Phonemic fluency quantity and quality: Comparing patients with PSP, Parkinson's disease and focal frontal and subcortical lesions

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Abstract

Progressive supranuclear palsy (PSP) can be difficult to distinguish from Parkinson's disease (PD), but has a much graver prognosis. PSP is characterised severely reduced output on measures of phonemic fluency, suggesting that it may be a specific marker of PSP. However, reduced phonemic fluency has also been noted in PD, and very few studies have actually compared phonemic fluency in PSP and PD. Although anecdotal reports suggest that phonemic fluency output in PSP may have specific characteristics, with more low-frequency words and perseverative errors, no study to date has formally explored this. Further investigation into phonemic fluency output and its cognitive and neuroanatomical correlates is now critical for improving our understanding of the verbal fluency in PSP. In this study, we compared phonemic fluency characteristics (including quantity, frequency and error rates) in patients with PSP, PD and focal frontal or subcortical lesions, and age- and education-matched healthy controls. We then compared these characteristics with performance on extensive neuropsychological testing. We found that PSP patients generated significantly fewer words than patients with PD and patients with right frontal focal lesions, and healthy controls. Phonemic fluency was also significantly reduced in patients with left frontal and subcortical focal lesions. However, there were no significant group differences in word frequency or error rates. Phonemic fluency was best predicted by performance on the Vocabulary and Hayling neuropsychological tests. We argue that these findings provide important evidence that reduced phonemic fluency is a hallmark of PSP and argue that the specificity of this impairment betrays an underlying impairment in energization, reflecting dysfunction of left frontal and subcortical networks.

Key words

Progressive supranuclear palsy; Parkinson's disease; Verbal fluency; Energization.

1. Introduction

Progressive supranuclear palsy (PSP) is a fatal neurodegenerative disease, with motor, ocular and cognitive features. It is defined by the intracerebral aggregation of microtubule-associated protein tau and its diagnosis can only be made post-mortem, upon neuropathological examination (Höglinger et al., 2017). It is increasingly recognised that PSP reflects a broad spectrum of diverse phenotypes (Ali et al., 2019), which may be difficult to distinguish from Parkinson's disease (PD; Poewe & Wenning, 2002). Indeed, both PSP and PD are complex neurodegenerative disorders characterised by motor and non-motor symptoms (Höglinger et al., 2017; Postuma et al., 2015). The non-motor symptoms include cognitive impairment and behavioural disorders, which are associated with reduced quality of life (Duncan et al., 2014; Schrag et al., 2003). However, PSP has a significantly worse prognosis, with more rapid and aggressive progression (Poewe & Wenning, 2002). Therefore, early detection is crucial for enabling access to appropriate interventions and support, as well as identifying patients suitable for clinical trials.

One striking characteristic of PSP is difficulty with propositional speech (Robinson et al., 2006). Families often describe a marked reduction in speech and initiation of conversations (Barker et al., 2018), with clinical reports of stuttering (Barker et al., 2018; Williams et al., 2007), palilalia (Barker et al., 2018; Cordato et al., 2006) and echolalia (Della Sala & Spinnler, 1998; Josephs & Duffy, 2008). In severe cases, this speech impairment can be described as dynamic aphasia (Robinson et al., 2006), where there is a striking reduction in propositional speech despite intact core language functions, such as naming, repetition and comprehension (Esmonde et al., 1996; Robinson et al., 2006; Robinson et al., 2015). Alongside this, there is also evidence of a behavioural adynamia, with reports of an apathetic syndome (Aarsland et al., 2001; Litvan et al., 1996), although this can present separately (Pellicano et al., 2017).

Upon formal testing, these everyday difficulties with propositional speech in PSP usually translate into severely reduced verbal fluency (Robinson et al., 2006), with greater impairment on phonemic rather than category fluency tasks (Bak et al., 2005; Rittman et al., 2013). Although reduced phonemic fluency has also been noted in PD (Henry & Crawford, 2004), very few studies have directly compared verbal fluency in PSP and PD. Of these, several have failed to examine phonemic fluency on its own, combining it with category fluency (Pillon et al., 1986; Rittman et al., 2013), and/or omitting to include a healthy control group (Pellicano et al., 2017; Pillon et al., 1995; Santangelo et al., 2018; Soliveri et al., 2000). When phonemic fluency alone has been examined, all studies have reported significant reductions in PSP relative to PD and healthy controls (Cordato et al., 2006; Foley et al., 2018; Lange et al., 2003). Indeed, phonemic fluency has been found to be the best discriminator between PSP and PD (Foley et al., 2018; Rittman et al., 2013), suggesting that this brief, but sensitive test may be invaluable for the early detection of PSP.

Yet, beyond total number of words generated, no study to date has explored how phonemic fluency output differs between PSP and PD. Phonemic fluency is thought to draw upon a number of different cognitive processes, including generation and selection (e.g. Robinson, 2013), with both types of deficits documented in single case studies of PSP (Robinson et al., 2015). However, we have yet to identify if there is a typical pattern of deficits specific to PSP, and how this might relate to wider cognitive performance.

Similarly, it is known that phonemic fluency involves several different neuroanatomical areas, including left frontal regions (Baldo et al., 2006; Costafreda et al., 2006; Robinson et al., 2012; Schmidt et al., 2019), especially the left inferior frontal gyrus (e.g. Robinson et al., 2012; Cipolotti et al, 2020), and subcortical regions (Ellfolk et al., 2013), but we have very limited understanding of which brain region underlies the phonemic fluency deficit in PSP. Previous research has suggested that although both PSP and PD involve the subcortex, only

PSP involves additional symmetrical atrophy of the frontal cortex (Cordato et al., 2005) and midbrain (Albrecht et al., 2019; Yang et al., 2014), likely disrupting important connections with frontal regions (Cummings, 1993). These findings suggest that PSP may involve frontal dysfunction arising from both direct cortical atrophy and indirect dysfunctional brain circuitry: a combination not present in PD (Cordato et al., 2005). A recent small region of interest study by Magdalinou and colleagues (2018) found sentence completion tasks to be associated with the left inferior frontal and posterior superior temporal gyri, but this study combined patients with PSP and corticobasal syndrome together, preventing identification of the brain regions specific to PSP. Thus, further investigation into phonemic fluency output and its cognitive and neuroanatomical correlates is now critical for improving our understanding of PSP to help support its early detection.

Interestingly, anecdotal reports have suggested that phonemic fluency output in PSP may indeed have specific and revealing characteristics. Firstly, Rittman and colleagues (2013) observed that patients with PSP may produce a "small number of low-frequency words (e.g. 'perambulator') rather than high-frequency words (e.g. 'put', 'people')" (p.4), which they suggest may reflect disruption of strategic word retrieval. However, this intriguing proposal has yet to be formally investigated.

Generation of any word on a fluency task is thought to involve 'energization' reflecting activation of the superior medial frontal lobes (Shallice et al., 2008), and access to temporal lobe lexical representations (Lambon Ralph et al., 1998). Access to low-frequency words, or those acquired later in life, is impaired in patients with deficient semantic lexical representations in the context of wider linguistic impairment arising from temporal lobe pathology (Bell et al., 2000; Barbarotto et al., 1995; Hirsh & Funnell, 1995). To date, there have been no accounts of the reverse: patients demonstrating greater difficulty generating

high-frequency words, or those acquired earlier in life, and hence no investigation of their cognitive and neuroanatomical correlates.

Secondly, a few case studies have suggested that patients with PSP may make an increased number of perseverative errors, generating more repetitions and permutations of the same word (Esmonde et al., 1996; Robinson et al., 2006). It has been argued that such errors signal difficulty with word selection, as has been documented following subcortical damage (Robinson, 2013). Although fluency errors have been investigated in other pathologies (Thompson et al., 2005; Woods et al., 2004) only one study that we are aware of has formally investigated these in PSP. Rosser and Hodges (1994) reported a higher proportion of perseveration errors on both phonemic and category fluency tasks in 10 PSP patients compared with patients with Alzheimer's disease, Huntington's disease and healthy controls, but with no significant group differences. However, this study combined both repetition and permutation errors together, perhaps masking any specific findings. Furthermore, this study did not examine the use of proper nouns or profanities, which are also thought to be errors and have been found to be markers of frontal involvement in other studies (Crowe, 1992; Ringman et al., 2010). Moreover, none of these studies examined how proportional error rates relate to performance on other measures of cognitive performance, precluding further insights into their underlying mechanisms.

These initial investigations into characteristics of words generated during fluency tasks raise the interesting possibility that deeper examination of phonemic fluency output may provide new insights into the cognitive and neuroanatomical mechanisms underlying the striking phonemic fluency deficit observed in PSP. Therefore, in this study we examined the phonemic fluency output in PSP patients and how this differed from patients with PD or focal brain lesions in left or right frontal regions or subcortical areas, and from age- and education-matched healthy controls. We sought to determine: (1) the quantity, frequency, age-of-

acquisition and error rates (including proper nouns and profanities) of words generated in a phonemic fluency task by patients with PSP, PD, focal brain lesions (left and right frontal, and subcortical) and healthy controls; and (2) how these fluency characteristics correlate with performance on intellectual, linguistic and executive variables, in order to elucidate further the cognitive and neuroanatomical mechanisms underlying the verbal adynamia seen in PSP.

2. Methods

2.1 Participants

All patients were recruited from the National Hospital for Neurology and Neurosurgery (NHNN), Queen Square, London.

The 23 PSP patients (15 male) were diagnosed using NINDS-SPSP criteria (Litvan, et al., 1996), with supportive MRI findings of midbrain atrophy in 60.87 % (n = 14) of all patients. All patients were followed-up for a minimum of three years to confirm diagnosis, and up until death (n = 19; M = 6.81 years onset, range = 3 – 15 years, SD = 2.57) or discontinuation of care at Queen Square (n = 2; M = 10.5 years, range = 8 – 13 years). They had a mean illness duration of 3.26 years (range = 1 – 10 years, SD = 2.51). Eleven of the patients were on dopaminergic drugs for motor symptoms, with a mean levodopa equivalent daily dose (LEDD) of 428.36 (SD = 252.80).

The 26 PD patients (18 male) fulfilled Queen Square Brain Bank criteria for PD. They had a mean illness duration of 8.31 years (range = 1 – 22 years, SD = 4.80) and mean LEDD of 826.84.

The 44 patients with focal brain lesions (23 male) were identified on the basis of detailed anatomical localization using standard atlases, as described previously (e.g. Murphy et al., 2013). Left frontal (LF) lesions (n = 16) had been caused by brain tumour (n = 12) or stroke (n = 4), and had a mean duration of 6.62 years since first presentation (range = 1 month to 20 years, SD = 6.94 years). The scans of eight of these were sufficiently high-resolution to enable voxel-based lesion mapping, which revealed a mean of 4552.12 total voxels affected, including 3766.98 in the grey matter. Right frontal (RF) lesions (n = 14) had been caused by brain tumour (n = 6) or stroke (n = 8); and had a mean duration of 4.67 years since first

presentation (range = 1 month to 17 years, *SD* = 5.86 years). Eight had high-resolution scans available and voxel-based lesion mapping revealed a mean of 4547.73 total voxels affected, including 3608.77 in the grey matter. Subcortical (SC) lesions (*n* = 14) had been caused by brain tumour (*n* = 5) and stroke (*n* = 9), and had a mean duration of 1.47 years since first presentation (range = 1 month to 10 years, *SD* = 3.22). Eight had high-resolution scans available, with a mean of 1243.28 total voxels affected, including 973.50 in the grey matter.

The 35 age-matched healthy controls (21 male) were recruited through NHNN or the Psychology Department of the University of Edinburgh. No participant had significant neurological or psychiatric history.

All participants had an absence of psychiatric disorders that might confound the results, history of alcohol or substance abuse, or previous neurological disorder.

The research was done in accordance with the Declaration of Helsinki and approved by the NRES Committee London – Queen Square and the University of Edinburgh's Department of Psychology Ethics Committee.

2.2 Measures

2.2.1 Background neuropsychological tests

All patients were administered a battery of neuropsychological tests. Current level of intellectual functioning was assessed using six subtests from the Wechsler Adult Intelligence Scale – Third Edition (WAIS-III; Wechsler, 1997), pro-rated to generate scores for both verbal (VIQ) and nonverbal performance intellectual abilities (PIQ), using the method described previously (Foley et al., 2018). The National Adult Reading Test (NART; Nelson, 1982) was used in order to estimate the premorbid level of intellectual functioning, by

generating each patient's predicted Full-Scale IQ (PFSIQ). Language functioning was assessed using the Vocabulary and Similarities subtests from the WAIS-III (Wechsler, 1997), and the Graded Naming Test (McKenna & Warrington, 1983). Executive functioning was assessed using the Digit Span subtest from the WAIS-III (Wechsler, 1997) and the Hayling Sentence Completion Test (Burgess & Shallice, 1997). PSP and PD patients also underwent mood assessments using the Hospital Anxiety and Depression Scale (Zigmond & Snaith, 1983) and the Apathy Evaluation Scale (Marin et al., 1991).

2.2.2 Phonemic fluency

All participants were asked to name as many different words that start with the letter 'S' as they could within 60 seconds. Instructions emphasised that the words should not include repetitions, permutations (e.g. 'have' and then 'having') or proper nouns (e.g. 'Sarah' or 'Spain'). All responses generated by the participant were written down, in order, by the experimenter. These words were then examined in the following ways:

2.2.2.1 Word quantity

Number of words generated minus number of errors made was calculated to provide an overall measure of word quantity.

2.2.2.2 Word frequency

Frequency of each word generated was obtained from the Celex database, extracted through the MCWord online programme (www.neuro.mcw.edu/mcword). This database of

17,900,000 words provides word frequencies of both written and spoken text combined, with counts ranging from 0 to 1,168,607. Words not included in the Celex database (e.g. supercalifragilisticexpialidocious; 1.39 % of our sample) were assigned a frequency of zero.

Number of low frequency words, as defined as having a frequency below one, was also calculated. This number was then divided by the total number of words generated to provide a proportional score of low frequency words.

2.2.2.3 Word age-of-acquisition

Age-of-acquisition of each word generated was determined by obtaining ratings from the Kuperman et al. (2012) norms (www.crr.urgent.be). Words not included in this database (5.23 % of our sample) were not assigned an age-of-acquisition rating and excluded from further analysis.

2.2.2.4 Word error rates

Number of repetitions, permutations and proper noun errors were noted and then summed to provide a total number of errors overall. These were then divided by the total number of words generated to provide proportional scores of total errors overall, repetitions, permutations and proper noun errors. The number of profanities uttered was also noted and divided by the total number of words generated to provide a proportional score of profanities uttered.

2.3 Statistical analysis

Mean and raw scores were calculated for each of the measures listed. Normality of distribution was assessed using the Kolmogorov-Smirnov test and, if significant, by examining the z-scores for skewness and kurtosis. Homogeneity of variance was assessed using Levene's test. All data met the assumptions of normality and homogeneity of variance, unless otherwise stated. Scores were compared across patient groups using *t*-tests, Mann-Whitney *U* tests, analyses of variance (ANOVAs), using Welch's *F* when insufficient homogeneity of variance, or Kruskal-Wallis Tests, as appropriate.

The relationship between phonemic fluency and other variables was compared using Pearson and Spearman correlational analyses, as appropriate. Finally, a backwards regression analysis was used to determine the predictive value of specific neuropsychological variables upon phonemic fluency. Post hoc analyses were adjusted for multiple comparisons using Bonferroni correction. All analyses were conducted using IBM SPSS Statistics Data Editor version 24.

3. Results

3.1 Participants

Mean age, years of education and NART PFSIQ scores in all patient groups and healthy controls can be found in Table 1.

--Table 1 around here--

ANOVAs revealed no significant group differences in age (F (5, 44.27) = 1.73, p = .15), education (F (5, 117) = 0.86, p =.51), or NART PFSIQ (F (5, 42.08) = 0.27, p = .93). There was also no significant difference in gender distribution (χ^2 (5) = 10.04, p = .07).

There was a significant group difference in disease duration (F (5, 117) = 15.51, p < .001, η^2_{partial} = .40), with the PD patients having significantly longer disease durations than PSP and subcortical lesion patients (p < .001). PSP patients also had significantly lower LEDDs than PD patients (U = 51.00, p < .05). When size of focal brain lesions was compared, there were no significant group differences in either mean number of total voxels (F (2, 21) = 1.70, p = .21) or grey matter voxels affected (F (12, 21) = 1.87, p = .18).

3.2 Background neuropsychological tests

Mean scores on measures of intellectual, linguistic and executive functioning in each patient group can be found in Table 2.

--Table 2 around here--

ANOVAs revealed no significant group differences in intellectual functioning [VIQ (F (4, 80) = 1.56, p = .19), PIQ (F (4, 77) = 1.80, p =.14)]. There were also no significant group differences on either the GNT (F (5, 106) = 0.92, p = .47) or the Hayling [suppression RT (F (5, 24.29) = 0.27, p = 29), suppression errors (F (5, 26.16) = 0.34, p = 89). However, there was a significant group difference in Vocabulary (F (4, 77) = 2.57, p < .05, $\eta^2_{partial}$= .12). Pairwise comparisons between patient groups revealed that both PSP and LF patients had significantly lower Vocabulary scores than PD patients (p < .05), but these were no longer significant after Bonferroni adjustment for multiple comparisons (adjusted alpha level of .01). There was a significant group difference in Similarities (F (4, 78) = 2.93, p < .05, $\eta^2_{partial}$ = .13) and pairwise comparisons revealed that PSP patients had significantly lower Similarities scores than PD and subcortical patients (both p < .01). There was also a significant group difference in Digit Span (F (4, 78) = 2.95, p < .05, $\eta^2_{partial}$ = .13) and pairwise comparisons revealed that PSP patients had significantly lower Digit Span scores than subcortical patients (p < .01).

Unfortunately, HADS and AES scores were not available for all PSP patients, with only nine of the 23 patients completing these assessments in comparison to 22 of the PD patients. However, a higher proportion of PSP patients (85.7 %) endorsed clinically significant levels of apathy than PD patients (36.4%; χ^2 (1) = 5.18, p < .05, φ = .42). A higher proportion of PSP patients also endorsed anxiety and depression (anxiety: 66.7%; depression: 55.6 %) than PD patients (anxiety: 40.0 %; depression: 40.0 %), but this was not statistically significant.

3.3 Phonemic fluency

Mean word quantity, frequency, age-of-acquisition of words generated on the fluency task can be found in Table 3.

--Table 3 around here--

3.3.1 Word quantity

There was a significant group difference in mean word quantity (F (5, 122) = 16.45, p < .001, $\eta^2_{partial}$ = .40). Relative to healthy controls, quantity of 'S' words generated was significantly smaller in the PSP (p < .001), left frontal (p < .001) and subcortical patient groups (p <.01). Pairwise comparisons between patient groups revealed that the PSP patients generated significantly fewer words than PD patients (p < .001) and right frontal patients (p < .01), and left frontal patients generated significantly fewer words than PD patients (p <.01).

Correlational analyses revealed that word quantity was not related to age (r = -.08, p = .35), education (r = .03, p = .74) or disease duration (r = -.06, p = .51), but was significantly correlated with NART PFSIQ (r = .22, p < .05) and LEDD (r = .44, p < .05). On background neuropsychological assessments, word quantity was correlated with performance on measures of intellectual (VIQ: r = .40, p <.001; PIQ: r = .33, p < .01), linguistic (Vocabulary: r = .38, p <.001; Similarities: r = .40, p <.001; GNT: r = .26, p <.001) and executive function (Digit Span: ρ = .38, p < .001; Hayling suppression response time: r = -.36, p <.01). However, associations with NART PFSIQ, LEDD and GNT were no longer significant after Bonferroni adjustment for multiple comparisons (adjusted alpha level of .005). In our limited analyses, word quantity was not correlated with either apathy (ρ = -.22, p = .27) or anxiety (ρ = -.15, p

= .29), and although was negatively correlated with depression (ρ = - .36, p < .01), this was no longer significant after Bonferroni adjustment for multiple comparisons (adjusted alpha level of .005).

In order to determine which of the remaining covariates (VIQ, PIQ, Vocabulary, Similarities, Digit Span and Hayling suppression response time) were predictive of phonemic fluency word quantity, multiple regression analysis was conducted. There was no evidence of multicollinearity (VIF = 1.00; Tolerance = 1.00). The initial variance explained by the model, with all potential covariates, was 11.6%, which was not significant. However, using a backwards method, a significant model emerged (F (2, 54) = 6.00, p < .01), with incremental increases in variance explained (Model 2: Vocabulary, Hayling suppression response time, VIQ, PIQ, Similarities: adjusted R^2 = .133; Model 3: Vocabulary, Hayling suppression response time, PIQ, Similarities: adjusted R^2 = .148; Model 4: Vocabulary, Hayling suppression response time, PIQ: adjusted R^2 = .148). The final model consisted of Vocabulary and Hayling suppression response time, which together accounted for 15.2 % (unadjusted R^2 = .182) of the variance in number of words generated (Table 4).

--Table 4 around here--

3.3.2 Word frequency

There were no significant group differences in mean word frequency (F (5, 51.73) = 2.08, p < .08), or low frequency words generated [mean number (F (5, 122) = 1.65, p = .15), mean proportion (F (5, 42.24) = 0.41, p = .84)].

When word frequency was split by the healthy control median (22.84), PSP patients were found to have generated a similar percentage of words in the lower half (46.33 %) relative to healthy controls (49.75 %). When compared with other patient groups, the PSP patients' percentage of lower frequency words was similar to PD (46.55 %), left frontal (49.79 %) and subcortical patients (50.63 %), but less than the right frontal patients, who generated slightly more words with lower frequencies (54.35 %).

Correlational analyses also revealed the proportion of low frequency words was not related to age (ρ = -.09, p = .30), education (ρ = .11, p = .24) or disease duration (ρ = -.02, p = .87), but was positively correlated NART PFSIQ (ρ = .21, p < .05). Proportion of low frequency words generated was also positively correlated with performance on a couple of measures of linguistic function (Vocabulary: ρ = .27, p < .05; GNT: ρ = .27, p <.01), but no measure of executive function. However, after Bonferroni adjustment for multiple comparisons (adjusted alpha level of .005), percentage of low frequency words remained significantly associated with GNT performance only, indicating that those who generated more low frequency words performed better on the GNT.

In our limited analyses, proportion of low frequency words was negatively correlated with apathy (ρ = -.38, p < .05), but this was no longer significant after Bonferroni adjustment for multiple comparisons (adjusted alpha level of .005). Proportion of low frequency words was not correlated with either anxiety (ρ = .04, p = .77) or depression (ρ = .07, p = .62).

3.3.3 Word age-of acquisition

There were no significant differences in mean age-of-acquisition (F (5, 122) = 2.14, p = .81.

3.3.4 Word error rates

Mean word error rates on the fluency task can be found in Table 5.

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There were no significant group differences in mean proportion of total errors overall F (5, 118) = 0.66, p = .65) or individual error types [repetitions (F (5, 40.24) = .87, p = .50), permutations (F (5, 118) = 1.10, p = .36), proper nouns (H (5) = .5.02, p = .41)], or profanities generated (H (5) = 3.18, p = .67).

Neither errors nor profanities proportional scores were correlated with age, education or NART PFSIQ. Neither errors nor profanities proportional scores were correlated with performance on any of the neuropsychological assessments, or with apathy, anxiety or depression.

4. Discussion

This study aimed to characterise the verbal fluency impairment in PSP. Previous studies have suggested that reduced phonemic fluency to be the neuropsychological hallmark of PSP (Bak et al., 2005; Bak & Hodges, 1998; Brown et al., 2010; Burrell et al., 2018, Cordato et al., 2006; Foley et al., 2018; Rittman et al., 2013). Compared to healthy controls, patients with PD and patients with right frontal focal lesions, our PSP patients generated significantly fewer words. The PSP patients generated between two and 15 words, which is below the mean number generated by healthy controls (16.91). Over a third of PSP patients generated fewer than seven words, whereas no patient with PD did. The group difference in verbal fluency represented a large sized effect, with diagnosis accounting for 40% of all the variance. The only other significant group differences on background neuropsychological tests were on Similarities and Digit Span. The group differences on these tests were only medium sized, with diagnosis accounting for 13% of all the variance. Therefore, we suggest that the present study confirms the finding that verbal fluency is severely reduced in PSP. This alongside reduced spontaneous speech and initiation of conversation, reveals the verbal adynamia of PSP.

Phonemic fluency was also significantly reduced in patients with left frontal and subcortical focal lesions. Although these lesions arose from different pathologies, these findings are in line with earlier studies (Baldo et al., 2006; Costafreda et al., 2006; Robinson et al., 2012; Schmidt et al., 2019) that suggest left frontal and subcortical areas are critical for phonemic fluency. PSP is associated with atrophy of the frontal lobes (Brenneis et al., 2004; Cordato et al., 2002, 2005; Ghosh et al., 2012; Price et al., 2004) and basal ganglia (Alexander et al., 1986; Burciu et al., 2015; Cordato et al., 2005). Therefore, we suggest that in PSP it is the combination of damage to frontal and subcortical areas that is associated with the striking fluency deficit (Robinson et al., 2015).

Phonemic fluency was correlated with performance on a range of measures of intellectual, linguistic and executive function, but best predicted by performance on Vocabulary and the Hayling. Previous studies have also found phonemic fluency to be correlated with measures of language and executive functioning (e.g. Aita et al., 2018), and PSP patients have previously been found to demonstrate reduced Vocabulary (Josephs & Duffy, 2008; Paviour et al, 2006) and extended suppression response times on the Hayling (Barker et al., 2018; Millar et al., 2006; Robinson et al., 2006; 2015). It may be argued that the cognitive processes involved in these two tests are somewhat similar to those in propositional speech. Both require un-cued initiation of a verbal response while sustaining attention to the overall task, and both necessitate frequent shifts in attention with each question. Alexander (2006) suggests that deficits in energization would lead to significant delays and pauses on such tasks, and these have been described on other measures of propositional speech (Robinson et al., 2006).

A couple of studies have also suggested that Vocabulary performance (Paviour et al., 2006) and Hayling suppression response times (Cipolotti et al., 2016) are associated with frontal regions, which is thought to be the anatomical substrate of energization (Stuss & Alexander, 2007). Therefore, we suggest that the neuropsychological deficits, particularly in phonemic fluency, Vocabulary and the Hayling, may reflect a more general impairment in energization, which gives rise to the verbal adynamia observed in PSP.

A general impairment in energization may also explain the apathetic syndrome witnessed in high rates in this study and in previous investigations (Aarsland et al., 2001; Litvan et al., 1996). Although we were not able to provide full details on our patients' apathy and mood ratings, our analyses indicated that verbal generation was not correlated with apathy. This is in line with recent pilot data we have collected in 177 PD patients. Of these, 26 (14.7%) demonstrated apathy on the Apathy Evaluation Scale, and nearly half (49.7%) indicated

mood disorder on the Hospital Anxiety and Depression Scale. After appropriate adjustment for multiple comparisons, our analyses revealed no significant difference in phonemic fluency in PD patients with pure apathy (n = 5) than both the PD patients with pure mood disorder (n = 67) and PD patients without apathy or mood disorder (n = 84; Foley & Cipolotti, unpublished data). However, future research may wish to examine this further, to understand the nature of the relationship between these two purported manifestations of deficient energization.

In contrast to the marked reductions in phonemic fluency quantity, we found no significant group differences in word frequency or age-of-acquisition. PSP patients generated words of a similar frequency and age-of-acquisition to all other patient groups and healthy controls. Moreover, our correlational analyses revealed that generating a higher proportion of low-frequency words was associated with better naming performance on the GNT. This refutes the suggestion that producing a higher proportion of low-frequency words reflects disruption of strategic word retrieval (Rittman et al., 2013). Rather, it suggests the opposite: higher proportion of low-frequency words reflects superior word retrieval.

This is consistent with previous research that patients with temporal lobe pathology generate words of a higher mean frequency and acquired earlier in life than healthy controls (Bell et al., 2000; Barbarotto et al., 1995; Hirsh & Funnell, 1995). These findings were documented in the context of wider linguistic impairment and always impaired naming. In contrast, naming in our PSP patients was intact. Thus, we may conclude that access to low-frequency words requires intact semantic representations, which we have demonstrated to be unaffected by PSP, accounting for the normal frequency of words generated on our phonemic fluency task.

We also found no evidence of increased errorful responding in PSP. Although previous single case or small case series have reported perseverative responding in PSP (Esmonde et al., 1996; Robinson et al. 2006), our larger study did not support this. This suggests that there is no basic impairment in word selection in PSP. Our PSP patients were able to monitor words generated to ensure they remain relevant and appropriate, confirming that this function remains intact in PSP.

The present study was not without its limitations. Firstly, we used only one measure of phonemic fluency. It would have been useful to examine fluency characteristics across different measures of phonemic and semantic fluency, and across different 15 second epochs, to understand more fully the nature of the fluency deficit. Secondly, it would have been useful to have further clinical information about our patients. We did not have information about severity of motor symptoms and activities of daily living, and we had only limited information about the presence of mood disorders. Furthermore, for the majority of PSP patients included in this study, we did not have subgroupings available. Future research should seek to determine how these important variables may contribute to verbal fluency performance, including how the findings differ in those with PSP-Richardson syndrome, PSP-parkinsonism and PSP-progressive gait freezing (Williams & Lees, 2009), as well as in those with early and late onset (Jabbari et al., 2019). Thirdly, as our data were cross-sectional, with relatively small sample sizes, and without embedded validity tests, we must be tentative about the strength of the inferences drawn.

Notwithstanding these limitations, this study provides important evidence that reduced phonemic fluency is a hallmark of PSP, distinguishing it from PD. This reduction in verbal fluency word quantity is not accompanied by changes in word frequency or errors: PSP patients produce fewer, but similar words to all other patient groups tested. We suggest that

the specificity of this impairment betrays an underlying deficit in energization, likely reflecting dysfunction of left frontal and subcortical networks.

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Tables

Table 1: Demographics of each participant group (*M* ± *SD*).

	PSP (n=23)	*PD (n=26)*	*LF (n=16)*	*RF (n=14)*	*SC (n=14)*	*Controls (n=35)*
Age (years)	66.13 ± 6.65	64.15 ± 7.81	62.00± 7.55	64.00 ± 10.94	60.00 ± 11.48	66.47 ± 4.93
Education (years)	13.83 ± 3.99	12.81 ± 2.37	14.00 ± 2.86	12.64 ± 2.81	13.92 ± 3.38	12.66 ± 3.12
NART PFSIQ	107.86 ± 12.85	108.96 ± 11.01	110.94 ± 12.09	109.00 ± 9.74	102.00 ± 31.62	107.83 ± 9.86

PSP: progressive supranuclear palsy; PD: Parkinson's disease; LF: left frontal: RF: right frontal; SC: subcortical.

Table 2: Neuropsychological performance of each patient group (*M* ± *SD*).

		PSP (n=23)	*PD (n=26)*	*LF (n=16)*	*RF (n=14)*	*SC (n=14)*
IQ	VIQ	96.83 ± 14.07	103.62 ± 10.90	103.17 ± 15.37	104.42 ± 12.90	107.33 ± 14.66
	PIQ	89.68 ± 17.49	96.92 ± 18.39	104.58 ± 15.38	95.91 ± 11.56	99.00 ± 11.25
Language	Vocabulary	41.52 ± 12.54	50.38 ± 10.12	38.60 ± 14.24	44.27 ± 13.91	45.92 ± 10.19
	GNT	22.45 ± 4.82	22.08 ± 4.01	20.75 ± 5.40	19.86 ± 3.84	21.64 ± 5.26
	Similarities	18.30 ± 6.28	22.65 ± 4.54	21.30 ± 5.42	20.92 ± 3.63	23.42 ± 4.81
Executive	Digit Span	14.30 ± 4.47	14.92 ± 3.43	15.10 ± 2.89	18.25 ± 5.15	17.83 ± 4.26
	Hayling suppression RT (s)	84.55 ± 79.66	56.00 ± 46.41	67.89 ± 80.52	55.09 ± 40.40	59.00 ± 44.90
	Hayling suppression errors	13.36 ± 12.28	10.96 ± 11.13	8.44 ± 10.10	12.45 ± 19.60	7.71 ± 9.48

PSP: progressive supranuclear palsy; PD: Parkinson's disease; LF: left frontal: RF: right frontal; SC: subcortical; VIQ, PIQ: Wechsler Adult Intelligence Scale – Third Edition, Verbal IQ, Performance IQ; GNT: Graded Naming Test; Hayling suppression RT: Hayling suppression response time.

Table 3: Phonemic fluency word quantity, frequency and age-of-acquisition of each participant group ($M \pm SD$).

		PSP (n=23)	*PD (n=26)*	*LF (n=16)*	*RF (n=14)*	*SC (n=14)*	*Controls (n=35)*
Mean word quantity		**7.57 ± 3.42*[a, b, c]**	14.69 ± 3.96	**10.06± 5.99*[a, b]**	13.14 ± 3.06*[a]	**11.50 ± 4.42*[a]**	16.91 ± 4.20
Mean word frequency		92.73 ± 100.58	74.16 ± 42.23	69.75 ± 47.89	53.91 ± 30.94	53.53 ± 19.85	82.78 ± 73.13
Low frequency words (<1)	Mean number	0.83 ± 0.89	1.35 ± 1.02	1.06 ± 1.44	1.29 ± 0.83	1.21 ± 1.31	1.69 ± 1.37
	Mean proportion (%)	11.47 ± 12.77	9.01 ± 6.44	8.99 ± 12.27	9.50 ± 7.97	10.20 ± 12.22	10.72 ± 8.69
Mean word age-of-acquisition		6.62 ± 0.96	6.88 ± 0.85	6.72 ± 1.32	6.51 ± 0.77	6.47 ± 0.93	6.65 ± 0.94

*$p < .05$; [a] compared with healthy controls; [b] compared with PD patients; [c] compared with right frontal patients; PSP: progressive supranuclear palsy; PD: Parkinson's disease; LF: left frontal: RF: right frontal; SC: subcortical.

Table 4: Predictors of phonemic fluency word quantity

	B	*SEB*	*B 95% CI*	*Zero-order correlations*	*β*	*β 95% CI*
Constant	8.986	2.498	3.977, 13.995			
Vocabulary	0.114	0.050	0.013, 0.214	.279	.279	.032, .524
Hayling supresssion RT	-0.027	0.010	0.011, -0.047	-.322	-.322	.013, -.561

CI: confidence interval

e

Table 5: Phonemic fluency error rates (*M* ± *SD*).

	PSP (n = 23)	*PD (n = 26)*	*LF (n = 16)*	*RF (n = 14)*	*SC (n = 14)*	*Controls (n = 35)*
Total errors overall – mean proportion (%)	8.92 ± 10.91	7.18 ± 9.42	7.04 ± 8.41	6.15 ± 9.62	8.53 ± 17.84	11.12 ± 14.00
Repetitions – mean proportion (%)	1.42 ± 3.79	1.89 ± 3.86	3.05 ± 0.51	2.66 ± 6.26	4.83 ± 13.83	1.54 ± 2.77
Permutations – mean proportion (%)	6.05 ± 9.46	5.29 ± 9.00	5.33 ± 9.12	2.69 ± 4.52	3.10 ± 7.24	8.56 ± 12.40
Proper nouns – mean proportion (%)	1.45 ± 6.95	0	0	0.79 ± 2.97	0.60 ± 2.23	0.83 ± 2.64
Profanities – mean proportion (%)	0.54 ± 2.60	0	0	0	0.09 ± 3.34	0.33 ± 1.35

PSP: progressive supranuclear palsy; PD: Parkinson's disease; LF: left frontal: RF: right frontal; SC: subcortical.