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Neuroanatomical correlates of phonologic errors in logopenic progressive aphasia

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Abstract

While phonologic errors may be one of the salient features of the logopenic variant of primary progressive aphasia (lvPPA), sparse data are available on their neuroimaging correlates. The purpose of this study was to identify brain regions associated with different types of phonologic errors across several tasks for participants with lvPPA. Correlational analyses between phonologic errors across tasks most likely to elicit such errors and specific left hemisphere gray matter volume regions were conducted for 20 participants. Findings point to the inferior parietal lobe and supramarginal gyrus as being the most relevant correlates. Atrophy in these regions may increase the likelihood of making phonologic errors in lvPPA, particularly substitution error types. Our results provide support for neuroanatomical correlates of phonologic errors in the parietal region, which is consistent with previous findings of temporoparietal cortex involvement/atrophy in lvPPA.

Keywords

logopenic progressive aphasia; primary progressive aphasia; phonologic errors; neuroimaging; neuroanatomical correlates

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1. Introduction

Primary progressive aphasia (PPA) consists of impaired language abilities, in the absence of other cognitive deficits, as the presenting sign of a neurodegenerative disease (Gorno-Tempini et al., 2011; Mesulam, 2001). The consensus criteria for PPA by Gorno-Tempini et al. (2011) recognize three main variants: logopenic, semantic, and nonfluent. Alternative ways of classifying PPA subtypes have also been proposed (e.g., Botha, et al., 2015). Specific to the logopenic variant (lvPPA) are salient clinical characteristics consisting of impairments in word retrieval and sentence repetition, and the presence of at least three of the following four features: phonologic errors during naming and spontaneous speech tasks, spared comprehension of single words or object knowledge, spared motor speech abilities, and/or absence of agrammatism (Gorno-Tempini et al., 2011). Neuroimaging studies of lvPPA (Beck et al., 2008; GornoTempini et al., 2008, 2011; Josephs et al., 2010; Krishnan et al., 2017; Madhavan et al., 2013; Mesulam et al., 2009; Rohrer et al., 2010, 2013) demonstrate that there are left greater than right hemisphere abnormalities, with marked atrophy in the lateral temporoparietal cortex, often also involving the precuneus and frontal lobes, with relative sparing of the medial temporal lobe.

According to the consensus criteria (Gorno-Tempini et al., 2011), phonologic errors are one of the salient features that may occur, though are not required, for a diagnosis of lvPPA. Unfortunately, phonologic errors are typically loosely defined, and inconsistent terminology is used (e.g., simply mentioned as occurring frequently or infrequently during certain tasks and sometimes reported to consistent of omissions, substitutions, or additions of nondistorted sounds) (Bonner, Ash, & Grossman, 2010; Gorno-Tempini et al., 2004, 2008; Leyton, Ballard, Piguet, & Hodges, 2014; Leyton et al., 2015; Mesulam et al., 2009; Rogalski et al., 2011; Wilson et al., 2010), making comparisons across studies difficult. Only a few recent studies have described and analyzed phonologic errors in detail (Dalton, Schultz, Henry, Hillis, & Richardson, 2018; Henry et al., 2016; Petroi, Duffy, Strand, & Josephs, 2014). Petroi et al. (2014) provided support for the existing consensus criteria (Botha et al., 2015; Gorno-Tempini et al., 2011) by demonstrating that all 22 participants with lvPPA made some phonologic errors, with the presence or absence of those errors varying across tasks. Other factors influencing the frequency of errors were the nature and complexity of the tasks, overall aphasia severity, and possibly education. Tasks most sensitive to eliciting a significant proportion of phonologic errors were reading nonwords and irregular words (Western Aphasia Battery-Revised (WAB); Kertesz, 2007), repetition of multisyllabic words, and the 15-item Boston-Naming Test (BNT) (Lansing, Ivnik, Cullum & Randolph, 1999).

Sparse data are available on neuroimaging correlates of phonologic errors, especially over a variety of tasks designed to elicit such errors. In general, core regions associated with phonological processing impairments in lvPPA are the temporoparietal junction as well as the retrosplenial region/posterior cingulate cortex, with disease progression involving the spread of atrophy to the inferior frontal regions (Awad, Warren, Scott, Turkheimer, & Wise, 2007; Rohrer et al., 2008; Rohrer et al., 2010). Prior studies that have analyzed neuroimaging correlates in lvPPA (Brambati, Ogar, Neuhaus, Miller, & Gorno-Tempini, 2009) and stroke-induced aphasia (e.g., Baldo, Katseff, & Dronkers, 2012) have primarily

focused on response accuracy, or have focused on general phonological skill across PPA variants (Henry et al., 2016). Yet accuracy of responses alone and general descriptions of the adequacy/inadequacy of phonological processing may be insufficient for examining the relationship between phonologic impairment and its underlying neuroanatomical correlates in lvPPA.

This study extends our previous research (Petroi et al., 2014), which described the types of language tasks that were most likely to elicit phonologic errors in lvPPA, by examining neuroanatomical correlates across both speaking task and type of error. Its purpose was to examine and describe the relationship between phonologic errors and affected brain regions on diverse spoken language tasks, a relationship which has not been examined for individuals with lvPPA. Understanding these brain-behavior relationships will increase knowledge of the biological underpinnings of phonologic errors and help to explain heterogeneity in clinical presentation across participants with lvPPA. An atlas-based parcellation technique was used to identify which regional gray matter volumes correlated with phonologic errors across four tasks.

Neuroimaging studies have shown that lvPPA is characteristically associated with atrophy of the left lateral temporal and parietal lobes (Beck et al., 2008; Gorno-Tempini et al., 2008, 2011; Josephs et al., 2010; Krishnan et al., 2017; Madhavan et al., 2013; Mesulam et al., 2009; Rohrer et al., 2010, 2013), and a number of studies point to areas within the temporal and parietal lobes as being important in the phonological processing of speech production in normal individuals and lesion studies (Hickok, 2009; Hickok & Poeppel, 2007). Hence, we aimed to specifically assess the degree to which volume of the temporal and parietal regions would correlate with tasks most likely to elicit a high frequency of phonologic errors (reading nonwords and irregular words, repetition of multisyllabic words, and the 15-item BNT) and with specific phonologic error types (substitutions, omissions, and additions). Because the left inferior frontal lobe (e.g., Broca's area) is assumed to be part of the articulatory (motor) network (Hickok & Poeppel, 2007) and may have some some relevance to phonological processing, we also assessed the degree to which that region was associated with phonological errors in a secondary analysis. It was not included in the primary analysis because it is thought to have greater activation during general task processing and increased task load, and may reflect working memory, attention, and executive function processing (Graves, Rutvik, Humphries, Seidenberg, & Binder, 2010). To our knowledge, this is the first study to examine a variety of language tasks to determine whether frequency of phonologic errors reveals differences in neuroanatomical correlates in lvPP.

2. Materials and Methods

2.1 Participants

This study was completed as part of a National Institutes of Health (NIH) funded investigation examining PPA and its variants. The study was approved by the Mayo Clinic Institutional Review Board, and informed consent was obtained from all participants.

Twenty participants with lvPPA were consecutively recruited from the Department of Neurology, Mayo Clinic, Rochester, MN. They were a subset of the twenty-two participants

included in the Petroi et al. (2014) study. Two of those participants (i.e., 17 and 19) were not included in the present study: the former was excluded due to movement on the MRI and the latter due to diagnostic uncertainty given the MRI findings. A diagnosis of lvPPA was generally compatible with the previously published consensus criteria (Gorno-Tempini et al., 2011), consistent with updated considerations (Botha, et al., 2015), and based on the results of extensive language evaluation described previously (Petroi et al., 2014). The participants consisted of nine males and eleven females with a mean age of 66.5 (range = 47 to 85). All participants had language difficulties as their initial symptom and primary presenting complaint. There were no findings on neurological examination or neuroimaging studies indicative of a nondegenerative etiology. The pattern of phonologic errors of the one participant who was left-handed did not substantially depart from the patterns of the other participants nor did her neuroimaging findings, which showed left-sided temporoparietal atrophy.

The language testing protocol consisted of the WAB Part 1 and portions of the Reading and Writing sections of Part 2; the Token Test, Part V (DeRenzi & Vignolo, 1962); a 15-item BNT; an action (verb) fluency task (Woods et al., 2005); and a letter (FAS) fluency task (Loonstra, Tarlow, & Sellers, 2001). Motor speech as well as phonologic production abilities were judged based on spoken language tasks from the WAB along with other tasks that included speech alternating motion rates, speech sequential motion rates, vowel prolongation, multisyllabic word and sentence repetition, and a conversational speech sample.

Consistent with the diagnosis of lvPPA, participants exhibited varying degrees of pauses for word retrieval difficulties, impaired naming without obvious loss of word meaning, phonologic errors, impaired comprehension of phrases and sentences, and impaired repetition of spoken language. There was no evidence of agrammatism. Phonologic errors could be present, but they were not a requirement for the diagnosis of lvPPA. Consistent with the currently accepted criteria for a motor speech disorder diagnosis (Duffy, 2020; McNeil, Robin, & Schmidt, 2009; Wambaugh, Duffy, McNeil, Robin, & Rogers, 2006), no participant was judged to have apraxia of speech or dysarthria. The diagnosis of lvPPA for the participants was arrived at by consensus of two experienced speech-language pathologists (JRD and EAS) who agreed on the diagnosis with a high degree of confidence in all cases based on test results and review of video recordings of the formal testing. Table 1 summarizes participant characteristics. Supplementary Table S1, provides the findings from the WAB, and supplementary Table S2 summarizes participant performance on other language measures.

Participants also underwent detailed neurological examination by a neurologist (KAJ) specialized in neurodegenerative diseases including PPA, with the examination including testing of behavioral, cognitive, functional, and motor performance. Neuropsychological testing was administered by a psychometrist and overseen by a clinical neuropsychologist (MMM). Neuroimaging results (described below) supported the clinical diagnosis of lvPPA in that they were consistent with those found in previous studies of lvPPA (Beck et al., 2008; Gorno-Tempini et al., 2008, 2011; Josephs et al., 2010; Krishnan et al., 2017; Madhavan et al., 2013; Mesulam et al., 2009; Rohrer et al., 2010, 2013).

2.2 Methods for Evaluating Phonologic Errors

Phonologic errors were defined as phoneme substitutions, omissions, additions, and transpositions within recognizable utterances. Supplementary Table S3 provides definitions and examples of each type of error. To be consistent with our Petroi et al. (2014) study, the term phonologic errors is used here; it can be used interchangeably with phonological and phonemic errors. Based on our initial data (Petroi et al., 2014), tasks for which phonologic errors were analyzed consisted of several subtests of the WAB: picture description, repetition, animal fluency, reading irregular words (e.g., yacht, debt, courageous), and reading nonwords (e.g., dosh, aponster, limponit). Also analyzed were responses to the 15-item BNT, action fluency, letter fluency, and an unpublished multisyllabic word repetition task requiring three repetitions of each word in a set of 13 complex multisyllabic words (e.g., specific, catastrophe, aluminum). Criteria were previously established (Petroi et al., 2014) for determining the maximum number of phonemes that could be substituted, omitted, added, and/or transposed within a given response based on the number of phonemes in the target and the number of errors elicited (e.g., the maximum number of acceptable errors was one for a two or three phoneme word (e.g., /haɪk/ for kite /kaɪt/), and the maximum number of acceptable errors was two for a four to six phoneme word (e.g, /kɪtnaɪp/ for catnip / kætnɪp/), yet still be included in the phonologic error analysis. A coding manual was developed to ensure that judgments consistently matched the criteria for the presence and type of phonologic errors. The total number of utterances and total number of phonologic errors produced by each participant were recorded for each task, with transcribed errors (using the International Phonetic Alphabet) and ratings being based on the review of video recordings of all participants. Items coded for data analysis included percent of target words containing phonologic errors and broad type of phonologic error (i.e., substitution, omission, addition, or transposition).

Normalized frequencies (reported as a percentage) of specific types of phonologic errors were derived for each participant by dividing the number of recorded instances of each type of phonologic error by the total number of task-relevant words (or target words, as applicable, in contrast to nonrelevant words, e.g., verbal asides) produced per task. In some cases, normalized frequencies were aggregated across multiple tasks by summing the total number of each type of phonologic error across the tasks of interest and dividing those sums by the total number of task-relevant words produced across those same tasks. Only one instance of each type of phonologic error was counted per given target word, irrespective of the number of times each error type occurred per word. For example, if a word had two substitutions and three omissions, only one substitution and one omission were recorded to indicate the presence of that type of error in the response. Details pertaining to types and examples of phonologic errors as well as more specific methods for evaluating phonologic errors have been described previously (Petroi et al., 2014).

Our previous study (Petroi et al., 2014) revealed that some language tasks elicited more phonologic errors than others (i.e., were most sensitive to phonological production problems). For example, the findings suggested that picture description and word fluency tasks were less likely than naming, repetition, and reading tasks to elicit phonologic errors. It may be that open-ended tasks permitted participants to avoid words they anticipated to be

phonologically challenging, and as such may have reduced the frequency of phonologic errors. Thus, it was determined that neuroimaging correlates of phonologic errors would be best identified by examining the four tasks (hereafter referred to as “sensitive tasks”) that elicited the greatest number of such errors: two subtests of the WAB—reading irregular words and reading nonwords, the 15-item BNT, and a multisyllabic word repetition task.

2.3 Neuroimaging Analyses

All participants had volumetric magnetic resonance imaging (MRI) performed at 3T using a standardized protocol at baseline. A 3D magnetization prepared rapid acquisition gradient echo (MPRAGE) was performed using the following parameters: TR/TE/T1, 2300/3/900 ms; flip angle 8°, 26-cm FOV; 256 × 256 in-plane matrix with a phase FOV of 0.94, voxel sizes of 1×1×1.2mm. All MPRAGE images underwent pre-processing correction for gradient non-linearity and intensity non-uniformity. Regional gray matter volumes were calculated using atlas-based parcellation in SPM5 and the automated anatomical labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002). All MPRAGE scans and the AAL atlas were spatially normalized to a customized template using the unified segmentation tool in SPM5 (Ashburner & Friston, 2005). The customized template was created using 200 cognitively normal controls and 200 participants with dementia, as previously described (Vemuri et al., 2008). To create the template, all 400 scans were normalized to the Montreal Neurological Institute template and segmented using unified segmentation. Average probability maps of gray matter, white matter, and cerebrospinal fluid (CSF) were created and smoothed using 8 mm full-width at half maximum smoothing kernel to create customized tissue probability maps. Images from all participants in the current study were then normalized and segmented using unified segmentation and these customized tissue probability maps. Then, for each participant, the inverse transformation was applied to the atlas in custom template space in order to warp the atlas to the participant’s native anatomical space, and each native-space MRI was segmented into gray matter, white matter, and CSF.

The gray matter probability maps for each participant were thresholded to create a binary mask and were multiplied by the native-space AAL atlas to generate a custom gray matter atlas for each subject, parcellated into different regions-of-interest (ROI). Only left hemisphere regions were assessed as there is leftward asymmetry in lvPPA and as language is lateralized primarily to this hemisphere. In addition, total intracranial volume was measured to allow the correction for head size. The five brain regions identified as important for lvPPA included in this analysis were the lateral temporal cortex (including inferior, middle and superior temporal gyri), superior parietal lobe, inferior parietal lobe, supramarginal gyrus, and angular gyrus. These regions typically show the most severe abnormalities on neuroimaging in lvPPA and are important for normal phonological processing (Beck et al., 2008; Gorno-Tempini et al., 2008, 2011; Josephs et al., 2010; Krishnan et al., 2017; Madhavan et al., 2013; Mesulam et al., 2009; Rohrer et al., 2010, 2013). We merged the inferior, middle and superior temporal ROIs into one lateral temporal ROI in our primary analysis in order to reduce the number of statistical comparisons performed, reducing the number of type 1 errors. However, we also report the findings separately for each temporal gyri. In an additional secondary analysis, we assessed the

inferior frontal lobe (i.e., Broca's area) given its potential role in phonological processing. Supplementary Figure S1 provides a rendering of the ROIs included in the study.

2.4 Statistical Analyses

All regional gray matter volumes were divided by the total intracranial volume and then converted to age-corrected z-scores representing the degree of abnormality compared to a healthy, cognitively normal control cohort (n = 75, 40 females, mean age 71 (range = 51 to 89)). Gray matter values were negative as they represented atrophy compared to controls who had smaller z-scores. Significant findings would therefore reveal that as the normalized frequency of the phonologic errors increases, the gray matter scores decrease. We fitted linear regression using age as a predictor and mean gray matter volume as an outcome. We then extracted the intercept (beta0), slope (beta1), and residual standard error (sigma) from the model. The age-adjusted z-score was calculated as follows: (mean volume – (beta0 + beta1*age))/sigma. This step allowed us to correct for any age effects on each regional brain volume with these age effects estimated in a healthy aging population. This is prefereable to trying to estimate the influence of age on brain volume within the lvPPA participants who also show disease-related volume loss.

Spearman rank correlation coefficients were calculated to identify potential relationships between regional gray matter volumes and normalized frequencies of phonologic errors across the four sensitive tasks as well as between gray matter volumes and specific phonologic error types (i.e., substitution, omission, addition, and transposition errors). Using the Benjamini and Hochberg procedure (Benjamini & Hochberg, 1995) to correct for multiple comparisons, significance thresholds for the individual correlation tests were established based on a maximum allowed false discovery rate (FDR) of $q \leq 0.05$. Controlling for FDR using this approach instead of the family wise error rate was selected because of the generally higher sensitivity of FDR approaches. As a major goal of this study was to inform future research efforts, it was felt that the 'cost' of false negatives (Linquist & Mejia, 2015) (in the form of potentially unexplored avenues of research) was high enough to justify using the FDR approach, despite the higher potential for type 1 errors. Age, gender, education, and disease duration were ruled out as confounding factors using univariate, unadjusted tests of association with gray matter z-scores, including Spearman rank correlation coefficients and the Wilcoxon rank sum test. A p value of < 0.05 was considered significant for all unadjusted comparisons. All calculations were performed using the SAS v9.3 software suite (SAS Foundation, Cary, NC).

3. Results

3.1 Neuroanatomical Correlations for Sensitive Tasks

Table 2 summarizes the neuroanatomical correlates for phonologic errors across the four sensitive tasks. There were moderately high negative correlations between normalized frequencies of phonologic errors for repetition of multisyllabic words and the superior and inferior parietal lobes and the supramarginal gyrus, though those findings did not survive corrections for multiple comparisons. No significant or meaningful correlations were found between other sensitive tasks and any gray matter regions. There were also no significant

correlations when analyzing the superior, middle, and inferior temporal gyri separately ($p > .05$). As a secondary analysis, examination of the inferior frontal region did not reveal significant correlations ($p > .05$) as was hypothesized.

3.2 Neuroanatomical Correlations for Types of Phonologic Errors

Table 3 summarizes the results for neuroanatomical correlates for types of phonologic errors across the four sensitive tasks. Moderate negative correlations were found between substitution, omission, and addition errors and the superior and inferior parietal lobes. Substitution errors were additionally significantly correlated with the supramarginal gyrus. There were no significant correlations for transposition errors. When correcting for multiple comparisons, moderate negative correlations were found between substitution errors and the inferior parietal lobe and supramarginal gyrus. This relationship is depicted in the scatter plot in Supplementary Figure S2. No significant correlations for addition or omission errors survived corrections for multiple comparisons.

Table 4 summarizes the normalized frequency of phonologic error types across all sensitive tasks. There was a higher normalized frequency of errors for sensitive tasks compared to all nine tasks from the Petroi et al. (2014) study. For these sensitive tasks, correlations were larger for error types that occurred more frequently (Table 5 in that study) and that were more broadly distributed. This was particularly evident for substitutions errors (mean = 21.1%, SD = 16.5%, range = 2.7 to 58.3).

4. Discussion

4.1 Neuroanatomical Correlates

This study sought to identify brain regions that are meaningfully associated with phonologic errors produced by people with lvPPA. The findings demonstrate associations across the parietal regions assessed, with the inferior parietal lobe and supramarginal gyrus yielding the strongest correlations. Correlations between the inferior parietal lobe and supramarginal gyrus and substitution errors seem to be particularly relevant as they survived corrections for multiple comparisons. Thus, the greater the atrophy in these regions, the more likely that individuals with lvPPA will make phonologic errors, especially substitutions. Though this study was not intended to examine the causal relationships of these findings, it can be inferred that the inferior parietal lobe and supramarginal gyrus play a pertinent role in phonological processing. The results may also suggest that participants with lvPPA that show predominant parietal patterns of neurodegeneration may be more likely to exhibit phonologic errors than participants with more temporal predominant patterns (Krishnan et al., 2017), although this hypothesis will need to be tested in a larger cohort. While not surviving corrections for multiple comparisons, correlations were also found between the superior as well as inferior parietal lobe and substitution, addition, and omission errors.

While no previous study has examined the neuroanatomical correlates of phonological errors in lvPPA, a number of neuroimaging studies suggest that phonological processing involves the supramarginal gyrus (the left or bilateral suprmarginal gyrus have been implicated), temporoparietal regions, and the posterior inferior frontal gyrus (Graves et al., 2010; Price,

2012; Price & Mechelli, 2005). Specifically, the left supramarginal gyrus is activated during phonological storage in verbal working memory tasks (Paulesu, Frith, & Frackowiak, 1993; Ravizza, Delgado, Chein, Becker, & Fiez, 2004). Studies have also found left posterior superior temporal gyrus region activation in accessing lexical phonology (Baldo & Dronkers, 2006; Buchsbaum & D'Esposito, 2008; Graves, Grabowski, Mehta, & Gordon, 2007; Graves, Grabowski, Mehta, & Gupta, 2008). Additionally, Hickok and colleagues identified the Sylvian-parietal-temporal area (Spt), located primarily in the region of the left Sylvian fissure at the parietal lobe and temporal lobe boundary (roughly corresponding to Brodmann area 40 and including portions of the supramarginal gyrus), as playing a role in phonological processing (e.g., Buchsbaum, Humphries, & Hickok, 2001; Hickok, 2014; Hickok & Poeppel, 2004, 2007).

Temporoparietal regions have been correlated with repetition errors in persons with stroke-induced aphasia as well (Baldo et al., 2012; Benson, 1979; Damasio, 1981; Mendez & Geehan, 1988). In line with neuroimaging findings in lvPPA, lesions associated with conduction aphasia are localized to the left superior temporal gyrus and inferior parietal cortex, including the supramarginal gyrus (Benson, 1979; Damasio H & Damasio AR, 1980; Dronkers & Baldo, 2009; Green & Howes, 1977). Explanations of phonologic impairments and neuroanatomical abnormalities associated with traditional aphasia classifications, particularly conduction aphasia (Buchsbaum & D'Esposito, 2008; Buchsbaum, Baldo, Okada, Berman, Dronkers, & D'Esposito, 2011; Hickok, 2009; Hickok et al., 2003; Hickok & Poeppel, 2004, 2007), are consistent with the language features and areas of atrophy in lvPPA. Based on prior studies (Budd et al., 2010; Burns & Canter, 1977; Goodglass, 1992; Gorno-Tempini et al., 2011; Kohn, 1984; Kohn & Goodglass, 1985; Patterson et al., 2006; Wilson et al., 2010), we hypothesized in our original study (Petroi et al., 2014) that participants with lvPPA would demonstrate more phonologic errors on specific tasks: repetition of multisyllabic words, reading tasks, and the 15-item BNT. While significant correlations between repetition of multisyllabic words and regions of the parietal lobes and supramarginal gyrus in the current study were found to be significant, they did not survive corrections for multiple comparisons. Multisyllabic word repetition likely places heavier demands on phonological skills and little or no demands on lexical retrieval, or may provide greater opportunities to make phonologic errors; whereas, errors on the be BNT are likely strongly influenced by lexical retrieval demands. This might explain why the BNT did not correlate with the above anatomic areas. Furhter research may be needed to explore why reading tasks were not significantly associated with these brain regions. Nonetheless, the current results would support previous findings of temporoparietal region involvement in repetition tasks in the presence of phonological impairment and may imply that inferior parietal lobe and supramarginal gyrus atrophy is associated with a greater likelihood of phonologic substitution errors.

Moreover, correlations between substitution errors and the inferior parietal lobe and supramarginal gyrus appeared to be the most relevant in the current study as they survived corrections for multiple comparisons. Sound substitutions have been found to occur in people with stroke-induced aphasia and in other studies examining lvPPA. Irrespective of type of stroke-induced aphasia (e.g., conduction, Broca's, Wernicke's), analyses of phonologic errors indicate that substitutions constitute the majority of error types (Ardila &

Rosselli, 1993; Burns & Canter 1977), which we also found to be the case across tasks in lvPPA in our prior study (Petroi et al., 2014). Such errors, especially in conduction aphasia, are likely to occur with greater frequency during phrase/sentence repetition, spontaneous speech, picture naming, oral reading tasks, and multisyllabic word production, with errors increasing as complexity of words increase and in low frequency words (Burns & Canter 1977; Goodglass, 1992; Kohn, 1984; Kohn & Goodglass, 1985). However, while phonologic errors can be a feature of lvPPA, they have been only vaguely described as present during single word production, multisyllabic word/sentence repetition, and naming (Croot, Ballard, Leyton, & Hodges, 2012; Gorno-Tempini et al., 2008; Leyton et al., 2015; Leyton, Hsieh, Mioshi, & Hodges, 2013; Rohrer et al., 2010). Only recently (Dalton et al., 2018; Henry et al., 2016; Petroi et al., 2014) have such errors been investigated more thoroughly in lvPPA. The results of this study support the value of explicitly identifying the presence versus absence and task specificity of phonologic errors associated with PPA, particularly its logopenic variant. Such description may eventually help to refine clinical diagnostic criteria and has implications for neuroimaging localization.

Variability in types of tasks used and task analysis may account for some of the differences in the temporoparietal associations found across studies for phonologically-based responses or errors. This may have some bearing on neuroanatomical correlations for repetition of multisyllabic words, which in the current study did not survive when correcting for multiple comparisons. We also did not find evidence of a relationship between temporal lobe atrophy and phonologic errors. Even so, inclusion of sensitive tasks as opposed to those eliciting minimal phonologic errors failed to yield associations with the temporal lobe. Certainly, hypotheses related to the function of particular temporoparietal regions in lvPPA remain to be further defined and investigated. Thus far, there is evidence to support clinical heterogeneity within lvPPA that may reflect differences in severity and spread of neurodegeneration in the language network (e.g., Leyton et al., 2015; Leyton, Hsieh, Mioshi, & Hodges, 2013; Machulda et al., 2013).

4.2 Study Considerations

Some strengths as well as limitations of the current study should be considered. Strengths include the examination of the frequency of different types of phonologic errors across several language tasks, in comparison to many studies that simply noted the presence versus absence of phonologic errors without regard to task or error type. Particular regions within the parietal cortex were studied to better understand which areas may be relevant in phonologic processing in lvPPA. To our knowledge, this is the first study to investigate a variety of language tasks to determine whether frequency of phonologic errors reveals differences in neuroanatomical correlates across speaking tasks and phonologic error types in lvPPA. The number of participants may have limited the power in our correlation analyses At the same time, this study included a relatively large cohort of participants. In the previous description of the study cohort (Petroi et al., 2014), frequencies of phonologic errors were summarized at the level of the entire cohort (e.g. 47% of all errors committed by the entire cohort during the BNT task were substitution type errors). In this study, we summarized participant-level data to examine associations between task performance and other participant specific features, including gray matter deficit data.

Several of the correlations did not survive when correcting for multiple comparisons. However, it can be contended that there is no need to make adjustments as there will be fewer interpretation errors when the data being evaluated are observations of nature rather than random numbers (Rothman, 1990). Since empirical research is intended to understand phenomena through observation and experience, adjusting may result in missing important findings, particularly in an exploratory analysis. Some caution also should be taken when interpreting the results given the limitations associated with correlational analyses. While one subregion may not be independent from atrophy in adjacent regions, it was difficult to account for this statistically with a cohort of 20 participants. Other relevant specific temporoparietal gray matter regions are worth considering in future studies as well. Examining subdivisions of temporal regions into anterior and posterior components along with better understanding the role of input and output systems may also prove useful (Hickok, 2009; Hickok & Poeppel, 2007). Further, as noted previously (Petroi et al., 2014), frequency or severity of phonologic errors may have been underestimated because not all phonologic errors per given target word were counted and because neologisms were excluded; those scoring decisions may have influenced neuroanatomical correlations.

In terms of future directions, more theory-driven investigations of the mechanisms underlying phonologic errors associated with lvPPA and how other behavioral attributes (e.g., words produced, syntactic complexity, retrieval abilities) interact with phonologic errors may help inform future assessment and intervention approaches. Longitudinal examination of the relationship between phonologic error frequency and rate of overall clinical decline in lvPPA may also have implications for counseling and management.

5. Conclusion

The current study investigated brain regions associated with phonologic errors in individuals with lvPPA. The most relevant findings suggest that phonologic errors are associated with atrophy in the inferior parietal lobe and supramarginal gyrus and that sound substitutions are the most frequent relevant phonologic error type. These results are consistent with previous findings that involvement of the temporoparietal cortex is associated with some of the characteristic language deficits found in lvPPA.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Declaration of Interest

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Highlights

- This study examined neuroimaging correlates of phonologic errors in lvPPA.
- The inferior parietal lobe and supramarginal gyrus had the strongest correlates.
- Atrophy was associated with a greater likelihood of substitution errors in lvPPA.
- Thus, specific parietal region atrophy may increase phonologic errors in lvPPA.
- The results support prior findings of temporoparietal cortex atrophy in lvPPA.

Statement of Significance

This study aimed to assess the degree to which volume of the temporoparietal region is associated with phonologic errors in lvPPA. To our knowledge, this is the first study examining various language tasks to determine whether phonologic error frequency reveals differences in neuroanatomical correlates across speaking task and error types.

Table 1.

Participant characteristics

No. and sex of participants	Handedness		Age (years)	Onset age (years)	Illness duration (years)	Education (years)
20 (M=9, F=11)	Right=19 left=1					
		M (*SD*)	66.5 (10.5)	63.1 (10.3)	3.4 (1.3)	14.8 (2.6)
		Mdn	68.0	65.0	3.5	14.0
		Range	47 to 85	43 to 80	1 to 5	12 to 20

Table 2.

Neuroanatomical correlates (r_s) for phonologic errors across sensitive tasks

Sensitive tasks	Gray matter regions					
	Superior parietal	**Inferior parietal**	**Supramarginal gyrus**	**Angular gyrus**	**Angular gyrus**	**Mean gray matter**
Reading nonwords	−0.331	−0.319	−0.376	−0.285	−0.178	−0.319
p value	0.152	0.170	0.101	0.223	0.452	0.169
Reading irregular words	−0.398	−0.363	−0.219	−0.192	−0.017	−0.221
p value	0.081	0.115	0.352	0.416	0.942	0.349
Repetition of multisyllabic words	−0.493	−0.523	−0.474	−0.397	−0.294	−0.368
p value	0.027*	0.017*	0.034*	0.082	0.209	0.110
Boston Naming Test	−0.057	−0.195	−0.126	−0.046	0.100	−0.044
p value	0.808	0.408	0.595	0.846	0.675	0.851

* $p < 0.05$

Table 3.

Neuroanatomical correlates (r_s) for types of phonologic errors

Phonologic error types	Gray matter regions					
	Superior parietal	Inferior parietal	Inferior parietal	Angular Gyrus	Lateral temporal	Mean gray matter
Substitutions	−0.552	−0.617	−0.622	−0.439	−0.342	−0.473
p value	0.012 *	0.004 *†	0.003 *†	0.053	0.140	0.035 *
Omissions	−0.460	−0.482	−0.440	−0.365	−0.189	−0.312
p value	0.041 *	0.031 *	0.052	0.114	0.425	0.180
Additions	−0.512	−0.518	−0.393	−0.384	−0.254	−0.396
p value	0.021 *	0.019 *	0.086	0.094	0.279	0.084
Transpositions	−0.348	−0.133	−0.040	−0.189	−0.078	−0.144
p value	0.133	0.578	0.866	0.424	0.743	0.544
Total phonologic errors	−0.543	−0.595	−0.550	−0.432	−0.289	−0.433
p value	0.013 *	0.006 *†	0.012 *	0.057	0.217	0.057

* $p < 0.05$.

Note.

† = survived corrections for multiple comparisons (FDR limit set at $q \leq 0.05$)

Table 4.

Normalized frequencies of phonologic error types across sensitive tasks and all tasks

Error type across tasks	*Normalized frequency of errors/Mean* (SD) (percent)	Range of normalized frequencies (percent)
Sensitive tasks		
Substitution errors	21.1 (16.5)	2.7 to 58.3
Omission errors	14.8 (12.2)	0.0 to 39.6
Addition errors	10.0 (9.4)	0.0 to 33.3
Transposition errors	1.2 (1.4)	0.0 to 4.8
All tasks		
Substitution errors	7.8 (6.9)	1.1 to 27.8
Omission errors	5.4 (5.4)	0.0 to 18.4
Addition errors	3.4 (3.9)	0.0 to 16.5
Transposition errors	0.4 (0.5)	0.0 to 1.7