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Phonological processing in primary progressive aphasia

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Abstract

Individuals with primary progressive aphasia (PPA) show selective breakdown in regions within the proposed dorsal (articulatory-phonological) and ventral (lexical-semantic) pathways involved in language processing. Phonological short-term memory impairment, which has been attributed to selective damage to dorsal pathway structures, is considered to be a distinctive feature of the logopenic variant of PPA. By contrast, phonological abilities are considered to be relatively spared in the semantic variant and are largely unexplored in the nonfluent/agrammatic variant. Comprehensive assessment of phonological ability in the three variants of PPA has not been undertaken. We investigated phonological processing skills in a group of participants with PPA as well as healthy controls, with the goal of identifying whether patterns of performance support the dorsal versus ventral functional-anatomical framework and to discern whether phonological ability differs amongst PPA subtypes. We also explored the neural bases of phonological performance using voxel-based morphometry (VBM). Phonological performance was impaired in patients with damage to dorsal pathway structures (nonfluent/agrammatic and logopenic variants), with logopenic participants demonstrating particular difficulty on tasks involving nonwords. Binary logistic regression revealed that select phonological tasks predicted diagnostic group membership in the less fluent variants of PPA with a high degree of accuracy, particularly in conjunction with a motor speech measure. Brain-behavior correlations indicated a significant association between the integrity of gray matter in frontal and temporoparietal regions of the left hemisphere and phonological skill. Findings confirm the critical role of dorsal stream structures in phonological processing and demonstrate unique patterns of impaired phonological processing in logopenic and nonfluent/agrammatic variants of PPA.

Introduction

Primary progressive aphasia (PPA) is a debilitating condition wherein speech and language deteriorate as a result of neurodegenerative disease. Epidemiological data for PPA

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specifically are not available. However, incidence and prevalence of frontotemporal dementia (of which nonfluent and semantic variants of PPA are subtypes) are thought to be equal or greater than Alzheimer's disease amongst early onset (less than 60 years of age) dementias (Kirshner, 2014) with language variants accounting for approximately 43% of cases (Johnson et al., 2005). Three variants of PPA are now recognized, each of which shows a unique constellation of speech-language deficits and pattern of underlying atrophy in the brain (Gorno-Tempini et al., 2011). The nonfluent/agrammatic type presents with syntactic and motor speech deficits and fronto-insular atrophy in the left hemisphere (Gorno-Tempini et al., 2004; Grossman et al., 1996). The semantic variant is characterized by degradation of semantic knowledge in the context of anterior and inferior temporal lobe atrophy (typically left hemisphere greater than right) (Gorno-Tempini et al., 2004; Hodges, Patterson, Oxbury, & Funnell, 1992). Finally, the more recently characterized logopenic variant demonstrates impairments in naming and repetition (Gorno-Tempini et al., 2008; Rohrer et al., 2010). This variant, associated with atrophy of temporoparietal regions in the left hemisphere, has also been referred to as the "phonological" variant of PPA due to deficits on tasks that require short-term phonological storage (i.e., the "phonological loop") and to the presence of phonological paraphasias in connected speech (Gorno-Tempini et al., 2008; Henry & Gorno-Tempini, 2010; Leyton, Ballard, Piguet, & Hodges, 2014; Wilson et al., 2010).

Current models of the functional neuroanatomy of language propose two pathways by which speech and language are processed in the brain (Hickok & Poeppel, 2007; Saur et al., 2008; Ueno, Saito, Rogers, & Lambon Ralph, 2011). A dorsal pathway involving left temporoparietal and frontal perisylvian structures is thought to be involved, broadly, in articulatory-phonological processing and a ventral language pathway, in the left middle and inferior temporal lobes, is considered crucial for lexical-semantic processing (Hickok & Poeppel, 2007; Lambon Ralph, Sage, Jones, & Mayberry, 2010).

Within the dorsal network, phonological processes are distributed over anterior and posterior perisylvian regions, which have been implicated in unique but complementary and highly interactive roles. The classic "phonological loop" literature implicates posterior temporoparietal cortex in short-term phonological storage, whereas frontal cortices are thought to support subvocal phonological rehearsal that serves to refresh the store (Baddeley, 2003). A more recent and elaborated model of the dorsal articulatory-phonological pathway, the State Feedback Control (SFC) Model (and its extension, the Hierarchical State Feedback Control Model), proposes the existence of motor-phonological and auditory-phonological representations of speech, supported by left inferior frontal and superior temporal cortices, respectively (Hickok, 2012; Hickok, 2014). Transcoding between these motor and auditory phonological codes occurs in left temporoparietal cortex (in an area referred to as Spt). This model, which focuses on volitional speech production, does not address phonological storage or manipulation, per se; however, functional neuroimaging research supports the idea that the aforementioned left frontal and temporoparietal regions are cooperatively and interactively engaged during tasks that require maintenance and manipulation of phonological information (Buchsbaum & D'Esposito, 2008; Champod & Petrides, 2010; Marvel & Desmond, 2012; Peschke, Ziegler, Eisenberger, & Baumgaertner, 2012). Previous work in individuals with aphasia and phonological impairment caused by stroke has not revealed significant differences in performance in those with anterior versus posterior left

perisylvian lesions on phonological processing tasks (Rapcsak et al., 2009), suggesting that damage anywhere within the dorsal phonological-articulatory stream may produce phonological deficits. Nonetheless, it may be the case that individuals with anterior (frontal) damage within this network versus those with posterior (temporoparietal) damage have difficulty with phonological tasks for different underlying reasons.

In a previous study, we demonstrated that performance in specific language domains correlates with the structural integrity of dorsal (phonological) and ventral (semantic) systems in a mixed group of individuals with PPA (Henry, Beeson, Alexander, & Rapcsak, 2012). We found that gray matter volumes in left frontal and temporoparietal cortices correlated with performance on phonological tasks. Conversely, volumes in left angular and anterior temporal cortices correlated with performance on semantic measures. While confirming the general functional-anatomical separation of the dual processing streams, the study did not allow examination of relative performance across the three diagnostic variants of PPA.

Although semantic processing has been extensively examined in all three PPA variants, little research has explored phonological processing ability by PPA subtype. A phonological-short-term storage deficit has been considered a distinctive feature of logopenic patients, who demonstrate impaired comprehension and repetition of sentences as well as reduced digit, letter, and word span (Rohrer et al., 2010; Gorno-Tempini et al., 2008). Logopenic patients also fail to show the classic “phonological similarity effect,” wherein strings of phonologically dissimilar letters are more accurately repeated than phonologically similar strings, a pattern thought to reflect degradation of the “store” component of the phonological loop (Gorno-Tempini et al., 2008). There has been relatively little investigation of phonological ability in nonfluent/agrammatic patients; however, they have demonstrated abnormal phonological facilitation effects during naming trials (Mack et al., 2013). Mack et al. showed that agrammatic patients exhibited naming facilitation with presentation of phonologically related words at a later time window than logopenic or control participants, suggesting impaired or delayed phonological encoding as an underlying cause for naming difficulty. Finally, individuals with semantic variant PPA have shown relative preservation of phonological processing, at least early in the disease course when damage is largely confined to anterior and inferior temporal regions (Jefferies, Jones, Bateman, & Lambon Ralph, 2005). Whereas this body of work suggests that phonological processing is impaired in logopenic and perhaps nonfluent/agrammatic patients, to our knowledge, no study has directly compared performance across the three variants on tasks designed to assess perception, storage, manipulation, and production of phonological information.

In this study, we investigated phonological processing in a large cohort of individuals with PPA, with the following aims: to further assess the validity of the dorsal-ventral pathway distinction in language processing; to compare phonological processing ability across PPA variants; and to determine the clinical utility of phonological tasks in differential diagnosis by PPA variant. We used a brief battery of tasks involving both spoken and written language. Based on previous work, we selected three subtests from the *Arizona Phonological Battery* that have proven particularly sensitive to phonological impairment in individuals with aphasia caused by stroke, as well as individuals with PPA (Beeson et al., 2010; Henry et al.,

2012; Rapcsak et al., 2009). Written language measures included reading and spelling of nonwords (Rapcsak et al., 2009). Given the well-established loci of anatomical damage in the subtypes of PPA, we hypothesized that patients with damage to the dorsal pathway (nonfluent/agrammatic and logopenic variants) would show greater impairment on phonological processing tasks, whereas patients with damage to the ventral pathway (semantic variant) would show relative preservation of phonological abilities. Further, given that individuals with logopenic PPA have damage to posterior perisylvian structures implicated in primary storage and transcoding of phonological information as well as a pattern of language features consistent with a phonological deficit (e.g., repetition, span, and nonword reading deficits) (Brambati, Ogar, Neuhaus, Miller, & Gorno-Tempini, 2009; Gorno-Tempini et al., 2008), we predicted that this variant would show greatest impairment on phonological measures. Finally, we directly examined cortical regions involved in phonological processing using voxel-based morphometry (VBM). We predicted that these analyses would confirm significant involvement of left perisylvian (frontal and temporoparietal) cortical regions in phonological processing ability.

Methods

Participants

Thirty-six individuals with PPA (12 individuals with semantic, 12 with logopenic, and 12 with nonfluent/agrammatic variant PPA) and 13 healthy controls were included in the study. All participants gave written informed consent and the UCSF Committee on Human Research approved all study procedures. In order to be included in the study, participants with language impairment met current diagnostic criteria for PPA (Gorno-Tempini et al., 2011). A PPA diagnosis required progressive deterioration of speech-language functions, with deficits largely restricted to these domains during early stages of the disease. Patients were diagnosed with non-fluent/agrammatic, semantic or logopenic variant of PPA based on current guidelines (Gorno-Tempini et al., 2011). Diagnosis by variant was reached by consensus, following a multi-disciplinary evaluation comprising language and neuropsychological testing (see Table 1 for assessments) and neurological examination. Structural neuroimaging (MRI) was conducted for all participants, but was not considered for diagnosis. At the time of the study, participants with PPA were required to score 10 or greater on the *Mini Mental State Examination* (*MMSE*). Additionally, they had to demonstrate adequate motor speech ability to perform spoken phonological tasks, including: correct repetition of up to three syllables without error (as measured by the *Western Aphasia Battery* repetition subtest) (Kertesz, 1982) and apraxia of speech and dysarthria ratings of 4 (moderate) or less on the *Motor Speech Evaluation (MSE)* (Wertz, LaPointe, & Rosenbek, 1984). In order to ensure adequate perceptual abilities, potential participants could report no unaided hearing impairment and were required to perform at 85% or better on a test of 20 auditory minimal pair judgments in words and nonwords (adapted from *PALPA* subtests 1 and 2) (Kay, Lesser, & Coltheart, 1992). A total of 66 individuals were evaluated for participation in this study and 17 were excluded. Of those, 12 were individuals with the nonfluent variant of PPA (seven did not meet the motor speech criteria; one individual scored less than 10 on the *MMSE*, and four had unaided hearing loss). Five individuals with

the logopenic variant were excluded (three with a score of less than 10 on the *MMSE* and two with hearing loss).

Healthy controls were screened for history of neurological or psychological illness and scored within normal limits on a neuropsychological screen (> 27 on the *MMSE*). Demographic characteristics for participants and relevant cognitive and speech-language measures are reported in Table 1.

Speech-language measures

In addition to the standard UCSF Memory and Aging Center speech-language assessments detailed elsewhere (Gorno-Tempini et al., 2004), each individual was administered three phonological tasks from the *Arizona Phonological Battery* (Beeson, Rising, Kim, & Rapcsak, 2010; Henry, Beeson, Alexander, & Rapcsak, 2012; Rapcsak et al., 2009). Tasks included phoneme deletion, phoneme blending, and phoneme replacement, in both words and phonologically plausible nonwords (see Table 2 for sample items). A speech-language pathologist (MH or MB) conducted all testing with patients, and research assistants tested healthy controls. Each session was videotaped. Responses were transcribed and scored online and videotapes were reviewed for accuracy of coding. For each of the phonological tasks, three practice items were given prior to administration of experimental items. Scores were calculated for each of the deletion, blending, and replacement tests, as well as a summary score that equaled total percent correct on all three phonological tasks. As in previous studies, motor speech was characterized using the *Motor Speech Evaluation* (*MSE*), designed to detect characteristics of apraxia of speech (AOS) and dysarthria (Wertz, LaPointe, & Rosenbek, 1984) via tasks of increasing difficulty (from simple phonation and production of monosyllables, to repetition of multisyllabic words and sentences).

Written language measures consisted of oral reading and writing to dictation of 80 real words (40 regularly spelled and 40 irregularly spelled) and 20 phonologically-plausible nonwords, whose linguistic characteristics have been described previously (Henry, Beeson, Alexander, & Rapcsak, 2012; Rapcsak et al., 2009). Performance on written language measures was available for a subset of participants (reading = 10 logopenic PPA, 11 nonfluent/agrammatic PPA, 12 semantic PPA, 12 healthy controls; spelling = 9 logopenic PPA, 9 nonfluent/agrammatic PPA, 12 semantic PPA, 12 healthy controls). Nonword reading/spelling was of particular importance, as pronunciations and written renditions must be derived phonologically. For this reason, we were also interested in the relative performance of our participants on nonword stimuli relative to real words across spoken and written tasks. In order to examine the effect of stimulus type on performance, we calculated lexicality effect sizes by subtracting nonword score from real word score. An effect of lexicality, or word versus nonword status, is observed when letter combinations with a lexical representation are read/spelled/repeated correctly, whereas unfamiliar but pronounceable letter combinations are produced less accurately. This derived measure serves as an index of phonological impairment. We compared the size of this effect across groups and tasks (phonological battery and written language). Scores on the phonological tasks and the reading and spelling trials were examined across clinical subgroups using analysis of variance (ANOVA). Sidak's procedure was used to adjust alpha for follow-up contrasts. We

also directly compared real word to nonword performance on tasks within each diagnostic group using *t*-tests.

In order to determine whether any of our spoken or written phonological measures might be a positive predictor of PPA variant diagnosis, *independently of* other speech-language measures, we entered all phonological test scores and reading and spelling of nonwords into a forward, stepwise binary logistic regression. This analysis used the likelihood ratio method and a $p<0.05$ criterion for inclusion of variables in the model. Multicollinearity was assessed using variance inflation factor (<10 considered acceptable) (Field, 2009). Logopenic and nonfluent/agrammatic patients were the focus of this analysis, as these groups may be difficult to distinguish behaviorally (both groups present with speech sound errors and reduced fluency of language output). Group membership (logopenic versus nonfluent/agrammatic) served as dependent variable for this analysis. We followed this with an analysis in which other standard speech-language measures were added to the previous model (in addition to the phonological tasks) in a stepwise fashion (scores reported in Table 1; including *Boston Naming Test*, *WAB* fluency rating, *WAB* repetition, *WAB* sequential commands, and AOS/dysarthria rating from the *Motor Speech Evaluation*). This analysis was intended to determine how phonological measures might contribute to differential diagnosis *in conjunction with* standard speech-language measures. Significance of changes in the model's predictive accuracy were assessed by comparing the log-likelihood of each new model with that of the previous model (this statistic has a chi-square distribution).

Neuroimaging and brain-behavior correlations

Patients underwent high resolution structural MRI scanning on a Siemens 3 Tesla (3T) Trio scanner using a T1-weighted 3D magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence with the following parameters: slice thickness = 1 mm; FOV = 256 × 256 mm; matrix = 256 × 256; TR = 2300 ms; TE = 2.98 ms; flip angle = 9°. All image processing and analysis were performed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8) and Matlab version 7.10 (The MathWorks, Inc.). All T1 structural images were segmented and bias-corrected, then registered to Montreal Neurological Institute (MNI) space through an affine and a non-linear deformation. The non-linear deformation parameters were calculated with the high dimensional diffeomorphic anatomical registration through exponentiated lie (DARTEL) algorithm and the predefined templates within the SPM DARTEL toolbox (Ashburner, 2007). The voxel-based morphometry (VBM) analysis was conducted using modulated grey matter images, with voxel values multiplied by Jacobian determinants derived from the spatial normalization in order to preserve the total amount of grey matter from the original images. Modulated images were smoothed with a Gaussian kernel (10 mm FWHM).

We examined the relation between regional gray matter volumes and phonological summary score, as well as reading and spelling of nonwords, with age, sex, and total intracranial volume included in the model as covariates. Motor speech rating from the MSE (AOS rating plus dysarthria rating) was included as an additional covariate in the phonological summary score analysis. Threshold for significance was set at $p<0.001$ and correction for multiple comparisons was achieved by permutation analysis, as described previously (Wilson et al.,

2010). Subsequently, we examined the unique requirements of specific phonological subtests (deletion, blending and replacement tasks) within the broader phonological network by examining the independent contribution of frontal and temporoparietal regions of interest (ROIs) to phonological subtest performance. A frontal ROI was defined as regions where $t > 4$ in the phonology map in the inferior frontal gyrus, middle frontal gyrus, or precentral gyrus. A temporoparietal ROI was defined as regions where $t > 4$ in the phonology map in the superior temporal gyrus, supramarginal gyrus or inferior parietal lobule. Anatomical labels were from Tzourio-Mazoyer et al. (2002). We carried out three ANOVAs: one with each phonology measure as the dependent variable. In each ANOVA, the independent variables were mean grey matter volume in each of these two ROIs, along with covariates of age, sex, and total intracranial volume.

Results

Participant groups did not differ with regard to age or education (Table 1). Consistent with current criteria for PPA subtyping, individuals in the semantic group were impaired on confrontation naming on the *Boston Naming Test* (Kaplan, Goodglass, & Weintraub, 2001) and showed impaired single word comprehension on a shortened (16 item) version of the *Peabody Picture Vocabulary Test-Revised* (Dunn & Dunn, 1981; Kramer et al., 2003) relative to other participants. Individuals in the nonfluent/agrammatic group had significantly more severe ratings for apraxia of speech and dysarthria, and individuals with logopenic variant were impaired relative to the other groups on the *Western Aphasia Battery* (Kertesz, 1982) repetition subtest.

Phonological Performance

Phonological task performance in participants with PPA and healthy controls is presented in Figure 1 and Table 3. We conducted separate ANOVAs examining phonological test scores across the diagnostic groups, with follow-up contrasts conducted if the omnibus test was significant. The Sidak procedure was used to correct for multiple comparisons (adjusted alpha = $p < 0.009$). The ANOVA comparing overall phonological score was significant ($F(3,45) = 13.99$, $p < 0.001$) and follow-up contrasts revealed significantly worse performance in logopenic patients relative to controls and semantic patients as well as worse performance in nonfluent/agrammatic patients relative to controls and semantic patients. Nonfluent/agrammatic and logopenic patients were not significantly different.

An effect of diagnostic group was revealed by the ANOVAs examining phoneme deletion in nonwords ($F(3,45) = 8.21$, $p < 0.001$) and words ($F(3,45) = 7.27$, $p < 0.001$) and follow-up contrasts identified worse performance in logopenic participants relative to all other groups on these tasks. Group differences were also observed on the phoneme blending in nonword ($F(3,45) = 9.48$, $p < 0.001$) and word ($F(3,45) = 9.22$, $p < 0.001$) tests and phoneme replacement in nonword ($F(3,45) = 16.75$, $p < 0.001$) and word ($F(3,45) = 9.07$, $p < 0.001$) tests. Follow-up contrasts revealed that logopenic and nonfluent participants performed worse than semantic patients and controls, but did not differ significantly.

Written Language Battery Performance

Reading and spelling scores by word type are presented in Figure 2 and Table 3. Nonword performance was of particular importance due to high phonological processing demands. ANOVAs revealed a significant group effect for nonword spelling but not reading ($F(3,39) = 16.08$, $p < 0.001$) and follow-up contrasts revealed that logopenic patients were significantly impaired relative to nonfluent/agrammatic, semantic, and control groups on this measure.

Word versus nonword performance across tasks

Lexicality effect sizes (word score minus nonword score) were calculated for reading/spelling (averaged) and phonological tasks (Figure 3). Semantic variant participants showed a reverse lexicality effect, with nonword spelling performance superior to real word performance (due to impaired irregular word reading/spelling, or surface dyslexia/dysgraphia). As such, this group was excluded from the analysis in order to avoid biasing the results. The reading/spelling lexicality effect size analysis did not reveal a significant effect of group ($F(2,25)=3.05$, $p = 0.065$). By contrast, the ANOVA for the lexicality effect from the spoken phonological tasks revealed a significant effect of group ($F(3,45) = 4.74$, $p = 0.006$), with follow-up contrasts (adjusted alpha: $p < 0.009$) showing a significantly larger effect in logopenic participants relative to the semantic variant group ($p = 0.006$) and healthy controls ($p = 0.004$). Direct comparisons of real word versus nonword performance were conducted for each task using paired *t*-tests, revealing a significant decrement in nonword compared to real word performance on the following tasks in the logopenic group: spelling ($t(8) = 2.38$, $p = 0.045$), phoneme deletion ($t(11) = 2.55$, $p = 0.027$) and phoneme replacement ($t(11) = 3.19$, $p = 0.009$). Significantly worse performance on nonwords relative to real words was not observed on any tasks in any of the other groups.

Phonology measures as predictors of clinical subtype: Nonfluent/agrammatic and logopenic patients

Because nonfluent/agrammatic and logopenic patients can be difficult to discriminate behaviorally due to overlapping clinical features, we sought to determine whether any of our phonological tasks might hold utility for predicting to which diagnostic group an individual belongs. As such, we conducted stepwise, forward, binary logistic regression with all phonological task scores and reading and spelling of nonwords as predictor variables. The overall fit of the final model was significant ($\chi^2(2) = 13.02$, $p = 0.001$) and two variables were kept in the model as significant predictors (at criterion of $p < 0.05$): nonword spelling and sound blending in nonwords, which together predicted group membership with 83.3% accuracy (Table 4). However, multicollinearity diagnostics indicated a variance inflation factor value of 11.15, which is considered to be outside of acceptable bounds for multicollinearity (Field, 2009). As such, we conducted the analysis again with only scores from the nonword versions of each task, as these were the more sensitive tasks across patient groups. This eliminated the problem of multicollinearity. The resulting model was virtually unchanged ($\chi^2(2) = 13.02$, $p = 0.001$; nonword spelling and sound blending in nonwords were kept in the model as significant predictors; the model showed 83.3% correct group assignment). In a separate logistic regression analysis, standard speech and language measures were added to this model in a stepwise manner, in order to determine the

predictive power of phonological scores in conjunction with widely used clinical measures. The addition of motor speech evaluation (AOS plus dysarthria) rating to the model resulted in a significant improvement in the model's predictive power ($\chi^2(1) = 11.94$, $p = 0.001$), with the resulting model ($\chi^2(3) = 24.95$, $p < 0.001$) showing improved prediction at 100% accuracy. Other speech-language measures (Repetition, Fluency, and Sequential Commands subtests from the *WAB* as well as *BNT* score) did not significantly improve the model's predictive accuracy based on the model chi-square statistic.

Neuroimaging and brain-behavior correlations

Imaging analysis using voxel-based morphometry (VBM) revealed a significant relationship between gray matter volumes and total phonology score in left frontal and temporoparietal regions (Figure 4; Table 5). Specifically, phonological score was associated with gray matter volumes in a large left hemisphere cluster including anterior regions (superior, middle, and inferior frontal gyri, insula, supplementary motor area, and precentral gyrus); posterior regions (postcentral gyrus, superior and inferior parietal lobe, temporoparietal junction, and superior temporal gyrus); as well as the occipital lobe and cingulate gyrus. Additional, smaller clusters were observed in the right superior and middle temporal gyri, the right inferior parietal lobe, and the thalamus.

VBM analyses for each of the three individual phonological tasks (not shown) revealed patterns highly similar to the overall phonological score, with involvement of left frontal as well as temporoparietal regions for each measure. To further investigate differential reliance of the three phonological measures on frontal and temporoparietal regions, we carried out a follow-up ROI analysis. Deletion scores were predicted by atrophy in the frontal ROI ($F(1, 43) = 7.57$, $p = 0.009$) and the parietal ROI made only a marginal independent contribution ($F(1, 43) = 2.93$, $p = 0.094$). Similarly, replacement scores were predicted by atrophy in the frontal ROI ($F(1, 43) = 16.37$, $p < 0.001$), but not independently by the temporoparietal ROI ($F(1, 43) < 1$). In contrast, blending scores were predicted independently by atrophy in the frontal ROI ($F(1, 43) = 8.92$, $p = 0.005$) as well as the temporoparietal ROI ($F(1, 43) = 5.98$, $p = 0.019$).

VBM analyses for reading and spelling of nonwords are presented in Figure 5 and Table 5. The nonword reading score was associated with gray matter volumes in the left superior and inferior parietal lobe, postcentral gyrus, middle temporal gyrus and occipital lobe. A smaller cluster was observed in the right parietal lobe and occipital lobe. The score for spelling nonwords was associated with volumes in left superior and inferior parietal lobe as well as precentral and postcentral gyri.

Discussion

Imaging studies in PPA have revealed that the three variants show selective degeneration of regions within the proposed dorsal (nonfluent and logopenic variants) and ventral (semantic variant) pathways involved in processing spoken language. Findings from our phonological tasks as well as from written language tasks confirm the dorsal (articulatory-phonological) versus ventral (lexical-semantic) stream distinction in a relatively large cohort of individuals with PPA. As predicted, patients with damage to the dorsal pathway showed impaired

performance on phonologically mediated tasks relative to both controls and patients with ventral pathway damage. Findings are in accordance with an increased prevalence of phonological paraphasias in the connected speech of individuals with nonfluent/agrammatic and logopenic variants of PPA (Wilson et al., 2010) and with previous work indicating abnormal phonological processing in these patient groups (Gorno-Tempini et al., 2008; Mack et al., 2013).

Logopenic patients demonstrate a characteristic pattern of atrophy affecting posterior perisylvian regions implicated in storage and transcoding of phonological codes, as well as a well-established speech-language profile characterized by difficulty with phonological processing (repetition, span, and nonword tasks) (Gorno-Tempini et al., 2008; Rohrer et al., 2010). As such, we predicted that the logopenic group would show poorer performance across spoken and written phonological measures relative to the other variants, including the nonfluent/agrammatic group. Counter to our prediction, the phonological summary score was not significantly different in logopenic versus nonfluent/agrammatic groups, indicating that damage to anterior or posterior perisylvian regions may cause significant impairment of spoken phonological task performance. The logopenic subgroup did demonstrate lower scores on the phoneme deletion tasks relative to nonfluent/agrammatic patients (and other participants). Further, nonword spelling was significantly worse in these patients relative to all other participants and, unlike other groups, they showed a significant decrement in nonword relative to real word performance for two of three spoken language measures as well as spelling.

The two less fluent variants of PPA (logopenic and nonfluent/agrammatic), both of which present with segmental speech sound errors and reductions in speech fluency, can be difficult to dissociate behaviorally, particularly in mild, early stages. Acoustic measures of speech production and speech sound error typing have proven useful in differentiating between these clinical subtypes (Ballard et al., 2014; Croot, Ballard, Leyton, & Hodges, 2012; Wilson et al., 2010). We were interested to discern whether any of our phonological tasks might be additional useful tools for differential diagnosis in PPA. We found that the two most discriminating tasks in our battery (nonword spelling and sound blending in nonwords), which together take less than 10 minutes to administer, distinguished between logopenic and nonfluent/agrammatic patients with 83% accuracy. This was striking, given that neither of these measures is currently used in diagnosis of PPA by variant. In conjunction with a rating for motor speech impairment (a more established measure for differentiating between PPA types), we were able to predict group membership without error. Thus, phonological processing tasks may play a role in helping to assign individuals with PPA to appropriate diagnostic sub-types, particularly in mild-to moderate stages of severity. Diagnosis by variant is particularly relevant given that PPA variant status is predictive of underlying pathology (Gorno-Tempini et al., 2011) and thus, important for determining candidacy for pharmacological and other treatments that may be forthcoming. Future studies with larger cohorts need to be conducted in order to confirm the adequacy of these and other measures for discriminating between variants and to determine relevant cutoff scores for aiding in individual diagnosis.

Brain-behavior correlations conducted via VBM confirmed the involvement of a primarily left hemisphere fronto-temporoparietal network in phonological processing for spoken phonology tasks. Overall, these findings are consistent with current models of the functional neuroanatomy of language (Hickok & Poeppel, 2004; Saur et al., 2008; Ueno, Saito, Rogers, & Lambon Ralph, 2011), previous functional imaging research (Price et al., 2012), prior work in PPA (Henry, Beeson, Alexander, & Rapcsak, 2012), and lesion data from individuals with phonological processing difficulties subsequent to stroke (Rapcsak et al., 2009). Lesion studies in patients, however, have not identified specific perisylvian sub-regions that are critical for different aspects of phonological processing. The phonological tasks employed in this study engage a number of procedures that may be collectively referred to as "phonological;" however, more specifically, they require processing of auditory input, assembly of phonological codes from sublexical information, short-term storage of phonological codes, manipulation of stored phonological representations, subvocal rehearsal, and ultimately, motor output. This study was not designed to explore these sub-processes or their neural bases via specific tasks. Nonetheless, the various tasks employed may place different demands on particular components within the phonological network. Consistent with this possibility were the unique patterns of impairment on individual tasks across PPA variants and partially distinct patterns of regional recruitment (revealed by VBM) within the phonological network for each task.

The temporo-parietal junction/ventral inferior parietal lobe was implicated in all of our measures using whole-brain VBM, confirming the area's critical role in execution of spoken and written phonological tasks. This region, which is consistently damaged in logopenic PPA, is thought to support transcoding of auditory into articulatory-verbal information (Hickok & Poeppel, 2007) and storage/maintenance of phonological information (Buchsbaum & D'Esposito, 2008; Jacquemot & Scott, 2006; Paulesu, Frith, & Frackowiak, 1993), processes that are common to all of our phonological measures. Accordingly, only logopenic patients were impaired across spoken and written phonological tasks. Dorsal inferior parietal lobe/intraparietal sulcus, also damaged in logopenic PPA, is thought to play a role in analysis and construction of syllable order (Moser, Baker, Sanchez, Rorden, & Fridriksson, 2009), attention to temporal order during verbal working memory tasks (Owen, McMillan, Laird, & Bullmore, 2005) and serial sublexical (sound-letter conversion) processes invoked during written language processing (Wilson et al., 2009). Consistent with this role were the results of VBM analyses for reading and spelling of nonwords, which revealed correlations between the dorsal inferior parietal lobe/intraparietal sulcus and sublexical written language skills. In addition, ROI analyses revealed a significant independent contribution of temporoparietal cortex to phoneme blending performance, a task which requires not only maintenance of phonological information, but attention to serial ordering of phonemes prior to transcoding into articulatory gestures associated with whole words/pseudowords. The finding that spelling of nonwords and sound blending in nonwords were the most discriminating clinical measures for differentiation of logopenic relative to nonfluent/agrammatic patients also supports a critical contribution of temporoparietal cortex to these tasks.

Left frontal cortex was also implicated in all spoken phonological subtests on whole brain VBM. Left middle and inferior frontal and premotor regions are thought to support overt and

covert articulatory processes as well as monitoring and manipulation of phonological material (Champod & Petrides, 2010; Marvel & Desmond, 2012; Peschke, Ziegler, Eisenberger, & Baumgaertner, 2012; Price, 2012). In order to rule out the possibility that impaired performance on spoken phonological tasks was related solely to motor output difficulty, we screened participants to confirm adequate speech production ability for repetition of up to three syllables without error. This rather conservative criterion served to ensure that all individuals were more than capable of providing the monosyllabic responses required for completion of spoken phonological tasks.

Importantly, however, impaired subvocal rehearsal and inner speech generation have been documented in stroke patients with apraxia of speech caused by stroke (Waters, Rochon, & Caplan, 1992) and anarthria (Cubelli & Nichelli, 1992) indicating that frontal cortices traditionally viewed as “motoric” likely play a role in both overt speech production as well as subvocal speech required for pre-articulatory maintenance and assembly of phonological codes. This can account for the significant correlations between phonological scores and frontal volumes even after controlling for motor speech scores (Figure 4) and for the results of ROI analyses indicating frontal involvement in all phonological subtests. In addition to subvocal rehearsal, each of our spoken phonological tasks requires fundamental alterations in phonological representations, involving both monitoring and manipulation of phonological strings, also considered to be frontally mediated processes (in conjunction with posterior perisylvian regions). In contrast to previous findings (Henry, Beeson, Alexander, & Rapcsak, 2012), we did not observe a significant frontal contribution to reading and spelling of nonwords, although nonword scores did correlate with frontal volumes at an uncorrected threshold ($p < 0.005$). It may be the case that left frontal cortex provides a greater contribution to spoken relative to written phonological tasks due to modality of output or to a greater reliance on frontally-mediated functions such as subvocal rehearsal during execution of these tasks.

In conclusion, our results confirm the selective impairment of dorsal articulatory-phonological processes in individuals with nonfluent/agrammatic and logopenic PPA and the sparing of this network in semantic variant PPA. We observed a striking impairment of phonological abilities across spoken and written tasks in individuals with the logopenic variant, supporting the assertion that language deficits in this patient group are phonological in nature. The contrast between the central phonological deficit in logopenic PPA and the sparing of phonological processing in semantic variant patients has implications for language treatment in these groups. Whereas both groups exhibit anomia as a primary characteristic, the underlying basis (semantic versus phonological) differs in each. As such, naming treatments may be designed to capitalize on the relative sparing of these core linguistic processes in each patient group (Henry et al., 2013). Our findings also document impaired phonological task performance in individuals with nonfluent/agrammatic variant, and suggest that phonological tasks engage frontal regions independently of their role in overt speech production. Specifically, they likely support subvocal rehearsal as well as manipulation and monitoring of phonological information. Finally, we have shown that phonological tasks (particularly those involving nonwords) have the potential to contribute to differential diagnosis in PPA and, as such, should be considered for inclusion in clinical assessment protocols.

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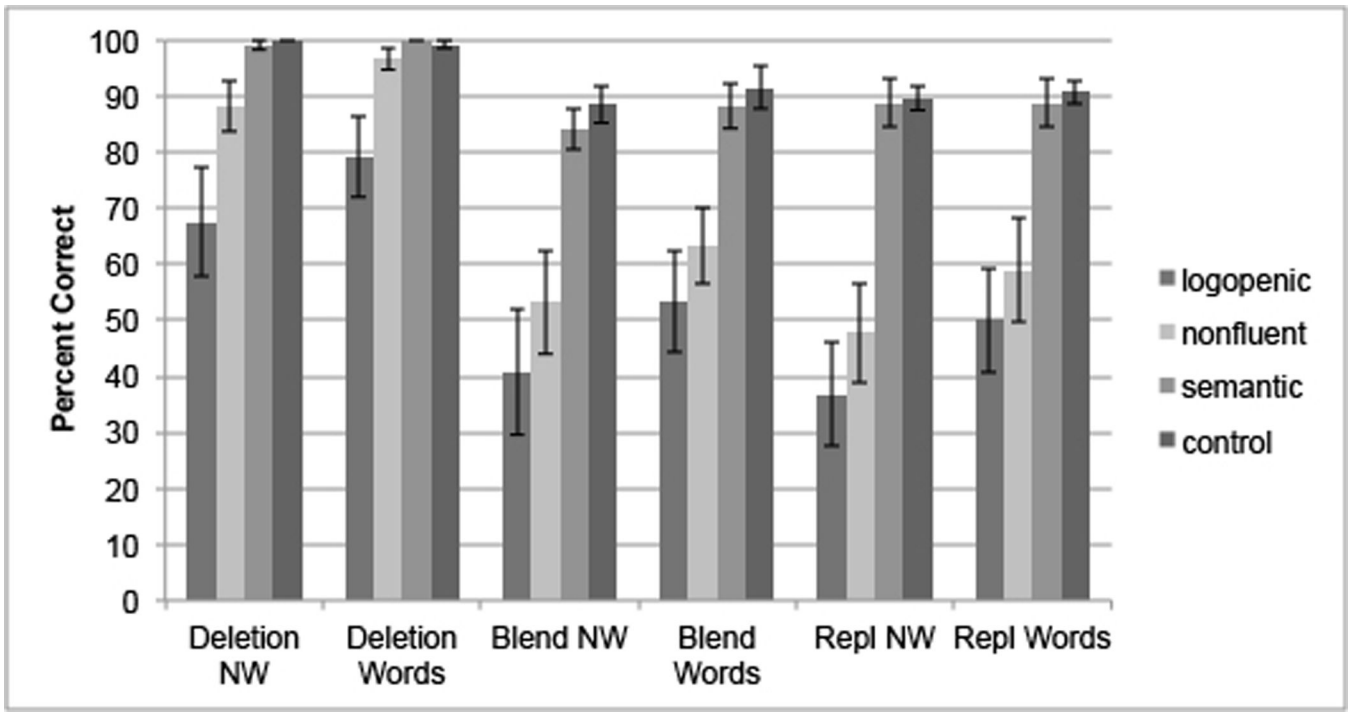

Figure 1.

Phonology scores in each PPA variant on tasks using nonword (NW) and word stimuli. Error bars represent standard errors. (Blend = Blending; Repl = Replacement)

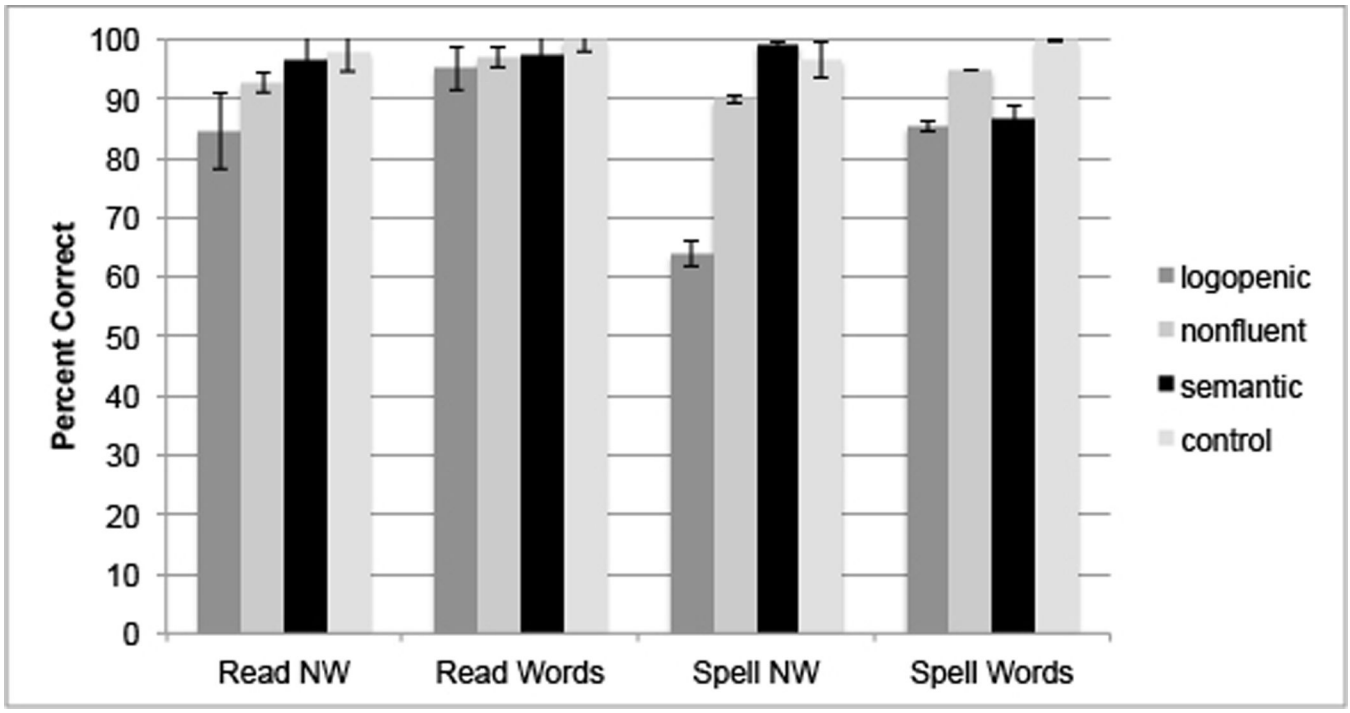

Figure 2.

Reading and spelling performance in PPA patients and healthy controls on word and nonword (NW) stimuli. Error bars represent standard errors

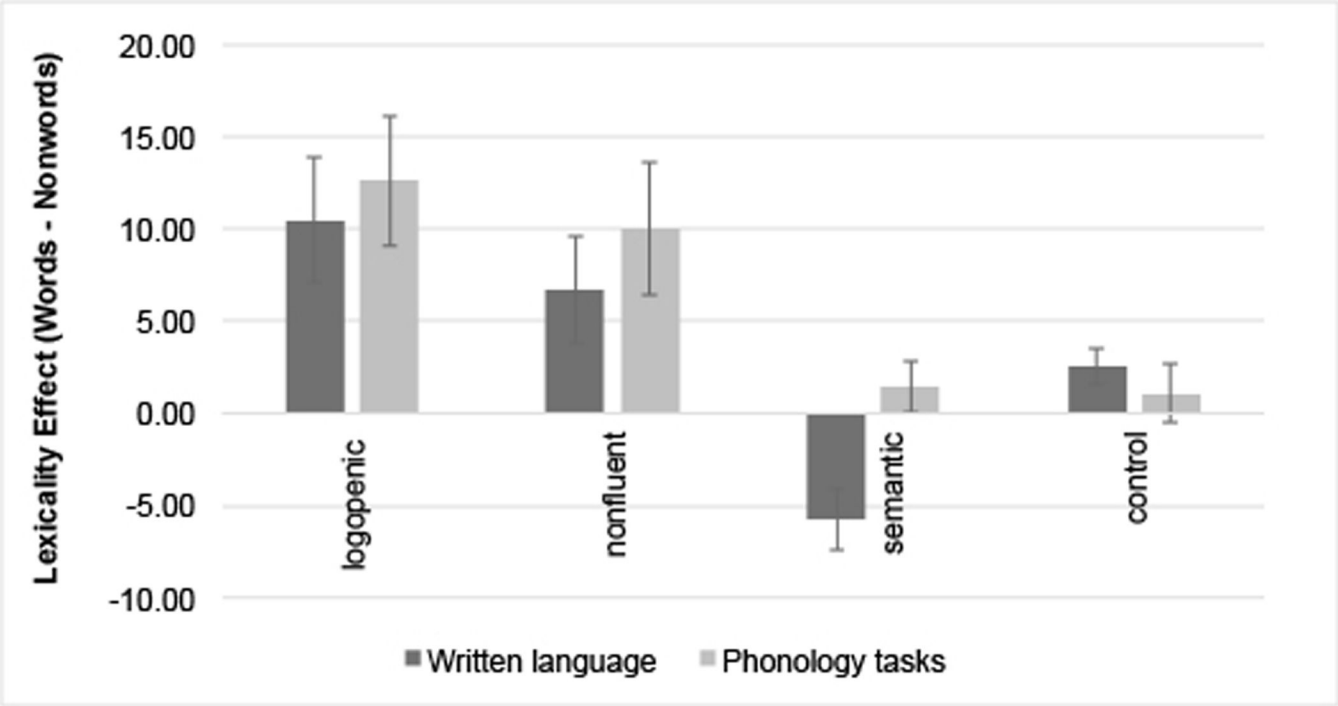

Figure 3.
Lexicality effect sizes for written language and phonology tasks. Error bars represent standard errors.

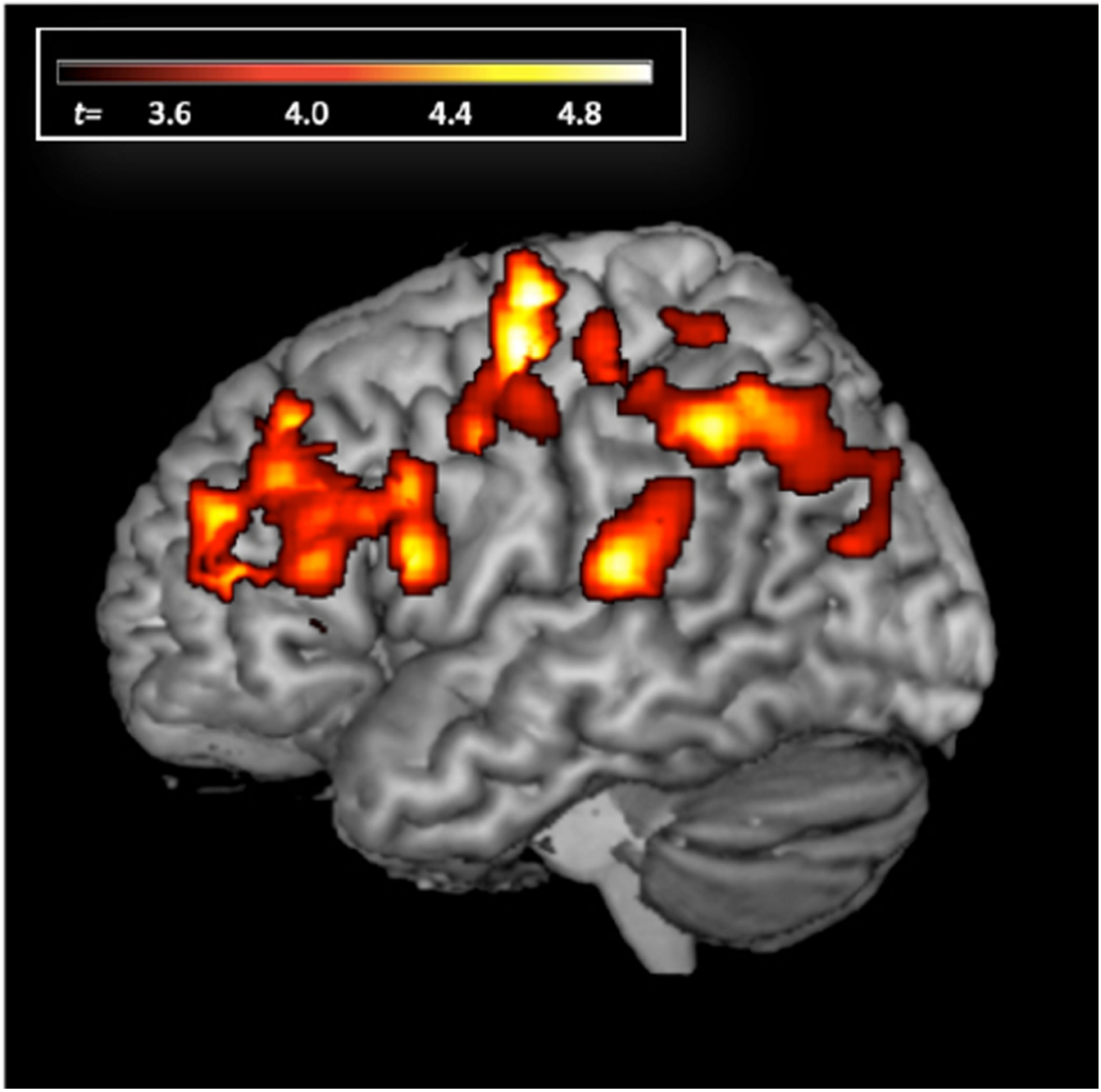

Figure 4.

Results of voxel-based morphometry (VBM; N=12 semantic variant; 12 logopenic variant; 12 nonfluent/agrammatic variant; 13 healthy controls) analysis examining relation between phonology score and gray matter volumes ($p<0.001$corrected for multiple comparisons based on cluster size; age, sex, total intracranial volume, motor speech score included as covariates)

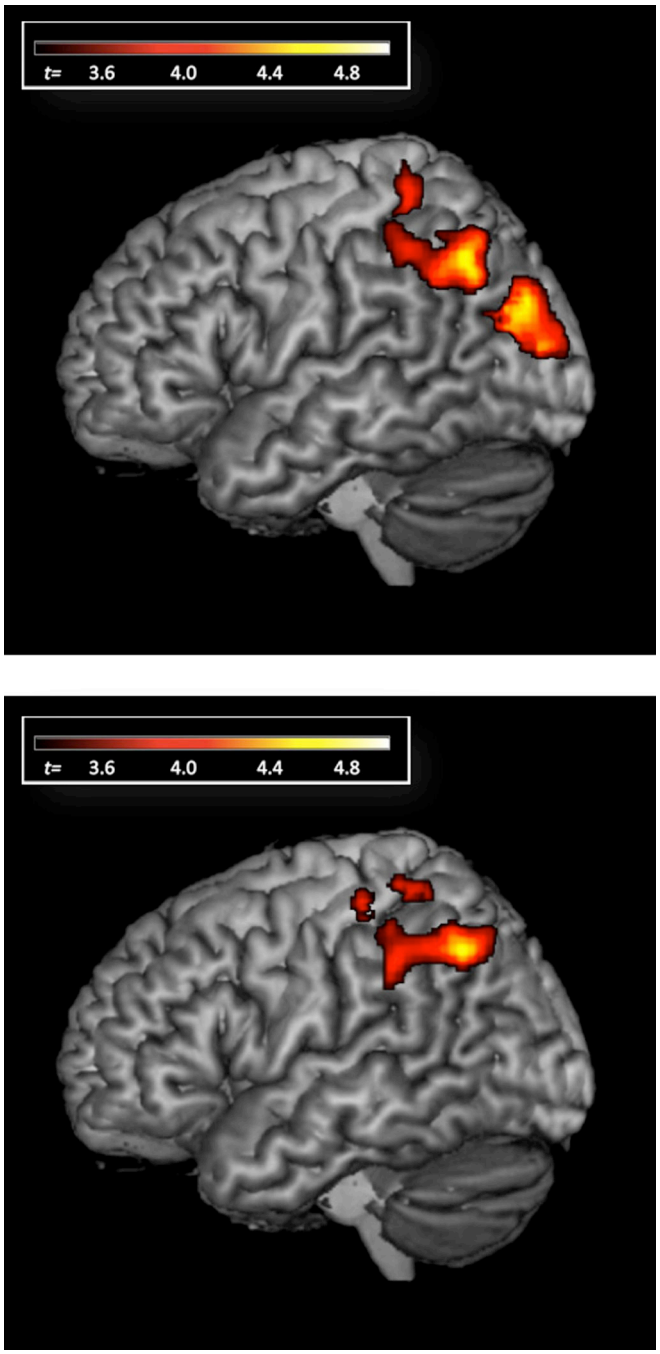

Figure 5.

Results of voxel-based morphometry (VBM) analysis examining relation between a) Reading nonword score and b) Spelling nonword score and gray matter volumes ($p<0.001$ corrected for multiple comparisons based on cluster size; age, sex, total intracranial volume included as covariates)

Table 1

Demographic information and cognitive scores (with standard deviation) for PPA groups and healthy controls

	LV (N=12)	NFV (N=12)	SV (N=12)	Control (N=13)
Demographic	62.75 (8.9)	70.08 (7.4)	63.00 (6.4)	66.46 (3.9)
Age				
Gender	2M: 10F	5M:7F	6M:6F	4M:9F
Education (yrs)	17.8 (1.1)	18.5 (1.8)	16.50 (2.7)	18.0 (3.8)
Handedness	9R;2L;1Amb	11R;1L	11R;1L	9R;4L
Mini Mental State Examination (30)	24.1 (5.5)[d]	27.4 (1.90)	27.4 (2.8)	29.6 (0.7)
Language and Speech				
Boston Naming Test (15)	9.8 (3.7)[b]	13.5 (1.6)	5.9 (3.0)[a,b]	
Fluency rating (WAB; 10)	8.8 (.9)	7.6 (1.8)[c]	9.0 (0.4)	
Repetition (WAB; 100)	78.6 (12.9)[b,c]	91.9 (5.8)	95.7 (4.6)	
Sequential Commands (WAB; 80)	72.6 (8.6)[c]	73.5 (8.3)	80.0 (0.0)	
Apraxia of speech rating (0–7)	0.3 (1.2)	1.9 (1.3)[a,c]	0.0	
Dysarthria rating (0–7)	0.0	2.1 (1.9)[a,c]	0.0	
PPVT-short (16)[e]	14.0 (2.1)	15.6 (.5)	10.5 (3.8)[a,b,d]	15.5 (0.7)
Working memory				
Digit span forward	4.3 (1.4)[c,d]	4.6 (1.0)[c,d]	7.1 (1.3)	7.5 (1.5)
Visuospatial function				
Benson figure copy (17)[e]	14.7 (2.6)	15.2 (1.2)	15.8 (.8)	15.4 (.5)
Visual memory				
Benson figure recall (17)[e]	6.0 (3.4)[b,d]	11.3 (2.5)	7.7 (4.8)	12.1 (2.9)
Verbal memory				
CVLT-SF Trials 1–4 (40)[e]	17.6 (8.5)	24.6 (5.8)	18.8 (5.9)	
CVLT-SF 30 sec free recall (10)[e]	4.9 (2.9)	6.3 (1.8)	3.8 (2.4)	
CVLT-SF 10 min free recall (10)[e]	3.5 (3.6)	5.8 (2.0)	2.4 (1.9)[b]	
Executive functions				
Digit span backward	2.9 (.9)[c,d]	3.9 (1.0)[c,d]	6.2 (1.8)	5.9 (1.5)
Modified Trails (lines per minute)[e]	15.8 (11.9)[d]	12.7 (8.8)[d]	25.3 (10.1)[d]	44.6 (16.0)

Group differences: significantly impaired relative to [a]logopenic, [b]nonfluent/agrammatic, [c]semantic and [d]control groups ($p < .05$ with Sidak correction)

[e]From Kramer, et al. (2003)

Amb =ambidextrous; F = female; M = male, LV = logopenic variant, NFV = nonfluent/agrammatic variant, SV = semantic variant; WAB = Western Aphasia Battery; PPVT = Peabody Picture Vocabulary Test; CVLT-SF = California Verbal Learning Test- UCSF version

Table 2

Sample tasks from the Arizona Phonological Battery (Beeson et al., 2010)

Task	Example
Phoneme deletion (n=10 words, 10 pseudowords)	Say “fat”…now take away “f” → “at” Say “zane”…now take away “z” → “ane”
Phoneme blending (n=10 words, 10 pseudowords)	Blend these sounds together /b/ /oi/ /l/ → “boil” /z/ /aI/ /p/ → “zipe”
Phoneme replacement (n=15 words, 15 pseudowords)	Say “mouth”…now change /th/ to /s/ → “mouse” Say “bazz”…now change /b/ to /d/ → “dazz”

Table 3

Mean scores (and standard deviations) for individual phonological subtests and written language tasks

	LV	NFV	SV	Control
Deletion NW	67.50 (33.61) *b,***c,d	88.33 (15.86)	99.17 (2.87)	100.00 (0.00)
Deletion Words	79.17 (24.66) **b,***c,d	96.67 (6.51)	100.00 (0.00)	99.23 (2.77)
Blend NW	40.83 (38.95) ***c,d	53.33 (31.14) *c,**d	84.17 (13.11)	88.46 (11.44)
Blend Words	53.33 (32.29) ***c,d	63.33 (23.48) *c,**d	88.33 (15.86)	91.54 (13.45)
Repl NW	36.67 (32.10) ***c,d	47.78 (30.86) ***c,d	88.89 (14.86)	89.74 (7.99)
Repl Words	50.01 (32.10) ***c,d	59.03 (32.38) **c,d	88.89 (15.13)	90.77 (7.95)
Total Phonology Score	52.98 (28.20) ***c,d	66.24 (21.56) **c,d	91.19 (9.11)	92.86 (4.16)
Read NW	84.5 (19.92)	92.73 (12.12)	96.67 (7.18)	97.92 (3.34)
Read Words	95.13 (5.25)	97.05 (5.76)	97.60 (2.53)	99.90 (0.36)
Spell NW	63.89 (26.07) ***b,c,d	90.00 (10.35)	99.17 (1.95)	96.67 (6.85)
Spell Words	85.42 (9.88) ***d	94.84 (5.53)	86.67 (10.74) ***d	99.79 (.49)

*p<0.009, **p<0.005, *** p<0.001 significantly impaired relative to [a]logopenic, [b]nonfluent/agrammatic, [c]semantic, [d]control group (Sidak-adjusted alpha = 0.009)

LV = logopenic variant, NFV = nonfluent/agrammatic variant, SV = semantic variant

Table 4

Classification tables showing results of binary logistic regression predicting logopenic versus nonfluent/agrammatic PPA group membership based on a) sound blending in nonwords and nonword spelling and b) sound blending in nonwords, nonword spelling, and motor speech rating (apraxia of speech plus dysarthria ratings from the *Motor Speech Evaluation*)

a.)

	Predicted Diagnostic Group		
	LV	**NFV**	**% correct**
LV	8	1	88.9
NFV	2	7	77.8
TOTAL			*83.3*

b.)

	Predicted Diagnostic Group		
	LV	**NFV**	**% correct**
LV	9	0	100
NFV	0	9	100
TOTAL			*100*

Table 5

Significant clusters and corresponding anatomical regions from phonology and written language VBM analyses

Cluster	Volume (mm^3)	Center of mass			Max *t*	p	Anatomical Regions
		x	y	z			
Phonology Score							
1	172200	−31	−18	37	5.37	0.003	LH: superior/middle/inferior frontal gyri; insula; precentral/postcentral gyri; inferior parietal lobe; superior parietal lobe; superior temporal gyrus; cingulate; supplementary motor area; rolandic operculum; precuneus; occipital lobe
2	29352	58	−18	−4	4.92	0.020	RH: superior/middle temporal gyri
3	27264	1	−18	4	4.89	0.021	thalamus
4	13696	55	−41	39	4.34	0.041	RH: inferior parietal lobe
Read Nonwords							
1	48504	−25	−51	49	5.45	0.012	LH: superior/inferior parietal lobe; precuneus; postcentral gyrus
2	25624	−25	−81	23	4.89	0.028	LH: occipital; cuneus; precuneus; middle temporal gyrus
3	15592	22	−70	27	5.09	0.041	RH: parietal; occipital; cuneus
Spell Nonwords							
1	18544	−44	−53	43	4.64	0.031	LH: superior/inferior parietal lobe
2	11920	−18	−47	59	4.56	0.047	LH: precentral/postcentral gyri; precuneus; superior parietal lobe

LH = left hemisphere; RH = right hemisphere