Published in final edited form as:
J Cogn Neurosci. 2012 February ; 24(2): 261–275. doi:10.1162/jocn_a_00153.

Written language impairments in primary progressive aphasia: A reflection of damage to central semantic and phonological processes

Maya L. Henry[1], **Pélagie M. Beeson**[2,3], **Gene E. Alexander**[4,5], and **Steven Z. Rapcsak**[2,3,6]

[1]Memory and Aging Center, Department of Neurology, University of California, San Francisco

[2]Department of Speech, Language, and Hearing Sciences, University of Arizona, Tucson, AZ

[3]Department of Neurology, University of Arizona, Tucson, AZ

[4]Department of Psychology, University of Arizona, Tucson, AZ

[5]Evelyn F. McKnight Brain Institute, University of Arizona, Tucson, AZ

[6]Neurology Section, Southern Arizona VA Health Care System, Tucson AZ

Abstract

Connectionist theories of language propose that written language deficits arise as a result of damage to semantic and phonological systems that also support spoken language production and comprehension, a view referred to as the "primary systems" hypothesis. The objective of the current study was to evaluate the primary systems account in a mixed group of individuals with primary progressive aphasia (PPA) by investigating the relation between measures of non-orthographic semantic and phonological processing and written language performance, and by examining whether common patterns of cortical atrophy underlie impairments in spoken versus written language domains. Individuals with PPA and healthy controls were administered a language battery including assessments of semantics, phonology, reading, and spelling. Voxel-based morphometry was used to examine the relation between gray matter volumes and language measures within brain regions previously implicated in semantic and phonological processing. In accordance with the primary systems account, our findings indicate that spoken language performance is strongly predictive of reading/spelling profile in individuals with PPA and suggest that common networks of critical left hemisphere regions support central semantic and phonological processes recruited for spoken and written language.

Introduction

Acquired disorders of reading (dyslexia) and spelling (dysgraphia) result from damage to distinct left-hemisphere cortical regions typically caused by stroke or neurodegenerative disease. These deficits are often discussed in the context of spoken language impairment, which is not surprising given that disorders of spoken and written language tend to co-occur in individual patients. However, there is disagreement regarding the interpretation of this association and the extent to which written language is supported by the same cognitive systems and neural networks as spoken language. According to dual-route models of written language processing, dyslexia and dysgraphia syndromes result from damage to procedures specific to reading and spelling, namely the non-lexical and lexical-nonsemantic routes

Address Correspondence to: Maya L. Henry, Ph.D, CCC-SLP, Memory and Aging Center, Department of Neurology, University of California, San Francisco, Ph: (415) 476-2912, mhenry@memory.ucsf.edu.

involved in subword versus whole-word level mappings between orthography and phonology (Coltheart, 2006). Dual-route theory predicts that impaired irregular word reading/spelling, or surface dyslexia/dysgraphia, and impaired nonword reading/spelling, or phonological dyslexia/dysgraphia, may occur independently of generalized semantic and phonological impairment. As such, the co-occurrence of written and spoken language deficits is considered coincidental and assumed to reflect simultaneous damage to anatomically contiguous but functionally distinct cortical regions (Blazely, Coltheart, & Casey, 2005; Coltheart, Tree, & Saunders, 2010). Support for this view comes from reports of isolated surface or phonological dyslexia/dysgraphia in the absence of more widespread semantic or phonological impairment (Blazely et al., 2005; Coltheart, 1996; Coltheart, 2006; Coltheart et al., 2010; Tree & Kay, 2006).

By contrast, the “primary systems” hypothesis, motivated by connectionist models of language processing, posits that the two major subtypes of central dyslexia/dysgraphia arise as a result of damage to central semantic and phonological representations that also support spoken language production and comprehension (Lambon Ralph & Patterson, 2005; Patterson & Lambon Ralph, 1999). Connectionist “triangle” models propose a graded division of labor between semantic and phonological contributions to written language processing, which varies as a function of stimulus type (Plaut, McClelland, Seidenberg, & Patterson, 1996; Woollams, Lambon Ralph, Plaut, & Patterson, 2007). In particular, semantic mediation is considered critical for reading/spelling irregular words, especially when items are low in frequency, whereas the integrity of phonological representations is particularly important for correct reading/spelling of nonwords. Brain damage can alter the balance between semantic and phonological contributions to language and, according to connectionist theory, this should be accompanied by a parallel shift in the efficiency of reading/spelling performance for irregular words versus nonwords. Thus, individuals with disproportionate semantic impairment are not only expected to show better performance on phonological relative to semantic tasks but also a relative advantage in processing nonwords compared to irregular words (i.e., profile of surface dyslexia/dysgraphia).By contrast, patients with primary phonological impairment and relatively preserved semantic ability should demonstrate an advantage on semantic relative to phonological measures, accompanied by a parallel shift toward better processing of irregular words compared to nonwords (i.e., profile of phonological dyslexia/dysgraphia).

The primary systems hypothesis is supported by reports that verbal and nonverbal tasks requiring semantic processing, as observed in individuals with the semantic variant of PPA, are often accompanied by surface dyslexia/dysgraphia (Graham, Patterson, & Hodges, 2000; Jefferies, Lambon Ralph, Jones, Bateman, & Patterson, 2004; Patterson & Hodges, 1992; Patterson et al., 2006; Woollams et al., 2007). In addition, irregular word performance in these patients has been shown to correlate with degree of semantic impairment (Brambati, Ogar, Neuhaus, Miller, & Gorno-Tempini, 2009; Graham et al., 2000; Patterson et al., 2006; Woollams et al., 2007), suggesting that spoken and written language deficits may arise from damage to central semantic representations. These findings are consistent with the view that semantic input is critical for accurate reading/spelling of irregular words, presumably because these items cannot be handled efficiently by the pathway relying on direct transcoding between phonology and orthography (Woollams et al., 2007). Similarly, individuals with phonological dyslexia/dysgraphia show disproportionate impairment in processing nonwords on both written and spoken language tasks (Crisp & Lambon Ralph, 2006; Jefferies, Sage, & Lambon Ralph, 2007; Patterson & Marcel, 1995; Patterson, Suzuki, & Wydell, 1996; Rapcsak et al., 2009). Furthermore, non-orthographic measures of phonological ability requiring the identification, manipulation, and maintenance of sub-lexical phonological information (e.g., phoneme segmentation, deletion, and blending) are predictive of reading/spelling performance, consistent with the notion that damage to a

central phonological system produces both spoken and written language deficits (Crisp & Lambon Ralph, 2006; Rapcsak et al., 2009).

At the neuroanatomical level, the primary systems hypothesis is supported by converging evidence from lesion-deficit correlation studies in neurological patients with surface or phonological dyslexia/dysgraphia and functional neuroimaging studies of semantic and phonological processing in healthy individuals. In particular, surface dyslexia/dysgraphia in patients with the semantic variant of PPA is associated with asymmetrical (left > right) atrophy of the anterior and inferolateral temporal lobes (Graham et al., 2000; Wilson et al., 2009; Woollams et al., 2007) and these same regions are activated in normal subjects during verbal and nonverbal tasks requiring semantic processing (Binder, Desai, Graves, & Conant, 2009; Binney, Embleton, Jefferies, Parker, & Lambon Ralph, 2010; Price, Moore, Humphreys, & Wise, 1997; Price, 1998; Rogers et al., 2006; Vandenberghe, Price, Wise, Josephs, & Frackowiak, 1996; Visser, Embleton, Jefferies, Parker, & Lambon Ralph, 2010; Visser, Jefferies, & Lambon Ralph, 2010; Woollams, Silani, Okada, Patterson, & Price, 2011). Similarly, functional imaging studies have provided evidence for the role of the angular gyrus in semantic processing (e.g., Binder et al., 2009, Vigneau et al., 2006) and damage involving this cortical region has also been associated with the profile of surface dyslexia/dysgraphia (Rapcsak & Beeson, 2002; Vanier & Caplan, 1985). On the other hand, lesions in phonological dyslexia/dysgraphia involve left perisylvian cortical regions, including inferior frontal gyrus, rolandic operculum, precentral gyrus, insula, supramarginal gyrus, and superior temporal gyrus (Brambati et al., 2009; Fiez, Tranel, Seager-Frerichs, & Damasio, 2006; Henry, Beeson, Stark, & Rapcsak, 2007; Rapcsak et al., 2009), that overlap with areas showing functional activation during spoken and written language tasks requiring phonological processing (Beeson & Rapcsak, 2003; Beeson et al., 2003; Binder & Price, 2001; Burton, LoCasto, Krebs-Noble, & Gullapalli, 2005; Heim, Opitz, Müller, & Friederici, 2003; Jobard, Crivello, & Tzourio-Mazoyer, 2003; Katzir, Misra, & Poldrack, 2005; Mechelli, Gorno-Tempini, & Price, 2003; Omura, Tsukamoto, Kotani, Ohgami, & Yoshikawa, 2004; Seki, Okada, Koeda, & Sadato, 2004; Vigneau et al., 2006).

The neuropsychological evidence in favor of the primary systems hypothesis is, however, still limited in several important ways. First, with few exceptions (e.g., (Brambati et al., 2009), the degree of quantitative and qualitative agreement between patterns of impairment across spoken and written language tasks has typically been examined in relatively homogeneous patient groups selected on the basis of clinical diagnosis (e.g., semantic variant PPA (Woollams et al., 2007)), specific reading/spelling profile (e.g., phonological or deep dyslexia (Crisp & Lambon Ralph, 2006; Jefferies et al., 2007)), or lesion location (Rapcsak et al., 2009) raising potential questions about the generalizability of the findings. Use of homogeneous samples could also limit the ability to detect significant effects due to restriction in the range of scores on semantic and phonological measures. In addition, most previous studies have examined only semantic or phonological task performance relative to written language profile (i.e., semantic processing in patients with surface dyslexia/dysgraphia and phonological processing in patients with phonological dyslexia/dysgraphia). There are, to our knowledge, no studies using both phonological and semantic assessments to predict written language abilities in a behaviorally and neuroanatomically diverse group of patients with acquired language impairment. Furthermore, studies to date have not included measures of both reading and spelling, with virtually no studies examining spelling performance in a mixed group of PPA patients relative to measures of semantics and phonological processing. Finally, very few group studies have examined the predictions of the primary systems hypothesis using both behavioral and neuroimaging data.

The goal of the present work was to evaluate the primary systems account in a mixed group of individuals with primary progressive aphasia (PPA) by examining the relation between

measures of non-orthographic semantic and phonological processing and reading/spelling performance. In addition, we performed exploratory analyses comparing patterns of cortical atrophy associated with abnormal performance on spoken versus written language tasks in order to examine whether damage to a common set of cortical regions causes impairments in both modalities. We hypothesized that, in accord with the primary systems account, written language performance would be predicted by non-orthographic measures of semantic and phonological processing. Furthermore, we predicted that non-orthographic measures of semantic processing and accuracy in reading/spelling irregular words would correlate with atrophy involving a common set of left extrasylvian temporo-parietal regions and that phonological processing and nonword reading/spelling performance would correlate with atrophy in overlapping regions within left perisylvian cortex.

Methods

Participants

Fifteen individuals with PPA and fifteen demographically matched normal controls were included in the study (Table 1). A PPA diagnosis was the only requirement for patient inclusion. Diagnosis was made based on neuropsychological testing and patient/caregiver interview. As recommended by current clinical and research criteria, diagnosis involved a two-stage process wherein patients were first determined to meet PPA criteria and subsequently diagnosed by variant. CCriteria for PPA diagnosis (Gorno-Tempini et al.,2011; Mesulam, 2001) indicate that aphasia must be the most prominent clinical feature at onset and throughout the early stages of the disease; that aphasic deficits should be the primary cause of limitations in activities of daily living; and that episodic memory, visual memory, and visuospatial impairments should not be prominent during initial stages of the disorder. Patients were subsequently diagnosed by PPA variant based on the following primary language features as well as secondary features outlined in the current criteria: individuals with agrammatic language and/or effortful, halting speech (apraxia) were classified as nonfluent variant; those with impaired confrontation naming and single-word comprehension were classified as semantic variant; and those with impaired word retrieval and phrase/sentence repetition were classified as logopenic variant.

Demographic characteristics for the PPA group are shown in Table 1. Normal control participants (n = 15; Table 1) did not differ from the patient group with regard to age ($p = 0.13$), education level ($p = 0.22$) or gender. All participants spoke English as their primary language. Control participants were screened for history of neurological or psychological illness, substance abuse, and dementia and were required to score ≥28/30 on the *MMSE*. Patients' mean *MMSE* score differed significantly from the control group ($p<0.001$), but is comparable to that reported in previous groups of PPA patients (e.g., (M. L. Gorno-Tempini et al., 2004; Grossman et al., 2004).

Test Battery

The following measures were used to characterize language performance in each domain (Table 2):

Assessment of Semantics—The picture version of the *Pyramids and Palm Trees Test* (*PPT*) (Howard & Patterson, 1992) was included as a measure of nonverbal semantic processing. Because semantic knowledge is critical for lexical retrieval, the 60-item *Boston Naming Test* (*BNT*) (Kaplan, Goodglass, & Weintraub, 2001) was used to assess spoken picture naming for items of increasing difficulty. Auditory comprehension was examined with the spoken word-picture matching and auditory synonym judgment tasks from the

Psycholinguistic Assessment of Language Processing in Aphasia (*PALPA, subtests 47 and 49 (20 items)*) (Kay, Lesser, & Coltheart, 1992).

Assessment of Phonology—The *Arizona Phonological Battery* (*APB*) (Beeson, Rising, Kim, & Rapcsak, 2010; Rapcsak et al., 2009) comprises non-orthographic tests that examine phonological manipulation (phoneme deletion, substitution, and blending) using both real word and nonword stimuli matched for syllable length and phonological complexity (see Table 3 for example tasks). Minimal pair discrimination was also included as a pure perceptual measure.

Assessment of Reading and Spelling—The *Arizona Battery of Reading and Spelling* (*ABRS*) (Beeson et al., 2010) consists of 40 regular words with predictable sound-to-letter correspondences (e.g., pine) and 40 irregular or exception words (e.g., choir), which cannot be spelled accurately by reliance on phoneme-to-grapheme conversion. Regular and irregular words are subdivided into 20 high and 20 low frequency items. Word length varies from four to seven letters. Nonword spelling and reading were tested using 20 items derived from real words by changing 1–2 letters (while maintaining phonological plausibility). Nonword stimuli were matched in length with real word stimuli. For spelling tasks, stimuli were presented verbally by the examiner and repeated by the participant prior to spelling in order to ensure that the stimulus was perceived correctly.

Calculation of composite scores for language measures

We derived behavioral composite measures representing the status of semantic and phonological processes by combining scores from several tasks in each language domain, as outlined above. For the spoken language measures1, individual tasks were first entered into a principal component analysis (using scores from the patient group only), in order to determine whether each task loaded with other tasks ostensibly measuring the same underlying construct (semantics or phonology). Although there is no such thing as a “pure” language task (e.g., picture naming undoubtedly involves both semantic and phonological processes), we expected that certain tasks would load more strongly with tasks tapping semantics and others with tasks requiring phonological processing. The analysis revealed only two factors with eigenvalues greater than one, presumably representing semantic and phonological components. Individual language tasks loaded in the expected manner relative to semantics versus phonology (Table 4). Subsequently, semantic and phonological composites were calculated by averaging percent correct across subtests for each participant. Because reading and spelling scores were highly correlated ($r = 0.78$, $p<0.0001$), performance was averaged across tasks to create a written language composite measure for each stimulus type (regular words, irregular words, and nonwords).

Calculation of behavioral “bias” measures

As described above, damage to critical left hemisphere cortical regions may result in a shift in the normal balance between semantic and phonological contributions to language processing. We quantified shifts in the balance between semantic and phonological contributions by calculating a spoken language “bias” measure, derived as semantic score *minus* phonology score. Because irregular and nonword performance are thought to reflect the integrity of semantic and phonological representations, respectively, the complementary written language bias measure was calculated as irregular word score *minus* nonword score.

[1]Note that although the majority of the tasks in our semantic battery required spoken language comprehension and/or production, we did include the picture version of the Pyramids and Palm Trees Test as a nonverbal measure of semantic processing. Given that verbal and nonverbal semantic processing are thought to be supported by common, amodal semantic representations, we will refer to this set of tasks as “spoken language measures” for the sake of brevity.

These derived measures have the additional benefit of revealing relative impairments across language tasks, while controlling for overall severity.

Neuroimaging

High-resolution T1-weighted MRI scans were obtained within one month of language testing for 11 of the 15 PPA patients and all normal controls (four PPA participants could not be scanned due to contraindications such as coronary artery stents, pacemakers, and claustrophobia). MRI scanning was conducted on a 3 Tesla (3T) General Electric Excite MRI scanner (Milwaukee, Wisconsin) using a 3D inversion recovery (IR) prepped spoiled-gradient-echo sequence (SPGR) with the following parameters: repetition time, TR = 7.4 ms; echo time, TE = 3.0 ms; inversion time, TI = 500 ms; flip angle = 15; field of view (FOV) = 26×26×19 cm; matrix size = 256×256×124; NEX = 1; acquisition time, TA = approximately 8 minutes. Resulting voxel dimensions were 1×1×1.5 (S/I, A/P, R/L, respectively). One PPA participant could not be scanned at 3 Tesla due to contraindications and was scanned on a GE 1.5T scanner using comparable parameters.

Voxel-based analysis of gray matter atrophy—Voxel-based morphometry (VBM), implemented with SPM5 software (Statistical Parametric Mapping; Wellcome Department of Cognitive Neurology) was used to derive segmented and smoothed gray matter maps for PPA patients and normal controls. Prior to processing, T1 images were evaluated for quality, including motion and other artifacts that could contribute to systematic registration biases. Images were then segmented into gray matter, white matter, and cerebrospinal fluid using the automated segmentation routines in SPM5 (Ashburner & Friston, 2005), augmented by the VBM5 toolbox available at http://dbm.neuro.uni-jena.de/vbm/vbm5-for-spm5/. Sample-specific customized priors were used. Voxel values in the segmented images were multiplied by Jacobians derived during spatial normalization to produce gray matter volume estimates (Good et al., 2001). Spatially normalized, segmented images were then smoothed with a 12 mm full-width-half-maximum (FWHM) Gaussian kernel. An estimate of total intracranial volume (eTIV) was computed by combining the gray matter, white matter, and cerebrospinal fluid segments derived from SPM VBM processing.

Statistical analyses

Repeated-measures ANOVA was used to evaluate between- and within-group differences on the semantic and phonological composite measures and to examine the effects of word type (regular words, irregular words, and nonwords) on written language performance. Multiple regression analyses were performed to investigate the semantic and phonological composites as predictors of written language performance and to examine the contribution of these variables across word types (regular words of high and low frequency, irregular words of high and low frequency, and nonwords) in the PPA group. Finally, the strength of the relationship between bias measures in spoken and written language in the PPA group was examined using simple regression analysis.

Imaging analyses

Gray matter volumes in PPA patients versus normal controls—For the imaging analyses, we tested the overall pattern of atrophy in the patient group (n=11) relative to the control group (n=15) using ANCOVA to compare gray matter volume at each voxel in the whole brain while controlling for age and eTIV. The resulting t-map was corrected for multiple comparisons by thresholding the image to control the False Discovery Rate (FDR) at a 0.01 significance level.

Neural correlates of spoken and written language measures—The relation between gray matter volumes within critical language regions and composite language scores was tested using multiple regression. Spoken language (semantics and phonology) and written language (irregular words and nonwords) composite scores for patients only were entered into four separate multiple regression models, assuming that decreased gray matter would be associated with diminished performance on each composite. Age and eTIV were entered as additional covariates. Regression analyses were limited to left hemisphere regions of interest (ROIs) implicated in semantic versus phonological processing by lesion-deficit studies of neurological patients as well as functional imaging studies of language in healthy individuals. In particular, we were interested in determining whether spoken and written language measures correlated with overlapping patterns of cortical atrophy within these pre-defined ROIs, which were used to define search regions for voxel-based effects. For these analyses we created a perisylvian "phonology ROI," which was used for testing correlations between atrophy and the phonological composite and nonword reading/spelling scores. This ROI included inferior frontal gyrus, rolandic operculum, precentral gyrus, insula, supramarginal gyrus, and superior temporal gyrus. Similarly, an extrasylvian "semantic ROI" was created for testing correlations between atrophy and the semantic composite and irregular word reading/spelling scores. The relevant regions included temporal pole, middle and inferior temporal gyri, fusiform gyrus, and angular gyrus. Masks were created using the aal atlas in PickAtlas software (Maldjian, Laurienti, Kraft, & Burdette, 2003). Due to the small size of the patient group and specific *a priori* hypotheses regarding the cortical regions involved, a threshold of $p<0.05$ (uncorrected) was applied.

Results

Group comparisons of composite language scores

Spoken language composite scores are presented in Table 5. A 2×2 repeated-measures ANOVA comparing performance on the spoken language measures revealed significant effects of group (PPA vs. control) ($F(1,28) = 44.16$, $p<0.001$) and language domain (semantics vs. phonology) ($F(1,28) = 7.04$, $p<0.05$). Post-hoc tests with Tukey's HSD correction for multiple comparisons revealed that patients were significantly impaired relative to controls on both the semantic ($p<0.01$) and phonological ($p<0.001$) composites. Semantic versus phonological composites did not differ significantly within either group ($p = 0.09$ and $p = 0.56$ respectively).

Written language composite scores are presented in Table 6. A 2×3 repeated-measures ANOVA comparing performance on the written language measures revealed significant effects of group ($F(1,28) = 15.93$, $p<0.001$) and word type ($F(2,56) = 11.33$, $p<0.001$), as well as a group-by-word type interaction ($F(2,56) = 6.647$, $p<0.005$). Post-hoc tests (Tukey's HSD-corrected) revealed that patients were significantly impaired relative to controls on irregular words ($p<0.05$). Performance on regular words and nonwords did not differ between patient and control groups ($p = 0.83$ and $p = 0.22$ respectively). Within-group contrasts revealed that, in the patient group, irregular word performance was significantly poorer than regular word performance ($p<0.001$) and nonword performance was also significantly poorer than regular word performance ($p<0.01$). There was no significant difference between irregular and non-word scores ($p = 0.29$). Written language performance of normal controls did not differ across stimulus types.

Spoken language composite measures as predictors of written language performance in PPA patients

Multiple regression analysis revealed that the combination of phonological and semantic scores accounted for a significant proportion of the variance ($R^2 = 0.62$, $p<0.01$) in overall

written language performance (total correct for word plus non-word stimuli, Table 7). The proportion of unique variance explained by semantic versus phonological predictors varied along a continuum relative to stimulus type, as predicted by connectionist models. In particular, reading/spelling accuracy for nonwords was predicted exclusively by the phonological composite, whereas real word reading/spelling was predicted by both semantic and phonological scores. Within the set of real words, phonology score accounted for a numerically greater proportion of variance than semantic score for regular words, and semantic score accounted for a numerically greater proportion of variance than phonology score for irregular word performance, particularly for low-frequency items.

Relation between spoken and written language bias measures in PPA patients

Figure 1 shows a regression graph with the spoken language bias measure (semantic composite *minus* phonological composite) plotted against the written language bias measure (irregular word score *minus* nonword score). Simple regression analysis indicated that the spoken language bias measure accounted for 69% of the variance in written language bias ($F(1,13) = 28.52$, $p < 0.001$).

Imaging analyses

Gray matter volumes in PPA patients versus normal controls—Results of the two-group comparison examining gray matter volume in the patient versus the control group are shown in Figure 2. This analysis revealed the typical pattern of regional cortical atrophy in PPA (M. L. Gorno-Tempini et al., 2004; Rohrer et al., 2010), with damage affecting both peri- and extrasylvian regions within the left-hemisphere language network as well as less extensive right hemisphere atrophy primarily in the frontal and temporal lobes.

Neural correlates of spoken and written language measures—Correlations between gray matter volumes and spoken language composite scores within specific language ROIs for the 11 individuals with PPA are shown in Figure 3. As predicted, the semantic composite correlated with gray matter volumes in the extrasylvian semantic ROI, which included the left temporal lobe and angular gyrus. The peak voxel in a large temporal lobe cluster was located in the temporal pole, with additional involvement of the middle and inferior temporal gyri and fusiform gyrus. A separate cluster was found in the angular gyrus. By contrast, phonological composite scores correlated with volumes throughout the perisylvian phonology ROI, with a peak in the inferior frontal gyrus and additional involvement of the precentral gyrus, rolandic operculum, insula, supramarginal gyrus, and superior temporal gyrus.

As reported above, multiple regression analyses examining spoken language measures as predictors of written language performance revealed both phonological and semantic contributions to irregular word reading and spelling. To test the predictions of the primary systems hypothesis, we were interested in determining whether a common set of cortical regions supported the semantic components of irregular word reading/spelling and performance on non-orthographic semantic tasks. In order to isolate the neural substrates of the semantic contribution to irregular word reading/spelling, we analyzed the relation between irregular word scores and gray matter volumes and included phonological composite score as an additional nuisance covariate. This analysis (Figure 4) revealed significant correlations in a subset of those areas implicated in non-orthographic semantic processing within the extrasylvian semantic ROI, specifically, portions of the temporal lobe including the temporal pole, anterior fusiform gyrus, and middle and inferior temporal gyri, as well as the angular gyrus. By contrast, similar to the phonological composite, nonword scores correlated significantly with gray matter volumes in the perisylvian phonology ROI. The peak voxel was located in the inferior frontal gyrus and additional areas of significant

correlation were found in precentral gyrus, rolandic operculum, insula, supramarginal gyrus, and superior temporal gyrus.

Discussion

The purpose of this study was to evaluate the relation between spoken and written language deficits in individuals with PPA. Specifically, we aimed to determine whether aphasia, dyslexia, and dysgraphia result from damage to common, modality-independent cognitive systems as opposed to separate systems supporting communication in each modality. The key research question was whether shifts in semantic versus phonological processing induced by brain damage would be accompanied by similar shifts in accuracy for reading/spelling irregular words versus nonwords, as predicted by connectionist models.

In our mixed cohort of PPA patients, non-orthographic semantic and phonological composite scores were highly predictive of written language performance. We found that the relative strength of semantic and phonological composites as predictors varied on a continuum with respect to stimulus type, with nonwords exclusively predicted by the phonology score. This confirms that nonword reading/spelling is reliant on sub-lexical phonological processes that are shared with those involved in speech production and perception (Crisp & Lambon Ralph, 2006; Rapcsak et al., 2009). Real word performance was predicted by both semantic and phonological composites, indicating that central semantic and phonological representations involved in spoken language also contribute to oral reading and writing-to-dictation of familiar words. Within the set of real words, the semantic composite accounted for the greatest relative proportion of variance for low-frequency irregular items, suggesting that input from the semantic system is especially critical for processing less familiar words with irregular/atypical phoneme-grapheme correspondences (Woollams et al., 2007; Woollams, Lambon Ralph, Plaut, & Patterson, 2010). By contrast, the phonology composite accounted for a numerically greater proportion of variance for regular words, which likely reflects the fact that words containing predictable phoneme-grapheme mappings can be more reliably processed using direct phonological-to-orthographic transcoding, rendering input from the semantic system less important. Unlike nonwords, however, semantic representations were recruited for regular word reading and spelling, suggesting that conceptual information plays a role in written language processing for all real words, even those with transparent sound-letter correspondences (Woollams et al., 2007).

In addition to the finding that spoken language performance predicts written language profile, we also observed that derived “bias” measures, which represent a shift in the normal balance between semantic and phonological contributions to language, were significantly correlated across spoken and written tasks. We found that relatively poorer performance on non-orthographic semantic measures was consistently associated with poorer performance on irregular word reading and spelling. Conversely, relatively poorer performance on non-orthographic phonological measures was consistently associated with poorer performance on nonword reading and spelling. Thus, our data suggest that changes in the division of labor between semantic and phonological processing produced by brain damage are associated with parallel shifts in the relative efficiency of reading/spelling performance for irregular words versus nonwords.

The results of the exploratory VBM analyses presented in this study suggest largely consistent relationships between atrophy pattern and behavioral profile for spoken and written language tasks within specific language ROIs. Irregular word reading/spelling performance correlated with atrophy in extrasylvian temporo-parietal cortical areas and a similar set of regions was associated with performance on our semantic battery, which did

not involve written language tasks. Significant findings in the temporal lobe are consistent with previous studies indicating temporal lobe involvement in irregular word reading/spelling and semantic task performance, suggesting a possible neuroanatomical substrate for the strong correlation between these behavioral measures in individuals with neurodegenerative disease (Brambati et al., 2009; Graham et al., 2000; Patterson et al., 2006; Woollams et al., 2007). Similarly, the demonstration of a correlation between atrophy in the angular gyrus and semantic composite and irregular word reading/spelling scores is consistent with previous reports of semantic impairment and surface dyslexia/dysgraphia in patients with focal damage to this region Rapcsak & Beeson, 2002; Vanier & Caplan, 1985). By contrast, nonword reading/spelling performance correlated with gray matter volumes in left perisylvian regions, which were also implicated in non-orthographic phonological processing tasks. These results are consistent with previous findings indicating an association between damage to left perisylvian cortex and impaired nonword reading/spelling (Brambati et al., 2009; Fiez et al., 2006; Henry et al., 2007; Rapcsak et al., 2009) and also with the strong correlation between general phonological impairment and written language performance in patients with phonological dyslexia/dysgraphia (Crisp & Lambon Ralph, 2006; Rapcsak et al., 2009). These findings indicate that differential damage to distinct left-hemisphere language networks results in parallel patterns of behavioral impairment across spoken and written language tasks.

Findings from this study are consistent with connectionist “triangle” models of language processing (Plaut et al., 1996; Harm and Seidenberg,1999, 2001; Seidenberg & McClelland, 1989; Welbourne and Lambon Ralph, 2007) and the primary systems view that disruption of modality independent semantic and phonological representations results in parallel impairments in spoken and written language. By contrast, some of our results are less adequately accounted for by dual-route models of reading/spelling. One of the critical differences between the triangle model and the dual-route cascaded (DRC) model of Coltheart et al. (2001) concerns the role of semantic representations in written language. According to the DRC model, semantic representations play no role in reading aloud and spelling to dictation, as these tasks can be performed successfully by relying on the lexical-nonsemantic route. Therefore, reading/spelling of irregular words can remain completely normal even in the presence of damage to the semantic system. Furthermore, any association between semantic impairment and defective reading/spelling of irregular words is thought to be a reflection of the anatomical contiguity of the brain regions that support semantic processing and those that are important for reading/spelling by the lexical-nonsemantic route (Blazely et al., 2005; Coltheart et al., 2010). Because the DRC model denies the involvement of semantic representations in written language processing, the model would not predict that semantic impairment and poor irregular word reading/spelling should correlate with damage to the same cortical regions. Rather, these deficits should correlate with simultaneous damage to functionally distinct but anatomically adjacent brain regions. Thus, our finding that damage to a common set of cortical regions underlies both semantic impairment and defective irregular word reading/spelling (suggesting that these functions have shared neural substrates) is inconsistent with the predictions of the DRC model.

By contrast, the well-documented association between phonological impairment and phonological dyslexia/dysgraphia is not necessarily incompatible with the functional architecture of the DRC model (Rapcsak et al., 2009). The non-lexical route of the DRC model (see Coltheart et al., 2001) comprises several different functional components (letters/graphemes, phoneme-grapheme rule system, and phonemes) and damage to any of these modules (some of which are non-phonological) could potentially result in a disproportionate impairment of nonword reading/spelling. Thus, there may be different subtypes of phonological dyslexia/dysgraphia depending on which processing component within the non-lexical route is damaged. Specifically, damage at the letter/grapheme level or to the

phoneme-grapheme rule system would result in poor nonword reading/spelling without generalized phonological impairment. There would also be a form of phonological dyslexia/dysgraphia, however, that would result from damage to the phoneme component of the model and, because phonemes are also involved in speech production/perception, damage at this level would produce general phonological impairment that would include phonological dyslexia/dysgraphia among its manifestations. Therefore, although proponents of the DRC model have made the claim that the association between general phonological impairment and phonological dyslexia/dysgraphia may simply reflect anatomical proximity of the regions important for phonological processing and nonword reading/spelling (Caccappolo-van Vliet, Miozzo, & Stern, 2004a; Caccappolo-van Vliet, Miozzo, & Stern, 2004b; Coltheart, 1996), the model allows for a subtype of phonological dyslexia/dysgraphia that is due to central phonological impairment (Nickels, Biedermann, Coltheart, Saunders, & Tree, 2008). As a result, our data demonstrating a behavioral and neuroanatomical association between general phonological impairment and phonological dyslexia/dysgraphia cannot be used to adjudicate between the DRC and triangle models. Overall, however, the combined findings of overlapping neural substrates for semantic tasks and irregular word reading/spelling and for phonological tasks and nonword reading/spelling are more parsimoniously accounted for by the triangle model and the primary systems view.

In summary, our study has provided behavioral and neuroanatomical evidence consistent with the primary systems hypothesis in a behaviorally diverse group of patients with PPA. Specifically, we demonstrated that written language performance can be reliably predicted by spoken language profile and that a shift in the division of labor between the core linguistic processes of semantics and phonology is accompanied by parallel shifts in the efficiency of irregular word versus nonword reading/spelling. We also presented preliminary findings suggesting that spoken and written language deficits have similar neuroanatomical correlates and are attributable to damage to critical left hemisphere regions that support central semantic and phonological networks. Collectively, these findings are consistent with the view that written language skills build on core cognitive and neural systems that initially support the development of spoken language production and comprehension (Harm & Seidenberg, 2004; Lambon Ralph & Patterson, 2005; Patterson & Lambon Ralph, 1999).

Finally, we wish to acknowledge certain limitations in the current study that warrant consideration. First, the brain-behavior relationships reported here were based on data from a relatively small sample of PPA patients which did not allow us to apply stringent statistical thresholds for the imaging analyses. Nonetheless, we observed distinct patterns of atrophy-behavior correlations for semantic versus phonological tasks and for irregular versus nonword reading/spelling that were consistent with our *a priori* hypotheses derived from lesion-deficit correlation studies in neurological patients and functional imaging studies of language processing in healthy individuals. Second, our patient group was not well distributed in terms of PPA subtype. In particular, our sample included only two individuals with the nonfluent variant of PPA (only one of whom could undergo MRI scanning). In order to draw conclusions regarding the general validity of the primary systems hypothesis in PPA, as well as patterns of cortical atrophy associated with language deficits in these patients, it would be preferable to have relatively even distribution across PPA variants. Future studies are needed with larger samples and a broader distribution of PPA patients to replicate and extend our findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by National Institutes of Health NIDCD grants F31DC009145, F32DC010945, R01DC008286, R01DC007646; NIA grants P30AG19610, P01AG019724, P50AG023501, R01AG025526; and NINDS grant R01NS050915, as well as the State of Arizona and Arizona Department of Health Services, Arizona Advanced Research Institute for Biomedical Imaging, and the Evelyn F. McKnight Brain Institute.

References

Ashburner J, Friston KJ. Unified segmentation. NeuroImage. 2005; 26(3):839–851. [PubMed: 15955494]

Beeson PM, Rapcsak SZ, Plante E, Chargualaf J, Chung A, Johnson S, et al. The neural substrates of writing: A functional magnetic resonance imaging study. Aphasiology. 2003; 17(6):647–665.

Beeson PM, Rapcsak SZ. The neural substrates of sublexical spelling. Journal of the International Neuropsychological Society. 2003; 9:304.

Beeson PM, Rising K, Kim ES, Rapcsak SZ. A treatment sequence for phonological alexia/agraphia. Journal of Speech, Language, and Hearing Research. 2010; 53(2):450–468.

Binder JR, Desai RH, Graves WW, Conant LL. Where is the semantic system? A critical review and meta-analysis of 120 functional neuroimaging studies. Cerebral Cortex. 2009; 19(12):2767–2796. [PubMed: 19329570]

Binder, JR.; Price, CJ. Functional neuroimaging of language. In: Cabeza, R.; Kingstone, A., editors. Handbook of functional neuroimaging of cognition. Cambridge, MA: MIT Press; 2001. p. 187-251.

Binney RJ, Embleton KV, Jefferies E, Parker GJM, Lambon Ralph MA. The ventral and inferolateral aspects of the anterior temporal lobe are crucial in semantic memory: Evidence from a novel direct comparison of distortion-corrected fMRI, rTMS, and semantic dementia. Cerebral Cortex. 2010; 20(11):2728–2738. [PubMed: 20190005]

Blazely A, Coltheart M, Casey B. Semantic impairment with and without surface dyslexia: Implications for models of reading. Cognitive Neuropsychology. 2005; 22(6):695–717. [PubMed: 21038273]

Brambati SM, Ogar J, Neuhaus J, Miller BL, Gorno-Tempini ML. Reading disorders in primary progressive aphasia: A behavioral and neuroimaging study. Neuropsychologia. 2009; 47(8–9): 1893–1900. [PubMed: 19428421]

Burton MW, LoCasto PC, Krebs-Noble D, Gullapalli RP. A systematic investigation of the functional neuroanatomy of auditory and visual phonological processing. NeuroImage. 2005; 26(3):647–661. [PubMed: 15955475]

Caccappolo-van Vliet EC, Miozzo M, Stern Y. Phonological dyslexia without phonological impairment? Cognitive Neuropsychology. 2004a; 21(8):820–839.

Caccappolo-van Vliet EC, Miozzo M, Stern Y. Phonological dyslexia. A test case for reading models. Psychological Science. 2004b; 15(9):583–590.

Coltheart M. Phonological dyslexia: Past and future issues. Cognitive Neuropsychology. 1996; 13(6): 749–762.

Coltheart M, Rastle K, Perry C, Langdon R, Ziegler J. The DRC model: A model of visual word recognition and reading aloud. Psychological Review. 2001; 108:204–258. [PubMed: 11212628]

Coltheart M. Acquired dyslexias and the computational modelling of reading. Cognitive Neuropsychology. 2006; 23(1):96–109. [PubMed: 21049323]

Coltheart M, Tree JJ, Saunders SJ. Computational modeling of reading in semantic dementia: Comment on woollams, lambon ralph, plaut, and patterson (2007). Psychological Review. 2010; 117(1):273–283. [PubMed: 20063974]

Crisp J, Lambon Ralph MA. Unlocking the nature of the Phonological–Deep dyslexia continuum: The keys to reading aloud are in phonology and semantics. Journal of Cognitive Neuroscience. 2006; 18(3):348–362. [PubMed: 16513001]

Fiez JA, Tranel D, Seager-Frerichs D, Damasio H. Specific reading and phonological processing deficits are associated with damage to the left frontal operculum. Cortex. 2006; 42(4):624–643. [PubMed: 16881271]

Good CD, Johnsrude IS, Ashburner J, Henson RNA, Friston KJ, Frackowiak RSJ. A voxel-based morphometric study of ageing in 465 normal adult human brains. NeuroImage. 2001; 14(1):21–36. [PubMed: 11525331]

Gorno-Tempini ML, Hillis AE, Weintraub S, Kertesz A, Mendez M, Cappa SF, et al. Classification of primary progressive aphasia and its variants. Neurology. 2011; 76(11):1006–1014. [PubMed: 21325651]

Gorno-Tempini ML, Dronkers NF, Rankin KP, Ogar JM, Phengrasamy L, Rosen HJ, et al. Cognition and anatomy in three variants of primary progressive aphasia. Annals of Neurology. 2004; 55(3): 335–346. [PubMed: 14991811]

Graham NL, Patterson K, Hodges JR. The impact of semantic memory impairment on spelling: Evidence from semantic dementia. Neuropsychologia. 2000; 38(2):143–163. [PubMed: 10660226]

Grossman M, McMillan C, Moore P, Ding L, Glosser G, Work M, et al. What's in a name: Voxel-based morphometric analyses of MRI and naming difficulty in Alzheimer's disease, frontotemporal dementia and corticobasal degeneration. Brain. 2004; 127(3):628–649. [PubMed: 14761903]

Harm MW, Seidenberg MS. Phonology, reading acquisition, and dyslexia: Insights from connectionist models. Psychological Review. 1999; 106(3):491–528. [PubMed: 10467896]

Harm MW, Seidenberg MS. Are there orthographic impairments in phonological dyslexia? Cognitive Neuropsychology. 2001; 18(1):71–92. [PubMed: 20945207]

Harm MW, Seidenberg MS. Computing the meanings of words in reading: Cooperative division of labor between visual and phonological processes. Psychological Review. 2004; 111(3):662–720. [PubMed: 15250780]

Heim S, Opitz B, Müller K, Friederici AD. Phonological processing during language production: FMRI evidence for a shared production-comprehension network. Cognitive Brain Research. 2003; 16(2):285–296. [PubMed: 12668238]

Henry ML, Beeson PM, Stark AJ, Rapcsak SZ. The role of left perisylvian cortical regions in spelling. Brain and Language. 2007; 100(1):44–52. [PubMed: 16890279]

Howard, D.; Patterson, K. Pyramids and palm trees: A test of semantic access from pictures and words. Bury St.Edmunds, UK: Thames Valley Test Company; 1992.

Jefferies E, Lambon Ralph MA, Jones R, Bateman D, Patterson K. Surface dyslexia in semantic dementia: A comparison of the influence of consistency and regularity. Neurocase. 2004; 10(4): 290–299. [PubMed: 15788266]

Jefferies E, Sage K, Lambon Ralph MA. Do deep dyslexia, dysphasia and dysgraphia share a common phonological impairment? Neuropsychologia. 2007; 45(7):1553–1570. [PubMed: 17227679]

Jobard G, Crivello F, Tzourio-Mazoyer N. Evaluation of the dual route theory of reading: A metanalysis of 35 neuroimaging studies. NeuroImage. 2003; 20(2):693–712. [PubMed: 14568445]

Kaplan, E.; Goodglass, H.; Weintraub, S. Boston Naming Test. Philadelphia: Lippincott, Williams and Wilkins; 2001.

Katzir T, Misra M, Poldrack RA. Imaging phonology without print: Assessing the neural correlates of phonemic awareness using fMRI. NeuroImage. 2005; 27(1):106–115. [PubMed: 15901490]

Kay, J.; Lesser, R.; Coltheart, M. PALPA: Psycholinguistic Assessments of Language Processing in Aphasia. Hove: Lawrence Erlbaum Associates Ltd; 1992.

Lambon Ralph, MA.; Patterson, K. Acquired disorders of reading. In: H, C.; Snowling, MJ., editors. The science of reading: A handbook. Oxford, UK: Blackwell Publishing, Ltd; 2005. p. 413-430.

Maldjian JA, Laurienti PJ, Kraft RA, Burdette JH. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. NeuroImage. 2003; 19(3):1233–1239. [PubMed: 12880848]

Mechelli A, Gorno-Tempini ML, Price CJ. Neuroimaging studies of word and pseudoword reading: Consistencies, inconsistencies, and limitations. Journal of Cognitive Neuroscience. 2003; 15(2): 260–271. [PubMed: 12676063]

Nickels L, Biedermann B, Coltheart M, Saunders S, Tree JJ. Computational modelling of phonological dyslexia: How does the DRC model fare? Cognitive Neuropsychology. 2008; 25(2):165–193. [PubMed: 18568812]

Omura K, Tsukamoto T, Kotani Y, Ohgami Y, Yoshikawa K. Neural correlates of phoneme-to-grapheme conversion. Neuroreport. 2004; 15(6):949–953. [PubMed: 15076713]

Patterson K, Hodges JR. Deterioration of word meaning: Implications for reading. Neuropsychologia. 1992; 30(12):1025–1040. [PubMed: 1484600]

Patterson K, Lambon Ralph MA. Selective disorders of reading? Current Opinion in Neurobiology. 1999; 9(2):235–239. [PubMed: 10322178]

Patterson K, Lambon Ralph MA, Jefferies E, Woollams A, Jones R, Hodges JR, et al. "Presemantic" cognition in semantic dementia: Six deficits in search of an explanation. Journal of Cognitive Neuroscience. 2006; 18(2):169–183. [PubMed: 16494679]

Patterson K, Marcel A. Phonological ALEXIA or PHONOLOGICAL alexia? Neurocase. 1995; 1(3): 251–257.

Patterson K, Suzuki T, Wydell TN. Interpreting a case of japanese phonological alexia: The key is in phonology. Cognitive Neuropsychology. 1996; 13(6):803–822.

Plaut DC, McClelland JL, Seidenberg MS, Patterson K. Understanding normal and impaired word reading: Computational principles in quasi-regular domains. Psychological Review. 1996; 103(1): 56–115. [PubMed: 8650300]

Price CJ. The functional anatomy of word comprehension and production. Trends in Cognitive Sciences. 1998; 2(8):281–288. [PubMed: 21227210]

Price CJ, Moore CJ, Humphreys GW, Wise RJS. Segregating semantic from phonological processes during reading. Journal of Cognitive Neuroscience. 1997; 9(6):727–733.

Rapcsak SZ, Beeson PM. Neuroanatomical correlates of spelling and writing. Handbook on Adult Language Disorders: Integrating Cognitive Neuropsychology, Neurology, and Rehabilitation. 2002:71–99.

Rapcsak SZ, Beeson PM, Henry ML, Leyden A, Kim E, Rising K, et al. Phonological dyslexia and dysgraphia: Cognitive mechanisms and neural substrates. Cortex. 2009; 45(5):575–591. [PubMed: 18625494]

Rogers TT, Hocking J, Noppeney U, Mechelli A, Gorno-Tempini ML, Patterson K, et al. The anterior temporal cortex and semantic memory: Reconciling findings from neuropsychology and functional imaging. Cognitive, Affective, and Behavioral Neuroscience. 2006; 6:201–213.

Rohrer JD, Ridgway GR, Crutch SJ, Hailstone J, Goll JC, Clarkson MJ, et al. Progressive logopenic/phonological aphasia: Erosion of the language network. NeuroImage. 2010; 49(1):984–993. [PubMed: 19679189]

Seidenberg MS, McClelland JL. A distributed, developmental model of word recognition and naming. Psychological Review. 1989; 96(4):523–568. [PubMed: 2798649]

Seki A, Okada T, Koeda T, Sadato N. Phonemic manipulation in japanese: An fMRI study. Brain Research. Cognitive Brain Research. 2004; 20(2):261–272. [PubMed: 15183397]

Tree JJ, Kay J. Phonological dyslexia and phonological impairment: An exception to the rule? Neuropsychologia. 2006; 44(14):2861–2873. [PubMed: 16879843]

Vandenberghe R, Price C, Wise R, Josephs O, Frackowiak RS. Functional anatomy of a common semantic system for words and pictures. Nature. 1996; 383(6597):254–256. [PubMed: 8805700]

Vanier, M.; Caplan, D. CT correlates of surface dyslexia. In: Patterson, K.; Marshall, JC.; Coltheart, M., editors. Surface dyslexia: Neuropsychological and cognitive studies of phonological reading. London: Lawrence Erlbaum; 1985. p. 511-525.

Vigneau M, Beaucousin V, Herve PY, Duffau H, Crivello F, Houde O, et al. Meta-analyzing left hemisphere language areas: Phonology, semantics, and sentence processing. NeuroImage. 2006; 30(4):1414–1432. [PubMed: 16413796]

Visser M, Embleton KV, Jefferies E, Parker GJ, Lambon Ralph MA. The inferior, anterior temporal lobes and semantic memory clarified: Novel evidence from distortion-corrected fMRI. Neuropsychologia. 2010; 48(6):1689–1696. [PubMed: 20176043]

Visser M, Jefferies E, Lambon Ralph MA. Semantic processing in the anterior temporal lobes: A meta-analysis of the functional neuroimaging literature. Journal of Cognitive Neuroscience. 2010; 22(6): 1083–1094. [PubMed: 19583477]

Welbourne SR, Lambon Ralph MA. Using parallel distributed processing models to simulate phonological dyslexia: The key role of plasticity-related recovery. Journal of Cognitive Neuroscience. 2007; 19(7):1125–1139. [PubMed: 17583989]

Wilson SM, Brambati SM, Henry RG, Handwerker DA, Agosta F, Miller BL, et al. The neural basis of surface dyslexia in semantic dementia. Brain. 2009; 132(1):71–86. [PubMed: 19022856]

Woollams AM, Lambon Ralph MA, Plaut DC, Patterson K. SD-squared: On the association between semantic dementia and surface dyslexia. Psychological Review. 2007; 114(2):316–339. [PubMed: 17500629]

Woollams AM, Lambon Ralph MA, Plaut DC, Patterson K. SD-squared revisited: Reply to coltheart, tree, and saunders (2010). Psychological Review. 2010; 117(1):273–281. [PubMed: 20063974]

Woollams AM, Silani G, Okada K, Patterson K, Price CJ. Word or word-like?. dissociating orthographic typicality from lexicality in the left occipito-temporal cortex. Journal of Cognitive Neuroscience. 2011; 23(4):992–1002. [PubMed: 20429854]

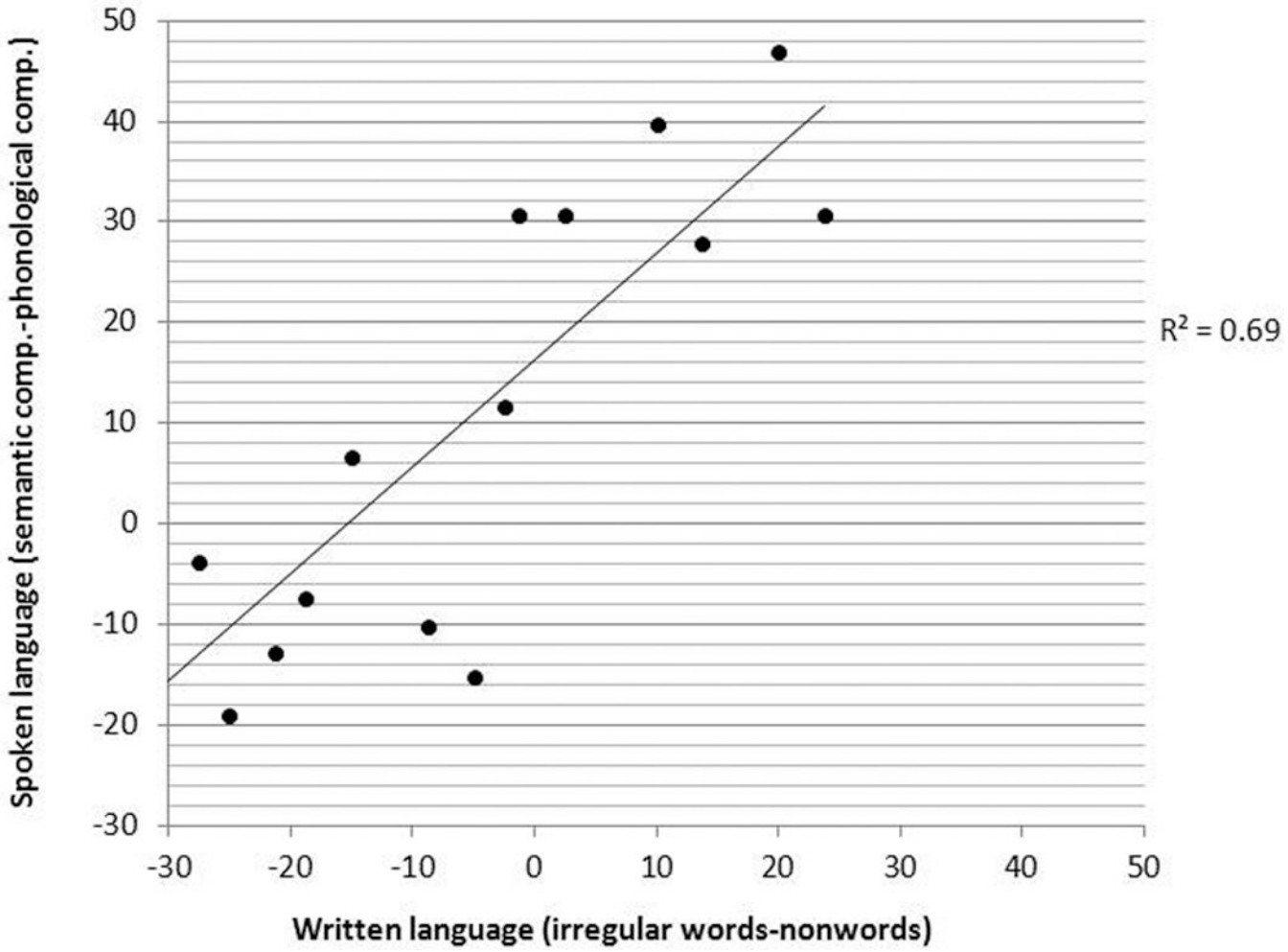

Figure 1.
Regression plot showing the relationship between spoken and written language bias measures in individuals with PPA.

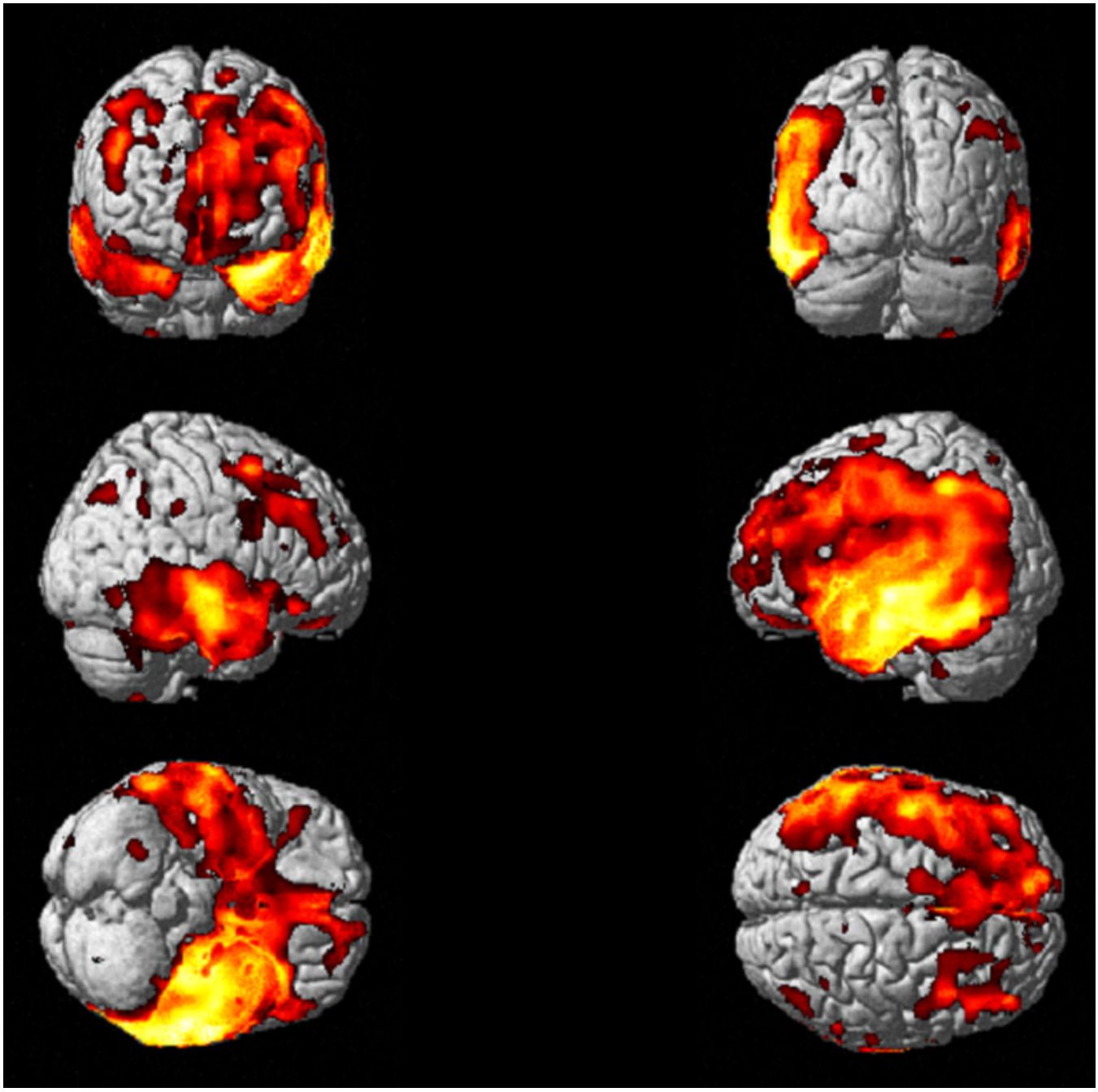

Figure 2.
Results of VBM analysis comparing gray matter volume in PPA patients (n = 11) versus controls (n = 15; q<0.01, FDR corrected

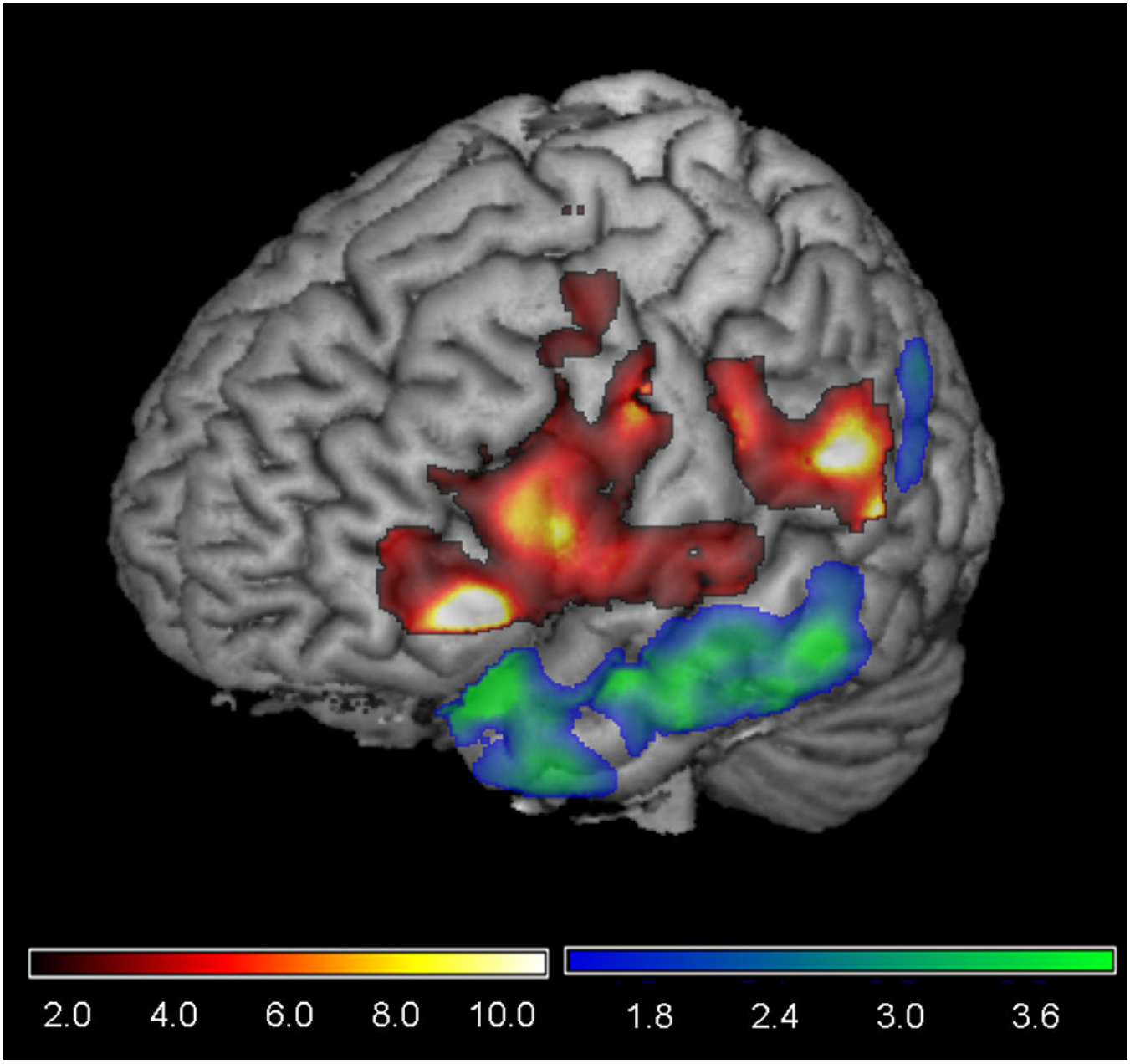

Figure 3.
Correlations between spoken language composite measures and gray matter volumes within language ROIs (color bars indicate t-values; cool colors = semantic composite; hot colors = phonological composite; $p<0.05$, uncorrected)

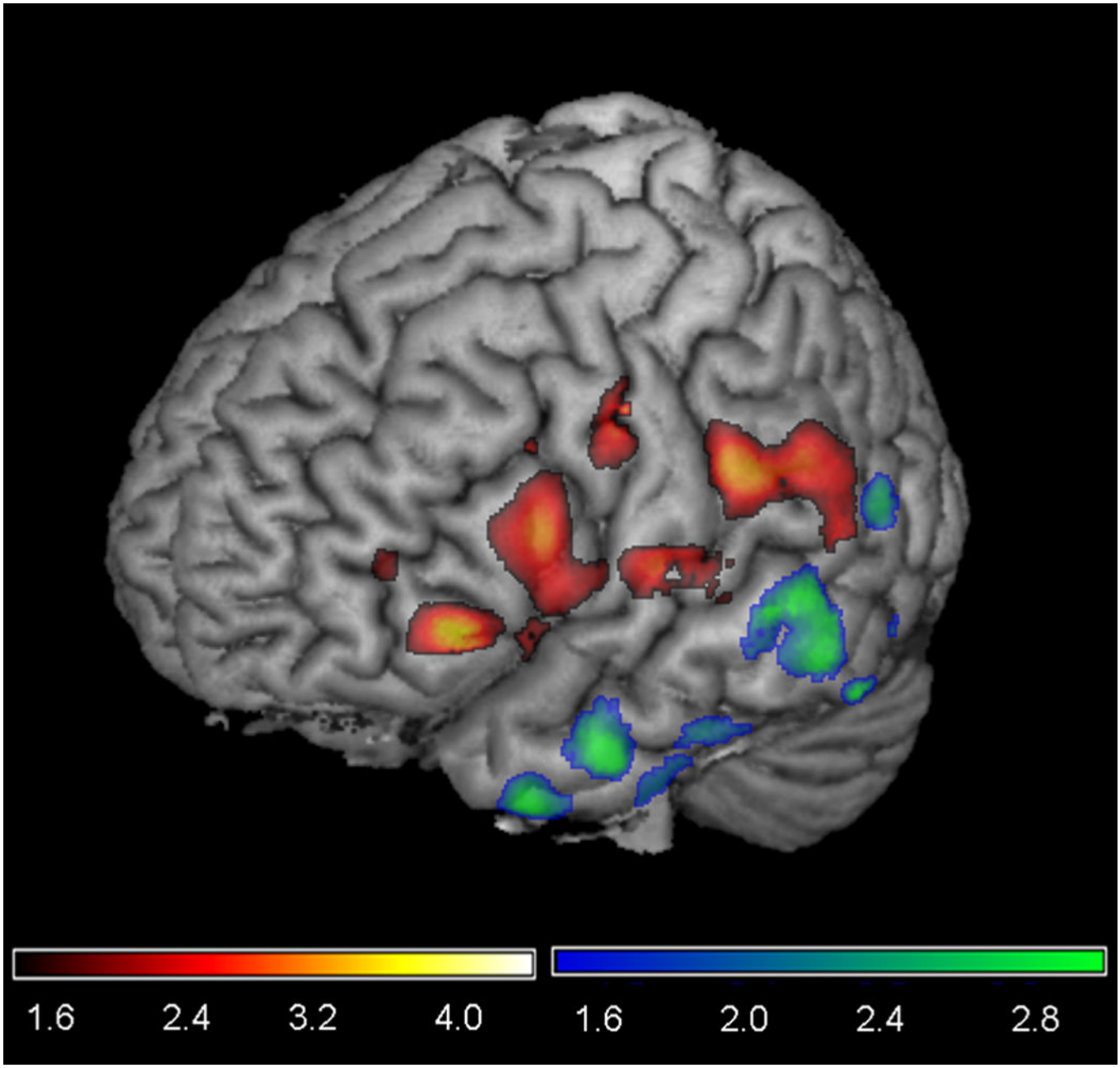

Figure 4.
Correlations between written language composite measures and gray matter volumes within language ROIs (color bars indicate t-values; cool colors = irregular word scores; hot colors = nonword scores, $p<0.05$, uncorrected)

Table 1

Characteristics of participants with PPA (n=15) and a group of normal controls (n=15)

	Age	Sex	Educ. (years)	Hand	Time Post Onset (years)	WAB Aphasia Quotient /100	PPA type	MMSE /30	MRI scan
PPA1	75	M	15	R	5	91.4	SV	30	yes
PPA2	80	M	16	R	2	86	NFV	26	no
PPA3	71	M	16	R	11	79.2	SV	20	no
PPA4	80	F	18	R	8	72.6	SV	24	yes
PPA5	73	F	18	R	6.5	76.5	LV	24	yes
PPA6	60	M	15	R	2	85.9	LV	27	no
PPA7	70	M	14	R	3.5	79.9	LV	26	no
PPA8	65	F	16	L	4.5	70.6	SV	23	yes
PPA9	71	F	14.5	R	5	98.2	SV	29	yes
PPA10	53	M	12	R	2.5	90.3	LV	26	yes
PPA11	76	M	15	R	2.5	90.6	LV	25	yes
PPA12	80	M	14.5	R	2	55.6	NFV	12	yes[¤]
PPA13	71	F	20.5	R	6	65.6	LV	12	yes
PPA14	70	M	18	R	2	93.6	LV	26	yes
PPA15	79	F	13	R	9	86.3	SV	27	yes
PPA mean (SD)	71.6 (7.7)	9M:6F	15.7 (2.1)	14R:1L	4.8 (2.9)	81.5 (11.7)		23.8 (5.4)	
NC Mean (SD)	67.8 (8.5)	8M:7F	16.9 (2.7)	14R:1L				29.2 (.9)	

Note:

[¤]Scanned at 1.5T, SV=semantic variant, LV=logopenic variant, NFV=nonfluent variant; NC=normal control; WAB=*Western Aphasia Battery*; MMSE=*Mini Mental State Exam*

Table 2

Assessment Battery

Language Domain	**Type of assessment**	**Tasks (# of items)**
Semantics	Verbal and nonverbal assessments of conceptual knowledge (includes comprehension and production tasks)	*Pyramids and Palm Trees Test* (52) *Boston Naming Test* (60) *PALPA 47*: Spoken word-to-picture match (40) *PALPA 49*: Auditory synonym judgment (subset of 20)
Phonology	Assessment of phonological processing (in nonorthographic tasks)	*Arizona Phonological Battery:* Phoneme deletion (20) Phoneme substitution (30) Phoneme blending (20) Minimal pair discrimination (40)
Written language	Spelling to dictation and oral reading	*Arizona Battery of Reading and Spelling:* Regular words (40) Irregular words (40) Nonwords (20)

Table 3

Example tasks from the Arizona Phonological Battery

Task	Instructions	Correct response
Phoneme deletion	Say “fat”→ now take away “f” Say “deek” →now take away “k”	“at” “dee”
Phoneme substitution	Say “not”→now change “n” to “h” Say “sar”→now change “s” to “v”	“hot” “var”
Phoneme blending	Put these sounds together to make a word: “b” – “oi” – “l” Put these sounds together to produce a made-up word: “f” -- “oo” – “m”	“boil” “foom”
Minimal pair discrimination	Do these words/made-up words sound the same? “tack” – “cat” “sape” – “sape”	“no” “yes”

Table 4

Results of principal component analysis for language tasks

	Factor loadings	
	Factor 1 (Semantics)	**Factor 2 (Phonology)**
PPT pictures	0.920	−0.067
BNT	0.952	0.055
PALPA 47 (spoken-word to picture matching)	0.818	0.041
PALPA 49 (auditory synonym judgment)	0.797	−0.003
Phoneme deletion	−0.113	0.788
Phoneme substitution	−0.405	0.819
Phoneme blending	0.191	0.876
Minimal pair discrimination	0.239	0.536

Direct Oblimin rotation applied to factors
PPT=Pyramids and Palm Trees Test
BNT=Boston Naming Test
Factor 1 (Semantics) eigenvalue = 3.32; % variance explained = 41.55
Factor 2 (Phonology) eigenvalue = 2.35; % variance explained = 29.41
Total variance explained by 2 factors = 70.96

Table 5

Spoken language composite scores (average percent correct across tasks)

	Semantic Composite	Phonological Composite	Bias score
PPA1	82.69	92.92	−10.23
PPA2	92.79	45.83	46.96
PPA3	60.30	64.17	−3.87
PPA4	54.10	73.13	−19.03
PPA5	88.96	58.33	30.63
PPA6	89.89	59.17	30.72
PPA7	90.77	60.00	30.77
PPA8	60.90	64.79	−3.89
PPA9	80.24	95.42	−15.18
PPA10	93.21	86.67	6.54
PPA11	79.95	87.29	−7.34
PPA12	65.45	37.50	27.95
PPA13	84.74	45.00	39.74
PPA14	96.54	85.00	11.54
PPA15	64.71	77.50	−12.79
PPA mean (SD)	79.02 (14.12)	68.85 (18.32)	10.17
NC mean (SD)	97.97 (1.09)	92.44 (5.60)	5.53

Table 6

Written language composite scores (average percent correct across reading and spelling tasks)

	Regular words			Irregular words			Real Words	Nonwords	Bias score
	HF (20)	LF (20)	Total (40)	HF (20)	LF (20)	Total (40)	Total (80)	(20)	
PPA1	100.00	97.50	98.75	97.50	80.00	88.75	93.75	97.50	−8.75
PPA2	97.50	80.00	88.75	75.00	60.00	67.50	78.13	47.50	20.00
PPA3	87.50	82.50	85.00	77.50	40.00	58.75	71.88	90.00	−31.25
PPA4	97.50	87.50	92.50	82.50	57.50	70.00	81.25	95.00	−25.00
PPA5	92.50	75.00	83.75	72.50	55.00	63.75	73.75	40.00	23.75
PPA6	100.00	97.50	98.75	95.00	85.00	90.00	94.33	87.50	2.50
PPA7	97.50	90.00	93.75	95.00	82.50	88.75	91.25	90.00	−1.25
PPA8	92.50	87.50	90.00	72.50	52.50	62.50	76.25	90.00	−27.50
PPA9	100.00	100.00	100.00	97.50	92.50	95.00	97.50	100.00	−5.00
PPA10	100.00	100.00	100.00	90.00	80.00	85.00	92.50	100.00	−15.00
PPA11	100.00	92.50	96.25	90.00	67.50	78.75	87.50	97.50	−18.75
PPA12	70.00	62.50	66.25	65.00	27.50	46.25	56.25	32.50	13.75
PPA13	97.50	97.50	97.50	97.50	77.50	87.50	92.50	77.50	10.00
PPA14	100.00	100.00	100.00	97.50	92.50	95.00	97.50	97.50	−2.50
PPA15	95.00	85.00	90.00	85.00	47.50	66.25	78.13	87.50	−21.25
PPA mean (SD)	95.17 (7.88)	89.00 (10.81)	92.08 (9.00)	86.00 (11.13)	66.50 (19.80)	76.25 (15.07)	84.17 (11.76)	82.00 (22.70)	−5.75
NC mean (SD)	100.00 (0.00)	99.67 (0.88)	99.83 (0.44)	99.17 (1.54)	96.83 (4.27)	98.00 (2.66)	98.29 (1.33)	97.00 (3.43)	1.00

Table 7

Results of multiple regression analyses examining semantic and phonological composites as predictors of written language measures in individuals with PPA

	ANOVA			Semantic Composite				Phonology Composite			
	r-square	*F*	sig.	Beta	*t*	sig.	square of part correl.	Beta	*t*	sig.	square of part correl.
All stimulus types	0.62	9.87	0.003	0.36	2.05	0.063	0.13	0.67	3.79	0.003	0.45
Nonwords	0.61	9.36	0.004	−0.1	−0.52	0.61	0.00	0.78	4.32	0.001	0.61
Real Words (all)	0.66	11.51	0.002	0.55	3.25	0.007	0.30	0.56	3.29	0.007	0.31
Reg words	0.60	9.02	0.004	0.42	2.29	0.041	0.17	0.62	3.41	0.005	0.39
HF reg	0.55	7.25	0.009	0.45	2.29	0.041	0.20	0.56	2.87	0.014	0.31
LF reg	0.57	7.91	0.006	0.37	1.95	0.075	0.14	0.63	3.32	0.006	0.40
Irreg words	0.66	11.72	0.002	0.61	3.62	0.004	0.37	0.50	2.95	0.012	0.25
HF irreg	0.52	6.54	0.012	0.46	2.29	0.041	0.21	0.53	2.63	0.022	0.27
LF irreg	0.71	14.50	0.001	0.67	4.29	0.001	0.45	0.46	2.94	0.012	0.21

Reg=regular, Irreg=irregular, HF=high frequency, LF=low frequency, part correl. = part (or semi-partial) correlation, the square of which represents the proportion of unique variance explained by each predictor; sig. = significance level (*p*)

Note: each line of the table represents a separate regression model.