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Phonological Short-Term Memory in Logopenic Variant Primary Progressive Aphasia and Mild Alzheimer's Disease

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Abstract

It has been argued that individuals with logopenic variant primary progressive aphasia (lvPPA) have an impairment of the phonological loop, which is a component of the short-term memory (STM) system. In contrast, this type of impairment is not thought to be present in mild typical Alzheimer's disease (AD). Thus, one would predict that people with lvPPA would score significantly lower than a matched AD group on tasks that require phonological STM. In the current study, an lvPPA group was compared with a mild AD group that was matched on age, education, and general cognitive functioning. For a subset of the tasks that involved pseudowords, the AD and lvPPA groups were compared to a healthy control group that was matched on age and education. The lvPPA group was more impaired than the AD group on all of the tasks that required phonological STM, including the pseudoword tasks, but there were no significant differences between these groups on tasks that required visuospatial STM. Compared to the healthy controls, the lvPPA group performed significantly worse on the repetition and reading of pseudowords, while the AD group did not differ significantly from the controls on these tasks. These findings are consistent with the hypothesis that phonological STM is impaired in lvPPA.

Keywords

primary progressive aphasia; Alzheimer's disease; short-term memory; phonological processing; visuospatial processing

1. Introduction

Logopenic variant primary progressive aphasia (lvPPA) is a clinical syndrome that involves impairment in word retrieval and repetition of phrases and sentences (Gorno-Tempini et al, 2011). Phonological speech errors may also occur. Single-word comprehension, object knowledge, motor speech, and grammar are typically spared. In a majority of cases, neuropathological and biomarker studies have associated lvPPA with an atypical presentation of Alzheimer's disease (Leyton et al., 2011; Mesulam et al., 2008; Mesulam et

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al., 2014; Rabinovici et al., 2008; Rohrer et al., 2010; Rohrer, Rossor, & Warren, 2012; Teichmann et al., 2013). In this atypical presentation, cortical atrophy is maximal within the left inferior parietal lobe and the left posterior superior temporal lobe (Gorno-Tempini et al., 2004, 2008; Josephs et al., 2013; Rohrer et al., 2010; Teichmann et al., 2013). In contrast, the typical presentation of Alzheimer's disease involves degeneration that originates within the medial temporal lobe (Braak & Braak, 1995; Delacourte et al., 1999).

Gorno-Tempini and colleagues (Gorno-Tempini et al., 2004, 2008) have argued that the core mechanism that underlies the lvPPA syndrome is an impairment of the phonological loop, a short-term storage system in Baddeley's model of working memory (Baddeley, 1992, 2003a, 2012). According to this model, the phonological loop comprises two components: the phonological store, which holds speech sounds for 1 to 2 seconds; and subvocal rehearsal, which can be utilized to refresh the speech sounds that are being held within the phonological store. The phonological store has been associated with left inferior parietal cortex, while subvocal rehearsal has been associated with left inferior frontal cortex (Baldo & Dronkers, 2006).

The existence of the phonological store is supported by the phonological similarity effect (Baddeley, 1966). This effect involves superior short-term recall of letter or word sequences with dissimilar phonology (e.g., *cow*, *bar*, *day*, *pit*), compared to letter or word sequences with similar phonology (e.g., *mad, mat, cap, cat*). The existence of subvocal rehearsal is supported by the word length effect (Baddeley, Thomson, & Buchanan, 1975). The word length effect involves superior short-term recall for word sequences that can be articulated quickly (e.g., *sum, wit, harm, bond*), compared to word sequences that require additional time for articulation (e.g., association, considerable, university, representative).

Consistent with the hypothesis that lvPPA involves an impaired phonological loop, individuals with lvPPA have exhibited deficits in digit, letter, and word span tasks (Crutch, Lehmann, Warren, & Rohrer, 2013; Foxe, Irish, Hodges, & Piguet, 2013; Gorno-Tempini et al., 2008; Leyton et al., 2014; Rohrer et al., 2010; Wilson et al., 2010). In this population, the phonological similarity effect has been found to be absent (Gorno-Tempini et al., 2008) or abnormal (Leyton et al., 2014), suggesting that the phonological store is impaired in lvPPA. In contrast, the word length effect is present in lvPPA, suggesting that subvocal rehearsal is relatively intact (Gorno-Tempini et al., 2008).

Unlike lvPPA, an impaired phonological loop is not thought to be present in mild typical Alzheimer's disease (AD; Foxe et al., 2013; Huntley & Howard, 2010; Leyton et al., 2014). Instead, performance on span tasks suggests that spatial STM is impaired in mild AD (Huntley & Howard, 2010). Performance on block design, a task that involves visuospatial processing, is also lower in mild AD, compared to age-matched controls (Caccappolo-van Vliet et al., 2003; Ennok, Anni, Burk, & Linnamagi, 2014). Therefore, one would predict that people with lvPPA would score significantly lower than a matched AD group on tasks that require phonological STM, and one would predict that individuals with mild AD would perform significantly worse than a matched lvPPA group on tasks that require spatial STM. The former prediction, but not the latter prediction, has been supported by the performance of matched lvPPA and AD groups on digit and spatial span tasks (Foxe et al., 2013).

Compared to the AD group, lvPPA participants performed significantly worse on forward and backward digit span, while the two groups did not differ on forward and backward spatial span.

In addition to phonological span tasks, individuals with lvPPA perform significantly worse than controls on repetition tasks, including single-word and sentence repetition (Crutch et al., 2013; Leyton et al., 2014; Rohrer et al., 2010) and pseudoword repetition (Crutch et al., 2013). Individuals with AD have scored lower than healthy controls on sentence repetition (Leyton et al., 2014), but they have also scored higher than those with lvPPA on both word and sentence repetition (Foxe et al., 2013). It remains to be seen if this repetition advantage extends to pseudowords. Since pseudowords are novel and meaningless stimuli that cannot be semantically recoded, the repetition of these items provides a purer test of phonological STM (Baddeley, Gathercole, & Papagno, 1998; Friedman, 1996). Furthermore, compared to word repetition, pseudoword repetition is dependent on larger areas of cortex within the left superior temporal gyrus and the left inferior parietal lobe (Baldo, Katseff, & Dronkers, 2012), suggesting that pseudoword repetition places a greater demand on phonological STM.

Pseudoword reading is another task that has been associated with phonological STM (Bisiacchi, Cipolotti, & Denes, 1989; Butterworth, Campbell, & Howard, 1986; Caramazza, Basili, Koller, & Berndt, 1981). In previous studies, individuals with lvPPA have had lower pseudoword reading accuracy than controls (Brambati, Ogar, Neuhaus, Miller, & Gorno-Tempini, 2009; Rohrer et al., 2010), suggesting that phonological alexia is present in lvPPA. Some have argued that the phenomenon of phonological alexia results from impairment in the ability to convert graphemes to phonemes (e.g., Beauvois & Derouesne, 1979; Coltheart, Rastle, Perry, Langdon, & Ziegler, 2001), while others have argued that phonological alexia results from a modality-independent phonological processing deficit (e.g., Friedman, 1995; Patterson, Suzuki, & Wydell, 1996). In lvPPA, phonological alexia could result from a failure to hold the correct sequence of phonemes within STM (cf. Bisiacchi et al., 1989; Friedman, 1996).

In the current study, we tested the prediction that people with lvPPA would score significantly lower than a matched AD group on tasks that require phonological STM, but not on tasks that require visuospatial STM. We included multiple tests that require either phonological or visuospatial STM, and we compared an lvPPA group with a mild AD group that was matched on age, education, and general cognition, as measured by the Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975). A subset of the phonological tests involved pseudoword tasks that are not widely available. For these tasks, the AD and lvPPA groups were compared to a healthy control group that was matched on age and education. It was predicted that the lvPPA group would perform significantly worse than the AD and control groups on tasks that require phonological STM, and it was predicted that the lvPPA and AD groups would not be significantly different on tasks that require visuospatial STM. In addition, it was predicted that the AD and control groups would have similar performance on the pseudoword tasks.

2. Method

2.1. Participants

Eleven lvPPA participants and 12 AD participants were diagnosed based on the current criteria (Gorno-Tempini et al., 2011; McKhann et al., 2011). The lvPPA and AD groups were matched on age, education, and MMSE (see Table 1). The healthy control group consisted of 16 participants who were matched on age and education, but scored significantly higher on the MMSE.

2.2. Procedure

The lvPPA and AD groups completed tasks that require phonological STM: forward and backward digit span, from the Wechsler Memory Scale (WMS; The Psychological Corporation, 1997b); BDAE word and sentence repetition subtests (Goodglass, Kaplan, & Barresi, 2001); pseudoword repetition; and reading pseudowords and matched real words. The lvPPA and AD groups also completed tasks that require visuospatial STM: forward and backward spatial span, from the WMS; and block design, from the Wechsler Adult Intelligence Scale (The Psychological Corporation, 1997a). The healthy control participants completed pseudoword repetition and the reading of pseudowords and matched real words.

The pseudoword repetition task included 10 pseudowords with one syllable (e.g., *zan*), 10 with three syllables (e.g., *banikim*), and 10 with five syllables (e.g., *janiliation*). The pseudoword and matched real word reading tasks each included 11 items that contained three phonemes and 9 items that contained four phonemes. The 20 pseudowords were created by changing the first letter of each matched real word (e.g., *tub* became *mub*).

At least one participant from each group did not complete every task. One of the 16 control participants did not complete pseudoword reading, and three control participants did not complete pseudoword repetition. In the lvPPA group, two of the 11 participants did not complete pseudoword repetition, due to experimenter error. Due to time constraints, two lvPPA participants did not complete block design, and one lvPPA participant did not complete pseudoword reading. In the AD group, one of the 12 participants did not complete pseudoword repetition or block design, due to experimenter error.

For the specific subgroups that completed each task, the independent-samples t test indicated that lvPPA, AD, and control subgroups did not differ on age or education. Furthermore, the control subgroups scored significantly higher on the MMSE compared to both lvPPA and AD subgroups, while comparisons of lvPPA and AD subgroups indicated that they were not significantly different on the MMSE.

3. Results

3.1. Digit and spatial span tasks

A 2 × 2 × 2 (Task × Direction × Group) mixed analysis of variance (ANOVA) was conducted on the raw accuracy data, which are presented in Figure 1. This analysis revealed significant main effects of Task, Direction, and Group. More importantly, there were significant interactions of Task × Group [$F(1, 21) = 5.57$, $p = .028$] and Direction × Group

[$F(1, 21) = 4.66$, $p = .043$]. The Task × Direction interaction was also significant [$F(1, 21) = 25.87$, $p < .001$], but this interaction is not relevant to the current study. The three-way interaction was not significant, $F(1, 21) = 0.12$, $p = .73$.

The Task × Group interaction was explored in two ways. First, the effect of Group was examined for each Task. For the digit span task, the AD group scored significantly higher than the lvPPA group, $t(21) = 3.31$, $p = .003$. In contrast, for the spatial span task, there was no significant difference between the two groups, $t(21) = 0.63$, $p = .534$. Second, the effect of Task was examined for each Group. For the AD group, performance was greater on digit span, $t(11) = 3.07$, $p = .011$. For the lvPPA group, there was no difference between the two span tasks, $t(10) = 0.64$, $p = .534$.

Similarly, the Direction × Group interaction was explored in two ways. First, the effect of Group was examined for each Direction. For the forward direction, the AD group scored significantly higher than the lvPPA group, $t(21) = 3.39$, $p = .003$. For the backward direction, the two groups were not significantly different, $t(21) = 1.20$, $p = .244$. Second, the effect of Direction was examined for each Group. For both groups, performance was greater in the forward direction [AD: $t(11) = 6.75$, $p < .001$; lvPPA: $t(10) = 2.90$, $p = .016$].

The mean scaled scores for each span task are presented in Figure 2. Compared to the lvPPA group, the AD group had a significantly higher scaled digit span score, $t(21) = 3.49$, $p = .002$. The AD group's mean scaled digit span score was in the average range ($M = 8.67$, $SD = 2.10$), while the lvPPA group's mean score was borderline impaired ($M = 5.82$, $SD = 1.78$). For spatial span, the AD and lvPPA groups were not significantly different, $t(21) = 0.22$, $p = .832$. Both groups scored in the low average range (AD: $M = 6.33$, $SD = 2.50$; lvPPA: $M = 6.09$, $SD = 2.91$).

3.2. Block design

The raw and scaled block design data are presented in Figure 3. The AD and lvPPA groups were not significantly different on block design, and this was true for both raw scores [$t(18) = 0.29$, $p = .773$] and scaled scores, $t(18) = 0.21$, $p = .836$. Both groups scored in the low average range (AD: $M = 6.36$, $SD = 2.58$; lvPPA: $M = 6.11$, $SD = 2.80$).

3.3. BDAE word and sentence repetition

The accuracy data are presented in Figure 4. The AD group scored significantly higher than the lvPPA group on both word repetition [$t(14.1) = 2.81$, $p = .014$[1]] and sentence repetition, $t(21) = 3.33$, $p = .003$.

3.4. Pseudoword repetition

The accuracy data for the three groups are presented in Figure 5. A 3 × 3 (Length × Group) mixed ANOVA was conducted, and the Greenhouse-Geisser correction was employed when Mauchly's Test indicated that sphericity was not present. The main effect of Length was significant [$F(1.6, 47.1) = 17.26$, $p < .001$], with accuracy decreasing as length increased.

[1]Corrected for unequal variances.

The main effect of Group was also significant [$F(2, 30) = 7.78$, $p = .002$], and the Length × Group interaction was significant, [$F(3.1, 47.1) = 4.79$, $p = .005$]. At each pseudoword length, the Tukey HSD post-hoc test indicated that the AD and control groups were not significantly different, while the lvPPA group scored significantly lower than the other two groups (see Table 2).

3.5. Pseudoword reading

Difference scores were calculated by subtracting each participant's matched real word score from his or her pseudoword score (see Figure 6). Thus, a more negative difference score indicates a greater difficulty with pseudoword reading, compared to the reading of matched real words. A between-subjects ANOVA revealed a significant effect of Group, $F(2, 34) = 6.15$, $p = .005$. The Tukey HSD test indicated that the lvPPA group's difference score was more negative than that of the AD group ($p = .034$) and the control group ($p = .005$), while the AD and control groups were not significantly different ($p = .763$).

4. Discussion

The goal of the current study was to test the hypothesis that phonological STM is impaired in lvPPA. Participants with lvPPA were compared to participants with mild AD who were matched on age, education, and general cognition, as measured by the MMSE. Participants completed multiple tasks that required phonological STM, in addition to tasks that required visuospatial STM. Healthy control participants completed a subset of the former tasks, namely those that involved pseudowords.

As predicted, the lvPPA participants were more impaired than the AD group on all of the tasks that required phonological STM, and there were no significant differences between these groups on the tasks that required visuospatial STM. Compared to the healthy controls, the lvPPA participants performed significantly worse on the pseudoword tasks. In contrast, the performance of the AD and control groups did not differ significantly on these tasks. These findings are consistent with the hypothesis that phonological STM is impaired in lvPPA.

Comparable to the findings of Foxe et al. (2013), the lvPPA and AD groups were not significantly different on tasks that require visuospatial STM. Both groups scored within the low average range for these tasks. These results are consistent with the patterns of functional connectivity that have been observed in participants with lvPPA and AD (Whitwell et al., 2015). Compared to healthy controls, both patient groups showed reduced functional connectivity in the right parietal lobe, which has been associated with visuospatial STM (Baddeley, 2003b; Smith & Jonides, 1997). In contrast, only the lvPPA group showed reduced functional connectivity in the left inferior parietal lobe, which has been associated with the phonological store (Baldo & Dronkers, 2006).

Similar to previous findings of impaired word and sentence repetition in lvPPA (Crutch et al., 2013; Foxe et al., 2013; Leyton et al., 2014; Rohrer et al., 2010), we found that the lvPPA group performed significantly worse on these tasks compared to the control and AD groups. Furthermore, the lvPPA group was also impaired on pseudoword repetition. In the latter task, the lvPPA group scored significantly lower than the other groups at every pseudoword length, but the lvPPA group's accuracy also decreased as pseudoword length increased, with 77% accuracy for one-syllable pseudowords and 49% accuracy for five-syllable pseudowords. This pattern could be due to an impaired phonological store (Baddeley, Gathercole, & Papagno, 1998; cf. Friedman, 1996). Alternatively, longer pseudowords could be more difficult to repeat because of an articulatory deficit. However, individuals with lvPPA do not typically have dysarthria or verbal apraxia. Thus, the latter interpretation is unlikely to be correct.

The lvPPA group had lower pseudoword reading accuracy than the other groups, while the AD and control groups were not significantly different. In contrast, Brambati et al. (2009) found that lvPPA and AD groups both performed significantly worse than a healthy control group on a pseudoword reading task. However, the average age of the AD group from the Brambati et al. study, which was composed primarily of individuals with early onset AD (EOAD), was lower than that of the AD group from the current study. Compared to late onset AD (LOAD), EOAD has been associated with greater bilateral temporoparietal atrophy (Frisoni et al., 2005; Frisoni et al., 2007). Thus, EOAD and lvPPA may be more phenotypically similar than LOAD and lvPPA.

In conclusion, the findings of this study are consistent with the hypothesis that phonological STM is impaired in lvPPA (Foxe et al., 2013; Gorno-Tempini et al., 2004, 2008; Leyton et al., 2014), although the exact nature of the impairment remains unclear. In contrast, phonological STM appears to be largely intact in mild typical AD (Huntley & Howard, 2010). This pattern extends to tasks that require the processing of novel and meaningless phonological representations that cannot be semantically recoded, such as the repetition and reading of pseudowords. However, individuals with lvPPA and mild AD appear to have comparable levels of low average performance on tasks that involve visuospatial STM.

5. Acknowledgements

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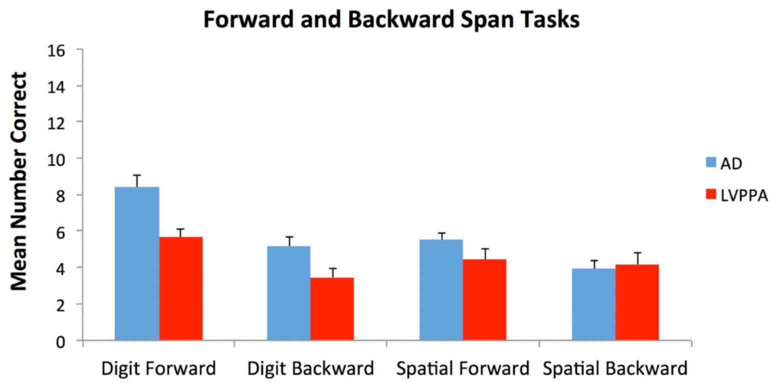

Figure 1.
Mean number of correct items on the forward and backward versions of the digit and spatial span tasks. For this figure and those that follow, the bars represent the standard error.

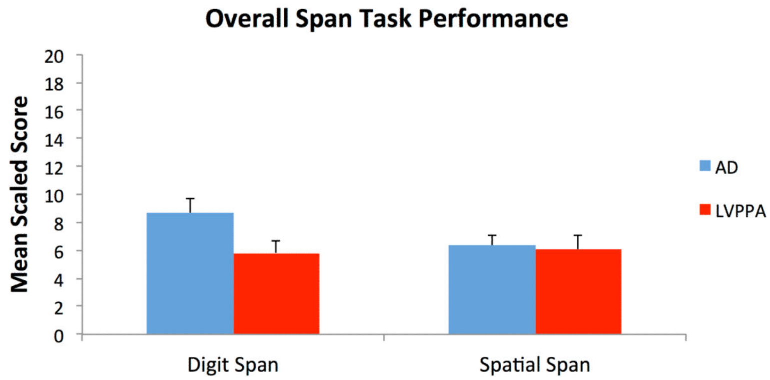

Figure 2.
Mean overall scaled scores for span tasks.

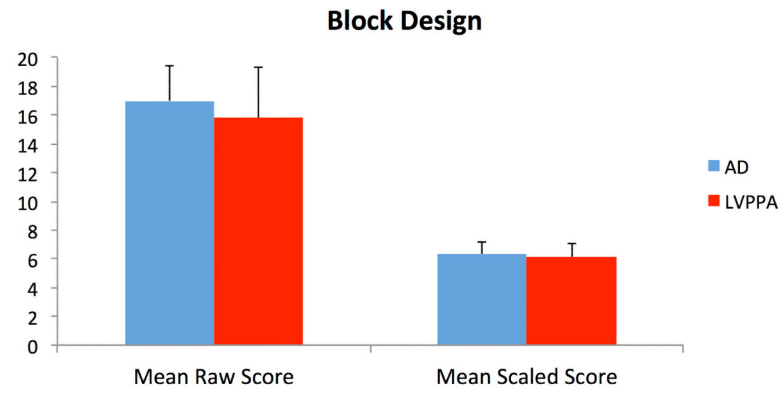

Figure 3.

Mean raw scores (left) and mean scaled scores (right) on the block design task.

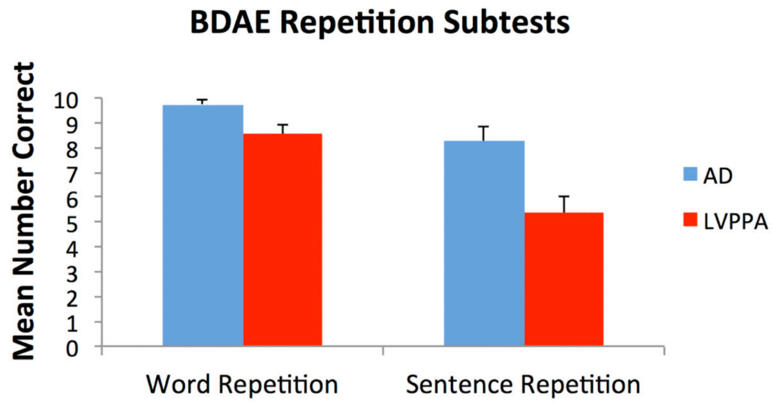

Figure 4.
Mean number of correct items on the BDAE word and sentence repetition subtests.

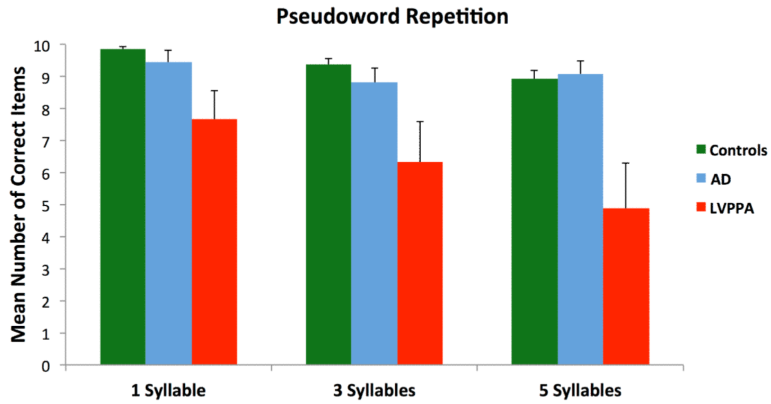

Figure 5.
Mean number of pseudowords repeated correctly at each syllable length.

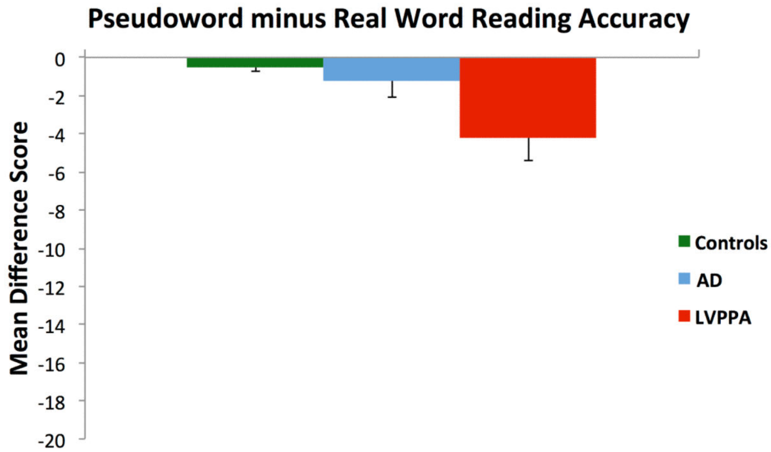

Figure 6.
Mean difference scores for pseudoword and matched real word reading.

Table 1

Demographic Data and MMSE Scores

	Mean (SD)			*p*-Values from Independent Samples *t* Test		
	Controls	**AD**	**lvPPA**	**Controls vs. AD**	**Controls vs. lvPPA**	**AD vs. lvPPA**
Sex (F:M)	8:8	7:5	7:4			
Age	71.2 (9.6)	69.7 (9.3)	70.7 (8.3)	.68	.90	.78
Education	17.6 (1.5)	17.0 (1.9)	17.3 (1.6)	.33	.56	.72
MMSE	29.3 (1.1)	22.4 (2.0)	22.1 (3.8)	< .001	< .001[a]	.80[a]

[a]Corrected for unequal variances.

Table 2

Pseudoword Repetition, p-Values from Tukey HSD Test

Comparison	1 Syllable	3 Syllables	5 Syllables
lvPPA vs. AD	.041	.041	.002
lvPPA vs. Controls	.008	.008	.002
AD vs. Controls	.813	.800	.984