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Verbal fluency in Huntington's disease: a longitudinal analysis of phonemic and semantic clustering and switching

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Abstract

Two underlying components of verbal fluency tasks have been identified as *clustering* (the ability to generate successive words within a sub-category) and *switching* (the ability to shift from one sub-category to another). Selective impairment of switching ability occurs in patients with frontostriatal pathology, whilst clustering ability is compromised with temporal lobe dysfunction. Letter fluency tasks have been shown to be especially sensitive to frontostriatal deficits, whereas, category fluency tasks tend to be compromised by temporal lobe pathology. This study examined two types of verbal fluency task (letter fluency and category fluency) using two levels of analysis (phonemic and semantic) for clustering and switching measures. The performance of 21 frontostriatally compromised Huntington's disease (HD) patients was followed over an average of 3.5 annual follow-up visits. HD patients showed a significant reduction of correctly generated words over time, together with a significant increase in word repetitions. Phonemic switching decreased significantly over time for both letter and category fluency. Semantic switching, however, remained stable over time for both verbal fluency tasks. Clustering (both semantic and phonemic) likewise remained stable and did not vary longitudinally for either letter or category fluency. Hence, phonemic switching alone drove verbal fluency performance and this selective impairment can be explained by the progressive involvement of frontostriatal circuitry in the natural progression of HD.

Keywords: Frontostriatal; Neuropsychology; Cognition; Response set; Motor; Functional assessment

1. Introduction

Verbal fluency is a commonly used neuropsychological test which examines the ability to spontaneously produce words orally within a fixed time span. There are two types of verbal fluency tasks, i.e. letter fluency (variously known in the literature as initial letter fluency, phonemic fluency, phonological fluency, formal fluency, letter-cue word generation) and category fluency (or semantic (category) fluency, semantic-cue word generation). For *letter* fluency, words must be produced according to *phonemic* constraints (i.e. exemplars beginning with a specified letter of the alphabet such as 'f'). For *category* fluency, words must be produced according to *semantic* constraints (i.e. exemplars which belong to a specified semantic category, such as 'animal'). The measure of performance most commonly used is the number of correctly generated words within 60 s. This measure is believed to tap frontal [9,10] and temporal [8,11,24] lobe function and is generally decreased in Huntington's disease (HD) patients relative to controls [5–7,36]. Indeed, there is some evidence for a decline in performance over time for letter [17] and category fluency in HD [2], despite the lack of cross-sectional difference for both letter and category fluency when comparing early versus late HD [5,6].

A qualitative examination of the sequence and nature of the actual words generated provides further insights on the different types of processes that occur in this task. Observation of clustering (where related words are produced rapidly one after the other) and switching (where there is a slight pause before another cluster of related words is produced) has led to the proposition that two distinct but complementary cognitive strategies (i.e. clustering and switching) are in operation during verbal fluency tasks [14,37,40]. This concept has been refined and operationalised by Troyer et al. [37] and subsequently used to investigate further the nature of verbal fluency performance in neurologically impaired patients [31,36]. Thus, the extent to which patients demonstrate

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clustering which involves either a phonemic (e.g. words beginning with 'fa_' or 'fi_') or semantic (e.g. farm animals or safari animals) sub-category search, and switching which involves a shift to a new sub-category (phonemic or semantic) can be compared to yield further insights into the possible pathophysiological substrates critical for performance of verbal fluency tasks.

The *letter* fluency task has been shown to be especially sensitive to frontostriatal pathology, such as that following PSP [33] and frontal lobe lesions [9,29]. *Category* fluency tasks tend to be compromised by temporal lobe deficits seen in Alzheimer's disease [19,27,33] and particularly in semantic dementia [18,20]. This difference may be explained by the type of search necessary to perform the fluency tasks. The category fluency task utilises a more familiar search strategy because of its reliance on meaning, where activation of the first prototypical exemplar automatically activates other semantically related words [22]. The letter fluency task, on the other hand, is based on the more artificial level of word representation rather than meaning and prompts a less familiar phonological search strategy through the mental lexicon to find novel category neighbours [33]. Another interesting finding emerging from the literature is that *switching* tends to be reduced in frontal patients [38], frontostriatal disorders (e.g. PD with dementia patients [39]) and even in a divided attention paradigm which simulates frontal dysfunction in healthy participants [37]. *Clustering*, however, is impaired in patients with temporal pathology [38] and with Alzheimer's disease [39]. Whilst this frontostriatal–temporal dichotomy is not always clear cut [36], it appears that brain pathology has a systematic impact on the type of cognitive process that becomes compromised in verbal fluency tasks.

Verbal memory tasks require the use of working memory to operationalise the cue and track the exemplars generated. Several other processes are common among fluency tasks, such as the direction of attention to the task, implementation of appropriate search strategies, word retrieval and finally articulation of the word [26]. However, different search strategies are employed. For the letter fluency task, a primarily phonemic search is utilised; a phonemic switching strategy is instrumental for high performance because of the many sub-categories available, e.g. by phonemically varying the stem component to generate words that begin with a particular initial letter (such as sa_, se_, si_, so_, su_, sc_, sh_, etc.). Due to the vast number of alphabetic permutations as well as the short 60 s duration of the task, the clustering strategy is comparatively less important [36]. For the category fluency task, however, a primarily semantic search takes place and is fundamentally hierarchical as it emphasises a semantic clustering strategy which looks for many same-level exemplars of a rather broad semantic sub-categories (e.g. farm animals, safari animals, jungle animals, reptiles, etc.). However, the semantic switching strategy is also utilised when a semantic sub-category is exhausted and, therefore, both switching and clustering are important [36].

In the earlier stages of HD, pathology begins at the dorsal caudate nucleus which is part of the dorsolateral prefrontal cortex loop and gradually spreads throughout the frontostriatal system, with only minimal impairment of the temporal lobes [16]. From this, several hypotheses emerge regarding the change in performance of verbal fluency tasks over the natural progression of the disease. Firstly, the use of the more frontally-mediated phonemic switching strategy important in letter fluency performance may be progressively reduced in HD patients due to increasing frontostriatal involment over time. Secondly, use of the more temporal lobe dependent semantic clustering strategy instrumental in the category fluency task may remain stable. Thirdly, it will be of interest to examine if there is also a progressive phonemic switching deficit in category fluency, where a primarily semantic search strategy is implemented. In other words, whether a generalised phonemic switching impairment occurs as the disease progresses.

Only the first hypothesis has been partially investigated in a study of longitudinal performance of HD patients in a letter fluency task. Rich et al. [31] found a deterioration of phonemic switching on the letter fluency task over time in HD patients but no reduction in clustering on the same task. However, to test the generality of the findings, category fluency must be examined as well. Therefore, this study aims to address this for the first time by examining the pattern of deterioration in clustering and switching ability by conducting phonemic *and* semantic analyses for *both* letter and category fluency tasks, over the course of longitudinal testing in patients with HD.

2. Methods

2.1. Participants

Twenty one patients (15 males and six females) with mild to moderate HD at baseline were followed longitudinally via yearly assessments. All these patients had a positive family history of HD and more than 36 CAG repeats upon genetic testing for the IT-15 mutation [15]. They all gave written consent to participate in this ethically approved study. At baseline, the patients' mean age was 47.8 years (S.D. = 10.6) and they scored an average of 28.4 (S.D. = 1.7) out of 30 on the mini mental state examination (MMSE), 110.3 (S.D. = 9.5) on the national adult reading test (NART) and 24.7 (S.D. = 14.2) for the unified HD rating scale (UHDRS) total motor score. As a result of the progressive nature of ongoing enrolment to the cohort, the number of follow-up assessments post-baseline varied but overall patients were followed up for an average of 3.5 (S.D. = 1.1) annual assessments.

2.2. Procedure

At annual assessments, patients performed two verbal fluency tasks. Firstly, the letter fluency task where they were

required to orally generate as many words (excluding proper nouns and variants of the same root word) which began with the letters 'f', 'a' and 's' for 60 s each [4]. Secondly, for the category fluency task, patients were required to name as many animals as they could within a 60 s duration [7]. All responses were recorded verbatim. The MMSE [13] and UHDRS motor examination [21] were also administered at each yearly assessment. For the most recent (endpoint) assessment, several other neuropsychological tests sensitive to frontostriatal impairment in HD were undertaken including the intra/extra dimensional (IDED) set-shifting task of the Cambridge neuropsychological test automated battery (CANTAB) [12], Stroop test [34] and Reitan trail-making test [30] to examine the *relationship* between these tests and the verbal fluency measures investigated in this study.

2.3. Scoring method

For both the letter and category fluency tasks the typical quantitative measure of total number of correct words within 60 s was scored. Additionally, four qualitative measures were made for each verbal fluency task. These measures comprised two types (i.e. phonemic and semantic) of clustering and switching scores as described below:

1. Phonemic clustering score
   Clusters were defined as sequences of words which began with either (a) at least the same first two letters (verbal fluency, e.g. fan, fast, family; category fluency, e.g. cat, camel, caterpillar), (b) words which differed by rhyme or only by one phoneme (verbal fluency, e.g. fan, fin, fun; category fluency, e.g. cat, rat, bat) or (c) were homophones (verbal fluency, e.g. sole, soul; does not occur in category fluency).
2. Semantic clustering score
   Clusters were defined as sequences of words which belong to the same semantic sub-category (verbal fluency, e.g. swim, sand, snorkel—all to do with the seaside; category fluency, e.g. cow, pig, goat—all farm animals).
3. Phonemic switching score
   Phonemic switches were defined as the number of transitions between phonemic clusters, including single words (verbal fluency, e.g. 'fat, fall, fit' has one phonemic switch, whilst 'far, farther, farthing' has no phonemic shift; category fluency, e.g. 'ant, antelope, fish' has one phonemic shift, while 'zebra, lion, tiger' has two phonemic shifts).
4. Semantic switching score
   Semantic switches were defined as the number of transitions between semantic clusters, including single words (verbal fluency, e.g. 'fat, fall, fit' has two semantic switches, whilst 'far, farther, farthing' one semantic shift; category fluency, e.g. 'ant, antelope, fish' has two semantic shifts, while 'zebra, lion, tiger' has no semantic shifts).

These scoring rules were devised by Troyer et al. [37] (refer to their Appendix for further details and scoring examples), where errors and repetitions were included in the analysis of the four qualitative scores above, but not for the total correct score for the letter fluency and category fluency tasks. This is because, while it is not valid to include errors for the quantitative measure of correctly produced words, errors may arise from a deficit in the underlying cognitive processes under scrutiny and should, therefore, be captured by the more qualitative analysis of clustering and switching scores. Larger clustering scores reflect increased cluster size, whilst larger switching scores a higher frequency of switches. These indices have been shown to have high interrater reliabilities (i.e. $r > 0.90$) [37].

2.4. Analysis

To maximise the inclusion of data collected for each patient and to minimise the variability that is common in this neurological group, performance over time was quantified by the means of calculating regression slopes utilising each annual assessment data point available for each individual patient. The assumption of linear decline is relevant and has been previously used for this population [23].There were at least three data points (yearly assessments) for any patient, hence yielding a robust regression line to depict the picture of possible deterioration, improvement or stable performance over time. The effect sizes for the mean of patients' regression scores for each measure was then tested for significance with α at 0.05 (two-tailed). As patients' successive performances over time was of interest, a healthy control group was not used [2,3].

A correlational analysis was performed between switching and clustering measures on both fluency tasks with neurological indices and other neuropsychological tests which are implicated in the concept of mental set switching and are known to be sensitive to frontal dysfunction. Spearman's correlation coefficients were computed based on patients' raw scores at their most recent assessment, respectively. End point rather than baseline scores were used in order to obtain a greater range of performance on each measure. As this was an exploratory analysis, a non-conservative approach was adopted and adjustment for multiple comparisons was not made in order to avoid type 1 error. However, exact levels of significance are reported in the text.

3. Results

For both letter and category fluency, HD patients showed a significant reduction of correct words over time (letter fluency mean regression slope $= -0.10$, $P = 0.039$; category fluency mean regression slope $= -0.08$, $P < 0.005$), together with a significant increase in repetitions (letter fluency mean regression slope $= 0.03$, $P < 0.050$; category fluency mean regression slope $= 0.01$, $P < 0.010$).

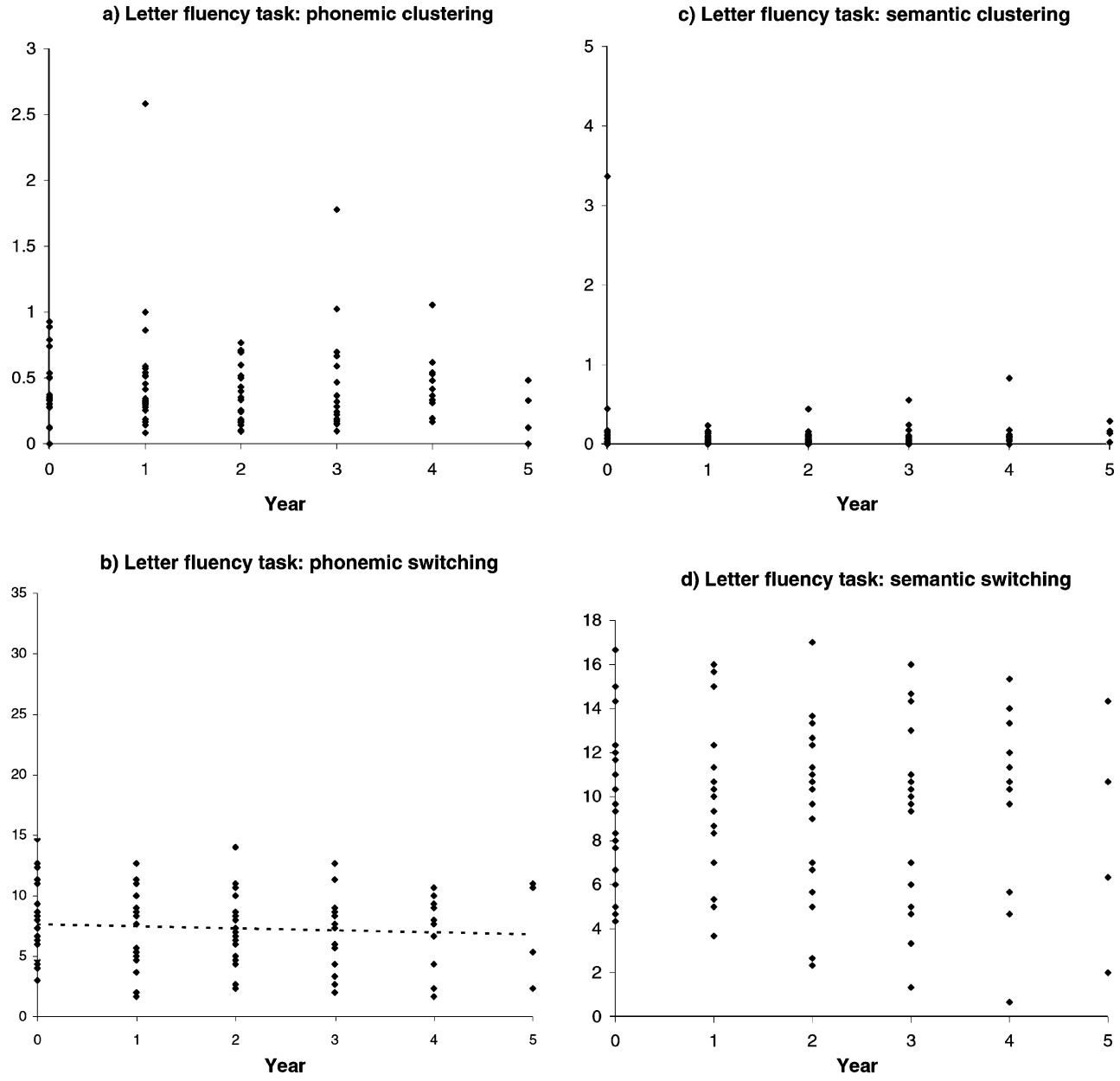

Fig. 1. Scatter plot of scores for (phonemic and semantic) clustering and switching for the letter fluency task.

Letter fluency errors, however, decreased over time (mean regression slope $= -0.03$, $P = 0.044$).

Figs. 1 and 2 illustrate individual HD patients' phonemic and semantic clustering and switching for the letter fluency and category fluency tasks. Generally, it shows that semantic clustering occurred more frequently for the semantic task and phonemic clustering for the phonemic letter fluency task. The regression slope for each patient's performance on each of the measures was obtained and from this the means were obtained and presented in Table 1. For measures where there was a significant change over time (phonemic switching in the letter fluency task and phonemic switching in the category fluency task), the mean regression slope for that measure was superimposed on the relevant scatter plot of scores (Figs. 1b and 2b, respectively). A key finding was that phonemic switching decreased significantly over time for letter (mean regression slope $= -0.06$, $P = 0.050$) and for category fluency (mean regression slope $= -0.08$, $P = 0.001$). Semantic switching however, remained stable over time for both fluency tasks. Likewise, clustering (semantic and phonemic) did not vary longitudinally for both letter and category fluency.

Spearman's correlation coefficients performed on patients' last assessment scores (end point data) are presented in Table 2. From this analysis, motor performance (UHDRS total: $r = -0.511$, $P = 0.018$; chorea: $r =$

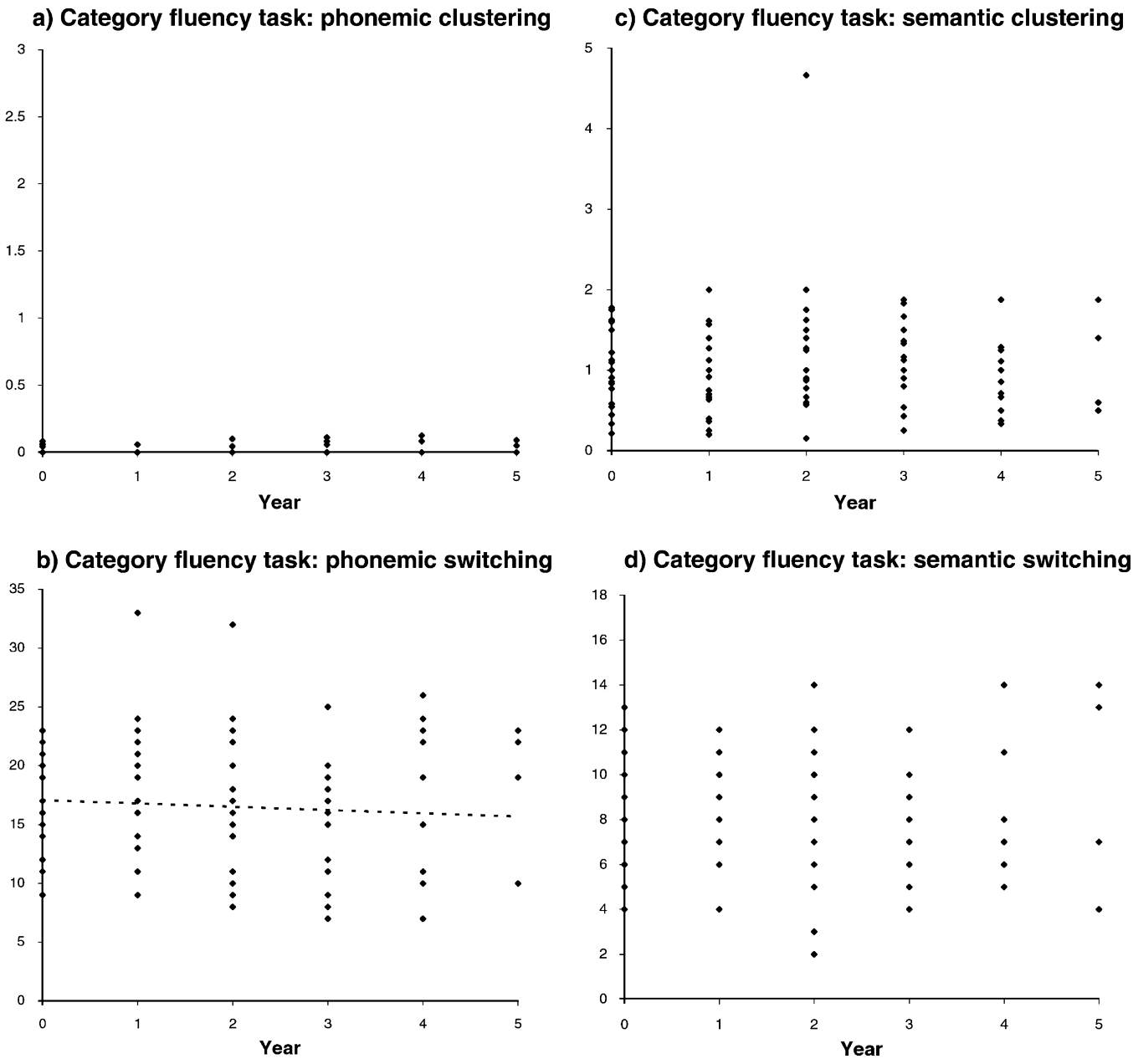

Fig. 2. Scatter plot of scores for (phonemic and semantic) clustering and switching for the category fluency task.

-0.558, $P = 0.009$; bradykinesia: $r = -0.467$, $P = 0.033$; total functional score: $r = -0.443$, $P = 0.045$) correlated with phonemic switching on the letter fluency task, such that low motor performance was related to low phonemic switching. Functional impairment in everyday living (total functional score: $r = -0.442$, $P = 0.046$; functional capacity: $r = -0.451$, $P = 0.040$) correlated with phonemic clustering in the letter fluency task such that impaired performance in one measure was associated with impaired performance in the other measure. General cognition as measured by the MMSE ($r = 0.447$, $P = 0.029$) correlated positively with the ability to perform semantic switching in the animal fluency task such that high MMSE scores were associated with high switching ability.

Both primary switching measures for the letter (phonemic switching) and animal (semantic switching) fluency tasks correlated with neuropsychological tasks which are influenced by frontal lobe functioning, such as the IDED set switching task, Stroop test and Reitan trail-making test. Specifically, phonemic switching for the letter fluency task correlated with the IDED task total error score ($r = -0.468$, $P = 0.032$), Stroop colour naming ($r = 0.553$, $P = 0.009$), Stroop word naming ($r = 0.591$, $P = 0.005$), Stroop interference ($r = 0.582$, $P = 0.006$), trails A ($r = -0.485$,

Table 1
Mean regression slopes on verbal fluency measures

	Mean regression slope	Standard error	Effect size	*P* value (two-tailed)
UHDRS total motor score	0.39	0.04	9.20	<0.005*
MMSE	−0.01	0.01	−0.55	0.582
Letter fluency				
Total score	−0.10	0.05	−2.08	0.039*
Total errors	−0.03	0.01	−2.02	0.044*
Total repetitions	0.03	0.01	2.17	0.030*
Phonemic clustering	0.00	0.00	1.54	0.124
Phonemic switching	−0.06	0.03	−1.96	0.050*
Semantic clustering	−0.01	0.01	−1.18	0.242
Semantic switching	−0.04	0.03	−1.43	0.153
Category fluency				
Total score	−0.08	0.02	−3.54	<0.005*
Total errors	0.00	0.00	−0.98	0.327
Total repetitions	0.02	0.01	2.46	0.014*
Phonemic clustering	0.00	0.00	0.01	0.992
Phonemic switching	−0.08	0.03	−2.58	0.010*
Semantic clustering	0.00	0.00	−0.40	0.689
Semantic switching	−0.03	0.02	−1.36	0.174

* Significant at $P < 0.05$.

$P = 0.026$) and trails B ($r = 0.471$, $P = 0.031$). Semantic switching for the animal fluency task correlated with the IDED task extra dimensional shift error ($r = 0.444$, $P = 0.044$), Stroop colour naming ($r = 0.584$, $P = 0.005$), Stroop word naming ($r = 0.582$, $P = 0.006$), Stroop interference ($r = 0.474$, $P = 0.030$) and trails B ($r = 0.495$, $P = 0.023$).

Secondary switching measures for the letter (semantic switching) and animal (phonemic tasks) fluency tasks also correlated with frontal neuropsychological tasks but on fewer measures. Specifically, semantic switching on the letter fluency task correlated with Stroop colour naming ($r = 0.503$, $P = 0.020$), Stroop word naming ($r = 0.601$, $P = 0.004$) and Stroop interference ($r = 0.509$,

Table 2
Correlations between (phonemic and semantic) clustering and switching measures with key neurological and neuropsychological indices

	Letter fluency task				Category fluency task			
	Phonemic clustering	Phonemic switching	Semantic clustering	Semantic switching	Phonemic clustering	Phonemic switching	Semantic clustering	Semantic switching
Neurological indices								
UHDRS								
Total motor score	0.25	−0.51*	0.16	−0.39	0.26	−0.39	−0.04	−0.35
Rigidity	0.05	−0.41	0.27	−0.38	0.35	−0.35	−0.16	−0.30
Chorea	0.32	−0.56*	0.05	−0.41	0.15	−0.41	0.11	−0.38
Bradykinesia	0.19	−0.47*	0.21	−0.38	0.27	−0.37	−0.06	−0.34
Total functional score	0.44*	−0.44*	−0.02	−0.30	−0.11	−0.42	−0.08	−0.43
Independence scale	−0.29	0.30	−0.04	0.18	0.01	0.30	0.13	0.31
Functional capacity	−0.45*	0.33	0.04	0.19	0.04	0.26	0.16	0.24
Neuropsychological indices								
MMSE	−0.02	0.34	−0.25	0.39	−0.05	0.38	−0.11	0.48*
IDED test								
Errors at ED stage	0.29	−0.15	0.00	−0.10	−0.08	−0.15	0.24	−0.44*
Latency at ED stage	0.32	−0.07	0.20	−0.06	0.01	−0.04	−0.30	0.07
Average errors (all stages)	0.35	−0.47*	0.11	−0.39	−0.08	−0.23	0.05	−0.35
Average latency (all stages)	0.32	−0.11	−0.05	−0.07	0.01	−0.18	−0.37	−0.04
Stroop test								
Colour naming	−0.19	0.55*	−0.13	0.50*	−0.06	0.57*	−0.03	0.58*
Word reading	0.11	0.59*	−0.22	0.60*	−0.18	0.51*	−0.04	0.58*
Interference	−0.11	0.58*	−0.24	0.51*	−0.021	0.46*	−0.03	0.47*
Reitan trail-making test								
Trails A	0.17	−0.48*	0.05	−0.40	0.08	−0.30	0.15	−0.41
Trails B	0.205	−0.47*	−0.01	−0.38	0.00	−0.40	0.14	−0.49*

* Significant at $P < 0.05$.

$P = 0.019$). Phonemic switching on the semantic fluency task correlated with Stroop colour naming ($r = 0.567$, $P = 0.007$), Stroop word naming ($r = 0.507$, $P = 0.019$) and Stroop interference ($r = 0.459$, $P = 0.036$).

4. Discussion

This study examined the longitudinal performance of HD patients on measures of verbal fluency over an average duration of 3.5 annual assessments. A *quantitative* analysis of the total number of correctly produced words showed that the patients score deteriorated over time on both letter and category fluency tasks and they also produced more repetitions. This finding is consistent with the role of the frontal lobe in tests of verbal fluency [2,9,10,17] and provides further evidence that longitudinal deterioration *within* HD individuals occurs, even though this is not evident from studies utilising cross-sectional paradigms [5,6].

A *qualitative* scrutiny of the sequence of words generated showed that as predicted, phonemic switching (but not clustering) deteriorated over time in the letter fluency task, consistent with Rich et al. [31]. Furthermore, this progressive impairment in phonemic switching also occurred in the category fluency task, again in the absence of any progressive clustering impairment. The consistency of a progressive switching impairment across letter and category fluency extends Rich's [31] findings and provides further evidence for a deterioration in cognitive flexibility. The ability to freely switch between sub-categories in order to generate appropriate exemplars is crucial in the performance of these time-constrained fluency tasks. Progressive impairment to the switching process, in contrast to stable clustering, is entirely consistent with the disruption of the frontostriatal circuit in HD [31,37]. HD patients' ability to utilise a clustering strategy for phonemic and semantic searches are not compromised and neither is the capacity for switching semantic sub-categories. It appears that HD patients' letter and category fluency performance gradually declined because they are unable to *switch* to different *phonemic* sub-categories in order generate more words. Phonemic searches and as a consequence phonemic switching may be considered more artificial, less automatic and, therefore, more frontally-dependent in contrast to semantic searches which involve regions of the brain implicated with representation of semantic knowledge, notably the temporal lobes [22,26,33]. Reliance of fluency performance upon frontostriatal (particularly the dorsolateral prefrontal) areas has been demonstrated in recent imaging studies [1,35]. The impairment in switching between phonemic sub-categories could be construed as an inability to shift cognitive response set and would, therefore, be compatible with the theory of deficient inhibitory processes in frontostriatal diseases [32].

The correlational analysis showed that there appeared to be an association between performance on switching indices and on key neuropsychological tests known to be sensitive to frontostriatal impairment (such as the IDED set-shifting task, Stroop test and Reitan trail-making test). This consistent trend for impairment in shifting between cognitive sets demonstrated across a range of tasks further underpins the direct relevance of the dysfunctional frontostriatal circuit in the explanation of a switching deficit in verbal fluency tasks. Of interest was the trend for dissociation in the pattern of correlations of motor indices and the overall measure of cognition (MMSE), with type of switching. Motor indices correlated significantly with phonemic switching, whilst the MMSE score correlated with semantic switching. These findings may be accounted for by the common frontostriatal motor loop mediating both motor behaviour and phonemic switching in the more frontally dependant letter fluency task. Support for this view comes from Parkinson's disease patients with frontostriatal impairment who often demonstrate bradyphrenia (i.e. slowness of mental processing) in conjunction with bradykinesia (i.e. slowness of motor execution) [25,28].

In summary, this longitudinal study has provided new evidence in support of the progressive impairment of switching and preservation of clustering in HD patients' performance of verbal fluency tasks. Specifically, phonemic switching alone drives verbal fluency performance and is selectively impaired, presumably due to the frontostriatal pathophysiology of HD.

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