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Authors

Dial, Heather R
Europa, Eduardo
Grasso, Stephanie M
et al.

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Baseline structural imaging correlates of treatment outcomes in semantic variant primary progressive aphasia

Heather R. Dial[a,c,*], **Eduardo Europa**[b], **Stephanie M. Grasso**[c], **Maria Luisa Mandelli**[b], **Kristin M. Schaffer**[c], **H. Isabel Hubbard**[d], **Lisa D. Wauters**[c], **Lindsey Wineholt**[c], **Stephen M. Wilson**[e], **Maria Luisa Gorno-Tempini**[b], **Maya L. Henry**[c,f]

[a]Department of Communication Sciences and Disorders, University of Houston, Houston, TX, USA

[b]Memory and Aging Center, University of California, San Francisco. 675 Nelson Rising Lane (Suite 190), San Francisco, CA USA

[c]Department of Speech, Language and Hearing Sciences, University of Texas at Austin, 2504A Whitis Avenue (A1100), Austin, TX USA

[d]College of Health Sciences, University of Kentucky, 900 S. Limestone, Lexington, KY, USA

[e]Department of Hearing and Speech Sciences, Vanderbilt University Medical Center, 1215 21st Ave S, Nashville, TN 37232, USA

[f]Department of Neurology, Dell Medical School, University of Texas at Austin, Bldg. B, Stop Z0700, Austin, TX USA

Abstract

Semantic variant primary progressive aphasia (svPPA) is a neurodegenerative disorder characterized by a loss of semantic knowledge in the context of anterior temporal lobe atrophy

[*]*Corresponding author*. University of Houston, Department of Communication Sciences and Disorders. Melcher Life Sciences, Room M242, USA., hrdial@central.uh.edu (H.R. Dial).

Author contributions

Heather R. Dial: conceptualization, methodology, data curation, investigation, formal analysis, visualization, writing-original draft.
Eduardo E. Europa: conceptualization, methodology, investigation, formal analysis, writing-review & editing.
Stephanie M. Grasso: conceptualization, investigation, formal analysis, writing-review & editing.
Maria Luisa Mandelli: methodology, writing-review & editing.
Kristin Schaffer, H. Isabel Hubbard, Lisa Wauters, Lindsey Wineholt: investigation, writing-review & editing.
Stephen Wilson: methodology, writing-review & editing.
Maria Luisa Gorno-*Tempini*: funding acquisition, resources, writing-review & editing.
Maya L. Henry: conceptualization, methodology, funding acquisition, resources, supervision, writing-review & editing.

Declaration of interest

None.

TOP guidelines statement

The conditions of our ethics approval do not permit public archiving or sharing of the treatment study materials or the MRI data supporting this study with any individual outside the author team under any circumstances. However, the data analysis code can be found here: https://osf.io/u78hq/

Due to legal copyright restrictions, the clinical instruments used in this study are not publicly archived and can be obtained from the copyright holders in the cited references. No part of the study procedures or analyses were preregistered in an independent repository prior to the research being conducted. We report how we determined our sample size, all data exclusions (if any), all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cortex.2022.10.004.

(left > right). Core features of svPPA include anomia and single-word comprehension impairment. Despite growing evidence supporting treatment for anomia in svPPA, there is a paucity of research investigating neural mechanisms supporting treatment-induced gains and generalization to untrained items. In the current study, we examined the relation between the structural integrity of brain parenchyma (tissue inclusive of gray and white matter) at pre-treatment and treatment outcomes for trained and untrained items in a group of 19 individuals with svPPA who completed lexical retrieval treatment. Two structural neuroimaging approaches were used: an exploratory, whole-brain, voxel-wise approach and an *a priori* region of interest (ROI) approach. Based on previous research, bilateral temporal (inferior, middle, and superior temporal gyri), parietal (supramarginal and angular gyri), frontal (inferior and middle frontal gyri) and medial temporal (hippocampus and parahippocampal gyri) ROIs were selected from the Automated Anatomical Labeling (AAL) atlas. Analyses revealed improved naming of trained items and generalization to untrained items following treatment, providing converging evidence that individuals with svPPA can benefit from treatment for anomia. Better post-treatment naming accuracy was associated with the structural integrity of inferior parietal cortex and the hippocampus. Specifically, improved naming of trained items was related to the left supramarginal (phonological processing) and angular gyri (phonological and semantic processing), and improved naming of trained and untrained items was related to the left hippocampus (episodic, context-based memory). Future research should examine treatment outcomes in relation to pre-treatment functional and structural connectivity as well as changes in network dynamics following speech-language intervention to further elucidate the neural mechanisms underlying treatment response in svPPA and related disorders.

Keywords

Semantic variant primary; progressive aphasia; Lexical retrieval treatment; Magnetic resonance imaging; Anomia; Treatment outcomes

1. Introduction

Primary progressive aphasia (PPA) is a neurodegenerative disorder characterized by a gradual emergence of language deficits that worsen over time (Gorno-Tempini et al., 2011; Mesulam, 1982, 2001). General cognitive abilities are relatively spared in early stages of the disease, but non-language cognitive deficits emerge with disease progression (Cerami et al., 2017). There are three widely recognized clinical variants of PPA that differ in behavioral phenotype and underlying pattern of neurodegeneration (Gorno-Tempini et al., 2004, 2011). The current study presents findings from the semantic variant (svPPA, which overlaps diagnostically with semantic dementia), a syndrome characterized by a loss of core semantic knowledge. Behaviorally, this manifests as anomia, impaired single word comprehension, impaired object knowledge, and surface dyslexia/dysgraphia, with relatively spared phonological and syntactic processing. Brain atrophy is observed predominantly in the anterior temporal lobes and can extend posteriorly into inferior, middle, and superior temporal gyri, fusiform gyrus, amygdala, and hippocampus, and superiorly into the posterior insula (Gorno-Tempini et al., 2004; Mummery et al., 1999; Wisse et al., 2021). Bilateral

atrophy is usually observed, although there is a greater degree of atrophy in the language-dominant hemisphere (typically left > right).

Although there is a long history of research addressing speech-language treatment efficacy and neural contributors to recovery in stroke-induced aphasia, comparatively little is known regarding neural mechanisms that influence response to intervention in PPA. Unlike stroke-induced aphasia, continued decline in language abilities in PPA is inevitable, which has led to skepticism among medical providers regarding the efficacy of behavioral interventions in PPA (Taylor, Kingma, Croot, & Nickels, 2009). Despite such skepticism, evidence for the utility of speech-language treatment in PPA is growing (Cadório, Lousada, Martins, & Figueiredo, 2017; Carthery-Goulart et al., 2013; Cotelli et al., 2019; Volkmer, Spector, Meitanis, Warren, & Beeke, 2020; Wauters et al., 2021), along with our understanding of the neural mechanisms that support improved naming (Beeson et al., 2011; Cotelli et al., 2016; Dressel et al., 2010; Henry et al., 2018; Jokel et al., 2016; Marcotte, InéAnsaldo, & Mary Road, 2010; Paek, Murray, & Newman, 2021). In the current study, we sought to contribute to the evidence base regarding neural structures associated with treatment-induced gains in svPPA. Specifically, we examined the relation between the structural integrity of brain parenchyma (i.e., tissue inclusive of gray and white matter) at pre-treatment and post-treatment naming accuracy following a lexical retrieval intervention in individuals with mild-to-moderate svPPA.

1.1. Treatment for anomia in svPPA

The most common focus of speech-language intervention in svPPA is single word retrieval (Cadório et al., 2017; Carthery-Goulart et al., 2013; Volkmer et al., 2020; Wauters et al., 2021). One of the first accounts of improved single word retrieval in svPPA following targeted practice is that of patient D.M., presented by Graham and colleagues (Graham et al., 1999, 2001). D.M. self-initiated a home-based program consisting of repeated attempts to retrieve words in response to pictures in the Oxford English Picture Dictionary (Parnwell, 1977) and hand-written definitions contained in a notebook; both the Picture Dictionary and the notebook were organized by semantic category. When he was unable to recall a word, he would reveal the orthographic word form. D.M. demonstrated improved confrontation naming (Graham et al., 2001) and category fluency (Graham et al., 1999) for practiced items, which was surprising, as previous research suggested that individuals with svPPA could not relearn “forgotten” words (e.g., Graham & Hodges, 1997).

The body of research documenting effects of treatment for anomia in individuals with svPPA has grown in the decades following the seminal work of Graham and colleagues, providing support for the claim that individuals with svPPA can relearn targeted vocabulary (Beales, Cartwright, Whitworth, & Panegyres, 2016; Bier et al., 2009; Dial et al., 2019; Dressel et al., 2010; Frattali, 2004; Henry et al., 2008, 2013, 2019; Heredia, Sage, Lambon Ralph, & Berthier, 2009; Jokel & Anderson, 2012; Jokel et al., 2002, 2006, 2010, 2016; Meyer, Snider, Eckmann, & Friedman, 2015, 2017; Newhart et al., 2009; Robinson, Druks, Hodges, & Garrard, 2009; Savage et al., 2014; Snowden & Neary, 2002). Across the myriad treatment approaches, gains for trained items are nearly always reported immediately post-treatment. Differences exist, however, in the magnitude of the treatment effect, maintenance

of gains, and generalization to untrained items and contexts. Many of the treatment studies targeting anomia utilize repeated presentation of pictures paired with the spoken and/or orthographic word form (e.g., Heredia et al., 2009; Meyer et al., 2015, 2017), whereas other protocols incorporate self-cueing via retrieval of residual semantic, phonological, orthographic, and episodic information. These studies report both significant gains and maintenance beyond the immediate post-treatment period (Dressel et al., 2010; Henry et al., 2008, 2013, 2019; Jokel & Anderson, 2012; Jokel, Rochon, & Anderson, 2010; Savage et al., 2013; Savage et al., 2015), as well as generalization to untrained targets (Beales et al., 2016; Henry et al., 2008, 2013, 2019; Jokel & Anderson, 2012; Jokel et al., 2010; Savage et al., 2013). Questions remain, however, regarding the cognitive and neural processes supporting these observed gains.

1.2. Cognitive and linguistic processes supporting word relearning in svPPA

Potential underlying mechanisms supporting treatment-mediated improvements in naming in svPPA may be informed by models of single-word retrieval and previous research in svPPA. Single-word retrieval first involves the activation of a semantic concept (e.g., in response to a picture). Activation then spreads to the lexical level (lemma, phonological representations), followed by articulatory planning and production, with most models assuming some degree of interactivity between levels (Dell & O'Seaghdha, 1992; Dell, Schwartz, Martin, Saffran, & Gagnon, 1997; Goodglass, 1998; Levelt, 1999; Levelt, Roelofs, & Meyer, 1999). Single-word retrieval deficits in svPPA are associated with damage to one or both of the first two stages of the lexical retrieval hierarchy: either a failure to activate a robust semantic concept due to a loss of core semantic knowledge or a failure to activate the lexical representation due to weakening of the link between the semantic and lexical levels (Wilson, Dehollain, Ferrieux, Christensen, & Teichmann, 2017).

It is likely that improved naming following treatment for anomia in svPPA is supported by several cognitive and linguistic processes including, but not limited to, phonological processing, residual semantic knowledge, and episodic memory. Phonological processing is relatively spared in svPPA (Agosta et al., 2010; Battistella et al., 2019; Henry et al., 2016; Jefferies, Jones, Bateman, & Ralph, 2005) and is necessarily implicated in treatment for anomia (i.e., by pairing a picture with either a spoken word that must be repeated or a written word that must be read aloud). As semantic memory degrades, individuals with svPPA may become more dependent upon phonological processing. For example, individuals with svPPA rely on phonological processing to perform tasks like irregular word reading, leading to surface dyslexia (Wilson et al., 2009), and immediate serial recall, leading to the production of words that are phonologically similar to target words (Jefferies et al., 2005). In an interactive system, phonological processing feeds back to the semantic level, increasing activation for residual semantic concepts associated with the word and strengthening the connection between the two levels. This mechanism may underlie some of the improvements observed in svPPA following treatment, particularly for trained items. Generalization to untrained items may also be supported by such a mechanism, especially for strategic interventions focused on phonemic self-cueing that are designed to capitalize on existing connections between residual semantic concepts and phonological representations

(Best, Herbert, Hickin, Osborne, & Howard, 2010; Best, Howard, Bruce, & Gatehouse, 2008; Bruce & Howard, 1987; Lorenz & Nickels, 2007; Wambaugh et al., 2001).

In addition to relatively spared phonological processing, individuals with svPPA may take advantage of residual semantic knowledge to support word retrieval. For words with residual semantic knowledge, failed lexical retrieval attempts are due in part to a weakening of the link between the lexical and semantic levels (e.g., Wilson et al., 2017). Thus, by targeting items with residual semantic knowledge, the link between the verbal label and the semantic concept can be strengthened, thereby supporting improved naming. In fact, Graham et al. (1999) proposed that D.M.'s residual semantic knowledge for practiced items, combined with the emphasis on semantic category during practice, may be the reason he was able to relearn and maintain previously "forgotten" vocabulary. Further evidence for the role of residual semantic knowledge in word relearning in svPPA comes from a series of studies from Jokel et al. (2002; 2006; 2010). In these studies, individuals with svPPA underwent treatment targeting words for which they either did or did not have residual semantic knowledge. Significant gains immediately following treatment were observed for both types of items, but treatment effects were larger and maintained longer for items with residual semantic knowledge. As such, treatment approaches that incorporate retrieval of residual semantic information may facilitate maintenance (e.g., as in Beales et al., 2016; Dressel et al., 2010; Henry et al., 2008/2013/2019; Jokel & Anderson, 2012; Jokel et al., 2010) and generalization to untrained exemplars (e.g., Hoffman, Clarke, Jones, & Noonan, 2015) in svPPA. This is likely to be of most benefit for trained items, but generalization to untrained items (not just untrained exemplars of trained items) may also be observed if there is a strategic component designed to facilitate the transfer of strategies from trained to untrained items.

Whereas the availability of residual semantic knowledge likely enables more robust and generalizable gains that are maintained for longer periods of time, episodic memory is proposed to play an important role in supporting improved word retrieval immediately following treatment (e.g., Beales et al., 2016; Bier et al., 2009; Frattali et al., 2004; Graham et al., 1999; Henry et al., 2008; Heredia et al., 2009; Jokel et al., 2016; Mayberry et al., 2011a/2011b; Snowden & Neary, 2002). Graham et al. (1999) were the first to propose this episodic memory hypothesis, which was derived from the complementary systems theory of knowledge acquisition (e.g., Alvarez & Squire, 1994; Mcclelland, Mcnaughton, & O'reilly, 1995). This theory posits that initial learning is accomplished via the hippocampal complex (i.e., medial temporal lobe structures), which allows for rapid acquisition of memories and reduces the likelihood of confusing newly acquired memories by storing new items as sparse, non-overlapping representations. Over time, memories are consolidated into the neocortex, where representations are more distributed and where memories with shared features have overlapping representations. Because the greatest atrophy is observed in temporal neocortex in svPPA, individuals with svPPA are less able to rely on the neocortical structures that are necessary for memory consolidation, which may lead to an increased reliance on episodic memory for word relearning, supported by the hippocampal complex. In other words, lexical retrieval interventions may shift the reliance on the connection between semantic memory and phonological representations to an alternative route that relies on episodic memory. Specifically, the connections between episodic memory and

lexical-phonological representations may be strengthened for trained items and capitalized upon for both trained and untrained items. The hippocampal complex, however, can only accommodate a limited amount of episodic information, leading to rapid forgetting of relearned words, as was the case for D.M (Graham et al., 1999). The increased reliance on episodic memory for word relearning in svPPA also leads to context-dependent effects, such as difficulty producing a trained word when its picture is presented on a different colored background (Snowden & Neary, 2002) or when using an untrained exemplar of a trained item (Hoffman et al., 2015; Mayberry et al., 2011).

In sum, improved naming following treatment for anomia in individuals with svPPA is supported by a combination of phonological, semantic, and episodic processes. It may be the case that phonological processing and episodic memory support immediate gains and are recruited irrespective of whether there is residual semantic knowledge for a given word. However, for words with residual semantic knowledge, semantic memory is recruited, providing additional support, and leading to larger, longer lasting gains that are more likely to generalize to novel exemplars and contexts.

1.3. Neural bases of treatment-induced gains in PPA

Structural and functional neuroimaging also provide insight into the cognitive processes supporting positive treatment outcomes in svPPA. If phonological processing, residual semantic knowledge, and episodic memory are key contributors to word relearning in svPPA, then the structural and functional integrity of neuroanatomical regions supporting these processes should be related to treatment outcomes. Imaging research addressing language treatment is relatively sparse in stroke-induced aphasia and even more limited in PPA. To our knowledge, at the time of this writing there are only five functional neuroimaging studies that have examined neural activation at pre- and post-treatment in PPA (Beeson et al., 2011; Dressel et al., 2010; Jokel et al., 2016; Marcotte et al., 2010; Paek et al., 2021) and three structural neuroimaging studies that have utilized voxel-based morphometry (VBM) to examine the structural integrity of gray matter at pre-treatment in relation to treatment outcomes in PPA (Cotelli et al., 2016; Henry et al., 2018; Meyer, Faria, Tippett, Hillis, & Friedman, 2017). All three PPA subtypes have been examined, with variations in methodology, participant profile, and treatment approach across studies. A summary of these studies is presented in Table 1.

These previous imaging studies in PPA indicate that positive treatment outcomes are supported by the functional and structural integrity of relatively spared left hemisphere language regions and homologous areas in the right hemisphere, as well as structures related to executive function. Findings across studies vary as a function of PPA subtype and the nature of the intervention, indicating that the specific regions supporting improved function following treatment depend, in part, on clinical phenotype and the treatment paradigm. In the present study, we sought to extend previous findings by examining the relation between the structural integrity of brain parenchyma at baseline and gains in naming following lexical retrieval intervention in the largest sample of individuals with svPPA to-date.

1.4. Current study

In the current study, we sought to identify the neural conditions under which treatment-induced gains in naming are observed for individuals with svPPA. To do so, we examined the relation between structural integrity of brain parenchyma and naming treatment outcomes for trained and untrained items in a group of 19 individuals with svPPA. Two structural neuroimaging approaches were used: an exploratory whole-brain, voxel-wise (VBM) approach, and an *a priori* region of interest (ROI) approach.

The lexical retrieval treatment employed for this study incorporates components of several approaches that have proven successful in improving lexical retrieval in individuals with aphasia. These include semantic feature analysis and phonemic/orthographic cueing. Semantic feature analysis requires individuals to retrieve salient semantic features in response to a picture, thereby encouraging the retrieval of residual semantic knowledge while also strengthening the connection between the semantic and lexical levels (Boyle, 2004; Boyle & Coelho, 1995; Coelho, McHugh, & Boyle, 2000). Phonemic/orthographic cueing involves eliciting (or providing, if necessary) the initial sound/letter of a target word, encouraging partial retrieval of the lexical representation to facilitate access to the lexical representation and strengthen the link between semantic and lexical levels (Best et al., 2008, 2010; Bruce & Howard, 1987; Lorenz & Nickels, 2007; Wambaugh et al., 2001). By incorporating these treatment approaches that target multiple levels of processing into a single intervention cascade, this intervention has the potential to benefit persons with different underlying causes of anomia (e.g., persons with semantic or phonological impairment or both). Additionally, the training approach encourages retrieval of residual semantic and/or word form knowledge via self-cueing strategies, which is expected to facilitate not only improved retrieval of targeted vocabulary, but generalized improvement in word retrieval for untrained items as well. Our prior studies have confirmed that these predictions hold true, with improved naming of trained as well as untrained items in persons with both logopenic and semantic variants of PPA (Dial et al., 2019; Henry et al., 2019). Accordingly, in this study, we predicted improved naming of trained items as well as generalization to untrained items (with greater gains for trained items relative to untrained items) in participants with svPPA.

We examined treatment outcomes in relation to four hypothesis-driven families of ROIs grouped based on function and anatomical location. Specifically, we predicted that post-treatment naming accuracy would be related to the structural integrity of: a) bilateral temporal lobe structures, given their role in lexical and semantic processing (e.g., Binder, Desai, Graves, & Conant, 2009; Démonet et al., 1992; Graves, Grabowski, Mehta, & Gupta, 2008; Martin, Loring, Meador, & Lee, 1990) and based on previous findings in fMRI studies of treatment response in svPPA (Dressel et al., 2010; Jokel et al., 2016); b) bilateral parietal lobe structures, given their role in phonological processing (e.g., Baldo & Dronkers, 2006; Martin & Saffran, 1997; Yue, Martin, Hamilton, & Rose, 2019) and previous imaging studies of treatment response in svPPA (Dressel et al., 2010); c) bilateral frontal lobe structures, given their role in executive functions supporting lexical retrieval (e.g., Sharp, Scott, Cutler, & Wise, 2005; Turkeltaub, Messing, Norise, & Hamilton, 2011) and based on previous fMRI studies examining treatment response in svPPA and logopenic variant

PPA (lvPPA; Beeson et al., 2011; Dressel et al., 2010; Jokel et al., 2016); and d) bilateral hippocampus and para-hippocampal gyri (e.g., Corkin, 2002),[1] given their role in lexical retrieval (Hamamé Alario, Llorens, Liégeois-Chauvel, & Trébuchon-Da Fonseca, 2014) and treatment response in svPPA (e.g., Snowden & Neary, 2002). We did not have specific predictions for trained versus untrained sets of items.

2. Materials and methods

2.1. Participants

Participants were recruited through the Aphasia Research and Treatment Laboratory at the University of Texas at Austin (UT Austin) and the Memory and Aging Center at the University of California, San Francisco (UCSF). Written informed consent was obtained prior to participation, and study procedures were approved by the UT Austin and UCSF Institutional Review Boards. Nineteen individuals with a clinical diagnosis of svPPA (age in years: $M = 66.4$, $SD = 7.4$, range = 50.6 – 78.3) and Mini Mental State Exam (Folstein, Folstein, & Mchugh, 1975) scores greater than 15 were included in the current study (Henry et al., 2019). Confirmation of PPA diagnosis was made in accordance with current diagnostic criteria (Gorno-Tempini et al., 2011) following a comprehensive neurological, neuropsychological, and cognitive-linguistic assessment (Gorno-Tempini et al., 2004; Kramer et al., 2003). All participants met diagnostic criteria for svPPA, with poor confrontation naming and impaired single word comprehension in the presence of spared repetition, motor speech, and grammar. Demographic information and results of neuropsychological testing are presented in Table 2 (individual participant data are reported in Supplementary Table 1). The data reported in the current study were collected as part of a larger research project investigating the utility of lexical retrieval treatment in PPA (e.g., Henry et al., 2019).[2] In addition, data from 60 age-matched controls ($n = 30$ from UT Austin, age in years: $M = 65.4$, $SD = 4.8$, range = 60.1 – 79.7; $n = 30$ from UCSF, age in years: $M = 68.5$, $SD = 3.9$, range = 60.7 – 76.7) were used to identify regions of significant atrophy in the svPPA group using a two-sample t-test (Fig. 1; see Supplementary Materials).

Consistent with typical findings in svPPA (Gorno-Tempini et al., 2004, 2011; Mummery et al., 1999), structural brain imaging using VBM revealed atrophy in left inferolateral temporal, medial temporal, and orbitofrontal regions, and underlying white matter (see Supplementary Methods). Smaller clusters were also observed in right temporal, medial temporal, and frontal lobe structures, and underlying white matter, as well as bilaterally in the cerebellum.

2.2. Treatment materials and procedure

The lexical retrieval training (LRT) intervention implemented in the current study utilized a training cascade (modified from the Arizona Lexical Retrieval Cascade; Henry et al., 2013) designed to promote the use of self-cueing strategies capitalizing on residual semantic,

[1]Although traditional language models do not consider the hippocampus to be part of the language network, recent evidence suggests otherwise (e.g., Covington & Duff, 2016; Hamamé et al., 2014).

[2]Data from seven of the participants in the current study are presented in Henry et al. (2019), and data from the same seven participants and two additional participants are presented in Dial et al. (2019).

phonological, orthographic, and episodic knowledge. Four participants received LRT in person and 15 received LRT via telerehabilitation. Based on our recent work (Dial et al., 2019), mode of treatment delivery does not have a significant impact on treatment outcomes; therefore, this difference in treatment delivery modality is not considered further.

The data in the current study were derived from three variations of the treatment (LRT-1: $n = 3$, LRT-2: $n = 6$, and LRT-3: $n = 10$). The major components of LRT were consistent across the three variations. Importantly, the LRT protocol evolved over time, and was not modified based on participant characteristics. Systematic changes were implemented at various stages of the larger research program investigating language intervention in svPPA and lvPPA. The treatment protocols for all LRT variations involved the presentation of a personally relevant picture for naming (treatment target selection described below), followed by guided retrieval of semantic information, a second naming attempt, prompts for retrieval of phonemic and orthographic information (and provision of cues, if needed), spoken and written repetition of the target word, and retrieval of the spoken and written word from memory following a filled delay. All three LRT variations included daily home-based Copy and Recall practice (Beeson & Egnor, 2006) for items currently in treatment. For additional details on treatment procedures, see Supplementary Methods. Given the potential impact of LRT protocol variations on treatment outcomes, LRT protocol was included as a nuisance predictor in all statistical analyses (see section 2.4).

2.2.1. Treatment target selection—Items selected for treatment were tailored to each individual. Participants were asked to identify and take digital photographs of items that were difficult to name but functionally relevant (e.g., related to their home life, work, hobbies). Items that were unnamed on at least two of three pre-treatment probes, separated by at least a day, were eligible for treatment. Stock photos of common objects were used to supplement participant-provided items, if needed. Only items with residual semantic knowledge available to the participant were selected for treatment. During pre-treatment probes, if the participant indicated that they did not recognize an item and/or provided no relevant conceptual information in response to the picture of the item, either spontaneously or when queried, the item was excluded. Items eligible for treatment were randomly selected and divided into sets comprising five items (LRT-1: 4 trained sets, 1 untrained set; LRT-2 and LRT-3: 8 trained sets and 2 untrained sets) with all sets matched for several linguistic characteristics (i.e., word length, frequency, imageability, familiarity; Coltheart, 1981; Davies, 2009; Wilson, 1988).

2.3. VBM

2.3.1. Image acquisition—High resolution structural MRI scans were collected at UT Austin ($n = 9$ svPPA, $n = 30$ age-matched controls) and UCSF ($n = 10$ svPPA, $n = 30$ age-matched controls). Scans for PPA participants were obtained within two weeks of neuropsychological testing and between eight and 118 days prior to the treatment start date ($M = 28.7$ days, $SD = 6.2$ days). Scans were acquired on a Siemens 3T Skyra scanner equipped with a 64-channel head coil (UT Austin) or a Siemens 3T Trio scanner equipped with a 12-channel head coil (UCSF) using a T1-weighted MPRAGE sequence

(slice thickness = 1 mm, FOV read = 256 mm^2, matrix = 240 × 256, voxel size = 1 mm^3 isotropic, TR = 2300 ms, TE = 2.98 ms, flip angle = 9°).

2.3.2. Image preprocessing—All T1-weighted images were first visually assessed to ensure the absence of artifacts or excessive motion. The images were processed through the Computational Anatomy Toolbox (CAT12; http://www.neuro.uni-jena.de/cat/) in SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12) under MATLAB 2020a (Mathworks, Natick, MA). After bias-correction, the images were segmented into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF). The segmentation process was initialized using the standard SPM unified segmentation algorithm (Ashburner & Friston, 2005), followed by the CAT12 adaptive maximum a posteriori (AMAP) approach (Tohka, Zijdenbos, & Evans, 2004). The AMAP estimation is improved relative to the classic unified segmentation approach as it calculates partial volume estimates, thus minimizing partial volume effects. Segmented images were registered to MNI space using an affine deformation calculated using the high-dimensional diffeomorphic anatomical registration using exponentiated lie algebra (DARTEL) algorithm (Ashburner, 2007). Resulting images were modulated using the affine components and quality checked using visual inspection. Lastly, gray matter and white matter images were summed together using the imcalc function in SPM12 to obtain a map of brain parenchyma (Wilson, DeMarco et al., 2016; Wilson, Henry et al., 2010). Because atrophy affects both GM and WM, estimates of brain parenchyma tend to be more robust because they are less affected by the ability to detect the GM-WM boundary. The resulting images were smoothed with an 8 mm FWHM Gaussian kernel for whole-brain analyses and with a 4 mm FWHM Gaussian kernel for ROI analyses.

ROIs were defined using the Automated Anatomical Labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002) and tissue density was extracted from the brain parenchyma maps for each ROI using the SPM12 toolbox, MarsBaR (Brett, Anton, Valabregue, & Poline, 2002). We selected six temporal lobe ROIs (bilateral STG, MTG and ITG), four parietal lobe ROIs (bilateral angular gyri and SMG), six frontal lobe ROIs (bilateral IFG opercularis, IFG triangularis, and MFG), and four medial temporal lobe ROIs (bilateral hippocampi and para-hippocampal gyri). Examination of the segmentation results revealed that CSF was included in many of the hippocampal segments, leading to poor estimates of tissue density, especially for the most atrophic brains. As such, hippocampal segmentation was conducted in FIRST/FSL (Patenaude, Smith, Kennedy, & Jenkinson, 2011) and manually corrected by the first author and a trained research associate. Following manual correction, the first author and research associate met and reviewed the tracings, slice by slice, making corrections as needed. The fslstats function was then used to extract the hippocampal volumes (total number of voxels) for each participant.

2.4. Statistical analysis

2.4.1. Treatment outcomes—Treatment effects were examined using mixed-effects linear regression models implemented in the nlme package (Pinheiro, Bates, DebRoy, & Sarkar, 2021) in R (version 4.0.2). Naming accuracy (percent correct) was the outcome measure. For each of three pre-treatment naming attempts and two post-treatment naming attempts, accuracy data were averaged for trained sets and separately for untrained sets.

Thus, there were three pre-treatment and two-post treatment values in each model. Time point (pre-vs. post-treatment), Boston Naming Test score (BNT; Kaplan, Goodglass, & Weintraub, 1983), and LRT protocol, represented as two dummy coded variables (LRT-1: 0 or 1; LRT-2: 0 or 1), were included as fixed effects. BNT scores were included to control for severity of lexical retrieval impairment. Participant was included as a random intercept. Separate models were run for trained and untrained items. In addition, to directly compare treatment outcomes for trained and untrained items, a model was run that included the same fixed and random effects but also included an interaction term for time point and whether an item was trained or untrained. The data failed to meet the homogeneity of variance assumption, so cases were weighted by the inverse of the variance at each time point.

2.4.2. Whole-brain analysis—We examined the relation between the structural integrity of brain parenchyma at pre-treatment and treatment outcomes (change scores, calculated as average post-treatment score minus average pre-treatment score) for trained and untrained sets using a voxel-wise, whole-brain approach. Data were analyzed using the general linear regression model in SPM12 with change score as the outcome measure, scanner, BNT, and dummy-coded LRT protocol as covariates (LRT-1, 0 or 1; LRT-2, 0 or 1), and threshold for significance set at voxel-wise FWE-corrected $p < .05$ based on Gaussian random field theory. Head size was controlled for via global scaling by total intracranial volume (TIV).

2.4.3. ROI analysis—*A priori* hypotheses were investigated by examining treatment outcomes relative to the structural integrity of pre-defined ROIs (section 2.3.2) using mixed-effects linear regression. The outcome measure was naming accuracy (section 2.4.1). Fixed effects included scanner (UT Austin vs. UCSF), BNT,[3] LRT protocol (LRT-1, 0 or 1; LRT-2, 0 or 1), time point (pre-vs. post-treatment), TIV, ROI measure, and the interaction of time point and ROI measure. The ROI measure was operationally defined as tissue density for every ROI except the hippocampus, where volume in number of voxels was used. ROI tissue densities can only take values from 0 to 1, whereas hippocampal volumes can differ across individuals by thousands of voxels (left hippocampal volumes ranged from 1237 voxels to 3017 voxels in our sample). Because the ROI measures are on different scales, they were standardized. Participant was included as a random intercept. The effect of interest was the interaction of time point and ROI measure. To determine whether inclusion of this interaction term led to a significant improvement in the model, ANOVA was used to compare the “full” model to a “reduced” model that did not include the interaction term. A significant difference between the “full” and “reduced” model indicates that the structural integrity of the ROI is a significant neural correlate of post-treatment naming accuracy. Analyses were conducted separately for each ROI for trained and untrained sets.

[3]Our choice to use the Boston Naming Test to control for overall severity was motivated by the assumption that the Boston Naming Test would best estimate the severity of the lexical retrieval deficit. We ran additional analyses to confirm that our outcomes were not confounded with left anterior temporal lobe atrophy. In these analyses, we added left anterior temporal lobe (AAL region: superior temporal pole) tissue density to analyses for ROIs where the full model was significantly better than the reduced model. In all cases, the full model continued to significantly outperform the reduced model, suggesting that the findings reflect the unique contribution of the ROI of interest, not simply atrophy in the ATL.

We predicted that the structural integrity of an ROI would have no effect on pre-treatment naming accuracy because all participants were baselined to floor performance (see section 2.2.1. for details), whereas the structural integrity of an ROI would be related to higher post-treatment naming accuracy. To control for multiple comparisons, the threshold for statistical significance was set to false discovery rate (FDR) corrected $p < .05$ (Benjamini & Hochberg, 1995). FDR-correction was applied within each of the four families of regions (temporal ROIs, parietal ROIs, frontal ROIs, and medial temporal lobe ROIs) and for trained and untrained sets. The data failed to meet the homogeneity of variance assumption, so cases were weighted by the inverse of the variance at each time point.

3. Results

3.1. Treatment outcome results

Fig. 2 presents pre- and post-treatment accuracy for trained and untrained sets (averaged across the three pre-treatment and two post-treatment probes) for each participant (individual participant data for each of three pre-treatment and two post-treatment probes are presented in Supplementary Table 2). For untrained sets, one outlier was identified upon visual inspection of the quantile-quantile plot and removed from all subsequent analyses (Supplementary Figure 1). The main effect of time point was significant for both the trained and untrained models, such that individuals had significantly higher accuracy at post-treatment than at pre-treatment for trained ($\beta = 73.38$, SE = 4.58, $t(75) = 16.01$, $p < .001$, 95% CI [64.49, 82.27], $M_{pre} = 5.57$, $s_{pre} = 5.80$, $M_{post} = 78.90$, $s_{post} = 27.40$) and untrained sets ($\beta = 20.37$, SE = 4.10, $t(71) = 4.97$, $p < .001$, 95% CI [12.42, 28.32], $M_{pre} = 4.63$, $s_{pre} = 7.19$, $M_{post} = 25.00$, $s_{post} = 25.00$). The main effects of LRT-1 and LRT-2 were not significant for trained or untrained sets ($p > .05$). The main effect of BNT was not significant for trained sets ($p > .05$) but was significant for untrained sets ($\beta = .13$, SE = .05, $t(14) = 2.54$, $p = .023$, 95% CI [.02, .24]), suggesting that accurate naming of untrained sets diminishes with greater degree of lexical retrieval impairment. In the model comparing trained vs. untrained sets, the main effect of time was significant ($\beta = 124.91$, SE = 10.09, $t(159) = 12.38$, $p < .001$, 95% CI [105.37, 144.44], $M_{pre} = 4.95$, $s_{pre} = 6.43$, $M_{post} = 51.5$, $s_{post} = 37.2$) as was the interaction of time point and item type (trained vs. untrained; $\beta = -52.27$, SE = 6.38, $t(159) = -8.19$, $p < .001$, 95% CI [−64.62, −39.91]. The interaction reflects similar accuracy for trained and untrained items at pre-treatment and better accuracy for trained items than untrained items at post-treatment.

3.2. VBM results

There were no significant findings in the whole-brain, voxel-wise analysis examining the relation between the structural integrity of brain parenchyma at pre-treatment and treatment outcomes after correction for multiple comparisons. As such, we conducted a post hoc analysis wherein we examined outcomes with an uncorrected threshold set at $p < .005$ (see Supplementary Figure 2). For trained items, regions significantly related to treatment outcomes included left medial temporal lobe structures (hippocampus and para-hippocampal), bilateral parietal cortex (SMG, angular gyrus, superior parietal lobule), and right inferior frontal cortex. For untrained items, the left hippocampus was significantly related to treatment outcomes, as was bilateral parietal cortex.

3.3. ROI results

The results of ANOVAs comparing the "full" and "reduced" models are presented in Table 3. The inclusion of the interaction of time point and ROI measure improved model fit for the left SMG, left angular gyrus, and left hippocampus (FDR-corrected *P*'s < .05) for trained sets, and the left hippocampus for untrained sets (FDR-corrected $p < .05$). Parameters for models where the interaction term improved fit are presented in Table 4. Significant, positive beta weights were observed for the interaction of ROI measure and time point for each of these models (left SMG, left angular gyrus, and left hippocampus for trained sets, left hippocampus for untrained sets). These results indicate that greater structural integrity within these regions was related to better post-treatment naming accuracy.

4. Discussion

The evidence base documenting the value of restitutive language intervention in semantic variant primary progressive aphasia (svPPA) has grown in the two decades following the seminal work of Graham and colleagues. Although research supports the claim that individuals with svPPA can relearn targeted vocabulary, the cognitive and neural bases of improved word retrieval remain poorly understood. The goal of the current study was to identify neural regions whose structural integrity at pre-treatment was associated with post-treatment naming accuracy. We examined structural imaging metrics at pre-treatment in relation to treatment outcomes following a strategic lexical retrieval intervention in 19 individuals with svPPA. The behavioral findings demonstrate significant improvements for both trained and untrained items, with significantly larger gains for trained relative to untrained items, replicating our previous work (Henry et al., 2019) with a larger sample ($n = 9$ original study, $n = 10$ additional participants) and further confirming the utility of this intervention.

This is the largest study to-date that examines neural structures supporting improved naming following treatment in svPPA. Moreover, researchers have suggested a role for the hippocampus in supporting word relearning in svPPA (e.g., Graham et al., 1999; Snowden & Neary, 2002), but this is the first study to directly evaluate the relation between hippocampal volume and treatment outcomes in this population. Region of interest (ROI) analyses revealed that the structural integrity of the left supramarginal gyrus (SMG) and left angular gyrus was related to treatment outcomes for trained sets, and the left hippocampus was related to treatment outcomes for both trained and untrained sets; uncorrected VBM analyses provided converging evidence for these results. Taken together, these findings bolster the evidence base for restitutive interventions in this population and indicate a critical role for the left SMG, angular gyrus, and hippocampus in supporting treatment outcomes following lexical retrieval training in svPPA. In the following paragraphs, we discuss the potential role of these brain regions in supporting positive response to naming treatment in individuals with svPPA, with a focus on regions that were identified in both the ROI analyses and uncorrected VBM analyses.

The left SMG has been shown to support improved word retrieval post-treatment in stroke-induced aphasia, where increased left SMG activity has been observed following treatment that emphasizes phonological strategies for word retrieval (Léger et al., 2002;

Rochon et al., 2010; van Hees et al., 2014). Marcotte and Ansaldo (2010) also observed a relation between activity in the left inferior parietal lobe and lexical retrieval at pre- and post-treatment in nonfluent variant PPA. In svPPA, functional connectivity between left SMG and IFG is relatively preserved, reflecting relatively spared articulatory-phonological processing (Battistella et al., 2019). Moreover, individuals with svPPA may be described as "hyper-phonological," relying more heavily on phonological processing as semantic knowledge deteriorates. In the current study, phonological cueing strategies were embedded in the lexical retrieval training cascade, and the use of these phonological strategies may have been supported by the left SMG. In line with these observations, the degree of preservation of phonological processing, supported by left SMG, may be a key factor in lexical retrieval treatment outcomes in svPPA.

Contiguous with left SMG, the left angular gyrus is thought to support both phonological and semantic processing (Binder et al., 2009; Ripamonti et al., 2018). The integrity of the angular gyrus has been associated with phonological working memory in stroke-induced aphasia, with lesions in this region linked to single-word repetition deficits (Ripamonti et al., 2018). In the current study, word repetition was a critical component of treatment, as individuals were required to repeat target words during the training cascade. Recent work has also revealed spared functional connectivity between the left angular gyrus and IFG in svPPA (as was seen with left SMG), again supporting a relative preservation of articulatory-phonological processing (Battistella et al., 2019). With regard to semantic processing, Binder et al. (2009) have argued that the angular gyrus is critical for integration of complex concepts as well as retrieval of semantic information. Moreover, stronger connectivity between the left angular gyrus and middle temporal gyrus (MTG) is associated with better single-word comprehension in individuals with svPPA (Battistella et al., 2019). In the current study, systematic retrieval of semantic information was incorporated to promote self-cueing of target words. The angular gyrus may support the use of phonological and semantic cues to facilitate word retrieval in individuals with svPPA.

We also observed a significant association between the left hippocampus and treatment outcomes for trained and untrained items in the current study. The hippocampus has been shown to support word re-learning in stroke-induced aphasia (Meinzer et al., 2010; Menke et al., 2009), and researchers have claimed that, in svPPA, the burden for storing and retrieving lexical representations may gradually shift from semantic memory, supported by relatively atrophic neocortical structures, to episodic memory, supported by relatively preserved medial temporal lobe structures, including the hippocampus (Graham et al., 1999, 2001; Hoffman et al., 2015; Mayberry et al., 2011; Snowden & Neary, 2002). However, this view of neurally-dissociated episodic and semantic memory stores may be an oversimplification. In fact, the hippocampus has been implicated in the acquisition and retrieval of semantic memories (e.g., Duff, Covington, Hilverman, & Cohen, 2020; Gabrieli, Cohen, & Corkin, 1988), and recent functional neuroimaging work in svPPA has revealed recruitment of the hippocampus during an object knowledge task (Canu et al., 2020).

In the context of the current study, the hippocampus may support the use of semantic and episodic cues to facilitate word retrieval in individuals with svPPA. Along these lines, we posit an additional mechanism underlying the association between left hippocampal volume

and treatment outcomes. Specifically, better episodic memory, supported by the structural integrity of hippocampal structures, may facilitate application of rehearsed lexical retrieval strategies during attempts to retrieve words. That is, in addition to supporting retrieval of the word form itself, the hippocampus may support recall and utilization of the strategic aspects of the intervention, which could, in turn, facilitate word retrieval for trained and untrained targets. The significant relation between left but not right hippocampal volume and treatment outcomes may be attributed to the privileged connection between the left hippocampus and the left lateralized language system (Bonner-Jackson, Mahmoud, Miller, & Banks, 2015; Breitenstein et al., 2005).

Unlike previous studies, we did not find a significant association between treatment outcomes and the structural integrity of frontal (Beeson et al., 2011; Dressel et al., 2010; Jokel et al., 2016) or temporal ROIs (Dressel et al., 2010; Henry et al., 2018; Jokel et al., 2016; Marcotte & Ansaldo, 2010), nor in right hemisphere language homologues (although we did observe some evidence for right hemisphere homologues, primarily in frontal and parietal cortex, in our uncorrected VBM analysis). In several of the previous studies, it was only at post-treatment that significant activation was observed in these regions (Dressel et al., 2010; Jokel et al., 2016; Marcotte & Ansaldo, 2010), and by examining baseline structural MRI in relation to treatment response, we are not able to explore changes in network dynamics that support word-retrieval gains. Additionally, these previous studies utilized voxel-wise approaches, observing relatively small clusters that were related to treatment outcomes. AAL regions are relatively large by comparison and may not have been sensitive enough to detect smaller clusters. Moreover, prior studies did not control for multiple comparisons in their voxel-wise analysis, and thus, the results should be interpreted with caution. We attribute the lack of findings in the temporal lobe to the nature of selected stimuli. Specifically, all words included in trained and untrained sets were selected *if and only if* residual semantic knowledge was demonstrated in combination with a failed naming attempt on at least two of three pre-treatment probes. Thus, the experimental design manipulated pre-treatment naming accuracy to near floor across all participants, with evidence of residual semantic knowledge for every item included in trained and untrained sets. This manipulation may have minimized variability in the participants' ability to draw upon semantic information, since residual semantic information was available for every item. Lastly, it may be the case that we would see a role for temporal lobe structures if we examined long-term maintenance of gains, as some work has suggested that semantic knowledge is most critical for maintenance of gains beyond the immediate post-treatment period (e.g., Jokel et al., 2010).

4.1. Limitations and future directions

The current study was limited by the relatively small sample size, which likely hampered our ability to detect effects at the whole brain level. Other studies seeking to identify neural correlates of treatment-induced changes have restricted analysis to areas of significant atrophy relative to a control group (e.g., Meyer et al., 2017). This approach may attenuate the multiple comparisons problem by restricting analyses to a smaller number of voxels/regions. However, this approach precludes examination of relatively spared regions that could support treatment-induced changes. As such, we opted to utilize the whole brain

for our VBM analysis, and to supplement this analysis with the hypothesis-driven ROI approach, which mitigates the sample size issue.

In addition, given the heterogeneity that is observed in patients with severe brain abnormalities, the relatively small sample size increases the risk of identifying patterns that may not generalize to other individuals with svPPA. Thus, future research will benefit from larger samples to confirm and extend the findings of the current study. Relatedly, the ROIs derived from the AAL atlas are relatively large and therefore are likely to support multiple cognitive-linguistic processes. We elected to use these ROIs given the lack of previous research to motivate more granular predictions coupled with the relatively small sample size. The inclusion of a greater number of more constrained regions would have contributed to concerns regarding multiple comparisons. Additionally, our approach did not examine structural or functional connectivity between brain regions or evaluate activation of brain regions during language tasks. Future research should examine additional imaging modalities (e.g., fMRI and DTI) relative to treatment outcomes to determine whether these measures or changes therein may further elucidate the neural mechanisms supporting treatment response. Given that the structural integrity of the left SMG, angular gyrus, and hippocampus were related to improved post-treatment naming for trained items in the current study, targets for future functional and structural connectivity studies may include the hippocampal-parietal episodic memory network (Vincent et al., 2006) and the inferior longitudinal fasciculus (Maller et al., 2019), which connects the inferior parietal lobe to the hippocampus. Lastly, given that behavioral measures are more accessible to speech-language pathologists than neuroimaging in routine clinical practice, it will be important to consider the extent to which neural measures provide unique information to guide the selection of treatment approach(es) above-and-beyond commonly available behavioral indices. A larger sample would allow for the inclusion of additional cognitive-linguistic measures in the models, which would provide insight on this issue, and would allow for a more direct examination of the cognitive functions supporting improved naming following treatment.

Although the findings of the current study cannot definitively identify the cognitive mechanisms supporting naming gains following speech-language intervention, they do encourage the development and optimization of language interventions that emphasize the role of phonological processing, preserved semantic knowledge, and episodic memory in svPPA. This study may also inform treatment-candidacy decision-making. For example, behavioral or neural indicators of impaired episodic memory and phonological processing may warrant careful consideration as indicators of potential treatment benefit for this type of intervention.

5. Conclusion

Semantic variant PPA is characterized by a progressive loss of semantic knowledge. Due to the unique cognitive-linguistic profile observed in svPPA, particularly the loss of semantic knowledge, there has been skepticism regarding the utility of lexical retrieval intervention in this population. However, there is accumulating evidence supporting the benefit of language treatment in individuals with svPPA. It is generally accepted that residual semantic knowledge is critical for successful treatment for anomia, but additional cognitive and

neural processes supporting improved naming of trained items and generalization to untrained items remain poorly understood. Thus, we sought to identify baseline neural structures associated with recovered naming ability in svPPA. Post-treatment naming accuracy was related to the structural preservation of the left SMG, angular gyrus, and hippocampus for trained items, and the left hippocampus for untrained items. These results provide converging evidence that individuals with svPPA can benefit from treatment for anomia, and treatment-related gains may be supported by relatively spared left SMG (phonological processing), left angular gyrus (phonological and semantic processing), and left hippocampus (episodic, context-based memory). Although we did not directly examine cognitive predictors of treatment outcomes, the findings of this study provide a window into the cognitive mechanisms that support treatment in svPPA and serve as a theoretical basis motivating future studies. Future research should examine treatment outcomes in relation to cognitive predictors, pre-treatment functional and structural connectivity, as well as changes in network dynamics following speech-language intervention, in order to further elucidate the cognitive and neural mechanisms underlying naming treatment response in svPPA and related disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability

The data that has been used is confidential.

references

Agosta F, Henry RG, Migliaccio R, Neuhaus J, Miller BL, Dronkers NF, et al. (2010). Language networks in semantic dementia. Brain: a Journal of Neurology, 133(1), 286–299. 10.1093/brain/awp233 [PubMed: 19759202]

Alvarez P, & Squire LR (1994). Memory consolidation and the medial temporal lobe: A simple network model. Neurobiology, 91, 7041–7045. http://www.pnas.org/content/pnas/91/15/7041.full.pdf.

Ashburner J (2007). A fast diffeomorphic image registration algorithm. Neuroimage, 38(1), 95–113. 10.1016/j.neuroimage.2007.07.007 [PubMed: 17761438]

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

Baldo JV, & Dronkers NF (2006). The role of inferior parietal and inferior frontal cortex in working memory. Neuropsychology, 20(5), 529–538. 10.1037/0894-4105.20.5.529 [PubMed: 16938015]

Battistella G, Henry M, Gesierich B, Wilson SM, Borghesani V, Shwe W, et al. (2019). Differential intrinsic functional connectivity changes in semantic variant primary progressive aphasia. NeuroImage: Clinical, 22, Article 101797. 10.1016/j.nicl.2019.101797 [PubMed: 31146321]

Beales A, Cartwright J, Whitworth A, & Panegyres PK (2016). Exploring generalisation processes following lexical retrieval intervention in primary progressive aphasia. International Journal of Speech-Language Pathology, 18(3), 299–314. 10.3109/17549507.2016.1151936 [PubMed: 27063691]

Beeson PM, & Egnor H (2006). Combining treatment for written and spoken naming. Journal of the International Neuropsychological Society, 12(6), 816–827. 10.1017/S1355617706061005 [PubMed: 17064445]

Beeson PM, King RM, Bonakdarpour B, Henry ML, Cho H, & Rapcsak SZ (2011). Positive effects of language treatment for the logopenic variant of primary progressive aphasia. Journal of Molecular Neuroscience, 45(3), 724–736. 10.1007/s12031-011-9579-2 [PubMed: 21710364]

Beeson PM, & Rising K (2010). Arizona battery for reading and spelling

Benjamini Y, & Hochberg Y (1995). Controlling the false discovery rate: A practical and powerful approach to multiple testing. Source: Journal of the Royal Statistical Society. Series B (Methodological), 57(Issue 1).

Best W, Herbert R, Hickin J, Osborne F, & Howard D (2010). Phonological and orthographic facilitation of wordretrieval in aphasia: Immediate and delayed effects. Aphasiology, 16(1–2), 151–168. 10.1080/02687040143000483

Best W, Howard D, Bruce C, & Gatehouse C (2008). A treatment for anomia combining semantics, phonology and orthography. In Language disorders in children and adults: Psycholinguistic approaches to therapy (pp. 102–129). London, England: Whurr Publishers. 10.1002/9780470699157.ch7.

Bier N, Macoir J, Gagnon L, Van der Linden M, Louveaux SS, & Desrosiers J (2009). Known, lost, and recovered: Efficacy of formal-semantic therapy and spaced retrieval method in a case of semantic dementia. Aphasiology, 23(2), 210–235. 10.1080/00207590801942906

Binder JR, Desai RH, Graves WW, & Conant LL (2009). Where is the semantic system? A critical review and meta-analysis of 120 functional neuroimaging studies. Cerebral Cortex, 19(12), 2767–2796. 10.1093/cercor/bhp055 [PubMed: 19329570]

Bonner-Jackson A, Mahmoud S, Miller J, & Banks SJ (2015). Verbal and non-verbal memory and hippocampal volumes in a memory clinic population. Arthritis Research & Therapy, 7(1), 61. 10.1186/s13195-015-0147-9

Boyle M (2004). Semantic feature analysis treatment for anomia in two fluent aphasia syndromes. The American Journal of Surgical Pathology, 13(3), 236–249. 10.1044/1058-0360(2004/025

Boyle M, & Coelho CA (1995). Application of semantic feature analysis as a treatment for aphasic dysnomia. The American Journal of Surgical Pathology, 4(4), 94–98. 10.1044/1058-0360.0404.94

Breining BL, Lala T, Martıńez Cuitiño M, Manes F, Peristeri E, Tsapkini K, … Hillis AE (2015). A brief assessment of object semantics in primary progressive aphasia. Aphasiology, 29(4), 488–505.

Breitenstein C, Jansen A, Deppe M, Foerster AF, Sommer J, Wolbers T, et al. (2005). Hippocampus activity differentiates good from poor learners of a novel lexicon. Neuroimage, 25(3), 958–968. 10.1016/j.neuroimage.2004.12.019 [PubMed: 15808996]

Brett M, Anton JL, Valabregue R, & Poline JB (2002). Region of interest analysis using an SPM toolbox. Neuroimage, 16(2).

Bruce C, & Howard D (1987). Computer-generated phonemic cues: An effective aid for naming in aphasia. International Journal of Language & Communication Disorders, 22(3), 191–201. 10.3109/13682828709019862

Cadório I, Lousada M, Martins P, & Figueiredo D (2017). Generalization and maintenance of treatment gains in primary progressive aphasia (PPA): A systematic review. International journal of language & communication disorders, 52(5), 543–560. [PubMed: 28120406]

Canu E, Bessi V, Calderaro D, Simoni D, Castelnovo V, Leocadi M, et al. (2020). Early functional MRI changes in a prodromal semantic variant of primary progressive aphasia: A longitudinal case report. Journal of Neurology, 267(10), 3100–3104. 10.1007/s00415-020-10053-9 [PubMed: 32651673]

Carthery-Goulart MT, Silveira ADCD, Machado TH, Mansur LL, Parente MADMP, Senaha MLH, … Nitrini R (2013). Nonpharmacological interventions for cognitive impairments following primary progressive aphasia: A systematic review of the literature. Dementia & Neuropsychologia, 7, 122–131. [PubMed: 29213828]

Cerami C, Dodich A, Greco L, Iannaccone S, Magnani G, Marcone A, et al. (2017). The role of single-subject brain metabolic patterns in the early differential diagnosis of primary progressive aphasias and in prediction of progression to dementia. Journal of Alzheimer's Disease, 55, 183–197. 10.3233/JAD-160682

Coelho CA, McHugh RE, & Boyle M (2000). Semantic feature analysis as a treatment for aphasic dysnomia: A replication. Aphasiology, 14(2), 133–142. 10.1080/026870300401513

Coltheart M (1981). The mrc psycholinguistic database. The Quarterly Journal of Experimental Psychology Section A, 33(4), 497–505. 10.1080/14640748108400805

Corkin S (2002). What's new with the amnesic patient H.M.?, 3 www.nature.com/reviews/neuro.

Cotelli M, Manenti R, Ferrari C, Gobbi E, Macis A, & Cappa S (2019). Effectiveness of language training and non-invasive brain stimulation on oral and written naming performancce in primary progressive aphasia: A meta-analysis and systematic review. Neuroscience and Biobehavioral Reviews, 108, 498–525. 10.1016/j.neubiorev.2019.12.003 [PubMed: 31811834]

Cotelli M, Manenti R, Paternicó D, Cosseddu M, Brambilla M, Petesi M, et al. (2016). Grey matter density predicts the improvement of naming abilities after tDCS intervention in agrammatic variant of primary progressive aphasia. Brain Topography, 29(5), 738–751. 10.1007/s10548-016-0494-2 [PubMed: 27194245]

Covington NV, & Duff MC (2016). Expanding the language network: Direct contributions from the Hippocampus. In Trends in cognitive sciences (Vol. 20, pp. 869–870). Elsevier. 10.1016/j.tics.2016.10.006, 12. [PubMed: 27814958]

Davies M (2009). The 385þ million word Corpus of Contemporary American English (1990e2008þ): Design, architecture, and linguistic insights. International Journal of Corpus Linguistics, 14(2), 159–190. 10.1075/ijcl.14.2.02dav

Dell GS, & O'Seaghdha PG (1992). Stages of lexical access in language production. Cognition, 42(1–3), 287–314. [PubMed: 1582160]

Dell GS, Schwartz MF, Martin N, Saffran EM, & Gagnon DA (1997). Lexical access in aphasic and nonaphasic speakers. Psychological review, 104(4), 801. [PubMed: 9337631]

Démonet JF, Chollet F, Ramsay S, Cardebat D, Nespoulous JL, Wise R, et al. (1992). The anatomy of phonological and semantic processing in normal subjects. Brain: a Journal of Neurology, 115(6), 1753–1768. 10.1093/brain/115.6.1753 [PubMed: 1486459]

Dial HR, Hinshelwood HA, Grasso SM, Hubbard HI, Gorno-Tempini M-L, & Henry ML (2019). Investigating the utility of teletherapy in individuals with primary progressive aphasia. Clinical Interventions in Aging, 14. 10.2147/CIA.S178878

Dressel K, Huber W, Frings L, Kümmerer D, Saur D, Mader I, et al. (2010). Model-oriented naming therapy in semantic dementia: A single-case fMRI study. Aphasiology, 24(12), 1537–1558. 10.1080/02687038.2010.500567

Duff MC, Covington NV, Hilverman C, & Cohen NJ (2020). Semantic memory and the Hippocampus: Revisiting, reaffirming, and extending the reach of their critical relationship. In Frontiers in human neuroscience (Vol. 13) Frontiers Media S.A. 10.3389/fnhum.2019.00471.

Folstein MF, Folstein SE, & Mchugh PR (1975). MINI-MENTAL state: A practical method for grading the cognitive state of patients for the clinician. In Journal of psychiatric research (Vol. 12)Pergamon Press. http://home.uchicago.edu/~tmurray1/research/articles/printed and read/mini mental state_a practical method for grading the cognitive state of patients for the clinician.pdf.

Frattali C (2004). An errorless learning approach to treating dysnomia in frontotemporal dementia. ANCDS Bulletin Board (xiexxiv)

Gabrieli JDE, Cohen NJ, & Corkin S (1988). The impaired learning of semantic knowledge following bilateral medial temporal-lobe resection. BRAIN AND COGNITION, 7.

Goodglass H (1998). Stages of lexical retrieval. Aphasiology, 12(4–5), 287–298.

Gorno-Tempini ML, Dronkers NF, Rankin KP, Ogar JM, Phengrasamy L, Rosen HJ, et al. (2004). Cognition and anatomy in three variants of primary progressive aphasia. Annals of Neurology, 55(3), 335–346. 10.1002/ana.10825. [PubMed: 14991811]

Gorno-Tempini M, Hillis A, Weintraub S, Kertesz A, Mendez M, Cappa S, et al. (2011). Classification of primary progressive aphasia and its variants. Neurology, 76(11), 1006–1014. 10.1212/WNL.0b013e31821103e6 [PubMed: 21325651]

Graham KS, & Hodges JR (1997). Differentiating the roles of the hippocampal complex and the neocortex in long-term memory storage: Evidence from the study of semantic dementia and Alzheimer's disease. Neuropsychology, 11(1), 77–89. 10.1037/0894-4105.11.1.77 [PubMed: 9055272]

Graham KS, Patterson K, Pratt KH, & Hodges JR (1999). Relearning and subsequent forgetting of semantic category exemplars in a case of semantic dementia. Neuropsychology, 13(3), 359–380. 10.1037/0894-4105.13.3.359 [PubMed: 10447298]

Graham KS, Patterson K, Pratt KH, & Hodges JR (2001). Can repeated exposure to "forgotten" vocabulary help alleviate word-finding difficulties in semantic dementia? An illustrative case study. Neuropsychological Rehabilitation, 11(3e4), 429–454. 10.1080/09602010042000060

Graves WW, Grabowski TJ, Mehta S, & Gupta P (2008). The left posterior superior temporal gyrus participates specifically in accessing lexical phonology. Journal of Cognitive Neuroscience, 20(9), 1698–1710. 10.1162/jocn.2008.20113 [PubMed: 18345989]

Hamamé CM, Alario FX, Llorens A, Liégeois-Chauvel C, & Trébuchon-Da Fonseca A (2014). High frequency gamma activity in the left hippocampus predicts visual object naming performance. Brain and Language, 135, 104–114. 10.1016/j.bandl.2014.05.007 [PubMed: 25016093]

Henry M, Beeson P, & Rapcsak S (2008). Treatment for lexical retrieval in progressive aphasia. Aphasiology, 22(7–8), 826–838. 10.1080/02687030701820055 [PubMed: 20862210]

Henry ML, Hubbard HI, Grasso SM, Dial HR, Beeson PM, Miller BL, et al. (2019). Treatment for word retrieval in semantic and logopenic variants of primary progressive aphasia: Immediate and long-term outcomes. Journal of Speech, Language, and Hearing Research: JSLHR, 62(8). 10.1044/2018_JSLHR-L-18-0144

Henry ML, Hubbard HI, Grasso SM, Mandelli ML, Wilson SM, Sathishkumar MT, et al. (2018). Retraining speech production and fluency in non-fluent/agrammatic primary progressive aphasia. Brain: a Journal of Neurology, 141, 1799–1814. 10.1093/brain/awy101 [PubMed: 29718131]

Henry ML, Rising K, DeMarco AT, Miller BL, Gorno-Tempini ML, & Beeson PM (2013). Examining the value of lexical retrieval treatment in primary progressive aphasia: Two positive cases. Brain and Language, 127(2), 145–156. 10.1016/j.bandl.2013.05.018 [PubMed: 23871425]

Henry ML, Wilson SM, Babiak MC, Mandell ML, Beeson PM, Miller ZA, et al. (2016). Phonological processing in primary progressive aphasia. Journal of Cognitive Neuroscience, 28(2), 210–222. 10.1162/jocn_a_00901 [PubMed: 26544920]

Heredia CG, Sage K, Lambon Ralph MA, & Berthier ML (2009). Relearning and retention of verbal labels in a case of semantic dementia. Aphasiology, 23(2), 192–209. 10.1080/02687030801942999

Hoffman P, Clarke N, Jones RW, & Noonan KA (2015). Vocabulary relearning in semantic dementia: Positive and negative consequences of increasing variability in the learning experience. Neuropsychologia, 76, 240–253. 10.1016/j.neuropsychologia.2015.01.015 [PubMed: 25585251]

Jefferies E, Jones RW, Bateman D, & Ralph MAL (2005). A semantic contribution to nonword recall? Evidence for intact phonological processes in semantic dementia. Cognitive Neuropsychology, 22, 183–212. 10.1080/02643290442000068 [PubMed: 21038246]

Jokel R, & Anderson ND (2012). Quest for the best: Effects of errorless and active encoding on word re-learning in semantic dementia. Neuropsychological Rehabilitation, 22(2), 187–214. 10.1080/09602011.2011.639626 [PubMed: 22250922]

Jokel R, Kielar A, Anderson ND, Black SE, Rochon E, Graham S, et al. (2016). Behavioural and neuroimaging changes after naming therapy for semantic variant primary progressive aphasia. Neuropsychologia, 89, 191–216. 10.1016/j.neuropsychologia.2016.06.009 [PubMed: 27297727]

Jokel R, Rochon E, & Anderson ND (2010). Errorless learning of computer-generated words in a patient with semantic dementia. Neuropsychological Rehabilitation, 20(1), 16–41. 10.1080/09602010902879859 [PubMed: 19504403]

Jokel R, Rochon E, & Leonard C (2002). Therapy for anomia in semantic dementia. Brain and Cognition, 49(2), 241–244. https://europepmc.org/article/med/15259401. [PubMed: 15259401]

Jokel R, Rochon E, & Leonard C (2006). Treating anomia in semantic dementia: Improvement, maintenance, or both? Neuropsychological Rehabilitation, 16(3), 241–256. 10.1080/09602010500176757 [PubMed: 16835150]

Kaplan E, Goodglass H, & Weintraub S (1983). In Boston naming test Febiger L (ed.).

Kertesz A (2007). Western aphasia battery–revised

Knopman DS, Kramer JH, Boeve BF, Caselli RJ, Graff-Radford NR, Mendez MF, … Mercaldo N (2008). Development of methodology for conducting clinical trials in frontotemporal lobar degeneration. Brain: a Journal of Neurology, 131(11), 2957–2968. 10.1093/brain/awn234 [PubMed: 18829698]

Kramer JH, Jurik J, Sharon JS, Rankin KP, Rosen HJ, Johnson JK, et al. (2003). Distinctive neuropsychological patterns in frontotemporal dementia, semantic dementia, and Alzheimer disease. Cognitive and Behavioral Neurology: Official Journal of the Society for Behavioral and Cognitive Neurology, 16(4), 211–218. https://journals.lww.com/cogbehavneurol/Abstract/2003/12000/Distinctive_Neuropsychological_Patterns_in.2.aspx. [PubMed: 14665820]

Léger A, Démonet J-F, Ruff S, Aithamon B, Touyeras B, Puel M, et al. (2002). Neural substrates of spoken language rehabilitation in an aphasic patient: An fMRI study 10.1006/nimg.2002.1238

Levelt WJ, Roelofs A, & Meyer AS (1999). A theory of lexical access in speech production. The Behavioral and Brain Sciences, 22(1), 1–38. [PubMed: 11301520]

Lorenz A, & Nickels L (2007). Orthographic cueing in anomic aphasia: How does it work? Aphasiology, 21(6–8), 670–686.

Maller JJ, Welton T, Middione M, Callaghan FM, Rosenfeld JV, & Grieve SM (2019). Revealing the hippocampal connectome through super-resolution 1150-direction diffusion MRI. Scientific Reports, 9(1), 1–13. 10.1038/s41598-018-37905-9 [PubMed: 30626917]

Marcotte K, Iné Ansaldo A, & Mary Road Q (2010). The neural correlates of semantic feature analysis in chronic aphasia: Discordant patterns according to the etiology 10.1055/s-0029-1244953

Martin RC, Loring DW, Meador KJ, & Lee GP (1990). The effects of lateralized temporal lobe dysfunction on normal and semantic word fluency. Neuropsychologia, 28(8), 823–829. 10.1016/0028-3932(90)90006-A [PubMed: 2247208]

Martin N, & Saffran EM (1997). Language and auditory-verbal short-term memory impairments : Evidence for common underlying processes language and. In Cognitive neuropsychology (Vol. 14). 10.1080/026432997381402

Mayberry EJ, Sage K, Ehsan S, & Lambon Ralph MA (2011a). An emergent effect of phonemic cueing following relearning in semantic dementia. Aphasiology, 25(9), 1069–1077. 10.1080/02687038.2011.575203

Mayberry EJ, Sage K, Ehsan S, & Lambon Ralph MA (2011b). Relearning in semantic dementia reflects contributions from both medial temporal lobe episodic and degraded neocortical semantic systems: Evidence in support of the complementary learning systems theory. Neuropsychologia, 49(13), 3591–3598. 10.1016/j.neuropsychologia.2011.09.010 [PubMed: 21939679]

Mcclelland JL, Mcnaughton BL, & O ‘reilly RC (1995). Why there are complementary learning systems in the Hippocampus and neocortex: Insights from the successes and failures of connectionist models of learning and memory. Psychological Review, 102(3), 419–457. https://pdfs.semanticscholar.org/57f1/16f3e6780424463cc8416ce755a72f873aa9.pdf. [PubMed: 7624455]

Meinzer M, Mohammadi S, Kugel H, Schiffbauer H, Flöel A, Albers J, et al. (2010). Integrity of the hippocampus and surrounding white matter is correlated with language training success in aphasia. Neuroimage, 53(1), 283–290. 10.1016/j.neuroimage.2010.06.004 [PubMed: 20541018]

Menke R, Meinzer M, Kugel H, Deppe M, Baumgärtner A, Schiffbauer H, et al. (2009). Imaging short- and long-term training success in chronic aphasia. BMC Neuroscience, 10(1), 118. 10.1186/1471-2202-10-118 [PubMed: 19772660]

Mesulam M (1982). Slowly progressive aphasia without generalized dementia. Annals of Neurology, 11, 592–598. [PubMed: 7114808]

Mesulam MM (2001). Primary progressive aphasia. In Annals of neurology (Vol. 49). 10.1002/ana.21451.A

Meyer AM, Faria AV, Tippett DC, Hillis AE, & Friedman RB (2017). The relationship between baseline volume in temporal areas and post-treatment naming accuracy in primary progressive aphasia. Aphasiology, 31(9), 1059–1077. 10.1080/02687038.2017.1296557 [PubMed: 29628604]

Meyer AM, Snider SF, Eckmann CB, & Friedman RB (2015). Prophylactic treatments for anomia in the logopenic variant of primary progressive aphasia: Cross-language transfer. Aphasiology, 29, 1062–1081. 10.1080/02687038.2015.1028327 [PubMed: 26257456]

Mummery CJ, Patterson K, Wise RJS, Vandenbergh R, Price CJ, & Hodges JR (1999). Disrupted temporal lobe connections in semantic dementia. Brain: a Journal of Neurology, 122(1), 61–73. 10.1093/brain/122.1.61 [PubMed: 10050895]

Newhart M, Davis C, Kannan V, Heidler-Gary J, Cloutman L, Hillis AE, et al. (2009). Therapy for naming deficits in two variants of primary progressive aphasia. Aphasiology, 23(7–8), 823–834. 10.1080/02687030802661762

Paek EJ, Murray LL, & Newman SD (2021). Effects of concurrent action and object naming treatment on naming skills and functional brain activation patterns in primary progressive aphasia: An fMRI study with a case-series design. Brain and Language, 218, Article 104950. [PubMed: 33836414]

Parnwell EC (1977). Oxford English picture dictionary Oxford University Press.

Patenaude B, Smith SM, Kennedy DN, & Jenkinson M (2011). A Bayesian model of shape and appearance for subcortical brain segmentation. Neuroimage, 56(3), 907–922. 10.1016/j.neuroimage.2011.02.046 [PubMed: 21352927]

Pinheiro J, Bates D, DebRoy S, & Sarkar D (2021). nlme: Linear and nonlinear mixed effects models

Ripamonti E, Frustaci M, Zonca G, Aggujaro S, Molteni F, & Luzzatti C (2018). Disentangling phonological and articulatory processing: A neuroanatomical study in aphasia. Neuropsychologia, 121, 175–185. 10.1016/j.neuropsychologia.2018.10.015 [PubMed: 30367847]

Robinson S, Druks J, Hodges J, & Garrard P (2009). The treatment of object naming, definition, and object use in semantic dementia: The effectiveness of errorless learning. Aphasiology, 23(6), 749–775. 10.1080/02687030802235195

Rochon E, Leonard C, Burianova H, Laird L, Soros P, Graham S, et al. (2010). Neural changes after phonological treatment for anomia: An fMRI study. Brain and Language, 114(3), 164–179. 10.1016/j.bandl.2010.05.005 [PubMed: 20547416]

Savage SA, Ballard KJ, Piguet O, & Hodges JR (2013). Bringing words back to mind - improving word production in semantic dementia. Cortex; a Journal Devoted To the Study of the Nervous System and Behavior, 49(7), 1823–1832. 10.1016/j.cortex.2012.09.014 [PubMed: 23127420]

Savage SA, Piguet O, & Hodges JR (2014). Giving words new life: Generalization of word retraining outcomes in semantic dementia. Journal of Alzheimer's Disease, 40(2), 309–317. 10.3233/JAD-131826

Savage SA, Piguet O, & Hodges JR (2015). Cognitive intervention in semantic dementia maintaining words over time. Alzheimer Disease and Associated Disorders, 29(1), 55–62. 10.1097/WAD.0000000000000053 [PubMed: 25037030]

Sharp DJ, Scott SK, Cutler A, & Wise RJS (2005). Lexical retrieval constrained by sound structure: The role of the left inferior frontal gyrus. Brain and Language, 92(3), 309–319. 10.1016/J.BANDL.2004.07.002 [PubMed: 15721963]

Snowden JS, & Neary D (2002). Relearning of verbal labels in semantic dementia. Neuropsychologia, 40(10), 1715–1728. 10.1016/S0028-3932(02)00031-3 [PubMed: 11992659]

Staffaroni AM, Ljubenkov PA, Kornak J, Cobigo Y, Datta S, Marx G, & Rosen HJ (2019). Longitudinal multimodal imaging and clinical endpoints for frontotemporal dementia clinical trials. Brain: a Journal of Neurology, 142(2), 443–459. 10.1093/brain/awy319 [PubMed: 30698757]

Taylor C, Kingma RM, Croot K, & Nickels L (2009). Speech pathology services for primary progressive aphasia: Exploring an emerging area of practice. Aphasiology, 23(2), 161–174. 10.1080/02687030801943039

Tohka J, Zijdenbos A, & Evans A (2004). Fast and robust parameter estimation for statistical partial volume models in brain MRI. Neuroimage, 23(1), 84–97. [PubMed: 15325355]

Turkeltaub PE, Messing S, Norise C, & Hamilton RH (2011). Are networks for residual language function and recovery consistent across aphasic patients? Neurology, 76(20), 1726–1734. 10.1212/WNL.0b013e31821a44c1 [PubMed: 21576689]

Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, et al. (2002). Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage 10.1006/nimg.2001.0978

van Hees S, McMahon K, Angwin A, de Zubicaray G, Read S, & Copland DA (2014). A functional MRI study of the relationship between naming treatment outcomes and resting state functional connectivity in post-stroke aphasia: Resting-State fMRI and Aphasia Treatment. Human Brain Mapping, 35(8), 3919–3931. 10.1002/hbm.22448 [PubMed: 24453137]

Vincent JL, Snyder AZ, Fox MD, Shannon BJ, Andrews JR, Raichle ME, et al. (2006). Coherent spontaneous activity identifies a hippocampal-parietal memory network. Journal of Neurophysiology, 96(6), 3517–3531. 10.1152/jn.00048.2006 [PubMed: 16899645]

Volkmer A, Spector A, Meitanis V, Warren JD, & Beeke S (2020). Effects of functional communication interventions for people with primary progressive aphasia and their caregivers: A systematic review. Aging & Mental Health, 24(9), 1381–1393. [PubMed: 31134821]

Wambaugh JL, Linebaugh CW, Doyle PJ, Martinez AL, Kalinyak-Fliszar M, & Spencer KA (2001). Effects of two cueing treatments on lexical retrieval in aphasic speakers with different levels of deficit. Aphasiology, 15(10–11), 933–950.

Wauters L, Ballard K, Clark H, Croot K, Dial H, Duffy J, et al. (2021). A systematic review of behavioral treatment for PPA/PPAOS: Major trends and future directions. Round table presentation Clinical Aphasiology Conference. (Virtual conference). Q4

Wilson M (1988). MRC psycholinguistic database: Machine-useable dictionary, Version 2.00. Behavior Research Methods, Instruments, & Computers, 20(1), 6–10.

Wilson SM, Brambati SM, Henry RG, Handwerker DA, Agosta F, Miller BL, et al. (2009). The neural basis of surface dyslexia in semantic dementia. Brain: a Journal of Neurology, 132(1), 71–86. 10.1093/brain/awn300 [PubMed: 19022856]

Wilson SM, Dehollain C, Ferrieux S, Christensen LE, & Teichmann M (2017). Lexical access in semantic variant PPA: Evidence for a post-semantic contribution to naming deficits. Neuropsychologia, 106, 90–99. [PubMed: 28867555]

Wilson SM, DeMarco AT, Henry ML, Gesierich B, Babiak M, Miller BL, et al. (2016). Variable disruption of a syntactic processing network in primary progressive aphasia. Brain: a Journal of Neurology, 139(11), 2994–3006. [PubMed: 27554388]

Wilson SM, Dronkers NF, Ogar JM, Jang J, Growdon ME, Agosta F, … Gorno-Tempini ML (2010a). Neural correlates of syntactic processing in the nonfluent variant of primary progressive aphasia. Journal of Neuroscience, 30(50), 16845–16854. 10.1523/JNEUROSCI.2547-10.2010 [PubMed: 21159955]

Wilson SM, Henry ML, Besbris M, Ogar JM, Dronkers NF, Jarrold W, et al. (2010). Connected speech production in three variants of primary progressive aphasia. Brain: a Journal of Neurology, 133, 2069–2088. [PubMed: 20542982]

Wisse LEM, Ungrady MB, Ittyerah R, Lim SA, Yushkevich PA, Wolk DA, et al. (2021). Cross-sectional and longitudinal medial temporal lobe subregional atrophy patterns in semantic variant primary progressive aphasia. Neurobiology of Aging, 98, 231–241. 10.1016/j.neurobiolaging.2020.11.012 [PubMed: 33341654]

Yue Q, Martin RC, Hamilton AC, & Rose NS (2019). Non-perceptual regions in the left inferior parietal lobe support phonological short-term memory: Evidence for a buffer account? Cerebral Cortex, 29(4), 1398–1413. 10.1093/cercor/bhy037 [PubMed: 29522178]

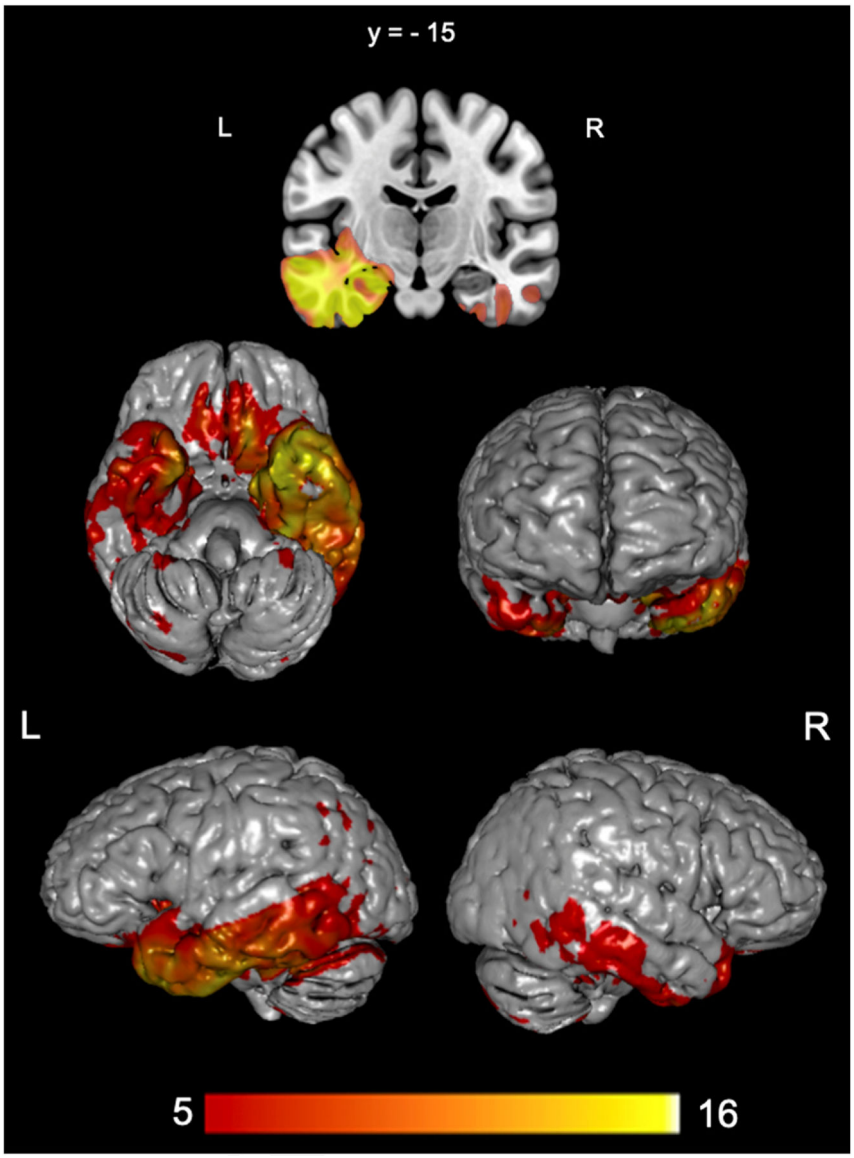

Fig. 1 –.

Voxel-based morphometry (VBM) results showing atrophy in individuals with svPPA (n = 19) relative to controls (n = 60). VBM was conducted using a two-sample t-test with *FWE*-corrected $p < .05$ and global scaling by total intracranial volume. Analysis controlled for age, sex, and scanner (n = 30 controls and n = 10 individuals with svPPA scanned at UCSF; n = 30 controls and n = 9 individuals with svPPA scanned at UT Austin). Top center: coronal slice at $y = -15$; top left: inferior surface view; top right: anterior surface view; bottom left: left hemisphere surface view; bottom right: right hemisphere surface view. Colorbar reflects t-values.

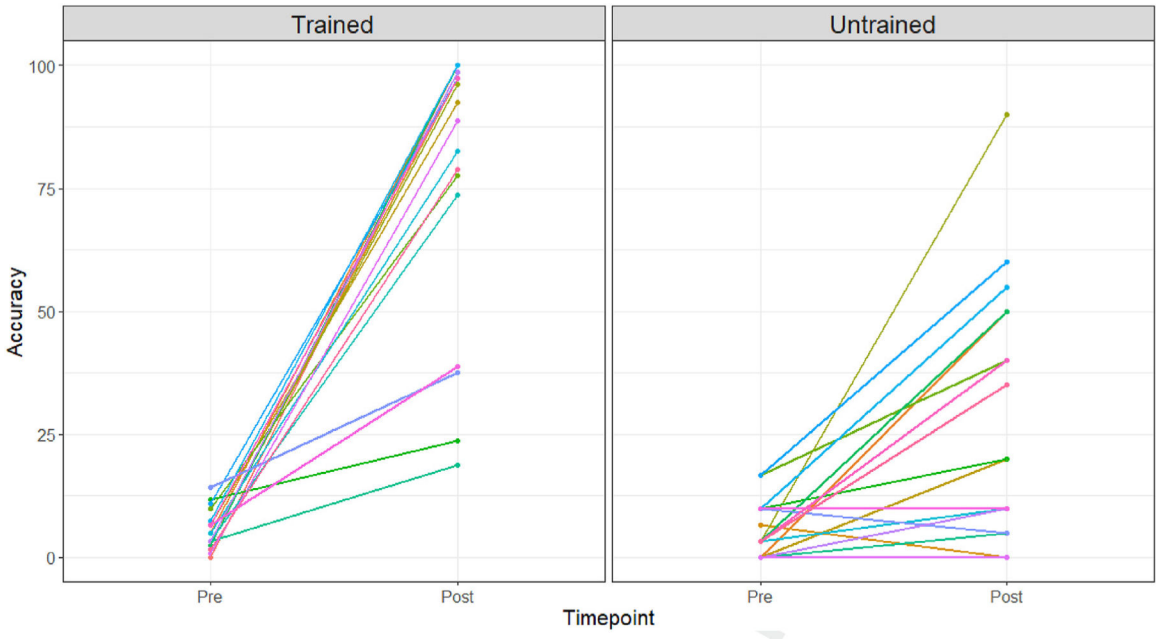

Fig. 2 –.

Mean accuracy across probes for trained and untrained sets at pre- and post-treatment for each participant. Left panel: trained items; right panel: untrained items. Each colored line represents a single participant.

Table 1 –

Research studies examining neuroimaging in relation to speech-language intervention outcomes in primary progressive aphasia.

Study	PPA Subtype(s)	Treatment Approach and Total Time in Treatment	Neuroimaging Method	Summary of Findings	Potential Limitations
Marcotte & Ansaldo, (2010)	*n* = 1 nfvPPA	Semantic feature analysis, three 1-h sessions per week for three weeks	fMRI, picture naming task	Activation for correctly named trained items in bilateral superior and inferior parietal lobes at pre- and post-treatment. Right parahippocampal gyrus and left superior and middle temporal gyri at post-treatment.	No statistical comparison between pre- and post-treatment activation patterns. No correction for multiple comparisons in fMRI analysis. Single case study.
Dressel et al., (2010)	*n* = 1 svPPA	Phonological and semantic cueing hierarchies, five sessions per week for four weeks (length of each session not reported)	fMRI, picture naming task	Activation for items correctly named at post-treatment but incorrectly named at pre-treatment in left middle frontal gyrus and right temporal pole, superior temporal gyrus, middle temporal gyrus, inferior temporal gyrus, inferior frontal gyrus, middle frontal gyrus, superior frontal gyrus and supramarginal gyrus.	No correction for multiple comparisons in fMRI analysis. Single case study.
Beeson et al., (2011)	*n* = 1 lvPPA	Generative naming and semantic elaboration, six 2-h sessions per week for two weeks	fMRI, picture naming task	Activation for naming of untrained items in bilateral pre- and post–central gyri, posterior superior temporal gyrus, and ventrolateral temporo-occipital regions at pre- and post-treatment. Left dorsolateral prefrontal cortex at post-treatment.	No discussion of naming performance during fMRI task. Single case study.
Jokel et al., (2016)	*n* = 4 svPPA	Picture presented with its name and phonological (first letter/sound or syllable) or semantic (descriptors) information, Two 1-h sessions per week for ten weeks	fMRI, rhyme and synonymy judgment tasks for nonwords and words, respectively	Group level: Greater activation at post-treatment relative to pre-treatment in a small cluster in right posterior inferior frontal gyrus for rhyme and synonymy judgment. Single-subject level: All participants had greater activation at post-treatment relative to pre-treatment within right temporal regions including the fusiform gyrus, inferior temporal gyrus, middle temporal gyrus, and/or superior temporal gyrus (regions varied by participant and task).	Did not utilize the trained task (naming) during fMRI. Instead, used tasks that do not require lexical retrieval. Findings may reflect general reorganization of the language network, but unclear if the findings are directly related to lexical retrieval. When no voxels survived correction for multiple comparisons in fMRI analysis, uncorrected results were reported. Relatively small sample.
Cotelli et al., (2016)	*n* = 18 nfvPPA	Repetition, oral naming, and reading, paired with tDCS over left dorsolateral prefrontal cortex, Five 25-min sessions per week for two weeks	VBM	Pre-treatment gray matter volumes in left fusiform gyrus, left middle temporal gyrus, and right inferior temporal gyrus correlated with gains in naming for trained items.	Findings may be specific to treatment approaches incorporating neuromodulation. No correction for multiple comparisons in VBM analysis.
Meyer et al., (2017)	*n* = 7 nfvPPA, *n* = 9 lvPPA, *n* = 5 svPPA	Repetition or written production of target words paired with a picture, two clinician-guided sessions per week for four weeks (length of each session not reported), followed by five months of home-based practice	VBM	Gray matter volumes in left temporal pole and left inferior temporal gyrus correlated with naming of untrained items at post-treatment produced with high accuracy at pre-treatment (left temporal pole) or low accuracy at pre-treatment (left inferior temporal gyrus).	Post-treatment naming accuracy used in analyses without controlling for pre-treatment accuracy. All three PPA subtypes included in same analysis and only regions that were significantly atrophic at group level were examined (a limitation because regional atrophy patterns differ across PPA subtypes).
Henry et al., (2018)	*n* = 10 nfvPPA	Video-implemented script training in aphasia (unison production with an audiovisual model), two 1-h sessions per week for four to six weeks	VBM	Regions of interest derived from a left inferior frontal gyrus seeded network in control participants. A region in left posterior inferior/middle temporal gyrus correlated with treatment effect size for trained items, controlling for overall aphasia severity.	Relatively small sample and relatively large regions of interest.

Study	PPA Subtype(s)	Treatment Approach and Total Time in Treatment	Neuroimaging Method	Summary of Findings	Potential Limitations
Paek et al., (2021)	*n* = 1 nfvPPA, *n* = 1 svPPA	Semantic feature analysis, semantic comprehension training, phonological component analysis, definitions, memory game, charades, “go fish”, speeded confrontation naming. Phonological and semantic cueing hierarchy, two 1-h sessions per week for 8 weeks.	fMRI, picture naming task	Increased post-treatment activation in bilateral inferior temporal, middle temporal, and occipital cortex; left superior and inferior parietal gyri, inferior frontal lobe, and posterior superior temporal gyrus for participant with nfvPPA; and left middle and inferior temporal; bilateral anterior frontal, primary motor and occipital cortex for participant with svPPA.	No correction for multiple comparisons in fMRI analysis. fMRI control condition was rest. Relatively small sample, data analyzed as single cases (*n* = 2).

Notes: PPA = primary progressive aphasia, nfvPPA = nonfluent variant primary progressive aphasia, lvPPA = logopenic variant primary progressive aphasia, sv = semantic variant primary progressive aphasia, fMRI = functional magnetic resonance imaging, tDCS = transcranial direct current stimulation, VBM = voxel-based morphometry, h = hour

Table 2 –

Demographic characteristics and pre-treatment performance on neuropsychological assessments of cognitive and linguistic processing.

	Mean (Range)	Standard Deviation
Demographics		
Age (years)	66.37 (50.64–78.28)	7.37
Sex (F/M)	12/7	–
Handedness (Right/Left)	18/1	–
Education (years)	17.16 (12–21)	2.43
General Cognition		
Mini Mental State Examination (30)[a]	25 (16–28)	3.59
Verbal Memory		
California Verbal Learning Test Total (36)[a]	17.37 (8–30)	5.99
California Verbal Learning Test Recall (9)[a]	1.95 (0–6)	2.20
Visuospatial Memory		
Complex Figure Copy (17)[a]	15.89 (13–17)	1.20
Complex Figure Recall (17)[a]	9.37 (2–14)	3.30
Complex Figure Recognition (Correct/Incorrect)[a]	17/2	–
Phonological Working Memory		
Forward Digit Span[a]	6.53 (5–9)	1.07
Backward Digit Span[a]	4.74 (0–8)	1.79
Western Aphasia Battery-Revised Repetition (100)[b]	92.32 (80–100)	6.36
Single Word Comprehension		
Peabody Picture Vocabulary Test Short (16)[a]	8.05 (0–16)	4.31
Verbal Fluency		
Letter: D[a]	7.53 (0–22)	4.74
Category: Animals[a]	7.63 (3–18)	4.00
Aphasia Severity		
Western Aphasia Battery-Revised Aphasia Quotient (100)	83.59 (60.90–94.00)	8.85

	Mean (Range)	Standard Deviation
Object Knowledge		
Pyramids & Palm Trees Test: Pictures (14)[c]	11.38 (8–14)	2.28
Naming		
Boston Naming Test (%)[a]	24.91 (6.67–60.00)	18.84
Syntactic Processing		
Auditory Sentence-Picture Matching (%)[d]	96.36 (68.75–100.00)	7.31
Reading/Spelling		
Regular, High Frequency Word Reading (%)[e]	96.49 (55.56–100.00)	10.51
Regular, Low Frequency Word Reading (%)[e]	92.78 (44.44–100.00)	13.56
Irregular, High Frequency Word Reading (%)[e]	74.71 (33.33–100.00)	19.94
Irregular, Low Frequency Word Reading (%)[e]	56.46 (.00–100.00)	28.16
Pseudoword Reading (%)[e]	80.41 (.00–100.00)	24.99
Regular, High Frequency Word Spelling (%)[e]	63.01 (.00–100.00)	27.66
Regular, Low Frequency Word Spelling (%)[e]	59.53 (.00–95.00)	24.43
Irregular, High Frequency Word Spelling (%)[e]	31.52 (.00–95.00)	34.03
Irregular, Low Frequency Word Spelling (%)[e]	30.70 (.00–90.00)	22.61
Pseudoword Spelling (%)[e]	61.99 (.00–100.00)	27.56

Notes: For tasks presenting percentages instead of raw scores, a different number of items was completed across participants (e.g., if they reached ceiling performance on one section of the assessment, they moved directly to another section). Percentages are reported to collapse data across participants.

[a]Assessments from neuropsychological battery described in Kramer et al. (2003), Knopman et al. (2008), and Staffaroni et al. (2019).

[b]From Kertesz (2007).

[c]Pyramids and Palm Trees only available for $n = 17$. This 14-item short version was developed by Breining et al. (2015) from the standard 52-items version.

[d]From Wilson, Dronkers et al. (2010).

[e]Adapted from the Arizona Battery for Reading and Spelling (Beeson & Rising, 2010).

Table 3 –

Results for ANOVA comparing “full” and “reduced” models for each ROI for trained and untrained sets.

	Trained		Untrained	
	Likelihood Ratio	**Uncorrected *p*-value**	**Likelihood Ratio**	**Uncorrected *p*-value**
Temporal ROIs				
L STG	1.41	.2343	.90	.3426
R STG	.01	.9173	1.09	.2973
L MTG	.24	.6217	.14	.7089
R MTG	.61	.4366	.78	.3783
L ITG	.01	.9172	.00	.9469
R ITG	.06	.8127	.59	.4412
Parietal ROIs				
L SMG	5.47	.0194*	.73	.3927
R SMG	.09	.7624	1.53	.2167
L angular gyrus	5.54	.0186*	.52	.4689
R angular gyrus	3.48	.0620	1.12	.2907
L IFG opercularis	.46	.4988	.72	.3946
R IFG opercularis	2.43	.1187	.24	.6257
L IFG triangularis	1.00	.3171	4.47	.0344
R IFG triangularis	1.28	.2579	3.26	.0708
L MFG	1.06	.3022	1.70	.1924
R MFG	.02	.9025	6.91	.0086
Medial Temporal Lobe ROIs				
L hippocampus	6.72	.0095*	6.31	.0120*
R hippocampus	.89	.3461	1.27	.2605
L parahippocampal gyrus	2.55	.1105	1.14	.2867
R parahippocampal gyrus	.11	.7456	.62	.4306

Notes:

*Significant with FDR-correction ($p < .05$).

L = left, R = right, STG = superior temporal gyrus, MTG = middle temporal gyrus, ITG = inferior temporal gyrus, IFG = inferior frontal gyrus, MFG = middle frontal gyrus, SMG = supramarginal gyrus

Table 4 –

Model parameters for the interaction of ROI volume and time point for trained and untrained sets where the addition of the interaction term improved model fit.

	β estimate	SE	95% CI	t	dF	p
Trained						
L SMG	10.25	4.45	[1.82, 18.69]	2.30	74	.0240
L angular gyrus	10.45	4.50	[1.91, 18.99]	2.32	74	.0231
L hippocampus	11.15	4.33	[2.94, 19.36]	2.57	74	.0120
Untrained						
L hippocampus	8.09	3.26	[1.92, 14.27]	2.48	70	.0156

Notes: L = left, SMG = supramarginal gyrus.