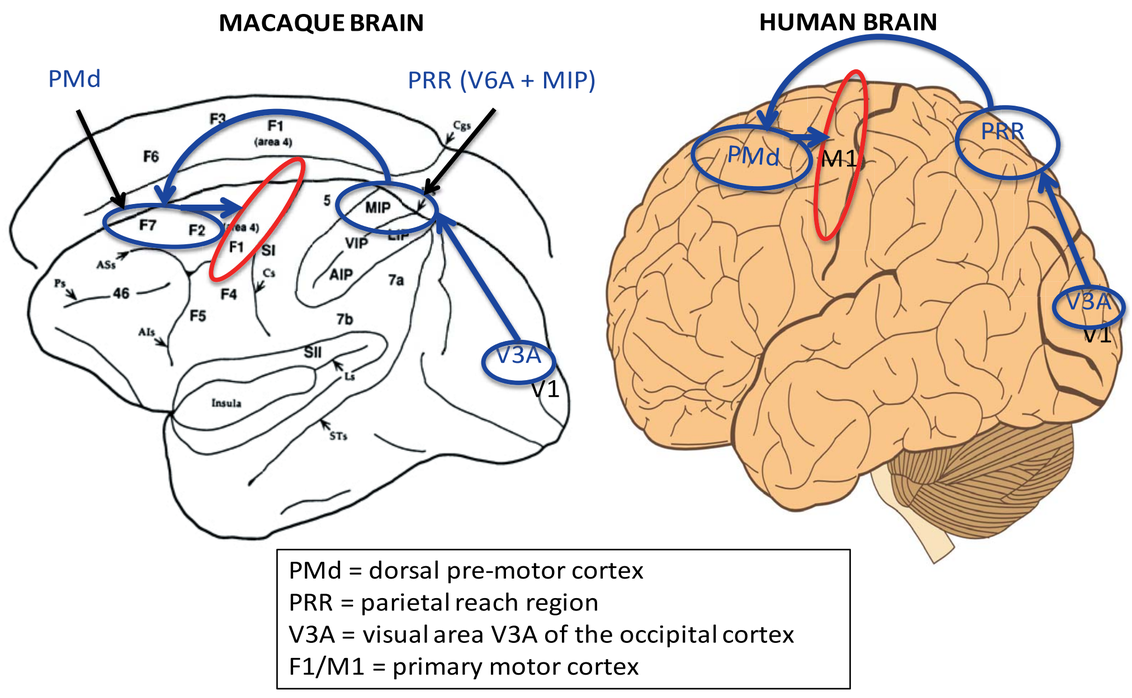

Figure 1: The reach pathway in the macaque and human - Visual information passes from the primary visual cortex (V1) to visual area V3A and then to the parietal reach region (PRR) containing visual area V6A, the major parietal node of reaching. Information then passes to the dorsal pre-motor cortex (PMd) and finally to the primary motor cortex (F1/M1) to generate a motor action.

Reach has previously been studied in PD-NC and there is evidence of a greater reliance on visual feedback to guide the reaching arm compared to healthy controls (HC) [2]. Reach has not been studied in PD-MCI or PDD.

We hypothesised that a progressive dependence on visual feedback to guide reach would be demonstrated across the PD cognitive groups.

Methods: Fifty-five PD subjects and 19 HC performed a reaching task under three conditions at a natural speed (Figure 2):

- full vision (FULL)
- towards an illuminated target in a darkened room (VIS)
- with eyes closed (MEM)

All PD subjects were tested whilst on. The PD subjects were classified into PD-NC (n =22), PD-MCI (n = 23) and PDD (n =10) according to MDS PD-MCI level 1 diagnostic criteria [3] (Table 1).

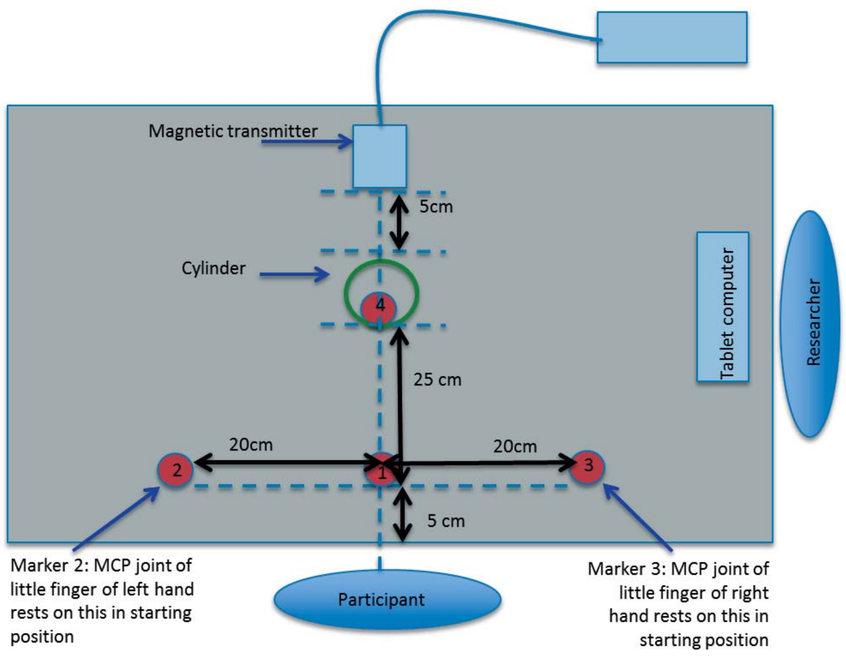

Figure 2: A schematic diagram of the experimental set-up. Not to scale.

Cognitive group	Diagnostic criteria
PD-NC	MoCA score ≥ 26
PD-MCI	MoCA score <26, global CDR 0 – 0.5
PDD	MoCA score <26, global CDR ≥ 1

Table 1: PD subjects were classified into cogntive groups using a combination of the MoCA score and the Clinical Dementia Rating (CDR) global score.

Movement sensing equipment was used and calculated kinematic parameters were compared using standard statistical tests.

Results: Age, MDS-UPDRS motor score and levodopa equivalent daily dose were not significantly different between the PD groups. PDD had significantly longer duration of disease and average Montreal Cognitive Assessment (MoCA) score was significantly different between the PD groups (Table 2).

	HC	PD-NC	PD-MCI	PDD	p1	p2
Age, years	63.8 (7.9, 50-75)	66.5 (9.4, 44-84)	70.0 (8.0, 47-85)	72.6 (5.3, 64-83)	0.328	
Gender, M:F	4: 15	16: 6	14: 9	6: 4	**0.002**	0.700
Handedness, R:L	15:4	20: 2	20: 3	8: 2	0.390	0.677
Disease duration, years	-	5.1 (3.7, 0.5-15)	5.7 (4.0, 0.5-15)	10.5 (6.4, 1.0-20)	-	**0.007**
MDS-UPDRS Part 3 score	-	25.9 (11.0, 3-49)	28.3 (11.5, 7-52)	34.4 (12.8, 12-57)	-	0.155
LEDD, mg/day	-	656.0 (621.7, 0-2836.3)	632.5 (492.8, 100.0-2046.5)	835.8 (636.3, 0-2210.0)	-	0.630
MoCA score	27.9 (1.5, 26-30)	26.9 (1.1, 26-29)	22.1 (2.3, 17-25)	17.6 (4.0, 12-23)	**0.09**	**<0.001**

Table 2: Demographic details of the HC and PD cogntive groups (SD, range). Abbreviations: p1 = statistical difference between HC and PD-NC.; p2 = statistical difference between the three PD cogntive groups; LEDD = levodopa equivalent daily dose.

PD-NC had a significantly longer movement time (MT), the major surrogate marker of reach, compared to HC in MEM but not in FULL or VIS. PDD had the longest MT in all three conditions compared to PD-NC and PD-MCI with a trend towards significance in MEM (Figure 3).

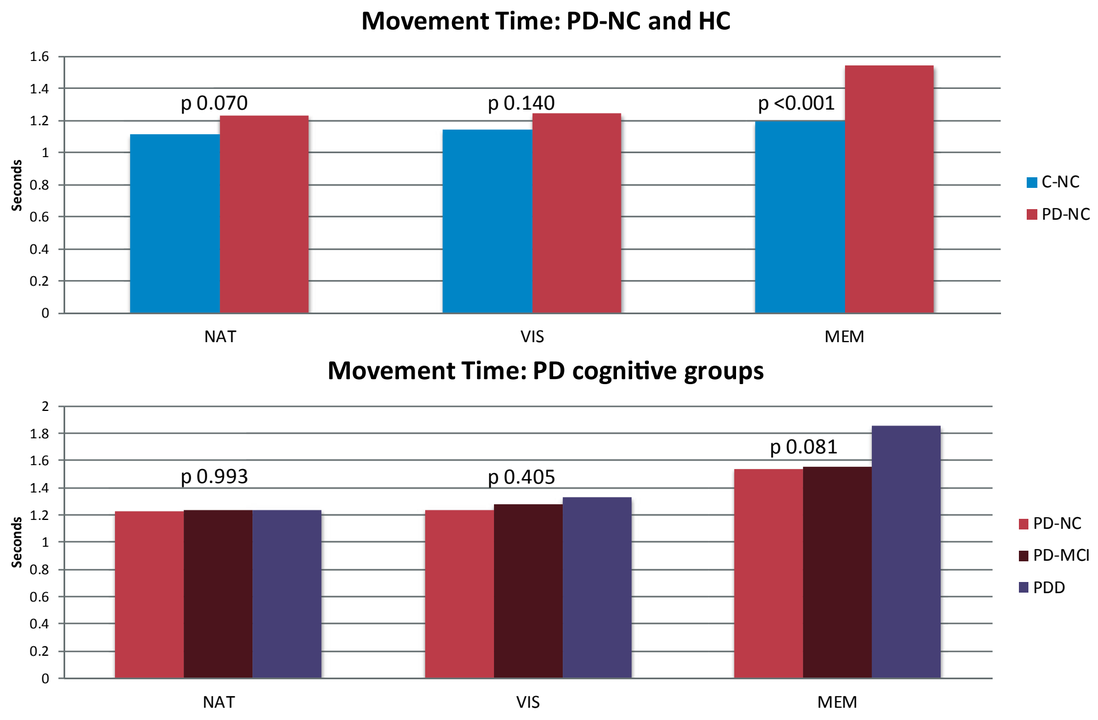

Figure 3: Movement time – the prinicple kinematic marker of reach – between HC and PD-NC and the PD cogntive groups.

In addition, times to attain peak acceleration, velocity and deceleration were significantly different between the PD groups in MEM and were longest for PDD (Table 3).

There were no significant differences in kinematic reach parameters between PD-NC and PD-MCI in any condition.

	PD-NC	PD-MCI	PDD	p
Movement Time, s	1.54 (0.45, 0.88 - 3.08)	1.55 (0.70, 0.86 - 4.15)	1.85 (0.69, 1.00 - 3.15)	0.081
Peak Acceleration, mm/s2	1613.6 (1.44, 713.4 - 3866.1)	1630.4 (1.24, 953.4 - 2556.7)	1246.0 (1.50, 572.5 - 2591.5)	**0.07**
Time to Peak Acceleration, s	0.41 (0.09, 0.30 - 0.63)	0.45 (0.19, 0.26 - 1.02)	0.57 (0.21, 0.34 - 1.10)	**0.01**
Peak Velocity, mm/s	604.4 (1.37, 301.9 - 1286.9)	592.9 (1.29, 33.6 - 972.6)	511.8 (1.48, 237.5 - 953.4)	0.140
Time to Peak Velocity, s	0.61 (0.17, 0.39 - 1.18)	0.62 (0.28, 0.37 - 1.42)	0.81 (0.29, 0.47 - 1.48)	**0.002**

Table 3: Calculated kinematic parameters in MEM for the PD cogntive groups (SD, range).

Conclusions: The only condition that resulted in a slower reach for PD-NC compared to HC was MEM. The kinematic parameters of reach suggest that PDD were more affected by MEM than PD-NC and PD-MCI.

Our results suggest a spectrum of increased reliance on visual feedback to guide reach: HC < PD-NC < PDD

Potential explanations for this include:

- **Progressive impairment of visual spatial memory in PD**
- **Progressive reliance on external stimulation to facilitate movement in PD**
- **Primary damage to visual area V6A via direct infiltration of alpha-synuclein and/or Alzheimer's disease related pathology**

References:

1) Pitzalis S et al. The human homologue of macaque area V6A. *NeuroImage* 2013: 82; 517-30.
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3) Litvan I et al. Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines. *Movement Disorders* 2012: 27; 349-356.