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Comparing Individuals With PPA to Individuals With AD: Cognitive and Linguistic Profiles

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Primary Progressive Aphasia (PPA) is a degenerative condition characterized by the progressive loss of language function. In PPA, aphasia is the most prominent deficit at onset. On the other hand, memory deficits are the hallmark of Alzheimer's disease (AD). The first aim of the study was to establish differences on neuropsychological testing and connected speech production between Greek-speaking individuals with AD and PPA. The second aim was to investigate the executive deficit involvement in the two conditions. Ten individuals with PPA and 9 individuals with AD took part in a comprehensive cognitive-linguistic evaluation. Fifteen demographically matched neurologically healthy adults served as controls. Participants were evaluated using a battery of neuropsychological measures. Quantitative production analysis and acoustic analysis were performed to calculate narrative and temporal measures of the participants' speech. Participants with PPA differed significantly from participants with AD on linguistic measures. They performed worse on the long frequent sentences' subtest of the Sentence Repetition Test and they produced fewer narrative and unique words in picture description. They also produced shorter, less elaborated sentences, and made more phonological errors. The two groups did not differ significantly on memory, executive, visuospatial and semantic composite measures. Compared to neurotypical adults, participants with AD were impaired in memory, and executive function. They also exhibited lexical retrieval difficulties, as well as difficulties in linguistic tasks with an increased processing load. Participants with PPA performed within normal limits on the delay conditions of episodic memory measures. However, they too were impaired in executive tasks, especially for short-term memory and verbal fluency. The production of phonological errors, difficulty in repeating long frequent sentences, and the production of simple and short sentences has differentiated participants PPA not only from neurotypical controls but also from participants with AD. No single measure could differentiate the AD group from the other two groups. These findings should be interpreted with caution considering the small sample size.

Keywords: executive, language, aphasia, Greek, primary progressive aphasia, logopenic, semantic, Alzheimer's

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INTRODUCTION

Aphasia is an impairment of language which affects the production and/or comprehension of speech, as well as the ability to read or write. Aphasia can result from a variety of causes including stroke, brain tumor, head injury and dementia. Dementia is an umbrella term used to describe syndromes which affect cognitive, social, and functional abilities (World Health Organization, 2012). Alzheimer's disease (AD) is the most common form of dementia. Another less common form of dementia is Primary Progressive Aphasia (PPA), a degenerative condition characterized by progressive loss of language function. In PPA, aphasia is the most prominent deficit at onset (Mesulam, 2001), but there may be subtle evidence of deficits in other domains, reflecting a spread of the disease to areas adjacent in the language network. Nevertheless, these types of non-language deficits do not restrict daily living activities to a significant degree.

PPA is classified into three variants, the logopenic variant of PPA (lvPPA), the nonfluent agrammatic variant of PPA (nfvPPA), and the semantic variant of PPA (svPPA). Each PPA variant has a distinct clinical, neuropathological and neuroimaging profile (Gorno-Tempini et al., 2011). The characteristic clinical profiles of PPA variants include linguistic, as well as non-linguistic features, namely apraxia in nfvPPA, behavioral changes in svPPA and working memory deficits in lvPPA (Harris et al., 2019). The profiles evolve with disease progression and other domains are increasingly affected, most notably behavior and executive functions.

Executive functions comprise a set of cognitive processes that enable us to adjust our behavior to environmental demands. According to a widely accepted framework, three core executive functions, i.e. inhibition, working memory and cognitive flexibility, set the basis for other higher-order executive functions such as problem solving, reasoning and planning (Diamond, 2013). Impairment of executive function has been shown to play an important role in aphasia recovery and rehabilitation in stroke aphasia (El Hachioui et al., 2014; Geranmayeh et al., 2017; Simic et al., 2020), as well as management of language disorders in persons with PPA (Beeson et al., 2011; Henry et al., 2019).

Initial reports of symptoms in PPA have typically focused on analyzing language function. However, neuropsychological testing has revealed additional executive impairment in PPA variants (Kamath et al., 2019, 2020). Individuals with nfvPPA have shown executive deficits on verbal tasks of working memory, verbal fluency, as well as on non-verbal tasks of mental flexibility and abstract reasoning (Macoir et al., 2017). There are nonetheless reports of unimpaired non-verbal executive functioning (e.g., Butts et al., 2015), even though executive functions seem to decline over the course of the disease (Libon et al., 2009). In svPPA, a person may have difficulty comprehending instructions and/or stimuli due to the underlying semantic impairment. This difficulty affects performance on neuropsychological tests. Mixed results have been reported about the presence of executive deficits in the early stages of this variant and the progression of the decline (Macoir et al., 2017). In lvPPA, executive deficits have been found on the Trail-Making Test (TMT) (Butts et al., 2015) and time to complete part B of the TMT is significantly slower than in svPPA. Moreover, working memory in lvPPA seems to be more affected than in nfvPPA and svPPA (Eikelboom et al., 2018). More research, however, is needed to better describe executive decline in lvPPA (Macoir et al., 2017).

Memory deficits, on the other hand, are the hallmark of AD, even though other cognitive domains such as orientation, visuospatial abilities, executive function, and language may also be affected. A recent systematic review of executive functions in AD (Guarino et al., 2019) has highlighted the importance of incorporating executive tasks in a neuropsychological evaluation, as executive functions can be impaired from the mildest stages. Working memory, inhibitory and attentional abilities are compromised to a greater extent (Amieva et al., 2004; Collette et al., 2009; Tse et al., 2010) and have been linked to degeneration of the prefrontal cortex (Salat et al., 2001; Stuss, 2011). Language problems in AD have been associated with semantic and pragmatic processing deficits. People with AD may have word-finding difficulties or make semantic paraphasias. They may also have trouble participating in conversations and may repeat themselves. Lexical retrieval deficits have been reported both in formal testing and connected speech production (Kavé and Goral, 2018). The phonological and syntactic level of language processing seems to be more resilient (Ferris and Farlow, 2013). However, reduced syntactic complexity, morphosyntactic impairment, as well as phonetic and phonological manifestations have been documented in AD (Ahmed et al., 2012; Cera et al., 2018; Fyndanis et al., 2018). Linguistic deficits in AD have been commonly linked to working memory impairment and decreased processing speed (Jokel et al., 2019; Boxtel and Lawyer, 2021).

Individuals with a neurodegenerative disease may present with impaired performance on executive measures as a consequence of an underlying executive deficit or even due to the linguistically demanding nature of the task used to evaluate executive function. In fact, it is difficult to devise "pure" tasks able to evaluate a specific process in isolation from other cognitive processes. Even though the complex relationship between language and executive function has yet to be unraveled, evidence suggests that executive deficits associated with language may be domain-general rather than domain-specific (e.g., Kuzmina and Weekes, 2017; Murray, 2017). In healthy individuals, greater recruitment of executive function seems to be related with more demanding language activities, whereas, in individuals with brain lesions, with more severe pathology as a means of compensating for linguistic deficits (Gonçalves et al., 2018).

Differentiating between PPA and AD is clinically valuable for disease management. The two conditions resemble each other more in the later stages as the diseases evolve. Information about typical performance on specific neuropsychological and linguistic tasks is invaluable in documenting deficits in PPA and AD, differentiating between the two conditions and monitoring changes over time.

Diagnosing PPA is often challenging and there is no agreement on how language assessment should be performed. Different research groups employ different methodologies and several instruments have been used for the overall description of speech and language abilities in PPA and the evaluation of individual cognitive domains. A published review of the

neuropsychological tests that have been developed for the assessment of speech and language disorders in PPA (Battista et al., 2017) has provided information about the available neuropsychological tools in English. More recently, tests have been developed for the evaluation of PPA in other languages, French, for example (Epelbaum et al., 2021). The situation is more complicated in languages like Greek where available tools for the assessment of speech and language in PPA are extremely limited (Peristeri et al., 2021). More research has been conducted regarding cognitive functioning. Current research has yet to explore which instruments or battery of tests can be used to evaluate language and cognitive performance in Greek-speaking individuals with PPA.

Thus, the main aim of this study was to establish differences between Greek-speaking individuals with AD and PPA on a comprehensive battery of tests to inform clinical practice. A secondary aim was to examine the executive deficit involvement in these two degenerative conditions, as executive function and linguistic ability are closely related.

Summarizing the evidence, we would expect to find more severe linguistic deficits in individuals with PPA. We would also expect individuals with AD to be more affected in cognitive measures tapping into memory in comparison to individuals with PPA. Finally, some degree of executive deficit would be expected in both conditions.

TABLE 1 | Years post onset, communicative, general cognitive, neuropsychiatric, and functional status of the participants.

Group (Max. Score)	Years post-onset	BDAE severity (/5)	MMSE (/30)	NPI (/144)	NPI impact (/60)	FRS (/100)
Neurotypical						
Mean		5.00	28.87			
Median		5.00	29.00			
SD		0.00	1.06			
AD						
Mean	3.22	4.78	24.89**	13.60	8.00	77.84
Median	3.00	5.00	26.00	14.00	7.00	92.86
SD	1.54	0.44	2.47	13.43	7.48	28.53
PPA						
Mean	2.10	3.44***	24.30**	4.25	3.38	79.78
Median	2.00	3.50	25.00	4.50	2.00	80.00
SD	0.77	0.97	3.65	2.12	3.74	15.69
AD vs PPA	ns	**	ns	ns	ns	ns

***, ***Significant at the 0.01, and 0.001 level respectively (2-tailed).*

BDAE, Boston Diagnostic Aphasia Examination severity scale: evaluates the severity of the communication difficulties; MMSE, Mini Mental State Examination: evaluates general cognitive status; NPI, Neuropsychiatric Inventory: evaluates the presence, severity, and impact of neuropsychiatric symptoms; FRS, Frontotemporal dementia Rating Scale: evaluates functional status; vs, versus; ns, non-significant.

MATERIALS AND METHODS

Participants

A total of 34 individuals (12 male and 22 female) participated in this study. The control group consisted of 15 neurotypical adults with a mean age of 67.93 ($SD = 6.17$) years and a mean of 13.13 ($SD = 3.482$) years of education. The AD group consisted of 9 participants (mean age 76.22, $SD = 6.833$ and mean years of education 12.67, $SD = 4.153$). Ten individuals participated in the PPA group (mean age 66.80, $SD = 7.525$ with mean years of education 13.60, $SD = 4.088$). Three of the participants with PPA met the criteria for svPPA, six for lvPPA and one had a mixed PPA phenotype.

General cognitive status, as indicated by scores on the Mini-Mental State Examination (MMSE) (Folstein et al., 1975; Fountoulakis et al., 2000; Solias et al., 2014), was similar for participants with AD and PPA (see **Table 1**). There was a statistically significant difference in age between the groups [$H(2) = 7.943$, $p = 0.019$] with a median of 69 years for neurotypical controls, 69.5 for the PPA group and 75 for the AD group. *Post-hoc* analysis revealed that the AD group was significantly older than the control group ($U = 10.867$, $z = 2.595$, $p = 0.028$), but not significantly older than the PPA group ($U = 10.900$, $z = 2.389$, $p = 0.051$). The three groups did not differ significantly in education and gender composition. Information about years post-onset, communication abilities, general cognitive functioning, neuropsychiatric, and functional status of the three groups can be found in **Table 1**.

All participants were right-handed, apart from one neurotypical male who was ambidextrous. All individuals were native Greek speakers. They all reported to have normal or corrected-to-normal vision and hearing.

Procedure

Participants with PPA were recruited through the memory clinic of the Dementia Day Care Center (DDCC) of the Athens Alzheimer's Association and referral from other memory clinics and specialists (neurologists and psychiatrists) working in the private sector. As a result, referral data were not uniform. Enrollment was consecutive.

All participants with AD were diagnosed at the DDCC using a neuropsychological battery which included the MMSE, the Addenbrooke's Cognitive Examination (ACE) (Mioshi et al., 2006; Konstantinopoulou et al., 2011), the Greek Verbal Learning Test (GVLT) (Vlahou et al., 2013), the Georgia Complex Figure Test (Loring and Meador, 2003), the Frontal Assessment Battery (FAB) (Dubois et al., 2000), the short form of the Geriatric Depression Scale (GDS) (Sheikh and Yesavage, 1986; Fountoulakis et al., 1999) or the Beck Depression Inventory (BDI) (Beck et al., 1996; Giannakou et al., 2013) for participants younger than 65 years.

The diagnosis of PPA and AD was based on neurological examination, standard neuropsychological testing and brain imaging according to currently acceptable research criteria (Gorno-Tempini et al., 2011; McKhann et al., 2011; Albert et al., 2013; Chare et al., 2014). The presence of other major systemic, psychiatric, or neurological diseases, uncorrected visual and hearing impairment and difficulty completing the assessment procedure constituted reasons for exclusion from participating in the study. Participants had to be in the mild or moderate

stage of the disease, as specified by severity ratings (Clinical Dementia Rating – CDR score < 3 and Boston Diagnostic Aphasia Examination – BDAE severity scale >3). Moreover, they should have at least 6 years of formal education and be native Greek speakers.

Assessment was completed over 3 or 4 hourly sessions depending on disease severity and practical issues, such as fatigue and time constraints. Assessment of the neurotypical individuals was completed in two 90-minutes-sessions.

The study was approved by the ethics committee of the Athens Alzheimer's Association and research was conducted in accordance with the principles of the Declaration of Helsinki and the European General Data Protection Regulation (GDPR). All participants provided written informed consent.

Assessment Battery

Participants were evaluated using a comprehensive battery of neuropsychological tests. The assessment battery included neuropsychological tools for the evaluation of speech, language, and other cognitive functions. Linguistic assessment targeted auditory comprehension, naming, repetition, reading, writing, and narrative production. In addition, information about the level of functioning and the presence of neuropsychiatric symptoms was collected by each participant's primary caregiver.

Cognitive Assessment

The *MMSE* was administered to all participants as a measure of general cognitive functioning. Attention and executive functioning was assessed by the *Trail Making Test (TMT)* (Corrigan and Hinkeldey, 1987; Zalonis et al., 2008). The TMT-A evaluates scanning and visuomotor tracking. It was employed to measure information processing speed. The TMT-B was used to assess divided attention and cognitive flexibility. For data analysis, the scores were reversed. Actual completion time was deducted from the maximum allowed time for completion, that is, 180s for TMA-A and 300 for TMA-B. In this way, higher scores reflect better performance. The *Verbal Fluency Test* (Kosmidis et al., 2004) was included as a measure of executive function. Phonemic (letter) and semantic (category) fluency was assessed using 3 letters and 3 categories, respectively. A total score was calculated based on the number of responses for each verbal fluency category. The *Clock Drawing Test (CDT)* (Bozikas et al., 2008) which measures both executive and visuospatial abilities was also administered adopting the scoring scheme of the original validation study. The *Forward* and *Backward Digit Span* (DGS) tasks from the WAIS-IV were used as measures of short-term auditory memory and verbal working memory, respectively. The delayed conditions of *5-Words Test* (Dubois et al., 2002; Economou et al., 2016), the *5-Objects Test* (Papageorgiou et al., 2014) and the *Benson Figure Test* (Possin et al., 2011) were administered in order to assess auditory and visuospatial memory, whereas the copy condition of Benson Figure Test to assess visuospatial processing. The 5-Words Test uses written words which are encoded using explicit semantic information. The 5-Objects Test has been developed as a measure of non-verbal episodic memory and is based on recalling the position of 5 objects. Finally, the picture version of the *Pyramids and Palm Trees Test (PPTT)* (Howard and Patterson, 1992) was included as a measure of semantic abilities. In this test a person needs to identify two semantically related pictures in the presence of a third distractor. A short form of the PPTT (Breining et al., 2015) was previously administered to a small number of Greek-speaking individuals with svPPA and found to be culturally appropriate. The complete version was administered to all participants, but scores were calculated for both versions.

Linguistic Assessment

Linguistic assessment included six subsets of the Greek version of the *BDAE-short form* (Goodglass and Kaplan, 1983) to assess naming (the short form of Boston Naming Test), *Narrative writing*, auditory processing (*Commands and Complex Ideational Material)* and reading comprehension (*Word and picture matching* and *Sentence comprehension)*. The subset *Embedded Sentences* from the BDAE-3 includes 10 reversible sentences (subject object relative clauses) and was selected as a measure of syntactic comprehension. The 45-item version of the *Boston Naming Test (BNT)* validated in Greek by Simos et al. (Simos et al., 2011) was used to assess confrontation naming. This version includes 12 out of the 15 items that make up the BNT short form. The additional stimuli were added in the assessment battery to enable comparison of the two versions. The *Sentence Repetition Test* by Bayles et al. (Bayles et al., 1996) was adapted to Greek and was used to examine the effect of sentence frequency and length, as well as semantic content on repetition. It consists of 25 sentences organized in 5 sets: short meaningful, short non-meaningful, long meaningful, long non-meaningful and long frequent sentences. The short form of the *Peabody Picture Vocabulary Test (PPVT)* (Simos et al., 2014), a spoken word-picture matching test consisting of 32 items, was used for assessing single word comprehension. *Reading fluency* (Simos et al., 2013) for words and non-words was assessed in two tasks, in which the participant has to read as quickly as possible a list of words and non-words. Performance is evaluated by counting the number of items that have been read correctly in 45 seconds. Twenty words (10 high frequency and 10 low frequency words) and 14 matched non-words were selected for assessing spelling (Sideridis et al., 2008; Simos et al., 2013). Narrative *writing* was evaluated using the *"Cookie Theft"* picture and scoring instructions from the BDAE. Finally, a *Grammaticality Judgment test* (unpublished) was used to assess receptive ability and knowledge of tense and agreement. The test consists of 80 sentences: 40 sentences are included in the agreement condition (20 sentences for person; 20 sentences for number agreement) and 40 in the tense condition (20 sentences for past; 20 sentences for future tense). Half of the sentences were well-formed and half ill-formed. In this task, participants must decide on the grammatical status of each sentence.

Concerning connected speech analysis, the Quantitative Production Analysis (QPA) (Saffran et al., 1989; Gordon, 2006; Varkanitsa, 2012) was selected for the quantification of fluency, discourse, lexical and grammatical production. The procedure was employed for the analysis of two narrative productions from a picture description task ("Cookie Theft" from the BDAE) and a story retell task (from the Multilingual Assessment

Instrument for Narratives - MAIN) (Gagarina et al., 2019). Detailed information about the QPA and the connected speech analysis procedure employed in this study can be found in Karpathiou et al. (2018).

Motor Speech Assessment

Motor speech evaluation included oral motor assessment, maximum phonation time, diadochokinetic (DDK) rates, repetition of utterances of increasing articulatory complexity (two-syllable words, polysyllabic words, sentences) and passage reading (Wertz et al., 1984). The test was informally adapted to Greek. Acoustic analysis was performed using the Praat software (Boersma, 2001) in order to calculate temporal measures for diadochokinetic rates, passage reading and sentence repetition. The *Western Aphasia Battery (WAB) apraxia* subtest (Kertesz, 1982) was also used to assess face and limb ideomotor apraxia.

Neuropsychiatric Evaluation

Mood was evaluated through the use of a 15-item questionnaire, the short form of the Geriatric Depression Scale (GDS) or the Beck Depression Inventory (BDI) for younger individuals (<65years). For data analysis, scores on the BDI were rescaled to match the GDS scoring system. Scores were reversed so that higher scores indicate fewer reported depressive symptoms. The new combined variable was labeled *Mood Scale*.

The *Neuropsychiatric Inventory (NPI)* (Cummings et al., 1994) has been widely used to measure the frequency and severity of neuropsychiatric symptoms in PPA. The NPI assesses 12 domains: delusions, hallucinations, agitation-aggression, depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behavior, sleep, and appetite. Each domain is scored for its frequency, its severity, and the distress that the symptom causes to the caregiver. Higher scores indicate more

TABLE 2 | Group results for the cognitive-linguistic battery.

Task (Max. Score)	Neurotypical group ($n = 15$)		AD ($n = 9$) vs. control group		PPA ($n = 10$) vs. control group		AD vs PPA
	Mean	SD	Mean	SD	Mean	SD	
MMSE (/30)	28.87	1.06	24.89**	2.47	24.30**	3.65	ns
Executive functioning							
Trail making test A (/180)	107.33	14.03	46.44**	46.00	64.53*	36.84	ns
Trail making test B (/300)	204.53	40.26	34.00**	44.79	72.68*	76.67	ns
Digit span total (/32)	14.33	2.41	11.44	2.70	10.80*	3.65	ns
Forward (/16)	8.80	1.57	7.44	1.59	6.40*	2.07	ns
Backward (/16)	5.53	1.68	4.00	1.50	4.40	2.12	ns
Verbal fluency test	94.60	18.41	54.56*	11.90	37.80**	12.09	ns
Letter	36.53	7.11	26.00	8.93	17.50***	5.64	ns
Category	58.07	15.47	28.56*	11.01	20.30**	8.43	ns
Memory							
5-words test (/20)	19.07	1.39	11.33**	4.64	14.90*	5.07	ns
Delayed recall (/10)	9.27	1.28	4.33***	2.96	7.20	2.94	ns
Free delayed recall (/5)	4.40	0.99	1.44***	1.33	3.10	1.91	ns
Cued delayed recall (/5)	4.87	0.35	2.89**	1.83	4.10	1.10	ns
5-objects test (/25)	24.87	0.52	20.11**	5.97	22.50	3.89	ns
Delayed recall (/5)	4.93	0.26	3.89	1.69	4.80	0.42	ns
Benson figure delayed recall (/17)	13.20	2.54	6.44***	3.28	8.50*	4.88	ns
Visuospatial functioning							
Benson figure copy (/17)	15.80	1.21	15.11	1.69	16.30	1.49	ns
Clock drawing test (/15)	14.40	0.63	11.67*	2.74	12.20	3.49	ns
Object semantics							
Pyramids and palm trees test (52)	50.27	1.534	48.78	2.95	44.40**	5.91	ns
Pyramids and palm trees test (14)	14.00	0.00	13.33	0.87	12.70***	1.16	ns
Mood							
Mood scale (/15)	13.47	2.67	10.89	3.48	13.50	0.97	ns
Praxis							
Western aphasia battery–apraxia subtest (/60)	59.93	0.26	58.11*	1.83	55.90***	2.42	ns

*, **, ***Significant at the 0.05, 0.01, and 0.001 level respectively (2-tailed).
Pairwise comparisons performed with Kruskal-Wallis H (df = 2) and post-hoc Mann-Whitney U tests (df = 1).
Ns, non-significant.

severe deficits and distress. The Greek version of NPI (Politis et al., 2004) was used in this study.

Functional Assessment

The *Frontotemporal Dementia Rating Scale (FRS)* (Mioshi et al., 2010; Maiovis et al., 2016) was used as a measure of severity and functional ability. Scoring is based on the reported frequency of behaviors and daily activities explored by a 30-item caregiver questionnaire.

Statistical Analysis

As the number of participants in each group was small, the most appropriate statistical test was the non-parametric Kruskal-Wallis H test. In cases where the test was significant, a series of 3 Mann-Whitney *U post-hoc* tests were conducted to compare pairs of groups. The corrected α value ($\alpha = 0.016$) was used to interpret the results. In order to determine whether the distributions in each group had the same variability, the corresponding histograms were visually inspected. Median and mean ranks are reported accordingly.

Z-scores were computed for each variable and averaged to yield a composite score for executive, memory, visuospatial, semantic, and linguistic measures. Mean *z*-scores were compared across groups using Welch's ANOVA due to unequal variances and sample size. The Games-Howell correction was used for *post-hoc* pairwise comparisons between groups. Correlations between cognitive and linguistic measures were performed using the Pearson correlation coefficients with Bonferroni corrections for multiple comparisons.

RESULTS

Several differences were found among the groups that participated in the study. Group results are presented in **Table 2** for cognitive measures and **Table 3** for speech and language measures. Statistically significant differences for narrative analysis measures are provided in **Table 4**.

Comparing Individuals With PPA to Neurotypical Adults

Concerning executive function, participants with PPA needed more time to complete the TMT, recalled shorter digit sequences and produced fewer words in both conditions of the Verbal Fluency Test. They were as a group less reliable in identifying semantic relations in the PPTT. Regarding memory, they performed worse than neurotypical controls on the figure delayed recall. Even though their performance was affected on the total score of the 5-Words Test, their performance was within normal limits for the delayed recall of words and objects' positioning.

As far as linguistic abilities are concerned, participants with PPA were found to be impaired on all sentence repetition tests, and the BNT. Spoken language comprehension was found to be impaired at the word level, as suggested by scores on the PPVT ($U = 13.55$, $z = 3.35$, $p = 0.02$) with a median of 24 correct compared to 30 for the neurotypical group. At the phrase level, the PPA group showed greater difficulty in following commands, processing complex ideational material and syntactically difficult sentences. Participants with PPA were impaired in understanding written sentences, detecting grammatical violations, reading and spelling real words, and narrative writing. Their articulation rate for passage reading was slower (mean rank = 9.44) compared to the neurotypical group (mean rank = 21.57), ($U = 11.92$, $z = 4.06$, $p = 0.01$). Speech rate may be affected by long pauses. Articulation rate on the other hand is computed by excluding silent pausing time. This measure better reflects speech motor execution, as speech rate involves motor, linguistic aspects of speech production (e.g., word-finding pauses) or non-linguistic processes (e.g., inattention).

Differences for fluency and narrative measures between the PPA and the control group that were found to be statistically significant are depicted in **Figures 1**, **2**.

Comparing Individuals With AD to Neurotypical Adults

Participants with AD performed worse than controls on all episodic memory measures and most executive measures with the exception of Digit Span tasks and the letter condition of the Verbal Fluency Test. They were impaired on the BNT, the long non-meaningful sentences of the SRT, the Reading Fluency Test both for words and non-words, the Grammaticality Judgment task, and the Narrative writing. Differences were also detected for articulation and speech rate, total dysfluencies, and percentage of narrative to total words in story retell, as well as total time, mean pause duration and pauses per total words, semantic errors and frequency of the words used in picture description. There was finally a statistically significant difference in the temporal measures for the production of two sentences from the motor speech evaluation.

Comparing Individuals With PPA to Individuals With AD

Even though differences did not reach statistical significance, participants with PPA, performed better than participants with AD on almost all the measures of the cognitive-linguistic battery that do not heavily rely on linguistic and semantic processing. They scored lower than participants with AD just on the forward condition of the DGS, both conditions of the VFT and the PPPT. The opposite pattern was observed on the linguistic battery. Participants with AD scored better on linguistic tests, with the exception of the Reading Fluency for words and non-words, and two motor speech measures (diadochokinetic rates and sentence duration per syllable). Finally, participants with AD scored better on almost all narrative measures.

Several measures have differentiated participants with PPA from participants with AD. Participants with PPA performed significantly worse than participants with AD on the long frequent sentences of the Sentence Repetition Test. They produced fewer narrative and unique words (type) in describing the "Cookie Theft" picture from the BDAE. In comparison to participants with AD, they produced shorter and less elaborated sentences, as measured by mean sentence length and sentence elaboration index in the story retell task. Finally, they made more phonological errors in both narrative tasks.

TABLE 3 | Group results for the speech and language assessment battery.

Task (Max. Score)	Neurotypical ($n = 15$)		AD ($n = 9$) vs. control group		PPA ($n = 10$) vs. control group		AD vs PPA
	Mean	SD	Mean	SD	Mean	SD	
Repetition							
BDAE sentence repetition (/2)	2.00	0.00	2.00	0.00	1.00***	0.48	**
Bayles sentence repetition (/340)	338.33	2.16	312.11**	33.39	217.80***	96.97	ns
Short meaningful (/50)	50.00	0.00	49.00	1.50	41.60***	11.00	ns
Short non-meaningful (/50)	50.00	0.00	48.67	2.24	40.60***	14.18	ns
Long meaningful (/80)	79.67	0.72	71.00	10.51	44.30***	26.52	ns
Long non-meaningful (/80)	78.80	1.82	65.89*	15.88	37.90***	28.54	ns
Long frequent (/80)	79.87	0.52	77.89	5.01	55.70***	22.69	*
Confrontation naming							
BNT (/45)	41.33	2.58	31.11**	9.09	20.90***	12.78	ns
BNT-short (/15)	14.87	0.35	12.11*	3.41	8.90***	3.41	ns
Auditory comprehension							
PPVT (/32)	28.80	2.86	26.00	4.58	21.50**	6.93	ns
BDAE commands (/10)	9.93	0.26	9.33	0.50	7.30***	1.89	ns
BDAE complex ideational material (/6)	5.67	0.62	4.78	1.20	3.30***	1.83	ns
Morphosyntactic processing							
BDAE-3 embedded sentences (/10)	9.73	0.46	8.67	1.32	7.50*	2.55	ns
Grammaticality judgment (/80)	78.27	2.19	72.89*	3.92	68.80***	7.04	ns
Reading							
BDAE word-picture matching (/4)	3.93	0.26	3.67	0.50	3.60	0.52	ns
BDAE sentence comprehension (/4)	4.00	0.00	3.78	0.44	3.50*	0.71	ns
Reading fluency words	81.87	8.92	60.56**	12.62	62.80**	13.93	ns
Reading fluency non-words	42.00	6.91	28.33**	8.31	35.80	6.29	ns
Writing							
Spelling words (/20)	18.07	1.53	15.22	3.56	12.20*	6.68	ns
Spelling non-words (/12)	11.40	0.63	11.33	1.12	9.80	3.74	ns
BDAE narrative writing (/11)	10.80	0.41	8.00***	1.41	7.10***	1.66	ns
Temporal measures of speech							
Reading passage speech rate	4.08	0.38	3.96	0.59	3.61	0.62	ns
Reading passage articulation rate	5.09	0.34	4.97	0.40	4.43**	0.60	ns
Sentence duration per syllable							
11-syllable sentence	0.20	0.03	0.32**	0.16	0.23	0.10	ns
12-syllable. sentence	0.19	0.03	0.25	0.06	0.19	0.08	ns
14-syllable sentence	0.17	0.03	0.20	0.03	0.19	0.11	ns
15-syllable sentence	0.17	0.02	0.19	0.06	0.15	0.09	ns
16-syllable sentence	0.17	0.03	0.20*	0.04	0.15	0.09	ns
Max phonation time mean	16.79	6.20	16.25	7.67	14.26	5.96	ns
Diadochokinetic rates							
pa (repetitions/syllable)	7.03	0.74	6.83	0.75	6.66	0.72	ns
ta (repetitions/syllable)	7.10	0.87	6.55	0.86	6.88	0.65	ns
ka (repetitions/syllable)	6.50	0.83	5.81	0.60	6.44	0.87	ns
pataka (repetitions/syllable)	6.96	0.72	7.02	1.62	8.64	3.97	ns

*, **, ***Significant at the 0.05, 0.01, and 0.001 level respectively (2-tailed).*

Pairwise comparisons performed with Kruskal-Wallis H (df = 2) and post-hoc Mann-Whitney U tests (df = 1).

BDAE, Boston Diagnostic Aphasia Examination; BNT, Boston Naming Test; PPVT, Peabody Picture Vocabulary Test; ns, non-significant.

Group Comparisons Using Mean *z*-Scores

Composite scores for executive, memory, visuospatial, semantic, and linguistic measures were compared across groups. Welch's Anova results and *post-hoc* group comparisons using the Games-Howell test are presented in **Table 5**. The only statistically significant difference that was detected

TABLE 4 | Statistically significant results for narrative measures.

Task (Max. Score)	Neurotypical ($n = 15$)		AD ($n = 9$) vs. control group		PPA ($n = 10$) vs. control group		AD vs PPA
	Mean	SD	Mean	SD	Mean	SD	
Story retell total time in s	72.94	16.92	102.33	32.11	142.28**	87.67	ns
Picture descr. total time in s	66.75	27.40	109.34	45.10	83.58*	27.27	ns
Story retell articulation rate (wpm)	174.71	28.25	143.99*	20.68	147.51	32.44	ns
Story retell speech rate (wpm)	133.93	24.91	94.62*	33.71	91.56*	31.39	ns
Picture descr. speech rate (wpm)	124.82	19.99	95.27	27.38	86.71**	31.40	ns
Picture descr. mean pause duration	0.87	0.20	1.47***	0.33	1.30**	0.28	ns
Picture descr. pauses ptw	0.05	0.03	0.11*	0.06	0.12**	0.06	ns
Story retell total dysfluencies ptw	0.12	0.06	0.24*	0.15	0.28**	0.12	ns
Picture descr. number of narrative Ws	96.40	38.77	92.44	25.80	55.00**	18.79	*
Picture descr. number of type Ws	65.53	19.42	57.89	11.05	39.60**	13.24	*
Story retell number of type Ws	75.07	14.52	59.89	12.82	57.8*	16.96	ns
Story retell narrative words/total Ws	0.87	0.07	0.72*	0.13	0.62**	0.21	ns
Story retell typetoken ratio SqR	6.37	0.49	5.80	0.41	5.54*	0.82	ns
Picture descr. type token ratio SqR	6.20	1.85	6.04	0.42	5.28**	0.96	ns
Picture descr. mean logarithmic frequency of narrative words	2.66	0.10	2.78*	0.09	2.88**	0.15	ns
Picture descr. mean sentence length	7.54	1.73	6.29	1.26	5.19**	1.17	ns
Story retell mean sentence length	8.97	1.83	8.23	1.46	6.14*	1.11	*
Picture descr. sentence elaboration index	2.25	0.66	1.77	0.57	1.16**	0.51	ns
Story retell sentence elaboration index	2.12	0.31	1.90	0.27	1.37***	0.31	*
Story retell embedding index	0.61	0.22	0.40	0.14	0.29***	0.10	ns

*, **, ***Significant at the 0.05. 0.01 and 0.001 level respectively (2-tailed).
Pairwise comparisons performed with Kruskal-Wallis H (df = 2) and post-hoc Mann-Whitney U tests (df = 1).
Descr., description; s, seconds; ns, non-significant; wpm, words per minute; ptw, per total word; Ws, words; SqR, square root.

between the AD and the PPA group was for the language composite measure.

Correlations Between Linguistic and Cognitive Composite Scores

A statistically significant correlation between the executive and the language composite measures was found for participants with PPA ($r = 0.86$, $p = 0.001$). For participants with AD, the correlation between the executive and the language z scores was not significant ($r = 0.47$, $p = 0.202$). No other significant correlations were detected between cognitive and linguistic measures.

DISCUSSION

The present study examined the cognitive and linguistic abilities of Greek-speaking individuals with AD and PPA. A group of neurotypical adults served as a control group. The first aim of the study was to compare their performance on a comprehensive battery of tests to inform clinicians about test selection. A secondary aim was to evaluate the executive impairment component to shed light on its involvement in linguistic deficits.

The two groups differed significantly on linguistic measures. Participants with PPA did not differ significantly from participants with AD on executive, memory, visuospatial functioning, and object semantics, as shown by comparing their composite mean z scores. Both groups differed from the control group on executive function, language, and memory. Participants with PPA were also impaired in semantics. Concerning linguistic assessment, production of phonological errors, difficulty in repeating long frequent sentences, and production of simple and short sentences has differentiated the participants with PPA not only from the neurotypical group but from participants with AD as well.

Even though both groups were impaired on measures of executive function to a similar extent, the pattern of deficits was different in each group. Participants with PPA scored better than participants with AD in the TMT and the CDT, which are non-verbal, but worse on the DGS and the VF tests. Moreover, the results of this study indicate that there is a relation between executive function and linguistic ability in individuals with PPA. No relation was found concerning individuals with AD. This suggests that linguistic and executive tasks measure, at least to some degree, different constructs. At first glance, the association between language and executive skills in this study seems to indicate an interrelation between language ability and domain-general cognitive processing. Individuals with PPA may exhibit executive deficits early in the course of the disease (Harciarek and Cosentino, 2013; Macoir et al., 2017) and while executive deficits have been linked to language impairments, evidence suggests that nonverbal executive tasks

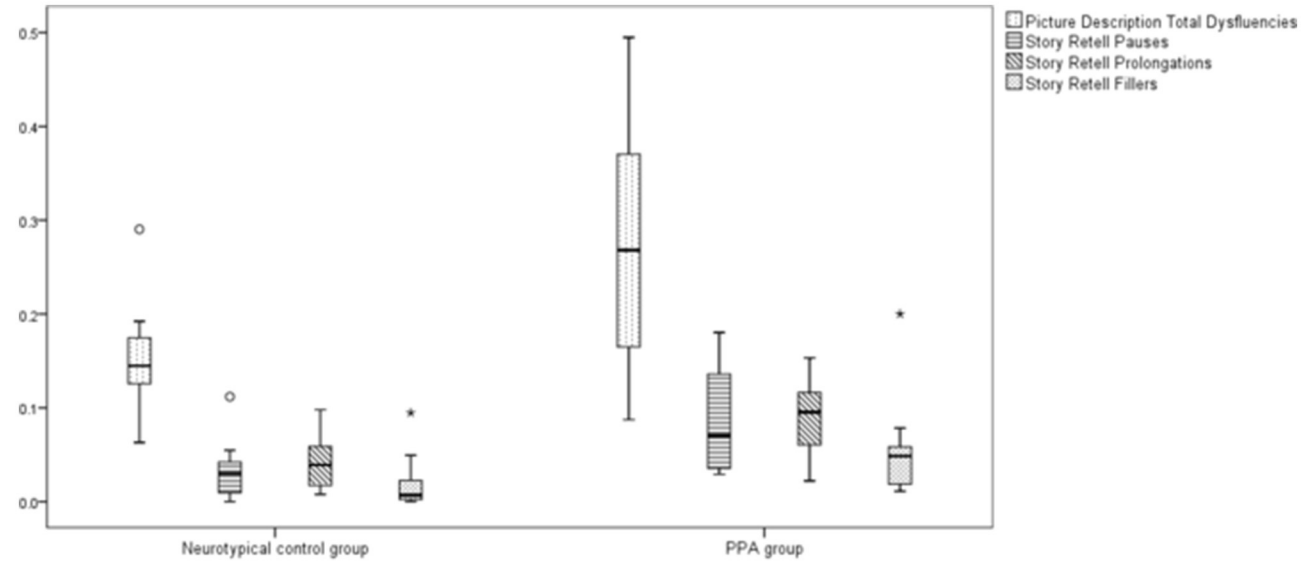

FIGURE 1 | Differences between individuals with PPA and neurotypical adults for fluency measures.

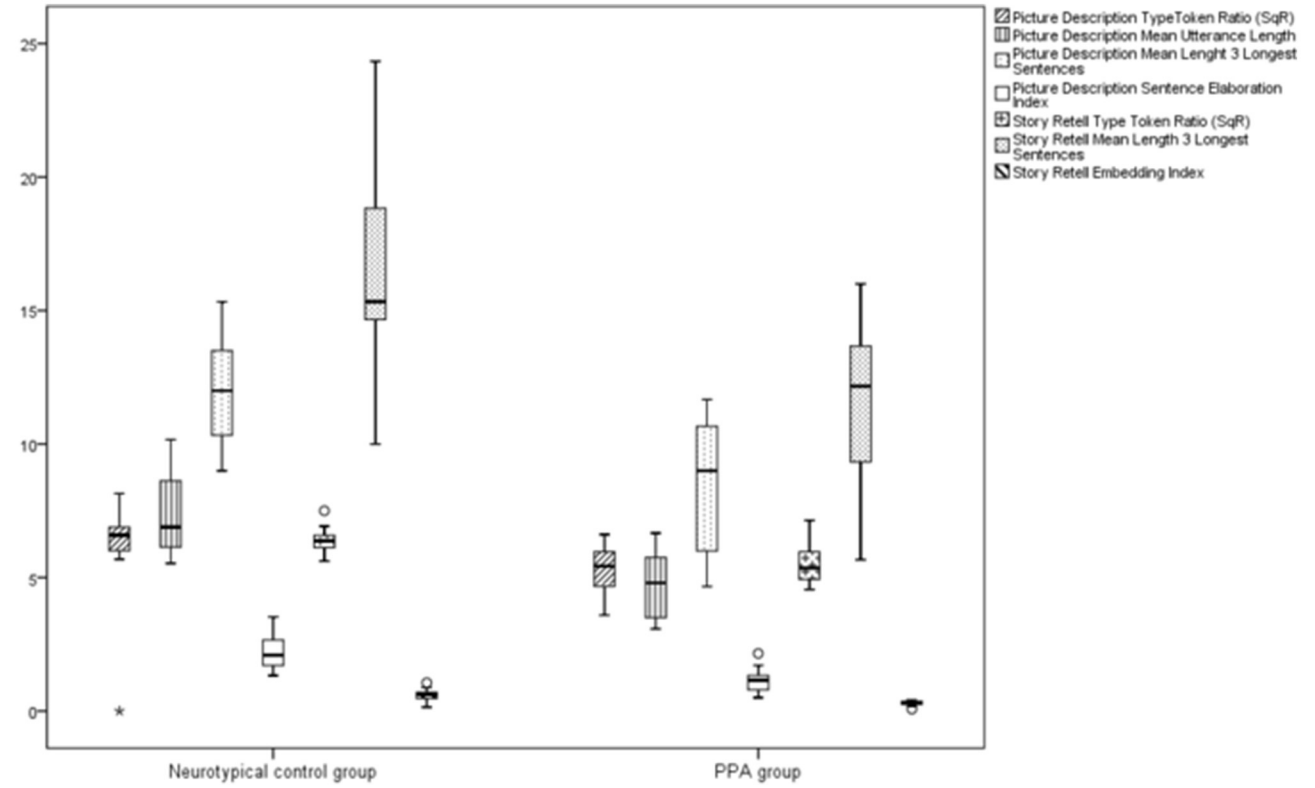

FIGURE 2 | Differences between individuals with PPA and neurotypical adults for narrative measures.

are also affected (Macoir et al., 2017). However, the executive tasks that were included in the assessment battery are not "pure". For example, the TMT relies on fine-motor skills and visual scanning, and the VF test on phonological and semantic processing. Verbal executive tasks may be useful for evaluating verbal abilities but are less useful for drawing conclusions about

TABLE 5 | Group comparisons with mean *z*-scores.

Area of functioning Mean *z*-scores	Group	*Mean*	*SD*	Welch Anova *F*	*df1*	*df2*	Sig.	Pairwise comparison	Games-Howell *post-hoc* Sig.
Executive	AD	−2.33	0.82	41.42	2	14.50	0.000	Neurotypical-AD	0.000
	PPA	−2.28	1.08					Neurotypical-PPA	0.000
								AD-PPA	0.999
Memory	AD	−3.52	3.10	8.71	2	12.63	0.004	Neurotypical-AD	0.022
	PPA	−1.33	1,42					Neurotypical-PPA	0.042
								AD-PPA	0.173
Language	AD	−2.55	1.54	21.05	2	11.89	0.000	Neurotypical-AD	0.002
	PPA	−8.06	5.49					Neurotypical-PPA	0.003
								AD-PPA	0.029
Semantic	AD	−0.97	1,92	5.14	2	13.42	0.022	Neurotypical-AD	0.374
	PPA	−3.83	3.85					Neurotypical-PPA	0.030
								AD-PPA	0.133
Visuospatial	AD	−0.57	1.40	1.25	2	16.61	0.312	Neurotypical-AD	ns
	PPA	0.41	1.24					Neurotypical-PPA	ns
								AD-PPA	ns

Df, degrees of freedom; Sig., significant; ns, non-significant.

the association between language performance and cognitive functioning. Nevertheless, the fact that the executive and linguistic composite measures were correlated in the PPA and not the AD group may reflect the linguistic load of the tests used and the recruitment of executive processes to compensate for the difficulties faced by the participants with PPA. This compensatory mechanism has been put forward to account for over-reliance on executive processing under demanding conditions (Gonçalves et al., 2018). Selecting simple, nonverbal executive function tasks seems preferable for documenting executive deficits, examining their contributions to language performance, and planning intervention in individuals with degenerative diseases.

The AD group was the only group that differed from controls on measures of episodic memory. Even though the PPA group scored lower than controls on the 5-Words Test (total score), the group's performance on the delayed conditions was similar to controls. The total score of the 5-Words Test combines scores from encoding, consolidation, and retrieval conditions. An impaired total score, in the presence of intact delayed recall ability, may be attributed to reduced short-term memory capacity as suggested by the group's low forward-DGS score and difficulties in almost all repetition tasks. These results are heavily influenced by the composition of the PPA group and more specifically by the larger proportion of individuals with the logopenic variant. Impaired short-term memory is considered to underly difficulties in lvPPA which is characterized by impaired sentence repetition and word retrieval deficits. Individuals with the semantic variant did not have repetition nor short-term memory deficits. This is consistent with previous studies which underly the differential nature of short-term memory deficits in PPA variants (Foxe et al., 2021).

The opposite pattern can be noted for the semantic tasks. Difficulties with non-verbal semantic associations and single-word comprehension can be attributed to the inclusion of individuals with the semantic variant of PPA. To be classified as svPPA, a person must be impaired in single-word comprehension and confrontation naming. Additional features of this variant include impaired object knowledge, surface dyslexia or dysgraphia, spared repetition, grammaticality, and motor speech abilities.

The PPA group did not include participants with the third PPA variant, the nfvPPA. The diagnosis of nfvPPA is based on either agrammatism in language production or apraxia of speech and impaired comprehension of syntactically complex structures.

Results concerning praxis and visuospatial functioning are consistent with previous research. On the WAB Apraxia subtest both the AD and PPA groups performed significantly lower compared to the control group. Limb apraxia has been documented in AD and lvPPA (Ahmed et al., 2016). Johnen et al. (2018) using a tool that assesses limb apraxia and buccofacial apraxia concluded that AD, nfvPPA and svPPA have different praxis profiles which contribute to differential diagnosis. Participants with PPA did not differ from neurotypical adults on visuospatial construction measures, i.e., figure copy and CDT). Nevertheless, they were impaired on the delayed recall condition of the Benson Figure Test, albeit to a lesser extent than participants with AD. Research has shown that visual memory may be impaired in both lvPPA and svPPA (Watson et al., 2018) and that participants with lvPPA and AD can be equally impaired (Foxe et al., 2013).

Several measures of language comprehension have been found to differ between the PPA and the neurotypical group. Performance of the PPA group on following commands, understanding complex auditory material, embedded sentences, and processing written sentences is not necessarily related to agrammatism. Concerning receptive language, sentence

comprehension deficits in the logopenic variant are frequently reported and have been associated with short-term memory demands for sentence processing (Wilson et al., 2012). As Ash et al. (2019) point out, impaired grammaticality with disease progression in lvPPA contributes to difficulty in distinguishing lvPPA from nfvPPA. As there were no participants with the nonfluent/agrammatic variant in our sample, other underlying deficits, such as single word comprehension deficits relevant to participants with svPPA or short-term and working memory difficulties pertinent to participants with lvPPA provide a more likely explanation for the observed difficulties. In the same way, difficulties in detecting grammatical violations are most probably associated with reduced working memory capacity. Indeed, concerning the PPA group, performance on the grammaticality judgement task was significantly correlated with the backward condition of the DGS and the B form of TMT.

The timed and temporal measures used in the battery suggest slower motor ability for the participants with AD. This is more clearly reflected in slower articulation rate which does not include pauses and hesitations. The AD group was older than the control group and speech rate and articulatory movement have been found to decline as a function of age (Bilodeau-Mercure et al., 2015). Slower articulation rate was found for narrative production and may have contributed to lower scores on the two reading fluency tasks. However, DDK rates and speech rate for passage reading was within normal limits. This suggests an additional processing difficulty factor imposed by the nature of the reading fluency task, where participants are asked to read as fast as possible a list of words and non-words, and discourse demands. Passafiume et al. (2000) have also reported longer reading latency in participants with AD than in normal subjects for words and non-words.

Participants with AD did not encounter any difficulty with spelling words and non-words. Previous studies have revealed variable spelling abilities in AD. Hughes et al. (1997), for example, found no spelling impairment in mild AD. Other studies (e.g., González-Nosti et al., 2020) have documented difficulties with spelling in the earliest stages of AD. Differences between studies may be explained by task selection and cross-linguistic factors, such as the degree of orthographic transparency of each language.

Reading and spelling performance of the PPA group was mildly impaired for real words. Reading fluency and spelling for non-words were within normal limits. Intact spelling performance with non-words, reflects spare phonology to orthography conversion, and reliance on sub-lexical mechanisms to spell. This explanation also accommodates impaired performance with real words. The words that have been selected for spelling assessment were highly dependent on the ability to access stored orthographic representations (e.g., "αλλιώτικος" —different, "διευθυντής" —director). Surface dysgraphia, i.e., difficulty with exceptional, low-frequency words and regularization errors, is one of the hallmarks of svPPA. Nevertheless, it is the second most common pattern of spelling impairment in the logopenic variant of PPA (Graham, 2014).

The inclusion of connected speech measures has proven valuable. Concerning narrative production, the PPA group was impaired in discourse and sentence productivity measures but did not differ from the neurotypical control group in measures of grammatical accuracy. The increased proportion of dysfluencies and more specifically of pauses, prolongations, and fillers together with the lower number and proportion of unique words can be attributed to lexical difficulties. For the AD group, increased duration of pauses, proportion of pauses, semantic errors, use of higher frequency words and incomplete sentences in the picture description task are indicative of word-finding difficulties. This is also supported by lower scores on the naming test. These results are in line with the findings of a recent meta-analysis concerning connected speech in AD (Kavé and Goral, 2018). Taken together, results of the AD group support the presence of memory, executive and lexical retrieval deficits.

Some of the findings of this study have practical implications for clinicians working with individuals with degenerative diseases. First, both the long and short forms of the BNT and the PPTT that have been used in the assessment battery have led to similar results. This suggest that the short forms of these tests can be used in busy settings. Second, the long frequent sentences subset of the SRT has differentiated participants with PPA from participants with AD. Increased processing difficulty with the long non-meaningful sentences subset resulted in impaired performance compared to controls. Given the fact that the entire test is quite long and, in our experience, demanding for individuals with more pronounced deficits, the use of the long frequent sentences' subtest may be preferable in the clinical setting. Third, the assessment battery revealed difficulty with sentences with increased articulatory complexity, as shown by the temporal measures of sentence production during the motor speech assessment. It must be noted that this is a common finding in participants with severe co-existing repetition deficits and has been previously reported (Duffy et al., 2017). Thus, repetition of single multisyllabic words seems to be more reliable for evaluating motor speech function. Finally, the study provides a reference group for potential useful comparisons. A clinician may compare an individual with PPA or AD with this reference group and establish a *z*-score profile and an indication of the severity of a cognitive-linguistic disorder.

The main limitation of the study is the small sample size. This is particularly relevant to the extensive assessment battery. Another limitation was the fact that the non-fluent variant of PPA was not represented in the PPA group. Fluency and grammatical measures may have been more impaired with the inclusion of individuals with nfvPPA. Difficulty recruiting individuals with this variant has been reported before (Epelbaum et al., 2021). Furthermore, the composition of the PPA group was unbalanced in respect to the number of participants with the logopenic and the semantic variant. However, the same may also be true for the AD group. The group is not homogeneous and different single or multiple deficits were documented for participants with AD. For example, one participant with a prominent memory deficit was also impaired in language measures at a similar degree to some of the participants with PPA. These limitations arise from the difficulty to include individuals with PPA in clinical research and the consecutive recruitment method that was employed. PPA is a rare disorder with a prevalence that is estimated in the range of 1.1–6 per 100.000 (Grossman, 2014). In addition to that, many

individuals with PPA receive a diagnosis when they are no longer in the early stages of the disease and cannot thus participate in diagnostic studies. This may be related to the delay in seeking medical attention, or even to limitations of the health system (Bertsias et al., 2020).

Finally, it must be noted that the AD group was older than the control group. Participants with PPA were also younger than the participants with AD, but the age difference did not reach statistical significance. This is because the control group was matched demographically to the PPA group and age of onset of PPA is typically younger than AD.

CONCLUSION

Neuropsychological testing combined with narrative analysis has documented language and other cognitive deficits in participants with lvPPA, svPPA and AD. Participants with AD were impaired in memory, and executive function. Moreover, they exhibited lexical retrieval difficulties, as well as difficulties in linguistic tasks with an increased processing load such as repetition of long non-meaningful sentences and fast reading of words and non-words. Participants with PPA were also affected on verbal executive function measures, reflecting the linguistic load of the tests used and the recruitment of executive processes to compensate for their difficulties. Naming, single word comprehension, auditory comprehension of complex material, repetition, reading, and writing were all affected.

The most informative measures in differentiating participants with lvPPA and svPPA from participants with AD, were sentence repetition, phonological errors, mean sentence length and sentence elaboration index in a connected speech sample. These findings should be interpreted with caution given the small sample size.

Speech and language deficits may be the core features of Primary Progressive Aphasia (PPA), but other cognitive domains are also affected, especially with disease progression. In order to develop an accurate profile of deficit patterns in PPA variants, linguistic and additional neuropsychological testing should uncover manifestation of all symptoms.

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 Athens Alzheimer Association. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

NK and MK designed the study. NK was responsible for data collection, data analysis, and drafting the manuscript. MK critically revised the work. Both gave their final approval of the version to be published.

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