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Short communication

# A novel bedside task to tap inhibitory dysfunction and fronto-striatal atrophy in Parkinson's disease

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ABSTRACT

*Background:* Given the heterogeneity of mild cognitive deficits in non-demented Parkinson's disease (PD), sensitive and anatomically specific behavioural measures are crucial when evaluating cognition in this patient group. Inhibitory dysfunction is one such deficit increasingly being recognised in non-demented PD; however, few clinical measures exist to detect it and its associated fronto-striatal pathology.

*Methods:* In 50 non-demented PD patients and 27 controls we employ a novel measure, the Excluded Letter Fluency (ELF) test, to objectively assess inhibitory dysfunction. ELF results were also contrasted with an established inhibitory measure (Hayling Test) and covaried against grey matter atrophy via voxel-based morphometry analysis in a subset of patients.

*Results:* The findings show that patients made significantly more rule-break errors than controls on the ELF and this measure was more sensitive than the Hayling in detecting inhibitory dysfunction, classifying over 76% of patients in logistic regression analysis. Importantly, ELF rule-break errors correlated with grey matter atrophy in known inhibitory-control regions (orbitofrontal cortex, inferior frontal gyrus and ventral striatum).

*Conclusions:* The ELF is a brief bedside task that efficiently detects inhibitory dysfunction in non-demented PD. The utility of this novel behavioural measure is further substantiated by its anatomical specificity for fronto-striatal inhibitory control regions.



## 1. Introduction

Among the heterogeneous cognitive deficits that occur in non-demented Parkinson's disease (PD), there is mounting evidence to suggest inhibitory deficits in this patient group [1]. This is not surprising as both action-response inhibition and cognitive/behavioural inhibitory processes are mediated via fronto-striatal neural circuits known to be dysfunctional in PD. Studies using experimental measures of inhibition have revealed impairments in PD and linked these to dysfunction in inhibitory control brain regions [2–4]. Importantly, these regions, including orbitofrontal cortex and ventral striatum, differ from those regions implicated in working memory (i.e. dorsolateral/ventrolateral prefrontal cortex and dorsal striatum [5]), suggesting that inhibitory deficits are dissociable from the more general multi-tasking deficits seen in PD. However, the experimental paradigms employed to assess inhibitory processes typically require complex computerised set-ups and a large number of trials, which are not feasible in a clinical setting for routine assessment of cognitive function in PD patients.

In the current study, we introduce a novel, validated clinical measure—the Excluded Letter Fluency (ELF) task—to detect inhibition deficits in PD. We determine the concurrent validity of the ELF by contrasting it against the well-established Hayling Test of inhibitory function and cross-validate our behavioural findings by exploring whether the ELF is tapping into neuroanatomical abnormalities in fronto-striatal inhibitory control regions via voxel-based morphometry. We predict that the ELF, as a very demanding inhibitory measure, will detect inhibitory deficits in non-demented PD and emerge as an effective clinical tool to employ in the cognitive assessment of these patients.

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## 2. Methods

### 2.1. Case selection

Fifty non-demented PD patients were consecutively recruited from the Brain and Mind Institute Parkinson's Disease Research Clinic; all satisfied UKPDS Brain Bank criteria for diagnosis of PD; were between Hoehn and Yahr stages I and III and were assessed with the Mini Mental State Examination (MMSE). Patients performed behavioural testing in the ON state, having taken their usual medications. (For medication details, see Supplement). Twenty seven age- and education-matched controls were selected from a volunteer panel. The study was approved by the Human Ethics Committees of the Central and South Eastern Sydney Area Health Services and the Universities of Sydney and New South Wales.

### 2.2. Behavioural testing

Order of administration of the two behavioural tasks was randomised across participants and they were administered on the same day. For the ELF [6] subjects were given three trials of 90 s each to produce as many words as possible that did not contain a specified letter: "A", then "E" and "I". They were instructed that the words must be longer than three letters and they could not be proper nouns or derivations of the same word-stem (e.g. 'drive', 'driver', 'driving'). Subjects were provided with examples of inappropriate words and then asked to give words without the letter "S" as a practice. In between trials they were reminded of the rules. The ELF is represented by an overall correct score and two error scores: rule-violations (i.e. words containing the excluded letter, proper nouns, derivations of the same word stem and words with three letters or less) and repetitions. We further explored the rule-violations score in an imaging analysis.

The Hayling Test evaluates inhibitory control via a sentence completion task. The crucial second section contains 15 open-ended sentences that the subject must complete with a word unconnected in meaning, which requires inhibition of the prepotent response. We report response time for section two (Scaled score B), inhibition errors for section two (i.e. responses connected in meaning: AB Error Score) and overall scaled score. (For detailed explanation of the Hayling Test, see Supplement).

### 2.3. Behavioural analyses

Data were analysed using SPSS18.0 (SPSS Inc., Chicago, Ill., USA). Parametric demographic and clinical data were compared across groups via one-way ANOVAs followed by Tukey post-hoc tests. A priori, inhibitory control variables were checked for normality via Kolmogorov–Smirnov tests. Variables showing non-parametric distribution were analysed via Chi-square, Kruskal–Wallis and Mann–Whitney *U* tests. Pearson correlations were used to compare inhibitory control measures. We employed backwards Wald stepwise binary logistic regression analysis to determine the efficacy of inhibitory control variables in predicting group membership.

### 2.4. Imaging acquisition and voxel-based morphometry (VBM) analysis

A subset of 12 PD patients and 15 controls were scanned and included in a VBM analysis to determine the relationship between ELF rule-violations and grey matter atrophy. A region-of-interest mask for prefrontal and striatal brain regions was created and the relationship between ELF performance and grey matter intensity was considered significant at $p < 0.05$ False Discovery Rate (FDR) corrected for each voxel and a cluster extent threshold of at least 20 contiguous voxels. (For details, see Appendix).

## 3. Results

### 3.1. Demographics, clinical characteristics and screening measures

Participant groups did not differ in age or education ($p$ values $> 0.1$). Patient MMSE scores were significantly lower than the controls ($p < 0.01$), although still well above the cut-off for dementia [7] (See Table 1).

Independent *t*-tests revealed no differences in demographics or clinical characteristics between the overall PD sample ($n = 50$) and the group that underwent further imaging analysis ($n = 12$) and there were no differences between the overall control group ($n = 27$) and the subset with imaging ($n = 15$) ($p$ values $> 0.1$).

### 3.2. Inhibitory control measures

On the ELF, patients and controls did not differ with respect to total amount of words produced over the three trials or their repetition errors ($p$ values $> 0.1$). However, PD patients made significantly more rule-violations than controls ($p < 0.000$). On the Hayling, there was no difference between the groups for inhibition time (Scaled Score B) or overall scaled score ($p$ values $> 0.1$), but PD patients committed significantly more inhibition errors (AB Error Score) compared to controls ($p < 0.01$). (See Table 1).

Independent *t*-tests showed that the overall PD and control samples versus the subsets included in the imaging analysis did not differ on any inhibitory control measures ($p$ values $> 0.1$).

### 3.3. Concurrent validity and classification sensitivity of the ELF measure

Pearson correlation analysis for PD patients and controls revealed a strong positive relationship between failures of inhibitory control on the ELF (rule-violation score) and inhibitory failures on the Hayling (AB score) ($r = 0.368$, $p < 0.01$).

Entering the ELF rule-violation and Hayling AB scores in backwards step-wise regression produced a significant model [$\chi^2 = 21.402$, $p < 0.000$, Nagelkerke's $R^2 = 0.390$] with only the ELF rule-violation score emerging as a significant predictor variable [$\beta = -0.299$, $p < 0.01$] and 76.6% of PD patients being distinguished from controls on this measure alone.

### 3.4. VBM − correlation with ELF inhibition score

We entered ELF rule-violation scores as covariates in the design matrix of the VBM analysis. PD patients' rule-violations covaried with grey matter atrophy in medial orbitofrontal cortex (OFC), left inferior frontal gyrus (IFG) and right nucleus accumbens (ventral striatum − VS). (See Supplementary Fig. 1 and Supplementary Table 1).

## 4. Discussion

Our results unequivocally show that the ELF is a sensitive measure to assess inhibitory dysfunction in non-demented PD patients, with good anatomical specificity for inhibitory-control brain regions.

On the ELF test PD patients made significantly more rule-violations than controls, indicating deficits in inhibitory control

**Table 1**
Mean (SD) values for controls and PD patients on demographics, clinical characteristics and measures of inhibitory control.

| Demographics, clinical characteristics and behavioural results | Controls | PD | $F/\chi^2$ values |
|---|---|---|---|
| *N* | 27 | 50 | – |
| Sex (M:F) | 16:11 | 34:16 | – |
| Age (years) | 65.6 (6.7) | 63.8 (7.7) | n.s. |
| Education (years) | 14.0 (3.2) | 13.4 (2.6) | n.s. |
| MMSE (max. 30) | 29.4 (0.81) | 28.0 (2.0) | ** |
| Disease duration (years since diagnosis) | – | 5.8 (4.4) | – |
| Hoehn & Yahr stage | – | 2.1 (0.46) | – |
| Dopamine dose equivalent (mg/day) | – | 775.6 (545.5) | – |
| Excluded letter fluency | | | |
| Total correct | 46.5 (12.8) | 47.7 (12.1) | n.s. |
| Rule-violations[a] | 4.1 (3.1) | 8.2 (5.3) | *** |
| Repetitions[a] | 0.70 (1.0) | 0.96 (1.6) | n.s. |
| Hayling test | | | |
| Scaled score B (inhibition time)[a] | 5.9 (1.0) | 5.7 (0.8) | n.s. |
| AB score (inhibition errors)[a] | 3.0 (5.5) | 10.0 (12.0) | ** |
| Scaled score overall[a] | 6.4 (1.2) | 5.8 (1.2) | n.s. |

n.s. = non significant; *** = $p < 0.001$; ** = $p < 0.01$; * = $p < 0.05$.
MMSE = Mini-Mental State Examination.
[a] *F* values indicate significant differences across groups, otherwise due to unequal variance $\chi^2$ indicates differences across groups.