

Characterization Of Cognitive Decline Over 5 Years in an Incident Parkinson's Disease Cohort: Results from the CamPaIGN Study

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Introduction

Methods

Results

Discussion

- Parkinson's disease (PD) is associated with significant cognitive decline affecting multiple domains.
- Development of treatments for cognitive function are hindered by the complex nature of the cognitive changes, which are affected by factors such as disease severity, differential pathology and medication use.
- In a population-representative, incident PD cohort (CamPaIGN), we have previously reported a cumulative dementia incidence of 46% over 10 years, and demonstrated that posterior cortical deficits (i.e. semantic fluency and pentagon copying test) at diagnosis are the best neuropsychological predictors of this outcome (Williams-Gray et al., 2009, Williams-Gray et al., 2013).
- Here we report in more detail how cognitive performance in multiple domains changes over the first 5 years from diagnosis in a more cognitively able subgroup of the CamPaIGN cohort and assess the effects of medication and relationship with day to day function.

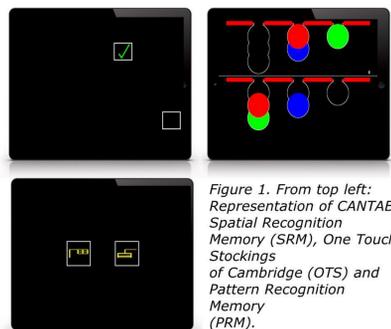


Figure 1. From top left: Representation of CANTAB Spatial Recognition Memory (SRM), One Touch Stockings of Cambridge (OTS) and Pattern Recognition Memory (PRM).

- 142 participants were included in the study at baseline and were assessed on the Unified Parkinson's Disease Rating Scale (UPDRS) and the Schwab & England (S&E) Activities of Daily Living scale. 78 of the 101 participants remaining in the study (77.2%) were able to carry out computerized testing at mean 5.2 year follow up. At baseline, there was no difference in baseline UPDRS (Motor) score or time from diagnosis, but the completer group were significantly younger than the group as a whole (Table 1).
- Participants also carried out a neuropsychological assessment lasting approximately 1 hour including the Mini Mental State Examination (MMSE), computerized CANTAB tests (Spatial Recognition Memory, SRM; Pattern Recognition Memory, PRM; and One Touch Stockings of Cambridge (OTS), a planning task based on the Tower of London task, Figure 1), semantic fluency (naming animals in 90 secs) and phonemic fluency (words beginning with F, A, S, for one min each), and pentagon copying.
- Data are described at baseline, mean 3.5 year follow up and mean 5.2 year follow up, with a detailed analysis of performance on individual tests for those patients who were able to complete a full neuropsychological battery at all time points ('completer subgroup'). The analyses presented in this poster focus on the completer cohort (N=78).
- Statistical analysis was conducted using repeated measures mixed modelling in SPSS 21. Models were adjusted for baseline age, gender and level of education. Significance was set at $p \leq 0.05$.

- At baseline, there was a significant difference in age and MMSE between the completer cohort and the group as a whole (Table 1). Furthermore, significantly better performance was observed on all neuropsychological tasks ($p < 0.05$) except for SRM in the completer group (data not shown). Across the entire group ($n=142$), there was a significant decrease in MMSE across 5 years ($p < 0.01$), but no change in the completer subgroup ($p=0.17$), (Figure 2A). Similarly, there was a significant change in the whole group for pentagon copying over 5 years ($p=0.04$), but not in the completer subgroup.
- In the completer subgroup, there were significant time-dependent deteriorations in semantic fluency, SRM and OTS with effect sizes of moderate magnitude ($d = -0.36$ to -0.49) (Figure 2B and 3). There were no significant changes in phonemic fluency or PRM (Table 2).
- S&E Activities of Daily Living significantly changed over the 5 years in both the whole group and the completer subgroup ($p < 0.01$). S&E change over time in completers correlated with OTS performance change over time (but not semantic fluency or SRM) ($r = .34$, $p = 0.04$), with 11.6% of the variance in the change in activities of daily living is accounted for by the relationship with OTS performance (Figure 3B).
- There was a negative correlation between change over 5 years in UPDRS (Motor) and change over 5 years in semantic fluency ($r = -.28$, $p = 0.02$) and OTS performance ($r = -.26$, $p = 0.03$), but not SRM.
- There was no association between changes over 5 years in OTS, SRM, PRM or semantic fluency performance and L-Dopa equivalent dose (mg/day) at the Year 5 visit.

- We have described the profile of cognitive change using a neuropsychological battery encompassing multiple domains in an incident PD cohort over the first 5 years from diagnosis.
- In the more cognitively-able group (i.e. 78 of the 101 remaining participants) able to complete testing to 5 years (completers), there was no change in MMSE over 5 years, but a significant decline in spatial recognition memory (SRM), and planning/executive function (OTS) known to be associated frontostriatal and dopamine function.
- Cognitive decline over 5 years was not influenced by L-Dopa equivalent dose at the year 5 time point in the completers.
- These findings demonstrate that; (i) in a typical, community-based cohort of PD patients, a significant proportion are unable to complete full neuropsychological testing within 5 years of diagnosis with implications for studies aiming to characterise PD-MCI, (ii) A selective progressive impairment in frontostriatal function occurs over the first 5 years in seemingly 'cognitively-able' PD patients with stable MMSE scores, supporting the hypothesis that the frontostriatal syndrome in PD evolves separately from a more posterior cortical dementing process (Williams-Gray et al., 2007; Robbins and Cools, 2014), (iii), This frontostriatal impairment is associated with a reduction in functional independence and is therefore of functional relevance to patients, and (iv), Frontostriatal impairments could be a target for pro-cognitive drug discovery programs in PD or PD-MCI.

Baseline Characteristics	Whole Group (N=142)		Completers (N=78)	
	Mean	SD	Mean	SD
Age (years)	70.4	9.6	66.4**	9.7
Gender (% male)	56.3	-	56.4	-
Time from diagnosis (years)	0.3	0.4	0.2	0.3
MMSE	28.0	1.5	28.5**	1.3
UPDRSM (max 56)	26.4	12.5	24.1	10.9
L-dopa equivalent dose (mg/day)	176.8	244.7	213.2	282.2
Education > 10 years (%)	44.4	-	53.8	-

Table 1. Baseline characteristics of both the whole group and the completer subgroup (who remained in the study and could perform the CANTAB tasks at the five year time point). MMSE= Mini Mental State Examination; UPDRSM= Unified PD rating scale motor subscale * $p < 0.05$, ** $p < 0.01$.

COMPLETERS (N=78)	Baseline Mean	SD	Year 3.5 Mean	SD	Year 5.2 Mean	SD
Age (y)	66.4	9.7	69.7	9.5	71.4	9.6
Time from diagnosis (y)	0.2	0.3	3.5	0.7	5.2	0.4
MMSE (max 30)	28.5	1.3	28.5	1.4	28.2	1.9
CANTAB OTS (max 14)	10.6	2.6	9.8	2.9	9.6	3.1
CANTAB PRM (max 24)	19.6	2.6	20.4	2.6	19.8	2.9
CANTAB SRM (max 20)	15.6	2.9	15.1	2.8	14.6	2.5
Phonemic Fluency	36.5	12.4	39.1	12.3	38.1	15.6
Semantic Fluency	22.3	7.4	20.5	5.8	19.5	6.5
Pentagon copying	1.9	0.4	1.8	0.6	1.9	0.4
Schwab and England	0.81	0.2	0.77	0.2	0.69	0.2
UPDRSM (max 56)	24.1	10.9	27.8	11.9	33.8	12.9

Table 2. Change over time demographic information and cognitive tasks scores in the completer subgroup. OTS: One Touch Stockings of Cambridge, PRM: pattern recognition memory, SRM: spatial recognition memory. MMSE: Mini Mental State Exam; UPDRSM; Unified Parkinson's disease rating scale motor subscale.

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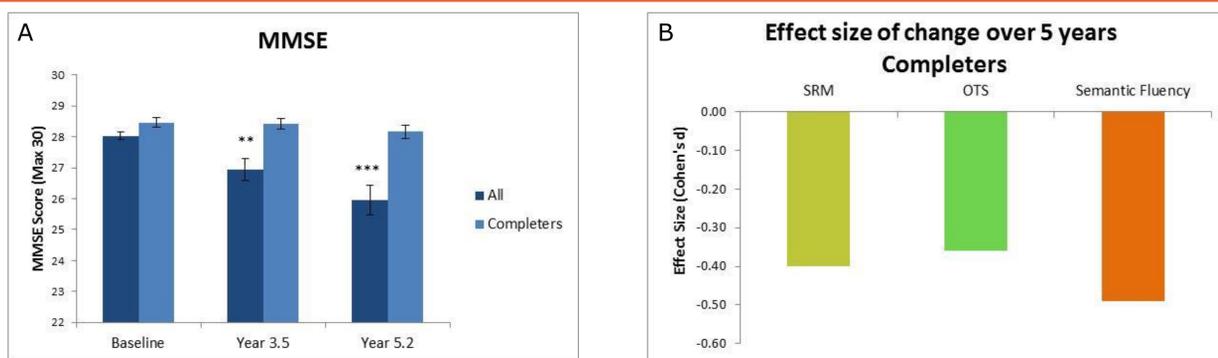


Figure 2(A). MMSE scores over three time points for scores for the whole group (All $n=142$) and completers ($n=78$). Asterisks indicate within-group change from baseline. (B) The magnitude of significant changes in CANTAB SRM and OTS and semantic fluency in completers over a mean 5.2 years are displayed as effect sizes. Data shown as mean \pm SEM; ** $p < 0.01$, *** $p < 0.001$

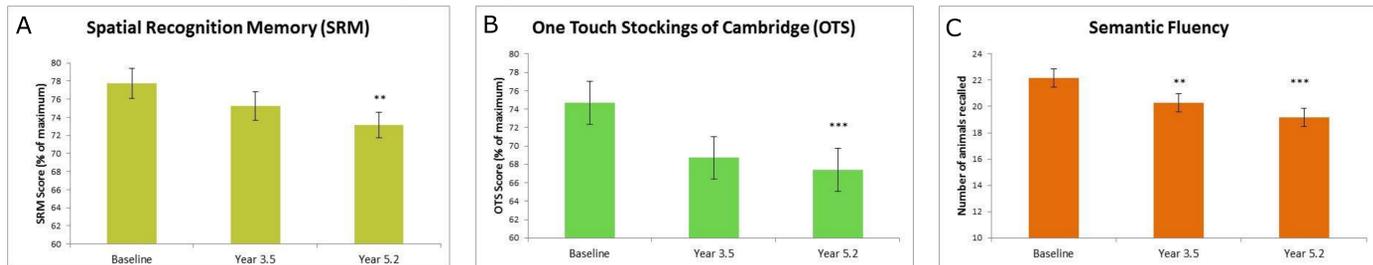


Figure 3 (A,B,C). Mean scores for (A) CANTAB SRM, (B) CANTAB OTS and (C) semantic fluency over mean 5.2 years for the completer cohort. Asterisks denote statistical significance for within-group change in score since baseline. Data shown as mean \pm SEM; ** $p < 0.01$, *** $p < 0.001$.

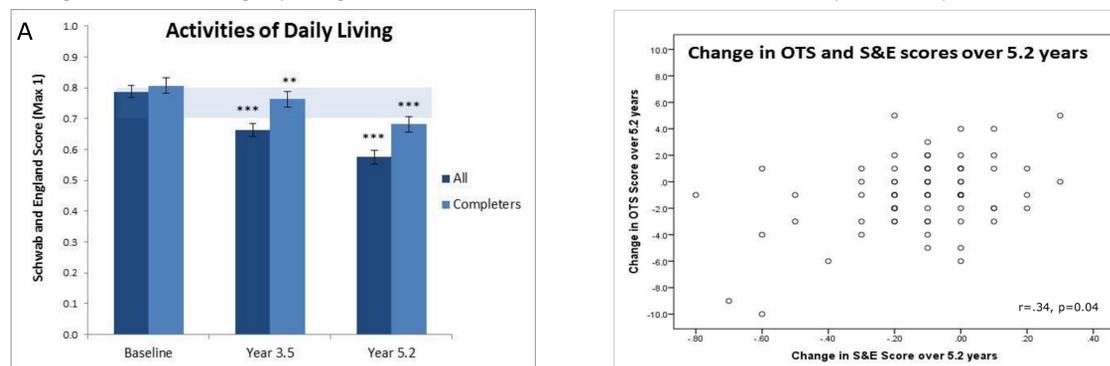


Figure 4 (A) Change in Schwab and England Activities of Daily Living Scale over 5 years in the whole group and completer subgroup. The pale blue bar represents a functional change from 'completely independent' (.8) to 'not completely independent' (.7). Stars represent significance for within-group change in score since baseline. (B). Relationship between change over time in OTS and change over time in S&E for the completers. ** $p < 0.01$, *** $p < 0.001$.