THE UNUSUAL SUSPECTS: LINGUISTIC DEFICITS IN NON-LANGUAGE-DOMINANT NEURODEGENERATIVE DISEASES

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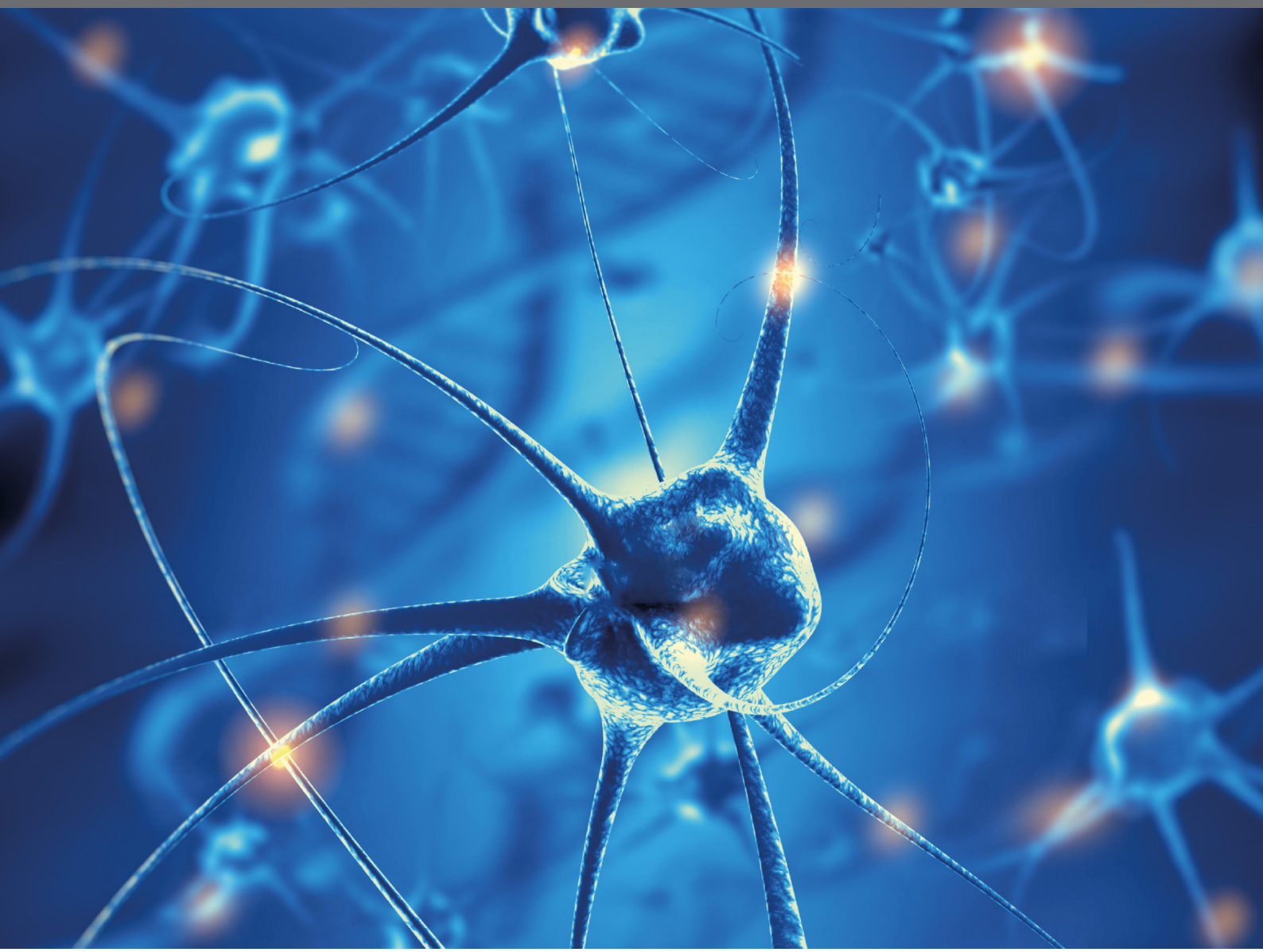

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THE UNUSUAL SUSPECTS: LINGUISTIC DEFICITS IN NON-LANGUAGE-DOMINANT NEURODEGENERATIVE DISEASES

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PARKINSON'S DISEASE

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EDITORIAL
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Editorial: The Unusual Suspects: Linguistic Deficits in Non-Language-Dominant Neurodegenerative Diseases

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Editorial on the Research Topic

The Unusual Suspects: Linguistic Deficits in Non-Language-Dominant Neurodegenerative Diseases

Discussions on linguistic deficits in neurodegenerative diseases are often circumscribed to primary progressive aphasia. Yet, verbal dysfunctions are also pervasive across neurodegenerative diseases typified by mnesic, socio-cognitive, or motoric alterations (García et al., 2022). This has been shown, for instance, in Alzheimer's disease (AD) (Taler and Phillips, 2008), behavioral variant frontotemporal dementia (bvFTD) (Geraudie et al., 2021a,b)(Geraudie et al., 2021a,b), progressive supranuclear palsy syndrome (PSPs) (Peterson et al., 2021), corticobasal syndrome (CBS) (Peterson et al., 2021), and Parkinson's disease (PD) (Birba et al., 2017). With a few exceptions (Boschi et al., 2017; García et al., 2022), however, relevant evidence has been compiled for each disorder separately, failing to foreground the transnosological import of language assessments in behavioral neurology. The present Research Topic directly addresses this need.

We bring together ten articles examining language difficulties in the abovementioned conditions. The evidence spans diverse linguistic dimensions (cutting across phonological, lexico-semantic, syntactic, and discursive-pragmatic levels), language families (Germanic, Indo-Aryan, Romance, Uralic), and methods (standardized batteries, experimental tasks, and spontaneous discourse analysis, in some cases combined with neuroimaging measures). Contributions are organized in three sets, dealing with (i) AD and mild cognitive impairment (MCI), (ii) frontotemporal lobar degeneration syndromes, and (iii) PD.

Opening the first set, Kaskikallio et al. examined neural correlates of verbal fluency in Finnish speakers with either AD or MCI alongside healthy participants. Behavioral outcomes were associated with white matter hyperintensities in bilateral fronto-parieto-occipital as well as right temporal regions, suggesting that vocabulary search difficulties involve cross-lobar axonal disruptions.

The second report, by Itaguchi et al., zoomed into animal fluency in Spanish-speaking AD patients. Relative to controls, these patients exhibited more intrusions at the start of the task and more perseverations toward the end. Patients with high error rates presented with marked alterations along left frontal tracts, reinforcing the importance of white matter integrity for fluency performance. Moving onto the textual domain, Bose et al. analyzed aspects of connected speech in Bengali speakers with AD. In addition to reduced speech rate, semantic richness, and sentential complexity, patients exhibited fewer pronouns—the opposite of what is typically reported in English speakers. This observation invites much-needed comparisons between well-documented and under-researched languages. For their part, Maziero et al. assessed textual inference skills in Portuguese speakers with MCI. Deficits were observed in subgroups with amnestic and non-amnestic profiles, best predicted by verbal memory in the former and semantic knowledge in the latter. These results suggest that pragmatic skills may be affected in persons at increased risk for AD and associated with diverse components of declarative memory.

The second set deals with frontotemporal lobar degeneration. Berthier et al. report on two Spanish speakers with PSPs and echolalic dynamic aphasia. Verbal production deficits and echolalic behaviors (including echoing approval) were observed alongside inhibitory, socio-cognitive, and psychiatric alterations. Both patients presented with atrophy of the midbrain tegmentum and the superior medial frontal cortex. The authors surmise that abnormalities in these regions would involve inhibitory deficiencies compromising language control. Additional insights are provided by Peterson et al., who assessed general language skills in English speakers with PSPs and CBS. Both groups exhibited similar deficits across subtests of motor speech as well as phonological, semantic, and syntactic skills. Though less severe, these impairments resembled those of patients with non-fluent variant primary progressive aphasia. Impairments were associated with left frontal, striatal, and temporal abnormalities, suggesting shared neurolinguistic patterns across the three groups. Finally, Ruiz-Garcia et al. compared semantic and grammatical features of sentence production in English speakers with bvFTD and AD. The former group wrote longer sentences, more often addressed to the examiner and focused on interpersonal relationships. Such difficulties were associated with general cognitive status in AD, but not in bvFTD. Thus, overlooked sentential features might inform differential characterizations in these populations.

The section on PD opens with a study on semantic memory and lexical availability in Spanish (Cardona et al.). The authors observed impaired naming (in response to pictorial and verbal cues) and impoverished lexical access in larger and smaller semantic fields. Difficulties were prominent for non-living entities, yielding high classification between patients and controls. Results are interpreted as a disruption of categorization skills and embodied mechanisms. Embodied considerations also figure prominently in Baez et al. study on Spanish speakers with PD. Two sentence-level tasks revealed difficulties in specific syntactic functions (functional-role assignment) and socio-emotional dimensions (*Schadenfreude*), irrespective of overall cognitive and affective status. Classification between patients and controls was improved when these measures were considered jointly, highlighting the usefulness of multidimensional language assessments in the disease. The relevance of embodied approaches to PD is further emphasized by Gianelli et al. Their mini-review compiles evidence from action fluency and action naming studies revealing partly selective deficits in early-stage patients. Action-semantic tasks are thus proposed as a complement to standard clinical assessments and interventions in PD.

Collectively, these articles illustrate the multilevel, cross-linguistic, and transnosological importance of linguistic assessments in non-primarily linguistic neurodegenerative diseases. Systematic speech and language evaluations can promote fine-grained characterizations of each disorder, inform neurocognitive models, and even nurture the quest for transdiagnostic and disease-specific markers –a most pressing task given the escalating growth of neurodegeneration worldwide. May this Research Topic inspire future work in the same direction.

AUTHOR CONTRIBUTIONS

AG wrote the manuscript. AI, BM, and MG revised the manuscript. All authors approved submission of the manuscript.

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ORIGINAL RESEARCH
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Effects of White Matter Hyperintensities on Verbal Fluency in Healthy Older Adults and MCI/AD

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Background: White matter hyperintensities (WMHs) are markers for cerebrovascular pathology, which are frequently seen in patients with mild cognitive impairment (MCI) and Alzheimer's disease (AD). Verbal fluency is often impaired especially in AD, but little research has been conducted concerning the specific effects of WMH on verbal fluency in MCI and AD.

Objective: Our aim was to examine the relationship between WMH and verbal fluency in healthy old age and pathological aging (MCI/AD) using quantified MRI data.

Methods: Measures for semantic and phonemic fluency as well as quantified MRI imaging data from a sample of 42 cognitively healthy older adults and 44 patients with MCI/AD (total n = 86) were utilized. Analyses were performed both using the total sample that contained seven left-handed/ambidextrous participants, as well with a sample containing only right-handed participants (n = 79) in order to guard against possible confounding effects regarding language lateralization.

Results: After controlling for age and education and adjusting for multiple correction, WMH in the bilateral frontal and parieto-occipital areas as well as the right temporal area were associated with semantic fluency in cognitively healthy and MCI/AD patients but only in the models containing solely right-handed participants.

Conclusion: The results indicate that white matter pathology in both frontal and parieto-occipital cerebral areas may have associations with impaired semantic fluency in right-handed older adults. However, elevated levels of WMH do not seem to be associated with cumulative effects on verbal fluency impairment in patients with MCI or AD. Further studies on the subject are needed.

Keywords: verbal fluency, white matter hyperintensities, Alzheimer's disease, mild cognitive impairment, vascular cognitive impairment

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INTRODUCTION

Aging is often accompanied by vascular changes in cerebral white matter (WM) (Feigin et al., 2003), which typically show up as white matter hyperintensities (WMHs) when magnetic resonance imaging (MRI) is utilized (Pantoni et al., 2007). These cerebrovascular changes can have a variety of effects on cognitive functions, including impairments to information processing speed, executive

functions, working memory, episodic memory, as well as linguistic functions (de Groot et al., 2000; Gunning-Dixon and Raz, 2000; Nordahl et al., 2005, 2006; Au et al., 2006; Pantoni et al., 2007; Zhou and Jia, 2009; Chin et al., 2012; Jokinen et al., 2012; Maillard et al., 2012; Lampe et al., 2019).

Cerebrovascular pathology and Alzheimer's disease (AD) are intertwined in several respects, as both share common risk factors (Duron and Hanon, 2008) and often overlap and co-occur (Toledo et al., 2013). Furthermore, the risk for developing AD is increased by vascular diseases and elevated WMH (Breteler, 2000; Wolf et al., 2000; Prins et al., 2004), whereas AD patients exhibit elevated levels of cerebral WM pathology (Brickman, 2013) as well as degeneration in specific WM tracts (Mito et al., 2018). Thus, it is of critical importance to study the effects of WM pathology on cognition in AD as well as in mild cognitive impairment (MCI), which is often an early stage of AD. However, the topic has received considerably less attention than the association between gray matter morphology and cognition (for exceptions, see Brickman et al., 2008; Brickman, 2013; Ramirez et al., 2014; Bilello et al., 2015; Mito et al., 2018; Kaskikallio et al., 2019a,b).

A deficit that occurs fairly early in AD is impaired word finding (Farrell et al., 2014). Word generation is commonly measured by verbal fluency (VF) tasks that involve generating words according to cues within a preset time interval: category cues are used for semantic fluency and letter cues for phonological fluency (Lezak et al., 2012). Verbal fluency tasks require using a variety of executive control processes (e.g., focusing on the task, updating material, inhibiting irrelevant responses) and are thus also seen as effective probes for executive functioning (Henry and Crawford, 2004). Overall, AD patients appear to exhibit larger impairments in semantic fluency than in phonological fluency (Henry et al., 2004). This likely reflects the deterioration of the semantic memory store traditionally linked to accumulating neuropathological changes in AD (Chertkow and Bub, 1990; Hodges et al., 1992).

Functional neuroimaging studies have indicated that VF tasks rely on relatively left-lateralized cortical networks (Birn et al., 2010), involving the frontal and temporal regions, anterior cingulate, superior parietal cortex, left hippocampus, thalamus, and cerebellum (Phelps et al., 1997; Gourovitch et al., 2000; Abrahams et al., 2003; Costafreda et al., 2006; Robinson et al., 2012; Biesbroek et al., 2016). Furthermore, the right hemisphere has been suggested to be more involved in semantic fluency tasks over phonological fluency tasks in a number of studies (Schlösser et al., 1998; Donnelly et al., 2011; Glikmann-Johnston et al., 2015). More specifically, areas in the left inferior/middle frontal cortex seem to contribute to both types of fluency (Costafreda et al., 2006; Wagner et al., 2014; Schmidt et al., 2019). However, phonological fluency seems to rely relatively more on the left frontal cortex (presumably reflecting the need for additional strategic effort) and semantic fluency relatively more on the left temporal cortex (presumably reflecting the need for retrieval from semantic memory) (Henry and Crawford, 2004; Baldo et al., 2006, 2010). Since phonological tasks require more effort and executive control, they are expected to impose more substantial demands on planning and strategy formation than semantic fluency tasks, which can rely more on utilizing pre-existing semantic networks (Henry and Crawford, 2004). Nonetheless, various retrieval strategies can be used in both types of tasks.

According to the dual stream model, the system for processing auditory speech involves two language streams that diverge from the superior temporal gyrus (Hickok and Poeppel, 2007; Saur et al., 2008). A left-dominant dorsal stream connects the superior temporal lobe and posterior frontal premotor association cortices via the arcuate fasciculus and superior longitudinal fasciculus, facilitating sensorimotor language production. On the other hand, a bilateral ventral language stream connects the superior and middle temporal lobe with the ventrolateral prefrontal cortex via the extreme capsule and the middle/inferior longitudinal fasciculi, extracting meaning from sounds (Hickok and Poeppel, 2007; Saur et al., 2008). The microstructural integrity of WM tracts from both pathways has been associated with VF performance in studies that have included healthy adolescents and adults as well as various clinical populations. These tracts include the left arcuate fasciculus and the bilateral superior longitudinal fasciculus for the dorsal stream (Peters et al., 2012; Allendorfer et al., 2016; Rodríguez-Aranda et al., 2016; Blecher et al., 2019), and the bilateral inferior longitudinal fasciculus for the ventral stream (Allendorfer et al., 2016; Rodríguez-Aranda et al., 2016; Blecher et al., 2019). Associations have also been reported for the bilateral frontal aslant track (Catani et al., 2013; Kinoshita et al., 2015; Blecher et al., 2019) and the corpus callosum (Rodríguez-Aranda et al., 2016).

Although numerous studies have been published on the neuroanatomic correlates of VF, research about the neurocorrelations between WM and VF in MCI and AD populations has been fairly limited. Studies utilizing diffusion tensor imaging have reported associations between semantic fluency and WM microstructure measures in the corpus callosum, right anterior periventricular, and posterior periventricular regions (Kavcic et al., 2008; Chen et al., 2009). Likewise, Rodríguez-Aranda et al. (2016) reported associations between semantic fluency and a bilateral network of WM tracts (uncinate fasciculus, inferior fronto-occipital fasciculus, forceps minor, and corpus callosum) as well as phonological fluency and several left-hemisphere tracts (anterior thalamic radiation, superior longitudinal fasciculus, inferior longitudinal fasciculus). Finally, Serra et al. (2010) reported that no significant associations exist for these groups specifically.

Overall, the research literature regarding the effects of WM pathology on verbal fluency in AD is quite limited, and previous studies have contained fairly small samples. We have previously examined effects of WM pathology on both general cognitive functioning (Kaskikallio et al., 2019a) as well as on specific cognitive domains (Kaskikallio et al., 2019b, 2020) in cognitively healthy adults and patients with MCI or AD. In these studies, verbal fluency was not included in the verbal function domain score (Kaskikallio et al., 2019b, 2020) due to relatively low shared variance with the other verbal tasks in factor analysis—thus supporting the view that VF tasks tap additional cognitive processes such as executive functions (e.g., Henry and Crawford, 2004; Aita et al., 2016). In this study, we investigated verbal fluency *per se*. The aim was to examine the associations between

WM pathology and VF in a sample consisting of a group of cognitively healthy older adults and a group of amnestic MCI and AD patients. A special focus was on examining possible group-wise effects, i.e., would there be differences in the effects of WM pathology between cognitively healthy and MCI/AD patients. The sample utilized here is a portion of the sample that has been used previously (Kaskikallio et al., 2019a, 2020), with the quantified MRI being utilized in Kaskikallio et al. (2019b).

MATERIALS AND METHODS

Participants

The data used in the current study were originally collected in the DEMPET and TWINPIB research projects over several years at the National PET-Centre in Turku, Finland (Kemppainen et al., 2006; Koivunen et al., 2011; Scheinin et al., 2011). The current sample is a portion of the one that has been utilized before, albeit with differing cognitive measurements and neuroimaging analysis methods (Kaskikallio et al., 2019a,b, 2020). The studies were carried out in accordance with relevant guidelines and regulations and were approved by the Joint Ethical Committee of the University of Turku and Turku University City Hospital. The participants received oral and written information about the study and gave informed consent.

The Petersen et al. (2001) criteria were used for diagnosing MCI, whereas patients with AD fulfilled the Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV) criteria for dementia as well as the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for probable AD (McKhann et al., 1984). Controlled concomitant metabolic and cardiovascular diseases were allowed, but participants with Type I diabetes were excluded. Furthermore, a minimum score of 25 in the Mini-Mental State Exam was required for inclusion into the cognitively healthy group. Patients with MCI were of the amnestic type, which is typically characterized by episodic memory impairment. The time lag between MRI data acquisition and neuropsychological testing was 1 week, on average, and 2 weeks at the at the most. From the original sample of 148 participants, 62 participants had to be excluded due to insufficient MRI data quality for quantification. The final sample consisted of 42 cognitively healthy adults, 14 patients with MCI, and 30 patients with AD. The MCI and AD subgroups were pooled together into due to relatively small group sizes. Further details can be found in Kaskikallio et al. (2019a).

Demographic characteristics of study participants are reported in **Table 1**. The cognitively healthy and patient (MCI + AD) groups were similar with regard to age [$t(84) = -0.463$, $p = 0.645$], education ($U = 855.500$, $z = -0.653$, $p = 0.514$) and gender distribution [$\chi^2(2) = 0.385$, $p = 0.535$]. However, age and education were kept as covariates, as they traditionally have strong associations with cognitive performance. Furthermore, the patient group had lower Mini-Mental State Exam scores than the cognitively healthy group [$t(83) = 4.846$, $p < 0.001$]. Finally, three participants reported being left-handed and four ambidextrous. As we did not want to limit the sample size any further, it was decided to run the analyses both with and without these participants in order to guard against possible confounding effects regarding language lateralization (e.g., Szaflarski et al., 2002).

Verbal Fluency Measures

Measures for semantic fluency (animals) and phonological fluency ("S") were administered. The participants were asked to orally produce as many words as they could for the span of 1 min. The total number of correct responses was reported. Cognitively healthy controls had the best performances in all word fluency measures, although no statistically significant differences were found between the groups (see **Table 2**).

MRI Acquisition

A 1.5T Philips Intera (Best, the Netherlands) was used for MRI acquisition. White matter hyperintensities were analyzed using three-dimensional (3D) T1 FFE transaxial (TR/TE 25/5, 58 ms; slice thickness, 2 mm; matrix, 512 × 512) and 2D fluid attenuated

TABLE 1 | Demographic and clinical characteristics of study participants.

	All	Cognitively healthy	Patient group (MCI/AD)
n	86	42	44
Women%	41.9%	45.2%	38.6%
Age M (SD), years	71.76 (4.73)	71.52 (5.20)	71.00 (4.40)
MMSE Score M (SD)	25.81 (3.57)	27.50 (1.40)	24.16 (4.24)[a]
Right-handed	79	38	41
Left-handed	3	1	2
Ambidextreous	4	3	1
Education level			
Primary school	43	20	23
Vocational school	32	15	17
Upper secondary	2	2	0
Academic degree	9	5	4

MCI, mild cognitive impairment; AD, Alzheimer's disease; MMSE, Mini-Mental State Exam.
[a]Data are missing from one participant in the patient group.

TABLE 2 | Word fluency performances in whole sample and in subgroups.

Word fluency measure	All	Cognitively healthy	Patient group (MCI + AD)	Group difference[a]
All participants (n = 86)				
Semantic fluency	21.55 (6.62)	22.36 (5.39)	20.77 (7.59)	$p > 0.05$
Phonological fluency	13.37 (6.51)	14.43 (6.03)	12.36 (6.86)	$p > 0.05$
Right-handed only (n = 79)				
Semantic fluency	21.67 (6.78)	22.50 (5.59)	20.90 (7.71)	$p > 0.05$
Phonological fluency	13.38 (6.47)	14.34 (5.93)	12.49 (6.89)	$p > 0.05$

MCI, mild cognitive impairment; AD, Alzheimer's disease.
Means are reported first, followed by standard deviations in brackets.
[a]Student's T-test was used to study differences between groups.

inversion recovery (FLAIR) coronal (TR/TE, 11,000/140 ms; slice thickness, 5 mm; matrix, 512 × 512) images. The same sequences were applied to the whole sample. White matter hyperintensities were segmented according to the method presented in Wang et al. (2012). This quantified MRI data has been utilized and details reported previously in Kaskikallio et al. (2020). Comparisons between the cognitively healthy and patient subgroups did not yield statistically significant differences in WMH volumes, although the patient groups exhibited systematically higher mean volumes than the cognitively healthy group.

Statistical Analysis

Several multiple linear regression analyses were performed for testing the main research questions. For each regression model, age and level of education were entered as control variables in step 1, after which a measure for WMH in each anatomical region of interest was added as a dependent in step 2. Semantic fluency or phonological fluency was set as the independent variable for each analysis. Separate analyses were conducted for the eight anatomical regions of interest (left frontal, right frontal, left parieto-occipital, right parieto-occipital, left temporal, right temporal, bilateral frontal, bilateral parieto-occipital).

Analyses including the whole sample were run first, followed by analyses containing only right-handed participants. Type I errors due to multiple testing were controlled by using the Benjamini–Hochsberg procedure (Benjamini and Hochberg, 1995). A false discovery error rate of 0.05 was used to produce adjusted *p*-values for each step 2 predictor variable, against which the original *p*-values were compared against. The procedure was performed to the nine predictor variables for each hypothesis family (semantic fluency/phonological fluency) for both the total sample and the sample containing only right-handed participants. For those regression models that remained significant after correction, further subgroup analyses were performed separately for the control group and the patient group (MCI + AD). The same procedure to guard against multiple hypothesis testing was performed at this stage. Data analysis was done with the IBM SPSS statistics software v. 24.

RESULTS

Analyses concerning the total sample (controls, MCI/AD) and containing right-handed, ambidextrous, and left-handed participants (n = 86) were performed first, followed by identical analyses performed on a sample containing only right-handed participants (n = 79) (see **Table 3** for main analyses). Age and education were controlled for in step 1 of each model.

In the whole sample, increased WMH volumes in both the frontal and parieto-occipital areas, bilaterally, were significantly associated with worse performance in the semantic fluency task, although these associations did not survive correction for multiple testing. In the sample containing only right-handed participants, the results were similar, i.e., WMH volumes in frontal and parieto-occipital areas, bilaterally, were associated with lower semantic fluency performance (see **Figure 1**). Additionally, a significant association was seen between increased WMH volumes in the right temporal lobe and worse performance in the semantic fluency task only in the right-handed participants. The models concerning right-handed participants remained significant after correcting for multiple testing except for the association between left parieto-occipital WMH and semantic fluency.

As only the models concerning right-handed participants survived correction for multiple testing, left-handed/ambidextrous participants were excluded from the follow-up subgroup analyses. These concerned the areas that were significantly associated with semantic fluency after correction (left and right frontal, right parieto-occipital, right temporal) and were run separately for the cognitively healthy and MCI/AD subgroups. However, no significant associations were found concerning these subgroups.

DISCUSSION

The results indicated that increases in frontal and parieto-occipital WMH volumes, bilaterally, were associated with decreases in semantic fluency when all groups were included (healthy controls + MCI/AD patients). As we preferred to keep the sample size as large as possible, these analyses contained all the participants (including a few left-handed and ambidextrous ones). In order to guard against possible confounding effects regarding language lateralization, additional analyses were performed with only right-handed participants. However, after correcting for multiple testing, only the models concerning the right-handed participants remained significant (all except left parieto-occipital WMH, although bilateral parieto-occipital WMH remained significant). No significant group-specific effects in the control or patient groups specifically were seen.

The indications regarding an association between both frontal and parieto-occipital WMH with decreased semantic fluency are generally in line with previous findings: Verbal fluency performance has been linked with a network of frontal and parietal cortical regions, in addition to the temporal lobe and other subcortical structures such as the anterior cingulate, left hippocampus, thalamus, and cerebellum (Phelps et al., 1997; Gourovitch et al., 2000; Abrahams et al., 2003; Costafreda et al., 2006; Robinson et al., 2012; Biesbroek et al., 2016). However, previous studies have often shown more left lateralized associations for VF, whereas the associations seen here seemed to be bilateral. We would argue that left lateralized networks and certain cortical areas most certainly play a key role in VF tasks but also that VF tasks may rely on a broader bilateral network. This might apply more to semantic fluency, as some investigators have suggested a larger involvement for the right hemisphere in semantic fluency tasks over phonological tasks (Schlösser et al., 1998; Donnelly et al., 2011; Glikmann-Johnston et al., 2015). Indeed, in the current study, right temporal WMH volumes seemed to be associated with decreased semantic fluency performance in right-handed participants.

Related to this, a number of studies on various clinical groups have implicated the right hemisphere in VF tasks: Impaired VF performance has often been reported in patients with right frontal

TABLE 3 | Regression models predicting word fluency performance from white matter hyperintensities.

Independent variables	All participants (n = 86)						Only right-handed (n = 79)					
	Semantic fluency			Phonological fluency			Semantic fluency			Phonological fluency		
	R^2	$p\Delta R^2$	B (95% CI)	R^2	$p\Delta R^2$	B (95% CI)	R^2	$p\Delta R^2$	B (95% CI)	R^2	$p\Delta R^2$	B (95% CI)
Step 1												
Model 1 (M1): age and education	0.089	0.021		0.211	0.000		0.085	0.034		0.240	0.000	
Step 2												
M1 + frontal L WMH	**0.139**	**0.032**	**–0.98 (–1.88, –0.09)**	0.231	0.150	–0.61 (–1.44, 0.26)	**0.146**	**0.024**	**–1.13 (–2.11, –0.16)***	0.253	0.253	–0.50 (–1.38, 0.37)
M1 + frontal R WMH	**0.136**	**0.039**	**–0.67 (–1.31, –0.04)**	0.231	0.153	–0.43 (–1.02, 0.16)	**0.141**	**0.030**	**–0.78 (–1.49, –0.08)***	0.253	0.248	–0.37 (–1.00, 0.26)
M1 + frontal L + R WMH	**0.139**	**0.033**	**–0.42 (–0.79, –0.04)**	0.232	0.144	–0.26 (–0.61, 0.09)	**0.145**	**0.024**	**–0.48 (–0.90, –0.06)***	0.254	0.240	–0.22 (–0.59, 0.15)
M1 + temporal L WMH	0.100	0.329	–0.93 (–0.28, 0.95)	0.215	0.524	–0.56 (–2.28, 1.17)	0.100	0.264	–1.12 (–3.10, 0.86)	0.245	0.455	–0.65 (–2.39, 1.08)
M1 + temporal R WMH	0.125	0.071	–1.43 (–2.97, 0.12)	0.222	0.303	–0.75 (–2.19, 0.69)	**0.144**	**0.025**	**–2.01 (–3.76, –0.25)***	0.261	0.145	–1.15 (–2.70, 0.41)
M1 + Temporal L + R WMH	0.115	0.130	–0.69 (–1.59, 0.21)	0.219	0.367	–0.38 (–1.21, 0.45)	0.124	0.071	–0.91 (–1.89, 0.08)	0.254	0.235	–0.52 (–1.39, 0.35)
M1 + parieto-occipital L WMH	**0.133**	**0.046**	**–0.72 (–1.42, –0.01)**	0.246	0.057	–0.63 (–1.27, 0.02)	**0.134**	**0.043**	**–0.75 (–1.48, –0.03)**	0.275	0.058	–0.61 (–1.25, 0.02)
M1 + parieto-occipital R WMH	**0.161**	**0.010**	**–0.75 (–1.31, –0.19)**	0.238	0.094	–0.45 (–0.98, 0.08)	**0.168**	**0.008**	**–0.80 (–1.38, –0.22)***	0.270	0.084	–0.45 (–0.98, 0.06)
M1 + Parieto-occipital L + R WMH	**0.151**	**0.017**	**–0.39 (–0.71, –0.07)**	0.243	0.068	–0.28 (–1.57, 0.02)	**0.155**	**0.015**	**–0.42 (–0.75, –0.08)***	0.274	0.064	–0.28 (–0.57, 0.02)

Separate models have been run for each ROI and cognitive variable. In every model, education and age were entered as control variables in step 1 and the volume of white matter intensities in step 2. The amount of explained variance (R^2) for each model is reported with the corresponding p-value ($p\Delta R^2$) for the difference in explained variance between model 1 and the current model. Coefficients (B) with 95% CIs are also provided.
WMH, white matter hyperintensity; L, left; R, right.
**These predictors remained significant after correcting for multiple testing.*
Models that were initially significant (i.e., before correcting for multiple testing) have been bolded.

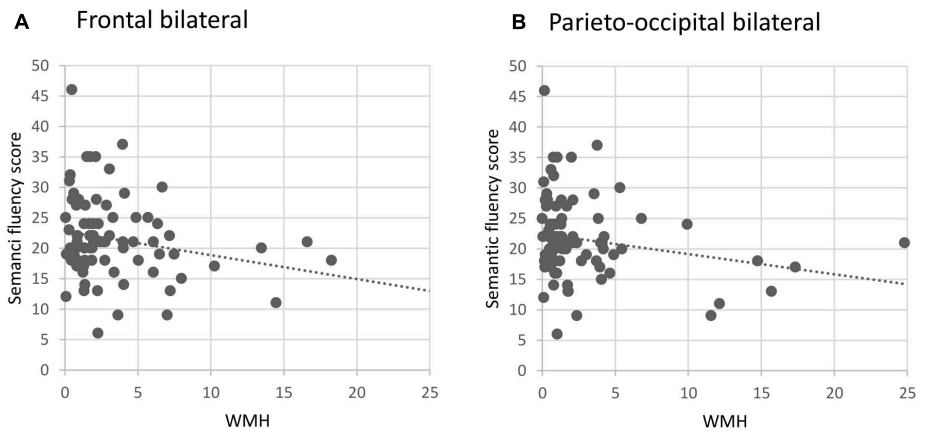

FIGURE 1 | Semantic fluency as a function of bilateral **(A)** frontal and **(B)** parieto-occipital white matter hyperintensities in right-handed participants (n = 79). WMH, white matter hyperintensities (ml).

lesions (Perret, 1974; Martin et al., 1990; Loring et al., 1994; Robinson et al., 2012), with a recent study identifying the right inferior frontal gyrus as an important area for semantic fluency (Biesbroek et al., 2016). As for WM tracks, VF impairments have also been associated bilaterally with the inferior fronto-occipital fasciculus and the superior longitudinal fasciculus in MS patients (Blecher et al., 2019) and in a pooled sample of healthy old adults and early AD patients (Rodríguez-Aranda et al., 2016). It is also important to note that the degree of lateralization most likely depends on age, as functional neuroimaging studies on older

participant have indicated a general reduction in hemispheric specialization in favor of more bilateral activation (Reuter-Lorenz et al., 2000; Cabeza, 2002). This age-related restructuring of the neural architecture has been posited to occur primarily by recruiting additional cortical areas to preserve performance and has been documented not only in VF tasks (Meinzer et al., 2012; La et al., 2016) and overt naming (Wierenga et al., 2008) but also in other cognitive functions such as the ventral visual system (Park et al., 2004) and the motor system (Carp et al., 2011). Furthermore, some investigators have speculated that the involvement of the right hemisphere in semantic fluency tasks may reflect the utilization of visuospatial mental imaging strategies for these tasks (Biesbroek et al., 2016; Gordon et al., 2018). Finally, it is important to note that only the models that included solely right-handed participants remained significant after multiple testing correction. This is discussed further in the limitations section.

Regarding the results, there are a number of null findings that need addressing. Possibly, the most relevant one is that no group-specific associations were seen for the MCI/AD patient group. This is in contrast with our previous results, as we have previously reported indications of a cumulative effect of WM pathology in the frontal areas on general cognitive functioning in AD patients specifically (Kaskikallio et al., 2019b). We have also found indications of similar group-specific cumulative effects of frontal and temporal WMH volumes on processing speed (Kaskikallio et al., 2019a, 2020). The results in the present study do not support the notion that WM pathology would have group-specific/cumulative effects on VF in MCI and AD patients, contrasting some earlier findings that have been reported (Kavcic et al., 2008; Chen et al., 2009). On the other hand, these studies contained more limited sample sizes and also focused on analyzing specific WM tracts, whereas the current study utilized volumetric WMH measurements of larger lobar areas. Despite the fact that our sample size was larger than those in previous studies, it could still be too small to detect smaller effects (see *Limitations*). Two other null findings should also be mentioned: (Feigin et al., 2003) no significant associations were found between VF tasks and left temporal WMH in the main analyses, although the region has been implicated heavily with semantic fluency tasks (Pantoni et al., 2007; Schmidt et al., 2019) no significant associations were seen between phonological fluency and WMH in any region. Possible reasons for these are discussed in section "Limitations and Recommendations."

Although the cognitively healthy controls had, on average, higher VF performances that MCI/AD patients, the differences were not statistically significant. The difference was significant in the original sample, but regrettably, a number of participants had to be dropped due to inadequate imaging resolution for quantitative imaging analysis. Overall, the MCI/AD group utilized in the final sample has relatively good cognitive performance (a MMSE mean score of 24.16), which is also reflected as higher VF performance [compare with, for example, a study by Rinehardt et al. (2014), where VF performance of MCI and AD patients is on a notably lower level compared to the present study]. It should also be noted that since there were no significant differences in VF scores and WMH distributions between the subgroups, it is very likely that the AD patients included in the final sample (which formed the majority of the patient subgroup) were in relatively early phases of disease progression at the time of data collection.

Thus, although word finding difficulties can appear relatively early in AD and they are generally associated with VF scores (Farrell et al., 2014), these hindrances might not necessarily translate to significant deficits in VF for every patient. This implies that, in these cases, semantic information structures might still be relatively intact and accessible, although it is important to remember that VF performance is likely affected by a number of other components, including cognitive flexibility and strategy utilization, working memory, speed of processing and lexical retrieval, as well as basic linguistic abilities (Rinehardt et al., 2014; Whiteside et al., 2016; Schmidt et al., 2017; Gordon et al., 2018). From a methodological standpoint, it is worth noting that although VF tasks demand the retrieval of specific responses, they are less constrained than naming tasks for example (Gordon et al., 2018): If a certain word is not remembered in a VF task, a synonym can be used instead. In these cases, underlying vocabulary knowledge might be used to compensate for difficulties in word retrieval (Gordon et al., 2018). A related finding is that reading and writing habits, which are *per se* linked with vocabulary (Stanovich and Cunningham, 1992; Marulis and Neuman, 2010; Dylman et al., 2020), seem to be associated with VF performance in both cognitively healthy adults (Pawlowski et al., 2012) and patients with AD (Tessaro et al., 2020). In at least non-clinical participants, the effect seems to be even more stronger than education (Pawlowski et al., 2012). Another methodological issue to consider is the fact that differences exist regarding the cue content (i.e., object categories and letter cues used in tasks), timing (e.g., 60 vs. 90 s), and performance outcomes (e.g., correct words in total time limit, correct words in certain time intervals, latency between words, semantic clustering, etc.) of VF tasks in different studies. Variation in the background variables discussed here might also partly contribute to the non-significant subgroup differences in VF performance in the current study. Finally, regarding the effects of concomitant vascular pathology, it might be the case that AD-related disease progression must be at a more advanced stage before concomitant vascular pathology starts to have a cumulative effect on VF performances.

LIMITATIONS AND RECOMMENDATIONS

We acknowledge that the study has a number of limitations. First, the sample size (and thus the statistical power to detect the effects reported) is not optimal, as a notable number of participants had to be excluded due to insufficient MR image quality for quantification. *Post hoc* calculations concerning effect sizes seen in step 2 of hierarchical regression models indicate that the statistical power of the current total sample size is somewhat below the gold standard of 0.80 (0.60 for frontal bilateral WMH and 0.77 for bilateral parieto-occipital WMH). Thus, the relatively limited size of the final sample might have an effect on the statistical power to detect smaller effects especially in the patient subgroup and might also explain the null findings mentioned previously. Despite the relatively

small sample size, our sample is still almost twice the size of previous published studies on the matter (Kavcic et al., 2008; Chen et al., 2009; Serra et al., 2010; Rodríguez-Aranda et al., 2016). Second, the diminished sample size also necessitated the merging of the MCI and AD patient subgroups, which, although being a fairly commonplace procedure in the literature, might not be the optimal solution. Third, since several hierarchical regression models have been run, the risk for family-wise Type I errors (detecting a false positive) is increased. We attempted to guard against false positives by using the Benjamini–Hochberg procedure. After correction, only analyses containing solely right-handed participants remained significant. It is possible that any confounding effects regarding language lateralization were nullified with the removal of left-handed/ambidextrous participants, leading to slightly stronger effects in the regression models. Regarding language lateralization, it is a well-known fact that right-handed participants are more homogeneous with regards to brain functions. As such, it is not surprising to have results change when non-right-handed participants are included or excluded from the analyses. Finally, the current study only utilized total performance scores for measuring VF. Complimentary methods for assessing VF, such as naming latency or semantic clustering, have also been developed.

Overall, further research is needed on the possible group-wise effects of WM pathology on VF in the MCI/AD continuum. As the current study contains a number of unexpected null results, we feel that it is important to keep in mind that a critical feature for research literature to be trustworthy is that "all studies with at least reasonable quality have been reported" (Cumming, 2013). This is especially important in order to minimize publication bias, i.e., the cherry picking of positive findings and the exclusion of null or ambivalent findings. As single studies are rarely final or conclusive, additional evidence is required in the form of replications, follow-up studies, and meta-analyses (Cumming, 2013). In the case of this study topic, future studies would do well to incorporate larger sample sizes and utilize heterogeneous measures for both imaging (e.g., diffusion tensor imaging of microstructural WM tract integrity and volumetric approximation of WMH) as well as for behavioral measurement (e.g., total performance scores, naming latency, semantic clustering). However, transparency about reporting the measures and calculations utilized in assessing VF should be an important goal, as differences here can lead to difficulties in interpreting and replicating the results. It would also be prudent to take into consideration the stage of disease progression in AD patients as well as measure/control background variables besides age and education, including linguistic abilities such as vocabulary and reading and writing habits. Due to the possibility of confounding effects, using solely right-handed participants might be recommendable.

CONCLUSION

In conclusion, as has been shown elsewhere, frontal and parieto-occipital WMH seem to have an effect on semantic fluency. Elevated levels of WMH, as measured by volumetric imaging methods, seem to affect VF performances of both cognitively healthy adults and patients with MCI or AD, i.e., no additive effects of WMH in the patient group were found in this study. However, more research is needed on the possible group-wise effects of WM pathology on VF in the MCI/AD continuum, as the current study has a number of limitations, including the suboptimal statistical power of the current sample to detect the reported effects as well as the merging of the MCI/AD subgroups for analysis. We expect that future studies will elucidate the subject matter further: follow-up studies should aim to replicate the findings, incorporate larger sample sizes, utilize more heterogeneous imaging and behavioral measures, and account for background variables such as AD progression, vocabulary abilities, and reading and writing habits.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Joint Ethical Committee of the University of Turku and Turku University City Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AK performed the statistical analyses and wrote the initial draft. PG-N and MK helped in data analysis, interpretation, and manuscript drafting. JR organized the data collection, and together with MK and PG-N handled the project administration and supervision, as well as contributed to the conception of the study. TT and RP performed the original visual magnetic resonance analyses. JL and JK developed the methodology for the quantitative magnetic resonance imaging analysis and performed the analyses. JR, TT, RP, JL, and JK critically reviewed the manuscript. All authors have made substantial and direct contributions to the work, have approved the final version of the work, and agree to be accountable for all aspects of the work.

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Evaluation of Error Production in Animal Fluency and Its Relationship to Frontal Tracts in Normal Aging and Mild Alzheimer's Disease: A Combined LDA and Time-Course Analysis Investigation

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Semantic verbal fluency (VF), assessed by animal category, is a task widely used for early detection of dementia. A feature not regularly assessed is the occurrence of errors such as perseverations and intrusions. So far, no investigation has analyzed the how and when of error occurrence during semantic VF in aging populations, together with their possible neural correlates. The present study aims to address the issue using a combined methodology based on latent Dirichlet allocation (LDA) analysis for word classification together with a time-course analysis identifying exact time of errors' occurrence. LDA is a modeling technique that discloses hidden semantic structures based on a given corpus of documents. We evaluated a sample of 66 participants divided into a healthy young group (n = 24), healthy older adult group (n = 23), and group of patients with mild Alzheimer's disease (AD) (n = 19). We performed DTI analyses to evaluate the white matter integrity of three frontal tracts purportedly underlying error commission: anterior thalamic radiation, frontal aslant tract, and uncinate fasciculus. Contrasts of DTI metrics were performed on the older groups who were further classified into high-error rate and low-error rate subgroups. Results demonstrated a unique deployment of error commission in the patient group characterized by high incidence of intrusions in the first 15 s and higher rate of perseverations toward the end of the trial. Healthy groups predominantly showed very low incidence of perseverations. The DTI analyses revealed that the patients with AD committing high-error rate presented significantly more degenerated frontal tracts in the left hemisphere. Thus, our findings demonstrated that the appearance of intrusions, together with left hemisphere degeneration of frontal tracts, is a pathognomic trait of mild AD. Furthermore, our data suggest that the error commission of patients with AD arises from executive and working memory impairments related partly to deteriorated left frontal tracts.

Keywords: semantic verbal fluency, perseverations, intrusions, time-course analysis, LDA, frontal tracts, executive dysfunction, mild Alzheimer's disease

INTRODUCTION

Besides memory complaints, one of the most characteristic dysfunctions in Alzheimer's disease (AD) is verbal deterioration. Verbal impairments are observed in the quantity, quality, and meaningfulness of verbal response as well as in the ability of verbal comprehension (Lezak, 1995). In particular, AD impairs verbal fluency (VF), which is the ability to generate words as fast as possible according to either a letter of the alphabet or a semantic category within a time limit, usually one minute. VF abilities are evaluated with tasks, such as the Controlled Oral Word Association Test (COWAT, Benton, 1967) for the assessment of phonemic fluency, or by categories, such as animals or supermarket items (see e.g., the Dementia Rating Scale, Mattis, 1976), for the assessment of semantic fluency. The semantic variant of VF has been largely used in the detection of dementia, as the disease causes degradation of the semantic store (Henry et al., 2004). Moreover, it has been reported that AD impairs particularly semantic fluency as compared to phonemic fluency (Laws et al., 2010). Impairments in semantic fluency comprise reduction in the number of correct responses and increment in errors, which are prominent in AD (Gomez and White, 2006) even in the early stages (Fagundo et al., 2008).

From a clinical point of view, identification of errors is of special importance. The reason is that reduced number of generated words occurs in parallel to the occurrence of errors, especially in neuropsychiatric disorders (Suhr and Jones, 1998; Neill et al., 2014). Most common error forms in VF comprise perseverations (i.e., repeated words) and intrusions (i.e., words not pertaining to a semantic category). Perseverations are defined as the continuation or repetition of an action, which has no relevance for the task at hand and becomes unsuitable (Sandson and Albert, 1984). According to an earlier study (Albert, 1989), perseverations are strongly related to neural alterations, and different types of perseverations have been proposed (Sandson and Albert, 1984). Although other forms of errors have been reported in the literature, such as unintelligible or wrong language errors (Roberts and Le Dorze, 1997), for the present investigation, we will only refer to the most common error forms produced in semantic VF, i.e., perseverations and intrusions.

Regarding intrusions, these can be defined as the unintentional recall of an incorrect verbal material for the task demanded (Fuld et al., 1982). Intrusions arise because of deficient lexicon and troubles in retrieval of information from semantic memory (Carlesimo and Oscarberman, 1992). Even if intrusions occur in normal aging (McDowd et al., 2011), a higher propensity of intrusions exist in AD (Hart et al., 1986; McDowd et al., 2011). A classification of intrusions has also been proposed depending on the type of stimuli (Loewenstein et al., 1991).

Perseverations and intrusions in semantic VF are regularly accounted for in the standard scoring of VF by simply reporting the total number of error occurrences (Strauss et al., 2006). Often, the total number of errors (i.e., perseverations + intrusions) are used to calculate a single error score, which is frequently excluded from data analysis (e.g., Rinehardt et al., 2014). However, some investigations report rate of occurrence for perseverations and intrusions separately (e.g., Raboutet et al., 2010). Although error propensity is a low base rate variable (Woods et al., 2004), quantification of total number of perseverations and/or intrusions committed in a minute allows for identification of pathological conditions such as AD (e.g., Ober et al., 1986; Pekkala et al., 2008). This practice has a clinical value. For instance, perseverations in semantic VF have been analyzed in more detail in aging and dementia studies. Pekkala et al. (2008) analyzed a type of perseverations in different VF categories in normal aging, and mild and moderate AD. These authors showed that recurrent and continuous perseverations increase during the course of AD. More recently, Pakhomov et al. (2018) applied longitudinally a computerized solution to assess recurrent perseverations in the "animal" category, which predicted cognitive impairment in a time of 5.5 years. In this line of investigation, Auriacombe et al. (2006) conducted a longitudinal study on a sample of patients with incident AD and age-matched controls. These authors accounted for both perseverations and intrusions to evaluate whether error production in semantic VF characterized different phases of the disease. Indeed, the findings showed that perseverations were a marker of AD at diagnosis time. The abovementioned studies bring out the importance of analyzing errors in semantic VF. However, the purpose and methods employed had clinical interests, and they were not designed to disclose the mechanisms behind error occurrence. In this regard, a search in the literature revealed one investigation by Miozzo et al. (2013) looking at the mechanisms behind perseverations in semantic VF in AD. This study applied a time-analysis approach, which revealed that perseverative answers took place after long lags from their first occurrence. Conclusions were that perseverations emerged because of executive dysfunction and memory deficits.

Although that evaluation of errors (mainly of perseverations) has shown diagnostic utility and promising findings, there is still a need to unveil the significance of both intrusions and perseverations in semantic VF errors in aging and AD. To the best of our knowledge, there are no previous investigations that have attempted to disentangle the underlying mechanisms of different types of errors in the mentioned populations. In fact, the majority of studies in the field uses error data only to obtain an accuracy score, i.e., correct number of generated words, which is the main outcome of semantic VF. Correct answers have been analyzed with different quantitative and qualitative methods. One of the first qualitative approaches was proposed by Troyer et al. (1997) who calculated clustering and switching scores based on correct answers produced. Subsequent studies have introduced time-course analyses (e.g., Demetriou and Holtzer, 2017), and computational (e.g., latent semantic analysis; e.g., Ledoux et al., 2014) and statistical techniques (e.g., multidimensional scaling; e.g., Weakley and Scmitter-Edgecombe, 2014) aiming to ameliorate the qualitative scrutiny of semantic VF performance. These methodologies have proven successful as they allow us to appraise qualitative differences of semantic word generation. Nonetheless, the application of these methods has not been implemented to analyze the errors in semantic VF.

Because the simple report of total number of errors cannot reveal the exact nature of cognitive deteriorations taking place, the present investigation will carry out a refined evaluation of

intrusions and perseverations during semantic VF in normal aging and mild AD. The primary purpose is to better understand the underlying cognitive mechanisms of errors. To achieve this objective, the application of different approaches and techniques is deemed necessary. As a first step, a behavioral analysis of the pattern of error generation seems appropriate. With this analysis, we wish to determine how and when semantic VF errors occur. To answer these questions, we need to establish the context in which errors are committed and code the exact time of error occurrence. Defining the context in which errors happen can help answer the "how," and this can be achieved by identification of *clusters* or bundles of semantically related words (Troyer et al., 1997). This strategy provides a structure of word generation (Zemla et al., 2020). Previous data have demonstrated that clusters in semantic VF significantly affect perseveration rate (Azuma, 2004). Therefore, we wish to evaluate whether the context (i.e., presence of clusters) plays a role in error production of both perseverations and intrusions. Regarding the second question of "when," we apply time-course analysis techniques to address the issue. In our previous study, we have demonstrated that calculation of in-between word intervals during VF is a relevant way to assess the information processing speed of word generation during VF in aging populations (Rodríguez-Aranda et al., 2016). In the present investigation, we use the same approach to register when errors take place. In addition, we go one step further by not only analyzing perseverations and intrusions behaviorally but also by looking at their neural correlates.

Since the pioneer study of Milner (1964), commission of errors has been linked to frontal lobe impairments. The emergence of imaging techniques in the last decade further allowed the identification of frontal pathways associated with verbal production impairments such as the frontal aslant tract (FAT), anterior thalamic radiation (ATR), and uncinate fasciculus (Catani et al., 2013; Cipolotti et al., 2020). Empirical data have shown the importance of these tracts with VF deficits in primary progressive aphasia (Catani et al., 2013). Also, their involvement is confirmed in studies stimulating electrically some of the mentioned tracts (i.e., the FAT) causing speech arrest (Chernoff et al., 2019). Similarly, lesion (e.g., (Kinoshita et al., 2015) and imaging studies (e.g., Sharp et al. (2010) have demonstrated the involvement of frontal pathways in word generation, verbal fluency, stuttering, and inhibitory abilities (for review see: Dick et al., 2019). Based on this evidence, it seems highly probable that commission of errors in semantic VF is related to the integrity of frontal lobe tracts, which are known to degenerate in very early phases of AD, including preclinical stages (Caballero et al., 2018).

Thus, the goal of the present study is two-fold: (a) perform a fine behavioral evaluation of the occurrence of perseverations and intrusions in semantic VF in the category most frequently employed for the assessment of dementia (Moreno-Martinez et al., 2017), namely "animals" (Ardila et al., 2006); and (b) assess frontal tracts purportedly associated to error behavior. Three groups of participants were included in the study: patients with mild AD, healthy age-matched older controls, and healthy younger adults.

To address the first goal of the study, we conducted a first stage where we combined computational automatization for classification of clusters (i.e., latent Dirichlet allocation method; Blei et al., 2003) in order to avoid idiosyncratic decisions together with a time-course analysis of word generation. Then, to address the second goal, we conducted a second stage of the study where we applied diffusion tensor imaging (DTI) techniques to evaluate the white matter integrity of frontal tracts of the participants. In this second stage, we assessed the structural status of frontal tracts as well as their relationship to error commission. For the assessment of the association between error occurrence and frontal tract integrity, only data from participants committing errors were analyzed. We expect that error behavior arises mainly in the patient group and, to some degree, in the older healthy controls. Moreover, we hypothesize that all subjects with high recurrence of errors, disregarding which group they belong to, will show compromised integrity of frontal tracts. However, we do expect that the healthy older controls will be less prone to committing errors, while the patients with AD are expected to show a high incidence of errors. Degree of tracts' deterioration is expected to be relative to degree of error incidence.

MATERIALS AND METHODS

Participants

An initial sample of seventy-two participants was recruited for the present study, with 24 subjects on each of the following groups: healthy young adults, healthy older adults, and patients with mild AD. Due to technical troubles, we did not have complete speech/spectographic data for one healthy older adult. Moreover, five of the patients turned out to have other etiologies than AD. Thus, the latter six individuals were excluded from the study.

Stage 1. Participants Included in the Behavioral Analyses of Errors

A sample of sixty-six Norwegian individuals was retained for the first stage of the study. Of these, 24 were healthy young adults (13 females, 11 males; age: M = 30.2 years, SD = 5.9), 23 were healthy older adults (9 females, 14 males; age: M = 67 years, SD = 8.2), and 19 were patients with mild AD (9 females, 10 males; age: M = 64 years, SD = 10.1). Inclusion of the younger group was deemed convenient in order to evaluate commission of errors and status of frontal tracts of the healthy older group. All the participants were right-handed native Norwegian speakers from North Norway. The patients were recruited at the University Hospital of North-Norway from the Neurology and Geriatrics departments. Only patients with mild AD were enrolled in the study. Following consensus criteria for mild AD (see, e.g., Versijpt et al., 2017), these patients had scores on the Mini Mental State Examination (MMSE) (Folstein et al., 1975) above 20. Each patient underwent standard clinical examinations for the detection of AD, including cerebrospinal fluid (CSF) concentrations of tau, phosphorylated tau, and β-amyloid. Diagnosis was settled by an experienced neurologist or/and geriatrician according to the DSM-IV and NINCDS-ADRDA (Mckhann et al., 1984) criteria for probable

AD. Importantly, all the patients were included in the study only upon verification of AD diagnosis after a year of the initial diagnosis.

The healthy older controls were community-dwelling persons recruited through advertisements in a local senior citizen center, flyers, and by means of word of mouth. This group was selected to match as much as possible the patient group for age and gender. Participants in the younger group were university students recruited through advertisements in the university campus. All the participants were tested for cognitive status with the MMSE and a comprehensive neuropsychological assessment. For controls, only participants with an MMSE score $\geq$ 28 and not depressed according to the adapted criteria (Rodríguez-Aranda, 2003) for the elderly on the Beck Depression Inventory (BDI) (Beck et al., 1988) were included in the study. The healthy controls had no history of psychiatric or neurological illness, tumors, or drug or alcohol abuse. A neuroradiologist screened the MR images for major pathologies such as infarctions or tumors. Involvement in the study was voluntary, and written consent was signed before testing. The healthy groups provided signed informed consent prior to participation in the study. As for the patients, only those individuals retaining the ability to give informed consent at the time of testing were enrolled in the investigation. An initial interview was conducted to obtain demographic information. The study was approved by the Regional Research Ethics Committee.

Stage 2. Participants Included in the Structural Assessment of Frontal Tracts and Their Relationship to Error Occurrence

All sixty-six participants included in the first stage of the study had MRI data enabling anatomical comparisons of the selected frontal tracts, which was deemed important to establish the status of tracts in the older groups relative to the younger individuals. Nevertheless, only the older groups were followed-up in this second stage, as the younger individuals committed almost no errors. Thus, the evaluation of the association between integrity of frontal tracts and recurrence of errors was performed exclusively on the healthy older adult group and mild AD group. Both older groups were further subdivided into low-error and high-error subgroups. Description of how we obtained the subdivisions is provided in the later section "Subdivision of Older Groups". Nine healthy older participants conformed to the control low-error subgroup ($Con_{low\text{-}error}$) (M age = 71.3, SD = 3.1; 5 females), while 14 were assigned to the control high-error subgroup ($Con_{high\text{-}error}$) (M age = 64.3, SD = 9.3; 4 females). As for the patients, 9 were allocated to the AD low-error subgroup ($AD_{low\text{-}error}$) (M age = 62.3, SD = 11.7; 5 females) and 10 to the AD high-error subgroup ($AD_{high\text{-}error}$) (M age = 65.6, SD = 8.7; 4 females).

Procedures Behavioral Analyses

Verbal Fluency Assessment Scoring and Classification of Errors

The "animals" category was chosen for the present study, as this is the category of semantic VF most reported in the literature that discerns between normal aging and dementia (Rofes et al., 2020). We evaluated this task in an adapted computerized version developed in our laboratory (for detailed description of the adaptation see Rodríguez-Aranda and Jakobsen, 2011). Shortly, the participants wore a headset with microphone for recording answers while they sat in front of a computer screen. The word "animals" (dyr in Norwegian) was presented *via* the E-prime software (Psychology Software Tools, Pittsburgh, PA, United States), and the participants were asked to start producing words belonging to the category within 1 min as fast as the word appeared on the screen. They were explicitly asked to generate different types of animals, as fast as possible, and not to repeat any exemplar. The word remained present on the screen during the whole trial.

Answers were recorded simultaneously on a computer program (CSL 4500, Kaypentax), on a digital recorder, and manually by the experimenter in charge of the testing. Thereafter, two different coders checked the answers to ensure reliability of the results. Next, the same coders carried out manually the regular scoring of correct answers, which is simply the accounting of total number of correct generated words belonging to the "animals" category. In addition, the coders identified perseverations and intrusions. An intrusion was defined as an answer that did not pertain to the "animals" category, while perseverations were words repeated at any point during the 1-min trial after the first production of the word in question (e.g., "tiger, car, elephant, lion, tiger"; car = 1 intrusion; tiger = 1 perseveration).

Identification of Clusters

A regular score in the evaluation of semantic VF is that of clustering (Troyer et al., 1997). During semantic VF performance, subjects produce words matching a given category, for instance, animals. Word generation takes place by producing subclassifications of the required category, for example: farm animals, birds, mammals, or four-legged animals. Thus, word production in semantic VF occurs through subgroups or clusters. According to Rofes et al. (2020), a cluster can be defined as group of words belonging to a semantic family, which is sub-categorized under the superordinate category. The methods employed for identification of clusters has varied, from subjective *ad-hoc* decisions of the human coder to analytic methods based on automatic speech transcription and machine learning classifiers (Montemurro, 2014; Holmlund et al., 2019). In this study, we apply the latent Dirichlet allocation (LDA) technique, which is a Bayesian method for topic extraction in sampling of documents (Blei et al., 2003). LDA is an ameliorate approach of probabilistic latent analysis (pLA), which in turn is an improved technique of latent semantic analysis (LSA) (Anaya, 2011; Rosenstein et al., 2015) widely used in psycholinguistic research (e.g., Pereira et al., 2013).

Latent Dirichlet Allocation Analysis

Latent Dirichlet allocation (LDA) is an information retrieval technique, which assumes that multiple abstract topics (latent semantic structure) exist in a document, and it extracts them quantitatively by calculating the probability of co-occurrence of words in a document. This type of model ignores the order of

words and for this reason, it is called "bag-of-words model" (Blei et al., 2003). According to LDA, a category is the highest concept assumed of a semantic structure (e.g., animals), while a subcategory is a subset in the semantic structure (e.g., sea animals or insects). Thus, LDA identifies through co-occurrence of words in documents specific "topics," which correspond to the concept of a "subcategory." Once identification of topics is performed by LDA, clusters can be defined in a sequence of VF responses. It is, therefore, important to note that "cluster" and "topic" cannot be interchangeably used.

Human evaluators rely on idiosyncratic beliefs to classify a word as pertaining or not to the animal category based on what a specific person knows about "animals." However, because LDA is not based on such notions, it enables us to appraise whether wrong answers are actually semantically or lexically related to the generated topics. The topic identification based on LDA likely corresponds to the classification by animal subcategories but not necessarily corresponds to them in the same way that human coders would appraise.

Estimation of Topic Probabilities and Clusters by Latent Dirichlet Allocation Analysis

In the present study, we used 180 unique words in LDA analysis that were produced by our participants. We intentionally included wrong words (i.e., intrusions; e.g., rose) to assess semantic associations *vis-à-vis* "error" responses. We used the Norwegian version of the Wikipedia database (nowiki-20181020-pages-articles.xml.bz2, 495,898 articles) as a dataset. However, we reduced the document dataset to 80,405 articles containing only the response words. In this regard, the use of LDA is advantageous, as this technique creates a generalizable model to unknown data that suits the relatively limited number of articles available in Norwegian. According to the method of Blei et al. (2003), we conducted LDA analyses on the data using Rstan with the following parameters: number of topics = 3-15 and α = 0.2, 0.3, 0.4, 0.5, and 1. Thus, we obtained 65 possible models ($3 \times 15 = 65$), and then we selected a model with the number of topics = 14 and α = 0.3 based on leave-one-out cross-validation (LOOCV) to define the model. Based on the selected model, we calculated topic probability, which is the probability of the existence of a latent topic when a specific word appears in a document. One word has multiple topic probabilities. In the present model, 14 topic probabilities were obtained, which connected to 14 possible subcategories. The sum of the topic probabilities for a word is 1 (100%). The word list and topic probabilities of the model used in the study are provided as **Supplementary Material** (see **Supplementary Data File 1**).

Definition of Clusters by LDA Analysis and Error Identification

In this study, a cluster in VF responses was defined based on topic probability; when topic probabilities to the same topic are higher than the criteria ($= 1/14 \times 0.5$) in two consecutive word responses. The criterium of two consecutive responses was adopted in agreement with suggested norms by Troyer et al. (1997) and Rich et al. (1999). After identification of the clusters by LDA, we were able to locate the errors in the timeline of execution extracted from the time-course analysis. In addition, we counted the number of responses within a cluster, that is, the number of responses constituting a cluster. Note that it is possible that multiple topic probabilities exceed the clustering criteria within one cluster because of the definition of topic probability. In other words, an ongoing topic can overlap and transpose to another topic within a cluster. As an example, we present the following sequence: "monkey (topic 3), gorilla (topic 3) chimpanzee (topic 3 and 9), kangaroo (topics 8 and 9)." This group of words is considered a cluster, while the transposition from topics 3 to 9 occurs at "chimpanzee."

Time-Course Analyses

The deployment in time of all answers, including perseverations and intrusions, was analyzed with a speech lab system (CSL 4500, Kaypentax). In this analysis, the acoustic signal is visually and auditorily examined to settle the exact time of occurrence of each intrusion and perseveration all along the 1-min trial of the execution.

Two types of time-course analyses were conducted. First, we applied a strategy widely used in the literature (e.g., Rosen, 1980; Crowe, 1998; Kim et al., 2011), consisting of partitioning the VF trial into15-s phases to analyze performance by time period. We, thus, quantified the total number of responses (i.e., correct responses + errors) and types of errors (i.e., intrusions vs. perseverations) separately by phase and by group. The rationale was to obtain patterns of performance in overall word production and most importantly in error production as a function of time for each specific group. Previous research (e.g., Rohrer et al., 1999) focusing only on the time course of correct word production might have led to incomplete or wrong conclusions, as VF performance was only partially analyzed, that is, the occurrence of errors was not included. This selective way of analyzing VF might have prevented us from delineating important aspects of the processing speed issue in aging and dementia.

Keeping this line of reasoning, we conducted a second strategy where we calculated in-between intervals of errors. This procedure enabled us to test whether the incidence of errors had a relationship to the time used to produce the inaccuracies. This second approach aims, from a different perspective, to assess the role of processing speed in error occurrence. To achieve this goal, complementary information related to the number of correct words generated between errors was needed. Therefore, we quantified the total number of words produced amid error occurrences. If correct words are produced in between errors at a similar rate across the trial in all the groups, it will discard slowing of processing speed as a central factor of group differences. Thus, calculation of in-between error intervals was restricted to what we considered the best three alternatives presenting comprehensible information: (a) between same perseveration (i.e., same repeated word); (b) between intrusions; and (c) between errors of any type (i.e., "intrusion-intrusion," "intrusion-perseveration," "perseveration-perseveration," and

"perseveration-intrusion"). For calculations of (b) and (c), we excluded data with only one error.

Statistical Analyses for Behavioral Data

One-way between-subject ANOVAs were conducted to show group differences in demographic variables and in the number of responses, perseverations, and intrusions. According to initial sample size calculations for a three-level one-way ANOVA, we needed 24 individuals in each group to attain 85% statistical power and reach large effect sizes (f = 0.4) at a significance level of 0.05. Significant interactions or main effects involving group differences were followed up with appropriate *post-hoc* analyses. Chi-square tests were performed to detect possible differences in error production among the groups, and to detect differences in the time course between the two types of errors. Furthermore, correlation coefficients were calculated to quantify the relationship among the number of responses, errors, and topics.

Procedure DTI of Frontal Tracts and Their Association to Errors

MRI Acquisition

The participants were scanned in a 1.5T Phillips Intera MR scanner. Diffusion-weighted images were obtained using a single-shot SE-EPI sequence with TE/TR = 79/11,663 ms, SENSE acceleration factor 2, FOV 252 X 252 mm, and in-plane resolution 2.25 X 2.25 mm^2 in 70 axial slices (slice thickness of 2.25 mm). Diffusion gradients were applied in 15 directions with b = 1,000 s/mm^2, and a volume without diffusion weighting was acquired. Two common DTI metrics were assessed: fractional anisotropy (FA), which denotes the strength of diffusion directionality, and mean diffusivity MD, which indicates the overall rate of diffusivity (Madden and Parks, 2017). In aging, a decrement in FA has been reported, which often is coupled with an increment in MD (de Groot et al., 2016). These events suggest degeneration in white matter in terms of tissue loss and replacement of the damaged tissue by free water (Pfefferbaum and Sullivan, 2003). Of interest for the present study is that the magnitude of FA and MD changes is reported to be greater in AD than in normal aging (Caballero et al., 2018).

DTI Preprocessing

Preprocessing and statistical analysis of the DTI data were performed using the FSL software library (v5.0.9). The diffusion-weighted images were corrected for motion and eddy currents using FLIRT (Jenkinson and Smith, 2001). A brain mask was created per participant using BET (Smith, 2002). Diffusion tensor, fractional anisotropy (FA), and mean diffusivity (MD) were calculated using the DTIFIT tool of FMRIB's Diffusion Toolbox of FSL.

Anatomical Comparison of Frontal Tracts

Anatomical comparisons of the three initial groups were deemed appropriate to understand the status of frontal tracts of the older groups relative to the younger adults. In this way, we could appreciate the degree of tract deterioration in the patients with AD relative to the older control, and in the healthy older adults relative to the younger participants. Thereafter, we proceeded to evaluate the relationship between frontal tract integrity and error commission in four subgroups of the older participants (mild AD and healthy older controls).

Evaluation of Frontal Tract Status and Their Relationship to Errors in the Older Groups

The younger adult group committed practically no errors, and for this reason, this group was excluded in this part of the analyses. An overview and explanation of the reasons for exclusion can be found in **Supplementary Material**. The older groups were then subdivided into low-error and high-error subgroups.

Subdivisions of Older Groups

Because of scarce availability of error data, we subdivided the patients and older controls relying on the total score of errors, that is, on the sum of both intrusions and perseverations. The reasons for this decision are methodical and theoretical. To begin with, it is not reasonable to consider a division of groups based on type of errors because of the low number of occurrence by error type. As for the theoretical standpoint, the literature suggests that both intrusions (e.g., Desgranges et al., 2002) and perseverations (e.g., Corrivetti et al., 2019) are related to frontal impairments. Thus, it seems logical to evaluate the integrity of frontal tracts in relation to general error production. Subgrouping of the older and AD groups was based on a cut-off point using the median of total errors (intrusions + perseverations) from each group. The median values employed were 0.5 for the older adults and 1 for the patients with AD. Thus, any participant showing a score equal or above the respective value for his/her group was assigned to the "high-error subgroup," while those having a score below the median value were assigned to the "low-error subgroup."

Statistical Analysis for Imaging Data

Voxelwise statistical analyses of the FA and MD data were carried out using TBSS (Tract-Based Spatial Statistics, version 1.2; Smith et al., 2006), part of FSL (Smith et al., 2004). Two sets of analyses were performed. For the first set, an anatomical evaluation of the tracts was conducted across groups without subdivisions, and the younger group was included. Hence, the younger group, the healthy older controls, and patients with AD were compared. The reason to include the younger group in this initial stage was for evaluation of the integrity of the tracts of the older controls. Thus, FA and MD data of the three groups were aligned into the FMRIB58_FA standard space using the nonlinear registration tool FNIRT (Andersson et al., 2007; Andersson et al., 2007). The comparisons were performed along the three selected frontal tracts: (1) anterior thalamic radiation (ATR), (2) frontal aslant tract (FAT), and (3) uncinate fasciculus (UNC).

For the second set of analyses, comparisons between the four subgroups of older controls and patients were performed. Again, we evaluated the selected tracts FAT, ATR, and UNC. For these comparisons, FA and MD data were aligned to the most representative image of the sample, because all the images corresponded to seniors. In this second set of analyses, we conducted two DTI solutions. The first solution was conducted

voxel-wise within each tract and separated by hemisphere. Voxel-wise statistics were performed with the Randomize tool (v2.5; part of FSL), a permutation-based method (Winkler et al., 2014). We used 5,000 iterations, a threshold-free cluster enhancement for multiple comparison correction and a significance threshold of $p < 0.05$ for all the statistics. Age and sex were included as confounders in all the analyses. Since there were no differences in education between the healthy older adults and patients with AD, this variable was not entered as a confounder. In the second solution, we performed a global assessment of complete tracts by multivariate analysis using the SPSS software (version 24) to test interaction effects on the mean values of FA and MD across all the voxels of each tract. In this way, possible interactions by group, sex, age, tract, and hemisphere were tested. Because of multiple comparisons, the Sidak correction was applied.

RESULTS

Behavioral Analyses

Demographics

Demographic characteristics of the groups are shown in **Table 1**. Since some of the initial participants were excluded from the study, we calculated the statistical power of our remaining sample. Although this calculation of unbalanced ANOVA is not straightforward, the sample sizes in the one-way three-level analysis (n = 19, 23, and 24) were large enough to detect large effect sizes ($f > 0.4$) with a statistical power of = 0.8. Hence, significant differences among the groups were found for MMSE (F (2, 63) = 26.5, $p < 0.001$, $\eta_p^2 = 0.45$) in which the patients with AD presented considerably lower scores than the healthier groups. It is noteworthy that the older controls had a very similar score on MMSE than the younger adults. Years of education showed significant group differences (F (2, 63) = 19, $p < 0.001$, $\eta_p^2 = 0.38$), as both the older groups had less formal schooling than the younger participants. Evidently there were significant group differences in age (F (2, 63) = 148.2, $p < 0.001$, $\eta_p^2 = 0.82$), but not in sex (χ^2 (2) = 1.1, $p = 0.56$, NS). Regarding age and years of education, multiple comparisons showed significant differences between the young and the two older groups for education ($t(63) = 5.65$; $t(63) = 4.95$; $p < 0.05$), whereas the healthy older and AD groups did not differ significantly in age ($t(63) = 2.99$, $p = 0.24$) or education ($t(63) = 1.04$, $p = 0.3$).

Standard Scores for Semantic Verbal Fluency

Table 2 presents standard results for the "animals" category in terms of mean values for total number of correct responses, intrusions, and errors generated during the whole minute by group. The results showed significant group differences in correct number of answers (F (2,63) = 16.06, $p < 0.001$, $\eta_p^2 = 0.34$) and intrusions (F (2,63) = 5.43, $p < 0.01$, $\eta_p^2 = 0.14$). Group contrasts for perseverations did not yield significant differences (F (2,63) = 2.22, $p = 0.11$, NS, $\eta_p^2 = 0.07$). The multiple comparisons with Holm's method showed significant group differences for correct answers between the patient group and both healthy groups ($p < 0.05$). The same *post hoc* analysis revealed that group differences for intrusions were significant between the patient group and both healthy groups ($p < 0.05$).

LDA Analysis

Cluster Identification

Using the LDA technique, fourteen topics were extracted. Thereafter, the clusters were defined in a sequence of VF responses based on topic probability. A summed topic probability is the aggregated value of topic probabilities of a set of responses pertaining to a topic. In the following section, we present summed topic probabilities exclusive to errors. The corresponding results of summed topic probabilities to correct responses can be found in **Supplementary Material I**, which help understand the distribution of topics by type of generated word (correct vs. errors).

Error Production by Topic Probability

Perseverations: patterns of summed topic probabilities differ across groups (**Figure 1A**). This is true for topic 2 in the young adults, for topics 2 and 8 in the older controls, and topics 8 and 9 in the patients with AD. From the analyses of cluster identification, it became evident that more than half of the perseverations were produced within a cluster, which means 64% in the young group, 55% in the older adults, and 62% in patients with AD.

Intrusions: **Figure 1B** shows that the patient group mostly committed intrusions with the highest summed topic probability in topic 8. About half of the intrusions (56%) were found within clusters in the AD group. These results showed as a whole that more errors of any type were produced in topics with more words (to appraise this statement, refer to **Supplementary Material 1**).

Relationship Between Clusters and Errors in Topic Probability

Figure 2 shows the relationship between the summed topic probabilities for the topic model and the two types of errors (perseverations and intrusions). These analyses are of importance, as they allow us to assess the degree of association between errors and the 14 generated topics. The correlation coefficients between the summed topic probabilities

TABLE 1 | Demographics, MMSE scores by group.[a]

	Young group (n = 24)	Healthy older group (n = 23)	Mild AD Patients (n = 19)	F(2, 63)	p-value
Female	13 (54.16%)[a]	9 (39.13%)	9 (47.36%)		
Age (years)	30.2 (5.9)	67.0 (8.2)	64.0 (10.1)	148.2	**0.001**
Education	17.1 (2.3)	12.1 (3.7)	11.0 (3.5)	19.0	**0.001**
MMSE	28.9 (0.9)	28.7 (0.7)	25.0 (3.4)	26.5	**0.001**

NB: MMSE = Mini-Mental State Examination. [a]Mean (SD) or N (%). Bold values indicate that they are statistically significant ($p < 0.05$).

TABLE 2 | Means and SD for standard scores of the "animal" category in the 1-min trial.[a]

	Young group (n = 24)	Healthy older group (n = 23)	Mild AD Patients (n = 19)	F (2, 63)[a]	p-value
Total number correct answers	20.6 (1.0)	18.8 (1.4)	12.9 (0.97)	14.9	**0.001**
Total number of intrusions	0.00 (0.00)	0.09 (0.28)	0.95 (1.87)	3.8	**0.01**
Total number of perseverations	0.46 (0.66)	0.87 (1.49)	1.26 (1.59)	3.0	0.11

M = Mean, SD = standard deviation. Significant values are presented in bold. [a]Mean (SD).

for perseverations and topic model on each topic were r = 0.22, 0.60, and 0.79 in the younger, older, and AD groups, respectively (**Figure 2A**). The correlation coefficients (r) between the summed topic probabilities for intrusions and the topic model in each topic for the patients was 0.60 (**Figure 2B**). Similarly, the positive relationship between the errors and the topic model in the summed topic probabilities are also observed in within-cluster errors (**Figures 2C,D**). The reader should note that in the intrusion panels (**Figures 2B,D**) only the summed topic probabilities for the AD group are presented, because the healthy groups never or scarcely produced intrusion errors. Some of the intrusions committed by the healthy older adults, ("kemse" and "lojør") and AD group ("rosebed" and "pusi") were not factual words; hence, they were not included in any topic probability.

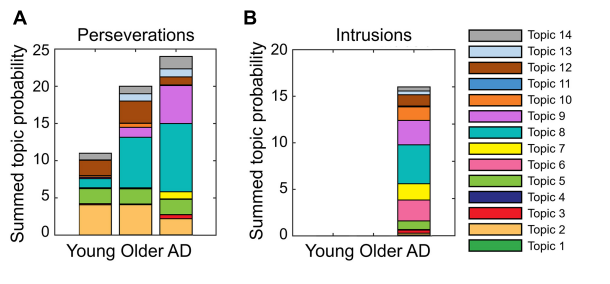

FIGURE 1 | Proportion of summed topic probabilities for each topic in **(A)** perseverations and **(B)** intrusions. Note that the intrusions committed by healthy older adults, ("kemse" and "lojør") are unknown utterances. As such, they are not found in Wikipedia articles, and accordingly, they have no topic probabilities. Likewise, two out of the 18 intrusions committed by patients with Alzheimer's disease (AD) ("rose bed" and "pusi") were not found in the Norwegian Wikipedia articles.

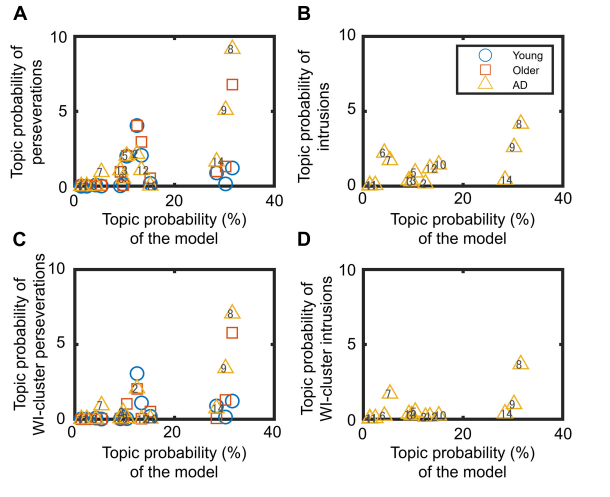

FIGURE 2 | Relationship between summed topic probabilities of the topic model and errors: **(A,C)** perseverations and **(B,D)** intrusions. Panels **(C,D)** concern within-cluster (WI-cluster) errors. Each marker indicates the data for one topic (from 1 to 14 topics).

Time-Course Analyses

Generation of Total Number of Responses by 15-s Phase, by Group

The illustration on the deployment in time of total number of generated words including errors across the 4 phases is presented in **Supplementary Material** (**Supplementary Figure 2**). The results showed that word production decreased as time passed in all the groups. A two-factor ANOVA revealed a significant main effect of group (F (2, 63) = 9.91, $p < 0.001$, η_p^2 = 0.24) and phase (F (3, 189) = 55.9, $p < 0.001$, η_p^2 = 0.47), but the interaction effect was not significant (F (6, 189) = 2.08, p = 0.057, η_p^2 = 0.06). *Post hoc* calculations revealed that the number of responses of the AD group was significantly lower than that of the young and older groups (t (63) = 4.31; t (63) = 3.29) but did not differ between the latter two groups (t (63) = 1.03). The analysis also showed significant differences among all the phases (t (63) = 4.4 for phases 1 and 2; t (63) = 4.86 for phases 2 and 3; t (63) = 2.97 for phases 3 and 4; t (63) = 9.41 for phases 1 and 3; t (63) = 11.68 for phases 1 and 4; t (63) = 4.86 for phases 2 and 3; $p < 0.05$).

Perseverations and Intrusions by 15-s Phase, by Group

Figure 3 shows the time course of the total number of errors in the four phases. To detect differences in the time course of two types of errors, chi-square tests were conducted. Whereas the tests did not find any statistical differences between the total number of errors and phases in younger and older groups ($\chi^2(3)$ = NA, p = NA, w = NA; $\chi^2(3)$ = 1.73, p = 0.63, w = 0.28), a significant difference in the time course among the errors in the AD group ($\chi^2(3)$ = 14.4, p = 0.002, w = 0.61) was found. A residual analysis revealed significant differences in phases 1 and 4 ($p < 0.05$).

In-Between Intervals of Errors

In-between intervals of perseverations: this calculation was performed by measuring the time interval between a generated word and the repetition of the same word (e.g., time between "lion and lion" or "fish and fish"). For these data, we considered 9 younger adults (M = 24.2 s, SD = 16.88), 12 healthy older adults (M = 21.64 s, SD = 13.69), and 10 patients with mild

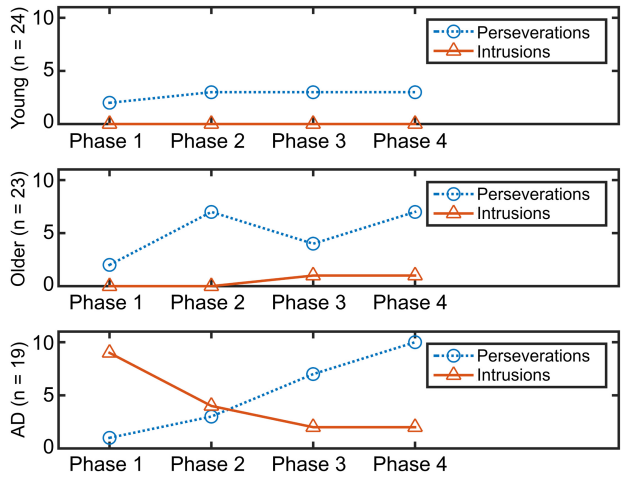

FIGURE 3 | Time course of each error in four phases.

AD (M = 22.81 s, SD = 8.09). A one-way ANOVA showed no significant group differences (F (2, 28) = 0.09; p = 0.91, NS, η_p^2 = 0.01).

In-between intervals of intrusions: this measurement was not carried out because of restricted amount of data. None of the younger participants committed intrusions, while only 2 older adults committed 2 intrusions. From the patient group, there were 18 intrusions, and only 2 participants had enough data to compute the in-between interval calculation.

In-between intervals of any error type: for these data, 9 younger adults (M = 31.11 s, SD = 16.56), 14 healthy older adults (M = 33.86 s, SD = 13.74), and 15 patients with mild AD (M = 31.56 s, SD = 13.55) were available. A one-way ANOVA showed no significant group differences (F (2, 35) = 0.13; p = 0.88, NS, η_p^2 = 0.01).

These analyses consistently showed that there were no practical differences in error intervals among the groups. Note that the statistical power in these analyses is low because of limited sample sizes in each group. Therefore, effect sizes are particularly important.

Word Production Within Intervals of Error Production

Because of availability of data, only the total number of produced words during in-between intervals of perseverations and of any error type was possible to analyze. The results concerning perseverations demonstrated that the 9 younger adults (M = 7.1 words, SD = 5.4), 12 healthy older adults (M = 7.6 words, SD = 3.5), and 10 patients with mild AD (M = 6.1 words, SD = 3.2) generated a similar number of responses. A one-way ANOVA showed no significant group differences (F (2, 28) = 0.38; p = 0.68, NS, η_p^2 = 0.03). As for the number of words in between intervals of any error type, we obtained limited data. Only 2 younger adults (M = 4.5 words, SD = 0.71) and 3 healthy older adults (M = 4.56 words, SD = 5.6) had useful outcomes for this analysis, while there were data available from the 10 patients with mild AD (M = 2.43 words, SD = 3.23). The corresponding one-way ANOVA showed no significant group differences (F (2, 12) = 0.56, p = 0.58, NS, η_p^2 = 0.09). Again, due to low statistical power in these analyses, effect sizes are of relevance.

DTI Analyses

Anatomical Comparisons of Frontal Tracts Among Young, Older, and Mild AD Groups

The analyses of FA and MD values in the frontal tracts comparing the young adults, healthy controls, and patients with AD are presented in **Supplementary Table 1**. The young adults showed increased FA compared to the healthy seniors and patients with AD, separately, in bilateral ATR and FAT, and in left UNC. The healthy seniors showed larger FA than the patients with AD only in the left ATR. For MD, the healthy seniors compared to the young adults, showed increase in the right FAT. The patients with AD presented increased MD in right ATR and left FAT compared to the young adults. Compared to the healthy seniors, the patients with AD showed increased MD in bilateral FAT, and left ATR and UNC. For all the comparisons, p-level was set at 0.05.

Assessment of the Integrity of Frontal Tracts and Errors in Older Subgroups

In this section, we will present VF results pertaining to the fours subgroups from the older groups. Complete data of error commission ratio of the original three groups (young, healthy older, and patients with mild AD) can be found in **Supplementary Material II** and **Supplementary Figure 3**.

Error scores across the four subgroups were as follows: $Con_{low\text{-}error}$, M = 0, SD = 0; $Con_{high\text{-}error}$, M = 0.8, SD = 0.8; $AD_{low\text{-}error}$, M = 0.3, SD = 0.3; and $AD_{high\text{-}error}$, M = 1.85, SD = 0.8. A chi-squared test conducted on the four subgroups of older controls and patients showed no group differences for sex (χ^2 (3) = 2.38, p = 0.5, NS). Similarly, a one-way ANOVA showed no significant differences for age (F (3, 38) = 1.76, p = 0.17, NS) or education (F (3, 38) = 1.3, p = 0.29, NS).

The voxel-wise comparisons among the four subgroups only showed differences in MD measures of the frontal tracts. In the comparisons between the high-error groups, $AD_{high\text{-}error}$ showed increased MD values in left ATR (**Figure 4A**) and UNC (**Figure 4C**), and bilateral FAT (**Figure 4B**) compared to $Con_{high\text{-}error}$ ($p < 0.05$, d = 2.34). Moreover, $AD_{low\text{-}error}$ also showed marginally larger MD measures than $Con_{high\text{-}error}$ in the left UNC ($p < 0.05$, d = 2.42; **Figure 5**).

The results from the multivariate analysis on FA and MD measures per hemisphere and tract by subgroups (second solution) are shown in **Table 3**. These data revealed main effects of age (p = 0.041, η_p^2 = 0.166), group (p = 0.005, η_p^2 = 0.235), and tract (p = 0.001, η_p^2 = 0.4), but no main effect of hemisphere (p = 0.99) or sex (p = 0.51). Specifically, the three main effects were present in MD measures (p = 0.022, η_p^2 = 0.138; p = 0.017, η_p^2 = 0.242; and p = 0.003, η_p^2 = 0.196, respectively; see bottom part of **Table 3**).

Also, there was a significant tract*hemisphere interaction (p = 0.018, η_p^2 = 0.081), indicating that the occurrence of differences in integrity between hemispheres depended on the tract analyzed. The right showed better integrity than

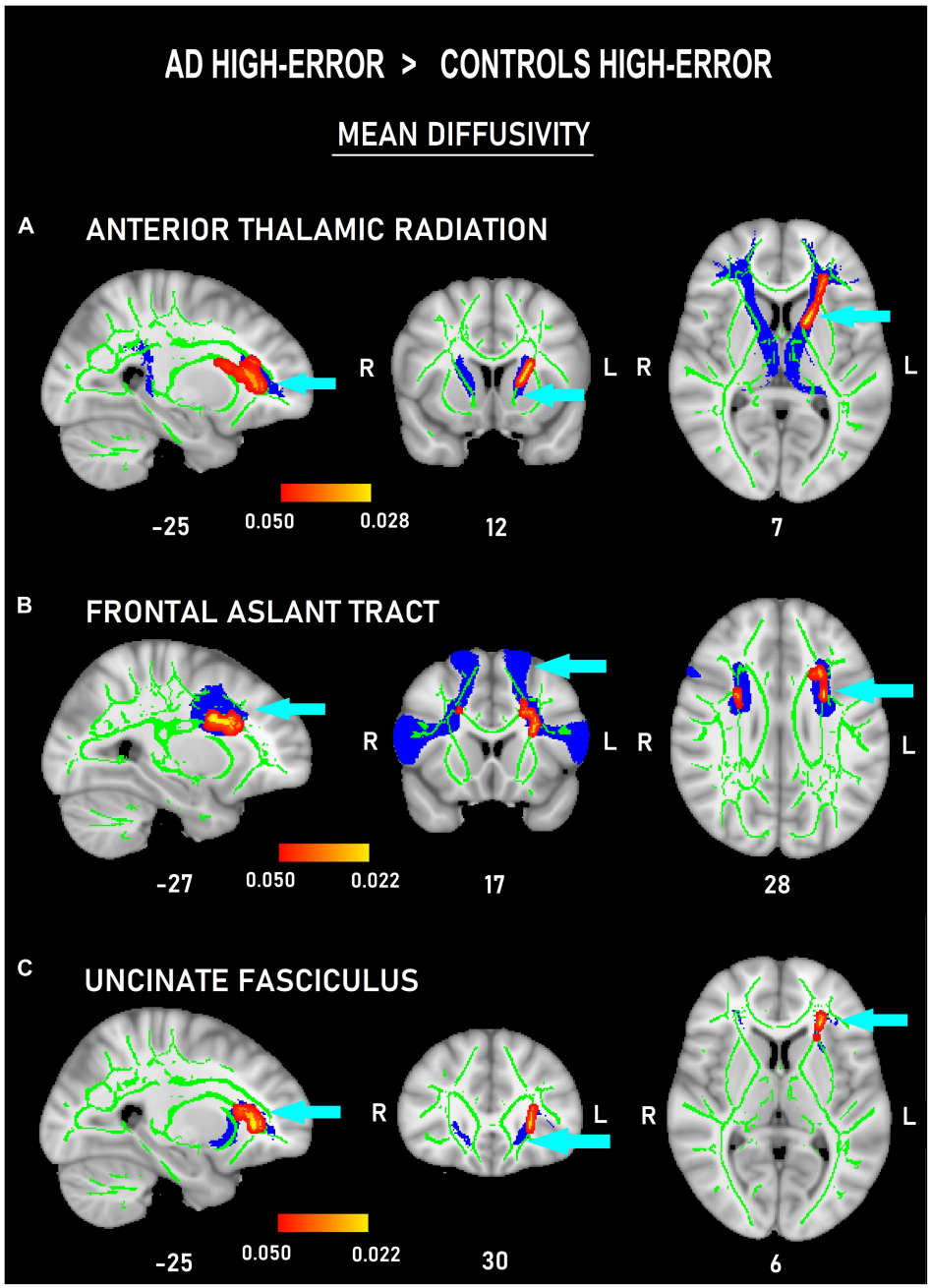

FIGURE 4 | Probability maps of tract-based spatial statistics showing clusters with increased mean diffusivity in patients with AD committing a high number of errors versus controls committing a high number of errors in three frontal white-matter tracts: anterior thalamic radiation **(A)**, frontal aslant tract **(B)**, and uncinate **(C)** fasciculus. Sagittal **(left)**, coronal **(middle)**, and axial **(right)** radiological views with corresponding MNI coordinates. Red-yellow shade bars indicate the significant *p* value ranges for every tract. The fractional anisotropy skeleton is shown in green. The area corresponding to each tract is shown in blue.

the left hemisphere, with specific differences in MD of the FAT (p = 0.013, η_p^2 = 0.137). There was also a significant hemisphere*sex interaction (p = 0.032, η_p^2 = 0.179), where differences between hemispheres were more pronounced in men. Also, this interaction specifically occurred in MD of the FAT (p = 0.014, η_p^2 = 0.157). *Post hoc* pair-wise comparisons showed that group differences only existed in MD of the FAT between $AD_{high\text{-}error}$ and both $Con_{low\text{-}error}$ (p = 0.041) and $AD_{low\text{-}error}$ (p = 0.04).

Otherwise, no effects for the interaction tract*group (p = 0.066), tract*age (p = 0.21), tract*sex (p = 0.231), group*hemisphere (p = 0.482), hemisphere*age (p = 0.637), tract*group*hemisphere (p = 0.895), and tract*hemisphere*age (p = 0.438) were found.

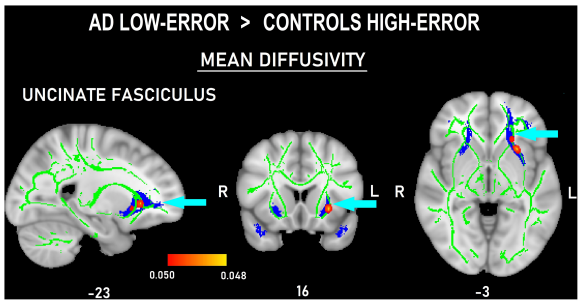

FIGURE 5 | Probability map of tract-based spatial statistics in the uncinate fasciculus showing clusters with increased mean diffusivity in patients with AD committing a low number of errors compared to controls committing a high number of errors. Sagittal **(left)**, coronal **(middle)**, and axial **(right)** radiological views with corresponding MNI coordinates. The red-yellow shade bar indicates the significant *p* value range. The fractional anisotropy skeleton is shown in green. The area corresponding to the uncinate fasciculus is shown in blue.

DISCUSSION

Behavioral Analyses

The results from the standard scores for animal VF agree with earlier reports (Crowe, 1998; Demetriou and Holtzer, 2017), in which younger participants outperform healthy older adults and patients with AD with regard to correct number of words and considerably fewer errors. In turn, the healthy older group committed more errors than the younger adults, especially perseverations, and generated less number of correct answers. However, as expected, the older adults outperformed the AD group who showed significant decline in word production and higher number of errors in both types. Of importance is that group comparisons for type of error showed that only number of intrusions was significantly different among the groups. As for the time-course analysis, it was observed that word production declined progressively along the 1-min trial across all the groups in a very similar way, but at lower rates for the older adults relative to the younger ones and even lower levels for the patients relative to the healthy elders.

Furthermore, the application of LDA showed that the pattern of the production of topics did not differ among the groups. However, there were specific topics that were more recurrently produced in the older groups, and some of them presented higher incidence of errors. In other words, mostly, frequent topics contained high occurrence of errors.

According to the literature, word production related to large semantic categories, such as "animals" poses difficulties for working memory load and causes higher perseveration rates (Azuma, 2004). Our data revealed that most perseverations (60%) happened within clusters, and a possible explanation for this finding is that generation of errors was triggered by strong lexical connections evoked by specific topics. This occurs in both the healthy subjects and patients with AD. Indeed, different studies have suggested that high frequent words are more prone to induce the appearance of perseverations (Miozzo et al., 2013), and that the animal category accounts among the most frequent categories for the evaluation of semantic VF (Ardila et al., 2006).

It is suggested that most perseverations are caused by limitations in working memory capacity and self-monitoring (Rosen and Engle, 1997). Hence, perseverative responses are more frequent in older adults (Ramage et al., 1999) and in populations suffering from memory and executive disorders such as patients with AD (Azuma, 2004). The present data mainly confirm all the above assertions. As for the intrusions, we found that even though some of the older adults committed few intrusions, the patient group generated primarily this type

TABLE 3 | Comparisons for the integrity of three frontal tracts between the subgroups of older controls and patients.

		$Con_{low\text{-}error}$ (n = 9)		$Con_{high\text{-}error}$ (n = 14)		$AD_{low\text{-}error}$ (n = 9)		$AD_{high\text{-}error}$ (n = 10)		MANCOVA	Interactions	GroupContrasts
		M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	Age / Group / Tract	Tract*Hemisphere / Hemisphere*Sex	1vs4 / 3vs4
Fractional Anisotropy												
Anterior Thalamic Radiation	R	0.3952	0.0209	0.4047	0.0199	0.3962	0.0211	0.3962	0.0205	ns / ns / ns	ns / ns	ns / ns
	L	0.3991	0.0176	0.4031	0.0164	0.3949	0.0252	0.3899	0.0237			
Frontal Aslant Tract	R	0.3623	0.0249	0.3756	0.0210	0.3616	0.0206	0.3678	0.0226			
	L	0.3780	0.0184	0.3831	0.0216	0.3685	0.0197	0.3790	0.0199			
Uncinate Tract	R	0.3769	0.0396	0.3884	0.0233	0.3733	0.0273	0.3829	0.0260			
	L	0.3857	0.0284	0.3935	0.0264	0.3758	0.0323	0.3853	0.0287			
Mean Diffusivity												
Anterior Thalamic Radiation	R	0.0009	0.0001	0.0009	0.0001	0.0009	0.0001	0.0008	0.0000	0.022 / 0.017 / 0.003	0.013 / 0.014	0.041 / 0.040
	L	0.0009	0.0001	0.0009	0.0001	0.0009	0.0001	0.0009	0.0001			
Frontal Aslant Tract	R	0.0008	0.0000	0.0008	0.0000	0.0009	0.0001	0.0008	0.0000			
	L	0.0008	0.0000	0.0008	0.0000	0.0008	0.0000	0.0008	0.0000			
Uncinate Tract	R	0.0009	0.0000	0.0009	0.0000	0.0009	0.0001	0.0008	0.0000			
	L	0.0008	0.0000	0.0008	0.0000	0.0008	0.0001	0.0008	0.0000			
								Main effects Multivariate Analysis		0.041 / 0.005 / 0.001	0.018 / 0.032	

$Con_{low\text{-}error}$ = control low-error subgroup; $Con_{high\text{-}error}$ = control high-error subgroup; $AD_{low\text{-}error}$ = AD low-error subgroup; $AD_{high\text{-}error}$ = AD high-error subgroup. For the multivariate analysis, only significant comparisons and interactions are presented, $p < 0.05$.

of error. Again, the LDA analysis showed that almost 60% of the intrusions were found within the clusters. This finding provides support to the idea that even if the deficits in semantic knowledge are present in mild AD, some semantic associations are still preserved (Paganelli et al., 2003). For this reason, production of wrong answers is detected by LDA analyses as conceptually related.

Regarding results from to the time-course analyses, we found a unique pattern of error generation in the patients with AD. While the younger and healthy older adults produced perseverations at a similar rate all along the trial, the pattern of error generation of the patients clearly demonstrated higher incidence of perseverations at the end of the trial with high incidence of intrusions at the beginning of the execution. Whereas it is reasonable that the number of perseverations increases along the trial because of accentuated attentional deficits in the patient group (Miozzo et al., 2013), the high generation of intrusions in the initial stage is more conspicuous. Increased intrusions in AD have been reported in a variety of tasks (Loewenstein et al., 1991; Doubleday et al., 2002). However, to the best of our knowledge, there is no report analyzing the time occurrence of this pathological feature during verbal recall. Earlier studies proposed that commission of intrusions in AD occur because of retrieval difficulties (Desgranges et al., 2002) and inability to suppress inappropriate answers (Shindler et al., 1984). In Shindler et al. (1984) proposed a four-stage process for the occurrence of intrusions. Our study further demonstrates that the chain of events described by Shindler et al. (1984) occurs in the initial stage of word generation in subjects with mild AD.

By assembling the findings from the time-course and LDA analyses, it appears that when the AD group intends to retrieve words, a defective strategic search is launched, which produces semantically related errors (i.e., intrusions) at the same time that it intertwines with the highest possible production of correct words. According to the literature, even if semantic knowledge is degraded in the early stages of AD, some degree of lexical information is still preserved (Barbarotto et al., 1998); therefore, correct answers and semantically related errors appear. It is noteworthy mentioning that only through LDA analyses we can recognize that a great proportion of intrusions are conceptually associated to an animal subcategory. Identification of intrusions based on human coding will not be able to make this link. Thus, the fine analysis of errors by phases demonstrated that the percentage of intrusions relative to total words generated in phase 1 was 9.5% (0.47 intrusions/5 responses on average). Although the proportion is numerically low, it is a real burst of incorrect answers due to a defective lexical search in a degraded semantic system. Remarkably, this event only takes place during the first 15 s. This phenomenon of correct word and intrusion generation relies not only on defective retrieval of semantic information but also on loss of insight in the selection of responses proper to the early stages of AD (Moreaud et al., 2001; Paganelli et al., 2003). From phase 2, other impaired mechanisms take place in the patients with AD, where a more mixed outcome consisting of correct answers, intrusions, and perseverations appears. At this point, the propensity of perseverations begins to increase and reaches its highest levels in phase 4 where 31.3% of their total answers become perseverations (0.53 perseverations/1.68 responses on average). Thus, in the middle of the trial, a shift in activation of impaired mechanisms occurs where perseverations take over.

Now, we wish to draw attention to the findings from group comparisons on the in-between perseveration intervals. In the past, some authors have proposed that semantic memory impairments in mild AD during VF are related to retrieval slowing deficit (Rohrer et al., 1999; Nutter-Upham et al., 2008). Nevertheless, those studies were based on the number of correct generated responses without considering the errors. Thus, our analyses of the in-between error intervals showed no group differences in the in-between lags to generate errors, and the number of responses in these time windows were practically equal across groups, which gives no support to a retrieval slowing in AD.

DTI Findings and Assessment of the Relationship Between Frontal Tracts and Error Occurrence

The anatomical results demonstrated, as expected, that the younger adults had better white matter integrity than the healthy older controls in all the three tracts. As for the anatomical differences between the healthy controls and patients, only MD values bilaterally in FAT and in left ATR and left UNC were significantly higher in the patients. These data are worth noting, since an earlier comparison of whole brain white matter of these two specific samples did not show significant differences (Rodríguez-Aranda et al., 2016). In that study, only one single DTI measure, namely, the mode of anisotropy (MO) differentiated the groups. However, in the present study, by focusing on particular white matter tracts, mostly from the left hemisphere, we were able to observe anatomical group differences.

In addition, contrasts on the subclassifications of patients and controls demonstrated that the patients had more degenerated tracts than the healthy older adults who committed a high number of errors. Predominantly, these differences were on the left side, even though a small portion of the right FAT also differentiated the subgroups. First, our data showed that the patients with AD with high incidence of errors presented higher MD values in all the tracts. In accordance, a recent investigation (Chen et al., 2020) suggests higher vulnerability of white matter microstructure in the left hemisphere in individuals developing AD. Our findings agree with the suggestion of Chen et al. that white matter deterioration in the left hemisphere is an indication of early signs of the disease.

Furthermore, our results are in line with findings pointing to the association between degeneration of frontal pathways and verbal deficits in different older populations (Papagno, 2011; Kljajevic et al., 2016; Di Tella et al., 2020). More specifically, the fact that left ATR and left UNC were more deteriorated in the subgroup of patients committing more errors agrees with studies showing that brain lesions and electrical stimulation of

these tracts are involved in error commission. For instance, Han et al. (2013) demonstrated an association of lesions in the left ATR and left UNC with semantic deficits, while Mandonnet et al. (2019) showed that electrical stimulation of the striato-thalamic-cortical system, including the left ATR, evoked verbal perseverations. In addition, inclusion of the FAT in our study is notable, as this is a relatively new connective tract that is thought to have a key role in language (Catani et al., 2012). In a recent review, Dick et al. (2019) has proposed that the left FAT is involved in speech initiation, stuttering, lexical selection, and verbal fluency, and that the right FAT is involved in inhibitory control such as the stop of behavior. Accordingly, our data show that only the FAT had significantly higher MD values bilaterally in the AD subgroup with high error rate, which suggests that this specific pathway might be relevant for various processes subserving error commission in semantic fluency.

Moreover, the difference in MD values between the subgroup of patients with low-error rate and controls with high-error rate deserves attention. This patient subgroup had more deteriorated white matter of left UNC than the mentioned control subgroup. We consider this finding as relevant, since the UNC turns to be the only tract in our study showing significantly more white matter degeneration in the whole AD group. For this reason, we will discuss the importance of this tract in the commission of errors. On one hand, the literature highlights the role of the left UNC as a central pathway for semantic control and for general cognitive processes of inhibition and action selection (Duffau et al., 2009; Papagno, 2011). On the other hand, even if there is scarce number of studies addressing its role in error commission, there are data demonstrating that this tract is involved in the commission of semantic errors (Duffau et al., 2009; Sollmann et al., 2020). The UNC forms part of what is called an indirect way to the ventral semantic stream (Duffau et al., 2014). This pathway consists of the UNC linking the temporal pole with the inferior frontal gyrus *via* the pars orbitalis. It occurs that when electrically stimulated, areas conforming to the ventral semantic stream, semantic paraphasias (i.e., semantic errors) are evoked (Duffau et al., 2005). Thus, because the left UNC is the sole tract in which all the patients with AD show significantly higher MD values than the controls, it can be argued that this is the only tract involved in error commission in the whole AD group.

There are two remaining issues for discussion. First, we only obtained significant differences when contrasting the patient subgroups against the controls with high-error rate. We believe that these results are related to the composition of the older control subsamples. The subgroup of controls with high error rate comprises the majority of the healthy older participants ($n = 14$) with a higher number of males ($n = 10$), while the low-error control subgroup (total $n = 9$) has almost an equal number of males ($n = 4$) and females ($n = 5$). One would expect that older controls in the low-error subgroup may show unimpaired white matter integrity in all the tracts; therefore, significant differences should appear. However, this was not the case. Even though we controlled for gender in group comparisons at the second level of DTI analyses, we encountered a significant interaction with sex. This interaction yielded more asymmetric differences in MD values of all the three tracts in males than in females. Interestingly, control males in the high-error subgroup presented lower MDs in left hemisphere. Likewise, males in both subgroups of patients with AD showed this trend. Whether this asymmetry represents a real gender dimorphism or it relates to the peculiarity of our sample is difficult to establish, and future studies may pursue this line of inquiry with a larger number of participants. However, a definite contributing factor for the lack of group differences with the low-error rate subgroup of controls is that this subsample represents a group of individuals with more age-related deterioration on frontal white matter than the high-error subgroup, in spite of adequate VF performance. Such finding is not uncommon in research on aging, as many older participants considered cognitively normal present unnoticed clinical features similar to those of persons with dementia (Irwin et al., 2018).

The second issue is that group differences were found uniquely in the MD data. Usually, there is a tendency in aging studies in which white matter degeneration is expressed in terms of lower FA values coupled with higher MD values (Pini et al., 2016). However, this relationship is not always present (e.g., Huang et al., 2012; Chen et al., 2020). According to previous findings (Acosta-Cabronero et al., 2012), some DTI metrics are more sensitive to the early stages of AD, such as MD and axial diffusivity (DA). In our study, we confirm this assertion. Because MD is an average of the three eigenvectors calculated in DTI, increased MD values in our study cannot be translated into precise neurobiological changes; rather, these results indicate clear pathognomic signs of the selected frontal tracts, especially among patients committing the largest number of semantic VF errors.

General Discussion

The present study was conducted to better understand the occurrence of semantic VF errors in normal aging and mild AD through a combined methodology. Although important research on the topic has long existed (see e.g., Fuld et al., 1982; Shindler et al., 1984; Hart et al., 1986), to our knowledge, no investigation has addressed the how and when of various types of errors in semantic VF, and has attempted to link this phenomenon to its neural correlates.

Four main findings arise from the present study. First, we found that error occurrence in semantic VF is triggered by semantic associations in all the participants disregarding their group affiliation. The issue of semantic relatedness of verbal error production has been acknowledged in studies where object naming or semantic priming is assessed (e.g., Vitkovitch and Rutter, 2000). Disclosing the nature of error occurrence in tasks of free recall such as VF is not obvious, since errors can be classified as unrelated words by a human coder. Hence by LDA, it was possible to appraise that an important proportion of errors are semantically associated with animal subcategories, at least at a lexical level even in patients. These findings point to the existence of relationships between the errors and subcategories that arise when thinking about animals and go beyond the strict inclusion of specimens of a given taxonomy. The results advocate, on one hand, for the importance of including errors in these types of analyses to accurately evaluate semantic dynamics in VF. On the

other hand, the data inform us that the patients with mild AD are still preserving some degree of semantic network, which agrees with previous studies (Paganelli et al., 2003).

A second important finding relates to differences in error generation between the patients with AD and the healthy groups. We corroborated that perseverations were the sort of error most usually committed across the groups (Vitkovitch and Rutter, 2000). In healthy individuals of both age groups, perseverations were of little incidence but on most occasions, these were the only type of error committed. It is postulated that perseverations occurred because of reduction in language processing efficiency (Levelt, 1989), especially when people are under pressure to respond (Moses et al., 2004). Perseveration of words is more recurrent among healthy older participants who experience weakened working memory capacities (Ramage et al., 1999) and it is even more persistent in elders with mild AD (Kave and Heinik, 2017). Tentative explanations for the occurrence of perseverative answers in AD relate to impairment in lexical selection due to central executive dysfunction (Miozzo et al., 2013), attentional deficits (Rosen and Engle, 1997), and amnestic syndrome (Davis et al., 2002). Our findings agree with the proposal of Miozzo et al. (2013). However, they further suggest that perseverations during VF in mild AD are only an exacerbated deficit similar to the one occurring in normal aging, which does not represent a distinctive feature of the disease.

The third and probably most important finding of the present study concerns the occurrence of intrusions as a unique pathological feature of the AD group. Mostly, intrusions arise because of impaired semantic representations and impaired semantic knowledge (Paganelli et al., 2003). However, the mechanisms underlying intrusions are not solely related to memory retrieval (Shindler et al., 1984). Such assertion is supported by our time-course analysis, which points to deployment of different intertwined cognitive impairments all along VF performance. The impairments initially manifest as high incidence of intrusions due to semantic network abnormalities as well as deficient selection and judgment to generate appropriate responses. We consider that this initial stage poses a considerable effort in patients with mild AD as they try to activate memory search and word retrieval in a degraded semantic system (Paganelli et al., 2003). Consequently, the occurrence of intrusions takes place only during the first 15 s of the trial. From the second phase of the trial, the cognitive impairments that arise gradually are related to working memory deficits. These deficits are observed as lack of self-monitoring and difficulties to suppress already generated words, which emerge under conditions of fatigue or decreased attention (Hotz and Helmestabrooks, 1995). For this reason, a greater number of perseverations are observed at the end of the execution. Thus, in accordance with earlier suggestions (Davis et al., 2002), our findings reveal that perseverations and intrusions are consequences of different impaired mechanisms arising in different periods of task execution.

The fourth important finding in our study is regarding the confirmation of the hypothesis that white matter degeneration in frontal tracts is associated to error occurrence in mild AD. As expected, the selected frontal tracts (FAT, ATR, and UNC) were found to be significantly more deteriorated in the subgroup of patients committing high-error rate, and, specifically, they were more affected in the left hemisphere. This allows us to conclude that the selected tracts are of importance for the appearance of semantic VF errors in the patient group. In addition, the white matter integrity of the UNC also turned out to be significantly degraded among the subgroup of patients presenting low error rate, which suggests that deleterious changes in the microstructural properties of this specific tract underlie the commission of all type of errors (Von Der Heide et al., 2013).

Admittedly, the anatomical group differences encountered between the patient group and older controls can equally constitute just a coincidental event. However, the differences arise primarily in the left hemisphere of all the tracts, and a considerable body of data has reported these left hemisphere tracts as neural bases of general language functions (e.g., Chernoff et al., 2019; Dick et al., 2019) and language error commission (e.g., Han et al., 2013; Mandonnet et al., 2019). For this reason, we consider our findings rather connotative. Furthermore, we also corroborated that the healthy controls committing high-error rate showed significantly better tract integrity than the patients, which suggests that the appearance of intrusions in the patient group is related to higher deterioration of the mentioned tracts. It is worth noting that the vast majority of the healthy older adults committed very few errors. Thus, although we classified the older controls into "high and low-error subgroups," these participants committed predominantly only few perseverations and nearly no intrusions. Taken together the above facts, we confirmed that the healthy older adults free of cognitive impairments who commit higher frequency of perseverations also showed deteriorations in specific frontal tracts (i.e., FAT) as compared to the younger individuals.

Limitations

Some limitations of the present study should be acknowledged. First, we operated with a rather limited number of subjects, which were further reduced in the second stage of the study. Thus, the issue of low statistical power is present, and caution is demanded for generalization of the data. Furthermore, we did not conduct an analysis based on subtypes of perseverations and intrusions. As mentioned in the introduction, taxonomies for each type of error have been suggested (e.g., Sandson and Albert, 1984; Loewenstein et al., 1991). In turn, the various types of perseverations and intrusions are thought to reflect different cognitive impairments (Fischer-Baum et al., 2016). Thus, it would be advantageous that future research considers various subcategories of errors in a larger group of subjects to improve the understanding of the present findings. Finally, it is important to stress that degeneration of other connective pathways, such as those underlying the ventral semantic stream network (Duffau et al., 2014), might be equally involved in error commission during semantic VF. Nevertheless, the latter is not in disagreement with the view that deleterious changes in the ATR, FAT, and UNC are implicated in the commission of errors in mild AD.

CONCLUSION

Our findings demonstrate that error production in mild AD during a 1-min trial of semantic verbal fluency follows a unique deployment of different error types that varies as a function of trial progression. This pattern of error occurrence clearly differentiates patients from healthy controls not only because of the way of deployment but also the presence of intrusions, which is a pathognomic trait proper to mild stages of AD (Loewenstein et al., 1991). Thus, our data document that intrusions and perseverations arise at different points in time, and that their emergence principally depends on executive functions and working memory impairments. Finally, our study strengthens the view that significant white matter deterioration of left frontal tracts exists in mild AD that corresponds to increased rate of semantic VF errors.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because of the restrictions imposed by the Regional Research Ethics Committee. Requests to access the datasets should be directed to CR-A, claudia.rodriguez-aranda@uit.no.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Regional Research Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CR-A and YI contributed to the conception and design of the study. CR-A collected data. KW and SJ recruited and assessed the patient group. CR-A and SC-C organized the MRI database. YI, CR-A, and SC-C performed the statistical analyses. YI, SC-C, and CR-A wrote the first draft of the manuscript. KW and SJ revised the intellectual content. All authors contributed to manuscript revision, and read and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2021.710938/full#supplementary-material

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Connected Speech Characteristics of Bengali Speakers With Alzheimer's Disease: Evidence for Language-Specific Diagnostic Markers

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Background and aim: Speech and language characteristics of connected speech provide a valuable tool for identifying, diagnosing and monitoring progression in Alzheimer's Disease (AD). Our knowledge of linguistic features of connected speech in AD is primarily derived from English speakers; very little is known regarding patterns of linguistic deficits in speakers of other languages, such as Bengali. Bengali is a highly inflected pro-drop language from the Indo-Aryan language family. It is the seventh most spoken language in the world, yet to date, no studies have investigated the profile of linguistic impairments in Bengali speakers with AD. The aim of this study was to characterize connected speech production and identify the linguistic features affected in Bengali speakers with AD.

Methods: Participants were six Bengali speaking AD patients and eight matched controls from the urban metropolis, Kolkata, India. Narrative samples were elicited in Bengali using the Frog Story. Samples were analyzed using the Quantitative Production Analysis and the Correct Information Unit analyses to quantify six different aspects of speech production: speech rate, structural and syntactic measures, lexical measures, morphological and inflectional measures, semantic measures and measure of spontaneity and fluency disruptions.

Results and conclusions: In line with the extant literature from English speakers, the Bengali AD participants demonstrated decreased speech rate, simplicity of sentence forms and structures, and reduced semantic content. Critically, differences with English speakers' literature emerged in the domains of Bengali specific linguistic features, such as the pro-drop nature of Bengali and its inflectional properties of nominal and verbal systems. Bengali AD participants produced fewer pronouns, which is in direct contrast with the overuse of pronouns by English AD participants. No obvious difficulty in producing nominal and verbal inflections was evident. However, differences in the type of noun inflections were evident; these were characterized by simpler inflectional features

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used by AD speakers. This study represents the first of its kind to characterize connected speech production in Bengali AD participants and is a significant step forward toward the development of language-specific clinical markers in AD. It also provides a framework for cross-linguistic comparisons across structurally distinct and under-explored languages.

Keywords: speech analysis, Bengali, pronoun, semantic, Alzheimer's disease, connected speech, syntax, micro-linguistics

INTRODUCTION

Language assessment has a crucial role in the clinical diagnosis of several forms of dementia (Taler and Philips, 2008; Macoir et al., 2015). In Alzheimer's Disease (AD) language has been shown to decline in the pre-symptomatic stages (Snowdon et al., 1996; Ahmed et al., 2013); it is the central feature of primary progressive aphasias (Gorno-Tempini et al., 2011; Grossman, 2012), and acts as a supplementary marker in young onset AD (Crutch et al., 2013). As such, clinical assessment of language has become routine in the diagnostic workup; which commonly use assessment of confrontation naming, verbal fluency; and analysis of spontaneous or connected speech. Connected speech samples elicited *via* picture descriptions, narratives, or interviews have been proven to be better ecological approximations of language production in everyday context. Connected speech goes beyond single-word productions and involves ongoing interactions among diverse cognitive processes including semantic storage and retrieval, executive functions, and memory processes (Ahmed et al., 2013; Mueller et al., 2018; Slegers et al., 2018). Importantly, connected speech samples provide detailed information about processing at several linguistic levels, such as phonetic, phonological, lexico-semantic, syntactic, and discourse-pragmatic; allowing deeper analysis of domains of interest (Boschi et al., 2017).

Recent literature reviews on the linguistic characteristics of connected speech in AD point to a pattern of deficit in several domains including speech rate, syntactic structure and complexity, lexical content, semantic content and efficiency, as well as spontaneity and fluency of speech (Boschi et al., 2017; Mueller et al., 2018; Slegers et al., 2018; Filiou et al., 2020). Specifically, the key features that distinguish AD from healthy control participants are: reduced speech rate and spontaneity including increased repetitions and revisions; simplified syntax and sentence structures including shorter and grammatically simpler sentences; word finding difficulties and increased use of pronouns; inflectional errors in nouns and verbs; and reduced semantic content of speech and uninformative speech with low idea density and efficiency.

With the advantages of quick administration, relatively low burden on the participant, ability to distinguish amongst dementia pathologies, and its use as a marker for disease progression, the evaluation and identification of connected speech characteristics has generated intense interest in dementia research (Gorno-Tempini et al., 2011; Ahmed et al., 2013; Boschi et al., 2017; Mueller et al., 2018; Slegers et al., 2018; Filiou et al., 2020). The progress in the field is encouraging, however, a significant drawback remains with regard to the diversity of languages studied, and how fragmentation of linguistic features differs across different languages (Beveridge and Bak, 2011). Our understanding of linguistic breakdown in dementia is, therefore, limited as the vast majority of studies have been conducted in English speaking participants, with only a few studies in French, Spanish, Brazilian Portuguese, Chinese, Japanese, Hebrew, Iranian, Finnish, Italian, and German (Boschi et al., 2017; Filiou et al., 2020). However, it is well-known from research in language impairments and neurological diseases that language impairments depend on how the system can break down, which in turn is determined by the structure of the language system (Paradis, 1988). For example, syntactic disorders apparent at the surface of a speaker's grammar are dependent on the underlying structure of the specific language. Languages, such as Italian, Spanish, and Bengali are pro-drop languages, that is, they allow speakers to "drop" the subject pronoun if the subject can be inferred from the context. To illustrate, if a Bengali speaker stated, "āmār mā bijñāni" ("My mother is a scientist"), his or her next sentence could be "iunivārsitite kāj karen" ("Works at the university") in which the pronoun "she" is excluded. Conversely, English, is a non-pro-drop language, that is, speakers must use the subject regardless of the availability of the referent in the context.

This feature becomes all the more important given that one salient marker of language breakdown in AD is the over production of pronouns, such as *he*, *she*, *they*, *it*, rather than use of the specific name or nouns (March et al., 2006; Ahmed et al., 2013; Jarrold et al., 2014; Fraser et al., 2016 for English; Kavé and Levy, 2003; Kavé and Goral, 2016, for Hebrew). However, it remains to be determined if in pro-drop languages individuals with AD would show a similar over production of pronouns or a different pattern might emerge, given that a pronoun is not essential for correct and grammatical production of sentences.

Another feature of note is inflection abilities in AD. Whilst many studies with English speaking AD individuals have shown difficulty with verb inflections in connected speech (e.g., Sajjadi et al., 2012; Ahmed et al., 2013); other studies in English and other languages have not shown difficulty in inflectional morphology for individuals with AD [e.g., Kavé and Levy, 2003; see Auclair-Ouellet (2015) for a review of inflectional morphology in dementia].

There is a critical need to determine language-specific features to accurately describe and understand the linguistic impairments of individuals with AD across different languages. These lines of research will inform assessment procedures, which in turn would lead to more accurate clinical diagnosis of

these language users. Compared to English and some European languages, there remains a distinct absence of research evidence documenting the markers associated with language decline in South Asian languages (e.g., Bengali, Urdu, Hindi, Punjabi, Nepalese, and Tamil). The expected growth in neurodegenerative diseases, such as AD will be in low and middle income South Asian and Western Pacific countries including China and India (Prince et al., 2015; Alzheimer's Disease International, 2021). English is not the primary language of use in these countries. Therefore, it is important to identify, characterize, and analyze the linguistic features of connected speech among individuals with dementia from non-English speaking populations. Evaluation of the linguistic profiles of individuals with AD who speak different languages is also key to improve our core theoretical understanding of linguistic impairments across different dementia pathologies. Furthermore, this knowledge has the potential to inform the development and provision of equitable clinical services for the assessment, diagnosis and management for these individuals. The current study fills a significant gap in the research literature and aims to identify and characterize linguistic features of connected speech in Bengali speakers with a clinical diagnosis of AD.

Bengali (also known as Bangla) belongs to the Aryan branch of the Indo-Iranian of the Indo-European group of languages. It is the national language of Bangladesh (first language of 142 million speakers, 98.8% of the total population, Bangladesh Census, 2011) and the official language of three states of India, West Bengal, Tripura, and Assam (first language of 97 million speakers, 8.3% of the total population, India Census, 2011). Bengali is also spoken by the significant global Bengali diaspora (Indian and Bangladeshi) in the United States, the United Kingdom, the Middle East and many Western countries. Bengali is currently ranked as the seventh most spoken language in the world; more than 265 million people speak Bengali as their first or second language in their everyday life. Despite the large number of Bengali speakers there are only handful of studies involving Bengali speakers with neurological impairments (e.g., Lahiri et al., 2019; Patra et al., 2020), and remains one of the under-represented and under-explored world languages in neurological research (Beveridge and Bak, 2011).

In the following section, we highlight the features of Bengali that are relevant for characterization of connected speech production in AD in the domains of syntax, lexicon, and morphology. **Table 1** provides a summary of these features and draws attention to the specific differences with English. This table is not intended to include an exhaustive account of all aspects of Bengali, but provides relevant information for characterizing connected speech in the context of AD.

To understand the linguistic characteristics of a language, it is useful to consider language typology. It has been shown that word order patterns, such as SOV (Subject Object Verb, in Bengali, Farsi, Hindi, Sanskrit, Latin, and Japanese) or patterns such as SVO (English, Dutch, Italian, Spanish, and Russian) may go hand-in-hand with other language features, such as the existence of pre- or postpositions, the placing of determiners before or after nouns, the presence or absence of pro-drop and of dative subjects, although the clustering of language features is highly complex (Thompson, 2010). Another classifying distinction between languages, which links in with the word order system, is the amount of grammatical inflection. Modern English is predominantly an analytic language, which means that it is made up mainly of free lexical units and there is little remaining inflection. Bengali is a highly inflected language with verbal conjugation according to person, tense, aspect, auxiliary marker, honorification, and particles; and number, particle, and case marking for nouns and pronouns (Dash, 2005, 2015). The inflectional nature of words determines the syntactic roles of the constituents of a sentence. The extent of inflection in a language is usually related to the flexibility of word order. Therefore, in Bengali the SOV order is not mandatory and word order is not rigid. In contrast, English follows a relatively rigid word order.

As mentioned earlier, Bengali is a pro-drop language, allowing omission of personal pronouns in the subject position. Pro-drop occurs in languages with unambiguous conjugational systems where person information is given in the verb inflection. The rules for pro-drop occurrence are context-based. Where the referent is clear from the context, subjects can be dropped. The following are examples of pro-drop sentences produced by participants of this current research:

Example 1:'tār nām chhila phreṭi' "His name was Freddy"
'khub bhālobāsto or dui peṭke' "Deeply loved his two pets": Subject dropped

Example 2: 'maumāchhi tāder tāṛā kare' "Bees attack them"
'gāchher guṛite uṭhe paṭe' "Climb up on a log": Subject dropped

This pro-drop property of Bengali has important consequences for the amount of pronouns that are produced by speakers in their connected speech.

In terms of lexical distribution, Bengali words belong to seven parts-of-speech: nouns, verbs, adjectives, adverbs, pronouns, postpositions and indeclinables. These grammatical classes can be also organized in terms of open class words (i.e., nouns, verb, adjective, and adverb) and closed class words (i.e., pronoun, postpositions, and indeclinable). Nouns, pronouns, adjectives, verbs and adverbs are inflected in Bengali, whilst indeclinables and postpositions are not.

Bengali nouns are inflected for number, definiteness, gender (rarely), case, and particles. The inflections are tagged in an ordered agglutinative manner to the right side of the nouns to generate the final form.

Stem	Definiteness	Final Form
din	-ta	dinta
day	-the	the day

Stem	Plural	Case	Particle	Final Form
din	-guli-	-ke-	-o	dingulikeo
day	-s	-to accusative	Emphatic	to days also

For the inflected noun "*dingulikeo*", there are three inflections. These three inflections have a fixed order *dingulikeo* (<din + -guli + -ke + -o) and using them in different orders (e.g., <din +-ke + -o+ guli, or <din -o+ +-ke + guli) will generate

TABLE 1 | Summary of relevant linguistic features (syntactic, lexical, and morphology) for Bengali and its contrast with English.

Syntactic features	**Bengali**	**English**
Canonical word order	SOV	SVO
Flexibility of word order	Fluid word order at least for canonical forms	Rigid word order for unambiguous sentence construction
Branching	Left branching	Right branching
Passive constructions	Rare to non-existent	Passive constructions are common
Lexical categories		
Open-class words		
Nouns	Present	Present
Verbs	Present	Present
Compound verbs	Frequent	Infrequent
Adjectives	Present	Present
Adverbs	Present	Present
Closed-class words		
Pronouns	Present, pro-drop, similar inflectional system to noun	Present, very limited inflections
Prepositions	Absent	Present
Postpositions	Present	Absent
Auxiliaries	Not present as a word class but represented in the inflectional properties of nouns, verbs, and pronouns	Present
Reduplication	Pervasive usage	Rarely
Morphological properties		
Nominal morphology	Highly inflected morphology	Limited inflectional morphology
Nouns can be inflected for:		
Number	Marked with suffix	Marked with suffix
Definiteness markers	Marked with suffix	Use of a determiner
Case	Marked with suffix	Not marked
Gender (rarely)	Marked with suffix	Not marked
Particles	Marked with suffix	Not marked
Verbal morphology	Highly inflected morphology	Limited inflectional morphology
Auxiliary verbs	Absent	Present
Verbs can be inflected for:		
Tense	Marked with suffix	Marked with suffix
Aspect	Marked with suffix	Marked with auxiliary
Person	Marked with suffix	Marked with suffix but limited
Number	Not marked	Marked with suffix, limited to third person singular
Honorification	Marked with suffix	Not marked
Particles (emphatic and negative)	Marked with suffix	Expressed analytically

erroneous forms. Pronouns use a similar set of inflections to nouns.

Bengali verb morphology is extensive and complex, verbs can be inflected for person, tense, aspect, honorification, and particles. In Bengali verbs, person, tense and aspect information are mandatory, whilst honorification and particles can also be added. However, verb inflections do not change with the number and gender of the subject. In contrast to English, Bengali does not have the word classes of auxiliaries, modals, and aspect markers as lexical entities but these are incorporated as inflections on the verbs. To illustrate, the English phrase *He/She/They has/have been writing* is expressed by a single conjugated form */likhechhe/* in Bengali. Similar to nouns, the inflections are added in a specific order with the verb root to generate the final conjugated form. These conjugated forms generate a complete sense of action as well as aspectual, temporal, and spatial information within the form. Due to the composite nature of inflected Bengali verbs, there is no possibility of dropping a part of an inflection as this will generate an invalid form.

Root	Auxiliary	Tense	Person	Final Form
dekh	-chh-	-il-	-ām-	dekhchhilām
see	-do	-past	- first person (singular/plural)	I was seeing

Root	Aspect	Auxiliary	Tense	Person	Final Form
dekh	-e-	-chh-	-il-	-ām-	dekhechhilām
see	-perfect	-do	-past	- first person (singular/plural)	I had done

Bengali has a high occurrence of compound verbs, which is also a prominent feature in many South Asian languages, such as Hindi (Koul, 2008). A compound verb is a two or multiword compound formed by combining a sequence of two or more verbs to act as a single verb to express a single sense or meaning (e.g., *dhare rākh* "catch", *uṭhe paṛ* "rise", *śuye paṛ* "lie down", *bale phel* "speak").

In contrast to English, Bengali has fewer word classes within the closed-class category (Bengali: pronouns, postpositions, indeclinables vs. English: prepositions, determiners, pronouns, conjunctions, modals, auxiliaries). Bengali postpositions are similar to prepositions in English. Postpositions occur immediately after a noun or a pronoun to denote spatial, temporal, situational, locational, directional, and conditional information with other words used in a sentence (e.g., *bābār kāchhe* "near father", *gharer madhye* "in house", *hāt diye* "by hand", *dupurer pare* "after noon", *rāstār dhāre* "beside road"). Akin to English word classes of conjunctions and disjunctions, Bengali has a lexical category collectively known as indeclinables 'abyay' which are, in principle, not capable of being inflected (e.g., *ār* "and", *ebaṃ* "and", *bā* "or", *kintu* "but", *athabā* "or").

A frequent feature of Bengali and in many Indian languages is reduplication. Reduplication is a process by which a word is duplicated—wholly or partially—to generate a new word that is different in form and adds new sense in meaning. Reduplication serves multiple semantic functions, such as sense of multiplicity, continuation of action, recurrence of an event or emotional state (e.g., *hāśi* "smile" → *hāśihāśi* "smiling"; *ghuṭ* "dark" → *ghuṭghuṭe* "pitch dark"; → *ghar* "house" *ghar ghar* "in every house"; *din* "day" → *din din* "day by day"). Reduplication can happen to words of all parts-of-speech, although it is more common for open class words.

As can be seen from the above mentioned linguistic features of Bengali, there are distinct differences from English, which can impact manifestation of linguistic impairments in AD. Despite recognition that linguistic impairments are important markers for AD, very little is known regarding patterns of linguistic deficits in speakers of languages other than English. The literature is non-existent with this regard in South Asian languages (e.g., Bengali, Hindi, Urdu, and Punjabi). This research fills a significant gap in the literature and aims to identify linguistic features of connected speech in Bengali speakers with a clinical diagnosis of AD. We used the Frog Story narrative task ("Frog, Where are You?," Mayer, 1969) to elicit connected speech samples from Bengali AD and matched healthy controls. The multidimensional nature of connected speech and the large number of different variables for analysis that are reported in the literature makes it challenging to decide the best variables to choose to characterize production. The most often used multidimensional analysis framework has been a variant of the Quantitative Production Analysis (QPA; Berndt et al., 2000). In addition, researchers have augmented the QPA with other measures, such as semantic content analysis to capture the semantic breakdown (e.g., Croisile et al., 1996; Ahmed et al., 2013). We implemented and adapted the QPA analysis framework for Bengali as well as used semantic content analysis using the Correct Information Unit analyses (CIU; Nicholas and Brookshire, 1993). As detailed linguistic analysis in Bengali has not yet been reported in connected speech data from neurological impairments, we saw value in covering an exhaustive range of variables in relevant domains to ensure broad range of linguistic features of Bengali are explored. To capture linguistic features specific to Bengali, we supplemented the QPA by adding additional variables (e.g., elaboration of the inflectional morphology for nouns and verbs, inclusion of lexical categories, such as postpositions).

The main objective of the present study was to identify the features of connected speech in the domains of—speech rate, syntactic and grammatical parameters, lexical content, morphological features, semantic content and disruption to fluency and spontaneity—that may be affected in Bengali speakers with AD.

MATERIALS AND METHODS

Ethics Statement

This study was carried out with ethical clearance from the School of Psychology and Clinical Language Sciences, University of Reading (Ref: 2017-035-AB). Participation was voluntary and written consent was obtained from all participants prior to commencement of the study. For participants with AD, consent and information forms were adapted to facilitate comprehension. All participants were able to self-consent to the study.

Participants

Participants were six right-handed Bengali speaking adults with a clinical diagnosis of AD and eight age-, gender-, education-, and language-matched healthy control participants (HC). Participants were recruited from the Neuropsychology and Clinical Psychology Unit, Duttanagar Mental Health Centre, Kolkata, India. Control participants were recruited from a volunteer participant pool. Exclusion criteria for both groups included a known history of alcohol or drug abuse, or a history of other neurological or psychiatric illness, or <10 years of education.

Background assessments. For each participant detailed demographic information was obtained. The level of general cognitive functioning was measured using the adapted Kolkata Cognitive Screening Battery, an adapted Bengali version of Mini-Mental State Examination (BMSE; Das et al., 2006), the Bengali adapted version of Addenbrooke's Cognitive Examination (ACE)-III (Hsieh et al., 2013) and the Clinical Dementia Rating Scale (CDR; Morris, 1993). The CDR is a measure of dementia severity based on the individual's cognitive and daily functions across six domains, which included memory, orientation, judgement and problem solving, community affairs, home and hobbies, and personal care. In addition, the Instrumental Activities of Daily Living Scale for Elderly (IADL-EDR; Mathuranath et al., 2005) assessed patient's ability to undertake day-to-day activities which include cognitive activities (e.g., managing finances, taking medication), social and recreational activities (e.g., looking after grandchildren, pursuing hobbies), community activities (e.g., shopping, travel), household activities (e.g., meal preparation, laundry) and self-care activities

(e.g., shaving, personal care). There were 11 items in this scale which were rated for their relevance, levels of impairment, and whether difficulties were caused by cognitive or physical problems. Subsequently, a composite score is derived which indicates the overall physical and cognitive disability. All HC were free of cognitive symptoms or neurological illnesses, and performed within the normal range in KCSB, ACE-III, CDR, and IALD-EDR.

Participants with AD (AD01, AD03, AD04, AD06, AD07, and AD09) were diagnosed by experienced behavioral neurologist and neuropsychologists (fifth and sixth author; AD, RN) using the NINCDS/ADRAA criteria (Mckhann et al., 1984; McKhann et al., 2011). **Table 2** provides both AD and HC participants' demographic details and the results of the neuropsychological tests. All participants were Bengali-English sequential bilinguals. They were all native speakers of Bengali and were living in a predominantly Bengali speaking context, using Bengali at home and at work. They were professionally engaged prior to the onset of AD: AD01 was a retired clerk in insurance company; AD03 was a retired electrical supervisor; AD04 managed a farming business; AD06 was a retired tax consultant; AD07 was a homemaker; AD09 was a retired high school teacher. With the exception of AD07 with moderate dementia (i.e., CDR global score of 2), all other AD participants had mild dementia (i.e., CDR global score of 1). At the time of the study, all participants were living with their families in the urban metropolis of Kolkata in eastern India.

Experimental Task

A narrative sample in Bengali was elicited using the story book: "Frog, Where Are you?" (Mayer, 1969). Most literature in English speakers with dementias have been elicited using the Cinderella Story retelling narrative task (Kavé et al., 2007; Fraser et al., 2014); whilst the Frog Story has been used by few researchers (e.g., Ash et al., 2007; Ash and Grossman, 2015). For Bengali speakers living in Kolkata, India, it was unlikely that they would know all details of the Cinderella story even if they knew the broad idea of the story. The story of Cinderella is not ingrained in their cultural repertoire as in English speaking or Western countries. We used the Frog Story because we wanted to use a task that would capture relevant and appropriate concepts, and be also culturally acceptable. The stimulus has been successfully used with different types of dementias (Ash et al., 2007).

Prior to administering the narrative task, participants were given a brief background about the story and were told that the main characters of the story are a boy, his dog, and a frog. The story is about a boy who is searching for his missing frog along with his dog. Participants were instructed to look through the picture book and then asked to narrate a story based on the picture book using sentences. Participants could keep the book with them while narrating the story. Tester interruptions were kept to a minimum, other than occasional prompts and generic encouragement. No feedback was provided during the elicitation. Instructions for testing and feedback where written down for the tester to ensure consistency in instruction across participants. The narrative productions were recorded using the digital audio recorder Olympus voice recorder WS-833 for subsequent verbatim orthographic transcription. Excerpts of transcripts from two AD participants (AD03 and AD09) and two HC participants are provided in the **Table 3**.

Quantitative Analysis of Narrative Speech

Using the QPA and the CIU analyses we calculated a set of measures for each narrative sample. CIUs are a widely used metric in narrative analysis that assesses the informativeness and efficiency of information conveyed through connected speech (e.g., Carlomagno et al., 2005). The multidimensional nature of connected speech analysis and the large number of different variables used by researchers makes the choosing of appropriate variables to report a challenging task. The measures for this research were in keeping with the recommendations from recent reviews for domains that are essential for characterizing AD speech (Slegers et al., 2018; Filiou et al., 2020). They aimed at quantifying six different aspects of speech production: 1. speech rate; 2. structural and syntactic measures; 3. lexical measures; 4. morphological and inflectional measures; 5. semantic measures (CIU analysis); and 6. measure of spontaneity and fluency disruptions (Wilson et al., 2010; Ahmed et al., 2013; Fraser et al., 2016; Boschi et al., 2017; Slegers et al., 2018; Filiou et al., 2020).

To derive these measures, the narrative samples were transcribed verbatim, segmented and analyzed in accordance with the procedures identical to those used in the QPA (Berndt et al., 2000). As in the original QPA, utterances were defined as segments of running speech that were syntactically and/or prosodically coherent. Placement of sentence boundaries was guided by semantic, syntactic and prosodic features. An utterance did not have to constitute a fully grammatical sentence. Using the QPA rules of extracting the narrative core, words that did not contribute to the narrative were removed, that is, repetitions, repairs, examiner's prompts, discourse markers, non-words (Rochon et al., 2000 for specific steps in extracting the narrative words; please see Berndt et al., 2000). Both the first and second author performed the narrative core extraction individually for all the 14 speech samples. Consensus for any disagreements in narrative core extraction and utterance segmentation were achieved through review of the QPA rules, and re-listening of the audio samples.

The total narrative duration and total number of words produced by each participant were recorded. The minimum length of speech sample for obtaining meaningful results from a narrative production has been widely debated (e.g., Berndt et al., 2000; Sajjadi et al., 2012). The QPA analysis protocol recommends a corpus of 150 words for obtaining meaningful results (Saffran et al., 1989; Berndt et al., 2000). Previous research with different sample lengths have shown that a 150 narrative word corpus produced an adequate and reliable analysis (Sajjadi et al., 2012). To ensure that sample length would not influence the results, we performed our planned analyses using the full sample and ∼150-word sample for two AD and two HC participants. The proportional variables on QPA and CIU analyses showed similar, if not identical values for the two sample lengths. Therefore, following recommendation from the literature and to keep the sample length consistent across participants, we derived the measures after extracting 150 ± 10 narrative words.

TABLE 2 | Demographic characteristics and neuropsychological data on the various background measures for each individual with Alzheimer's Disease (AD) as well as Mean and SD of AD and Healthy Controls (HC) groups.

	Individual cases						Group means						Results of statistical tests		
	AD01	AD03	AD04	AD06	AD07	AD09	Alzheimer's Disease (AD)		Healthy Control (HC)						
							Mean	SD	Mean	SD	Min	Max	*z*-value	*p*-value	Effect size
Demographic information															
Age at the time of study (years)	67	76	78	51	71	56	66.5	10.89	71.7	4.2	67	78	−0.650	0.516	−0.17
Education (years)	15	14	10	15	17	17	14.7	2.58	16.1	1.2	15	18	−1.088	0.277	−0.29
Duration of symptoms (months)	36	36	24	12	30	48	31.0	12.25							
Age at the onset of symptoms (years)	64	73	76	50	68.5	52	63.9	10.82							
Sex	F	M	M	M	F	F									
Handedness	R	R	R	R	R	R									
General cognitive functioning															
Bengali Mini-Mental State Examination[a] (/30)	22	20	20	22	14	16	19.0	3.29	30.0	0	30	30	−3.441	**0.001**	−0.92
ACE-III, Bengali adapted (/100)[b]	49	40	45	73	27	31	44.2	16.38	92.7	2.3	89	96	−3.102	**0.002**	−0.83
Attention (/18)	11	10	11	13	7	8	10.0	2.19	17.7	0.7	16	18	−3.229	**0.001**	−0.86
Memory (/26)	10	9	12	16	3	4	9.0	4.90	25.3	0.7	24	26	−3.147	**0.002**	−0.84
Fluency (/14)	4	1	0	9	1	1	2.7	3.39	8.0	1.0	7	10	−2.292	**0.022**	−0.61
Language (/26)	16	12	15	24	9	15	15.2	5.04	25.9	0.3	25	26	−3.313	**0.001**	−0.89
Visuoconstructional (/16)	9	8	7	11	7	3	7.5	2.66	15.8	0.4	15	16	−3.233	**0.001**	−0.86
Clinical Dementia Rating (CDR)[c]	1	1	1	1	2	1	1.2	0.41	0.0	0	0	0	−3.528	**0.000**	−0.94
Instrumental Activities of Daily Living Scale in Elderly (IADL-EDR)[d] (% impairment)	20	50	CNT[e]	11	81	36	39.6	27.56	0.0	0	0	0	−3.338	**0.001**	−0.93

[a] *Das et al. (2006).*
[b] *Hsieh et al. (2013).*
[c] *Morris (1993) (CDR score of 0 = no dementia, 0.5 = questionable dementia, 1.0 = mild dementia, 2.0 = moderate dementia, 3 = severe dementia).*
[d] *Mathuranath et al. (2005) (a score >16 is in the impaired range with higher value representing higher level of impairment).*
[e] *Could not be tested.*
Bold font in p-values indicate significant difference between HC and AD groups.

TABLE 3 | Illustrative samples of the Frog Story narration by two individuals with Alzheimer's Disease (AD) and one Healthy Controls (HC).

Bengali orthographic transcription	Transliteration with Indic Roman	English translation	Comment
AD03 was a 76 year old man who retired several years ago as an electrical supervisor. He had an undergraduate degree with further technical qualifications. He presented to the clinic in Kolkata with a 3 years history of symptoms. He and his family described forgetfulness about meals consumed and the content of recent conversations, difficulty recognizing his own home, and aggression toward family members when in disagreement.			
একটা ছেলে	ekṭā chhele	A boy	Utterance, verb missing
এটা একটা কুকুর … কুকুর ও বা সামথিং এলস্ … বেড়াল	etā ekṭā kukur… kukur o bā something else… beṛāl	This is a dog dog or something else a cat	Repetition and revision
এটা ফ্রগ … হ্যাঁ ব্যাঙ	eṭā frog… hyā byāṇ	This frog	Utterance, verb missing, revision
কুকুর ছেলে ডগ … এই তিন জন	kukur chhele dog … ei tin jan	dog boy dog… these three people	Utterance, verb and predicate missing
আরেকটা ঘর	ārekṭā ghar	Another room	Utterance, verb missing
ঘরে কিছু জিনিস এখানে পড়ে আছে	ghare kichhu jinis ekhāne paṭe āchhe	Somethings are scattered here in the room	Correct sentence but unspecific subject
এখানে একটা শেড আছে	ekhāne ektā śeḍ ācche	There is a shade here	Correct short sentence, use of "āchhe" (i.e., is or has) is of similar pattern to previous construction
এই একটা জানলা আছে বন্ধ আছে	ei ekṭā jānlā ācche bandha āchhe	That is a window… closed	Correct sentence, use of "āchhe" (i.e., is or has) is of similar pattern to previous construction
দুটো একটা তিনটে চারটে জানলা আছে	duṭo ektā tiṇṭe chārṭe jānlā āchhe	Two one three four windows are there	Wrong order of cardinal adjectives, use of "āchhe" (i.e., is or has) is of similar pattern to previous construction
খোলা যায়	kholā ẏāy	Can be opened	Object missing
ছেলেটা বসে আর কুকুরটা এখানে দাঁড়িয়ে দেখছে	chheleṭā base ār kukurṭā ekhāne dāṭiye dekhchhe	The boy sitting and the dog is seeing standing here	Compound construction but verb missing with the subject in the first noun phrase.
ছেলেটাও দেখছে	chheleṭāo dekhchhe	The boy is also seeing	Short sentence
AD09 was a 56 year old woman who took voluntary retirement from her job as a English teacher for high school children following difficulties in coping with the cognitive demands of her job. She had a 4 year history of symptoms including forgetfulness about recent conversations, remembering to convey messages or what she had for meals, as well as remembering what she read. She also experienced word-finding difficulties, and showed increased dependence on her husband for decision making, along with increased topographical difficulties.			
ঘরে জানলা	ghare jānlā	Windows in the room	Utterance, verb missing
বাইরে উমম চাঁদ দেখা যাচ্ছে	bāire umm chād dekhā ẏāchchhe	Moon is visible outside	Short sentence
নিচে এখানে একটা কুকুর অঅঅ বসে আছে	niche ekhāne ekṭā kukur aaa base āchhe	A dog is sitting below	Short sentence
তার নিচে এখানে একটা ব্যাঙের মতো …. ব্যাঙ বসে আছে	tār niche ekhāne ekṭā byāṛer mato… byāṭ base āchhe	Under this, a frog like frog is sitting there	Revision
পেছনে খাটটা রয়েছে	pechhane khāṭṭā rayechhe	The cot is at the back	Short sentence
ওখানে বালিশ রা… রাখা রয়েছে … হুমম আর ইয়ে বালিশ রাখা রয়েছে	okhāne bāliś rā… rākhā rayechhe… humm ār iye bāliś rākhā rayechhe	There pillow, kept.. a pillow is there	Repetitions and revisions, short sentence, use of the same verb token "rayechhe" (is there)
আলো জ্বলছে ওপরে	ālo jvalchhe opare	Light is burning at the top	Short sentence

(Continued)

TABLE 3 | Continued

Bengali orthographic transcription	Transliteration with Indic Roman	English translation	Comment
এখান থেকে একটা	ekhān theke ekṭā	something from there	Vague utterance, subject and predicate missing
আর তারপর এখানে বালিশ রয়েছে	ār tārpar ekhāne bāliś rayechhe	And then after …a pillow is there	Short sentence, use of the same verb token "rayechhe" (is there)
বালিশের নিচে সোফা আর এটা রয়েছে … মমম … এখানে সোফার এটা মমম	bāliśer niche sophā ār eṭā rayechhe… mmm...ekhāne sophār eṭā mmm	Sofa is under the pillow…is there…here sofa's	Utterance, revisions
নিচে বাচ্চাটা রয়েছে	niche bāchchāṭā rayechhe	The boy is under there	Short sentence, use of the same verb token "rayechhe" (is there)
আর ওই ওর সঙ্গে ব্যাঙটাও নিচে রয়েছে	ār oi or saṭge byāṭāo niche rayechhe	and that..The frog is also with him under there	Use of the same verb token "rayechhe" (is there)
HC09, 68 year old woman who was a homemaker with 15 years of education (BA degree)			
এই গল্পটা হচ্ছে একটা বাচ্ছা ও তার পালিত দুই পশুর।	ei galpaṭā hachchhe ekṭā bāchchā o tār pālita dui paśur	This is the story of a boy and his two pet animals.	Coordinated noun phrases, compound sentence.
বাচ্চাটার দুই পালিত - একটা কুকুর আর একটা ব্যাঙ।	bāchchāṭār dui pālita ekṭā kukur ār ekṭā byāṭ	The boy has two pets, a dog and a frog.	Coordinated noun phrases.
বাচ্ছাটা এদেরকে নিজের বন্ধু মনে করত।	bāchchātā ederke nijer bandhu mane karta	The boy used to think them as his friends.	
এদের সাথে খেলত আর নিজের রুমএ রাখত।	eder sāthe khelta ār nijer rume rākhta	He used to play with them and keep them in his room.	Pro-drop compound sentence
ব্যাঙটাকে বাচ্চাটা একটা জারএর মধ্যে শুতে দিত।	byāṭāke bāchchāṭā ekṭā jārer madhye śute dita	The boy used to keep the frog inside a jar.	
একদিন রাতের বেলায় ব্যাঙটা সেই জার থেকে বেরিয়ে চলে যায় বাইরে।	ekdin rāter belāy byāṭā sei jār theke beriye chale ýāy bāire	One night the frog goes out after coming out of the jar.	Flexible word order, postposition at the terminal position. Embedded sentence
বাচ্চাটা তখন ঘুমচ্ছিল	bāchchāṭā takhan ghumachchhila	The boy was sleeping then.	
সে কিছু টের পায়নি	se kichhu ṛer pāyni	He did not know anything (about it).	
তার কুকুরটাও ঘুমলচ্ছিল।	tār kukurṭāo ghumachchhila	His dog was also sleeping.	
সকালবেলা বাচ্চাটা উঠে দেখে যে ব্যাঙটা তার জারএর মধ্যে নেই।	sakālbelā bāchchāṭā uṭhe dekhe ýe byāẹā tār jārer madhye nei	In the morning the boy finds that the frog is not inside the jar.	Embedded sentence
সে চারিদিকে ব্যাঙটাকে খুঁজতে শুরু করে দেয়।	se chāridike byātāke khūjte śuru kare dey	He starts searching for the frog all around him.	Embedded sentence

The excerpts are the first 12 sentences or utterances from their transcripts.

Using the QPA analysis framework, the narrative samples were analyzed for various measures: structural and syntactic, lexical, and morphological measures (Berndt et al., 2000). Specific linguistic features of Bengali (e.g., postpositions, number of reduplications, number of verbal compounds, verbal, and nominal morphology) were captured by including additional variables to the analysis scheme (see **Table 4**). We followed the QPA rules for deriving each of these variables; any exception made to the QPA rules to accommodate the characteristics of Bengali is indicated. Semantic content was analyzed using the CIU analyses. The complete list of different variables derived from the analyses is presented in **Table 4**. The following section provides a brief description of the domains used for characterizing the speech samples between the two groups.

Speech rate (words per minute). Speech rate was defined as the number of words per minute. That is, the total number of words produced in the narrative divided by the total duration of the narrative.

Structural and syntactic measures. This domain measured length, complexity and grammaticality of sentences to capture the structural and syntactic aspects of speech production. Four measures were drawn from various raw structural and syntactic measures (i.e., proportion of words in sentences, mean sentence length, proportion of well-formed sentences, embedding index).

Lexical measures. This domain captured subjects' production of various types of lexical items across the entire extracted narrative words, independent of utterance type. These measures included: number of narrative words (NW), number of open class, closed class words, number of nouns (N), verbs (V), compound verbs (CV), non-finite verbs (NF), matrix verbs (MV), adjectives, adverbs, personal pronouns (P), postpositions (PP), and reduplications. A wide range of proportional measures were generated on the basis of these counts of lexical items; full range reported in the **Table 4**. For this study, we limit reporting and analyzing to a set of variables indicated by check mark () in **Table 4**. The choice for these variables were motivated by findings in the literature that have been shown to demonstrate dependable differences in connected speech between AD and healthy controls (Slegers et al., 2018; Filiou et al., 2020).

Morphological and inflectional measures. To capture the richness and intricacies of the noun and verb inflectional system in Bengali, we generated measures described below. For nominal inflections, we determined the total number of nouns, number of nouns in their base form (i.e., uninflected forms), number of nouns that are possible to be inflected, and number of nouns with appropriate inflections. Additionally, we counted the number of inflections on each noun (i.e., one, two, >two) and the type of those inflections (i.e., definiteness markers vs. case markers, including accusative, genitive, locative). From these count measures, we derived six variables for noun inflections as indicated in **Table 4**. For verbs, we determined the total number of verbs, number of inflectable verbs, number of inflected verbs with appropriate inflections, and inflection score. From these count measures, verb inflection index and inflection complexity score were calculated to capture inflectional properties of the verbs.

Semantic measures (CIU analysis). Semantic content of the narrative samples was quantified separately using the CIU measures. Words and CIUs were identified from each narrative sample following the procedures outlined by Nicholas and Brookshire (1993). For CIU analysis we used the length of the sample that were used for QPA analysis, rather than the whole sample. Three measures were derived from the CIU analysis: number of CIUs, idea density and idea efficiency.

Measures of spontaneity and fluency disruptions. Given that difficulties with fluency and spontaneity have been identified as a salient measure to capture characteristics of AD speech output (Croisile et al., 1996; Ehrlich et al., 1997; De Lira et al., 2011; Slegers et al., 2018), we included a measure called total count of disruption to spontaneity and fluency. This measure included the total number of repetitions, revisions, and reformulations in the narrative sample.

Statistical Analysis

We approached the analysis in two ways: group and case-series analyses. This is a new set of data in a language that has not been investigated before, thus it is important to capture both group level as well as individual level performance. For the group comparisons, non-parametric versions of independent samples t-test (Mann-Whitney *U*-test) were used for the selected variables. Given the explorative nature of this study and that finding might be informative for under-researched clinical population and potential for future larger scale studies in this area (Perneger, 1998; Feise, 2002), we report findings with exact p-values (both at $p \leq 0.01$ and $p \leq 0.05$) and effect sizes for readers to appreciate the strength of these effects. It has been suggested that over-correction of alpha level risks the chance of increasing type II errors (i.e., rejecting significant findings) especially for under-represented clinical populations and hard to recruit populations (Feise, 2002; Streiner, 2009; Streiner and Norman, 2011). Perneger (1998) maintains that over correction leads to a situation where "The likelihood of type II errors is increased, so that truly important differences are deemed non-significant" (p. 1237).

For this research to achieve a balance between Type I and Type II errors (Perneger, 1998; Feise, 2002), and to be erring on caution, we corrected the *p*-value by four ($p \leq 0.05/4 = 0.012$) for family wise multiple comparisons. The determination of what makes a family for multiple comparison is difficult and ambiguous (Perneger, 1998), especially in a multidimensional phenomenon such as connected speech. The denominator of four is based on the aspects captured by each linguistic domain of the connected speech (i.e., speech rate and spontaneity; structural, syntactic and morphosyntactic measures; lexical measures; and semantic content). Based on the linguistic theories independence across various linguistic domains can be robustly debated, for example, modularity between semantics-syntax, or between semantic-conceptual (Jackendoff, 1972; Caramazza and Zurif, 1976; Moscovitch and Umilta, 1990). Given the inter-correlation of variables amongst linguistic domains, we use four broad domains as family to strike balance between caution and overly conservative interrogation of data.

TABLE 4 | Summary of the variables that were derived from the narrative production across the six domains of speech production.

	Linguistic feature	Definition/how to measure
	Speech Rate	
	Duration of the narrative (m, sec) sec	The amount of time in the sample containing both speech and pauses. Excluded from the duration were all periods during which the examiner is speaking (Berndt et al., 2000; Rochon et al., 2000)
✓	Total number of words	Total number of words produced by the participants. Indistinct strings of phonemes and discourse markers such as emm, aahh, uuh were excluded from the word count (Rochon et al., 2000; Sajjadi et al., 2012).
✓	Words per minute	Speech rate was defined as the number of words per minute. This measure was calculated on the entire speech sample rather than the 150-word narrative sample that is used to calculate all other measures. We calculated the time from the end of the tester's instructions to the end of participants' production. Number of words was calculated by tallying the total number of uttered words including repetitions, corrections, restarts, and paraphasias as well as patients' direct responses to the questions. Indistinct strings of phonemes and discourse markers such as emm, aahh, uuh were excluded from the word count (Rochon et al., 2000; Sajjadi et al., 2012). Timing and words of the examiner's speech were excluded from the speech rate measure.
	Structural and syntactic measures	
✓	Proportion of words in sentences	Total number of words in utterances that were sentences divided total number of sentences.
✓	Mean sentence length	The average number of words produced per sentence.
✓	Proportion well-formed sentence	Total number of well-formed sentences divided by the total number of sentences. As Bengali allows greater flexibility in word order, we recorded the type of errors produced in ill-formed sentences.
✓	Embedding Index	Total number of embeddings divided by the total number of sentences. This measure provides a quantification for utterance complexity. Fewer embeddings would imply less complex utterances.
	Lexical measures	
	Number of narrative words (NW)	The number of narrative words were obtained from the transcribed sample after removing habitual starters, stereotype story phrases, examiner's prompts, discourse markers, nonwords, coordinating conjunctions, participants' direct responses to specific questions, comments made by the participant, repetition, and repairs (Berndt et al., 2000). The first 150±10 narrative words were used for the QPA analysis.
	Number of open class words	Sum of all open class words, that is, nouns, verbs, adjectives, and adverbs.
	Number of closed class words	Sum of all closed class words, that is, pronouns, postpositions, and indeclinables.
	Proportion of open class words	Total number of open class words divided by total number of narrative words.
	Proportion of closed class words	Total number of closed class words divided by total number of narrative words.
✓	Proportion of noun (N/NW)	Total number of nouns divided by total number of narrative words.
	Proportion of noun (N/N+V)	Total number of nouns as a proportion of total number of nouns and verbs.
	Noun – verb ratio	Total number of nouns divided by total number of verbs.
	Proportion of noun (N/N+P)	Total number of nouns as a proportion of total number of nouns and pronouns.
✓	Proportion of pronoun (P/NW)	Total number of personal pronouns divided by total number of narrative words.
✓	Proportion of pronoun to noun (P/P+N)	Total number of personal pronouns as a proportion of total number of pronouns and nouns.
✓	Proportion of verb (V/NW)	Total number of verbs divided by total number of narrative words.
	Proportion of verb (V/V+N)	Total number of verbs as proportion of total number of verbs and nouns.
✓	Proportion of non-finite verb (NF/all V)	Total number of non-finite verbs divided by total number of all verbs.
✓	Proportion of matrix verb (MV/all V)	Total number of matrix verbs divided by total number of all verbs.
✓	Proportion of compound verb (CV/all V)	Total number of compound verbs divided by total number of all verbs. This is a Bengali specific characteristic.
	Proportion of adjective (Adj/NW)	Total number of adjectives divided by total number of narrative words.
	Proportion of adverb (Adv/NW)	Total number of adverbs divided by total number of narrative words.
✓	Proportion of postposition (PP/NW)	Total number of postpositions divided by total number of narrative words.
✓	Number of reduplication	Total number of reduplications in the narrative sample. Since the sample size is similar across participants (i.e., ∼150 words), the count measure is reported.
	Morphological and inflectional measures	
	Nominal inflections	
✓	Noun inflection index	Total number of appropriately inflected nouns to the number of nouns that are possible to be inflected. This could be conceptually thought of noun determiner index in English.
✓	Proportion of inflected noun	Total number of inflected nouns to the total number of nouns produced in the narrative.
✓	Proportion of noun with one inflection	Total number of inflected nouns with one inflection to the total number of all inflected nouns.
✓	Proportion of noun with two or more inflections	Total number of inflected nouns with two or more inflections to the total number of all inflected nouns.

(Continued)

TABLE 4 | Continued

	Linguistic feature	Definition/how to measure
✓	Rate of definiteness marker (DM/all N*100)	Total number of nouns inflected with definiteness or number marking to the total number of nouns.
✓	Rate of case markers (CM/all N*100)	Total number of nouns inflected with case marking to the total number of nouns.
✓	Proportion of definiteness marker (DM/N with 1 inflection*100)	Total number of nouns with definiteness marker divided by the total number nouns with single inflections * 100 (e.g., AD04 proportion of definiteness markers 23/35= 65.7%).
✓	Proportion of case markings (CM/N with 1 inflection*100)	Total number of nouns with case markers to the total number of nouns with single inflection*100 (e.g., AD04 proportion of case markers 12/35= 34.3%).
	Verbal inflections	
✓	Verb inflection index	Total number of appropriately inflected verbs to the number of verbs that are possible to be inflected. This is conceptually similar to the verb inflection index of the QPA in English.
	Inflection score	It is the sum of total number of tense, aspect and person inflections for the inflected verbs.
✓	Inflection complexity score	It is the ratio of inflection score divided by total number of matrix verb minus 1 (Inflection complexity score=Inflection score/total number of matrix verbs – 1). Inflection complexity score is similar to the auxiliary complexity index in the QPA framework.
	Semantic measures (CIU analysis)	
	Word count	To be included in the word count, words had to be accurate, relevant, and informative relative to the eliciting stimuli, and did not have to be used in a grammatically accurate manner (Nicholas and Brookshire, 1993).
✓	Number of CIU	The total number of intelligible, accurate and informative words that were relevant to the Frog story Nicholas and Brookshire, 1993.
✓	Idea density (CIU%)	Total number of CIUs (i.e., semantic units) divided by the total number of words used in the sample.
✓	Idea efficiency (CIUs per minute)	Total number of CIUs (i.e., semantic units) divided by the duration of the sample used for calculation of the CIUs.
	Measures of spontaneity and fluency disruptions	
✓	Repetitions	Total number words or whole phrases repeated. For example, whole word (e.g., the <boy> boy was searching for his frog) or phrase-level repetitions (e.g., <The boy>... The boy was searching for his frog). Reduplication of words which is natural phenomenon in Bengali was not considered as repetition (e.g., *āste āste* "slowly").
✓	Revisions	These include when the speaker changes something (usually the syntax) of an utterance but maintains the same idea. It could be word (e.g., a <frog>..dog) or phrase (e.g., <The boy is> …They boy was very upset to not find his frog) revisions.
✓	Reformulations	These included full and complete reformulations of the message without any specific corrections. For example: "<They boy was searching>...uh he decided to return to the pond".
✓	Total count of disruption of spontaneity	Sum of count of repetitions, revisions and reformulations.

The check mark (✓) indicates the variables utilized to compare between the groups in this study.

We implemented Crawford and colleague's single-subject statistical method of comparing a single case to a small control group (at least five) to identify differences between each AD participant and controls (e.g., Crawford and Garthwaite, 2002, 2006; Crawford et al., 2010). This was motivated to facilitate understanding of individual variation and to capture the heterogeneity of the AD population.

RESULTS

Table 5 provides the mean group data from AD and HC participants; individual data for all six AD participants across different variables; results of group statistics (*p*-values and effect sizes); and results of the single-subject statistics. The readers are encouraged to review **Table 3** of illustrative examples of narrative production of AD and HC participants. **Table 6** provides the summary of the key findings across the six domains of speech and language production, and information on the proportion of AD individuals who showed similar results to the group differences (i.e., proportion of AD individuals who were significantly different from the controls).

In terms of rate and spontaneity of speech, compared to the HC, AD individuals produced a slower rate of speech with higher number of disruptions to spontaneity and fluency of speech. **Table 5** indicates that revisions caused the most common type of disruption to the spontaneity of speech. Individual level analyses revealed that slow speech rate was observed in majority of AD participants (five out of six) and disrupted spontaneity was evident for three out of six participants.

In terms of syntactic and structural features, compared to the HC, AD individuals produced shorter (smaller mean sentence length), grammatically simpler (lower embedding indexes), and less well-formed sentences. Individual level analyses revealed that shorter length and lower embedding index was present in all of our AD participants. In contrast, ill-formed sentences were observed only in two of the six participants. Some sources of ill-formedness of the sentences were: Unclear or missing subjects,

TABLE 5 | Individual raw scores for each AD participant, and mean group data from Alzheimer's Disease (AD) and Healthy Controls (HC) across all the connected speech variables along with the results of statistical analysis.

	Variables	Individual AD participants						AD group		HC group		Statistical tests		
		AD01	AD03	AD04	AD06	AD07	AD09	Mean	SD	Mean	SD	*z*-value	*p*-value	Effect size
	Speech rate													
	Duration of the narrative, sec (s)	269	509	466	294	87	764	398.20	234.60	201.13	50.90	−1.94	0.053	−0.52
✓	Total number of words	320	406	229	276	164	537	322.00	133.43	466.00	211.98	−1.42	0.156	−0.38
✓	Words per minute	71.3	48.2	29.35	56.3	113	42.2	60.07	29.52	135.92	31.89	−2.97	**0.003**	−0.79
	Structural and syntactic measures													
	Number of sentences	38	32	34	23	15	38	30.00	9.19	19.63	2.83	−1.94	0.052	−0.52
	Number of topic/comment utterances	4	9	6	5	4	11	6.50	2.88	2.63	2.26	−2.21	**0.027**	−0.59
	Number of embeddings	1	0	0	1	2	0	0.67	0.82	9.38	2.56	−3.12	**0.002**	−0.83
	Number of well-formed sentences	28	28	28	13	13	33	23.83	8.61	18.13	3.14	−1.05	0.294	−0.28
	Number of words in sentence	148	138	138	120	68	127	123.17	28.72	147.50	12.20	−1.94	0.052	−0.52
	Number of words in topic or comments	12	29	21	18	14	32	21.00	8.05	10.38	10.50	−1.88	0.061	−0.50
✓	Proportion of words in sentences	0.93	0.83	0.87	0.87	0.84	0.80	0.85	0.04	0.93	0.07	−1.94	0.052	−0.52
✓	Mean sentence length	3.89	4.31	4.06	5.22	4.53	3.34	4.23	0.63	7.59	0.73	−3.10	**0.002**	−0.83
✓	Proportion of well-formed sentences	0.74	0.88	0.82	0.57	0.87	0.87	0.79	0.12	0.92	0.07	−2.53	**0.011**	−0.68
✓	Embedding index	0.03	0.00	0.00	0.04	0.13	0.00	0.03	0.05	0.50	0.18	−3.11	**0.002**	−0.83
	Lexical measures													
	Number of narrative words (NW)	160	167	159	138	81	159	144.00	32.37	158.00	6.00	−0.26	0.795	−0.07
	Number of open class words	130	131	126	109	69	136	116.83	25.20	120.00	6.99	−0.65	0.516	−0.17
	Number of closed class words	30	36	33	29	12	23	27.17	8.61	38.00	7.15	−2.13	**0.033**	−0.57
	Proportion of open class word	0.81	0.78	0.79	0.79	0.85	0.86	0.81	0.03	0.76	0.04	−2.14	**0.033**	−0.57
	Proportion of closed class words	0.19	0.22	0.21	0.21	0.15	0.14	0.19	0.03	0.24	0.04	−2.14	**0.033**	−0.57
	Number of nouns (N)	62	52	61	41	23	51	48.33	14.58	52.75	4.62	−0.32	0.746	−0.09
	Number of verbs (V)	43	41	42	39	20	45	38.33	9.20	37.38	6.14	−0.84	0.40	−0.23
	Number of nonfinite verbs (NF)	9	9	8	15	3	4	8.00	4.29	14.25	3.37	−2.14	0.033	−0.57
	Number of matrix verbs (MV)	33	32	34	24	17	41	30.17	8.42	23.13	4.42	−1.82	0.069	−0.49
	Number of compound verbs (CV)	22	9	13	11	9	15	13.17	4.92	12.25	4.13	−0.07	0.948	−0.02
	Number of adjectives (Adj)	2	30	8	9	10	19.00	13.00	9.96	14.25	2.92	−0.84	0.401	−0.22
	Number of adverbs (Adv)	5	5	3	6	4	7.00	5.00	1.41	4.50	3.25	−1.18	0.238	−0.32
	Number of all pronouns	5	11	13	17	6	7.00	9.83	4.67	19.25	5.26	−2.59	**0.010**	−0.69
	Number of demonstrative pronouns	1	7	5	1	1	1.00	2.67	2.66	2.88	1.73	−0.66	0.510	−0.18
	Number of personal pronouns (P)	4	4	8	16	5	6	7.17	4.58	16.38	4.66	−2.66	**0.008**	−0.71
	Number of postpositions (PP)	20	10	15	12	6	19.00	13.67	5.39	12.13	3.91	−0.78	0.438	−0.21
✓	Number of reduplication	0	0	1	1	1	0	0.50	0.55	3.00	2.78	−1.99	**0.046**	−0.53
	Proportional measures from lexical counts													
✓	Proportion of noun (N/all NW)	0.39	0.31	0.38	0.30	0.28	0.32	0.33	0.04	0.33	0.03	−0.71	0.476	−0.19

(Continued)

TABLE 5 | Continued

	Variables	Individual AD participants						AD group		HC group		Statistical tests		
		AD01	AD03	AD04	AD06	AD07	AD09	Mean	SD	Mean	SD	*z*-value	*p*-value	Effect size
	Proportion of noun (N/N+V)	0.59	0.56	0.59	0.51	0.53	0.53	0.55	0.03	0.59	0.04	−1.57	0.118	−0.42
	Noun – verb ratio: #N/#V	1.44	1.27	1.45	1.05	1.15	1.13	1.25	0.17	1.44	0.21	−1.43	0.154	−0.38
	Proportion of noun (N/N+P)	0.94	0.93	0.88	0.72	0.82	0.89	0.86	0.08	0.76	0.06	−2.13	**0.033**	−0.57
✓	Proportion of pronoun (P/all NW)	0.03	0.02	0.05	0.12	0.06	0.04	0.05	0.03	0.10	0.03	−2.27	**0.023**	−0.61
✓	Proportion of pronoun to noun (P/P+N)	0.06	0.07	0.12	0.28	0.18	0.11	0.14	0.08	0.24	0.06	−2.13	**0.033**	−0.57
✓	Proportion of verb (V/all NW)	0.27	0.25	0.26	0.28	0.25	0.28	0.27	0.02	0.24	0.04	−1.43	0.152	−0.38
	Proportion of verb (V/V+N)	0.41	0.44	0.41	0.49	0.47	0.47	0.45	0.03	0.41	0.04	−1.57	0.118	−0.42
✓	Proportion of nonfinite verb (NF/all V)	0.21	0.22	0.19	0.38	0.15	0.09	0.21	0.10	0.38	0.07	−2.79	**0.005**	−0.75
✓	Porportion of matrix verb (MV/all V)	0.77	0.78	0.81	0.62	0.85	0.91	0.79	0.10	0.62	0.07	−2.73	**0.006**	−0.73
✓	Proportion of compound verb (CV/all V)	0.51	0.22	0.31	0.28	0.45	0.33	0.35	0.11	0.34	0.12	−0.26	0.796	−0.07
	Proportion of adjective (Adj/NW)	0.01	0.18	0.05	0.07	0.12	0.12	0.09	0.06	0.09	0.02	−0.13	0.897	−0.04
	Proportion of adverb (Adv/NW)	0.03	0.03	0.02	0.04	0.05	0.04	0.04	0.01	0.03	0.02	−1.18	0.236	−0.32
✓	Proportion of postposition (PP/NW)	0.13	0.06	0.09	0.09	0.07	0.12	0.09	0.03	0.08	0.02	−1.31	0.192	−0.35
	Morphological and inflectional measures													
	Nouns inflections													
	Total number of nouns	62	52	61	41	23	51	48.33	14.58	52.75	4.62	−0.32	0.746	−0.09
	Number of nouns in base form	14	29	15	19	7	25	18.17	7.96	22.38	6.67	−1.18	0.240	−0.31
	Number of nouns possible to be inflected	48	23	45	22.00	16	26	30.00	13.22	30.38	4.47	−0.91	0.364	−0.24
	Appropriate noun inflection	47	23	45	22.00	16	24	29.50	13.10	30.38	4.47	−0.97	0.330	−0.26
✓	Noun inflection index	0.98	1.00	1.00	1.00	1.00	0.92	0.98	0.03	1.00	0.00	−1.70	0.090	−0.45
	Noun inflection type													0.00
	Total number of inflected nouns	48	23	45	22	16	24	29.67	13.37	30.38	4.47	−0.97	0.330	−0.26
	N with 1 inflection	36	18	35	18	14	22	23.83	9.39	25.50	3.07	−0.91	0.364	−0.24
	N with 2 inflections	10	5	10	4	2	2	5.50	3.67	5.57	2.94	0.00	1.000	0.00
	N with >2 inflections													0.00
✓	Proportion of inflected nouns	77.4	44.2	73.8	53.7	69.6	47.1	60.95	14.39	58.05	10.72	−0.26	0.796	−0.07
✓	Proportion of noun with 1 inflection	0.75	0.78	0.78	0.82	0.88	0.92	0.82	0.06	0.85	0.09	−0.58	0.559	−0.16
✓	Proportion of noun with 2 or > inflections	0.21	0.22	0.22	0.18	0.13	0.08	0.17	0.06	0.18	0.07	−0.39	0.697	−0.10
	Inflection type: Definiteness marker (DM)	24	14	23	5	8	16	14.83	7.96	6.88	2.85	−1.88	0.060	−0.50
	Inflection type: Case markers (CM)	12	4	12	13	6	6	8.83	3.54	18.50	3.89	−2.79	**0.005**	−0.75
	Rate of Definiteness marker (DM/all N*100)	38.7	26.9	37.7	9.8	34.8	31.4	29.87	10.76	13.08	5.55	−2.45	**0.014**	−0.66
	Rate of case markers (CM/all N*100)	17.7	9.6	19.7	31.7	26.1	11.8	19.43	8.40	35.11	6.87	−2.84	**0.005**	−0.76
✓	Proportion of Definiteness marker (DM/N with 1 inflection*100)	66.7	77.8	65.7	22.2	57.1	72.7	60.38	19.95	27.09	12.07	−2.45	**0.014**	−0.66
✓	Proportion of case markings (CM/N with 1 inflection*100)	30.56	27.78	34.29	72.22	42.86	27.27	39.16	17.18	72.44	12.56	−2.71	**0.007**	−0.72

(Continued)

TABLE 5 | Continued

	Variables	Individual AD participants						AD group		HC group		Statistical tests		
		AD01	AD03	AD04	AD06	AD07	AD09	Mean	SD	Mean	SD	*z*-value	*p*-value	Effect size
	Verb inflections													
	Number of verbs	43	41	42	39	20	45	38.33	9.20	37.38	6.14	−0.84	0.40	−0.23
	Number of inflectable verbs	43	41	42	39	20	45	38.33	9.20	37.38	6.14	−0.84	0.40	−0.23
	Number of inflectable verbs inflected	43	41	42	39	20	45	38.33	9.20	37.38	6.14	−0.84	0.40	−0.23
✓	Verb inflection index	1	1	1	1	1	1	1.00	0.00	1.00	0.00	0.00	1	0.00
	Inflection score (IS)	98	96	102	72	51	123	90.33	25.21	69.00	12.63	−1.75	0.081	−0.47
	Tense	33	32	34	24	17	41	30.17	8.42	23.13	4.42			
	Aspect	32	32	34	24	17	41	30.00	8.37	23.13	4.42			
	Person	33	32	34	24	17	41	30.17	8.42	23.13	4.42			
✓	Verb complexity score (IS/MV-1)	1.97	2.00	2.00	2.00	2.00	2.00	1.99	0.01	1.99	0.04	−0.11	0.916	−0.03
	Semantic measures													
	Word count	205	241	192	233	155	289	219.17	46.05	178.50	13.04	−2.01	**0.045**	−0.54
	Duration of the narrative for the CIU analysis (sec)	249	193	352	238	81	254	227.80	88.80	100.63	14.38	−2.20	**0.028**	−0.59
✓	Number of CIU	159	154	147	133	78	143	135.67	29.65	161.63	5.71	−2.61	**0.009**	−0.70
✓	CIU% (Idea density)	77.56	63.90	76.56	57.08	50.32	49.48	62.48	12.44	90.87	5.54	−3.10	**0.002**	−0.83
✓	CIUs per minute (Idea efficiency)	49.4	47.87	25.05	33.53	57.8	33.78	41.23	12.34	98.24	15.93	−3.10	**0.002**	−0.83
	Measures of spontaneity and fluency disruptions													
	Repetition	2	6	0	5	0	4	2.83	2.56	0.75	1.04	−1.61	0.108	−0.43
	Revisions	5	6	8	10	5	17	8.50	4.59	2.25	2.55	−2.69	**0.007**	−0.72
	Reformulations	0	0	0	0	0	0	0.00	0.00	0.13	0.35	−0.87	0.386	−0.23
✓	Total count of disruption of spontaneity and fluency	7	12	8	15	5	21	11.33	5.96	3.13	2.90	−2.67	**0.008**	−0.71

Gray shaded cells represent significant difference ($p < 0.05$) in single-subject statistics, where individual AD's score was significantly different than the HC group mean. The check marked variables are used for group comparison in this study.

Crawford and Howell (1998) statistical test was used to compare each AD's score with the HC group. Singlism.exe program (2002) was used to compute the statistics.

Bold font in p-values indicate significant difference between HC and AD groups.

despite pro-drop being allowed in Bengali; incomplete sentences; missing coordinating conjuncts; correct but overuse of a specific marker; subject, object or verb on some occasions replaced by fillers or particles. **Table 3** provides illustrative examples of these errors.

In the domain of lexical measures, compared to the HC, AD individuals showed reduced proportion of pronouns, decreased proportion of nonfinite verbs, increased proportion of matrix verbs, and fewer reduplications. All other distributions and proportions of lexical items were comparable between the two groups. Individual level analyses revealed change in the proportion of pronouns (four out of six), matrix verbs (five out of six), and nonfinite verbs (five out of six) in majority of the AD participants (see **Table 5**).

For the morphological and inflectional measures, AD and HC participants demonstrated equivalent inflectional indices both for nouns and verbs. This implies that AD participants were able to provide correct and appropriate inflections for the nouns and verbs they produced. Further, AD participants could also produce similar proportion of inflected nouns and similar proportion of nouns with one or two inflections (see **Table 5**). However, contrast could be observed between the two groups in terms of the type of noun inflections: AD participants produced higher proportion of definiteness markers, whilst HC produced greater proportion of case markings. The pattern of higher proportion of definiteness markers for nouns and lower proportion of case markers were observed for five out six AD participants. AD participants did not show any difference in the inflectional complexity scores for verbs, indicating that they could produce similar quantity of inflections compared to the controls. In the domain of semantic content and CIU analyses, compared to the HC, AD individuals showed fewer CIUs, lower idea density and idea efficiency. Individual level analyses revealed every AD participant had lower idea density and efficiency (six out of six). It is worth noting that the relationship between overall dementia severity and deficits in connected speech is far from straightforward. With the exception of one AD participant, AD07, who had a dementia rating of two, all other five participants evidenced a severity rating of one (i.e., mild). Despite AD07 demonstrating more severe dementia compared to the others in the group, she did not necessarily show more severe deficits on connected speech variables.

In summary, from **Table 6** we can see that the parameters which most prominently distinguished AD from the HC with large effect sizes and were impaired in majority of AD participants (at least four out of six) include: slowed speech rate; shorter sentence length; fewer embeddings; decreased proportion of pronouns; increased proportion of matrix verb with decreased proportion of non-finite verbs; decreased proportion of case marking for nouns with increased proportion of definiteness markers; and semantically reduced idea density and idea efficiency. In addition, disruption in spontaneity and fluency, decreased numbers of reduplications, and decreased proportion of well-formed sentences showed significant group differences with fewer AD participants.

DISCUSSION

We undertook this research to characterize connected speech production and identify linguistic features of Bengali AD participants. The impetus for this work was driven by the fact that an accumulating body of research has shown that speech and language characteristics of connected speech provide a valuable tool for identifying, diagnosing and monitoring progression in AD. However, our knowledge of linguistic features of connected speech in AD is primarily derived from English speakers. This is a problematic situation. The world is full of languages that are linguistically different from English. In fact, the majority of world's population do not speak English as their primary language. Therefore, there is an urgent need to investigate whether linguistic features that are used for characterizing AD in English will be relevant for structurally distinct languages. This is what we set out to find in speakers of Bengali, a pro-drop, Indo-Aryan language, and which is the seventh most spoken language in the world.

The key findings indicate that Bengali AD participants showed both similarities to findings reported from English speaking AD subjects as well as language specific differences from English. Similarities with English speaking literature were decreased speech rate, simplicity of sentence forms and structures, and reduced semantic content.

Critically, differences with English speakers' literature emerged in the domains of linguistic features where Bengali differs, such as pro-drop nature of the language and inflectional properties of nominal and verbal systems. Specifically, Bengali AD participants produced fewer pronouns, which is in contrast with a key feature of English AD speakers who produce an abundance of pronouns in connected speech. Despite Bengali being a highly inflected language, our AD participants showed a similar amount of noun and verb inflections without any obvious difficulties. However, differences did appear in the type of noun inflections that the AD speakers used, in most instances choosing simpler inflectional features.

Overall, connected speech production in these AD participants was characterized by the use of simpler, less complex and operationally less demanding options, with impoverished semantic content. They used shorter and simpler sentences with reduced rate of speech and reduced spontaneity, using fewer pronouns, fewer reduplications, and demonstrated a lack of difficulty with the quantity of noun and verb inflections produced but using inflections that are simpler. In the following paragraphs, we discuss the findings in detail and highlight how this research provides seminal evidence to build future research with different languages.

The finding that our AD participants produced a slower rate with higher number of disruptions to spontaneity because of revisions corroborates existing literature (Sajjadi et al., 2012; Forbes-McKay et al., 2013; Ash and Grossman, 2015). They produced significantly shorter sentences, which were grammatically simpler with minimal embeddings, and at times also fewer well-formed sentences. The majority of AD participants in our study showed difficulty with speech rate (5/6), shorter MLU (6/6), and fewer sentence embeddings (6/6)

TABLE 6 | Summary of the key findings across the six domains of speech and language production, and information on the proportion of AD individuals who showed similar results to the group differences.

Variables	Alzheimer's Disease (AD)		Healthy Control (HC)		Between group significant difference	Direction of effect for AD	Effect size	Number (proportion) of AD participants showing sign difference (total N=6)	*z*-value	*p*-value	Effect size
	Mean	SD	Mean	SD							
Speech rate											
Total number of words	322.00	133.43	466.00	211.98	✗				−1.420	0.156	−0.38
Words per minute	60.07	29.52	135.92	31.89	✓	decreased	Large	5 (83%)	−2.969	0.003	−0.79
Structural and syntactic measures											
Proportion of words in sentences	0.86	0.05	0.80	0.15	✗				−1.941	0.052	−0.52
Mean sentence length	4.26	0.64	7.68	0.82	✓	shorter	Large	6 (100%)	−3.098	0.002	−0.83
Proportion of well-formed sentences	0.79	0.13	0.95	0.06	✓	lesser	Large	2 (33%)	−2.529	0.011	−0.68
Embedding index	0.03	0.05	0.60	0.22	✓	lower	Large	6 (100%)	−3.112	0.002	−0.83
Lexical measures											
Proportion of noun (N/all NW)	0.33	0.04	0.33	0.03	✗				−0.713	0.476	−0.191
Proportion of pronoun (P/all NW)	0.05	0.03	0.10	0.03	✓	decreased	medium	3 (50%)	−2.274	0.023	−0.61
Proportion of pronoun to noun (P/P+N)	0.14	0.08	0.24	0.06	✓	decreased	medium	4 (67%)	−2.132	0.033	−0.57
Proportion of verb (V/all NW)	0.27	0.02	0.24	0.04	✗				−1.431	0.152	−0.382
Proportion of nonfinite verb (NF/all V)	0.21	0.10	0.38	0.07	✓	decreased	large	5 (83%)	−2.791	0.005	−0.75
Porportion of matrix verb (MV/all V)	0.79	0.10	0.62	0.07	✓	increased	large	5 (83%)	−2.726	0.006	−0.73
Proportion of compound verb (CV/all V)	0.35	0.11	0.34	0.12	✗				−0.258	0.796	−0.07
Proportion of postposition (PP/NW)	0.09	0.03	0.08	0.02	✗				−1.31	0.192	−0.35
Number of reduplication	0.50	0.55	3.00	2.78	✓	decreased	medium	3 (50%)	−1.994	0.046	−0.533
Morphological and inflectional measures											
Nouns inflections											
Noun inflection index	0.98	0.03	1.00	0.00	✗				−1.695	0.090	−0.45
Proportion of inflected nouns	60.95	14.39	58.05	10.72	✗				−0.258	0.796	−0.07
Proportion of noun with 1 inflection	0.82	0.06	0.85	0.09	✗				−0.584	0.559	−0.16
Proportion of noun with 2 or more inflections	0.17	0.06	0.18	0.07	✗				−0.390	0.697	−0.10
Proportion of definiteness markers in %	60.38	19.95	27.09	12.07	✓	increased	medium	5 (83%)	−2.453	0.014	−0.656
Proportion of case markers in %	39.16	17.18	72.44	12.56	✓	decreased	large	5 (83%)	−2.711	0.007	−0.725
Verb inflections											
Verb inflection index	1.00	0.00	1.00	0.00	✗				0.000	1.00	0.000

(Continued)

TABLE 6 | Continued

Variables	Alzheimer's Disease (AD)		Healthy Control (HC)		Between group significant difference	Direction of effect for AD	Effect size	Number (proportion) of AD participants showing sign difference (total N=6)	*z*-value	*p*-value	Effect size
	Mean	SD	Mean	SD							
Verb complexity score	1.99	0.01	1.99	0.04	✗				−0.106	0.916	−0.028
Semantic measures											
Number of CIU	135.67	29.65	161.63	5.71	✓	fewer	medium	4 (67%)	−2.611	0.009	−0.70
CIU% (Idea density)	62.48	12.44	90.87	5.54	✓	decreased	large	6 (100%)	−3.102	0.002	−0.83
CIUs per minute (Idea efficiency)	41.23	12.34	98.24	15.93	✓	decreased	large	6 (100%)	−3.098	0.002	−0.83
Measures of spontaneity and fluency disruptions											
Total count of disruptions of fluency (repetition, revision, reformulations)	11.33	5.96	3.13	2.90	✓	greater	large	3 (50%)	−2.673	0.008	−0.71

Gray shading indicates significant group difference.

highlighting the consistency of these features across AD patients. Although poorly formed sentences showed a significant group difference, it arose from only two of the six participants (AD01, AD06). The reason for less well-formed sentences was because the sentences had missing or under specified lexical items, mostly objects or subjects but at times even verbs resulting in incomplete sentences. Recall that unlike English, Bengali allows a more flexible word order, it permits greater leeway to formulate grammatically correct and well-formed sentences. Despite this feature two of the AD participants produced significantly fewer well-formed sentences. These findings of simplified syntactic production are in concordance with AD connected speech literature (Ash et al., 2007; Cuetos et al., 2007; De Lira et al., 2011; Sajjadi et al., 2012; Ahmed et al., 2013; Forbes-McKay et al., 2013; Ash and Grossman, 2015; Fraser et al., 2016).

An interesting question arises as to why these AD participants were producing syntactically and grammatically simpler sentences. Prior AD literature suggests that participants have significant impairments in their memory processes, which contributes to their difficulty in syntactic operations (e.g., Waters et al., 1998). This could indeed be a possibility in our data as most of our participants have lower scores on background memory measures. Another contending explanation is that our AD participants demonstrated grammatical difficulty as noted by other authors (e.g., Fraser et al., 2016). Fraser et al. (2016) noted that the syntactic impairments in their AD participants' picture description had features similar to Broca's aphasia, but commented that "while these deficits resemble Broca's aphasia and progressive nonfluent aphasia in their form, they are less severe, seldom reaching the point of frank agrammatism or telegraphic speech seen in those disorders" (p. 414). The difficulty with syntax and grammar is evident in our participants if we carefully consider the lexical distribution of types of verbs in the narratives. The findings of fewer nonfinite verbs produced by the AD participants correspond to the associated lack of complexity and embedding of their sentences. However, when the embedded clauses were indeed produced, the verbs were appropriately marked for agreement. This suggests that the difficulty was is in the structural complexity of the sentence rather than in inflectional morphology. This is consistent with previous studies in languages with high inflectional morphology, in that, the inflectional morphology is spared in cases of language impairments (Leonard, 2000; Penke, 2009; Auclair-Ouellet et al., 2019). Instead, the participants with AD in our study produced shorter sentences with single matrix verbs. Individual level analyses revealed an increase in the proportion of matrix verb with a corresponding decrease in nonfinite verbs in the majority of the AD participants (see **Table 5**). Future research using sentence production and comprehension tasks, with different sentence types and varying syntactic complexity would be important to understand the mechanism that is underplaying in the production of syntactically simplified connected speech in AD.

In terms of lexical measures and distribution of various lexical classes, the most salient finding from this research is that Bengali speaking AD showed a reduced proportion of pronouns in their narrative samples. As a group, AD participants produced fewer

pronouns; four of the six participants produced significantly fewer pronouns compared to the controls; two produced similar number of pronouns to the controls. Importantly, none of them over produced pronouns. This finding is in stark contrast with the findings from English speaking AD participants where over production of pronouns is a distinctive feature (March et al., 2006; Ahmed et al., 2013; Jarrold et al., 2014; Fraser et al., 2016). Increased production of pronouns has also been reported from AD speakers of Hebrew (Kavé and Levy, 2003; Kavé and Goral, 2016). Recall that Bengali is a pro-drop language and allows dropping of the subject; the subject could be inferred from the other inflected parts of speech. Pro-drop is more common with inflectionally rich languages, where inflectional morphology could be used to infer the referent. In languages where subjects are obligatorily spelled out, such as in English, dropping the subject is not an option. Therefore, AD individuals of those languages such as English, will prefer pronouns over nouns as the former is semantically vague, more frequent in use and thus might be easier to retrieve. In contrast, Bengali allows null-subject (i.e., dropped subject). Participants can drop the subject as null subject is cognitively less costly (Bloom, 1990). However, in English when one has to produce something, a less costly option is usually opted for, which is over-producing the pronoun (Almor et al., 1999). One simple deduction can be drawn from this cross-linguistic observation: when a language allows the avoidance of a linguistic feature or structure, such as subject drop in Bengali, AD participants will avoid it as retrieving and producing the subjects is more demanding. In contrast, when a language does not allow the avoidance of a linguistic feature, such as the obligatory use of a subject in English, AD participants will opt for a cognitively less costly option, that is, the replacement of nouns with pronouns. The important implication for this finding is that over-production of pronouns, which is a characteristic feature in English, might not be a relevant linguistic marker for a pro-drop language, such as Bengali. Research investigating pronoun usage for AD speakers in other pro-drop languages will be of great importance to determine if this pattern holds true across languages.

Reduplication is a frequent lexical feature in Bengali which is employed by speakers to enhance senses of multiplicity, continuation of action, recurrent happening of an event, or emotional state. In a sense, it serves a semantic function but requires word formation processes to generate the reduplicated forms. Using reduplication allows the expression of a richer and enhanced sense of the concept or event; however, lack of use of reduplication is not a linguistic deficit. AD participants' use of fewer reduplications could be further evidence of their difficulty in using complex linguistic operations, in this case, the word formation processes. This could indicate that AD participants have difficulty with complex word formation processes. Reduced reduplication has been reported in individuals with aphasia speaking standard Indonesian (Anjarningsih et al., 2012).

In the context of semantic content analysis—idea density and idea efficiency—reflect the ability to produce relevant content efficiently at a discourse level. Unsurprisingly, results reveal that our AD participants generated less concise information as noted by reduced idea density indicating they needed more words to convey ideas. This resulted in characteristic features of "empty speech" and "non-specificity" of discourse in AD reported in the literature (e.g., Nicholas et al., 1985). Some of these features include empty phrases (e.g., *mane hacche* "it seems"), deictic terms (e.g., *edik odik* "this side that side", *tār pare* "then"), indefinite terms (e.g., *ekṭā* "one", *iye* "something"), and repetitions (e.g., *eṭā ekṭā kukur… kukur* "this one is dog…dog"). Along with reduced idea density, AD participants evidenced reduced rate at which meaningful information is conveyed over time, that is, reduced idea efficiency. All of our AD participants (six out of six) showed reduced idea density and idea efficiency in their narrative samples. Reduced information content resulting in limited idea density and idea efficiency is a consistent finding across AD connected speech studies (Nicholas et al., 1985; Croisile et al., 1996; Forbes-McKay and Venneri, 2005; Sajjadi et al., 2012; Ahmed et al., 2013; Forbes-McKay et al., 2013). This highlights the fact that irrespective of the language spoken by AD participants, difficulties in conveying ideas concisely and efficiently are a pervasive difficulty as noted across various production tasks such as conversations (e.g., Dijkstra et al., 2004); picture description (e.g., Ahmed et al., 2013), and interviews (Sajjadi et al., 2012).

Studies investigating morphosyntactic characteristics of connected speech by measuring differences in inflectional properties between AD and controls have been reported from English speakers [see Auclair-Ouellet (2015) for a systematic review of inflectional morphology in primary progressive aphasia and AD]. As English is not an inflectionally rich language, it offers limited opportunity to test morphosyntactic differences between control and AD. In contrast, Bengali has a rich inflectional system for nouns and verbs. The findings from this study show that AD participants and the controls produced comparable proportion of inflected nouns, as noted by the similar noun inflection index as well as comparable proportion of nouns with one and two inflections. This highlights that AD participants were able to produce noun inflections in similar quantity to the controls. This is in contrast with findings from English speaking subjects from the literature who have been reported to have difficulties with nouns with determiners (e.g., Ahmed et al., 2013). This finding is not surprising when viewed with the lens of the literature on acquisition of morphological markers in morphologically rich languages (e.g., Penke, 2012). It has been proposed that morphologically rich and agglutinative systems generally display a greater morphological transparency compared to inflection systems where the inflection is associated with changes to the stem. As such, in these morphologically richer languages, inflectional morphology is acquired earlier in comparison to languages with sparse inflectional morphology (Bates and MacWhinney, 1987; Dressler, 2010). Therefore, in our data preservation of inflectional abilities in AD participants could be a reflection of the stability of these patterns as they might have been acquired earlier.

Distinct differences do appear between the two groups when type of noun inflections was explored in detail (see **Figure 1**). In AD, definiteness markers were more prevalent in nouns; whilst case marking was under-used (e.g., case-marking *jāre* "in the jar"; *kukurke* "to the dog"; definiteness marking *jāta*

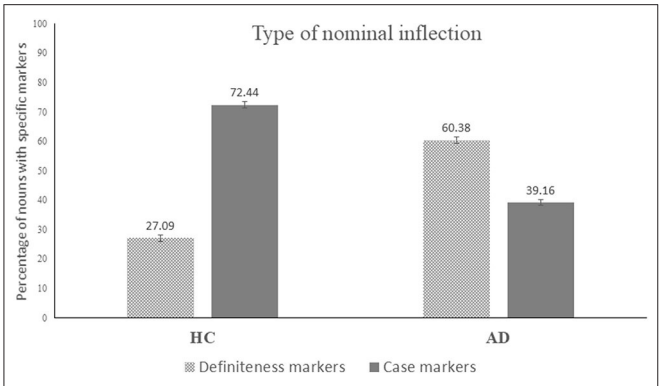

FIGURE 1 | Mean proportion of nouns with definiteness vs. case markers for Alzheimer's Disease (AD) and Healthy Controls (HC). Error bars represent standard error of mean.

"the jar"; *kukurta* "the dog"). Case marking is grammatical in nature and use of appropriate case markers requires complex morphosyntactic operations. The difficulty with case marking is an indication that AD participants' difficulties in production could be in using complex grammatical operations as use of appropriate case marking requires complex morphosyntactic processes. In contrast, definiteness marker is more semantic in nature and is used as a tool for over specifying a subject or object. This finding highlights the importance of digging deeper into the morphosyntax of languages to understand the core linguistic difficulties across languages, which has the potential to inform about underlying processes as well as aid in developing specific clinical markers for diagnosis.

In terms of verbal inflections, our AD participants showed no difficulty with generating appropriate inflections for verbs, as noted by verb inflection index and verb complexity score. Any verb they produced was correctly inflected for tense, aspect, and person. Qualitatively, they produced fewer variations in these features (see illustrative examples in **Table 3**) but overall, they could produce correctly inflected verbs. Research from German speakers with AD (Blanken et al., 1987) and Hebrew speakers with AD (Kavé and Levy, 2003) found no difference between AD and their control groups on verb inflectional abilities. This is in contrast with the greater number of inflectional errors in English-speaking AD patients (Altmann et al., 2001; Sajjadi et al., 2012; Ahmed et al., 2013), difficulty with inflected verbs, auxiliary verbs, gerunds or participles (Fraser et al., 2016); difficulty with verb tense use (Dijkstra et al., 2004) and difficulty with subject verb agreement (Kaprinis and Stavrakaki, 2007). This is an interesting point of discussion as languages such as Bengali, German, Hebrew, who have a more complex and richer verbal inflectional system than English was not precipitating more inflectional errors in AD speakers. The answer could be found in thinking about the nature of this complexity. In these languages, the verbal inflectional system is complex but regular and systematic. That complexity does not equate to difficulty has been shown in morphologically richer languages even in child acquisition literature (e.g., Penke, 2012). As argued earlier, the complex morphological structures that are acquired earlier might have been better preserved. We believe that a future line of research which systematically compares inflectional morphology and its breakdown across different languages stands to inform our understanding of core linguistic deficits across various dementia syndromes.

CONSIDERATIONS FOR FUTURE RESEARCH AND LIMITATIONS

In this section, we share our experiences and "lessons learnt" from embarking on connected speech research in an unexplored language, especially in determining an appropriate task and linguistic analysis framework for the data. Given that research is a resource intensive enterprise, we believe that documenting these observations would be useful for future researchers interested in similar research in neurological impairments in languages that have not yet been studied. We also highlight limitations of our current study and suggest future research directions.

First, if one is interested in characterizing linguistic patterns of connected speech in AD in a language, which has yet not been documented, the choice of task has important implications for the conclusions that could be drawn based on the findings. Picture description is quick and easy to administer. However, several studies with neurological impairments have reported that picture description often generates impoverished speech with limited types of sentence production, and patients often default to listing of the elements in the picture rather than producing "connected" speech *per se* (e.g., Olness, 2006; Armstrong et al., 2013). Interviews on the other hand are time-consuming and lack consistency across participants. It is ideal to use a linguistic task, which allows the person to generate connected speech samples with a story line (e.g., narrative story retell tasks). Grossman (2012) noted that connected speech features in dementia "are best quantified by a semi-structured protocol that is long enough to show the variety of utterances that can occur in spontaneous speech, yet is standardized enough so that all participants have an opportunity to produce speech prompted by the same content" (p. 546). The type of data generated in story narratives, such as Cinderella or Frog Story, affords opportunities to analyze connected speech both at micro- and macro-linguistic levels. It has also been suggested that it is prudent to use multiple elicitation methods in research studies to fully capture production differences across tasks (Boyle, 2015; Stark, 2019), which in turn can help decide the best task for clinical use. For our study, we used the Frog story as it allowed richer output and was culturally appropriate for our participants. Once a baseline of deficits is established in a new language using a semi-structured task, further research could be conducted to compare language production across different tasks (e.g., story narrative, picture description). Our current research focused on the micro-linguistic structures of production; macro-linguistic analysis of narratives remains a productive area of research in AD. Future research using multi-level analyses of micro-and macro-linguistic structures will further improve our understanding of connected speech profiles in AD.

Second, having an excellent team with interdisciplinary expertise is important. Critically, in-depth knowledge and understanding of linguistics of the language studied is essential.

Without the linguistic expertise, it is possible to miss important features of the language that could serve as linguistic markers of the impairments. As illustrated from the current research, the differences between AD and controls in the type of nominal inflections used highlights specific linguistic differences between the two groups; whilst restricting our analysis to overall noun inflection index would not have revealed the true nature of the deficits in AD participants. Future research that aims to characterize impairments in languages that have not been studied should strive to provide an exhaustive characterization of the linguistic features as these documentations over time could lead to a greater understanding of how different languages breakdown in AD.

Third, linked with the linguistic knowledge is the choice of analysis framework. We used the well-tested multidimensional analysis system of the QPA and augmented the framework with additional measures to capture Bengali specific linguistic features, as well as semantic content analysis. We found this approach useful, as it remained in line with the analysis framework that most researchers in this field are using (Slegers et al., 2018). Using a well-established method for analyzing and reporting data that is accessible to readers in the field would be an important consideration for future researchers. This will ensure that research findings from new languages remain comprehensible for readers who are non-speakers of those languages. We are happy to discuss and share with interested researchers the steps we followed in augmenting the QPA to suit the needs for Bengali.

Fourth, although it might be obvious, we emphasize the importance of clear task instructions and well-documented administration protocol especially for testing linguistically and culturally diverse populations. For example, bilingual clients who are proficient in both languages and in their naturalistic speech might code-switch effortlessly. In these instances, it will be beneficial to mention if the testing was conducted in bilingual vs. monolingual mode and how strictly those modes were followed. The corpus of language output, its analysis and interpretation would be different when bilinguals are allowed to use bilingual mode instead of monolingual mode. Future research with bilingual clients including various modes of elicitation stands to inform language processing and language control in them, and whether bilinguals can harness the power of two languages to provide a more productive output.

Fifth, recruiting a large sample of well-controlled and well-characterized clinical group remains a perennial difficulty for researchers. For this research we had six AD participants. A larger sample of AD participants would, of course, be desirable, although such number is not unusual in clinical studies particularly where participants belong to an under-represented group. The methodology was selected to mitigate challenges of generalization. As such, statistical analysis captured findings at both the group and individual levels, offering a comprehensive, detailed and nuanced approach to the profiling of linguistic impairments in a language which has not yet been linguistically studied in depth in neurological impairments. Future research with larger sample sizes with varying severity is desirable. As seen amongst the AD participants in this research that higher overall dementia severity did not necessarily reflect most difficulties in linguistic features. We urge caution in establishing direct link with overall dementia severity to the linguistic profiles of AD participants. In addition, consorted efforts for data sharing and data deposits amongst researchers and clinicians would enable collection of larger datasets.

Sixth, it is likely that non-English speakers would come from culturally diverse populations and perhaps from non-Western countries. In such situations the challenges of undertaking cross-cultural neuropsychological and neurolinguistic research should be acknowledged with clear mention of how tasks and tools used for profiling a client are appropriate and reliable. For instance, a published version of ACE for Bengali does not yet exist. Accordingly, the adapted version was used for this research, reliably adapted at the regional center we recruited from. Moreover, the population we recruited were highly educated pre-morbidly, and most were working professionally. Therefore, we did not face the typical challenges of testing lower literacy populations. However, going forward, having protocols and training in place to ensure reliability of methods for generating quality data will be of utmost importance.

SUMMARY AND CONCLUSIONS

In summary, in this research we characterize connected speech production in Bengali AD participants. Our research is the first of its kind to provide a comprehensive and detailed characterization of linguistic features in Bengali speaking AD individuals. Such detailed characterization in South Asian languages is currently non-existent. The findings highlight that Bengali AD participants showed both similarities to findings reported from English speaking AD subjects as well as language specific differences compared to English. Similarities with English speaking literature gravitated toward decreased speech rate, simplicity of sentence forms and structures, and reduced semantic content. Critically, differences with English speakers' literature emerged in the domains of Bengali specific linguistic features; fewer pronouns, fewer reduplications and a similar quantity of noun and verb inflections without obvious errors. Specifically, connected speech productions of Bengali AD participants were characterized by: impoverished semantic content with higher rate of disruption to spontaneity of speech and slower rate of speech; use of simpler, shorter and grammatically less complex sentences with limited embeddings; use of fewer pronouns and fewer reduplications; similar level of noun and verb inflections, but using inflections that are operationally simpler such as definiteness markers in nouns instead of case markers. This paints the picture of semantic difficulties along with differences in grammaticality of production where AD individuals choose simpler and operationally less demanding options.

This study is a significant step forward for improving both our theoretical understanding of linguistic deficits in AD and clinical implications of implementing these for improving diagnosis and monitoring progress in AD. Theoretically, this research contributes to the understanding of language impairments in neurodegenerative diseases; this could ultimately identify the

core underlying impairments that result in specific linguistic profiles. The study also provides a framework for cross-linguistic comparisons across structurally distinct and under-explored languages, and also challenges the notion that more complex morphology is more difficult for AD. This research begins to address the urgent need to develop language specific linguistic markers for AD, which in turn can aid in creating clinical guidance for assessment of this community of patients in dementia services to help with sensitive and, importantly specific diagnosis of dementia disorders.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of Reading (Ref: 2017-035-AB). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AB, AD, and SA: conceptualization. AD and RN: participant recruitment and data collection. AB, ND, and MD: linguistic framework development. AD, RN, AB, and SA: neuropsychological data coding and interpretation. AB, ND, MD, TD, YC, and SA: linguistic data coding and analysis. AB, YC, and TD: statistical analysis. AB, ND, SA, and MD: writing and critical review. All authors contributed to the article and approved the submitted version.

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Textual Inference Comprehension in Mild Cognitive Impairment: The Influence of Semantic Processing and Verbal Episodic Memory

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Language complaints, especially in complex tasks, may occur in mild cognitive impairment (MCI). Various language measures have been studied as cognitive predictors of MCI conversion to Alzheimer's type dementia. Understanding textual inferences is considered a high-demanding task that recruits multiple cognitive functions and, therefore, could be sensitive to detect decline in the early stages of MCI. Thus, we aimed to compare the performance of subjects with MCI to healthy elderly in a textual inference comprehension task and to determine the best predictors of performance in this ability considering one verbal episodic memory and two semantic tasks. We studied 99 individuals divided into three groups: (1) 23 individuals with amnestic mild cognitive impairment (aMCI), (2) 42 individuals with non-amnestic mild cognitive impairment (naMCI), (3), and (4) 34 cognitively healthy individuals for the control group (CG). A reduced version of The Implicit Management Test was used to assess different types of inferential reasoning in text reading. MCI patients performed poorer than healthy elderly, and there were no differences between MCI subgroups (amnestic and non-amnestic). The best predictors for inference-making were verbal memory in the aMCI and semantic tasks in the naMCI group. The results confirmed that the failure to understand textual inferences can be present in MCI and showed that different cognitive skills like semantic knowledge and verbal episodic memory are necessary for inference-making.

Keywords: mild cognitive impairment (MCI), inference, comprehension, text, semantic processing, verbal episodic memory

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INTRODUCTION

The concept of mild cognitive impairment (MCI) refers to an intermediate condition between normal cognition and early dementia, where individuals present some degree of cognitive impairment but maintain the preservation of functionality, progressing to full-blown dementia at a rate of 10–15% per year (Albert et al., 2011). MCI is classified as amnestic (a-MCI) and non-amnestic (naMCI) underpinned on memory damage (Kelley and Petersen, 2007). Impairment in episodic memory appears early in MCI patients who will develop Alzheimer's disease (AD) (McKhann et al., 2011).

Many pieces of research have been conducted for the early detection of cognitive decline in MCI (Vega and Newhouse, 2014; Chehrehnegar et al., 2019). Early detection provides better opportunities for pharmacological and non-pharmacological treatments and, therefore, may delay the evolution of the disease (Vega and Newhouse, 2014; Eshkoor et al., 2015; Zetterberg and Bendlin, 2021). Biomarkers of cerebral amyloid and tau deposition through cerebrospinal or neuroimaging studies are expensive, invasive, and unsuitable at the primary care level, especially in developing countries. Thus, the search for cognitive markers indicating the progression from MCI to dementia is of paramount importance (Briceño et al., 2020; Silva et al., 2020).

Compared to other cognitive domains, the linguistic decline in MCI is less studied, but various language measures are being identified as predictors of MCI conversion to AD (Belleville et al., 2017). Reports of language deficits include failures in several tasks such as, verbal fluency, confrontation naming, word definition, sentence comprehension, and repetition, and discourse production (Mueller et al., 2018; McCullough et al., 2019; de la Hoz et al., 2021). Non-literal language deficits as comprehension of proverbs, idiomatic expressions, and non-literal text were also identified in individuals with MCI (Cardoso et al., 2014). In this direction, studies show that the ability to understand inferences may also be affected in MCI (Schmitter-Edgecombe and Creamer, 2010; Gaudreau et al., 2015; Silagi et al., 2021).

Inferential processing is the ability to build mental representations for the complete comprehension of information that is heard or read, based on the application of personal knowledge added to the explicit information expressed, establishing associations and relations, allowing the comprehension of implicit information (Gutiérrez-Calvo, 1999).

Verbal and written communication requires different types of inferential reasoning. The continuous realization of inferences is critical to discourse comprehension since not all information is explicitly conveyed, and some degree of "predictions" and "deductions" about what the speaker or writer "really" means is often necessary to maximize communication effectiveness. The comprehension of inferences is based on well-developed semantic integration and verbal memory skills (Van Dijk and Kintsch, 1983; McNamara et al., 2007).

Thus, the ability to understand textual inferences is considered a high-demanding task that recruits multiple cognitive functions and, therefore, could be sensitive to detect cognitive decline in the early stages of MCI. Furthermore, considering the importance of early detection of decline in cognitive skills in a population facing increasingly more extended life expectancy and the pivotal role of inference comprehension in maintaining effective communication, we aimed to study the inferential comprehension from reading on a cohort of MCI patients. Therefore, we aimed to compare the performance of subjects with MCI to healthy elderly in a textual inference comprehension task and to determine the best predictors of performance in this ability considering one verbal episodic memory and two semantic tasks.

MATERIALS AND METHODS

Participants

We studied 99 elderly followed up at a Psychogeriatric outpatient clinic linked to a university hospital, aged between 60 and 90 years, who presented cognitive complaints or previous diagnosis of cognitive deficits, and a group of elderly engaged as volunteers in studies concerning cognition.

Individuals enrolled in the study were classified into three groups, paired according to age and educational level:

1. CG ($n = 34$): control group with cognitively healthy individuals;
2. aMCI ($n = 23$): individuals with amnestic mild cognitive impairment;
3. naMCI ($n = 42$): individuals with non-amnestic mild cognitive impairment;

First, all participants were evaluated by the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005; Memória et al., 2013) for general cognitive screening, the Geriatric Depression Scale-15 (GDS-15) (Sheikh and Yesavage, 1986; Almeida and Almeida, 1999) to detect depressive symptoms, and the Lawton and Brody Scale for Daily Life Activities (L and B) (Lawton and Brody, 1969; Santos and Júnior, 2012) to assess functional independence for instrumental activities of daily living. Subsequently, the participants were submitted to a neuropsychological assessment, composed of the following tests: Rivermead Behavioral Memory Test (RBMT) (Wilson et al., 1989; Yassuda et al., 2010); Trail Making Test (TMT) (Spreen and Strauss, 1998; Campanholo et al., 2014); Digit Span (DS) (Wechsler, 1997; Nascimento, 2004), FAS-COWA (Spreen and Strauss, 1998); Rey Auditory Verbal Learning Test (RAVLT) (Rey, 1964; Malloy-Diniz et al., 2007), and Rey-Osterrieth Complex Figure (ROCF) (Osterrieth, 1944; Oliveira et al., 2004).

MCI patients were selected based on the criteria of Albert et al. (2011), which cover: (1) cognitive complaint, preferably confirmed by a relative or close person; (2) objective cognitive impairment in one or more cognitive domains, with performance below the expected for peers in the same age range and educational level; (3) not being demented, with preserved simple activities of daily living.

This group was further subdivided into aMCI (evidence of episodic memory impairment) and naMCI (evidence of impairment in cognitive functions other than episodic memory). The inclusion criteria for the MCI subgroups were performance at least 1.5 SD below the mean score on one function and/or between 1 and 1.5 SD below the mean score in two neuropsychological tests of the same function (Petersen, 2004).

All patients diagnosed as MCI had their blood counts, biochemical and lipid profile, vitamin B12, folic acid, syphilis serology, and thyroid function tested and performed magnetic resonance imaging studies to rule out metabolic, infectious, and vascular etiologies for cognitive decline.

Participants with no previous complaints of cognitive decline and who performed normally on cognitive tests were allocated to the GC.

An experienced multidisciplinary team that included neurologists, geriatricians, neuropsychologists, and speech-language pathologists gave the final diagnosis for the groups.

The exclusion criteria for all groups were: being illiterate; having a health condition that could preclude the realization of neuropsychological tests (such as, non-correctable vision or hearing impairment); history or evidence of cerebrovascular injury, non-AD dementias, and other neurologic/psychiatric conditions that might impair cognition (such as, severe traumatic brain injury, epilepsy, depression, bipolar disorder, and psychosis).

The local Ethics Committee approved the study under protocol number CEP 3.318.162, and all participants or their proxies signed a consent form before enrollment in the study.

Instruments

After cognitive evaluation, the individuals were submitted to a protocol designed to assess inferential, semantic, and verbal episodic memory abilities.

Textual inference comprehension was assessed using The Implicit Management Test (IMT) (in the original French version, *La Gestion de l'Implicite*) (Duchêne May-Carle, 2000), adapted to Brazilian Portuguese (Silagi et al., 2014). The test evaluates the ability to comprehend inferences during reading activities and is designed to assess adult subjects with cognitive and/or communication complaints. The test was applied in a reduced-version containing ten texts consisting of short stories involving two people or describing a verbal interaction; individuals must read and answer three questions for each text. The only admissible answers are: "Yes", "No", or "I cannot answer." The texts contain explicit and implicit information, which is necessary for the correct interpretation during reading. The texts were available for the patients to consult while they answered the questions.

Questions regarding the texts are subdivided into five categories that require different types of inferential reasoning: (1) explicit–questions are answered by using information supplied in the text; no inference-making needed; (2) logical–questions are answered by using a cause-effect relationship with the information provided in the text, through formal reasoning; (3) distractor–questions that have "I cannot answer" as the only possible correct answer, as the information required for an appropriate answer cannot be extracted from the text either explicitly or implicitly; (4) pragmatic–questions are answered by using context and previous experience; and (5) "other"–questions require both logical and pragmatic reasoning. Examples of the different types of questions can be seen in **Table 1**.

Semantic tests included: (a) the Word-Picture Matching (WPM) Test (Weintraub, 2000). This test evaluates spoken word recognition and assesses the frequency of semantic errors in word comprehension. The stimuli consist of five displays, each one containing pictures of four objects that are semantically related. Each display is presented four times (once for each picture as the target) in a total of 20 trials. The presentation order of displays is pseudo-randomized so that no four-picture display appears in sequential trials. One point is given for each correct response given at the first attempt, which allows a maximum score of 20—"I do not know" is considered as an incorrect response; (b) the Semantic Associates Test (SA) (Weintraub, 2000). This test comprises16 displays containing three items presented as two pairs (one target and one distractor), which evaluates the functional, contextual and categorical relationship between the items. The individual is asked to look at the two pairs of pictures in each display (semantically related or non-related) and point to the matching set. For example, in a display containing the pairs: *sweater-blanket/sweater-pillow*, the correct answer is *sweater-blanket* (functional relationship); for the two pairs *sweater-chest/sweater-workbench*, the correct answer is *sweater-chest* (contextual relationship). One point is given for each correct match choice, which allows a maximum score of 16.

To assess verbal and non-verbal episodic memory, we used the Three-Words Three Shapes Test (3W3S) (Weintraub, 2000). The participants are asked to copy three words (*pride, hunger*, *station*) and three geometric shapes displayed on a sheet of paper and then reproduce them from memory to assess immediate and delayed recall (after five minutes, during which the individuals performed a task of picture description). The test provides scores for verbal memory (immediate and delayed recall for words; WImR and WDR, respectively) and non-verbal memory (immediate and delayed recall for shapes). We considered only the verbal memory scores in this study: each word correctly retrieved in each condition is scored as five, giving a total score of 15. The score of five for each correct word allows for deductions due to adding, subtracting, or substitution errors in writing.

Statistical Analysis

Intergroup comparison of means for demographic and clinical continuous variables was performed through one-way analysis of variance with Bonferroni's post-test. The Chi-Squared test was used to assess intergroup differences in sex distribution. Mixed-effects linear regression models were used to (a) determine the best predictors for IMT total scores and scores in each question subtype in the total sample, using such scores as dependent variables, schooling and scores on WPM, SA, subtests of the 3W3S as fixed-factors, and within-subjects differences in performance as a random effect; (b) determine the best predictor for IMT in each diagnostic subgroup using diagnosis as the dependent variable, schooling, and scores on WPM, SA, subtests of the 3W3S as fixed-factors, and within-subjects differences in performance as a random effect. Schooling was tested in interaction with all variables. The Akaike information criterion (AIC) was employed to compare the models and choose the best among them, which were those with the smaller AIC values. Model estimations were performed using restricted maximum likelihood (REML). Significance levels were set at $p < 0.05$ values. We used the SPSS® Statistics software version 25 for all analyses.

RESULTS

The demographic and clinical characteristics of the sample are shown in **Table 2**. There were no differences between groups

TABLE 1 | Types of questions in the implicit management test.

Type of question	Example
Explicit	Nadia called Lucas and told him: "My goodness, have you seen the time?", and Lucas answered: "Yes, I know, but I cannot find my car keys." *Has Lucas lost the keys to his car?*
Logical	My neighbor's cat never meows, except when it has not eaten for a long time. Today, I heard the cat meowing all morning. *Did my neighbor feed her cat this morning?*
Pragmatic	After the weather report, Brigitte said to herself: "I must not forget my umbrella tomorrow." *Does Brigitte like getting wet?*
Other	Peter says: "It costs a lot of money to go to Canada; I cannot go there right now." *Does Peter have much money right now?*
Distractor	Rose says to Suzanne: "Stop eating or you will put on weight!" and Suzanne replies: "So what, men like it." *Is Rose married?*

TABLE 2 | Demographic variables and performance on tests according to diagnostic group.

Variable	controls ($n = 34$)	aMCI($n = 23$)	naMCI ($n = 42$)	p-value	Multiple comparisons $p < 0.05$
Age (years)	70.8 (7.8)	70.6 (6.7)	69.7 (6.8)	0.768	NA
Schooling (years)	14.4 (3.0)	11.6 (4.7)	11.6 (4.7)	0.088	NA
Sex *F*	20	11	20	0.749	NA
M	14	12	22		
IMT	25.1 (2.4)	20.0 (7.3)	22.6 (4.2)	<0.001	CG ≠ aMCI, naMCI
Pragmatic	7.8 (1.2)	7.2 (1.9)	7.8 (1.4)	0.533	NA
Distractor	6.4 (0.8)	5.5 (1.7)	5.3 (2.2)	0.072	NA
Explicit	3.7 (0.4)	3.3 (0.9)	3.4 (0.8)	0.448	NA
Logical	4.1 (0.8)	3.3 (1.2)	3.5 (1.3)	0.044	CG ≠ aMCI
Other	3.3 (1.2)	2.8 (1.4)	2.6 (1.2)	0.115	NA
WPM	19.9 (0.1)	19.9 (0.0)	19.9 (0.2)	0.154	NA
SA	15.8 (0.5)	15.9 (0.8)	15.5 (1.5)	0.628	NA
3W3S					
WImR	13.9 (2.4)	12.3 (3.7)	10.3 (4.9)	0.004	CG ≠ naMCI
WDR	14.4 (1.9)	11.8 (5.5)	12.5 (3.6)	0.016	CG ≠ aMCI, naMCI

Data displayed as Mean (SD) except for sex (number of individuals); aMCI, amnestic mild cognitive impairment; naMCI, non-amnestic mild cognitive impairment; F, female; M, male; IMT, Implicit Management Test; WPM, Word-Picture Matching; SA, Semantic Associates; 3W3S, Three Words Three Shapes; WImR, Words Immediate Recall; WDR, Words Delayed Recall; NA, not applicable.

on age and sex. The complete neuropsychological evaluation is displayed in the **Appendix**.

The performance of the sample in the IMT, WPM, SA, and 3W3S tests is shown in **Table 2**. MCI patients performed worse than controls in the IMT total score; aMCI patients performed worse than controls in "logical" questions, though in the margin of statistical non-significance. In the 3W3S test, MCI patients performed worse than controls in WImR. There were no intergroup differences in the WPM and SA tests; aMCI and naMCI patients performed similarly in all tests.

Mixed-effect regression models showed that the best predictors for total IMT performance for the whole sample were schooling and the verbal episodic memory tasks; however, predictors changed according to the type of question: SA for pragmatic questions, schooling, SA and WDR for distractor questions, WPM for explicit questions, and schooling for logical questions. There were no predictors for "other" questions (**Table 3**). We also found different main predictors for inference-making performance across diagnostic groups. In the control group, schooling and WPM were the best predictors, with a trend for SA. The best predictor was verbal memory in the aMCI group, while in the naMCI group, inference-making skills were associated with semantic tasks (WPM and SA) (**Table 4**).

DISCUSSION

Inferential processing is a poorly explored ability in MCI. It is considered a complex linguistic skill, mainly in the context of text comprehension, as it depends on both linguistic and domain-general cognitive abilities. As it is a demanding skill, we hypothesized that the ability to understand inferences might already be impaired in patients with MCI and that possible changes in basic language processing and other cognitive functions could interfere with this ability. Thus, the aim of this study was to compare the performance of patients with MCI to a sample of healthy elderly in a textual reading task that requires the understanding of different types of inferences, as well as verifying whether semantic knowledge and episodic verbal memory would be predictors of this ability.

Performance on the Inference Comprehension, Semantic, and Episodic Verbal Memory Tasks

Regarding the performance of the groups in the inference comprehension test (IMT), we verified that the MCI group showed worse performance than controls in the total score. The aMCI group performed poorer than controls in "logical"

TABLE 3 | Mixed-effect linear regression for predictors of IMT scores according to the type of question in the whole sample.

Type of question/predictor	Estimated coefficient	SE	*F*	*t*	*p-value*	CI 95%	
						Lower bound	Upper bound
Total							
Schooling	0.35	0.10	10.95	3.31	0.001	0.14	0.57
WImR	0.28	0.10	7.26	2.69	0.009	0.07	0.49
WDR	0.31	0.12	6.82	2.61	0.011	0.07	0.56
Pragmatic							
SA	0.46	0.14	10.43	3.23	0.02	0.17	0.74
Distractor							
Schooling	0.15	0.40	14.43	3.79	<0.001	0.07	0.23
SA	0.39	0.14	7.28	2.70	0.008	0.10	0.68
WDR	0.11	0.04	7.44	2.72	0.008	0.03	0.20
Explicit							
WPM	1.29	0.39	10.81	3.28	0.001	0.50	2.07
Logical							
Schooling	0.06	0.02	5.60	2.36	0.02	0.01	0.12
WDR	0.08	0.03	6.68	2.58	0.01	0.02	0.15

Dependent Variable, Implicit Management Test (IMT); Standard Error; CI, Confidence Interval; WImR, Words Immediate Recall; WDR, Words Delayed Recall; SA, Semantic Associates; WPM, Word-Picture Matching+.

TABLE 4 | Mixed-effect linear regression for predictors of IMT scores by diagnostic group.

Group predictors	Estimated coefficient	SE	*F*	*t*	*p-value*	CI 95%	
						Lower bound	Upper bound
CG							
Schooling	0.44	0.14	9.76	3.12	0.00	0.15	0.74
WPM	−8.54	2.91	8.59	−2.93	0.00	−14.52	−2.55
SA	1.80	0.88	4.19	2.04	0.05	0.00	3.61
aMCI							
WImR	1.13	0.38	8.81	2.96	0.01	0.31	1.94
naMCI							
WPM	5.50	2.27	5.85	2.41	0.02	0.89	10.11
SA	1.19	0.38	9.69	3.31	0.00	0.41	1.97

Dependent Variable, Implicit Management Test (IMT); aMCI, amnestic mild cognitive impairment, naMCI, non-amnestic mild cognitive impairment; SE, Standard Error; CI, Confidence Interval; WPM, Word-Picture Matching; SA, Semantic Associates; WImR, Word Immediate Recall.

questions but with a *p*-value approaching the limit of statistic non-significance. The aMCI and naMCI groups performed similarly regarding total scores and subtypes of questions.

Few studies in the literature have addressed the performance of individuals with MCI in inference comprehension tasks. We found three studies that showed similar results about the difficulty of understanding inferences in subjects with MCI. Schmitter-Edgecombe and Creamer (2010) verified that aMCI subjects produced fewer inferences in a story comprehension task than controls and had more difficulties explaining story events and using preliminary text information to support inference generation. Similarly, Gaudreau et al. (2015) found that MCI participants were impaired in identifying ironic or sincere stories that required mental inference capacities, compared to control subjects. We found only one study that compared aMCI and naMCI on the ability to understand inferences. Silagi et al. (2021) evaluated a different cohort of MCI individuals with the same test used in our study (IMT). They found that MCI patients had difficulty understanding inferences compared to controls and the accuracy analyses showed that the total score in the IMT provided good sensitivity and specificity in discriminating MCI from normal individuals. However, they were also unable to differentiate the MCI subgroups from each other in the task.

As for the semantics tasks, all groups showed similar performance in the WPM and SA tests. We observed a ceiling-effect regarding performance in the WPM task in all groups. Semantic impairment has been widely reported in MCI in tasks ranging from verbal fluency, naming, and sentence comprehension (Emery, 2000; Balthazar et al., 2008; Rinehardt et al., 2014; Silagi et al., 2015). However, studies show that

the performance on isolated word comprehension and semantic association (as required in WPM and SA) are usually preserved in the patients until the early stages of AD, that is, the semantic impairments in MCI are associated with difficulty in lexical or lexico-phonological search, and in complex tasks involving a more fine-grained semantic decision, with basic semantic knowledge preserved (Ortiz and Bertolucci, 2005; Barbeau et al., 2012; Kirchberg et al., 2012; Tsantali et al., 2013; Venneri et al., 2018).

On the other hand, the verbal episodic memory tests (3W3S) were able to differentiate between controls and MCI as well established in the literature (Ding et al., 2019; Wasserman et al., 2019; Abraham et al., 2020; Silva et al., 2020).

Predictors of the Inference Comprehension Ability

Our mixed-effect model showed that schooling and verbal episodic memory tasks were the best predictors for inference-making performance in the whole sample. Regarding the predictors of the ability to understand inferences in different diagnostic groups, we found distinct profiles in healthy controls and MCI groups.

In the control group, schooling and WPM were the best predictors, with a trend for SA. A study with healthy subjects showed a strong effect of education on inference comprehension; individuals with higher educational levels had better performance than individuals with a lower educational level on the total score and across all question types of the inference test (Silagi et al., 2014). The authors discussed that schooling plays an essential role in developing several cognitive-linguistic skills, which support inferential reasoning (Ardila, 2005).

The influence of semantic knowledge was also proven in the ability to understand texts with inferences in healthy subjects (Yeari and van den Broek, 2015, 2016; Dong et al., 2020). Semantic integration is essential for inference making, and it occurs as a result of the activation of the semantic network that produces access to a word's meaning with consequent co-activation of words and meanings of the same semantic category. Inference-making is based on the existence of strong semantic associations with specific ideas conveyed by speech or text. Yeari and van den Broek (2015) found that robust associations between textual information and personal background knowledge result in a greater probability of the information being activated. This activation of inference from background knowledge is a function of the number and strength of semantic constraints imposed by the evoking text.

In the aMCI group, the best predictor of inference comprehension was verbal memory. The influence of episodic memory on the ability to understand inferences is well established and addressed by previous studies in subjects with MCI. Schmitter-Edgecombe and Creamer (2010) reported impairment in the production of inferences in MCI patients associated with poorer delayed verbal memory abilities. The authors argue that episodic memory influences inference comprehension because it helps create causal connections between different text parts and establish an integrated story. Similarly, Gaudreau et al. (2015) showed that the poorer comprehension of mental state inferences in the MCI population was correlated with episodic memory and executive functions difficulties. Finally, Silagi et al. (2021) found correlations between the scores in the inference comprehension task and RAVLT in an aMCI group, presupposing that the impairment in inference comprehension observed in this group was related to episodic memory failure. In contrast, they found correlations between the total test score and the TMT-A in the naMCI group, associating the poor inference comprehension in this group with failure in attention and executive functions (which we did not include in our mixed-effect models).

In our results, in the naMCI group, inference-making skills were associated with the semantic tasks (WPM and SA). According to Graesser et al. (1994), some types of inferences are built when long-term memory knowledge structures are activated and incorporated into the representation of the text's meaning. Van Dijk and Kintsch, 1983 establishes the relationship between inferential processing and how information is stored, highlighting that long-term memory is organized in semantic bundles, hierarchically ordered. Lastly, Rumelhart (1980) defines schema as the data structure for representing concepts stored in memory. Schemas represent knowledge about concepts, events, and actions. According to the author, the schema underlies a concept stored in memory, which generates meaning. Schemas allow access to information stored in memory while reading and building inferences.

As for the different types of IMT questions, we hypothesize that the main predictors reflect the nature of reasoning necessary to successfully identify and extract the information in order to answer the questions related to the texts:

(a) pragmatic inferences, which are based primarily on "world knowledge" (the non-linguistic information that helps a reader or listener interpret the meanings of words and sentences) were associated with SA. This task requires the evaluation of functional, contextual, or semantic-category relations between two words (presented as pictures), thus, assessing the integrity of the semantic network.
(b) distractor inferences were associated with schooling, SA, and verbal memory. This type of inference requires that the individual move from the interpretative approach to acknowledge that the only possible answer is "I cannot answer" since the information required for an appropriate answer cannot be extracted from the text either explicitly or implicitly.
(c) explicit inferences were associated primarily with verbal memory. These questions are answered using information supplied in the text; no inference-making is needed.
(d) logical inferences were associated with educational level. These questions are answered by using a cause-effect relationship with the text's information, employing formal reasoning.

This study belongs to a series in which we explore high-demanding language abilities, including inferential processing (both textual and visual) in the normal aging-AD continuum and stroke patients (Silagi et al., 2014, 2018, 2021). Based on

previous results in normal individuals and MCI patients, we traced some variables influencing performance in the IMT, including executive functions and episodic memory (Silagi et al., 2014, 2021). We then decided to proceed with our investigation focusing on the role of semantic abilities in inference-making by employing the WPM and SA tasks. An interesting finding in our study was that by conducting a complementary analysis of the "justifications" (that is, how the stimulus word "matched" the individual's response) in the SA task, we observed that many patients could not explain it or provided nonsense explanations, despite making the correct choice (data not shown). We believe that these observations point to a subtle impairment of semantic processing, albeit not sufficient to prevent a correct choice. We intend to explore these findings in subsequent studies.

This study has some limitations: its cross-sectional design and the need for a larger sample to include a higher number of variables in our predictive model. The latter was precluded by the Covid pandemic that impeded us from proceeding with the enrollment of patients. Another limitation is that, given the ceiling-effect observed in WPM, we could have obtained better results regarding the impact of this semantic ability on inference-making should we have used a more demanding task. More studies, preferably longitudinal, are needed to confirm the results.

FINAL COMMENTS

Individuals with MCI have difficulties in understanding inferences during reading. It was possible to differentiate MCI patients from cognitively healthy individuals, but it was not possible to differentiate aMCI from naMCI. Despite this, different predictors seem to influence the performance of groups in this skill. The best predictors for inference-making were verbal memory in the aMCI and semantic tasks in the naMCI group. The results confirmed that failure to perform textual inferences may be present in MCI and showed that different cognitive skills like semantic knowledge and verbal episodic memory are necessary for inference-making. It is also essential to understand the interaction among several basic cognitive abilities that, together, allow for the accomplishment of high-demanding cognitive tasks, such as, inference-making, in order to guide rehabilitation efforts according to the specificities of each patient's deficits.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee for the Analysis of Research Projects (CAPPesq) from Hospital das Clínicas, School of Medicine, University of São Paulo. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. MM: collected the language data and wrote part of the paper. AB: assisted with collection of language data. MC: collected neuropsychological data. MR: responsible for clinical evaluation, diagnosis, and carried out the statistical analysis. OF: supervised the data collection. MS: wrote the first draft of the manuscript. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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APPENDIX

TABLE A1 | Neuropsychological assessment of the sample.

Test	Control ($n = 34$)	aMCI($n = 23$)	naMCI ($n = 42$)	p-values	Multiple comparison ($p < 0.05$)
MoCA	27.6 (1.7)	23.1 (4.0)	24.4 (2.7)	<0.0001*	CG ≠ tMCI
GDS	3.8 (4.7)	10.1 (6.8)	7.8 (5.8)	<0.0001*	CG ≠ tMCI
L and B	26.6 (1.4)	25.7 (2.1)	26.1 (2.5)	0.370	NA
RBMT					
Screening	10.2 (1.7)	8.0 (2.6)	9.4 (1.9)	0.001*	CG ≠ aMCI
Profile	21.7 (2.4)	17.3 (4.4)	19.8 (3.1)	< 0.0001*	CG ≠ tMCI
TMT–A					
Errors	0 (0)	0.1 (0.5)	0.1 (0.4)	0.119	NA
Time	42.4 (13.2)	62.4 (35.7)	58.4 (25.6)	<0.0001*	CG ≠ tMCI
TMT–B					
Errors	0.4 (0.7)	1.2 (1.7)	1.1 (1.3)	0.119	NA
Time	87.7 (31.9)	143.3 (95.3)	138.0 (91.4)	0.005*	CG ≠ tMCI
Stroop					
Errors	1.3 (2.6)	2.2 (2.8)	1.6 (2.1)	0.567	NA
Time	29.2 (8.6)	40.1 (14.0)	37.3 (13.0)	0.005*	CG ≠ tMCI
DS					
Forward	9.0 (2.2)	8.3 (2.0)	7.6 (2.0)	0.059	NA
Backward	6.7 (1.4)	4.8 (1.8)	4.7 (1.9)	<0.0001*	CG ≠ tMCI
FAS-COWA	42.1 (8.5)	35.2 (11.1)	35.5 (11.5)	0.015*	CG ≠ tMCI
RAVLT					
Recall	10.2 (2.1)	4.5 (2.7)	7.9 (2.6)	<0.0001*	CG ≠ tMCI; aMCI ≠ naMCI
Total	47.9 (6.7)	33.2 (7.7)	38.5 (7.8)	<0.0001*	CG ≠ tMCI
ROCF					
Copy	41.0 (36.0)	36.5 (20.6)	31.9 (5.4)	0.001*	CG ≠ tMCI
Recall	20.7 (15.3)	17.86 (18.6)	13.4 (5.7)	0.001*	CG ≠ tMCI

Data presented as mean (SD); aMCI, amnestic mild cognitive impairment; naMCI, non-amnestic mild cognitive impairment; tMCI, total mild cognitive impairment (aMCI + naMCI); MoCA, Montreal Cognitive Assessment; GDS, Geriatric Depression Scale; L and B, Lawton and Brody Scale for Daily Life Activities; RBMT, Rivermead Behavioral Memory Test; TMT, Trail Making Test; DS, Digit Span; FAS-COWA, Controlled oral word association–letters F, A, S; RAVLT, Rey Auditory Verbal Learning Test; ROCF, Rey-Osterrieth Complex Figure; NA, not applicable.

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CASE REPORT
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Case Report: Barely Able to Speak, Can't Stop Echoing: Echolalic Dynamic Aphasia in Progressive Supranuclear Palsy

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The diagnostic criteria for progressive supranuclear palsy (PSP) incorporate two speech-language disturbances (SLDs), non-fluent/agrammatic primary progressive aphasia and progressive apraxia of speech, but overlook the inclusion of other SLDs, including dynamic aphasia (DA). Thus, there is a need to reappraise the broad spectrum of SLDs in PSP to include other presenting phenotypes. Here we report findings from the study of two elderly patients with PSP presenting with DA and irrepressible echolalia. Both patients had markedly impoverished verbal production, but their performance in other tasks (repetition and naming) and auditory comprehension were preserved or only mildly impaired. Experimental tests of DA revealed impaired word and sentence generation in response to verbal and non-verbal stimuli. Additional language and cognitive testing revealed different types of echolalia (mitigated, automatic, and echoing approval) as well as impaired inhibitory control and social cognition (mentalizing). Both patients had negative neuropsychiatric alterations (i.e., apathy, aspontaneity, and indifference/emotional flatness). Brain magnetic resonance imaging in both patients showed atrophy of the midbrain tegmentum and superior medial frontal cortex suggestive of PSP, yet further evaluation of the neural correlates using multimodal neuroimaging and neuropathological data was not performed. However, based on the already known neural basis of DA and echolalia in PSP and stroke, we suggest that, in the present cases, neurodegeneration in the midbrain tegmentum, superior medial frontal lobe, and caudate nucleus was responsible for DA and that decreased activity in these regions may play a permissive role for eliciting verbal echoing *via* disinhibition of the perisylvian speech-language network.

Keywords: dynamic aphasia, echolalia, progressive supranuclear palsy, primary progressive aphasia, inhibition deficits

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INTRODUCTION

The clinical features of speech-language disorders (SLDs) in primary progressive aphasias have recently been expanded to include echolalia (Ota et al., 2020), a hitherto forgotten language feature in these disorders (Torres-Prioris and Berthier, 2021). In the same line, the diagnostic criteria for SLDs in progressive supranuclear palsy (PSP) incorporate non-fluent/agrammatic primary progressive aphasia and progressive apraxia of speech (Boxer et al., 2017; Höglinger et al., 2017), yet overlooked alternate language phenotypes [e.g., dynamic aphasia (DA) and echolalia], which can also herald the onset of PSP (Ghika et al., 1995; Esmonde et al., 1996; Della Sala and Spinnler, 1998; Robinson et al., 2006, 2015; Rohrer et al., 2010; Perez et al., 2013; Fernández-Pajarín et al., 2015; Magdalinou et al., 2018). Therefore, it is essential to further delineate the broad spectrum of SLDs in PSP (Catricalà et al., 2019; Peterson et al., 2019) and in other degenerative non-PPA conditions (see Savage et al., 2021). In fact, the language profile of DA (specific deficits in the generation of novel verbal messages) (Luria and Tsvetkova, 1967) in PSP has been clearly delineated (Robinson et al., 2006, 2015), yet less well known is its relationship with concurrent echolalia (repetition of what has been heard) (e.g., Della Sala and Spinnler, 1998; Berthier et al., 2018a). Exploring this association is pertinent because the analysis of language and cognitive deficits in PSP may illuminate the predominant sites of heightened neurodegeneration. Language deficits in non-fluent/agrammatic primary progressive aphasia and progressive apraxia of speech related to PSP point to a predominant left perisylvian neurodegeneration (inferior frontal gyrus and posterior superior temporal gyrus) (Magdalinou et al., 2018) besides the rostral brainstem and basal ganglia involvement. It is also possible that echolalic DA in PSP may additionally involve the midline superior frontal cortex (Kleist, 1960; Ungvari and Rankin, 1990; Berthier, 1999; Rohrer et al., 2010; Perez et al., 2013). This topographical distribution of atrophic changes can account for impoverished speech production in DA, together with echolalia resulting from disinhibition of the mirror neuron system in the frontal and temporoparietal perisylvian cortex (Esmonde et al., 1996; Berthier et al., 2006, 2017, 2018a).

Here we report the findings from the study of two elderly PSP patients initially presenting echolalic DA. To gain further insight into the functional mechanisms underlying these language disorders, we evaluated these two patients with tests tapping language production deficits in DA (Robinson et al., 1998; Berthier et al., 2020). Other tests were also employed evaluating the permissive role of abnormal inhibitory control, social cognition (mentalizing), auditory comprehension, short-term verbal memory, echo awareness, and behavioral changes in the genesis of PSP-related echolalia (Berthier et al., 2017).

CASE DESCRIPTIONS

According to Movement Disorder Society criteria (Boxer et al., 2017; Höglinger et al., 2017) the two patients described below met the criteria for a diagnosis of *suggestive of PSP* (C1, PSP-SL) and their examination further provided helpful supplementary evidence (dysarthria, dysphagia, and midbrain tegmentum atrophy) that increased diagnostic confidence.

Patient 1 was a 71-year-old right-handed man presenting with a 4-year history of progressive decline in speech production. Two years after speech onset of speech production deficits, he suffered two falls and gradually developed motor slowness, difficulty turning over in bed, mild limb rigidity, and micrography. Neurological examination revealed reduced saccades in all directions, bilateral limb rigidity with reduced toe tapping, postural instability, and seborrhea. His family history was positive for Parkinsonism in several members. At the age of 50, his mother developed Parkinsonian symptoms with marked echolalia, eventually evolving into dementia. Two brothers of the patient were diagnosed with Parkinson's disease, and two maternal female cousins died from Parkinson's disease (autopsy was not performed). The patient's verbal production was slow, hesitant, and effortful with reduced phrase length and connective speech. Sentence construction and echolalic emissions occasionally sounded grammatically incorrect. For example, in response to the question "Do you have tremor?" the patient replied "Tremor? No need to have I." His spontaneous and responsive speech was continuously intermingled with echolalia, and his previously strong regional accent was replaced by a flat intonation devoid of emotional coloring (Berthier et al., 2015). Language initiation was extremely difficult, and the patient needed to stand up and move his right hand to start talking. At rest, he also had right-hand stereotypes. Auditory comprehension, repetition, and naming were preserved. Features consistent with PSP were confirmed with the Progressive Supranuclear Palsy Rating Scale (PSPRS) (Golbe and Ohman-Strickland, 2007; **Table 1**). A brain magnetic resonance imaging (MRI) showed moderate cortical, subcortical, and midbrain tegmentum atrophy (**Figure 1**). Treatments with carbidopa/levodopa (25/250 mg/tid) and amantadine (300 mg/bid) were unhelpful.

Patient 2 was a 73-year-old right-handed woman with a 5-year history of progressive decline in verbal communication, characterized by sparse and slow speech production. She did not speak unless addressed but produced stereotyped phrases, generated lengthy monologs, while echoing most of what she heard and completing simple open-ended sentences. It was also noticed that her regional accent was reverted to a previous variant learned during childhood (Roth et al., 1997). Her auditory comprehension and naming abilities were mildly impaired, but repetition was virtually intact. Two years after showing first deficits in spoken speech production, she suffered four falls in 1 year and developed apathy, bradyphrenia and emotional incontinence displaying uncontrollable episodes of crying and laughing. Neurological examination disclosed slow, hypometric saccades, decreased rate blink, bilateral limb rigidity with impaired finger and toe tapping, as well as tremor and bilateral hand grasping. She also showed neck rigidity, wide-based gait, postural instability, and problems arising from a chair and shortcomings on sitting down. Features consistent with PSP were revealed with the PSPRS (Golbe and Ohman-Strickland, 2007; **Table 1**).

TABLE 1 | Progressive supranuclear palsy rating scale (PSPRS).

PSPRS	Patient 1		Patient 2	
	Score	Abnormal exam	Score	Abnormal exam
History	4	Withdrawal, falls (<1 per month), urinary incontinence (few drops)	10	Withdrawal, dysphagia, slow dressing, falls (1–4 per month), and sleep difficulty
Mental exam	3	Bradyphrenia	9	Disorientation, bradyphrenia, emotional incontinence, and grasping behavior
Bulbar exam	1	Dysarthria	1	Dysphagia
Ocular motor exam	5	Voluntary upward, downward, and left and right saccades	2	Slow, hypometric saccades, decreased rate blink
Limb exam	3	Limb rigidity, toe tapping bilaterally	5	Limb rigidity, impaired finger and toe tapping, and tremor
Gait/midline exam	2	Arising from a chair	7	Neck rigidity, arising from a chair, wide-based gait, postural instability, awkward on sitting down
Total score	18		34	

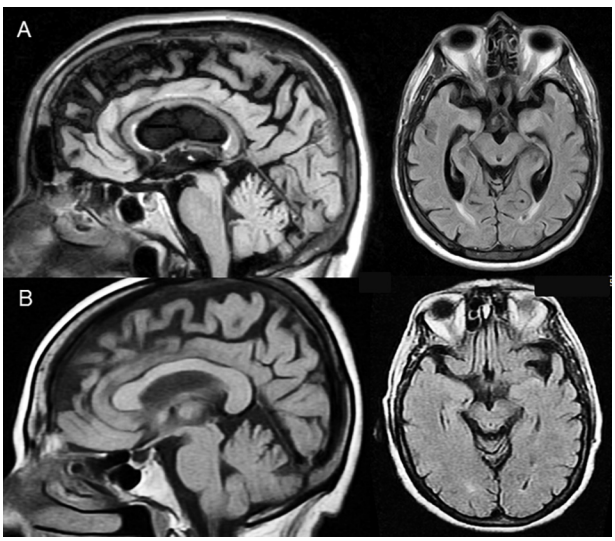

FIGURE 1 | Midsagittal (FLAIR sequences) slices show selective midbrain tegmentum atrophy with "Hummingbird sign" (flattening of the superior aspect of the midbrain tegmentum) in both patients. Axial slices (FLAIR sequences) additionally show a "Mickey Mouse sign" (reduction of the anteroposterior midline midbrain diameter) in patient 1 **(A)** and an incipient "Morning Glory sign" (loss of the lateral convex margin of the midbrain tegmentum) in patient 2 **(B)**, all of which are highly suggestive of PSP. Atrophy is also noted in the superior medial frontal cortex affecting the pre-supplementary motor area and the supplementary motor area, but the cingulate gyrus and the orbitofrontal cortex are preserved. Moderate atrophy of the body of the corpus callosum is seen in patient 1.

Family history was negative for movement disorders or dementia. A brain MRI showed moderate cortical, subcortical, and midbrain tegmentum atrophy (**Figure 1**). Treatments with carbidopa/levodopa (25/250 mg/tid) and amantadine (300 mg/bid) were unhelpful.

The two patients provided written informed consent after receiving a complete description of the study. Written informed consent for publication of any potentially identifiable data or images was also obtained. The Institutional Review Board of the University of Malaga approved this study.

TESTING OF COGNITION AND LANGUAGE

Methods

General cognition was evaluated with the Mini Mental State Examination (MMSE) (Folstein et al., 1975), and the Frontal Assessment Battery (FAB) was used to characterize the dysexecutive phenotype (Slachevsky et al., 2004). The profile and severity of aphasia was examined with the Western Aphasia Battery-Revised (WAB-R) (Kertesz and Raven, 2007). Analysis of informativeness in connected speech during picture description of the WAB-R was based on correct information units and related parameters using a rule-based scoring system (Nicholas and Brookshire, 1993). Phonemic fluency and semantic fluency were also evaluated (Borkowski et al., 1967; Kertesz and Raven, 2007).

Results

Results on cognition and language are shown in **Table 2**. Scores on the MMSE were normal in patient 1 and moderately impaired in patient 2. Both patients were impaired on the FAB, particularly on verbal fluency and motor series. On the WAB-R, both patients scored in the aphasic range (Aphasia Quotient of the WAB-R $\leq$ 93.8/100) showing a profile of transcortical motor aphasia (a profile comparable to DA). Analysis of connected speech showed reduced fluency and informativeness as well as pauses and perseverations. Both patients had marked reductions in phonemic and semantic fluencies.

TESTING OF DYNAMIC APHASIA

The clinical diagnosis of DA was established with the WAB-R (Kertesz and Raven, 2007) on the basis of reduced propositional speech with relative preservation or mild impairment of

TABLE 2 | Testing of cognition and language.

	Patient 1	Patient 2
Mini Mental State Examination (max.: 30)	28	21
Frontal Assessment Battery (FAB)		
FAB global score (max. = 18)	11	8
Similarities (max. = 3)	2	1
Verbal fluency (max. = 3)	0	0
Motor series (max. = 3)	0	0
Conflicting instructions (max. = 3)	3	1
Go-No-Go (max. = 3)	3	3
Prehension behavior (max. = 3)	3	3
Western Aphasia Battery-Revised (WAB-R)		
Fluency (max. = 10)	4	4
Comprehension (max. = 10)	9.0	8.7
Repetition (max. = 10)	9.4	9.6
Naming (max. = 10)	8.5	8.6
Aphasia Quotient (max. = 100)	79.8	77.8
Analysis of Picture Description (Picnic Scene – WAB-R)		
Duration of description (seconds)	200	40
Word count	86	60
Total Correct Information Units (CIU)	65	34
% CIU	76	57
Perseverations	0	2
Pauses (>3 s)	14	1
Phonological fluency (F.A.S.)	9	2
Semantic fluency (animals)	6 (<1% ile)*	6 (<1%ile)*

**Norms of healthy controls from Peña-Casanova et al. (2009a).*

comprehension, word and sentence repetition, as well as object naming (Luria and Tsvetkova, 1967; Lebrun, 1995). To better identify DA features, several experimental tests were also administered (see next).

Methods

The characteristics of DA were further evaluated using an adaptation of a series of experimental tests (see Robinson et al., 1998; Berthier et al., 2020). The scores obtained in our PSP patients in each of these tasks were compared to those obtained by a control group (five subjects) using a one-tailed Crawford's modified *t*-test. This test allows comparing outcomes from one or more individuals with results derived from small control samples (Crawford and Howell, 1998; Crawford and Garthwaite, 2002; Crawford et al., 2010). The following tests were administered: (A) generation of a single word to complete a sentence; (B) generation of a sentence from a single word; (C) generation of a sentence from a given sentence context; (D) generation of a sentence from a single picture; (E) generation of a sentence given a pictorial scene; (F) generation of sentences from a pictorial scene, "what might happen next?"; and (G) story generation from a pictorial context.

Results

Both patients were impaired in all experimental DA tests (**Table 3**). The two patients were mildly impaired when a single response was strongly suggested by the sentence frame (high constraint frames in test A), but even stronger impaired in generating words, and phrases when cued by a sentence frame allowing several response possibilities (low constraint frames in test A and tests B and C). They also showed abnormal response generation when the stimuli were non-verbal (pictures or pictorial scenes) (tests D, E, F, and G). It was noteworthy that on performing verbal tests (A, B, and C), both patients always automatically echoed the stimulus sentence first, followed by mitigated echolalia (e.g., test C, stimulus: "My cousin eats apples"; patient's 1 response: "*apple, your cousin eats apples*"). Automatic echolalia was also frequently heard (e.g., test C, stimulus: "the child paints a flower"; patient 1 response: "*the child paints a flower*") and several instances of self-contradictory responses (echoing approval). For instance, on replying to the question "Are you tired?" patient 1 replied: "*Yes, I'm not tired!*" Similarly, on completing the open-ended frame of test A: "It's good to be…," patient 2 stated "*tired, no! it's not good to be tired.*" Both patients produced many recurrent verbal perseverations of words and phrases.

MULTIDIMENTIONAL TESTING OF ECHOLALIA

Methods

The presence of different types of echolalia was elicited in two different contexts: amid a casual conversation and during the administration of WAB-R subtests (spontaneous speech, comprehension, repetition, and naming). The recent literature suggests that other cognitive domains, such as inhibitory control, social cognition (mental state attribution), auditory comprehension, auditory-verbal short-term memory, and awareness, may be dysfunctional in patients with echolalia (Berthier et al., 2017). Therefore, these domains were specifically evaluated in both patients. First, to test inhibitory control, the accuracy and latency in performing the Hayling Sentence Completion Test (HSCT) (Burgess and Shallice, 1996; Pérez-Pérez et al., 2016) were measured through *response initiation* (part A—complete an open-ended sentence with a related word) and *response inhibition* (part B—complete an open-ended sentence with an unrelated word). Moreover, since severe inhibition deficits in part B of the HSCT were evident in both patients (see section "Results" and **Table 4**), this part was administered using three different strategies to overcome inhibition failures (Robinson et al., 2016). Both patients were informed that after hearing a sentence frame, they needed to look around the room and say aloud the name of an object unrelated to the sentence meaning (strategy 1), or read a number (strategy 2) or a single word (strategy 3) written on a sheet of paper to complete it. Second, to test social cognition, the 10 histories of the Hinting task (HT) were used aimed to infer real intentions behind indirect speech utterances (mentalizing) (Corcoran et al., 1995; Gil et al., 2012). Third, auditory-verbal short-term memory and working memory were respectively evaluated with the forward and backward digit span test of the Wechsler Memory Scale (Wechsler, 2009). Fourth, the comprehension subtest of the WAB-R, resulting from the sum of Yes–No Questions, Auditory Word Recognition, and Sequential Commands subtests, was used to rate auditory comprehension. Finally, an informal interview was also performed to evaluate

TABLE 3 | Testing of dynamic aphasia with verbal and non-verbal stimuli.

Experimental testing					
	Patient 1	**Patient 2**	**Healthy controls (*n* = 5)**	**Statistics (Crawford's t, one tailed)**	
				Patient 1	**Patient 2**
Verbal tasks					
Test A. Generation of a single word to complete a sentence					
High constraint frames (max.: 20)	16 (0.80)	17 (0.85)	19.8 ± 0.48	−7.23; $p < 0.001$	−5.32; $p = 0.003$
Low constraint frames (max.: 20)	9 (0.45)	11 (0.55)	19.4 ± 0.89	−10.67; $p < 0.001$	−8.62; $p < 0.001$
Test B. Generation of a sentence from a single word (max.: 20)	11 (0.55)	6 (0.30)	19.4 ± 1.34	−5.72; $p = 0.002$	−9.13; $p < 0.001$
Test C. Generation of a sentence from a given sentence context (max.: 20)	1 (0.05)	5 (0.25)	19.6 ± 0.89	−19.08; $p < 0.001$	−14.97; $p < 0.001$
Non-verbal tasks					
Test D. Generation of a sentence from a single picture (max.: 10)	5 (0.50)	6 (0.60)	10 ± 0.0	—*	
Test E. Generation of a sentence given a pictorial scene (max.: 20)	9 (0.45)	4 (0.20)	19 ± 1.73	−5.27; $p = 0.003$	−7.91; $p < 0.001$
Test F. Generation of sentences from a pictorial scene. "what might happen next?" (max.: 20)	0 (0.0)	0 (0.0)	18.75 ± 0.96	−17.83; $p < 0.001$	−17.83; $p < 0.001$
Test G. Story generation from a pictorial context (max.: 10)	1 (0.10)	0 (0.0)	9.8 ± 0.45	−17.85; $p < 0.001$	−19.88; $p < 0.001$

**Test D shows no uncertainty, since standard deviation equals cero.*

TABLE 4 | Multidimensional Testing of Echolalia.

Tests	**Patient 1**			**Patient 2**		
	Accuracy/Proportion	**Latency (seconds)**		**Accuracy/Proportion**	**Latency (seconds)**	
		Correct	**Incorrect**		**Correct**	**Incorrect**
Hayling Sentence Completion Test (HSCT)						
Response initiation (part A) (max. = 15)	13 (0.87)	1.68	4.45	15 (1.0)	2.93	0
Response inhibition (part B) (max. = 15)	0 (0.00)	0	4.52	0 (0.00)	0	1.93
Strategies to Overcome Inhibition Failures						
HSCT – Overt object naming (max. = 15)	9 (0.60)	18.51	9.50	1 (0.06)	1.71	1.57
HSCT – Overt number reading (max. = 15)	14 (0.93)	4.63	4.78	1 (0.06)	1.40	2.81
HSCT – Overt word reading (max. = 15)	11 (0.73)	5.56	3.80	4 (0.27)	4.23	1.78

	Patient 1	**Controls***	**Patient 2**	**Controls***
Social cognition: Hinting Task (HT)	3	18.03 ± 1.39	5	18.03 ± 1.39
HT (questions: 2,3,6,7,9)	1	9.41 ± 0.85	2	9.41 ± 0.85
Auditory-verbal short-term memory				
Digit span				
Forward	4 (3th–5th%ile)**		4 (3th–5th%ile)	Not tested
Backward	3 (29th–30th%ile)		3 (29th–30th%ile)	Not tested
Auditory comprehension (WAB-R) (max = 10)	9		8.7	

**Controls from Gil et al. (2012). **Norms of healthy controls from Peña-Casanova et al. (2009b).*

the patients' awareness of echolalia and of other disinhibition disorders (hyperlexia and echographia).

Results

Echolalia was the most outstanding disinhibited behavior in both patients. On analyzing several subtests of the WAB-R, three echolalic subtypes emerged, namely mitigated echolalia (patient 1 = 19; patient 2 = 54), automatic echolalia (patient 1 = 16; patient 2 = 3), and echoing approval (patient 1 = 1; patient 2 = 1) (see the footnote[1]). Occasionally, when patient 1 produced mitigated

[1]Automatic echolalia refers to the immediate production of echoes in an impulsive, "parrot-like" manner. Mitigated echolalia refers to any language change in the

echolalia, part of the sentence was grammatically incorrect. All these subtypes of echolalia were also frequently observed in other verbal tasks (e.g., experimental DA tests), but no instances of ambient echolalia were heard. The result of the HSCT (accuracy and latency), used to test inhibitory control, is shown in **Table 4**. Average and perfect performances on the part A (response initiation) were found in patients 1 and 2, respectively, but their performance dropped dramatically on completing part B (response inhibition). To overcome inhibition failures found in part B of the HSCT [0.00], patient 1 used the three strategies [overt object naming (0.60), number reading (0.93), and word reading (0.73)] more efficiently, but at the expense of longer latencies (mean: 9.53 s). However, despite repeated explanations of how to perform the task, inhibition strategies were not useful in patient 2 [overt object naming (0.06), number reading (0.06), and word reading (0.27)]. On the HT, the two patients were markedly impaired in their ability to infer real intentions behind indirect speech utterances (mentalizing) (**Table 4**). Auditory short-term memory, working memory, and auditory language comprehension were slightly reduced in both patients. The two patients were fully aware of their echolalic behavior to the extent that both commented "I can't stop repeating what you say," but they had limited insight into other aspects of their disinhibited behavior (echographia, hyperlexia) (see below; see examples of echolalia in **Supplementary Material**).

Other disinhibited behaviors were also observed. Patient 1 showed echographia (automatic translation of visual and sometimes auditory stimuli into writing) on spontaneous writing (Pick, 1924; Berthier et al., 2006). Patient 2 showed poor control of inner speech manifested by impulsive figure naming presented during language testing and by describing aloud the actions of people in the room, even though she was not instructed to do so (Tanaka et al., 2000; Vercueil and Klinger, 2001). She commented "I can't remain silent. . . I feel obligated to speak and to describe what people do." She also incurred in long stereotyped monologs at night and occasionally read words impulsively written on commercial signs on the street (hyperlexia) (Suzuki et al., 2009). To unsuccessfully stop her comments, she frequently said, "Now, I shut up." Neither patient did show utilization behavior for common objects.

TESTING OF BEHAVIORAL ABNORMALITIES

Methods

Neuropsychiatric abnormalities are frequent in PSP, particularly apathy, depression, and sleeping problems (Kulisevsky et al., 2001; Gerstenecker et al., 2013). Negative symptoms and disinhibited behaviors were evaluated with the Frontal Behavioral Inventory (FBI) (Kertesz et al., 1997), whereas changes in the frequency and severity of five behaviors (eating and cooking, roaming, speaking, movement, and daily rhythm) were rated with the Stereotypy Rating Inventory (SRI) (Shigenobu et al., 2002). Both inventories were administered to a reliable caregiver.

Results

Both patients displayed negative symptoms. On the FBI, patient 1 obtained a low negative behavior score (6/36), showing mild changes in items evaluating apathy, indifference/emotional flatness, inflexibility, and comprehension and a moderate change in logopenia, but there were no signs of disinhibited behavior (disinhibition score: 0/36). On the same task, a higher negative behavior score (14/36) was found in patient 2, showing moderate changes in items rating apathy, aspontaneity, indifference/emotional flatness, inflexibility, disorganization, and personal neglect. Her disinhibition score was low (5/36) and pinpointed by perseverations and inappropriateness. On the SRI, patient 1 had stereotyped speaking (say the same things—frequency = 4; severity = 3), movements (right-hand stereotypes, touches persons, collects the same things—frequency = 4; severity = 2), and daily rhythm (fixed routines—frequency = 4; severity = 2). On the same inventory, patient 2 had stereotyped speaking (unable to remain silent, talks what she sees, talk about the same things—frequency = 4; severity = 3) and movements (sits on the same seat—frequency = 4; severity = 2).

DISCUSSION

The presenting phenotype of SLD in our PSP patients extends the boundaries of the recently developed PPA criteria (Boxer et al., 2017; Höglinger et al., 2017) to include DA. Furthermore, our study expands the phenotype of DA already described in PSP (Esmonde et al., 1996; Robinson et al., 2006, 2015; Magdalinou et al., 2018) by including different types of echolalia coexisting in the same patient (Ghika et al., 1995; Della Sala and Spinnler, 1998; Fernández-Pajarín et al., 2015). The latter finding is one strength of the present study because for the first time we reappraised echolalia using a multidimensional evaluation in an attempt to disentangle the relative contribution of various cognitive deficits underpinning such disinhibited verbal behavior (Berthier et al., 2017, 2018b).

Dynamic Aphasia

Language features in our patients were consistent with DA since they showed disproportionate deficit in both spontaneous speech and picture description, whereas the production of language in other verbal tests (repetition and naming) as well as auditory comprehension were average or slightly below average. Taking in consideration the characteristics of language and cognitive deficits found in our patients, we classify their DA as belonging to a *domain-general* subtype, a condition secondary to the involvement of frontal and subcortical areas (Robinson et al., 2006). Nevertheless, the production of ungrammatical sentences in both spoken language production and mitigated echolalia in patient 1 also suggests a *language-based* subtype (Robinson et al., 2006) due to involvement of the left anterior perisylvian language cortex (Magdalinou et al., 2018). Both patients showed severe impairments of volition and initiative, key features of

echoed emission for communicative purposes Echoing approval refers to the imitation of the affirmative or negative syntactical construction of questions or the intonation (Ghika et al., 1996; Berthier et al., 2018a).

DA associated to medial superior frontal lobe damage (Rohrer et al., 2010; Perez et al., 2013). Indeed, patient 1 felt forced to shake his right hand to initiate language production, a barely effective trick that unsuccessfully primed language activation in the left prefrontal cortex (Luria, 1970; Raymer et al., 2002). Similarly, patient 2 never initiated conversations or uttered words spontaneously. However, she impulsively described the actions performed by persons nearby or incurred in endless irrelevant monologs. Further support for the diagnosis of DA comes from the impaired performance of both patients on experimental DA tests, which disclosed widespread verbal generation deficits in response to verbal and non-verbal stimuli in comparison with healthy controls (Robinson et al., 1998, 2006, 2015). Such alterations may reflect the combination of the inability to generate verbal responses, impairments in energization (idea generation) (Barker et al., 2018), and in the generation of a fluent sequence of novel thoughts filled with perseverations (Robinson et al., 2006).

Our present findings suggest that neurodegeneration of the midbrain–basal ganglia–superior medial frontal cortex might be related to impaired discourse generation, thought sequencing, and verbal response selection on experimental DA tests (Magdalinou et al., 2018). The MRIs showed moderate atrophy in the superior medial frontal cortex and the midbrain tegmentum with the typical configuration described in PSP (Mueller et al., 2018) (see **Figure 1**). The atrophic changes in the pre-supplementary motor area and the supplementary motor area may account for the impairment in controlling shared representations (misunderstanding the intentions of others) (Frith and Frith, 2006; Brass et al., 2009) and evaluating outcomes (e.g., impaired reflection on one's own performance) (Passingham et al., 2010; Berthier et al., 2018a). Widespread white matter degeneration has been described in PSP (Zhang et al., 2016), and dysfunction of two white matter tracts traveling through the frontal substance may also play a role in language and cognitive deficits and in the behavior in PSP. Damage to the frontal aslant tract, a white matter bundle linking the superior medial frontal cortex with the pars opercularis of the inferior frontal gyrus, may be responsible for impaired verbal fluency and expression recognition of communicative intentions (Catani et al., 2013; Catani and Bambini, 2014). Moreover, the involvement of the frontostriatal tract, which connects the superior medial frontal cortex with the head of the caudate nucleus, could account for impaired initiation and preparation of speech movements and verbal fluency (Kinoshita et al., 2014) as well as of decreased motivation and goal-directed behavior (apathy) (Levy and Dubois, 2006; Lansdall et al., 2017).

Echolalia and Related Disinhibited Behaviors

On this ground, we also demonstrated that several types of verbal echoing (mitigated echolalia, automatic echolalia, and echoing approval)[2] occur in PSP-related DA and that they coexist with modality-specific utilization behaviors such as hyperlexia, hypernomia, and echographia (Ghika et al., 1995; Tanaka et al., 2000; Berthier et al., 2006). Altogether, these deficits may reflect a predominant disinhibition of the left perisylvian speech-language network, so that auditory and visual speech perceptions produce hyperexcitability of action-perception circuits including the perisylvian mirror neuron system involved in observation and speech imitation (Watkins et al., 2003; Berthier et al., 2006; Suzuki et al., 2009). There is evidence that modifying the neural activity of the pre-supplementary motor area and the supplementary motor area with non-invasive brain stimulation in healthy subjects induces echophenomena by impairing inhibitory control (Hsu et al., 2011; Finis et al., 2013). In complementary terms, stimulation over the left posterior inferior frontal gyrus facilitates speech repetition (Restle et al., 2012). Therefore, the integration of this information allows us to suggest that automatic activation within the left perisylvian speech-language network resulted from decreased tone in the superior medial frontal cortex and caudate nucleus. This functional uncoupling between areas may account for impaired inhibitory control and social cognition (mental state attribution) as well as for verbal and written echoing (echographia). Awareness of echolalia and related disinhibition activities was variable (preserved for echolalia, absent for hyperlexia and echographia).

One important limitation of our study was that we did not perform structural (voxel-based morphometry and diffusion tensor imaging) and functional neuroimaging (e.g., functional connectivity) necessary to examine the neural mechanisms underpinning echolalic DA. Therefore, further neuroimaging studies and histopathological identification of key areas with heightened neurodegeneration are required. Notice, however, that the main aim of our study was to examine in some detail the cognitive and behavioral mechanisms of DA and echolalia in PSP. Our language and cognitive findings suggest an imbalance between hypoactive midbrain–basal ganglia–superior medial frontal cortex circuits and hyperactive left inferior frontal and temporal superior gyri. To confirm this proposal, future studies may examine a dual dysfunctional mechanism, wherein damage to the midbrain, the superior medial frontal cortex, and the caudate nucleus decreases bottom-up processing causing DA and negative behaviors (apathy). Such damage, in turn, disrupts the top-down modulation of incoming multimodal stimuli in the left perisylvian speech-language network releasing echolalia and other disinhibited behaviors (Berthier et al., 2006).

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

No animal studies are presented in this manuscript. The studies involving human participants were reviewed

[2]Patient 1 also produced instances of mitigated echolalia composed of ungrammatical fragments, an abnormal language feature we termed "agrammatic echolalia."

and approved by Ethics Committee of the University of Malaga. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individuals for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

MB, FH, and GD developed the study concept and the study design. MB, FH, ÁB-C, DS-M, and LE performed testing and data collection. FH, ÁB-C, DS-M, and LE performed the data analysis and interpretation under the supervision of MB and GD. MB and GD drafted the manuscript. All authors provided critical revisions and contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2021.635896/full#supplementary-material

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frontiers in Aging Neuroscience

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Language Disorder in Progressive Supranuclear Palsy and Corticobasal Syndrome: Neural Correlates and Detection by the MLSE Screening Tool

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Background: Progressive supranuclear palsy (PSP) and corticobasal syndrome (CBS) affect speech and language as well as motor functions. Clinical and neuropathological data indicate a close relationship between these two disorders and the non-fluent variant of primary progressive aphasia (nfvPPA). We use the recently developed Mini Linguistic State Examination tool (MLSE) to study speech and language disorders in patients with PSP, CBS, and nfvPPA, in combination with structural magnetic resonance imaging (MRI).

Methods: Fifty-one patients (PSP N = 13, CBS N = 19, nfvPPA N = 19) and 30 age-matched controls completed the MLSE, the short form of the Boston Diagnostic Aphasia Examination (BDAE), and the Addenbrooke's Cognitive Examination III. Thirty-eight patients and all controls underwent structural MRI at 3 Tesla, with T1 and T2-weighted images processed by surface-based and subcortical segmentation within FreeSurfer 6.0.0 to extract cortical thickness and subcortical volumes. Morphometric differences were compared between groups and correlated with the severity of speech and language impairment.

Results: CBS and PSP patients showed impaired MLSE performance, compared to controls, with a similar language profile to nfvPPA, albeit less severe. All patient groups showed reduced cortical thickness in bilateral frontal regions and striatal volume. PSP and nfvPPA patients also showed reduced superior temporal cortical thickness, with additional thalamic and amygdalo-hippocampal volume reductions in nfvPPA. Multivariate analysis of brain-wide cortical thickness and subcortical volumes with MLSE domain scores revealed associations between performance on multiple speech and

language domains with atrophy of left-lateralised fronto-temporal cortex, amygdala, hippocampus, putamen, and caudate.

Conclusions: The effect of PSP and CBS on speech and language overlaps with nfvPPA. These three disorders cause a common anatomical pattern of atrophy in the left frontotemporal language network and striatum. The MLSE is a short clinical screening tool that can identify the language disorder of PSP and CBS, facilitating clinical management and patient access to future clinical trials.

Keywords: progressive supranuclear palsy, corticobasal syndrome, speech, language, aphasia

INTRODUCTION

Progressive supranuclear palsy (PSP) and corticobasal degeneration are primary degenerative tauopathies affecting movement and cognition (Litvan et al., 1996; Armstrong et al., 2013; Burrell et al., 2014; Höglinger et al., 2017). Speech and language deficits are common in both disorders, but their recognition has been hampered by the lack of a brief but sensitive clinical assessment tool (Peterson et al., 2019). In this article, we use the Mini Linguistic State Examination (MLSE; Patel et al., 2020) to investigate the range of speech and language deficits in PSP and the corticobasal syndrome (CBS), and their neural correlates in structural magnetic resonance imaging (MRI).

The classical phenotype of PSP, Richardson's syndrome, is characterised by vertical supranuclear gaze palsy, axial rigidity, and postural instability, with cognitive impairment (Steele et al., 1964; Litvan et al., 1996). Richardson's syndrome is highly suggestive of PSP pathology, however, other common phenotypes have been described, including a presentation with speech and language deficits (PSP-SL; Respondek and Höglinger, 2016; Höglinger et al., 2017). The clinical syndrome of CBS is characterised by the combination of motor deficits (progressive asymmetrical akinetic rigidity, dystonia, tremor, myoclonus) and cortical features (alien limb, apraxia, cortical sensory change; Riley and Lang, 1988; Boeve et al., 2003), with heterogeneity in the clinical presentations and underlying pathology (Armstrong et al., 2013; Alexander et al., 2014). CBS is commonly accompanied by impaired speech and language (Burrell et al., 2014; Peterson et al., 2019). Indeed, a non-fluent agrammatic presentation of CBS (CBS-NAV) is recognised in consensus clinical diagnostic criteria (Armstrong et al., 2013). Speech and language deficits also develop commonly in PSP and CBS after motor presentations (Catricalà et al., 2019; Dodich et al., 2019; Peterson et al., 2019; Murley et al., 2020).

The speech and language changes of PSP and CBS have much in common with the non-fluent variant of a primary progressive aphasia (nfvPPA). Indeed, there is considerable overlap in the criteria for diagnosing nfvPPA, PSP-SL, and CBS-NAV (Peterson et al., 2019). There is agrammatism, anomia, circumlocution, and impaired syntactic comprehension in the context of preserved single-word comprehension and object knowledge in patients with PSP-SL and CBS-NAV (Armstrong et al., 2013; Höglinger et al., 2017; Dodich et al., 2019), and subtle deficits in verbal production and sentence comprehension in PSP/CBS (Dodich et al., 2019). However, few studies have directly compared speech and language in PSP/CBS with nfvPPA. Burrell et al. (2018) found aphasic deficits on formal testing in PSP patients that were comparable in frequency and severity to those of an nfvPPA group. However, the PSP group were recruited mainly from a cognitive disorders clinic and may have overrepresented cognitive phenotypic presentations.

Although the speech and language changes of PSP and CBS have similarities to nfvPPA, it does not necessitate a common aetiology. However, there are overlapping neuropathological features including neuronal, oligodendroglial, and astrocytic inclusions that are immunoreactive for tau with 4 microtubule binding repeats (4R; Grossman, 2010; Dickson et al., 2011; Spinelli et al., 2017). PSP and CBS clinical signs often follow the presentation of nfvPPA (Kertesz and McMonagle, 2010; Santos-Santos et al., 2016; Cerami et al., 2017; Gazzina et al., 2019), or primary progressive apraxia of speech (Josephs et al., 2014). The clinical and pathological overlap of PSP, CBS, and nfvPPA underlies the concept of a continuous spectrum of 4R-Tauopathy disorders (Kertesz et al., 2005; Dickson et al., 2011; Murley et al., 2020) that extends to the functional anatomy of their cognitive deficits.

Here, we test the hypothesis that the three disorders have a common associated structural impairment in relation to their common effects on speech and language. The functional anatomy of language impairment in PSP and CBS has been identified by fluorodeoxyglucose positron emission tomography (Dodich et al., 2019). Patients with language presentations of these two conditions have hypometabolism in areas typical of nfvPPA (left fronto-insular and superior medial frontal cortex), whereas patients without language impairment showed predominant right-hemispheric involvement. At the group level, the disorders differ: PSP is associated with atrophy and hypometabolism of midbrain, striatal, and frontal regions, bilaterally (Kaat et al., 2011; Niccolini and Politis, 2016; Murley et al., 2020); CBS is associated with asymmetric hypometabolism and atrophy of frontoparietal cortex and basal ganglia (Niccolini and Politis, 2016; Murley et al., 2020); and nfvPPA is associated with atrophy and hypometabolism of the left frontal perisylvian region, anterior insula, and frontal operculum (Nestor et al., 2003; Gorno-Tempini et al., 2004; Preiß et al., 2019).

The MLSE was recently developed as a screening tool to identify and categorise speech and language deficits in

neurological disorders (Patel et al., 2020). We, therefore, used the MLSE to compare PSP, CBS, and nfvPPA. The speech and language symptoms of PSP and CBS have been difficult to assess and characterise in non-specialist settings because of the lack of a validated brief language screening test. The MLSE is accurate for the assessment of primary progressive aphasias (Patel et al., 2020) but its performance in other neurological disorders is yet to be assessed. We included patients with a range of PSP and CBS phenotypic presentations to reflect the range of cases presenting to cognitive and movement disorders clinics, noting that speech and language impairment occurs in PSP/CBS patients even in those who do not meet criteria for PSP-SL or CBS-NAV (Dodich et al., 2019).

This study had two key aims: (1) to use the MLSE to evaluate and compare linguistic impairment in PSP, CBS, and nfvPPA; and (2) to investigate brain structural correlates of speech and language deficits in PSP, CBS, and nfvPPA. We predicted that the language profile in PSP and CBS would resemble that seen in nfvPPA. We also predicted that performance on the MLSE would be associated with cortical atrophy in a left-lateralised language network, specifically, the inferior frontal cortex, associated with agrammatic and apraxic speech (Gorno-Tempini et al., 2004).

MATERIALS AND METHODS

Ethics

Ethical approval was obtained from the London-Chelsea Research Ethics Committee (REC reference: 16/LO/1735). The study was sponsored by St. George's, University of London. All participants provided written informed consent.

Participants

Fifty-one patients (PSP N = 13, CBS N = 19, nfvPPA N = 19) were recruited through specialist cognitive neurology clinics at Addenbrooke's Hospital, Cambridge (N = 33), St. George's Hospital, London (N = 13), and Manchester Royal Infirmary and its associated clinical providers (N = 5). Patients were included if they had a clinical diagnosis of PSP based on the 2017 Movement Disorder Society criteria (Höglinger et al., 2017), CBS based on the 2013 Armstrong et al. criteria (Armstrong et al., 2013), or nfvPPA based on the 2011 Gorno-Tempini criteria (Gorno-Tempini et al., 2011). Nine of the PSP patients had probable PSP-Richardson's syndrome; the other four included one each of probable PSP-progressive gait freezing (PSP-PGF), probable PSP-SL, possible PSP-ocular motor dysfunction (PSP-OM), and possible PSP. Eight CBS patients had probable CBS; the others had probable CBS-NAV (N = 6), possible CBS-NAV (1), probable CBS presenting as PSP syndrome (CBS-PSP) (1), and possible CBS (3). One nfvPPA patient declared a native language other than English but had been highly fluent in English since childhood and predominately used English in day-to-day life. Patients were excluded if they had advanced dementia and were unable to understand the purpose of the study or follow task instructions. As part of their clinical assessment, PSP and CBS patients completed the PSP Rating Scale (Golbe and Ohman-Strickland, 2007). Medication information was also collected for these groups.

Thirty healthy controls were recruited. Inclusion criteria for the healthy control group were: the absence of a diagnosis of any pathological process causing a cognitive disorder and/or subjectively reported cognitive decline; age between 40 and 75 years; English as a first language; willing to participate in a study investigating language and dementia. Healthy controls were recruited through the National Institute for Health Research "Join Dementia Research" register[1] in Cambridge and London, patients' relatives, and *via* local advertisement.

Cognitive and Language Assessment

Participants completed the Addenbrooke's Cognitive Examination—III (ACE-III; Hsieh et al., 2013), the short form of the Boston Diagnostic Aphasia Examination (BDAE; Goodglass et al., 2001), and the Mini Linguistic State Examination (MLSE; Patel et al., 2020). The short form of the BDAE, designed to assess language changes after focal brain damage (mainly stroke), was used to augment the MLSE assessment of language functions. A composite score was calculated from the following subtests of the short form of the BDAE, selected to overlap with the MLSE subtasks: single word repetition (max = 5), basic word discrimination (max = 16), sentence repetition (max = 2), the Boston Naming Test short form (max = 15), and basic oral word reading (max = 15), giving a maximum BDAE composite score of 53 to compare with the MLSE total score. Assessment sessions were video and/or audio recorded for offline scoring and analysis.

The MLSE is a brief language assessment tool designed for the assessment of progressive aphasia. It contains subtests which span the principal linguistic domains affected by PPA, as used to apply the diagnostic criteria (Gorno-Tempini et al., 2011): confrontation naming, repetition, word and sentence comprehension, semantic association, reading, writing and a connected speech task. Error-based scoring provides *domain scores* corresponding to key linguistic domains (motor speech, knowledge of phonological structure, semantic knowledge, syntactic knowledge, and auditory-verbal working memory) as well as an overall *total score* out of 100, with lower scores indicating poorer performance. The MLSE has shown high inter-rater agreement and diagnostic accuracy for the classification of primary progressive aphasic syndromes (>90% accuracy using random forest classification; Patel et al., 2020).

Data Management

Study data were collected and managed using the Research Electronic Data Capture tool, a secure, web-based software platform designed to support data capture for research studies, hosted at the University of Cambridge and at St. George's, University of London (Harris et al., 2009, 2019).

Magnetic Resonance Imaging Protocol

Thirty-eight (PSP N = 11, CBS N = 14, nfvPPA N = 13) patients and all controls underwent structural MRI at 3 Tesla with a T1-weighted magnetisation-prepared rapid acquisition gradient echo (MPRAGE) and T2-weighted sequences. Twenty-seven

[1] http://www.joindementiaresearch.nihr.ac.uk

patients (PSP $N = 9$, CBS $N = 9$, nfvPPA $N = 9$) and 20 controls were scanned at the Wolfson Brain Imaging Centre, University of Cambridge on a Siemens Prisma 3T MRI (T1 Sagittal iPAT 2 parameters: TR = 2,000 ms, TE = 2.93 ms, TA = 306 s, in-plane resolution = 1.1 × 1.1 mm, slice thickness = 1.1 mm, Inversion Time = 850 ms, Flip Angle = 8°; T2 Sagittal iPAT 2 parameters: TR = 3,200 ms, TE = 401 ms, TA = 283 s, in-plane resolution = 1.1 × 1.1 mm, slice thickness = 1.1 mm, Inversion Time = 850 ms, Flip Angle = 120°). Eleven patients (PSP $N = 2$, CBS $N = 5$, nfvPPA $N = 4$) and 10 controls were scanned at the St. George's Hospital Radiology Department on a Philips Achieva 3T MRI (T1 Sagittal SENSE parameters: TR = 6,600 – 6,900 ms, TE = 3.0–3.2 ms, in-plane resolution = 1.1 × 1.1 mm, slice thickness = 1.1 mm, Inversion Time = 850 ms, Flip Angle = 8°; T2 Sagittal SENSE parameters: TR = 2,200 ms, TE = 243 ms, in-plane resolution = 1.1 × 1.1 mm, slice thickness = 1.1 mm, Inversion Time = 850 ms, Flip Angle = 90°). Three patients were scanned at the Manchester Royal Infirmary site but were not included in the MRI analysis in part because no healthy volunteers were scanned at this site (i.e., unable to control for an effect of scanner difference). The remaining 10 patients either declined or were ineligible for MRI.

Analysis

Demographic, cognitive, and subcortical volumetric data were analysed using RStudio and R version 4.0.2. A chi-square test was conducted to investigate differences in sex distribution between groups. Since Levene's test showed that the variances for years of education and ACE-III score were not equal, Welch's ANOVA with Games-Howell *post hoc* test was used. Age, symptom duration, the BDAE composite score, MLSE total and MLSE domain scores, and volumes of thalamus, caudate, nucleus accumbens, and brainstem were not normally distributed. Therefore, the Kruskal-Wallis rank sum test was used, with *post hoc* pairwise comparisons by the Dunn test. Multiple testing correction was conducted using the Benjamini-Hochberg method (Benjamini and Hochberg, 1995). A corrected value of $p < 0.05$ following Benjamini-Hochberg correction was considered significant.

The T1- and T2-weighted images were processed using FreeSurfer 6.0.0 recon-all pipeline. The T2 volume was used to aid the definition of the pial surface. All images were reviewed to confirm accurate segmentation. Group differences in cortical thickness between each patient group and the control group were tested using a univariate analysis with the group as a factor. Sex and age were included as covariates of no interest. All tests were performed vertex-wise subject to clusterwise correction for multiple comparisons using FreeSurfer's mri_glmfit-sim for a permutation analysis with 10,000 randomisations and an initial uncorrected height threshold of $p < 0.01$. Non-parametric permutations analysis adequately controls for false positives at this height threshold (Greve and Fischl, 2018).

We examined the relationship between language impairments and imaging metrics using univariate and multivariate statistics. The univariate approach tested the relationship between MLSE total score and cortical thickness with gender and age as covariates of no interest. Correlational analyses for cortical thickness were performed at each vertex subject to clusterwise correction for multiple comparisons using a permutation analysis with 10,000 randomisations and an initial uncorrected height threshold of $p < 0.01$. Clusters surviving a two-sided corrected cluster threshold of $p < 0.05$ were deemed significant. To investigate the link between MLSE and subcortical brain regions, left and right subcortical structure volumes from FreeSurfer were combined. Partial correlations were used to investigate associations between volumes of subcortical structures with MLSE total score, covarying estimated total intracranial volume, age, and sex.

To assess the multivariate relationship between MLSE domain scores and brain structures, we adopted a two-level procedure (Tsvetanov et al., 2018, 2019; Passamonti et al., 2019). First, canonical correlation analysis (Hotelling, 1936) identified the linear relationship between the two multivariate datasets, namely structural values (cortical thickness and subcortical volume) and MLSE domain scores, providing pairs of latent variables (Structure-LV and MLSE-LV). Each latent variable is a linear combination of the original variables, optimised to maximise the correlation between each pair. Here, dataset 1 consisted of structural values of cortical thickness and subcortical volume [67 subjects × 83 nodes: 68 from the Desikan-Killiany Atlas and 15 (left and right: thalamus, caudate, putamen, pallidum, hippocampus, amygdala, and nucleus accumbens; and the brainstem) from the automatic subcortical segmentation atlas within FreeSurfer (Fischl et al., 2002)], and dataset 2 included MLSE domain scores (67 subjects × 5 domains). Covariates of no interest included scanner site, gender, age, and total intracranial volume. Next, we tested whether the identified relationship between the cortical thickness and subcortical volume profile (Structure-LV) and MLSE-LV was differentially expressed by groups. We performed a second-level analysis using multiple linear regression with a robust fitting algorithm as implemented in the Matlab fitlm.m function. Independent variables included subjects' brain structure scores from first level canonical correlation analysis, group information (patient vs. control) and their interaction (Structure-LV × Group). The dependent variable was subjects' MLSE-LV scores from the first-level analysis in the corresponding canonical correlation analysis.

RESULTS

Participant Demographics

Fifty-one patients (PSP $N = 13$, CBS $N = 19$, nfvPPA $N = 19$) and 30 controls completed the language assessment, as summarised in **Table 1**. The groups were similar in age and sex. The patient groups showed similar symptom duration ($F < 1$). There was a significant difference across the groups in years of education. *Post hoc* pairwise comparisons indicated that the control group had significantly more years of education than each patient group (all $p \leq 0.003$), but the patient groups did not differ from each other on this variable. There was a significant difference across the groups in ACE-III total score: higher in the control group than each patient group (all $p \leq 0.001$). In addition, the nfvPPA mean ACE-III total score was lower than PSP ($p = 0.019$).

Thirty-eight patients were included in the MRI analysis protocol. We compared those included vs. not-included in the MRI analysis in terms of demographic and cognitive measures (**Supplementary Table 1**). The included patients had higher ACE-III, BDAE composite, and MLSE total scores compared to not-included patients, but the two groups did not differ in sex distribution, age, years of education, or symptom duration.

Five (26%) CBS patients and six (46%) PSP patients were taking dopaminergic medication. Using the Tomlinson et al. (2010) formula, levodopa equivalent daily dose value for the CBS patients was 193 mg (SD = 88.6) and for the PSP patients was 345 mg (SD = 254.1). 15% of PSP and 11% of CBS patients were taking benzodiazepines, 23% of PSP and 11% of CBS patients were taking opiates, 31% of PSP and 11% of CBS patients were taking selective serotonin reuptake inhibitors, 31% of PSP and 11% of CBS patients were taking other antidepressants.

Language Scores

Figure 1 presents group performance for MLSE domains. There were differences in scores between the groups for MLSE total score ($\chi^2_{(3)}$ = 58.52, adjusted p < 0.001), motor speech ($\chi^2_{(3)}$ = 48.90, adjusted p < 0.001), phonological structure ($\chi^2_{(3)}$ = 47.56, adjusted p < 0.001), semantic knowledge ($\chi^2_{(3)}$ = 39.40, adjusted p < 0.001), syntactic knowledge ($\chi^2_{(3)}$ = 46.56, adjusted p < 0.001), and auditory-verbal working memory ($\chi^2_{(3)}$ = 8.16, adjusted p = 0.043). Results of *post hoc* pairwise comparisons using the Dunn test with Benjamini-Hochberg adjustment (Benjamini and Hochberg, 1995) are presented in **Figure 1**.

Each patient group performed worse than controls for MLSE total score and all MLSE subdomain scores apart from auditory-verbal working memory (after correction for multiple comparisons). The nfvPPA group scored lower than PSP and CBS groups on MLSE total score, with no significant difference between PSP and CBS. The PSP and CBS patients' MLSE subdomain scores were similar, while nfvPPA patients scored significantly lower than CBS patients for motor speech, PSP patients for semantic knowledge, and both PSP and CBS patients for phonological structure and syntactic knowledge.

There was a significant difference in BDAE composite score across the groups ($\chi^2_{(3)}$ = 46.63, corrected p < 0.001), with the control group scoring significantly higher than each patient group but with no significant differences between patient groups (see **Table 1**).

MLSE scores were converted to per cent scores to visualise the pattern of linguistic impairment across the groups. As shown in **Figure 2**, the *pattern* of impairment on MLSE subdomains is comparable across PSP, CBS and nfvPPA but with greater severity in the nfvPPA patients.

Imaging Results

There were differences in cortical thickness between controls and each patient group as shown in **Figure 3A**. All patient groups showed bilateral cortical thinning in medial and lateral frontal

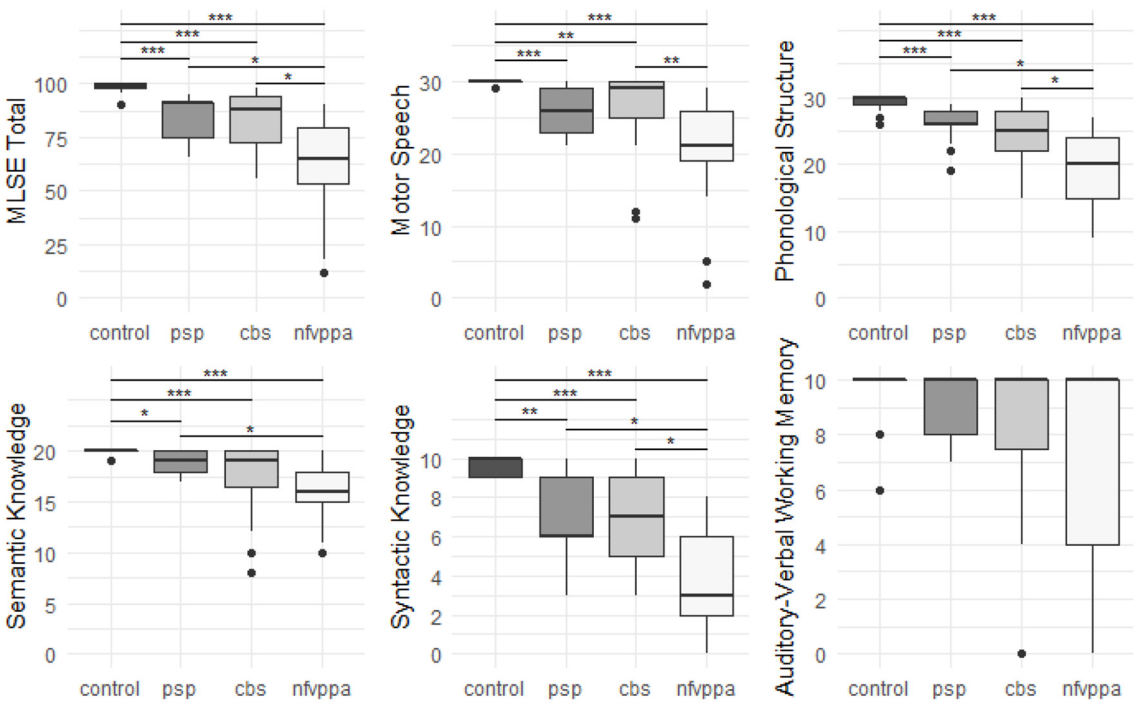

FIGURE 1 | Boxplots of group MLSE total and domain scores. The y-axes for each plot span the min to max scores. Significance markers represent adjusted *p* values from *post hoc* pairwise comparisons using the Dunn test with Benjamini-Hochberg adjustment. "***" = adjusted *p* value < 0.001, "**" = adjusted *p* value < 0.01, "*" = adjusted *p* value < 0.05.

TABLE 1 | Demographic information for the study cohort.

	Control	CBS	nfvPPA	PSP	Corrected P value
N	30	19	19	13	-
Sex (M/F)	18/12	11/8	7/12	8/5	0.452
Age Mean (SD)	66.60 (4.33)	70.37 (7.71)	70.42 (6.95)	69.23 (6.03)	0.063
Education (years) Mean (SD)	15.97 (3.33)	12.63 (2.83)	12.11 (2.16)	11.77 (1.74)	<0.001
Symptom duration (months) Mean (SD)	NA	49.47 (45.15)	35.63 (30.46)	45.62 (26.94)	0.590
ACE-III score Mean (SD)	95.97 (3.47)	74.37 (17.90)	57.47 (22.13)	77.15 (13.30)	<0.001
BDAE composite Mean (SD)	52.68 (0.50)	47.42 (5.88)	39.29 (12.51)	46.58 (6.93)	<0.001
PSP Rating Scale Mean (SD)	–	29.28 (18.17)	–	36.50 (16.15)	-

Note: corrected P values are the result of Chi-squared, Welch's ANOVA, or Kruskal-Wallis rank sum tests for each row with Benjamini-Hochberg adjustment.

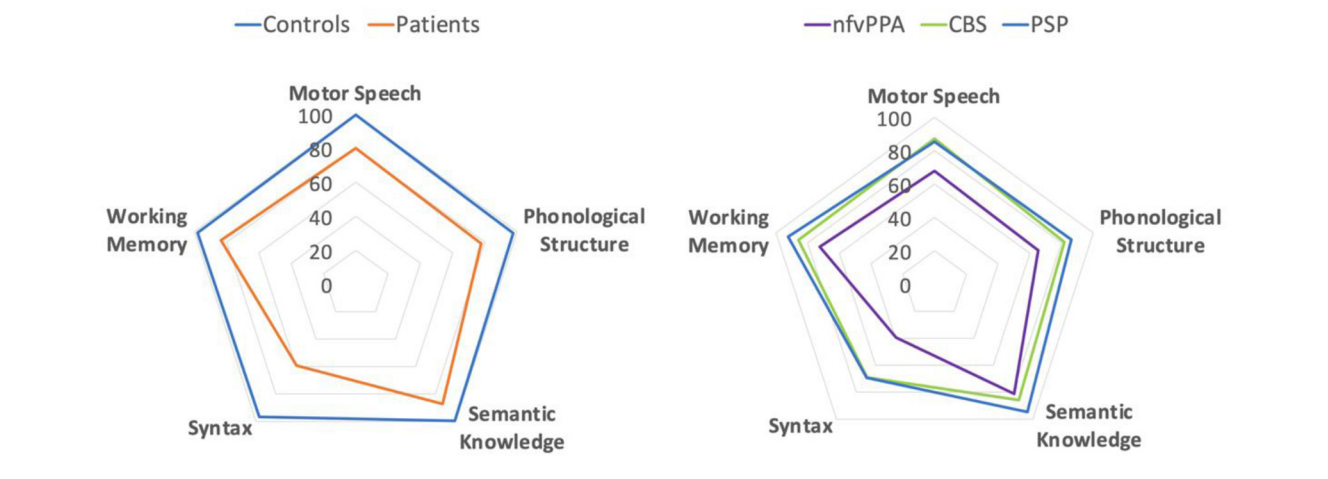

FIGURE 2 | Radar plots showing percentage scores for MLSE subdomains.

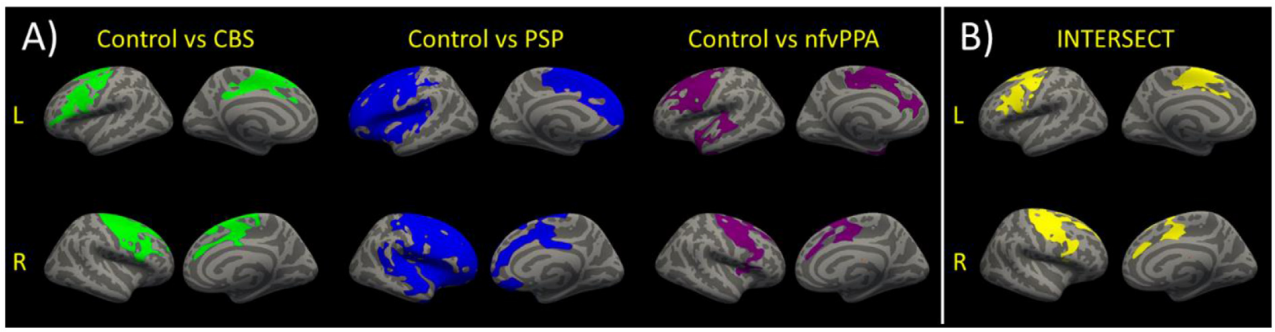

FIGURE 3 | **(A)** Reduced cortical thickness in each patient group vs. the control group. Clusters show regions of significant reductions in cortical thickness between each patient group and the controls following clusterwise correction at $p < 0.05$. **(B)** For visualisation purposes, the intersect of the clusters for the three group comparisons of cortical thickness is shown. The intersect shows overlapping regions of reduced cortical thickness in the three patients vs. controls comparisons.

regions. The overlap between each patient-control cluster and Desikan-Killiany atlas regions is presented in **Table 2**. We created the intersect of the three patient-control analyses clusters to illustrate the region of commonality using the 'labels_intersect' command in FreeSurfer (**Figure 3B**). Overlapping regions of cortical thinning in the three patient groups encompassed

inferior frontal, middle frontal, superior frontal, and precentral gyri (**Figure 3B**). The PSP and nfvPPA groups additionally showed cortical thinning in superior temporal regions, bilaterally in PSP and left–sided in nfvPPA. Correlational analysis between the MLSE total score and cortical thickness yielded no significant clusters following clusterwise correction.

There were group differences in subcortical volumes as shown in **Table 3**. All patient groups showed smaller putamen compared to controls. In addition, PSP patients showed reduced caudate volume compared to controls and reduced pallidum volume compared to all other groups; and nfvPPA patients showed reduced thalamus, caudate, and hippocampus volumes compared to controls and reduced amygdala volume compared to all other groups.

Partial correlations were conducted across the three patient groups to examine relationships between subcortical volumes and MLSE total score whilst controlling for estimated total intracranial volume, age and sex. There was a significant positive partial correlation between amygdala volume and MLSE total score ($r_{(33)} = 0.377$, $N = 38$, $p = 0.026$).

We assessed the multivariate relationship between MLSE domain scores and structural scores (cortical thickness and subcortical volumes) of 83 nodes across the brain using canonical correlation analysis. We identified one significant pair of latent variables (MLSE-LV and Structure-LV, $r = 0.5731$ $p < 0.001$; **Figure 4**). The Structure-LV expressed the highest loadings in the superior temporal cortex, prefrontal, inferior frontal and precentral regions, amygdala, hippocampus, putamen, and caudate, with a tendency for left lateralisation. The loading values for all structures are presented in **Supplementary Table 2**. The MLSE-LV expressed all domains, with the highest loadings on motor speech, phonology and syntax domains, followed by semantic and auditory-verbal working memory domains (**Figure 4A**). The positive loading values indicated that higher performance on MLSE domains (more so motor speech, phonology, and syntax domains) is associated with greater cortical thickness in the frontotemporal regions shown in **Figure 4B** and in volumes of the amygdala, hippocampus, putamen and caudate (**Figure 4C**), with a tendency for left lateralisation. The remaining four components were not significant (p values 0.250, 0.432, 0.136, 0.430 for components 2–5, respectively).

To test whether the observed relationship between MLSE-LV and Structure-LV is differentially expressed between controls and patients, we constructed a second-level regression model with robust error estimates by including Structure-LV subject scores, group information and their interaction term as independent variables and MLSE-LV as a dependent variable in addition to covariates of no interest (**Figure 4D**). We found evidence for a significant interaction ($r = 0.562$, $p = 0.006$) indicating a stronger relationship between MLSE-LV and Structure-LV in the patients relative to controls.

DISCUSSION

This study reveals the severity and structural correlates of language impairment in PSP and CBS, using the Mini Linguistic State Examination (MLSE). The PSP and CBS patients showed impaired performance on the MLSE domains of motor speech, phonological structure, semantic knowledge, and syntactic knowledge, but not auditory-verbal working memory. This pattern is similar to nfvPPA, consistent with previous reports of CBS-NAV or PSP-SL (Burrell et al., 2018; Catricalà et al., 2019; Dodich et al., 2019). PSP and CBS were similar to each other in the severity and range of language impairment.

We identified brain structural correlates of MLSE performance in PSP, CBS and nfvPPA. Multivariate analysis confirmed the association between a language component based on the MLSE domain scores (motor speech, phonology, and syntax loading most strongly) and a structural component (left-lateralised frontotemporal cortical thinning and subcortical atrophy). Further, we found cortical thinning common to all three patient groups in pre-frontal and precentral gyri. This accords with previous research showing that motor speech, phonology, and syntactic ability are the most affected linguistic domains in PSP, CBS, and nfvPPA (Burrell et al., 2018; Dodich et al., 2019; Peterson et al., 2019), and supports the sensitivity of MLSE to structural changes associated with language effects of PSP and CBS.

This atrophy is consistent with findings of hypometabolism in the left inferior frontal gyrus in patients with PSP-SL and CBS-NAV (Dodich et al., 2019), implicating this region in the emergence of a nfvPPA-type language profile. Despite this consistency, there is considerable heterogeneity in patterns of structural and functional impairment in these disorders. For example, some CBS patients show a pattern of language impairment resembling the logopenic variant of PPA, with impaired complex sentence repetition (Dodich et al., 2019), together with bilateral parietal hypometabolism, possibly reflecting underlying Alzheimer's disease pathology rather than corticobasal degeneration as the cause of CBS. Detailed analysis of linguistic impairment at the individual level in conjunction with pathological classification in PSP and CBS might provide more insight into the clinical-anatomical correlates of language impairment in these disorders.

The MLSE average assessment time was less than 20 min, but this was sufficient to confirm mild to moderate impairment in motor speech, semantic knowledge, phonological abilities, and syntactic ability in PSP and CBS (Burrell et al., 2018; Peterson et al., 2019). This confirms the MLSE as a quick language screening tool for patients with mixed cognitive and movement disorders. Many language tests assume good visual and motor functions (e.g., tasks featuring visual stimuli or which require writing). Such tasks might disadvantage PSP patients due to their oculomotor abnormalities or disadvantage both PSP and CBS patients due to motor deficits. This complicates interpretation of results from investigations of language in these disorders because scoring is often binary, the reasons for task failures can be unclear and can differ across disorders (Peterson et al., 2019; Picillo et al., 2019). The MLSE addresses this longstanding issue by incorporating an error-based scoring system to capture language-specific contributions to impaired test performance, enabling one to tease apart linguistic deficits from one another and from other impairments.

TABLE 2 | The overlap between each patient-control cortical thickness analysis cluster with Desikan-Killiany atlas regions shown in area mm^2 and percentage overlap.

Structure Name	Hemisphere	HC vs. CBS Cluster (Area mm^2, %)	HC vs. PSP Cluster (Area mm^2, %)	HC vs. nfvPPA Cluster (Area mm^2, %)
Frontal				
Superior Frontal	*Left*	3305, 50%	6322, 95%	3803, 57%
	Right	3884, 61%	4549, 72%	3059, 48%
Rostral Middle Frontal	*Left*	605, 13%	4549, 95%	1256, 26%
	Right	1171, 24%	4840, 98%	365, 7%
Caudal Middle Frontal	*Left*	1223, 57%	2072, 97%	1989, 93%
	Right	1749, 88%	1902, 95%	1198, 60%
Pars Opercularis	*Left*	660, 44%	1495, 100%	514, 34%
	Right	618, 48%	1231, 96%	711, 56%
Pars Triangularis	*Left*	216, 19%	1025, 92%	0
	Right	0	805, 64%	0
Pars Orbitalis	*Left*	0	259, 47%	0
	Right	0	643, 95%	0
Lateral Orbitofrontal	*Left*	0	1746, 82%	0
	Right	0	1146, 53%	0
Medial Orbitofrontal	*Left*	0	701, 46%	0
	Right	0	813, 54%	0
Precentral	*Left*	2698, 59%	4032, 88%	2951, 64%
	Right	3610, 77%	4386, 94%	2738, 59%
Paracentral	*Left*	332, 26%	538, 41%	505, 39%
	Right	503, 33%	287, 19%	169, 11%
Frontal Pole	*Left*	0	201, 100%	0
	Right	0	238, 92%	0
Rostral Anterior Cingulate	*Left*	0	350, 51%	245, 36%
	Right	0	162, 30%	0
Caudal Anterior Cingulate	*Left*	154, 24%	449, 69%	181, 28%
	Right	49, 7%	185, 26%	52, 7%
Parietal				
Superior Parietal	*Left*	0	0	0
	Right	0	0	0
Inferior Parietal	*Left*	0	0	0
	Right	0	289, 6%	0
Supramarginal	*Left*	0	1071, 29%	0
	Right	0	1270, 38%	0
Postcentral	*Left*	0	1883, 47%	0
	Right	0	2210, 58%	0
Precuneus	*Left*	0	0	0
	Right	0	0	0
Posterior Cingulate	*Left*	401, 34%	260, 22%	340, 29%
	Right	198, 17%	591, 50%	151, 13%
Isthmus Cingulate	*Left*	103, 11%	0	0
	Right	0	0	0
Temporal				
Superior Temporal	*Left*	0	1694, 50%	1910, 56%
	Right	0	2422, 76%	0
Middle Temporal	*Left*	0	0	216, 8%
	Right	0	453, 15%	0
Inferior Temporal	*Left*	0	0	600, 22%
	Right	0	185, 7%	0
Banks of the Superior Temporal Sulcus	*Left*	0	0	101, 10%
	Right	0	565, 64%	0
Fusiform	*Left*	0	0	469, 17%
	Right	0	0	0
Transverse Temporal	*Left*	0	433, 100%	280, 65%
	Right	0	303, 100%	0
Entorhinal	*Left*	0	0	224, 48%
	Right	0	0	0
Temporal Pole	*Left*	0	0	441, 94%
	Right	0	232, 52%	0
Parahippocampal	*Left*	0	0	0
	Right	0	0	0
Insula	*Left*	0	1715, 85%	294, 15%
	Right	0	1606, 87%	229, 12%

(Continued)

TABLE 2 | Continued

Structure Name	Hemisphere	HC vs. CBS Cluster (Area mm^2, %)	HC vs. PSP Cluster (Area mm^2, %)	HC vs. nfvPPA Cluster (Area mm^2, %)
Occipital				
Lateral Occipital	*Left*	0	0	0
	Right	0	0	0
Lingual	*Left*	0	0	0
	Right	0	0	0
Cuneus	*Left*	0	0	0
	Right	0	0	0
Pericalcarine	*Left*	0	0	0
	Right	0	0	0

Note: only regions with >5% overlap are shown.

TABLE 3 | Subcortical volumes.

	Control Mean (SD)	PSP Mean (SD)	CBS Mean (SD)	nfvPPA Mean (SD)
Thalamus	13.33 (1.47)	12.73 (3.84)	12.06 (1.69)	**11.74 (1.51)***
Caudate	6.85 (1.08)	**6.01 (1.27)***	6.39 (1.15)	**5.66 (0.82)***
Putamen	8.83 (1.05)	**6.87 (1.11)***	**7.85 (1.42)***	**7.21 (1.00)***
Pallidum	3.79 (0.43)	**2.86 (0.38)*,a,b**	3.70 (0.51)	3.53 (0.54)
Hippocampus	8.06 (0.85)	7.50 (0.86)	7.40 (1.10)	**7.11 (1.02)***
Amygdala	3.27 (0.45)	3.14 (0.38)	2.99 (0.46)	**2.50 (0.47)*,a,c**
Nucleus Accumbens	0.96 (0.13)	0.90 (0.35)	0.86 (0.18)	0.82 (0.17)
Brainstem	20.35 (2.17)	19.99 (4.87)	18.44 (2.17)	18.67 (2.85)

*Note: volumes are presented in millilitres and left and right combined. Multiple testing correction was conducted using the Benjamini-Hochberg method (Benjamini and Hochberg, 1995). A corrected value of $p < 0.05$ was considered significant. *Significantly reduced vs. controls, [a]significantly reduced vs. CBS, [b]significantly reduced vs. nfvPPA, [c]significantly reduced vs. PSP.*

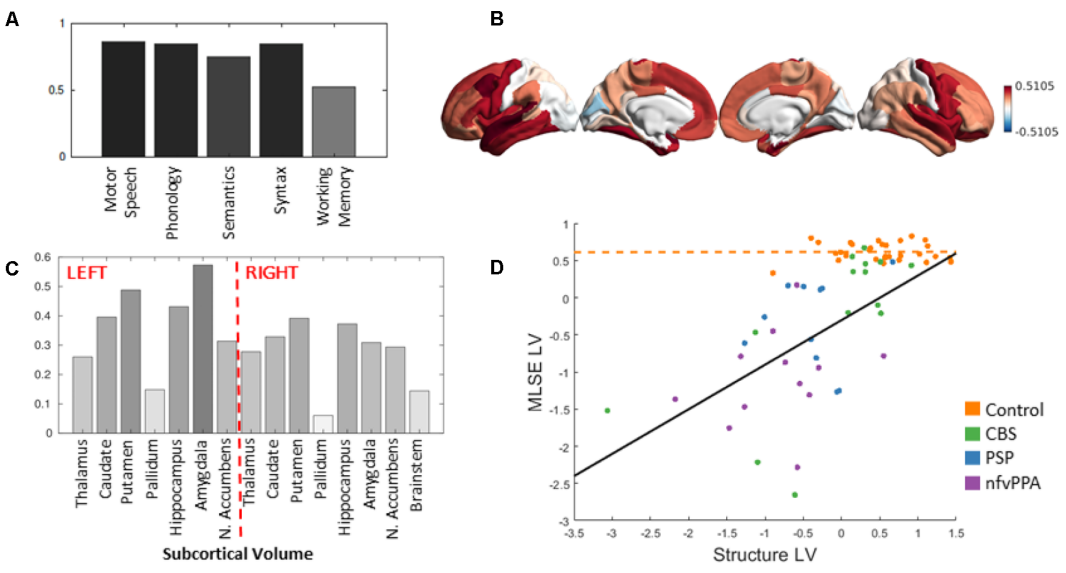

FIGURE 4 | **(A)** The MLSE latent variable (MLSE-LV) loadings. The MLSE-LV expressed all domains, with the highest loadings on motor speech, phonology and syntax, followed by semantic and auditory-verbal working memory domains. **(B)** and **(C)** The Structure latent variable (Structure-LV) loadings. The Structure-LV expressed high loadings in the superior temporal cortex, prefrontal, inferior frontal and precentral regions and in volumes of the amygdala, hippocampus, putamen and caudate, with a tendency for left lateralisation. **(D)** Visualisation of the interaction effect and the relationship between the MLSE-LV and the Structure-LV in the patients and controls. The relationship between MLSE-LV and Structure-LV was stronger in the patients relative to controls as visualised by black and orange trendlines, respectively, and confirmed formally by a significant interaction term ($r = 0.562$, $p = 0.006$). Corticobasal syndrome (CBS), progressive supranuclear palsy (PSP) and nfvPPA groups are colour coded.

There are limitations to the present study. We do not have pathological validation in our sample although clinicopathological correlations of PSP are very high (>90%; Gazzina et al., 2019). We have not examined phenotypic variance within groups other than language, due to the small group sizes and insufficient power but note that PSP and CBS can represent

diverse phenotypes. The small group sizes reflect the rarity of these conditions and it may be due to type II error that we were unable to detect between-patient-group differences in the relationship between MLSE performance and brain structure. Future studies with larger group sizes are needed to robustly evaluate potential group-specific effects and to replicate our findings. The study did not aim to dissect phenotype-specific patterns of atrophy of linguistic impairment, but rather exploit cohort variance to examine structure-function relationships. We recognise a possible selection bias for the patients scanned, with more severely impaired patients less likely to have undergone MRI. This is supported by the poorer cognitive and language performance in the patients who were not included in the MRI analysis. Thus, our imaging results may be more reflective of early-to-mid stage PSP/CBS/nfvPPA. Finally, the cross-sectional nature of this study precludes an interpretation of the progression of language profiles.

In conclusion, we find evidence for mild to moderate speech and language deficits in PSP and CBS which are similar in profile to nfvPPA. We have identified a shared anatomical substrate that correlates with linguistic impairment across these disorders, sensitive to MLSE profiling, consistent with the overlapping clinical and pathological spectrum of PSP, CBS, and nfvPPA.

DATA AVAILABILITY STATEMENT

We invite requests for the anonymised data for academic (non-commercialised) purposes, to the corresponding author. Data sharing may be subject to restrictions on some data types to protect confidentiality. Requests to access the datasets should be directed to james.rowe@mrc-cbu.cam.ac.uk.

ETHICS STATEMENT

The study was reviewed and approved by the London-Chelsea Research Ethics Committee (REC reference: 16/LO/1735).

AUTHOR CONTRIBUTIONS

KAP, NP, RI, SC, ML, KP, PG and JR contributed to conception and design of the study. KAP, NP and RI collected the data. KAP, PJ and KT performed the statistical analysis. SC, ML, KP, PG and JR supervised the project. KAP wrote the first draft of the manuscript. KT wrote sections of the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2021.675739/full#supplementary-material.

SUPPLEMENTARY TABLE 1 | Comparison between patients who were or were not included in the MRI analysis.

SUPPLEMENTARY TABLE 2 | The Structure-LV loading values of each structure (from the Desikan-Killiany atlas) and subcortical volumes, arranged from highest to lowest.

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frontiers in Aging Neuroscience

BRIEF RESEARCH REPORT
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Comparison of Behavior-Related Features in the MMSE Sentence in Behavioral Variant Frontotemporal Dementia and Alzheimer's Disease

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Background: Despite the ubiquity of cognitive assessments using the MMSE, there has been little investigation of currently unscored features of the MMSE sentence item relevant to behavior and language in patients with behavioral variant Frontotemporal Dementia (bvFTD) and Alzheimer's disease (AD).

Objective: To describe and compare the unscored content and grammar elements of the MMSE sentence item in patients with bvFTD and AD.

Methods: Categorization of predefined content and grammar elements of the MMSE sentence was performed by two blinded raters in patients with bvFTD (n = 74) and AD (n = 84). Chi-square and ANCOVAs were conducted to identify differences between the diagnostic groups. A multinomial logistic regression analysis was conducted to determine whether these features aid in the prediction of diagnosis of bvFTD or AD.

Results: A higher proportion of patients with bvFTD wrote sentences addressed to the examiner (22.7% vs. 4.7%, $X^2 = 11.272$, $p = 0.001$) and about interpersonal relationships (35.3% vs. 16.0%, $X^2 = 10.139$, $p = 0.017$) in comparison to those with AD. The number of words written was lower in patients with AD and was positively correlated with lower total MMSE scores in AD but not in bvFTD (AD: $r = 0.370$, $p < 0.001$; FTD: $r = 0.209$, $p = 0.07$). Assessment of the MMSE sentence content and grammar variables did not add to the prediction bvFTD or AD diagnosis beyond the variance explained by age and total MoCA score.

Conclusions: Patients with bvFTD and AD showed differences in aspects of the content of the written MMSE sentence item, though these differences did not aid in the diagnosis prediction.

Keywords: bvFTD, Alzheimer's disease, behavior, Mini-Mental State Examination sentence, writing content

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INTRODUCTION

In patients with behavioral variant Frontotemporal Dementia (bvFTD), scores on standard cognitive tests are often preserved, particularly in the early stages of the disease. However, it has been noted that qualitative aspects of cognitive testing are often abnormal in this population (Thompson et al., 2005) and are valuable for differentiation of dementia subtypes (Blair et al., 2006). Patients with bvFTD frequently score normally on the commonly used Mini Mental Status Examination (MMSE; Folstein et al., 1975) at the initial stages of the disease (Tan et al., 2013). However, information that may be gained from qualitative analysis of emotional aspects and linguistic elements of the MMSE written sentence task has been largely unexplored. It has been anecdotally observed that patients with different behavioral disturbances, for example during mania or depression, frequently write sentences with behaviorally relevant content, though empiric investigations of this phenomenon are limited.

bvFTD is a neurodegenerative disease characterized by behavioral changes secondary to apathy and empathy deficits, disinhibition, ritualistic behaviors, impulsivity, and executive cognitive impairment (Rascovsky et al., 2011). Although speech and language impairments have been explored in this population (Hardy et al., 2016; Geraudie et al., 2021), to our knowledge, there are no previous reports examining whether behavioral symptoms related to disinhibition and empathy may be detectable in written language samples from patients with bvFTD. While language, including writing, generally has been considered preserved in bvFTD, a subset of patients may develop language deficits, and many will display impaired word phonemic fluency (Rohrer et al., 2008). Further, as highlighted in a recent review, some patients with bvFTD also show language impairment in lexico-semantic, orthographic, and prosody domains (Geraudie et al., 2021). Further, as the MMSE is frequently used by primary health care providers and in other screening environments, whether the content of the MMSE sentence may help to differentiate patients with bvFTD from those with Alzheimer's disease (AD) yet has not been examined. In non-language variants of AD, language is generally preserved in the early stages of the disease, though some patients may display word finding difficulties and anomia (Ferris and Farlow, 2013).

The MMSE is one of the most popular cognitive screening tests and has been validated in several countries around the world (Ismail et al., 2010). One item evaluates a sentence written by the patient and awards 1 point if: (1) it is written spontaneously to the instruction "please write a sentence for me"; (2) contains a subject and a verb; and (3) is sensible. Content and other aspects of grammar are not evaluated. Prior studies have explored a limited number of unscored elements of the MMSE sentence in different geriatric populations. Findings have included an association between fewer words and lower total MMSE scores in general geriatric population patients (McCarthy et al., 2004), and in patients with FTD, Vascular dementia, AD, and Parkinson's disease in comparison with healthy control and MCI population (Corallo et al., 2019). In the same study, an association between the absence of abstract thinking and lower MMSE scores was found in Vascular Dementia and FTD patients, while the Parkinson's Disease population had increased frequency of concrete sentences; in general, patients with any kind of dementia displayed poorer abstraction in comparison to the healthy control and MCI groups. In another study performed in a general geriatric clinic, no correlations between the number of words and total MMSE scores were found, but higher scores on the 15-item Geriatric Depression Screening Scale (GDS) were correlated with shorter sentences and negative emotional polarity content (Press et al., 2012). Finally, in a study including patients with AD, Vascular dementia, Lewy body dementia, and unspecified dementia, a correlation was found between negative emotional polarity in the sentence and lower quality of life (Sniatecki et al., 2017).

The aim of this study was to characterize and compare the content and qualitative aspects of the MMSE sentence in patients with a clinical diagnosis of possible or probable bvFTD or AD. We hypothesized that in comparison to patients with AD, patients with bvFTD would show qualitative differences in the content of the MMSE sentence related to behavioral symptoms of bvFTD that potentially could be ascertained from the sentence alone (without the benefit of the behavioral observations such as impulsivity or ritualistic behaviors during the writing of the sentence). Thus, we focussed on content reflective of disinhibition and reduced empathy. We examined whether such differences would add to the diagnostic accuracy of a clinical diagnosis of bvFTD vs. AD, beyond that predicted by routine information typically present in primary health care settings (age, gender, MoCA total score), and therefore support the utility of considering one or more of the currently unscored MMSE sentence elements in triage and referral decisions.

MATERIALS AND METHODS

Population

The study sample was extracted retrospectively from the Cognitive Neurology and Alzheimer Research Centre Database in London, Ontario, Canada, from our records from January 2002 to September 2020. Inclusion criteria were a diagnosis of possible or probable bvFTD (Rascovsky et al., 2011) or AD (McKhann et al., 2011) and an available MMSE test including completion of the sentence item. Patients with structural brain lesions (tumor or stroke), patients with a previous diagnosis of schizophrenia or bipolar disorder with psychotic features, and patients who did not speak English as their first language were excluded. For the patients included in this study, the diagnosis of bvFTD or AD was based on a detailed history, neurologic examination, cognitive testing, brain imaging, and in some cases, genetic testing. In the clinic, given the availability of more extensive cognitive testing across the disease-relevant domains, as brief screening tests, the MMSE and MoCA are not the basis for diagnosis between bvFTD and AD but are used as markers of severity, particularly

for provincially mandated reported of driving concerns, and for longitudinal assessments. Clinical and cognitive testing data was obtained from the evaluation when a diagnosis of possible or probable AD or bvFTD was initially made. Neurological exam and diagnosis were performed by behavioral neurologists. The study was approved by the University of Western Ontario human subjects research ethics board (#R-11-510) and written informed consent was obtained from all participants. The study adhered to the guidelines of the Declaration of Helsinki.

Cognitive Screening Batteries and MMSE Sentence Exploration

Cognitive testing was performed by a trained psychometrician. The cognitive evaluation included the complete MMSE, Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005), and Beck Depression Inventory (BDI) total score (Beck et al., 1961), and typically also included immediate and delayed recall (adapted from the River Mead test), Trails A and B, naming from the Western Aphasia Battery or Boston naming test (15 items), letter and semantic fluency, and clock drawing.

To analyze the MMSE sentence, behaviural and grammatical variables were defined (see **Table 1**). Behavioral variables included: (a) Emotional polarity, coded as, negative emotion, neutral, or positive emotion; (b) Empathy, coded as empathic, neutral, or non-empathic sentence; (c) Abstraction, defined as the presence of ideas or concepts without physical referents (e.g., sentences about morality, love, etc.); (d) Disinhibition, defined as failure to suppress inappropriate information according to the clinical context; (e) Perseverations, defined as sentences with content related to other MMSE sections (example: "close your eyes"); and (f) Sentence addressed to the examiner. The behavioral variables (c–f) were coded as present or absent. Grammar variables evaluated included the number of words, nouns, verbs, adjectives, pronouns, adverbs, prepositions, grammatical form errors, spelling errors, and lexico-semantic errors. We also included allographic elements of case [normal, only upper case, only lower case, or a mixture of lower and upper case (e.g., ToDay is A good Day)] and font (cursive or printing letter or a mixture). As only a few sentences contained prepositions, these variables were binary coded (0 vs. $\geq$1 preposition). Grammatical form variables included: the presence of appropriate use of syntactic conjunctions, tenses, conditionals, subordinate clauses, and passive constructions (Boschi et al., 2017). Binary coding was used for grammatical form, spelling errors, lexico-semantic errors, font, and case variables. Finally, the four most common topics observed in the sentences were selected and categorized as: (1) Interpersonal relationships (example: "I love my wife"); (2) Self-descriptive interests (example: "I like to compost"), (3) Life events (example: "I went to see the doctor today") and (4) Weather (example "It is a sunny day").

All behavioral, topic, and grammar variables were rated by two independent raters blinded to diagnosis and the study hypothesis. Raters only had access to the MMSE sentence. Following the rating of the initial 30 participants, kappa statistics were performed, confirming inter-rater reliability (kappa values >0.60) for the content variables and topics, except for the perseveration content variable which had a kappa value less than 0.60 (see **Supplementary Table A**). After retraining and consensus scoring on points of discrepancy, raters completed the sentence scoring for all participants. The mean rating for grammar variables was used in the final analysis. For categorical variables, rating discrepancies were reviewed by the raters and a consensus rating was obtained according to previous training and definitions.

Statistical Analysis

Analyses were performed using SPSS version 26.0 (IBM, Armonk, NY, United States). Differences in demographics and cognitive testing scores between groups were determined by X^2-tests for categorical variables and *t*-tests for continuous variables. For the sentence variables, X^2-tests were conducted for categorical variables, and ANCOVAs including age and

TABLE 1 | Definitions and examples of content variables.

Content variable	Definition
Empathy	Identifying with others' feeling states. Patients with a lack of empathy display a diminished response to others' feelings and a diminished social interest or personal warmth, e.g., "I want to leave now".
Abstraction	Abstraction: Presence of ideas or concepts without physical referents. such as sentences about love, morality, democracy, freedom, etc. Lack of abstraction: sentences refer to objects that are available to the senses, e.g., "the grass is green".
Disinhibition	Sentences were categorized as disinhibited if the content represented a failure to suppress inappropriate information according to the clinical context. e.g., "I need new hair"
Emotional Polarity	Refers to the affective charge included in the sentence. Negative emotion polarity e.g., "Today is a bad day". Positive emotion polarity e.g., "Today is a wonderful day". Neutral e.g., "My name is Mike".
Sentence addressed to examiner	Refers to the direction of content to the evaluator. e.g., "You are a nice girl."
Perseverations	Sentences with content related to other MMSE sections, e.g., "No, if's, and's or but's", "Close your eyes".

TABLE 2 | Part A. Demographic and clinical characteristics of bvFTD and AD groups.

	bvFTD (*n* = 74)	AD (*n* = 84)	*t* value	*CI 95% (lower-upper)*	*p*-value
(A) Demographic and clinical characteristics					
Female, *n*(%)	31 (40.8%)	48 (55.8%)	3.645*	-	0.061
Age at time of diagnosis, mean (SD)	65 (9.78)	70.77 (9.74)	3.710	2.700–8.848	**<0.001**
Years of education, mean (SD)	13.05 (3.17)	12.88 (4.08)	−0.296	−1.319–0.976	0.764
Years of clinical symptoms, mean (SD)	3.56 (2.48)	2.87 (2.14)	−1.469	−1.624–0.242	0.145
MMSE score, mean (SD)	24.43 (6.09)	22.45 (5.58)	−2.159	−3.793 to −0.179	**0.033**
MoCA score, mean (SD)	19.94 (5.97)	14.39 (5.64)	−5.469	−7.550 to −3.539	**0.001**
Beck depression inventory, mean (SD)	11.87 (21.6)	11.22 (22.7)	−0.130	−10.666–9.355	0.897
(B) Grammar elements			***F* value**		
N. Words, mean (SD)	6.16 (3.30)	5.43 (2.16)	0.257	-	0.613**
N. Nouns, mean (SD)	1.64 (1.10)	1.40 (0.80)	0.898	-	0.345**
N. Verbs, mean (SD)	1.42 (1.00)	1.26 (0.86)	0.186	-	0.667**
N. Adjectives, mean (SD)	0.55 (0.63)	0.51 (0.58)	0.101	-	0.751**
N. Pronouns, mean (SD)	0.82 (0.75)	0.70 (0.61)	0.248	-	0.619**
N. Adverbs, mean (SD)	0.36 (0.56)	0.30 (0.47)	0.008	-	0.927**
N. of subjects with ≥ 1 Preposition (%)	27, (36%)	19, (22.6%)	3.450^{++}	-	0.063^{+}
Grammatical form errors, *n*(%)	19, (25%)	16, (18.8%)	0.900^{++}	-	0.343^{+}
Spelling errors, *n*(%)	20, (26.3%)	20, (23.3%)	0.203^{++}	-	0.652^{+}
Lexical-semantic errors, *n*(%)	9, (12%)	7, (8.2%)	2.259^{++}	-	0.520^{+}
Case, mixed features, *n*(%)	43, (56.6%)	55, (64%)	1.813^{++}	-	0.612
Font, cursive letter, *n* (%)	46, (53.5%)	33, (43.4%)	1.648^{++}	-	0.439

AD, Alzheimer Disease; bvFTD, behavioral variant Frontotemporal Dementia; MMSE, Mini Mental State Examination; MoCA, Montreal Cognitive Assessment Battery. Part A. Demographic and clinical characteristics. Student t-test was conducted for variables with exception of gender; for the later $*X^2$ *test was performed. Adjusted p-values ≤0.05 were considered statistically significant and are shown in bold. Part B. Grammar elements of the sentence in bvFTD and AD groups. N, number.* $**$*P-value of ANCOVA analysis using covariates (MMSE total score and age at first evaluation);* $^{+}$*p value for chi square analysis.* $^{++}X^2$ *value.*

MMSE total score as covariates were conducted for continuous variables. Pearson correlations were conducted to assess the relationship between the number of words and the MMSE total score. Two-tailed *p*-values ≤0.05 were considered statistically significant.

Finally, to determine if consideration of the MMSE sentence variables improved the prediction of FTD vs. AD dementia subtype beyond that obtained from age and cognitive screening test scores on the MoCA, the sentence variables found to be statistically significant in the initial analysis were included in a multinomial logistic regression model. Additionally, years of education and MoCA total score were included in the model as covariates. The total score on the MoCA test was selected as it better reflects disease severity across bvFTD and AD groups, particularly at early stages of bvFTD where it is more likely to detect impairments than the MMSE (Coleman et al., 2016)

RESULTS

Demographic and Cognitive Testing Data

One hundred and fifty-eight patients met the inclusion criteria. Participants in the bvFTD ($n = 74$) and AD groups ($n = 84$) were similar in gender distribution, years of education, years of clinical symptoms before diagnosis, and BDI total scores (see **Table 2**, part A). As expected, the mean age at the time of diagnosis was higher for the patients with AD compared to bvFTD. Scores on the cognitive testing screens were lower in the AD group than in bvFTD. Ten participants in the bvFTD group (13.5% of the sample) had a definite diagnosis due to a known mutation (six C9orf72, two MAPT, and two GRN). From the AD group, one patient had a PSEN 1 mutation.

Sentence Elements

The frequency of content variables and between group comparisons are shown in **Figure 1**. A higher proportion of patients with bvFTD wrote sentences addressed to the examiner in comparison to those with AD (22.7% vs. 4.7%, $X^2 = 11.272$, $p = 0.001$). There were no significant differences in the frequency of other content elements including disinhibition (21.3% vs. 12.9%, $X^2 = 2.000$ $p = 0.157$), perseverations (5.3% vs. 5.9%, $X^2 = 0.230$, $p = 0.880$), non-empathic sentences (4.0% vs. 3.5%, $X^2 = 2.770$ $p = 0.250$), negative emotional polarity (13.3% vs. 9.3%, $X^2 = 1.168$, $p = 0.558$), and lack of abstraction (28.0% vs. 31.0%, $X^2 = 0.166$, $p = 0.684$).

The proportion of sentence topics differed between the groups ($X^2 = 10.139$, $p = 0.017$; **Figure 1**). A greater number of patients with AD wrote sentences related to life events (27.2% vs. 11.8%,) and weather (24.7% vs. 20.6%) in comparison to the bvFTD group. A greater proportion of patients with bvFTD wrote about interpersonal relationships (35.3% vs. 16.0%), while a similar proportion was observed for self-descriptive interests (32.2% vs. 32.1%).

The total number of words written, classification of words written, grammatical form variables, lexico-semantic errors, and allographic elements (font and case) did not differ significantly between the groups (see **Table 2**, part B). The total number of words written was positively correlated with the MMSE total score for patients with AD ($r = 0.370$, CI 95% 0.197–0.506, $p < 0.001$), though the correlation did not reach significance in the bvFTD group ($r = 0.209$, CI 95% 0.072–0.344, $p = 0.07$).

The MMSE sentence variables showing significant group differences as described above (sentence addressed to the examiner and sentence topics) were then entered into a

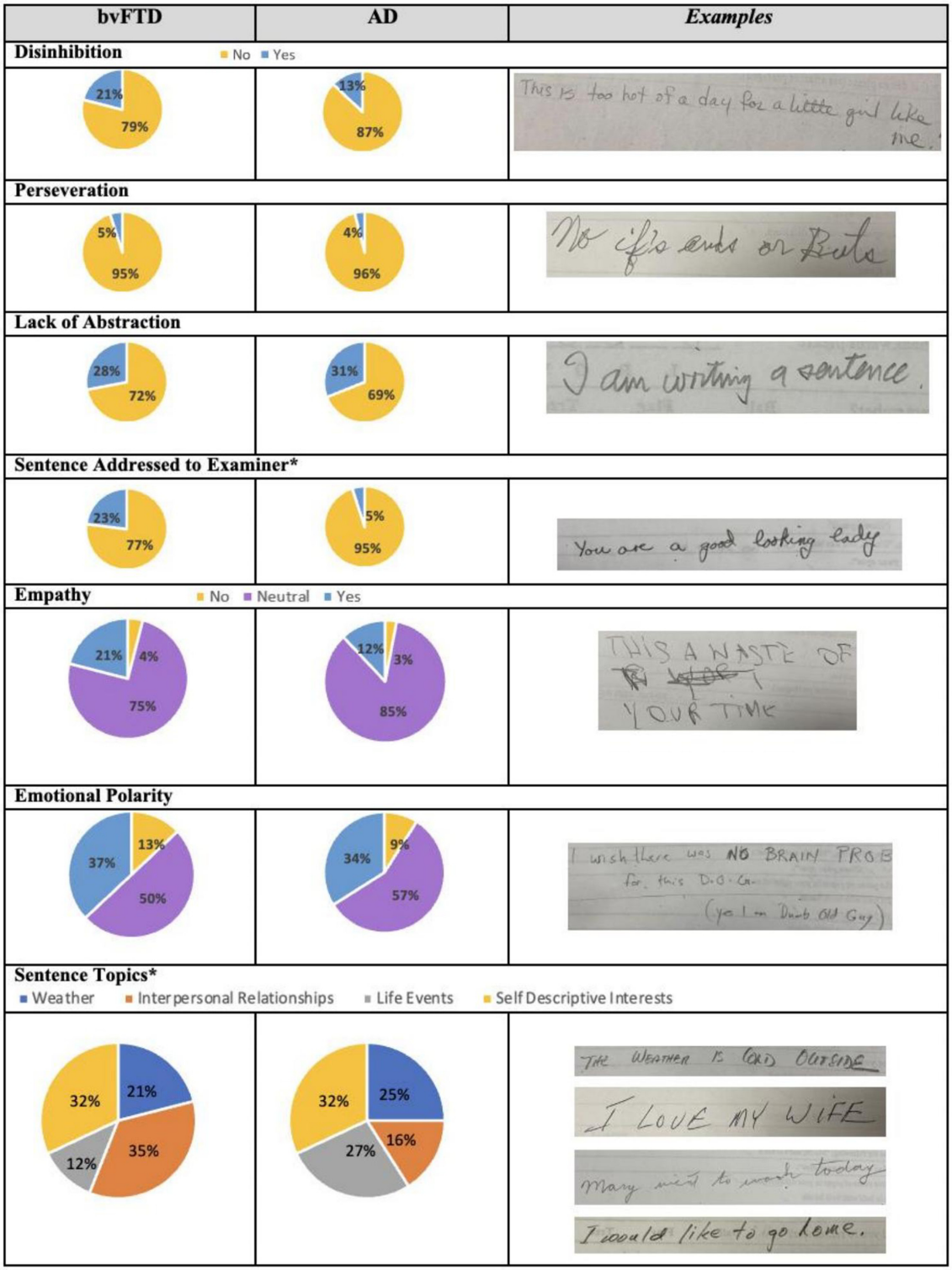

FIGURE 1 | Frequency and examples of sentence content and topics of the MMSE sentence in bvFTD and AD. bvFTD, behavioral variant Frontotemporal Dementia; AD, Alzheimer disease. *p-value <0.05. Examples in the last column are for: presence of disinhibition, presence of perseverations, lack of abstraction, presence of sentence addressed to the examiner, lack of empathy, and negative emotion polarity. Examples for sentence topics are displayed in the following order: weather, interpersonal relationships, life events, and self-descriptive interests.

TABLE 3 | Logistic regression model of MMSE sentence elements to predict bvFTD vs. AD diagnosis.

bvFTD*	b (SE)	*p*-value	Odds Ratio	95% CI Lower	95% CI Upper
Years of education	−0.154 (0.071)	**0.031**	0.857	0.745	0.986
MoCA score	0.189 (0.045)	**<0.001**	1.208	1.106	1.320
Interpersonal relationships	0.713 (0.713)	0.318	2.040	0.504	8.260
Timely life events	−0.283 (0.651)	0.664	0.753	0.210	2.700
Self-descriptive interests	0.797 (0.590)	0.176	2.219	0.669	7.049
Weather	0[b]				
Absence of sentence addressed to examiner	−1.532 (0.909)	0.092	0.216	0.036	1.282

Note. $R^2 = 0.27$ *(Cox and Snell), 0.37 (Nagelkerke). Model* $X^2_{(6)} = 37.944$, $p < 0.001$. **Reference category is Alzheimer Disease. p-values <0.05 were considered statistically significant and are shown in bold. b: this parameter was set to zero because it was redundant in the response category "Topics". b, unstandardized beta coefficient.*

multinomial logistic regression, with years of education and MoCA total score as covariates (see **Table 3**). The model was significant and predicted 37% of the diagnosis variance between the diagnostic groups (Nagelkerke $R^2 = 0.37$). However, none of the content variables contributed significantly to the group membership prediction.

DISCUSSION

To the best of our knowledge, this is the first study to examine whether abnormal behavioral symptoms of bvFTD are reflected in the content of the MMSE sentence item. Contrary to our initial hypothesis, when comparing sentence content from patients with bvFTD to those with AD, both groups overlapped considerably in the majority of MMSE sentence variables of interest. While a greater proportion of patients with bvFTD wrote sentences addressed to the examiner and wrote about interpersonal relationships, differences in the frequencies of these variables did not contribute significantly to predicting bvFTD vs. AD diagnosis.

The patterns observed are in keeping with the classic symptom profiles of bvFTD and AD. The larger proportion of patients with bvFTD addressing their sentence to the evaluator may reflect an environmental dependence-like phenomenon of behavioral disinhibition, where the evaluator is the most novel and salient stimulus in the room (Ghosh et al., 2013). Patients with AD wrote mainly about life events, likely reflecting the heightened representation of relatively preserved long–term memory processes in the context of short–term memory deficits (Weintraub et al., 2012), as most of the sentences related to this topic were descriptions of remote events or routines involving implicit memory processes.

Although these trends fit with predictions, the considerable overlap in the sentence content across the bvFTD and AD groups may reflect the mild stage at which the task was completed. The sentences included in this study were obtained from patients at their first presentation to the cognitive neurology clinic, typically during the initial stages of the disease, when disinhibition and related symptoms are mild or moderate. Further, in the early stages of bvFTD, the highly structured environment in a hospital clinic and cognitive testing room are known to influence the expression of behavioral changes, as patients are often able to conform to behavioral norms for limited periods of time (Snowden et al., 2001). Alternatively, it is possible that written language expression might not be a useful or reliable way to detect behavioral disinhibition, as the act of writing usually is not followed by an instant reinforcement and therefore represents an effortful "pure cognitive" task. Future prospective exploration of qualitative aspects of writing in bvFTD patients could include other features that may reflect impulsivity, such as the time spent in completing the task (e.g., less time in impulsive patients), and samples from more naturalistic settings, such as evaluation of email or texting content.

Patients with bvFTD wrote a greater number of words and grammar elements in comparison with the AD group. Patients with AD also had lower total scores in the MMSE, which was correlated with the number of words written. These results are consistent with previous reports in patients with cognitive decline, showing a positive correlation between the number of words in the MMSE sentence and the MMSE total score (McCarthy et al., 2004; Corallo et al., 2019).

Limitations of this study include the retrospective nature and cross-sectional design. While most of the patients were at the initial stages of disease when differences in performance may be more subtle, we considered this stage most relevant to assessing the value of the MMSE sentence task. Patients in the early stages of the disease are the population most commonly evaluated in primary care settings with cognitive screening tools like the MMSE, where quick assessments of aide diagnosis and direction of referrals are most valuable. While we used the MoCA to control potential differences in disease severity, other clinical measures of function and disease severity, beyond the MMSE and MoCA, were not available for much of this retrospective cohort. Additionally, we did not have data from a healthy control group to compare with the patient groups. Finally, although our inter-rater reliability was high for most of the variables, we observed some discrepancies in our evaluations for the content variables including disinhibition, empathy, and perseverations. Further standardization of these subjective elements may be beneficial given the subjective component of qualifying behavioral elements in a sentence.

In conclusion, patients with bvFTD and AD showed differences in aspects of the content of the written MMSE sentence item, though these differences did not aid in the prediction of diagnosis of bvFTD and AD beyond contributions of age and total MoCA scores. Further studies, including a healthy control group and other dementia subtypes, may be helpful to determine whether consideration of content elements of the MMSE sentence may aid in the differentiation of other dementia subtypes.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of Western Ontario human subjects research ethics board (#R-11-510). The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

EF, RR-G, SP, AR, and CS designed the study. EF and RR-G analyzed and interpreted the data. SY and LR rated all the variables. EF and SP evaluated all the patients. EF supervised the study. All the authors critically revised the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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BRIEF RESEARCH REPORT
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Semantic Memory and Lexical Availability in Parkinson's Disease: A Statistical Learning Study

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Parkinson's disease (PD) is a neurodegenerative disorder that causes a progressive impairment in motor and cognitive functions. Although semantic fluency deficits have been described in PD, more specific semantic memory (SM) and lexical availability (LA) domains have not been previously addressed. Here, we aimed to characterize the cognitive performance of PD patients in a set of SM and LA measures and determine the smallest set of neuropsychological (lexical, semantic, or executive) variables that most accurately classify groups. Thirty early-stage non-demented PD patients (age 35–75, 10 females) and thirty healthy controls (age 36–76, 12 females) were assessed via general cognitive, SM [three subtests of the CaGi battery including living (i.e., elephant) and non-living things (i.e., fork)], and LA (eliciting words from 10 semantic categories related to everyday life) measures. Results showed that PD patients performed lower than controls in two SM global scores (picture naming and naming in response to an oral description). This impairment was particularly pronounced in the non-living things subscale. Also, the number of words in the LA measure was inferior in PD patients than controls, in both larger and smaller semantic fields, showing a more inadequate recall strategy. Notably, the classification algorithms indicated that the SM task had high classification accuracy. In particular, the denomination of non-living things had a classification accuracy of ∼80%. These results suggest that frontostriatal deterioration in PD leads to search strategy deficits in SF and the potential disruption in semantic categorization. These findings are consistent with the embodied view of cognition.

Keywords: Parkinson's disease, semantic memory, verbal fluency, lexical availability, embodied cognition

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INTRODUCTION

How are concepts stored in our minds? Since the conceptual framework of Collins and Quillian (1969), theoretical approaches have emerged in the field of semantic memory (SM) (Tulving, 1972; Caramazza and Hillis, 1991; Ullman, 2001, 2004; Caramazza and Mahon, 2006; Gainotti, 2015; Kumar, 2021). Neuroimaging studies have highlighted the involvement of modality-specific

(sensory, cognitive, and motor) and multimodal neural circuits distributed in the frontal, temporal, and parietal cortex (Simons and Spiers, 2003; Binder and Desai, 2011; Quiroga, 2012). These findings have made it possible to identify a widely distributed cortical network associated with declarative memory.

Semantic fluency (SF) (Bousfield and Sedgewick, 1944) has been a classic SM measure in clinical and experimental neuropsychology. SF is the ability to identify specific categories (i.e., concepts, items, names, and objects) through association in a long-term memory store (Capitani et al., 2003; Robinson et al., 2012). Lexical availability (LA) tasks, which are typically used to identify the potential lexicon that a speaker possesses (of a mother tongue or a foreign language), have essentially the same features of the semantic fluency task (Hernández-Muñoz et al., 2014) with the critical addition of having defined categories (semantic fields) that are relevant to the everyday life of a speaking community, making them especially useful for SF studies.

The critical role of frontal and temporal cortical areas in SF performance has been well-studied. Neuropsychological studies have made it possible to partially identify the neural substrates of the conceptual organization and SM impairments' characteristics. Patients with frontal damage have shown monitoring deficits and poor strategies during the retrieval process (Warrington and Shallice, 1984; Baldo and Shimamura, 1998; Stuss et al., 1998; Troyer et al., 1998; Schwartz and Baldo, 2001; Fuster, 2008; Squire, 2009; Squire and Wixted, 2011; Robinson et al., 2012). These deficits have also been reported in the behavioral variant of frontotemporal dementia (bvFTD) (Burgess and Shallice, 1997; Mayr, 2002; Reverberi et al., 2006, 2014; Possin et al., 2013). Furthermore, temporal lobe damage has been associated with worse performance on semantic fluency tasks (Campanella et al., 2010). Similar findings have been reported in the semantic variant of primary progressive aphasia (sv-PPA) (Hodges et al., 1992; Catricalà et al., 2014; Reverberi et al., 2014; Migliaccio et al., 2016).

Semantic categorization (SC) is a fundamental ability to recognize and classify an object. Indeed, identifying whether a stimulus is a living or non-living object allows us to make inferences and predictions about its behavior and its relationship with the context (Binder and Desai, 2011). The dissociation between semantic categories has been previously addressed. In their seminal work, Damasio and Tranel (1993) reported the dissociated naming performance for objects and verbs in three patients with predominantly frontal or temporal lesions. Recently, the study of neurodegenerative motor disorders also supports the differential role of frontal (motor and premotor) areas in action-verb processing (De Renzi and Di Pellegrino, 1995; Bak et al., 2001, 2006). A relevant dissociation deficit found in PD patients is that of manipulated vs. non-manipulated object naming. These patients perform lower (i.e., accuracy of responses) than controls when naming manipulated objects, but their performance is similar when naming non-manipulated objects (Johari et al., 2019). Notably, response times in manipulated object naming tasks seem to improve in early PD patients receiving both pharmacological and subthalamic DBS treatment (but not pharmacological treatment alone), contrary to non-manipulated object naming. However, accuracy seems to improve for neither type of object (Phillips et al., 2012).

SM is not limited to cortical regions but also extends into the subcortical areas. Currently, it is recognized the role of the basal ganglia in SM (Copland, 2003; Crosson et al., 2003; Longworth et al., 2005; Cardona et al., 2013). Several studies have shown that SM is impaired in Parkinson's disease (PD) patients (Henry and Crawford, 2004; Kudlicka et al., 2011; Angwin et al., 2017). However, the cortico-subcortical circuits' role in PD in categorizing and storing information in the living vs. non-living categories is not clear.

The purpose of the present study was to characterize the cognitive performance of PD patients using a comprehensive set of LA and SM tasks that included living/non-living categories. Importantly, this study aimed to determine the smallest set of neuropsychological (executive, semantic, or lexical) variables that could better classify participants as being PD or control with high accuracy. To our knowledge, the current research is the first to study LA to explore semantic fluency in PD.

MATERIALS AND METHODS

Participants

The study comprised thirty early-stage non-demented PD patients and thirty healthy controls (all right-handed). PD patients' clinical diagnosis was established by an expert neurologist (J.D) following the United Kingdom PD Society Brain Bank Criteria (Hughes et al., 1992). Their motor symptoms and disease stage were assessed using the Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn and Elton, 1987) and the Hoehn and Yahr scale (H&Y) (Hoehn and Yahr, 1967), respectively. All patients were receiving antiparkinsonian therapy and evaluated during the "on" phase of their medication. Control subjects were matched for age, sex, and years of education (see **Table 1**).

No subject in any group presented a history of alcohol/drug abuse, physical or psychiatric conditions, or other neurological illnesses. Also, the groups were comparable in terms of their independent living skills and depressive symptoms, as measured with the Lawton Instrumental Activities of Daily Living Scale (IADL) (Lawton and Brody, 1969) and the Barthel Index for Activities of Daily Living (ADL) (Mahoney and Barthel, 1965), and the Geriatric Depression Scale (GDS) (Yesavage et al., 1982; Gomez-Angulo and Campo-Arias, 2011), respectively (see **Table 1**). All participants provided written informed consent in agreement with the Declaration of Helsinki. The Ethical Research Committee of Universidad del Valle (CIREH 203-015, CI 5278) approved all the study procedures.

Materials

General Cognitive State and Executive Functioning

The participant's general cognitive state was assessed using the Addenbrooke's Cognitive Examination Revised (ACE-R) (Sarasola et al., 2005; Mioshi et al., 2006; Reyes et al., 2009), which allows to simultaneously calculate the Mini-Mental State Examination (MMSE) (Folstein et al., 1975) score. This

TABLE 1 | Demographic, clinical, and neuropsychological data.

		PD patients (n = 30)	Controls (n = 30)	PD vs. controls			
		Median (±MAD)	Median (±MAD)	γ	df	p	ξ
Demographics							
Age (years)[a]		67 (6.67)	62.50 (8.15)	1.49	33.85	0.14	0.26
Sex (M: F)[b]		20:10	18:12	0.29		0.59	
Education (years)[a]		11 (4.45)	11 (2.97)	0.93	33.86	0.36	0.18
Clinical assessment							
Years since diagnosis[a]		2.8 (1.3)	–	–			
H&Y[a]		1.1 (0.3)	–	–			
UPDRS III[a]		25.47 (7.99)	–	–			
GDS[a]		1.50 (2.22)	2 (1.48)	0.83	33.93	0.41	0.17
IADL[a]		8 (0)	8 (0)	–[c]			
ADL[a]		100 (0)	100 (0)	–[c]			
Cognitive measures							
ACE-R[a]		92 (4.45)	92.50 (4.45)	0.95	34	0.35	0.19
MMSE[a]		28 (1.48)	28 (1.48)	0.76	33.96	0.45	0.20
IFS[a]		22 (1.48)	24 (1.48)	3.92	33.98	<0.001***	0.72
Semantic memory tasks							
Picture naming[a]	LT	23 (1.48)	23 (0.00)	0.95	28.28	0.35	0.26
	NLT	22 (1.48)	24 (0.00)	6.71	17	<0.001***	0.9
	Tools	11 (0.48)	12 (0)	8.95	17	<0.001***	0.76
	Non-tools	12 (0)	12 (0)	1.84	17	0.08	–
	Total score	45 (1.48)	47 (0.00)	5.14	22.23	<0.001***	0.66
Naming an oral description[a]	LT	21 (2.97)	22 (2.97)	1.77	32.45	0.09	0.38
	NLT	21.50 (2.22)	23.50 (0.74)	2.92	33.86	0.006**	0.46
	Tools	11 (1.48)	12 (0)	3.38	22.56	0.003**	0.69
	Non-tools	11 (1.48)	12 (0)	0.77	33.9	0.45	0.15
	Total score	43 (4.45)	45 (2.97)	2.31	28.66	0.03*	0.43
Word-picture matching[a]	LT	24 (0)	24 (0)	–[c]			
	NLT	24 (0)	24 (0)	1.16	17	0.26	–
	Tools	12 (0)	12 (0)	1.16	17	0.26	–
	Non-tools	12 (0)	12 (0)	–[c]			
	Total score	48 (0)	48 (0)	1.51	17	0.15	–
KDT[a]		48 (2.97)	50 (1.48)	2.13	25.85	0.04*	0.5
PPT[a]		50 (1.48)	51 (1.48)	1.25	34	0.22	0.21
Lexical fluency task							
Semantic category[a]	Body parts	20 (4.45)	24 (5.93)	2.12	27.8	0.04*	0.43
	Clothes	14 (2.97)	18.50 (5.19)	3.08	26.85	0.005**	0.56
	Parts of the house	15 (5.93)	20 (7.41)	1.95	30.7	0.06	0.36
	Furniture	10.50 (5.19)	11.50 (3.71)	0.27	28.77	0.79	0.05
	Food and drink	19 (5.93)	22 (7.41)	0.86	33.5	0.40	0.17
	Kitchen	16 (7.41)	16 (5.93)	0.16	33.08	0.87	0.03
	Town	14 (3.71)	17 (6.67)	1.49	34	0.14	0.29
	Countryside	10.50 (3.71)	12 (4.45)	1.49	33.47	0.15	0.31
	Animals	19 (4.45)	22 (5.93)	0.72	28.5	0.48	0.14
	Professions	14 (4.45)	14.50 (5.93)	0.33	30.23	0.75	0.06

Values are expressed as medians and median absolute deviations (MAD). PD, Parkinson's disease; H&Y, Hoehn and Yahr Scale (Hoehn and Yahr, 1967); UPDRS, Unified Parkinson's Disease Rating Scale (Fahn and Elton, 1987); GDS, Geriatric Depression Scale (Yesavage et al., 1982); IADL, Lawton Instrumental Activities of Daily Living Scale (Lawton and Brody, 1969); ADL, Barthel Index for Activities of Daily Living (Mahoney and Barthel, 1965); ACE-R, Addenbrooke's Cognitive Examination Revised (Mioshi et al., 2006); MMSE, Mini Mental State Examination (Folstein et al., 1975); IFS, INECO Frontal Screening battery (Torralva et al., 2009); LT, Living things; NLT, Non-living things; KDT, Kissing and Dancing Test (Bak and Hodges, 2003); PPT, Pyramids and Palm Trees (Howard and Patterson, 1992).

[a]p-values were calculated through the Yuen's test (γ).

[b]p-values were calculated through the chi-squared test (χ^2).

[c]In some cases, Yuen's test could not be conducted as the difference between medians, or the variance were 0. In those cases, the estimation of effect sizes was also impeded.

*Significance coding: *p < 0.05; **p < 0.01; ***p < 0.001.*

Alpha level was set at 0.05 for all analyses.

instrument has been extensively used in neurodegenerative diseases (Mioshi et al., 2006; McColgan et al., 2012; Hsieh et al., 2013). The maximum total score in the ACE-R is 100 points (see **Supplementary Section 1**).

Furthermore, subjects' executive functioning was examined through the INECO Frontal Screening (IFS) (Torralva et al., 2009), a validated test to measure executive dysfunction in neurodegeneration (Gleichgerrcht et al., 2011; Broche-Pérez et al., 2019; Moreira et al., 2019). This test comprises the following eight subtests: (1) motor programming (Luria series, "fist, edge, palm"); (2) conflicting instructions (hitting the table once when the administrator hits it twice, or hitting it twice when the administrator hits it only once); (3) motor inhibitory control; (4) numerical working memory (backward digit span); (5) verbal working memory (months backward); (6) spatial working memory (modified Corsi tapping test); (7) abstraction capacity (inferring the meaning of proverbs), and (8) verbal inhibitory control (modified Hayling test). The maximum total score in the IFS is 30 points.

Semantic Memory Tasks

CaGi Battery

The participants performed a previously Spanish adapted version (Moreno-Martínez and Rodríguez-Rojo, 2015; Navarro et al., 2020) of the CaGi battery (Catricalà et al., 2013), which has been widely used in neurodegenerative conditions (Catricalà et al., 2013, 2014, 2015; Della Rosa et al., 2014). This battery includes a set of 48 stimuli belonging to both living (12 animals and 12 vegetables) and non-living entities (12 tools and 12 non-tools).

Specifically, we used the following three subtests: (a) picture naming task, asking the participants to name colored pictures, (b) naming in response to an oral description requiring examinees to name each stimulus after listening to its verbal description (i.e., "*It grows in clusters, has a round shape, is used to make wine.*"), and (c) word-picture matching task, requiring subjects to select, from three pictures, the one corresponding to the spoken word. Correct and incorrect responses were assigned scores of 1 and 0, respectively. Thus, the maximum global score in each task is 48 points.

Pyramids and Palms Trees and Kissing and Dancing Tests

The subjects performed the picture version of two additional tasks assessing semantic memory for objects and actions: the Pyramids and Palms Trees test (PPT) (Howard and Patterson, 1992) and the Kissing and Dancing test (KDT) (Bak and Hodges, 2003). Both tests have been previously used in neurodegenerative diseases (Bak et al., 2001, 2006; Ibáñez et al., 2013). In the PPT, participants are shown 52 triplets of object drawings (1 target, 1 correct match semantically related, and 1 distractor non-semantically related) and asked to match the target picture with the one semantically related. The KDT task structure is analogous to the PPT, but stimuli consisted of pictures depicting actions instead of objects. In both tests, one point is earned for each correct answer, resulting in global scores out of 52.

Lexical Fluency Measures

LA was measured using 10 semantic categories (SC) of the Pan-Hispanic project (PPHDL available at www.dispolex.com), based on the indications for defining the fundamental lexicon of a language (Sánchez and Aguirre, 1992). SC represented an area related to everyday life, including (1) parts of the body, (2) clothes, (3) parts of the house, (4) furniture, (5) food and drinks, (6) kitchen, (7) town, (8) countryside, (9) animals, and (10) professions. In each SC, the participants were asked to orally generate words for 2 min, avoiding producing proper nouns or repeating words. The participants' answers were recorded and analyzed offline. One point was assigned for each correct generated word.

Statistical Analysis

Between-Group Comparisons and Statistical Learning Analysis

Normality was evaluated using the Shapiro-Wilk test. Since the assumption of normality was not met, we tried several transformations but none of them normalized the data, so we retained the original scores and proceeded using Yuen (1974)'s test (γ) for between groups comparisons of demographic and behavioral data. Sex was analyzed using the chi-squared test (χ^2). The statistical significance level was set at $p < 0.05$ for all analyses. Effect sizes were calculated through Wilcox and Tian'ξ (2011), implemented in the WRS2 package (Mair and Wilcox, 2020).

Additionally, statistical learning analyses were conducted to explore which measures best classify groups using the smallest possible set of variables. The predictors were categorized into demographic and neuropsychological (*dem/nepsy*) and lexical (*lex*) clusters. The *Dem/nepsy* cluster included age, years of education, sex, ACE-R, MMSE, IFS, working memory index, the CaGi battery total scores, and the living/non-living subscores, the KDT, and the PPT scores as predictors. The SC of the LA task was introduced as a covariate in this cluster. The *lex* cluster included log-frequency, number of letters, orthographic neighborhood, number of phonemes, number of syllables, familiarity, imageability, and concreteness as predictors.

Then, each cluster of variables was submitted to "one rule" (*1R*) (Holte, 1993) and Boruta (*B*) (Kursa and Rudnicki, 2010) classification algorithms, which rank the variables according to their classification accuracy (*1R*) and relative importance (*B*), respectively. The three strongest classifiers identified by each algorithm were kept.

Finally, four logistic regression models were conducted to ascertain which combination of variables had the highest predicting level (see **Table 2**). Each model included a combination of two of the strongest classifiers of the *dem/nepsy* and *lex* clusters as independent variables and group (PD patients and controls) as the dependent variable, following the structure $group \sim lex + dem/nepsy$. The models were fitted using the standard GLM with a binomial distribution (logit link function). The best classification model was represented via classification trees and spinograms (Everitt and Hothorn, 2014). All analyses were conducted using R version 3.6 (R Core Team., 2020). The R codes and data sets are available at https://figshare.com/projects/memory_and_lexicality_in_Parkinson/99800.

TABLE 2 | Logistic regression models combining the four variables suggested by the classification algorithms.

	Metrics				
Predictor variables	***z (p)***	**VIF**	***p-R²***	**AIC**	**BIC**
Denomination NLT + familiarity	Denomination NLT = −3.50 (0)	1	0.21	544.25	556.84
	Familiarity = −0.46 (0.65)	1			
Denomination NLT + imageability	Denomination NLT = −3.51 (0)	1	0.21	539.89	552.48
	Imageability = −2.47 (0.01)	1			
IFS total score + familiarity	IFS = −5.98 (0)	1	0.09	623.53	636.11
	Familiarity = −0.64 (0.53)	1			
IFS total score + imageability	IFS = −6.02 (0)	1	0.10	620.21	632.80
	Imageability = −1.71 (0.09)	1			

Abbreviations: g, group (Parkinson vs. Control); dnlt = denomination of non-living things; t.IFS, total_IFS; im, imageability; fa, familiarity. z (p), z-value and associated p-value; VIF, variance inflation factor; p-R^2, McFadden pseudo-R^2 (see Table 6 in Hemmert et al., 2018 for interpretation); AIC, Akaike information criterion; BIC, Bayesian information criterion. The model with the best fit is shaded in gray.

Lexical Availability Analysis

First Step

All perseverative responses were excluded. We used the lexical statistical program Dispolex (available at http://www.dispolex.com) following previous studies (Samper-Padilla, 1998; Bartol-Hernández and Hernández-Muñoz, 2003; Hernández-Muñoz et al., 2006, 2014; Mateus and Santiago, 2006; López-Morales, 2014). This program provided us: (a) the total number of words' occurrences (tokens), (b) each lexical unit (types) counts, (c) the average number of responses, and (d) the frequency and position of each word in each semantic category (LA index), and (e) the degree of coincidence in informants' word response (lexical cohesion index) (Echeverría, 1991; Hernández-Muñoz, 2010).

Second Step

In each category, words with a frequency of appearance lower than 4.17% (frequency equal to 1) were excluded. Subsequently, a lexical properties analysis was conducted by identifying: (a) orthographic structure: word frequency and number of letters, (b) orthographic neighborhoods: Levenshtein distance (Levenshtein, 1966), (c) phonological structure: number of phonemes and number of syllables, and (d) word's subjective ratings: familiarity, imageability, and concreteness.

These linguistic variables for Latin American Spanish were identified in the web interface to Spanish word frequency data and other word properties based on written and subtitle corpora (Duchon et al., 2013) (available at https://www.bcbl.eu/databases/espal/).

RESULTS

General Cognitive State

No between-group differences were observed in the ACE-R [$\gamma_{(34)} = 0.95$, $p = 0.35$, $\xi = 0.19$] and the MMSE [$\gamma_{(33.96)} = 0.76$, $p = 0.45$, $\xi = 0.20$] total scores. However, PD patients performed lower than controls in the IFS total score [$\gamma_{(33.98)} = 3.92$, $p < 0.001$, $\xi = 0.72$], the digits backward subtest [$\gamma_{(28.66)} = 2.65$, $p = 0.01$, $\xi = 0.44$], the working memory index [$\gamma_{(33.96)} = 2.22$, $p = 0.03$, $\xi = 0.46$], and marginally lower in the verbal inhibitory control subtest [$\gamma_{(33.31)} = 1.76$, $p = 0.09$, $\xi = 0.38$] (see **Table 1** and **Supplementary Table 1**).

Semantic Memory Tasks

CaGi Battery

Picture Naming Task

PD patients globally scored lower than controls [$\gamma_{(22.23)} = 5.14$, $p < 0.001$, $\xi = 0.66$]. Specifically, patients performed lower than controls in naming non-living things [$\gamma_{(17)} = 6.71$, $p < 0.001$, $\xi = 0.9$] and tools [$\gamma_{(17)} = 8.95$, $p < 0.001$, $\xi = 0.76$]. No significant between-group differences were observed in the denomination of living things [$\gamma_{(28.28)} = 0.95$, $p = 0.35$, $\xi = 0.26$] and non-tools [$\gamma_{(17)} = 1.84$, $p = 0.08$] (see **Table 1**).

Naming in Response to an Oral Description

PD patients globally performed lower than controls [$\gamma_{(28.66)} = 2.31$, $p = 0.03$, $\xi = 0.43$]. Particularly, patients exhibited lower scores in naming non-living things [$\gamma_{(33.86)} = 2.92$, $p = 0.006$, $\xi = 0.46$] and tools [$\gamma_{(22.56)} = 3.38$, $p = 0.003$, $\xi = 0.69$]. The groups' performance did not differ in naming living things [$\gamma_{(32.45)} = 1.77$, $p = 0.09$, $\xi = 0.38$] and non-tools [$\gamma_{(33.9)} = 0.77$, $p = 0.45$, $\xi = 0.15$] (see **Table 1**).

Word-Picture Matching

No significant differences between groups were observed in the global performance [$\gamma_{(17)} = 1.51$, $p = 0.15$], and the denomination of living things (equal medians), non-living [$\gamma_{(17)} = 1.16$; $p = 0.26$], tools [$\gamma_{(17)} = 1.16$, $p = 0.26$] and non-tools categories (equal medians) (see **Table 1**).

Pyramids and Palms Trees and Kissing and Dancing Tests

KDT total score was lower in PD patients than in controls [$\gamma_{(25.85)} = 2.13$, $p = 0.04$, $\xi = 0.5$], there being no significant between-group differences in the PPT scores [$\gamma_{(34)} = 1.25$, $p = 0.22$, $\xi = 0.21$] (see **Table 1**).

Lexical Fluency Performance

Qualitatively, PD patients exhibited a lower total number of words (tokens) in large (i.e., countryside) and small (i.e., parts

TABLE 3 | Results of the classification accuracies and variable's importance.

Variable cluster	Variable	Algorithm (ranks)	
		1R Classification accuracy (%)[a]	*B* Relative importance[b]
Demographic and neuropsychological *(dem/nepsy)*	Denomination of non-living things	79.59% (1)	26.54 (1)
	IFS total score	69.39 (3)	22.12 (2)
	Global denomination score	77.55% (2)	21.74 (3)
Lexical *(lex)*	Imageability	53.48% (2)	0.69 (3)
	Familiarity	54.49% (1)	0.75 (2)
	Levenshtein distance	52.65% (3)	
	Concreteness		1.71 (1)

The best three variables per classification algorithm are shown.
[a] *Values calculated through the one-rule (1R) algorithm.*
[b] *Values calculated through the Boruta (B) algorithm.*
In the case of the Lex variables, the B algorithm indicated that none of the variables was deemed necessary (see details in the ***Supplementary Material****).*
Note that in the case of dem/nepsy variables, all three variables were common to both classification algorithms, and while denomination of non-living things was the best according to each algorithm, IFS total score and global denomination score were equally valid; for simplicity though one of these was retained for further analyses. All variables retained for further analyses are shaded in gray. Empty cells are cases when the variables Levenshtein distance and concreteness had ranks above three and/or gave classification accuracies below 50%.

of the body) semantic categories (see **Supplementary Section 2.1** and **Supplementary Table 3**).

Lexical Units Index

In PD patients, the two SC with the most different lexical units corresponded to animals (79 lexical units) and food and drinks (74 lexical units). In contrast, the least productive SC were countryside (33 lexical units) and furniture (38 lexical units). In **Supplementary Table 3**, there was no direct relationship between general lexical productivity and word types (a measure of lexical richness).

In controls, the most productive SC with the highest number of word types were food and drinks (83 lexical units) and body parts (74 lexical units). Like the PD group, the least productive SC were countryside (42 tokens) and furniture (43 lexical units).

Lexical Availability Index and Lexical Cohesion Index

Results are summarized in **Supplementary Section 2.2, 2.3** and **Supplementary Tables 1, 2**.

Statistical Learning Analysis

In the *dem/nepsy* cluster, the denomination of non-living things, the global denomination score, and the total IFS score were the strongest variables for distinguishing between groups, correctly classifying 79.6% (58.3% of PD and 100% of controls), 77.5% (54.2% of PD patients and 100% of controls), and 69.4% (75% of PD patients and 64% of controls) of the overall cases, respectively. These variables also obtained the highest relative importance, only slightly varying in their order: denomination of non-living things (B = 26.54), total IFS score (B = 22.12), and global denomination score (B = 21.74) (see **Table 3**).

In the *lex* cluster, familiarity, imageability, and Levenshtein distance were the strongest predictors of group membership, successfully classifying 55% (58.8% of PD patients and 50% of controls), 53.5% (60% of PD patients and 48% of controls), and 52.7% (12.1% of PD patients and 91.6% of controls of the total cases, respectively. Besides, concreteness reached the highest relative importance (B = 1.71), followed by familiarity (B = 0.75) and imageability (B = 0.69) (see **Table 3**). Nevertheless, both classification algorithms indicated that these and other *lex* variables had classification accuracies near chance (*1R*) and low importance (*B*) (see **Table 3**).

Logistic Models

The model combining the denomination of non-living things ($z = -3.51$, $p < 0.01$) and imageability ($z = -2.47$, $p = 0.01$) reached the best fit (p-R^2 = 0.21, AIC = 539.89, BIC = 552.48) (see **Table 3**). However, this model was not pursued given the results of the classification algorithms regarding the *lex* variables; as shown in **Table 1**, all lexical variables had classification accuracies near chance (*1R* algorithm) and very low importance (*B* algorithm). Thus, the model *group* ∼ *dnlt* was examined via a classification tree and a spinogram.

The classification tree results suggested that when a person produces less than 24 denominations of non-living things, there is about an 85% chance of being classified as a PD patient. If the person produces about 24 or more denominations, the chances of the person being classified as a PD patient are about 9% (**Figure 1B**). The spinogram further corroborates these approximate likelihoods and provides the observed counts for different bins (**Figure 1A**). It is important to stress that the cut-offs are merely approximations and need to be revised within the task context.

DISCUSSION

This study aimed to characterize the cognitive performance of PD patients using a comprehensive set of lexical fluency and SM tasks and determine the smallest set of measures that best classify the groups. The classification algorithms indicated that some of the SM tasks had the highest classification accuracies while none of the executive or lexical variables had reliably classified groups.

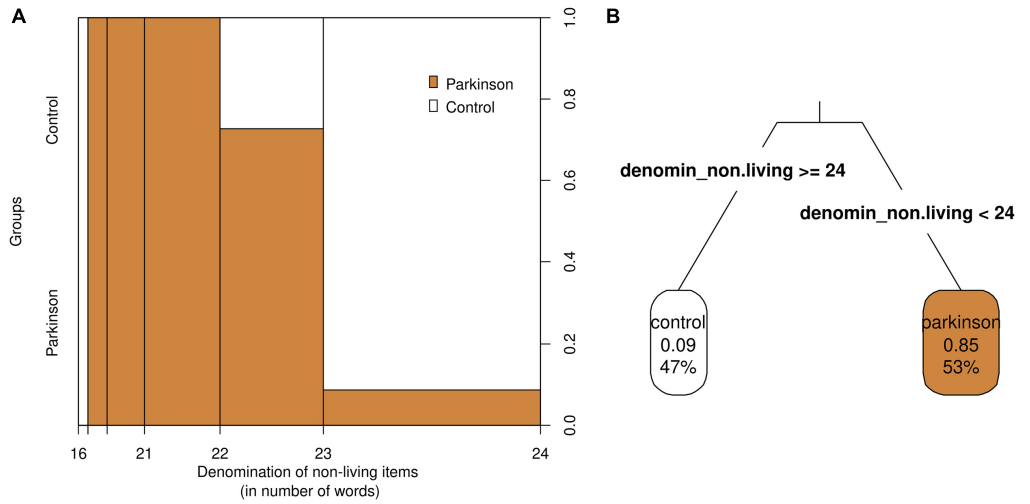

FIGURE 1 | Spinogram **(A)** and classification tree **(B)** of the model *group* ~ *dnlt*. **(A)** The widths of the bins in the *x*-axis in the spinogram represent the frequencies (number of participants that obtained a score) within each bin. For example, there were more observations between 23 and 24 denominations than between 16 and 21 denominations. Colors represent groups, white being for controls (always on top) and orange being for PD patients (always below). The right y-axis represents the proportion of subjects that belonged to each group in each of the bins. **(B)** The classification tree shows the likelihood of being classified as control or PD depending on a cut-off score of 24 in the denomination of non-living things subtask.

In particular, the "denomination of non-living things" had the highest classification accuracy of ∼80%.

Semantic Memory in PD

PD patients showed an inferior performance in two naming tasks of CaGi measures. In line with previous studies, significant differences were observed in the visual and auditory input tasks (Portin et al., 2000; Rosenthal et al., 2017; Salmazo-Silva et al., 2017). Importantly, this inferior performance was most notable in the SM category of non-living things.

From an embodied perspective (Tirado et al., 2018; Khatin-Zadeh et al., 2021), these results could be attributed to PD patients' difficulty to access manipulable objects' semantic representation. Previous studies suggest that PD is associated with deficits in the semantic representation of actions/verbs that imply movement (Cardona et al., 2014; Bocanegra et al., 2015; Melloni et al., 2015; Suárez-García et al., 2021) or functional manipulability (Péran et al., 2009; Herrera et al., 2012; Bocanegra et al., 2017). This poor PD performance is associated with the disrupting basal ganglia-frontal circuit activated during action processing and object manipulation tasks. It has been shown that this circuit participates in the crucial coupling between motor and linguistic information (Pulvermüller, 2005; Pulvermüller et al., 2005; Melloni et al., 2015) and that its disruption hinders such coupling (Ibáñez et al., 2013). However, as this study did not include neurophysiological/neuroimaging measures, further evidence is needed to support this view. As the semantics of manipulable objects entails body movement, deterioration of the mentioned circuit might explain why PD patients have a challenging time accessing these semantic representations. This is further confirmed by the findings in the tools' subcategory of the picture naming and naming on oral description tasks, in contrast to the non-tools subcategory (although there was a trend in the first task). These results converge with a growing corpus of research showing impairments in action semantics in PD and hint that the possibility of impairments in the semantic processing of non-living things is likely to be driven by the presence of motor representations (manipulability) in the semantic store of these objects.

As previous research has shown, manipulable objects naming is particularly impaired in PD (Johari et al., 2019). However, it might be possible to account for these deficits with techniques such as subthalamic DBS even in early PD (Phillips et al., 2012). The present findings also suggest that the comprehension of manipulable objects might deteriorate, so its treatment should also be explored through adjuvant electrical stimulation techniques.

Although PD patients did not present mild cognitive impairment, EF deficits were observed, especially in working memory and partially in verbal inhibitory control, as measured in the IFS scale by the digits backward task, and a shortened version of the Hayling test, respectively. These results agree with previous studies highlighting executive dysfunction as a frequent trait in PD's initial stage (Barone et al., 2011; Khoo et al., 2013; Liu et al., 2017). Furthermore, while the IFS global score reached a high classification accuracy, it was not superior to that of denomination of non-living things, hinting that these semantic deficits might be more characteristic to PD than executive deficits.

Lexical Availability in PD

Meta-analysis has shown that non-demented PD patients have semantic fluency impairments (Henry and Crawford, 2004; Kudlicka et al., 2011). Some authors suggest a selective lexical retrieval impairment in PD and frontal patients (Rogers et al., 1998; Silveri et al., 2017; Johari et al., 2019). Tagini et al. (2018)

speculate that this deterioration may be due to a low activation level (difficulty in initiation, bradyphrenia) that slows down the production rate throughout the task or a damaged semantic store.

No previous research has explored the lexical availability in PD. Our study's total number of words per semantic field was inferior in the PD group in both large and small semantic categories. These results indicate that PD patients present an overall more deficient search strategy in the semantic store and deficits in switching from one subcategory to another than controls. The inferior performance shown in these semantic categories is expectable given the delay of speech initiation, bradyphrenia, and the fact that PD patients perform worse than healthy controls in all categories, although not all of them reached statistical significance.

Semantic fluency tasks are less automatic than naming or matching tasks (Fernandino et al., 2013; Salmazo-Silva et al., 2017). Several cognitive domains contribute to performance on fluency tasks (Rosen and Engle, 1997; Reverberi et al., 2006, 2014; Unsworth et al., 2011; Robinson et al., 2012; Tagini et al., 2018). In this way, generating search strategies and concepts' internal organization is critical for satisfactory performance.

Limitations

This work has significant limitations. First, we did not use the complete CaGi battery, including the picture sorting, free generation of features, and sentence verification subtests due to the participants' fatigue and/or disinterest. Another limitation is the absence of the switching and clustering index. Without these analyses, semantic proximity is unknown, and therefore, it cannot be inferred whether the observed deficits are associated with alterations in strategic retrieval processing or monitoring deficits. These limitations prevent a broader interpretation of the results. Finally, we acknowledge that the levodopa equivalent dose is a highly relevant variable missing in this study since previous studies have shown an effect of dopaminergic medication in semantic processing related to action (Boulenger et al., 2008; De Letter et al., 2012, 2020).

CONCLUSION

To summarize, our results suggest that semantic memory is affected in early-stage non-demented PD patients. More importantly, a potential dissociation between living and non-living things categories was found, consistent with previous findings in the study of cognition in PD and the embodied perspective of cognition. Future studies involving neuroimaging techniques can provide fine-grained spatial and functional brain information.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/**Supplementary Material**.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethical Research Committee of Universidad del Valle (CIREH 203-015, CI 5278). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JFC, GM-F, and FM-R developed the study concept and the study design. JG-C, CT-L, LT, JC, JD, and TJ performed the testing and data collection. JFC, FM-R, JG-C, CT-L, and GM-F performed the data analysis and interpretation. JFC, JG-C, CT-L, HU, SC, AT, LG, and JC drafted the manuscript. NO-C, FM-R, and GM-F provided the critical revisions. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2021.697065/full#supplementary-material

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Classifying Parkinson's Disease Patients With Syntactic and Socio-emotional Verbal Measures

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Frontostriatal disorders, such as Parkinson's disease (PD), are characterized by progressive disruption of cortico-subcortical dopaminergic loops involved in diverse higher-order domains, including language. Indeed, syntactic and emotional language tasks have emerged as potential biomarkers of frontostriatal disturbances. However, relevant studies and models have typically considered these linguistic dimensions in isolation, overlooking the potential advantages of targeting multidimensional markers. Here, we examined whether patient classification can be improved through the *joint assessment* of both dimensions using sentential stimuli. We evaluated 31 early PD patients and 24 healthy controls *via* two syntactic measures (functional-role assignment, parsing of long-distance dependencies) and a verbal task tapping social emotions (envy, *Schadenfreude*) and compared their classification accuracy when analyzed in isolation and in combination. Complementarily, we replicated our approach to discriminate between patients on and off medication. Results showed that specific measures of each dimension were selectively impaired in PD. In particular, joint analysis of outcomes in functional-role assignment and *Schadenfreude* improved the classification accuracy of patients and controls, irrespective of their overall cognitive and affective state. These results suggest that multidimensional linguistic assessments may better capture the complexity and multi-functional impact of frontostriatal disruptions, highlighting their potential contributions in the ongoing quest for sensitive markers of PD.

Keywords: Parkinson's disease, sentential processing, multidimensional assessment, syntactic processing, social emotions

INTRODUCTION

Given the high prevalence of frontostriatal motor disorders in general, and Parkinson's disease (PD) in particular (Rossi et al., 2018), increasing efforts are being made to identify condition-sensitive markers (Delenclos et al., 2016). Cognitive evaluations prove highly useful, as they are inexpensive, non-invasive, and easily applicable (Bocanegra et al., 2015; García et al., 2017, 2018a). Frontostriatal circuits, which are crucially involved in motor function and become impaired early in PD (Samii et al., 2004; Rodriguez-Oroz et al., 2009), subserve multiple high-order functions, including decision-making, cognitive flexibility, attention, working memory, reward monitoring, motivation, error monitoring (Chudasama and Robbins, 2006; Morris et al., 2016; Birba et al., 2017), and, no less importantly, linguistic (Grossman et al., 2001; Ibáñez et al., 2013; Birba et al., 2017) and emotional (Takahashi et al., 2009; Baez et al., 2016, 2018) processing.

Candidate markers of frontostriatal disruptions have been obtained through separate assessments of specific verbal dimensions: syntax and emotional language processing (Paulmann et al., 2011; Bocanegra et al., 2015; Birba et al., 2017; Dissanayaka et al., 2017; García et al., 2017). Notwithstanding, most studies on PD have ignored the anatomical complexity and multifunctionality of frontostriatal circuits, considering language dimensions as compartmentalized (if not altogether modular) functions. This isolationist approach to cognitive processes precludes the identification of multidimensional markers, which are potentially more sensitive for the characterization and identification of PD patients. For instance, multidimensional linguistic (acoustic, prosodic, and semantic) markers surpass unidimensional ones in sorting between PD patients "on" and "off" medication (Norel et al., 2018). Despite recent calls for more integrative multidimensional frameworks to characterize cognitive processes (Ibáñez and García, 2018; Ibáñez, 2019) and their dysfunctions in neurological conditions (Caselli et al., 2014; Canevelli et al., 2015; Delenclos et al., 2016), no study in PD has yet explored whether patient classification can be improved through a joint assessment of syntactic and emotional language processing. Therein lies the aim of this article.

As shown in multiple studies, frontostriatal compromise can be robustly indexed through performance on syntactic processing tasks (for a review, see Birba et al., 2017). Notably, subtle deficits have been obtained through assessments of functional-role assignment (a predominantly sequential form of syntactic processing) and the establishment of long-distance dependencies (which distinctly taxes hierarchical processing mechanisms; Bocanegra et al., 2015; García et al., 2017). In frontostriatal disorders like PD and Huntington's disease (HD), these subdomains are affected in early stages irrespective of the patients' executive skills or overall cognitive status (Bocanegra et al., 2015; García et al., 2018b). Moreover, evidence from asymptomatic PD-mutation carriers indicates that functional-role assignment can be selectively disrupted in preclinical stages, even before other linguistic or extralinguistic domains are affected (García et al., 2017). Therefore, performance on this particular dimension emerges as a potentially sensitive marker of the disease.

Also, frontostriatal atrophy has been linked to emotional processing (Baez et al., 2016, 2017, 2018). In particular, patients with PD show impairments in emotional language comprehension (Zgaljardic et al., 2003; Pell and Monetta, 2008). Furthermore, subtle impairments in motor disorders have been revealed through verbal measures of *Schadenfreude* (pleasure at others' misfortunes). Response to sentences evoking *Schadenfreude* is selectively reduced upon frontostriatal atrophy (Baez et al., 2018). Alongside evidence of other emotional impairments in PD (Pell and Leonard, 2005; Ibarretxe-Bilbao et al., 2009), these findings suggest that verbal assessments of *Schadenfreude* could also reveal early deficits in this condition.

Notably, syntax and verbal emotion processing constitute different linguistic dimensions, characterized by dissimilar putative substrates [neostriatum for syntax (Szalisznyo et al., 2017), ventral striatum for *Schadenfreude* (Takahashi et al., 2009; Baez et al., 2018)], levels of automaticity [more automatic for syntax (Pulvermuller et al., 2008), more conscious for social emotions (Baez et al., 2017)], and connectivity patterns [increased connectivity between the striatum and Broca's area for syntax (Teichmann et al., 2015), higher connectivity between the ventral striatum and insular regions for social emotions (Paulus et al., 2018)]. However, the evidence above indicates that, beyond their disparity, both domains are sensitive to subtle disturbances in early disease stages, which likely attests to the anatomical (Chudasama and Robbins, 2006), neurochemical (Chudasama and Robbins, 2006), and functional (Grossman et al., 2001; Morris et al., 2016) complexity of frontostriatal circuits affected in PD. This opens a fertile path for research, since the classification of patients with neurodegenerative disorders (Devanand et al., 2008), including PD (Delenclos et al., 2016; Norel et al., 2018), may be improved through multidimensional assessments.

Here, our assessment of syntax included functional-role assignment and long-distance dependencies tasks. For the assessment of emotional language processing, we focused on social emotions given that their ecological relevance to characterizing daily interpersonal skills (Baez et al., 2017). In the latter case, we employed a validated paradigm (Baez et al., 2016, 2018; Santamaria-Garcia et al., 2017; Gomez-Carvajal et al., 2020) consisting of declarative affirmative sentences, which trigger *Schadenfreude* and envy (another social emotion acting as a control condition). Considering previous evidence, we hypothesized that combined measures of functional-role assignment and *Schadenfreude* would yield better patient discrimination relative to other syntactic and emotional dimensions. Moreover, given that levodopa bioavailability has been shown to modulate performance in different linguistic (Herrera and Cuetos, 2012; Herrera et al., 2012) and emotional (Lawrence et al., 2007; Mondillon et al., 2012) tasks, we conducted an exploratory comparison between PD patients in "on" and "off" stages of their medication (PD-on and PD-off, respectively). Briefly, this study aims to nurture an emergent trend highlighting the potential clinical benefits

of multidimensional assessments for the classification of PD patients.

MATERIALS AND METHODS

Participants

The study comprised 31 cognitively preserved PD patients and 24 healthy controls matched for age, sex, and years of education (**Table 1**). Patients were diagnosed according to the UK PD Society Brain Bank criteria (Hughes et al., 1992). Their motor symptoms were assessed with part III of the Unified Parkinson's Disease Rating Scale (UPDRS) and the Hoehn & Yahr scale (H&Y). All patients completed this initial assessment in the "on" stage of Levodopa. Then, for our core language protocol, the PD sample was subdivided into patients tested "on" (n = 15) and "off" (n = 16) medication. These subgroups were also paired in terms of age, sex, education, years since diagnosis, and UPDRS scores. To prevent biases in task administration, investigators were blinded to the patients' medication status.

All samples were also comparable in terms of their independent living skills and depressive symptoms, as measured with Lawton and Brody Index (L&B) and the Hamilton Depression Rating Scale (HDRS), respectively. They were also matched for the general cognitive state, as assessed *via* the Montreal Cognitive Assessment (MoCA), and executive function skills, as measured with the INECO Frontal Screening (IFS). The MoCA (Nasreddine et al., 2005) comprises evaluates attention, executive functions, memory, language, visuoconstructional and visuospatial skills, conceptual thinking, calculations, and orientation. The IFS battery (Torralva et al., 2009) includes the following eight subtests: (1) motor programing (Luria series, "fist, edge, palm"); (2) conflicting instructions (hitting the table once when the administrator hits it twice, or hitting it twice when the administrator hits it only once); (3) motor inhibitory control; (4) numerical working memory (backward digit span); (5) verbal working memory (months backward); (6) spatial working memory (modified Corsi tapping test); (7) abstraction capacity (inferring the meaning of proverbs); and (8) verbal inhibitory control (modified Hayling test). Importantly, all of these tests have proven sensitive to frontostriatal disorders, including PD (Nazem et al., 2009; Bocanegra et al., 2015). See details in **Table 1** and **Supplementary Data 1, 2**.

No subject in any group reported a history of alcohol/drug abuse, psychiatric conditions, or other neurological illnesses. All participants provided written consent in agreement with the Declaration of Helsinki. The Institutional Ethics Committee approved this study.

Materials

Syntactic Tasks

Syntactic comprehension was examined through the Touching A with B and the Embedded Sentences subtests of the Boston Diagnostic Aphasia Examination (Goodglass et al., 2000), which are sensitive to frontostriatal disorders (García et al., 2018b), including PD (Bocanegra et al., 2015; García et al., 2017). In both subtests, participants were required to select which of four pictures best represents a given utterance read by the examiner. In Touching A with B (12 items, maximum score = 12), each picture depicts the hand of a person holding or touching objects. The examiner read sentences including the verb *touching* in present participle form and two nouns that vary in syntactic function. In some sentences, both nouns are the direct object of *touching* (e.g., *Touching the spoon and the scissors*), while, in others, one of the nouns is a direct object and the other is an instrumental adjunct (e.g., *Touching the scissors with the comb*). Therefore, this task taps the syntactic domain of functional-role assignment (García et al., 2017, 2018b). In the Embedded Sentences subtest (10 items, maximum score = 10), stimuli consist in sentences including a restrictive relative clause as part of their subject (e.g., *The woman who is fat is kissing her husband*) or direct object (e.g., *The girl is chasing the boy who is wearing boots*). Thus, this subtest focuses on the processing of long-distance dependencies (García et al., 2017, 2018b).

Socio-emotional Language Task

Levels of *Schadenfreude* and envy were measured with a verbal task that proves sensitive to frontostriatal disorders (Baez et al., 2016, 2018; Santamaria-Garcia et al., 2017). Participants were first shown a real-life photograph and a brief description of two characters matched in age and sex with each participant. Then, in the first experimental block, participants read 15 sentences describing fortunate situations occurring to either of the two characters, and they indicated how much envy they felt for the character on a scale from 1 (no envy) to 9 (extreme envy). In the second block, participants were presented with 15 unfortunate situations involving either character and they rated their levels of *Schadenfreude* from 1 (no pleasure) to 9 (extreme pleasure). Furthermore, five neutral events were included in each block for control purposes. Considering that envy predicts the levels of *Schadenfreude* (Takahashi et al., 2009), the envy block was presented first. Situations were pseudorandomly distributed within each block. See details in **Supplementary Data 3**.

All stimuli in the envy and *Schadenfreude* blocks consisted of declarative affirmative sentences, with their main verb in active voice and past tense (more precisely, *pretérito perfecto indefinido*). Also, all sentences in both sets comprised two clauses (standing in either paratactic or hypotactic relation) with a strictly systematic syntactic pattern [i.e., (tacit) subject + verb + optional complement].

Statistical Analysis

Neuropsychological and behavioral data were analyzed using one-way ANOVAs. First, we compared the performance of all PD patients and all controls. Then, to assess the impact of medication state, we reiterated the analyses comparing PD-on vs. PD-off patients. Also, to control for the effect of general cognitive state, executive functions, and depressive symptoms on experimental results, we performed ANCOVA tests adjusted independently for total MoCA, IFS, and HDRS scores—for maximal informativeness, results are reported both before and after co-variation. Alpha levels were set at 0.05 for all analyses. Effect sizes were calculated through Cohen's d, with

TABLE 1 | Demographic and clinical characteristic of the participants.

	PD patients (*n* = 31) Mean (*SD*)	Controls (*n* = 24) Mean (*SD*)	PD-on (*n* = 15) Mean (*SD*)	PD-off (*n* = 16) Mean (*SD*)	PD vs. controls *p*-value	PD-on vs. PD-off *p*-value
Demographics						
Age (years)[a]	61.74 (5.14)	59.58 (7.22)	61.20 (6.19)	62.25 (4.07)	0.20	0.57
Sex (F:M)[b]	13:18	12:12	6:9	7:9	0.55	0.83
Education (years)[a]	11.77 (4.16)	12.21 (4.40)	12.31 (3.83)	11.20 (4.55)	0.71	0.46
Clinical assessment						
Years since diagnosis[a]	3.48 (1.48)	-	3.27 (1.39)	3.69 (1.59)	-	0.43
UPDRS-III[a]	18.68 (11.58)	-	21.93 (10.90)	15.63 (11.70)	-	0.13
L&B[a]	6.0 (1.48)	6.42 (1.56)	6.20 (1.52)	5.81 (1.47)	0.31	0.47
H&Y[a]	4.94 (3.08)	4.25 (3.14)	4.27 (2.82)	5.56 (3.27)	0.42	0.24
Cognitive assessment						
MoCA[a]	25.0 (2.35)	25.38 (2.37)	25.0 (2.51)	25.0 (2.28)	0.56	1.00
IFS[a]	22.65 (3.70)	24.25 (3.09)	23.33 (3.92)	22.0 (3.48)	0.09	0.32

PD, Parkinson's disease; PD-on, Parkinson's disease patients in the "on" state of medication; PD-off, Parkinson's disease patients in the "off" state of medication; UPDRS, Unified Parkinson's Disease Rating Scale; H&Y, Hoehn & Yahr Scale; L&B, Lawton and Brody Index; MoCA, Montreal Cognitive Assessment; IFS, INECO Frontal Screening battery. [a]p-values were calculated through one-way ANOVA. [b]p-values were calculated through the chi-squared test (X^2). Alpha level set at 0.05.

cut-offs of 0.20, 0.50, and 0.80 for small, middle, and large effects, respectively.

Additionally, we performed multiple group discriminant function analyses (MDAs) to determine which measures best discriminate between: (a) PD patients and controls; and (b) PD-on and PD-off patients. In the first two MDAs, only those measures yielding between-group differences were considered as predictors. We then conducted a third MDA including both predictors together.

Moreover, two receiver-operating characteristics (ROC) curves were used to determine which of the measures showing between-group differences afforded the greatest sensitivity and specificity to discriminate between: (a) PD patients vs. controls; and (b) PD-on vs. PD-off patients. ROC curve analyses were performed using the variables yielding differences between PD patients and controls, first separately and then jointly. The areas under the ROC curves (AUCs; 95% CI) were used as the measure of discriminatory accuracy. Additionally, sensitivity and specificity were calculated.

Moreover, for exploratory purposes, we conducted MDA and ROC analyses to discriminate between PD-on and PD-off patients. Whereas inferential analyses can only reveal significant or non-significant effects at the *group* level, these approaches generate measures of classification accuracy, sensitivity, and specificity. Therefore, they reveal the *subject-level* probability with which patients can be identified as being on or off medication, shedding light on the role of dopamine bioavailability in syntax and emotional language processing.

RESULTS

Syntactic Tasks

Relative to controls, PD patients obtained significantly lower scores in Touching A with B ($F_{(1,53)}$ = 10.81, p = 0.002, d = 0.91), but both groups performed similarly on the Embedded Sentences subtest ($F_{(1,53)}$ = 1.48, p = 0.22, d = 0.35)—see **Figure 1A1**, and **Supplementary Table 1**. Significant differences between groups in Touching A with B were preserved after removing an outlier from the PD group ($F_{(1,52)}$ = 10.75, p = 0.002, d = −0.89). Also, group differences in Touching A with B remained significant after co-varying for MoCA, IFS, and HDRS. Moreover, comparisons between PD-off and PD-on patients showed marginally poorer performance for the former on Touching A with B ($F_{(1,29)}$ = 3.37, p = 0.07, d = 0.66), alongside non-significant differences on the Embedded Sentences subtest ($F_{(1,29)}$ = 0.009, p = 0.92, d = 0.03)—see **Figure 1B1**, and **Supplementary Table 1**. The marginal differences between subgroups in Touching A with B remained similar after adjusting for MoCA, IFS, and HDRS.

Socio-emotional Language Task

Schadenfreude ratings were lower in PD patients than in controls ($F_{(1,53)}$ = 10.14, p = 0.002, d = 0.87), there being no significant between-group differences in ratings of envy ($F_{(1,53)}$ = 0.61, p = 0.439, d = 0.21) and neutral situations ($F_{(1,53)}$ = 0.18, p = 0.675, d = 0.12)—see **Figure 1A2**, and **Supplementary Table 1**. Significant differences between groups in *Schadenfreude* ratings were preserved after co-varying for MoCA, IFS, and HDRS. Also, *Schadenfreude* ratings were marginally lower for PD-off than PD-on patients ($F_{(1,29)}$ = 3.65, p = 0.06, d = 0.69), but no differences emerged between these groups' ratings of envy ($F_{(1,29)}$ = 0.003, p = 0.955, d = 0.02) and neutral situations ($F_{(1,29)}$ = 0.01, p = 0.910, d = 0.04)—see **Figure 1B2**, and **Supplementary Table 1**. Such marginal differences between subgroups in *Schadenfreude* ratings remained similar after co-variation with MoCA, IFS, and HDRS scores.

MDA Analyses

MDA Between PD Patients and Controls

Including the Touching A with B score as predictor, we obtained one discriminant function with a Wilkis's λ = 0.831, $\chi^2_{(1)}$ = 9.741, p = 0.002. This function correctly classified 67.3% of the cases (64.5% of PD patients and 70.8% of controls). Then, using *Schadenfreude* ratings as predictor, we obtained one discriminant function with a Wilkis's λ = 0.8.39,

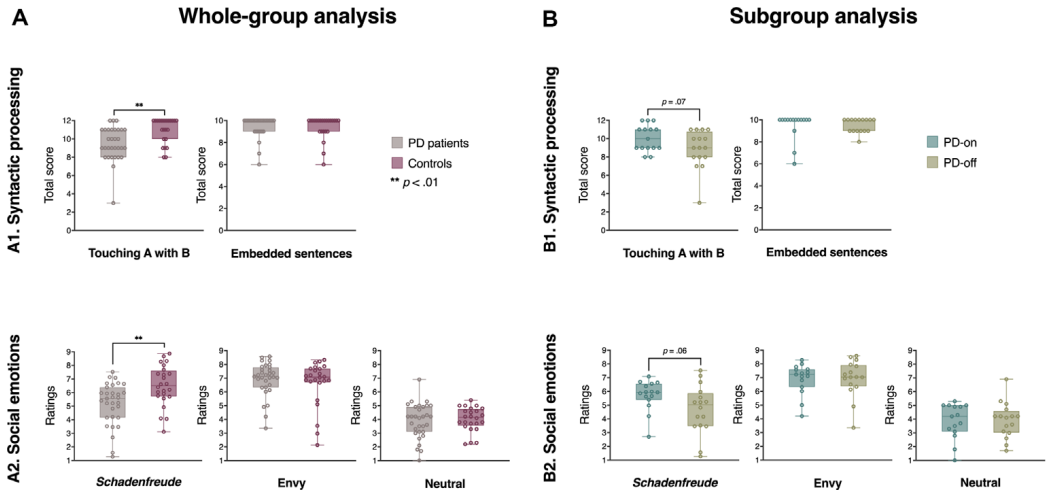

FIGURE 1 | Group results from the syntactic and social emotion tasks. **(A)** Whole-group comparison between Parkinson's disease (PD) patients and controls: **(A1)** syntactic processing scores; **(A2)** social emotion ratings. **(B)** Subgroup comparison between PD-on and PD-off patients: **(B1)** syntactic processing scores; **(B2)** social emotion ratings. Between-group comparisons were performed through one-way ANOVA.

$\chi^2_{(1)}$ = 9.192, p = 0.002. This function classified 63.6% of the cases into their respective groups (58.1% of PD patients and 70.8% of controls). Finally, when both domains were introduced as predictors, we obtained one discriminant function with a Wilkis's λ = 0.684, $X^2_{(2)}$ = 19.712, $p < 0.001$. The Touching A with B total score discriminated most reliably between PD patients and controls, followed by the *Schadenfreude* ratings. This function accounted for 100% of the total variance. This model showed the best classification accuracy across all three MDAs, successfully classifying 70.9% of the participants (67.7% of PD patients and 75.0% of controls)—**Figure 2A1**. Standardized coefficients of predictors included in each MDA are shown in **Supplementary Table 2**.

MDA Between PD-On and PD-Off Patients

Entering the Touching A with B score as predictor, we attained one discriminant function with a Wilkis's λ = 0.896, $X^2_{(1)}$ = 3.131, p = 0.07. This function classified 54.8% of the cases into their actual group (53.3% of PD-on and 56.3% of PD-off patients). Then using *Schadenfreude* ratings as predictor, we obtained one discriminant function with a Wilkis's λ = 0.888, $X^2_{(1)}$ = 3.383, p = 0.06. This function classified 64.5% of the cases into their corresponding group (80.0% of PD-on and 50.0% of PD-off patients). Finally, when both domains were included as predictors, one discriminant function was calculated with a Wilkis's λ = 0.762, $X^2_{(2)}$ = 7.611, p = 0.02. *Schadenfreude* ratings showed the best discrimination accuracy, followed by the Touching A with a B score. This function accounted for 100% of the total variance and showed the best classification accuracy, correctly classifying 74.2% of the cases (86.7% of PD-on and 62.5% of PD-off patients)—see **Figure 2B1**. Standardized coefficients of predictors included in each MDA are shown in **Supplementary Table 2**.

ROC Curve Analyses

ROC Curve Analysis Between PD Patients and Controls

At a cut-off of 11.5 points, Touching A with B scores yielded a sensitivity of 54.2% and a specificity of 90.3%. The AUC was 0.76 (CI: 0.62–0.89; p = 0.001). Then, at a cut-off of six points, *Schadenfreude* ratings showed a sensitivity of 66.7% and a specificity of 74.2%. The AUC was 0.73 (CI: 0.59–0.87; p = 0.003). The average of both domains showed the best discriminatory accuracy, reaching a sensitivity of 75% and a specificity of 80.7% at a cut-off of 8.3 points. The AUC was 0.83 (CI: 0.72–0.94; $p < 0.001$). The ROC curves for the three variables are illustrated in **Figure 2A2**.

ROC Curve Analysis Between PD-On and PD-Off Patients

At a cut-off score of 9.5 points, Touching A with B score showed a sensitivity of 56.3% and a specificity of 53.3%. The AUC was 0.67 (CI: 0.48–0.86; p = 0.10). Then, at a cut-off of 5.5 points, *Schadenfreude* ratings showed a sensitivity of 68.8% and a specificity of 73.3%. The AUC was 0.73 (CI: 0.50–0.90; p = 0.05). The average of both domains afforded the highest discriminatory accuracy, reaching a sensitivity of 62.5% and a specificity of 66.7% at a cut-off of 7.5 points. The AUC was 0.76 (CI: 0.59–0.93; p = 0.01). The ROC curves for the three variables are illustrated in **Figure 2B2**.

DISCUSSION

This report documents the first joint evaluation of two linguistic domains relying on frontostriatal circuits affected in PD: syntactic and verbal emotional processing. Patients exhibited selective impairments in specific measures of each dimension (functional-role assignment and *Schadenfreude*, respectively). More crucially, results from two analytical approaches

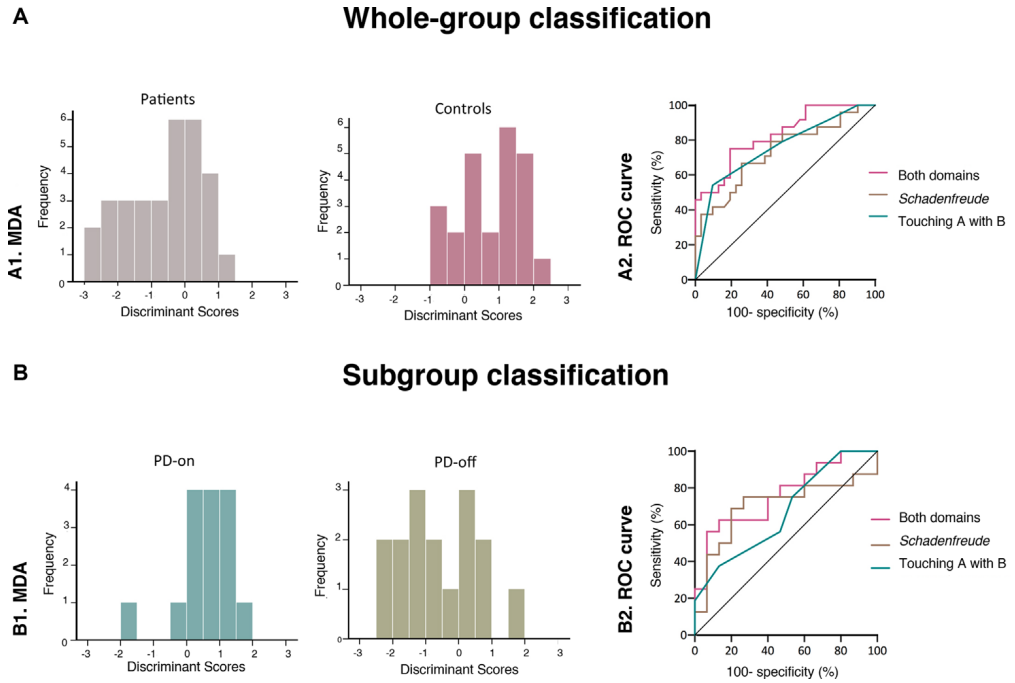

FIGURE 2 | Subject classification results. **(A)** Whole-group classification between PD patients and controls: **(A1)** histograms showing the distribution of Touching A with B and Schadenfreude discriminating scores; **(A2)** receiver-operating characteristics (ROC) curves for Touching A with B scores, Schadenfreude ratings, and the combination of both domains. **(B)** Subgroup classification between PD-on and PD-off patients: **(B1)** histograms showing the distribution of Touching A with B and Schadenfreude discriminating scores; **(B2)** ROC curves for Touching A with B scores, Schadenfreude ratings, and combined outcomes from both domains. Classification accuracies were calculated through the ROC curve and multiple group discriminant function analyses.

showed that individual patient classification improved when combining outcomes from both dimensions. These findings suggest that multidimensional linguistic assessments may better capture the complex and multifunctional impact of frontostriatal disruptions.

Frontostriatal disorders have been shown to impair syntactic comprehension and syntactic judgment skills (Bocanegra et al., 2015; García et al., 2018b; Johari et al., 2019; Whitfield and Gravelin, 2019; Melchionda et al., 2020). Here, we found that PD patients were impaired in Touching A with B but not in the Embedded Sentences subtest. This very dissociation has been observed in persons at risk for PD, even before the onset of other linguistic, cognitive, or motor impairments (García et al., 2017). As noted elsewhere (García et al., 2017, 2018b), the Touching A with B test taps functional-role assignment, a skill that rests mainly on sequential (as opposed to hierarchical) syntactic processes. In line with computational works suggesting that different sub-portions of the striatum play distinct roles during linguistic processing (Szalisznyo et al., 2017), this selective pattern might be partially explained by the nigral origins of frontostriatal deficits in PD (Birba et al., 2017). Also, this deficit was not associated with the patients' general cognitive state, executive skills, or depression symptoms. Such a result suggests that functional-role assignment deficits in PD may represent a primary dysfunction, rather than a secondary manifestation of unspecific cognitive/affective alterations. Still, further research is needed to clarify the role of different frontostriatal pathways in specific syntactic domains.

Regarding socio-emotional processing, PD patients reported lower levels of *Schadenfreude* than controls, despite null differences in ratings of envy and neutral situations. As was the case with syntactic outcomes, this pattern was not associated with the patients' overall cognitive status, executive functions, or depression symptoms, attesting to its potential primary (rather than epiphenomenal) nature. Our findings replicate findings from other frontostriatal disorders, such as HD (Baez et al., 2016, 2018). This attests to the intimate link between such circuits and this particular social emotion (Takahashi et al., 2009; Baez et al., 2018) as well as its underlying operations, such as reward processing and mentalizing abilities (Takahashi et al., 2009; Poletti et al., 2011). Those two operations are impaired in PD (Schott et al., 2007; Poletti et al., 2011), suggesting that the sensitivity of *Schadenfreude* as a marker of frontostriatal abnormalities might rest on multi-determined neurocognitive foundations. In particular, *Schadenfreude* levels have been associated with increased activity in the ventral striatum activity in healthy participants (Takahashi et al., 2009) and ventral striatum gray matter reduction in frontostriatal disorders (Baez et al., 2018). Reduced dopamine transporter density (Remy et al., 2005; Cilia et al., 2010) and reduced activity (Rao et al., 2010) in the ventral striatum have been previously reported in patients with PD. These functional abnormalities may underlie reduced *Schadenfreude* levels observed in PD patients. As a recent study

(Multani et al., 2019) reported associations between increased functional connectivity between opercular and insular cortices and socio-emotional processing in PD, future studies should investigate the structural and functional brain correlates (beyond frontostriatal pathways) of socio-emotional language processing in PD.

Interestingly, performance on Touching A with B tended to be poorer in PD-off relative to PD-on patients, there being no significant differences between such subgroups in the Embedded Sentences subtest. Tentatively, early deficits in the functional-role assignment may be associated not only with frontostriatal atrophy but also with dopamine bioavailability, as seen in other linguistic domains. PD-off patients exhibit more difficulties than PD-on patients in picture naming (Herrera and Cuetos, 2012), phonological and action fluency (Herrera et al., 2012), and sentence comprehension (Grossman et al., 2001) tasks. Also, we found marginally higher *Schadenfreude* ratings in PD-on compared to PD-off patients. Though not focused on *Schadenfreude*, previous studies suggest that dopamine therapy increases emotion recognition in PD (Dujardin et al., 2004; Mondillon et al., 2012; Dan et al., 2019). As stated above, *Schadenfreude* has been liked to ventral striatum activity and volume (Takahashi et al., 2009; Baez et al., 2018). Also, dopamine supplementation seems to improve functions mediated by dorsal striatum and to modulate ventral-striatal operations (Gotham et al., 1988; Kish et al., 1988; Macdonald and Monchi, 2011). Briefly, although present results should be taken with reservation given the moderate size of each patient subgroup, they invite new specific studies aimed to assess the role of dopamine in syntax and emotional language processing.

Yet, beyond those individual patterns, our core finding is that patient classification was boosted upon joint analysis of these sensitive measures. Specifically, an MDA including both dimensions successfully classified 70.9% of the participants while individual measures of functional-role assignment and *Schadenfreude* reached accuracies of 67.3% and 63.6%, respectively. Furthermore, ROC curves for the combination of both measures increased sensitivity and specificity values. Similarly, MDA and ROC analyses also showed that a combination of such measures improved classification between PD-on vs. PD-off patients. Taken together, these results suggest that multidimensional assessments can better capture the high complexity of frontostriatal networks, whose widespread anatomical distribution (Chudasama and Robbins, 2006), varied neurochemical dynamics (Chudasama and Robbins, 2006), and multiple connectivity patterns (Morris et al., 2016) render them putatively involved in diverse higher-order domains cutting across multiple subfunctions.

Note that similar classification accuracies have been reported by previous studies using cognitive measures in PD and other neurodegenerative diseases (Bennett et al., 2006; García et al., 2016; Tkaczynska et al., 2020). Indeed, our classification results are even higher than those of a recent study (Zimmerer et al., 2020) using linguistic measures to classify syndromes which primarily impair language (i.e., primary progressive aphasia). In line with previous results (Norel et al., 2018), our findings suggest that the joint assessment of different linguistic skills can boost the detection of PD cases, as observed for other domains in different neurodegenerative disorders (Caselli et al., 2014). Still, these outcomes do not yet warrant direct testing of our tools' clinical applicability. Rather, they lay the groundwork for more extensive research testing the translational utility of multidimensional assessments, in line with recent calls to validate inexpensive, non-invasive, patient-friendly markers of PD and other conditions (Canevelli et al., 2015; Delenclos et al., 2016).

Similarly, joint consideration of both dimensions also improved the classification of PD-on vs. PD-off patients, reaching an accuracy of 74.2%. However, the classification of PD-on patients (82.7%) was better than that of PD-off patients (62.5%). This probably reflects the multivariate nature of the MDA method, which combines independent variables to classify participants in different groups according to discriminant scores of selected predictors (Stevens, 2002). The cases are assigned to groups based on their discriminant scores and an appropriate decision rule. For example, in two-group discriminant analysis, a case will be assigned to the group whose centroid (the mean values for the discriminant scores for a particular group) is the closest. The fact that PD-off had worse classification than PD-on means that, in some PD-off patients, Touching A with B and *Schadenfreude* outcomes were similar to those of PD-on patients. This finding may be influenced by two factors. First, neuropsychological and clinical heterogeneity is a central characteristic of PD (Kehagia et al., 2010). Given that we used a between-group design, this heterogeneity could be reflected differently in either the PD-on or the PD-off groups. Second, the role of Levodopa withdrawal on syntax and *Schadenfreude* measures has not been established. Although some studies suggest that PD-off show lower performance than PD-on patients in syntax (Grossman et al., 2001) and emotion processing (Dujardin et al., 2004; Dan et al., 2019), others reported a comparable deficit in patients whatever the treatment condition (Sprengelmeyer et al., 2003). Our results suggest that scores in Touching A with B and *Schadenfreude* measures are lower among PD-off patients, but some of these patients performed similarly to those in the PD-on group. This heterogeneity among patients in the PD-off group could be associated with several individual factors such as disease severity (MacDonald et al., 2013) and levels of apathy or depression (Cohen et al., 2015). Future studies using larger samples of PD-on and PD-off patients should further investigate the role of dopamine withdrawal on linguistic and emotional domains, and the association of disease severity and neuropsychiatric symptoms on Levodopa response.

Despite differences in discrimination accuracy between PD-on and PD-off patients, overall, our results suggest that performance in syntactic and emotional language processing could be associated with dopamine bioavailability. Considering that ANOVAs failed to reveal significant differences between such groups, this finding carries a non-trivial methodological implication: estimations of subject-level classification probabilities may offer useful insights irrespective of group-level results. Indeed, a previous study assessing linguistic measures failed to find significant differences between PD patients and controls but showed that grammatical and sematic patterns

identified in monologues accurately discriminated between groups (García et al., 2016). Still, the association between dopamine bioavailability and performance in the syntactic and emotional language in PD should be more deeply assessed in future studies.

More generally, our results have theoretical implications. First, traditional frameworks in neuroscience and neuropsychology often favor rather modular accounts of particular linguistic domains. However, in daily interactions, different linguistic processes are intertwined and automatically interconnected with each other and with several other cognitive, affective, motoric, and even interoceptive functions (Ibáñez, 2019). The current multidimensional approach represents a viable approximation to circumvent such counterfactual ethos, in line with recent calls (Ibáñez and García, 2018; Ibáñez, 2019) for a more ecological, dynamic, and synergetic view of cognitive processes. Our results support novel frameworks pinpointing the multiple non-motor functions of the basal ganglia, crucially including linguistic and emotional processing (Eisinger et al., 2018). Accordingly, this work incarnates a concrete implementation of the emergent intercognitive agenda (Ibáñez, 2019) as an avenue towards more sophisticated conceptions of human cognition (Ibáñez and García, 2018).

Also, our results pave the way for developing multidimensional cognitive assessments to characterize and identify early PD patients, as highlighted in recent works (Canevelli et al., 2015; Delenclos et al., 2016). Such assessments may afford potential cognitive markers for detecting and tracking the progression of PD or other frontostriatal disorders, offering more robust approximations to the anatomical complexity and multifunctionality of frontostriatal circuits (Birba et al., 2017). Future studies should further investigate the potential use of combining linguistic and otherwise cognitive measures for early and preclinical PD detection. This is consistent with a recent theoretical perspective (Morese and Palermo, 2020) proposing an interdisciplinary vision in PD to encourage a richer discussion capable of generating new research and developing interventions to improve social and cognitive functioning in PD patients. Furthermore, as the results of a previous study in PD animal models (Ztaou et al., 2018) highlighted the relevance of striatal cholinergic interneurons in emotional and other non-motor deficits, future studies should also assess the role of cholinergic medication on emotional language processing in PD patients.

Some limitations of our work should be acknowledged. First, our sample size was relatively small. However, it proved similar to that of previous studies on linguistic (Grossman et al., 2000, 2002, 2003; Angwin et al., 2005, 2007; Bocanegra et al., 2015) and emotional (Breitenstein et al., 2001; Dara et al., 2008; Martínez-Corral et al., 2010) dimensions in PD. Future studies assessing PD patients with multidimensional assessments should include larger sample sizes. Second, we compared PD-on vs. PD-off patients using a between-subjects design. Future research should explore the role of dopamine medication using within-subject designs. Finally, as we did not include neuroimaging measures, our interpretations of the associations between the pathogenesis of PD and Touching A with B and *Schadenfreude* scores are hypothetical. Further research is needed to understand the complex relationship between frontostriatal pathways functioning in PD and different linguistic and emotional dimensions.

In sum, our study indicates that a joint evaluation of syntactic and socio-emotional language tasks can improve the classification accuracy of early PD patients. This result informs an emergent trend emphasizing the relevance of multidimensional cognitive examinations across frontostriatal disorders. Looking forward, new applications of this approach should be implemented to boost the ongoing quest for early markers of these conditions.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the Icesi University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SB, EH, HS-G, AI, and AG developed the study concept and the study design. EH, JC, and MP performed testing and data collection. SB, CT, and HS-G performed the data analysis and interpretation under the supervision of AI and AG. SB, EH, CT, and JC drafted the manuscript. MP, HS-G, AI, and AG provided critical revisions. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2020.586233/full#supplementary-material.

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MINI REVIEW
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Action Fluency in Parkinson's Disease: A Mini-Review and Viewpoint

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Increasing evidence shows that the typical motor symptoms of Parkinson's disease (PD) are often accompanied, if not preceded, by cognitive dysfunctions that are potentially linked to further complications of the disease. Notably, these cognitive dysfunctions appear to have a significant impact in the domain of action processing, as indicated by specific impairments for action-related stimuli in general, and verbs in particular. In this mini-review, we focus on the use of the action fluency test as a tool to investigate action processing, in PD patients. We discuss the current results within the embodied cognition framework and in relation to general action-related impairments in PD, while also providing an outlook on open issues and possible avenues for future research. We argue that jointly addressing action semantic processing and motor dysfunctions in PD patients could pave the way to interventions where the motor deficits are addressed to improve both motor and communicative skills since the early disease stages, with a likely significant impact on quality of life.

Keywords: Parkinson's disease, action fluency, action processing, embodied cognition, movement disorders

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INTRODUCTION

Increasing evidence shows that the typical motor symptoms of Parkinson's disease (PD) are often accompanied, if not preceded, by cognitive dysfunctions that are potentially linked to further complications of the disease, including developing dementia (Auclair-Ouellet et al., 2017). Notably, these cognitive dysfunctions appear to have a significant impact in the domain of action processing, as indicated by specific impairments for action-related stimuli in general, and verbs in particular (Cardona et al., 2013). While it is widely acknowledged that processing verbs is generally more difficult compared to nouns, regardless of their semantic content, evidence in the domain of embodied cognition suggests that PD patients might show a more specific impairment in this sense (Boulenger et al., 2008). In this framework, linguistic processing is thought to be grounded in sensorimotor processes in such a way that processing bodily action-related verbs or sentences (e.g., "to kick" or "I kick"), as well as concrete nouns (e.g., "ball"), is accompanied by sensory and motor activations congruent with their semantic content. Increasing evidence in healthy participants supports this view, both at the neural and the behavioral level (Pulvermüller, 2018), and more recently it has been shown that action-related verb processing, and to a lesser extent the

comprehension of concrete nouns might be specifically impaired in PD patients, with progressive decay of motor skills accompanied by category-specific linguistic deficits (Bocanegra et al., 2015). Notably, it has been shown that these category-specific deficits emerge in a wide range of tasks (Cardona et al., 2013; Gallese and Cuccio, 2018). When action naming tasks are considered, existing studies generally report worse performance for PD compared to healthy controls (Péran et al., 2009) and other patient groups (e.g., Alzheimer's disease; Rodríguez-Ferreiro et al., 2009). As to verb generation, PD patients typically show specific deficits for this category (Crescentini et al., 2008) while performing similarly to controls when nouns are considered (Péran et al., 2003). Interestingly, similar impairments have been shown not only when action-related words, and verbs in particular, are tested in isolation, but also when embedded in sentences (Cardona et al., 2014) and naturalistic texts (García et al., 2018).

It has thus been suggested that performance in tasks involving both comprehension and production might detect early impairments of the fronto-striatal loop, thus allowing to investigate how dopaminergic medication and other mechanisms might come into play to compensate for the progressive decay of action processing skills (Auclair-Ouellet et al., 2017). Furthermore, as these symptoms might severely impact communication abilities even in the first stages of the disease (Dadgar et al., 2013), early detection and full characterization of these deficits are crucial to improve the quality of life of these patients and design effective interventions. It is thus crucial to identify those tests that might be routinely used as screening tools allowing an early identification of specific action-related deficits and implementation of targeted interventions.

This review focuses on one example in this sense, i.e., the well-known action fluency task (Piatt et al., 1999a,b). By instructing participants to verbally report as many different actions they think people can do (e.g., "eat," "smell") in 1 min (Auclair-Ouellet et al., 2020), this test gives a fast and easy access to action word production and global action processing abilities. In this article, we will first review evidence from action fluency tests in general, then specifically address the use of this tool in PD patients within the embodied cognition framework and discuss the existing evidence providing a possible outlook for future research.

THE ACTION FLUENCY TEST

Action fluency tests were originally implemented (Piatt et al., 1999a,b) to assess whether the ability to generate verbs in the absence of prompting stimuli reflects a unique aspect of executive functioning typically neglected both by action naming tasks (i.e., verb retrieval, as opposed to object naming/noun retrieval), and by well-established fluency tasks based on prompting stimuli such as first letter or semantic domain (i.e., lexical and categorical fluency, respectively). Action fluency was indeed expected to tap both the generative-executive demands inherent in fluency compared with naming tasks, and the specific integrative-executive demands intrinsic to retrieving verbs (Grossman, 1998) compared to nouns or categories (Piatt et al., 1999a,b).

Several studies have provided multifaceted support to the possible uniqueness of verb generation, in terms of neuro-cognitive processing and sensitivity to pathology. First, data from healthy controls showed that its performance is significantly, but moderately, related to other executive metrics, and unrelated to measures of semantic or episodic memory (Piatt et al., 1999b) which suggests that action fluency taps unique abilities within the realm of executive functioning. Supporting this notion, a disproportionate impairment of action, compared with lexical and semantic, fluency was first observed in demented Parkinson's patients, compared both with non-demented patients and with elderly controls (Piatt et al., 1999a). Moreover, the lack of association between action fluency and dementia severity was suggestive of its specific sensitivity to the progressive fronto-striatal dysfunction of Parkinson's disease. While the authors of these studies generically suggested that action fluency is a valid measure of executive and language functions (e.g., Piatt et al., 2004), more recently its semantic-conceptual requirements have been interpreted within the embodied cognition framework, i.e., in terms of neural action representations generated from, and tightly connected with, sensorimotor experiences (Salmazo-Silva et al., 2017). A prominent impairment of action fluency in Parkinson's disease might thus reflect the adverse effect of basal ganglia damage on motor-language coupling (Melloni et al., 2015).

ACTION FLUENCY IN PARKINSON'S DISEASE

Differently from action naming, action fluency tasks require participants to produce verbs in absence of any visual aid. Piatt et al. (1999a) first tested this ability in absence of prompting stimuli (i.e., action fluency) in PD patients with and without dementia and in healthy controls, showing that this task is instrumental in differentiating between the two patient populations. Notably, other fluency tasks (e.g., lexical and categorical) often failed to account for such a difference, supporting the notion that appropriate action fluency tasks specifically tap into the disease's peculiar pathophysiology and deficits in executive functioning. These first results were supported by further data from the same group (Piatt et al., 2004) on healthy elderly controls. In this case, not only did the action fluency task prove its validity as a measure of executive functions, but the two measurements were significantly correlated, while appearing unrelated to semantic and episodic memory.

In this sense, an appropriate assessment of action fluency in PD patients necessarily requires disentangling these effects from those derived from other linguistic tasks (e.g., naming). Notably, direct comparisons between performance in fluency and naming tasks provided conflicting results. On the one hand, a few studies found no significant evidence of a clear distinction between action fluency and action naming (Rodríguez-Ferreiro et al., 2009). Bocanegra et al. (2017) compared PD participants with and

without mild cognitive impairment, as well as healthy volunteers, in a picture-naming task revealing that PD-MCI patients were selectively impaired in processing action verbs semantically implying a high level of motion. In line with these results, Salmazo-Silva et al. (2017) tested the variability of PD patients' impairments across a range of tasks focusing on action and object lexical and semantic processing with varying cognitive demands (verbal fluency, naming, and semantic association). Notably, while PD patients performed worse than controls in naming and association tasks, this did not hold for action fluency. The authors addressed these potentially conflicting results by highlighting the inherent confound posed by individual differences in the educational level. This factor might not only play a direct role in affecting performance in this specific task, but also in the preservation of executive functioning.

On the other hand, impairments in action fluency appeared to be more evident in comparison with lexical and semantic fluency. Rodrigues et al. (2015) directly compared action fluency scores with those derived from traditional fluency tests in PD in non-demented PD patients and healthy age- and education-matched controls. All participants were administered tests of letter, semantic, and action verbal fluency with significant differences between the two groups emerging only in the latter. Crucially, the fact that this specific deficit of verb vs. noun production appeared in PD patients without dementia – thus before any clear sign of cognitive impairment – supports the idea that a selective disruption in this domain is linked to fronto-striatal circuitry dysfunction (Fine et al., 2011). Notably, it has been proposed (Bocanegra et al., 2015) that while linguistic and semantic deficits in PD, specifically those related to action-verb production and action semantics, emerge very early during the first stages of the disease in absence of cognitive or executive dysfunctions, this is not the case for object semantics. Indeed, measures of executive functioning significantly predict impairments in this domain (Bocanegra et al., 2015). Similar results were obtained when testing PD patients without dementia and healthy controls longitudinally across several cognitive scales, as well as semantic, letter, and action fluency tasks (Signorini and Volpato, 2006). In this study, PD patients showed a consistent action fluency deficit in absence of other relevant cognitive disorders, thus supporting the notion that poor performance in this task can be interpreted as a sign of fronto-striatal damage.

Further evidence of a strong relationship between verb processing and motor functions was increasingly provided also by neuroimaging studies (York et al., 2014). By exploring the neural correlates of action-verb representations in PD with functional magnetic resonance imaging (*f*MRI), one of the early studies in this field (Péran et al., 2009) found a significant correlation between severity of the motor deficit (Unified Parkinson's Disease Rating Scale – UPDRS score) and brain activity during action verb generation in the pre- and post-central gyri bilaterally, left frontal operculum, left supplementary motor area, and right superior temporal cortex. More recently, Auclair-Ouellet et al. (2020) coupled the action fluency test with *f*MRI in PD patients to shed light on the relationship among these measures and personal characteristics, disease factors, cognition, and neural activity. While the action fluency scores remained independent of linguistic measures, this test allowed o identify a subset of patients with peculiar sex, age, global cognitive profile, executive function scores, and brain activity. Notably, when dividing patients into two subgroups characterized by normal and poor action fluency performance, the latter group had worse scores in both the cognitive and executive function domains, as well as decreased activity in fronto-temporal regions. In line with other studies (Abrevaya et al., 2016), this finding suggests that, to compensate for movement disorders, action-verb processing, and possibly action processing in general, may rely on less efficient non-motor semantic circuits. This proposal would thus imply the co-occurrence of preserved semantic knowledge and alteration in the neuro-cognitive mechanisms mediating the use of linguistic-induced motor brain activity to gain more efficient access to action semantics. Crucially, data from brain connectivity analyses showed that patients and controls shared similar patterns when processing nouns. However, this was not the case for action-related words, with patients appearing to rely more strongly than controls on temporal areas involved in amodal semantics, likely representing a compensatory mechanism for the reduced availability of more direct and efficient motor routes. Supporting evidence in this sense came also from studies investigating the effect of medication. It has indeed been shown (Herrera et al., 2012) that, when testing PD patients on- and off-dopamine treatment, patients in the off-state produce significantly fewer verbs in the action fluency task compared to controls, with significant differences also in the frequency of the produced words.

Finally, additional converging evidence was recently provided by a direct comparison of action verb knowledge in patients with PD and amyotrophic lateral sclerosis (ALS), two pathologies characterized by different anatomical substrates and clinical manifestations (Cousins et al., 2018). Patients were classified as having high or low motor impairments based on disease-specific functional scales and were tested on a verb production task focusing on body-related verbs (i.e., where the body is either as the agent of the action or as the theme). Interestingly, PD patients showed a similar impairment in production for all verb types, regardless of the role of the body, whereas ALS participants showed a specific dissociation between agent- and theme-related body verbs.

OUTLOOK AND FUTURE DEVELOPMENTS

We reviewed the use of action verbal fluency tests in investigating action processing in PD patients. While the existing literature on PD is still relatively limited, this test already showed its potential to highlight different facets of action processing impairments in this population, even compared to other fluency or naming tasks. Despite promising results, however, several open issues remain.

First, there is conflicting evidence concerning how performance in this test relates to naming tasks and other fluency assessments, as well as action processing in general. While this seems partially explained by the nature of the test, requiring participants to produce as many verbs referring to

actions as possible, further research should aim to place action verbal fluency tests within a broader assessment of action semantic processing. In this sense, performance in this specific task should be evaluated not only with respect to scores in similar tests, but also against patients' behavioral performance in tasks specifically designed to address motor-language coupling (Melloni et al., 2015). Preliminary evidence using an adapted version of the action-sentence compatibility effect (Cardona et al., 2014) suggests that this might indeed be a promising avenue (but see Morey et al., in press regarding limitations of this specific task).

With the aim of a more comprehensive characterization of the global profile of action-related impairments, research has so far mainly focused on the relationship between action fluency measures and other linguistic and executive function metrics pointing to a marked independence of this measure from scores in other tasks. However, future investigations will also have to consider a possible role of individual differences in driving action fluency results. As already highlighted in this review, fluency measures seem to be generally affected by several factors that go beyond disease stage and severity, including the educational and cognitive profile, as well as patients' age (Obeso et al., 2012). This appears particularly crucial for action fluency tests, also due to task complexity and its relative unconstrained structure. In this respect, an approach focusing on individual differences will necessarily have to deal not only with more general compensatory mechanisms, but also with individual strategies that patients are likely to implement as action-related impairments become more prominent and impact more strongly their quality of life.

In line with a more detailed characterization of PD patients and their deficits, it is worth noting that the evidence on the possible neural correlates of performance in the action fluency test is so far still limited. However, the global assessment of action processing in PD will necessarily require assessing not only how behavioral impairments correlate with regional changes in brain activity, but also how compensatory mechanisms and medication are at play at different stages of the disease, as the preliminary research reviewed here has shown. Ideally, in this approach the comparisons between different PD subgroups (e.g., with and without dementia), should be extended to involve also other pathologies with different anatomical substrates and possibly behavioral manifestations of action processing impairments.

Finally, further attention should be devoted to how scores in the action fluency and similar tests/tasks is linked to the overall motor and communicative abilities of the patient, as this is likely to have a great impact on their quality of life. In fact, communication deficits in PD likely derive from a combination of motor and cognitive impairments (Smith and Caplan, 2018) but the actual impact of these deficits on daily communication, and thus the possible measures to mitigate and counteract them, is still poorly investigated and understood.

In conclusion, jointly addressing action semantic processing and motor dysfunctions in PD patients could pave the way to interventions where the motor deficits are addressed with to improve both motor and communicative skills since the early disease stages, with a likely significant impact on quality of life.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

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