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Left frontotemporal effective connectivity during semantic feature judgments in patients with chronic aphasia and age-matched healthy controls

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Abstract

Traditional models of neural reorganization of language skills in patients with chronic stroke-induced aphasia (PWA) propose activation of reperfused or spared left hemisphere tissue results in the most favorable language outcomes. However, these models do not fully explain variable behavioral recovery patterns observed in chronic patients. Instead, investigation of connectivity patterns of critical network nodes may elucidate better-informed recovery models. In the present study, we combined fMRI and dynamic causal modeling (DCM) to examine effective connectivity of a simple three-node left hemisphere network during a semantic feature decision task in 25 PWA and 18 age-matched neurologically intact healthy controls. The DCM model space utilized in Meier, Kapse, & Kiran (2016), which was organized according to exogenous input to one of three regions (i.e., left inferior frontal gyrus, pars triangularis [LIFGtri], left posterior middle temporal gyrus [LpMTG], or left middle frontal gyrus [LMFG]) implicated in various levels of lexical-semantic processing, was interrogated. This model space included all possible combinations of uni- and bidirectional task-modulated connections between LIFGtri, LMFG and LpMTG, resulting in 72 individual models that were partitioned into three separate families (i.e., Family #1: Input to LIFGtri, Family #2: Input to LMFG, Family #3: Input to LpMTG). Family-wise Bayesian model selection revealed Family #2: Input to LMFG best fit both patient and control data at a group level. Both groups relied heavily on LMFG's modulation of the other two model regions. By contrast, between-group differences in task-modulated coupling of LIFGtri and LpMTG were observed. Within the patient group, the strength of activity in LIFGtri and connectivity of LpMTG→LIFGtri were positively associated with lexical-semantic abilities inside and outside of the scanner, whereas greater recruitment of LpMTG was associated with poorer lexical-semantic skills.

Keywords

connectivity; aphasia; lexical-semantics; dynamic causal modeling

1. Introduction

Approximately one-third of stroke survivors present with aphasia, a neurogenic communication disorder characterized by a constellation of deficits in multiple domains of

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language usually following infarct in the left middle cerebral artery (MCA) territory (Engelter et al., 2006; Flowers et al., 2016; Gialanella, Bertolinelli, Lissi, & Prometti, 2011; Laska, Hellblom, Murray, Kahan, & Von Arbin, 2001; Maas et al., 2012; Pedersen, Jørgensen, Nakayama, Raaschou, & Olsen, 1995; Wade, Hewer, David, & Enderby, 1986). Aphasia that persists into the chronic stage of recovery has devastating effects on patients' communication, participation in everyday activities and quality of life (Flowers et al., 2016; Gialanella et al., 2011; Hilari, Wiggins, Roy, Byng, & Smith, 2003; Lam & Wodchis, 2010). Research that elucidates patterns of co-occurring neural and behavioral recovery in persons with aphasia (PWA) is an essential resource for maximizing language recovery in these individuals as improved behavioral, neuromodulatory, and/or pharmaceutical treatments will naturally follow a better understanding of brain-behavior relationships in stroke aphasia. However, predictive computational models of aphasia recovery based on neural and demographic variables are only now emerging (e.g., Hope, Leff, & Price, 2018; Hope, Seghier, Leff, & Price, 2013; Price, Seghier, & Leff, 2010), and thus, predictions regarding treatment-related and spontaneous recovery potential for individual patients are currently unreliable (Charidimou et al., 2014; Heiss, 2017; Lazar, Speizer, Festa, Krakauer, & Marshall, 2008; Lazar & Antoniello, 2008; Lazar & Boehme, 2017; Price, Hope, & Seghier, 2017).

Traditional theories of neural reorganization in chronic aphasia (Anglade, Thiel, & Ansaldo, 2014; Heiss & Thiel, 2006) provide a general framework for understanding recovery by juxtaposing left versus right hemisphere recruitment for language. For example, Heiss and Thiel (2006) proposed a three-tiered framework of chronic aphasia in which optimal, satisfactory, and poor language recovery were associated with, respectively, preservation or reactivation of primary language areas; damage to primary language cortex but spared and functional secondary left hemisphere language areas; and extensive left hemisphere damage with reliance on the contralesional (but possibly ill-suited) right hemisphere to mediate language. However, the past 25 years of collective fMRI and PET research in aphasia has resulted in conflicting evidence for these patterns, particularly the contested role of the right hemisphere in aphasia recovery (see Cappa, 2011; Cocquyt, De Ley, Santens, Van Borsel, & De Letter, 2017; Crosson et al., 2007; Kiran, 2012; Meinzer, Harnish, Conway, & Crosson, 2011; Price & Crinion, 2005; Saur & Hartwigsen, 2012; Thompson & den Ouden, 2008; Zahn, Schwarz, & Huber, 2006 for reviews). Imaging findings accord with the general assertion that left hemisphere activation—and perilesional activity in particular—results in better language recovery in PWA (Fridriksson, Richardson, Fillmore, & Cai, 2012; Heiss, Kessler, Thiel, Ghaemi, & Karbe, 1999; Léger et al., 2002; Marcotte & Ansaldo, 2010; Meinzer et al., 2008; Meinzer & Breitenstein, 2008; Menke et al., 2009; Rosen et al., 2000; Szaflarski, Allendorfer, Banks, Vannest, & Holland, 2013; van Hees, McMahon, Angwin, de Zubicaray, & Copland, 2014; Vitali et al., 2007; Warburton, Price, Swinburn, & Wise, 1999; Winhuisen et al., 2007).

However, definitive evidence from the patient activation literature supporting Heiss and Thiel's (2006) distinction between optimal and satisfactory recovery patterns (i.e., activation of canonical language cortex versus activation of ipsilesional regions, respectively) has not been demonstrated. For example, certain studies (Abel, Weiller, Huber, Willmes, & Specht, 2015; Fridriksson, Bonilha, Baker, Moser, & Rorden, 2010; Sims et al., 2016) have shown

that patients with the most recovered language abilities recruit traditional perisylvian language regions (e.g., inferior frontal, superior and middle temporal, and angular and supramarginal gyri) as well as left hemisphere nodes outside of the canonical language network (e.g., superior and middle frontal gyri, superior parietal lobule). In a meta-analysis of 12 fMRI studies in PWA, Turkeltaub, Messing, Norise, and Hamilton (2011) discovered that across a variety of language tasks, PWA activated crucial language nodes homotopic to activation peaks observed in left inferior frontal gyrus pars opercularis (LIFGop), LIFG pars triangularis (LIFGtri), and left middle temporal gyrus (LMTG) in healthy controls. When the authors accounted for LIFG lesions, LH peaks were still found within canonical language regions but were shifted to functionally-homologous intact perilesional regions (i.e., LIFG pars orbitalis [LIFGorb]) or were recruited for a presumed different function (i.e., anterior insula). Critically, patients with and without lesions in LIFG showed activation in neighboring dorsolateral prefrontal cortex (i.e., LMFG), leading the authors to conclude that LMFG may be critical for supporting linguistic processes in some manner for PWA, regardless of lesion in LIFG. Within Heiss and Thiel's (2006) hierarchy of chronic aphasia recovery, LIFG and LMTG likely fall into the category of "classic" language regions whereas LMFG would probably be considered secondary left hemisphere language cortex. Nevertheless, the necessity of perisylvian and extrasylvian left hemisphere recruitment for optimal language recovery in PWA is reasonable given both the nature of linguistic deficits in PWA and the potential functional roles of these regions, as described below.

1.1. Aphasic deficits and the functional role of frontotemporal cortex for language

It has been proposed that deficits in PWA are a consequence of impaired controlled access to, rather than destruction of, linguistic representations (Corbett, Jefferies, & Lambon Ralph, 2009; Corbett, Jefferies, Ehsan, & Lambon Ralph, 2009; Crutch & Warrington, 2005; Gotts & Plaut, 2002; Hoffman, Jefferies, & Lambon Ralph, 2011; Jefferies, Baker, Doran, & Lambon Ralph, 2007; Jefferies, Patterson, & Lambon Ralph, 2008; Jefferies & Lambon Ralph, 2006; McCarthy & Warrington, 2016; Mirman & Britt, 2013; Rogers, Patterson, Jefferies, & Lambon Ralph, 2015; Thompson & Jefferies, 2013; Warrington, 1975; Warrington & Cipolotti, 1996; Warrington & Mccarthy, 1983, 1987). In the neuropsychological literature, the difference between representation and access deficits has been studied most often within the semantic system. Error analysis supports the existence of intact semantic knowledge in patients with stroke aphasia as PWA with semantic control deficits retrieve related but incorrect semantic information during tasks such as picture naming. For example, PWA often produce category coordinate errors (e.g., *'shorts'* for *'coat'*) or responses that fall outside of the intended category due to thematic associations (e.g., *'snow'* for a cold weather clothing). In addition, phonological cues improve word retrieval (e.g., correct naming of *'coat'* with a phonological cue of /k/) for these individuals while miscues result in paraphasias (e.g., incorrect naming of *'shorts'* for *'coat'* with phonological cue of /ʃ/) (Jefferies et al., 2008; Schwartz, 2013).

In alignment with the access deficit hypothesis, it stands to reason that beneficial neural reorganization of language in post-stroke aphasia involves the recruitment of and communication between regions implicated in access to and/or executive control of linguistic information. Neurocognitive models of healthy semantic processing (e.g., Binder

& Desai, 2011) confer an executive role to certain cortical regions, most often frontal cortex. Findings from seminal fMRI studies from the late 1990s and early 2000s support LIFG—and LIFGorb and LIFGtri in particular—in semantic access or control in cognitively demanding tasks (e.g., resolution of semantic ambiguity, selection of a target among semantic competitors, suppression of strong semantic associations with activation of weaker associations) (Badre & D'Esposito, 2007; Badre, Poldrack, Paré-Blagoev, Insler, & Wagner, 2005; Devlin, Matthews, & Rushworth, 2003; Gold & Buckner, 2002; Poldrack et al., 1999; Thompson-Schill, D'Esposito, Aguirre, & Farah, 1997; Wagner, Paré-Blagoev, Clark, & Poldrack, 2001). Lambon Ralph, Jefferies, Patterson, and Rogers (2016) proposed a larger semantic control network which includes not only LIFG but also the posterior LMTG (LpMTG), intraparietal sulcus (IPS), pre-supplementary motor area (pre-SMA), and medial prefrontal/anterior cingulate cortex (mPFC/ACC). Other work has suggested that a multiple demand (MD) network (including portions of the middle frontal gyrus [MFG], IFG pars opercularis [IFGop], the frontal operculum, anterior insula, dorsal ACC, SMA, and IPS) becomes active across a variety of tasks (e.g., verbal working memory, sentence comprehension, visual working memory, etc.) particularly when task difficulty increases (Duncan, 2010; Fedorenko, Behr, & Kanwisher, 2011; Fedorenko, Duncan, & Kanwisher, 2012; Fedorenko & Thompson-Schill, 2014).

Collectively, these papers highlight that regions implicated in domain-specific (i.e., semantic) and/or domain-general regions are activated in healthy individuals with increased executive processing demands. Given that PWA struggle with language, it is not inconceivable that regions that mediate executive processes would be crucial in patient networks. Alternatively, patients' reliance on regions typically associated with domain-specific (e.g., LIFGtri, LpMTG) or domain-general (e.g., LMFG) executive processing could reflect some undetermined—but possibly critical—consequence of stroke (e.g., reorganization of language to redundant systems, heightened cognitive control load due to concomitant cognitive deficits).

1.2. Domain specificity versus generality in aphasia

One critical question is if post-stroke language recovery—and lexical-semantic recovery in particular—must be mediated through reactivation of spared tissue in critical hubs associated with semantic representation or control or if redundant systems allow for domain-general MD regions to compensate for lost domain-specific systems. Recent work has illustrated that PWA rely on domain-general networks and/or connectivity between language and domain-general regions to a greater extent for language tasks compared to age-matched healthy controls (Geranmayeh, Chau, Wise, Leech, & Hampshire, 2017; Geranmayeh, Leech, & Wise, 2016; Sharp, Turkheimer, Bose, Scott, & Wise, 2010). Moreover, changes in activation in PWA following language therapy have been found not only in perisylvian language areas but also in other left hemisphere regions outside the canonical language network (e.g., Fridriksson, 2010; Fridriksson, Bonilha, Baker, Moser, & Rorden, 2010; Kiran, Meier, Kapse, & Glynn, 2015; Marcotte et al., 2012; Menke et al., 2009; Sandberg, Bohland, & Kiran, 2015). Unlike perisylvian language cortex—including the two regions most often implicated in semantic control (i.e., anterior LIFG and LpMTG)—MD regions such as LMFG fall on the outskirts of the MCA territory and may represent the only

remaining ipsilesional spared tissue available for bootstrapping linguistic processing in PWA. Therefore, informative conclusions regarding the neural reorganization of language in PWA would likely result from quantifying the extent of damage to canonical language regions, measuring the degree of activation or connectivity of regions within language and MD networks, and relating these neural metrics to specific linguistic skills.

To date, few researchers have made direct associations between lesion characteristics and PWA's activation or connectivity patterns during lexical-semantic processing. Of the limited existing studies, Griffis and colleagues (Griffis, Nenert, Allendorfer, & Szaflarski, 2017b; Griffis, Nenert, Allendorfer, Vannest, et al., 2017) found that patients with a greater amount of spared tissue in left temporoparietal cortex demonstrated greater activity in a canonical left frontoparietal semantic network and better performance on language tasks inside and outside of the scanner. In the same vein, Hallam et al. (2018) discovered that patients with semantic aphasia with damage to LIFG demonstrated greater activity in LpMTG relative to healthy individuals for a semantic control task. By contrast, Sims et al. (2016) found that greater damage to canonical anterior (i.e., LIFGorb) and posterior (i.e., angular/supramarginal gyri [LAG/LSMG] and LMTG) language cortex was associated with greater percent signal change for semantic decisions in bilateral dorsolateral and dorsomedial prefrontal cortex, regions most often implicated in domain-general cognitive control.

These collective findings suggest LIFGtri and LpMTG are integral for semantic processing and potentially play a critical role in domain-specific (i.e., semantic control) processing for individuals with aphasia. Likewise, a reliance on regions implicated in domain-general processes (e.g., LMFG) may be essential for the recovery of lexical-semantics in PWA. Nevertheless, the relative importance of canonical perisylvian regions versus traditional domain-general areas for lexical-semantic processing in PWA remains unknown.

1.3. Study aims

The present study aimed to extend previous work by interrogating functional integration (i.e., connectivity) of residual left hemisphere tissue in regions potentially most primed to mediate recovery of lexical-semantic skills in PWA. Specifically, we used a systematic approach for identifying regional activity during a semantic feature decision task in three left hemisphere regions of interest (ROIs): LIFGtri for its presumed role in controlled semantic access, LMFG for its presumed role in domain-general cognitive processes, and LpMTG for its assumed role in either semantic access and/or convergence of semantic information from modality-specific regions during semantic tasks. We used dynamic causal modeling (DCM; Friston, Harrison, & Penny, 2003) to investigate differences between PWA and age-matched healthy controls in effective connectivity of the LIFGtri-LMFG-LpMTG subnetwork and to determine relationships between connectivity parameters and lexical-semantic skills in PWA. To address these goals, we explored the DCM model space from Meier, Kapse, & Kiran (2016), in which exogenous task input was modeled to either LIFGtri, LMFG, or LpMTG and all possible combinations of task-modulated connections were specified to examine connectivity during lexical retrieval in PWA.

In Meier et al. (2016), we found that healthy controls demonstrated a preference for best-fit DCM models with input to LIFGtri whereas PWA preferred models with input to LMFG.

Furthermore, we found that the strength of several connections including LMFG was related to the amount of spared tissue in network nodes and naming abilities in PWA. As such, we hypothesized healthy controls in the present study would demonstrate a preference for DCM models with input to and the strongest connections from LIFGtri. Alternatively, if LIFGtri and LpMTG play a similar role in semantic access (Noonan et al., 2013; Lambon Ralph et al., 2016), we predicted no clear preference for models that emphasize input to either one of these two regions. For PWA, we hypothesized a high likelihood of local damage to and greater functional disconnection of LIFGtri and LpMTG. Similar to findings from Meier et al. (2016), we predicted that best-fit DCM models for PWA would include input to LMFG and that modulatory connections from LMFG to LIFGtri and/or LpMTG would be most predictive of lexical-semantic skills in the patient group.

2. Materials and methods

This study was conducted as part of a large, multi-site investigation of the neural bases of language recovery in individuals with chronic aphasia secondary to stroke (NIH/NIDCD grant 1P50DC012283) within the Center for the Neurobiology of Language Recovery (CNLR; http://cnlr.northwestern.edu/).

2.1. Participants

Thirty-two individuals with chronic aphasia (22M, mean age = 61.75 ± 11.26 years) following left middle cerebral artery MCA infarct and 21 neurologically intact healthy controls (10M, mean age = 59.61 ± 13.45 years) were recruited for the present study. Case history information including neurological history, age, handedness, race, and ethnicity was collected for all participants via questionnaire. None of the participants had major psychiatric disorders, neurological disease (besides stroke in PWA) or active medical conditions that would preclude participation. All participants primarily spoke English and had normal or corrected-to-normal vision and adequate hearing (i.e., bilateral threshold ≤ 40 dB at 500, 1000 and 4000 Hz). Enrolled patients presented with aphasia due to a single left hemisphere CVA[2] and were in the chronic phase of stroke recovery (mean post-stroke onset = 49.56 ± 48.93 months).

Final inclusion in the present study was determined based on fMRI data quality. Data were unusable for seven PWA and three controls due to artifacts from implanted material (n = 1 patient), low signal-to-noise from excessive motion (n = 6 PWA, 2 controls), and participant removal from the scanner due to claustrophobia prior to scan completion (n = 1 control). As such, behavioral and neuroimaging data were analyzed for 25 PWA (17M, mean age = 62.00 ± 11.77 years) and 18 healthy controls (10M; mean age = 60.35 ± 10.93 years). Of note, a subset of the participants in the current study[3] were included in Meier et al. (2016).

[2]Visual inspection of the T1-weighted images revealed three patients (i.e., P11, P18, and P19) exhibited right hemisphere ischemic changes of unknown etiology of the deep white matter abutting the lateral ventricles. As none of these participants had a known history of right hemisphere cortical infarct, their data were included in analyses within the present investigation.

[3]Behavioral and neuroimaging data pertaining to oral naming abilities and connectivity from 12 PWA (i.e., P1-P3, P5-P7, P9, P11-P13, P15 and P21) and 10 controls included in the present study were analyzed in the previous investigation.

Prior to scanning, PWA completed a behavioral testing battery that included the Western Aphasia Battery-Revised (WAB; Kertesz, 2007) to quantify overall aphasia severity per the Aphasia Quotient (AQ); the Pyramids and Palm Trees Test (PPT; Howard & Patterson, 1992) to assess nonverbal semantic association abilities, and subtest 51: Word Semantic Association from the Psycholinguistic Assessment of Language Processing in Aphasia (PALPA; Kay, Coltheart, & Lesser, 1992) to assess lexical-semantic association skills. Accuracy on PALPA 51 served as an outside-of-scanner proxy for lexical-semantic abilities. Lexical-semantic skills in general (and semantic feature processing in particular) were investigated due to the importance of semantic processes in single word production (Dell, Schwartz, Martin, Saffran, & Gagnon, 1997; Levelt, Roelofs, & Meyer, 1999; Schwartz, Dell, Martin, Gahl, & Sobel, 2006). Moreover, as part of the CNLR, many patients in the present study completed a 12-week language therapy that targeted word-retrieval deficits by training patients on semantic features of target items. While a detailed summary of the therapy is outside the scope of this paper, the results of the treatment portion of the study (see Gilmore, Meier, Johnson, & Kiran, 2018) additionally illustrate that semantic feature knowledge is critical for successful word retrieval in PWA. See Table 1 for stroke, demographic and testing information in the patient group.

Behavioral procedures for PWA were executed according to IRB protocols at Boston University. Neuroimaging procedures for all participants were performed according to IRB protocols at Massachusetts General Hospital.

2.2. MR data acquisition

Imaging data were collected at the Athinoula A. Martinos Center in Charlestown, MA, on a 3T Siemens Trio Tim scanner with a 20 channel head+neck coil. For all participants, a high resolution, T1-weighted 3D sagittal volume (parameters: TR/TE = 2300/2.91ms, T1 = 900ms, flip angle = 9°, matrix = 256×256mm, FOV = 256mm, slice thickness = $1mm^3$, 176 sagittal slices) and functional scans via a gradient echo T2*-weighted EPI sequence (parameters: TR/TE = 2570/30ms, flip angle = 90°, matrix = 80×78mm, FOV = 220×220mm, 40 axial, 3mm slices with 2×2×3mm voxels, parallel imaging with acceleration factor or 2) were acquired.

To measure the neural correlates of semantic processing, an event-related semantic feature verification task with a jittered inter-stimulus interval was used. Experimental stimuli included 108 real pictured items from three of five semantic categories (i.e., *birds*, *vegetables*, *furniture*, *clothing*, and *fruit*) that were balanced for familiarity, length, lexical frequency, and concreteness using the CELEX (Van der Wouden, 1990) and MRC Psycholinguistic (Coltheart, 1981) databases. Category assignment was pseudo-randomly counterbalanced across participants. Control stimuli included 36 scrambled, pixelated images in black and white or color. Trials were randomized and presented in two separate runs (i.e., 54 experimental and 18 control stimuli per run). During the task, an image appeared on the screen followed one second later by a written feature below the image. Features for the experimental items were based on results of a MTurk pilot study (https://www.mturk.com/mturk) in which participants decided whether a certain feature applied to a given item. Features were classified as being either related (i.e., contextual, characteristic,

physical, and functional features) or unrelated to the item. During the fMRI experiment, participants decided whether the written feature applied to the image and responded via a yes/no button press (see Figure 1A). Accuracy and reaction time (RT) data were collected and compared between groups using unequal variance Welch's t-tests. PWA were significantly less accurate than controls were in making semantic judgments during the fMRI task ($t(26.23) = -4.89$, $p < 0.001$; mean PWA accuracy: 72.38 ± 15.81%, mean control accuracy: 88.72 ± 3.47%) (Figure 1B). However, no significant differences in reaction times were noted between groups ($t(33.68) = 1.62$, $p = 0.11$; mean PWA RT: 1.89 ± 0.47 seconds, mean control RT: 1.72 ± 0.21 seconds) (Figure 1C).

2.3. MR data analysis

MR data were analyzed using SPM12 (Wellcome Trust Centre for Neuroimaging).

2.3.1. Preprocessing—A standard pipeline with additional steps for patient data was used to preprocess the MR data. First, slice timing correction with reference to the middle slice was performed to account for differences in the timing of slice acquisition. Next, realignment of functional scans to the mean image via 4th degree B-spline interpolation was performed, and functional and structural images were coregistered. Images were then segmented into gray matter, white matter and cerebrospinal fluid based on SPM12's tissue probability maps, and segmented functional and structural images were normalized to the MNI template. Last, data were smoothed using a relatively small smoothing kernel of 4mm. A smoothing kernel approximately twice the functional voxel dimensions has been recommended for patient data to increase the credibility of activation peaks obtained from 1st-level activation maps and to reduce the likelihood of activation shifting into lesioned areas (Meinzer et al., 2013). In addition, lesion masks were manually drawn in MRIcron (http://www.mccauslandcenter.sc.edu/mricro/mricron/) using each patient's T1-weighted structural image. Binarized lesion masks (in which lesioned voxels were deleted) and lesion maps (in which lesioned voxels were preserved) were included during preprocessing to improve coregistration and normalization of the patient data (Brett, Leff, Rorden, & Ashburner, 2001). Finally, the ArtRepair toolbox was used to account for large volume-to-volume motion; specifically, repaired functional files were used when repair reduced the standard deviation of the estimation error for the contrast of interest in the 1st-level general linear model (GLM) (Mazaika, Hoeft, Glover, & Reiss, 2009).

2.3.2. Localization of regional activity—The following procedures were performed to identify task activation in the three left hemisphere regions of interest (ROIs) for the effective connectivity analysis.

2.3.2.1. 1st-level analysis: For all participants, a 1st-level GLM was specified to obtain activation associated with semantic processing during the feature verification task. The GLM included the conditions *pictures* (i.e., experimental stimuli), *scrambled pictures* (i.e., control stimuli), and *fixation*. Stimulus onsets and durations for each condition were modeled and convolved with the canonical hemodynamic response function and its temporal derivative. The contrast of interest *pictures* – *scrambled pictures* was used to capture core processes involved in making semantic judgments (i.e., lexical-semantics, semantic control) while

controlling for visual and motor processes. Activation maps were obtained at an uncorrected threshold ($p < 0.001$) to identify peaks within each ROI for each participant.

2.3.2.2. 2nd-level analysis: As a critical data validation step prior to effective connectivity analysis, 2nd-level analyses were first performed for the contrast *pictures – scrambled pictures* using the Statistical nonparametric Mapping (SnPM) toolbox in SPM (http://warwick.ac.uk/snpm) to check whole-brain activation in patients and controls. Within each group, multi-subject one-sample t-tests with a cluster-defining threshold of $p < 0.01$ and F.W.E. cluster-corrected threshold of $p < 0.05$ over 10,000 permutations were conducted. The results of these analyses are shown in Supplemental Figure 1.

2.3.2.3. Definition of anatomically-constrained bounding masks: Masks within the anatomical boundaries of LIFGtri, LMFG and LpMTG were created to ensure that the signal extracted for the effective connectivity analysis was in a similar anatomical location across participants. First, one-sample t-test results in the control group at an uncorrected threshold ($p < 0.001$) were used to localize unique peak maxima within each region of interest (Figure 2A). The MNI coordinates corresponding to each peak were entered as the center input of rectangular bounding masks created in the MarsBaR toolbox (Brett, Anton, Valabregue, & Poline, 2002) for LIFGtri (mask dimensions: 35×35×35mm), LMFG (mask dimensions: 35×50×35mm) and LpMTG (mask dimensions: 35×50×35mm). Next, the rectangular masks were trimmed to fit the anatomical boundaries of each region per the SPM Anatomy toolbox (Eickhoff et al., 2005) (Figure 2B). To account for PWA's lesions (see Figure 2C for patient group lesion overlay), a manually-drawn lesion map for each patient (e.g., Figure 2D) was overlaid onto the bounding masks and lesioned voxels were subtracted from each mask. The amount of spared tissue within each anatomically constrained bounding mask was determined for each patient by subtracting their normalized lesion volume from the volume of the bounding mask and dividing that amount by the volume of the bounding mask (Figure 2E). Thus, bounding masks were tailored for each patient so that the area from which signal was extracted reflected tissue without frank damage from stroke (Figure 2F).

2.3.2.4. Extraction of contrast estimates: To assess potential between-group differences in activation strength within the three ROIs and the potential effects such differences might have on connectivity, contrast estimates for *pictures – scrambled pictures* were extracted from the 2nd-level one-sample t-tests from each anatomically constrained bounding mask with MarsBaR (Brett et al., 2002). Raw data with the grand mean scaled to zero were estimated for each participant. Differences in contrast estimates between groups were compared via a one-way MANOVA with participant group as the independent variable and regional contrast estimates as the dependent variables.

2.4. Effective connectivity analysis

Dynamic causal modeling (DCM) is a hypothesis-driven method of effective connectivity used to make inferences about how the coupling between modeled brain regions is influenced by an experimental task (Friston et al., 2003; Kahan & Foltynie, 2013; Seghier, Zeidman, Neufeld, Leff, & Price, 2010; Stephan et al., 2010; Stephan, Weiskopf, Drysdale, Robinson, & Friston, 2007). More specifically, DCM utilizes Bayesian estimations on

parameters of a dynamic multiple input-state-output model. The basic DCM implementation includes three main components: (1) inputs that are stimulus functions that correspond to external experimental manipulations (i.e., experimental task or conditions), (2) state variables that include neuronal and neurophysiological variables required to form outputs, and (3) outputs that correspond to hemodynamic responses in fMRI studies. DCM models five state variables for each region of interest. Neuronal activity within each region is fed forward into a hemodynamic balloon model that models four state variables (i.e., signal increases from vasodilation, blood inflow, changes in blood volume, and changes in deoxyhemoglobin). Observed changes in hemodynamic response are then linked to "hidden" neuronal states in the form of synaptic activity; as such, DCM allows for inferences about direct neural activity via the fifth and final state variable (Friston et al., 2003). Critically, three parameters within the neuronal state equation are estimated; specifically, differential equations within the DCM-A matrix model the intrinsic coupling between regions in the absence of task input; the DCM-B matrix models the change in the rate of coupling between regions induced by an external task; and the DCM-C matrix models exogenous perturbation of task input on a given region in the model. The remainder of this section describes the DCM implementation for the present study.

2.4.1. Model specification—The DCM model space from Meier et al. (2016) was utilized in the present study to test our hypotheses regarding dynamic connectivity during semantic judgments. As alluded to in the Introduction, prior fMRI studies have highlighted the importance of the three left hemisphere regions included in the model space (i.e., LIFGtri, LMFG, and LpMTG) for different cognitive functions during lexical-semantic processing in both healthy individuals and PWA. For this reason, Meier et al. (2016) constructed the model space to examine effective connectivity during overt picture naming, a task that has different (e.g., increased executive control during semantic selection) but overlapping (e.g., lexical-semantic processing) task demands as the semantic feature verification task. As such, comparing the results from these two investigations can provide additional insight into left hemisphere connectivity dynamics in chronic stroke patients.

Specification of the structure of the DCM-A, -B, and -C matrices followed Meier et al. (2016). In brief, fully inter-connected intrinsic connections were modeled in the DCM-A matrix given the robust network of white matter structures connecting these regions (Bajada et al., 2017; Catani & Mesulam, 2008; Catani, Howard, Pajevic, & Jones, 2002; Catani, Jones, & ffytche, 2005; Cloutman & Lambon Ralph, 2012; Dick, Bernal, & Tremblay, 2014; Frey, Campbell, Pike, & Petrides, 2008; Glasser & Rilling, 2008; Jung, Cloutman, Binney, & Lambon Ralph, 2017; Sarubbo, De Benedictis, Maldonado, Basso, & Duffau, 2013). The condition effect of *pictures* was systematically modeled onto connections between regions in the DCM-B matrix, such that all possible combinations of task modulation on uni- and bidirectional connections were specified. Last, direct task-induced perturbation from the *pictures* condition was modeled in the DCM-C matrix to one of the three regions within each model. Not only have other studies using DCM (Allen et al., 2008; den Ouden et al., 2012; Eickhoff, Heim, Zilles, & Amunts, 2009; Hartwigsen, Saur, Price, Baumgaertner, et al., 2013; Hartwigsen, Saur, Price, Ulmer, et al., 2013; Heim, Eickhoff, & Amunts, 2009; Seghier, Josse, Leff, & Price, 2011; Volz, Eickhoff, Pool, Fink, & Grefkes, 2015) similarly

modeled input to higher-level cortex, but also this implementation was particularly useful in the present sample of PWA as these individuals exhibited varying degrees of regional damage that may have influenced connectivity patterns. The final model space included 72 individual models and was partitioned into three families, with exogenous input modeled to LIFGtri for the first 24 models (i.e., Family #1), LMFG for the next 24 models (i.e., Family #2) and LpMTG for the final 24 models (i.e., Family #3) (see Supplemental Figure 2).

2.4.2. Volume of interest (VOI) extraction and model estimation—For each participant, peak maxima within the LIFGtri, LMFG and LpMTG bounding masks were identified from the 1st-level GLM at an uncorrected threshold ($p < 0.001$). If the local maxima within a given anatomical region fell outside the regional bounding mask, the MNI coordinates of the second or third most-active peaks at $p < 0.001$ or the strongest peak at a reduced threshold ($p < 0.01$) were identified. Volumes of interest (VOIs) were extracted as 8mm eigenvariate spheres surrounding the MNI coordinates of selected peaks. For PWA with less than approximately 50% spared tissue within a regional bounding mask who also did *not* exhibit perilesional activation within the mask, a noisy signal (i.e., at a threshold of uncorrected, $p = 1.0$) was extracted from the damaged region at the coordinates corresponding to the controls' regional peak. This method, which has been used in previous studies of network reorganization in stroke patients (Seghier, Bagdasaryan, Jung, & Price, 2014; Seghier et al., 2012), constitutes a good approximation of damage within the language system (Seghier et al., 2010) and allows for the inclusion of PWA who would otherwise be excluded from the DCM analysis. Following VOI extraction, models according to the model space were estimated for all participants. To minimize the complexity of the models while still capturing potential excitatory and inhibitory inter-regional modulation, a bilinear, deterministic two-state implementation was utilized.

2.4.3. DCM model and parameter inference—Inferences at the model and parameter levels were made to evaluate the DCM results. First, fixed effects Bayesian parameter averaging (BPA) was applied for each participant across outputs that corresponded to each run of the task. In the BPA analysis, the individual posterior densities from the two runs were combined by treating the posterior of one run as the prior for the other run (Stephan et al., 2010). This method was useful for obtaining one representative set of models for each participant. Next, to account for potential model structure uncertainty, a random-effects family-wise Bayesian model selection (BMS) procedure was used to establish which family of models best fit the data at both the individual and group levels (Penny et al., 2010). In this analysis, model inference is made on the posterior probability estimates of model family frequency, and as such, a model family's exceedance probability (xp) value reflects the certainty that a given family of models is more likely than other model families to fit the data (Stephan, Penny, Daunizeau, Moran, & Friston, 2009).

Because we expected best-fit families to differ between participant groups, we additionally applied Bayesian model averaging (BMA) across model families for parameter extraction. BMA resulted in one set of parameters that reflected weighted average connectivity of the six connections (i.e., LIFGtri→LMFG, LIFGtri→LpMTG, LMFG→LIFGtri, LMFG→LpMTG, LpMTG→LIFGtri, LpMTG→LMFG) wherein models with high

evidence for a participant contributed more greatly to the strength of task-modulated connections (measured by Ep.B values) than models with low evidence. One-sample t-tests were used to determine significant connections within each participant group. A one-way MANOVA was conducted to determine between-group differences in connection strength. In order to mitigate potential effects of regional activity to input regions influencing between-group differences, two-way MANOVAs with independent factors of group and regional activity within bounding regions (captured via contrast estimates described in section 2.3.2.4) were also conducted. Finally, backward stepwise regression was used to determine neural metrics (i.e., DCM parameters, contrast estimates) that were associated with lexical-semantic skills inside and outside of the scanner in the patient group.

3. Results

3.1. ROI analyses

The location of peak maxima was most similar between groups in the two frontal ROIs. Specifically, both groups showed peak activity in the dorsal portion of LIFGtri (MNI coordinates for controls: −45, 27, 18 and PWA: −51, 27, 21) and in LMFG bordering the precentral gyrus (MNI coordinates for controls: −39, 0, 60 and PWA: −36, −3, 60). While the left middle temporal peak was located in LpMTG in both groups, the patient group peak was superior to the controls' peak (MNI coordinates for controls: −57, −45, −6 and PWA: −57, −42, 6). The spatial extent of activity within the ROIs was smaller in LIFGtri and LpMTG and greater in LMFG in PWA compared to controls (Figure 3A). The overall MANOVA model testing for between-group differences in the strength of regional activity in the three anatomical bounding masks was not significant ($F(3,38) = 2.364$, Pillai's trace = 0.157, $p = 0.086$) (Figure 3B). The fact that the extent—but not strength—of activation differed between groups accords with the relative damage to LIFGtri and LpMTG and sparing of LMFG in the individuals with aphasia, as shown in Table 2.

Across the patient group, LpMTG was the most damaged anatomical ROI whereas LMFG was the most spared. Eleven PWA had approximately 50% or less spared tissue within at least one regional mask. Three individuals (i.e., P4, P12 and P16) had less than 50% spared tissue in two or all three ROI masks. Of the patients with highly damaged ROIs, noisy VOIs were extracted in LIFGtri for three PWA and in LpMTG for five PWA. Perilesional activity noted outside the boundaries of the masks was extracted for some PWA in order to maximize the number of functional peaks and connections. Ultimately, at least two functional peaks were extracted for all PWA excluding P12. This patient exhibited a high degree of damage to all three regions, and only one perilesional functional peak was identified; thus, this participant was excluded from the remaining analyses.

To ensure that all participants' regional peaks were proximal to the center of each regional mask, the distance between the control group's peaks (i.e., LIFGtri: −45, 27, 18; LMFG: −39, 0, 60; and LpMTG: −57, −45, −6) and each subject's corresponding regional peak was calculated for both PWA (Figure 4A) and controls (Figure 4B) using the distance formula:

$$d = \sqrt{(x_2 - x_1)^2 + (y_2 - y_1)^2 + (z_2 - z_1)^2}$$

There were no significant differences between groups in the distance between individual peaks and the control group's peak for LIFGtri ($t(36.55) = -1.261$, p = 0.215; controls' mean distance = 12.87 ± 3.88mm; PWA's mean distance = 11.27 ± 4.07mm) or LMFG ($t(35.841) = -0.022$, p = 0.983; controls' mean distance = 18.83 ± 6.55mm; PWA's mean distance = 18.76 ± 12.87mm). By contrast, the distance between the controls' LpMTG peak and individual LpMTG peaks approached significance wherein a greater mean distance was found for PWA compared to controls ($t(29.241) = 2.025$, p = 0.052; controls' mean distance = 16.03 ± 6.00mm; PWA's mean distance = 21.97 ± 11.50mm) (Figure 4C). The results are expected given the degree of damage to the LpMTG bounding mask across the patient group and the necessity of extracting perilesional peaks outside the mask for some PWA. Nevertheless, these collective results provide some certainty that potential between-group differences in connectivity were not solely due to between-group differences in the location of regional activity.

3.3. DCM model inference

In line with our hypotheses, the best-fit model family in the patient group was Family #2: Input to LMFG (xp = 0.837). Contrary to our hypotheses, Family #2 was also the model family that best characterized the control group's data (xp = 0.654). However, Family #2 was not uniformly the best family to model all controls' data, as evidenced by the exceedance probability value for Family #1: Input to LIFGtri at the group level (Figure 5). Three of the 72 individual models best characterized controls' data, including one fully-connected bidirectional model from Family #1: Input to LIFGtri (i.e., model #24 [xp = 0.297]) and two highly-connected bidirectional models from Family #2: Input to LMFG (i.e., models #42 [xp = 0.252] and #48 [xp = 0.265]). (See Supplemental Figure 2 for visualization of model #24 and Supplemental Figure 3 for visualization of models #42 and #48). While the exceedance probability for Family #2 was higher for the patient group, six PWA demonstrated a preference for Family #1: Input to LIFGtri and six PWA showed a preference for Family #3: Input to LpMTG at the single-subject level. Given the heterogeneity of model fit, averaged parameters weighed according to model evidence across all models (obtained via the BMA procedure) were extracted for further analysis.

3.4. DCM parameter inference

First, to validate the use of the noisy VOI methodology in a larger sample of stroke patients than has been explored previously, we performed an analysis with the subgroup of PWA for whom noisy VOIs were extracted. For this analysis, connections were coded as noisy if the noisy VOI was either the modulatory or the target region and as potentially functional if the noisy VOI was neither the modulatory nor the target region. For example, if a noisy VOI was extracted for LpMTG for a patient, connections involving LpMTG (i.e., LIFGtri→LpMTG, LMFG→LpMTG, LpMTG→LIFGtri, and LpMTG→LMFG) were coded as noisy, and connections without LpMTG (i.e., LIFGtri→LMFG and LMFG→LIFGtri) were considered potentially functional. A one-way ANOVA with connection type (i.e., noisy/functional) as the independent variable and the strength of task-modulated connections (i.e., Ep.B values) as the dependent variable revealed that potentially functional connections had significantly higher Ep.B values than noisy connections ($F(1,40) = 9.501$, p = 0.004), indicating that noisy signals did not artificially induce higher Ep.B values. Furthermore, across the entire

patient group, the amount of spared tissue within the anatomical bounding masks of driving regions was not associated with the strength of task-modulated connections (range: r = −0.034 – 0.368, p = 0.386 – 0.873 after FDR correction for multiple comparisons), indicating that patient connectivity was not merely a reflection of the integrity of network regions.

Next, modulatory connections within and between groups were further interrogated. In controls, significant connections per one-sample t-tests included LIFGtri→LpMTG ($t(17) = 2.928$, p = 0.019), LMFG→LIFGtri ($t(17) = 5.118$, p < 0.001) and LMFG→LpMTG ($t(17) = 4.800$, p < 0.001) after FDR correction for multiple tests (Figure 6A). After FDR correction, significant task-modulated connections for PWA also included LMFG→LIFGtri ($t(23) = 6.219$, p < 0.001) and LMFG→LpMTG ($t(23) = 4.725$, p < 0.001), as well as LpMTG→LIFGtri ($t(23) = 2.819$, p = 0.020) (Figure 6B). It should be noted that positive Ep.B values are typically interpreted as denoting an excitatory influence of one region on another, whereas negative values reflect inhibitory effects. Given that all significant Ep.B values were positive across groups, these results indicate that driving regions had an excitatory effect on target regions, where the greater the value, the stronger the effect.

Comparisons between groups in modulatory connections did not reach significance ($F(6,35) = 1.826$, p = 0.123). Given that the model space was structured according to exogenous input to ROIs, it stands to reason that regional activity may have influenced comparisons in connection strength between groups. In other words, we wanted to ensure that the null between-group result was not merely the consequence of the magnitude of activity in a given region, given that DCM connectivity parameters reflect how the rate of activity change in one region influences the rate of change in another region. Therefore, the previous analysis was re-run as three two-way MANOVAs with independent variables of group and contrast estimates from the LIFGtri, LMFG, or LpMTG bounding masks and dependent variables of Ep.B values per connection. In the models controlling for regional activation, the main effect of group still was not significant when contrast estimates from the LIFGtri ($F(6,34) = 1.903$, p = 0.109), LMFG ($F(6,34) = 1.803$, p = 0.128), and LpMTG ($F(6,34) = 1.804$, p = 0.128) masks were included in the models. The effect of activation in the bounding masks also was not significant in any model (LIFGtri beta weights: $F(6,34) = 1.573$, p = 0.185; LMFG beta weights: $F(6,34) = 0.821$, p = 0.562; LpMTG beta weights: $F(6,34) = 0.580$, p = 0.743). Despite the suprising lack of statistically-significant between-group differences in strength of connections, these results indicate that similarities in control and patient connectivity were not primarily driven by activation within the anatomical bounding masks.

3.5. Relationship between activation, connectivity, and behavior in PWA

Finally, the relationship between neural metrics and lexical-semantic skills was examined in the patient group. While interrogating within-scanner performance (via accuracy on the fMRI task) allowed for the tightest inferences regarding brain and behavior relationships, examining lexical-semantic skills outside the scanner (via accuracy on PALPA 51) avoided the potential confounds of practice effects (as PWA were trained extensively on the fMRI task before scanning) and reductions in patient accuracy due to time constraints imposed by the fMRI protocol. To ensure that accuracy on the fMRI task and PALPA 51 reflected a

similar (but not entirely overlapping) skill, we first conducted a Spearman correlation between these two behavioral metrics. A strong, positive correlation between patients' accuracy on the scanner task and their performance on PALPA 51 ($r = 0.770$, $p < 0.001$) was found. Therefore, each behavioral metric was entered into separate backward stepwise regression models as the dependent variable. The independent variables in each regression included Ep.B values for each connection and contrast estimates in the three anatomical bounding masks.

The final model predicting fMRI task accuracy from functional metrics was significant ($F(4,18) = 3.910$, $p = 0.019$, adjusted $R^2 = 0.346$) and included two of the six connections (i.e., LMFG→LpMTG and LpMTG→LIFGtri) and contrast estimates from the LIFGtri and LMFG masks as factors. Significant independent positive predictors of behavioral accuracy included the LpMTG→LIFGtri connection ($\beta = 0.415$, SE = 0.157, $t = 2.637$, $p = 0.017$) and LIFGtri beta weights ($\beta = 0.135$, SE = 0.056, $t = 2.416$, $p = 0.027$). In other words, greater excitatory coupling (indicated by higher Ep.B values) from LpMTG to LIFGtri and stronger activity within the LIFGtri mask were associated with better performance on the fMRI task (Figure 7A/B).

Similarly, the final model predicting PALPA 51 accuracy was significant ($F(4,19) = 7.613$, $p < 0.001$, adjusted $R^2 = 0.535$) and included two of the six connections (i.e., LMFG→LIFGtri and LpMTG→LIFGtri) as well as constrast estimates from the LIFGtri and LpMTG masks. As with fMRI task accuracy, significant positive predictors of semantic association skills per PALPA 51 were LpMTG→ LIFGtri ($\beta = 0.497$, SE = 0.176, $t = 2.830$, $p = 0.011$) and LIFGtri contrast estimates ($\beta = 0.125$, SE = 0.047, $t = 2.649$, $p = 0.016$). Contrast estimates extracted from the LpMTG bounding mask also significantly predicted PALPA 51 accuracy, but an inverse relationship was found ($\beta = -0.262$, SE = 0.068, $t = -3.867$, $p = 0.001$). In other words, greater activity within the LpMTG bounding mask was linked to *lower* accuracy on PALPA 51 (Figure 7C/D). In all, these results indicate that similar patterns of excitatory connectivity and stronger LIFGtri activity were linked to optimal patient performance on lexical-semantic tasks inside and outside of the scanner, whereas a dissociation in LpMTG activation and connectivity during lexical-semantic processing in PWA was observed.

4. Discussion

In this study, we investigated differences between healthy controls and a heterogeneous group of PWA in left hemisphere effective connectivity during a semantic feature judgment task. We also determined relationships between neural metrics and lexical-semantic processing abilities in the patient group. Using a systematic approach to localize activation and account for lesioned tissue in PWA, we found no differences between patients and controls in the strength of regional activity within anatomical bounding masks in LIFGtri, LMFG or LpMTG for semantic feature decisions. The DCM analysis revealed that the best-fit model family for both PWA and control group data was Family #2: Input to LMFG, although heterogeneity in model fit across groups was noted. At the connection level, modulation of LpMTG and LIFGtri by LMFG characterized the strongest connections in both participant groups. By contrast, the LIFGtri→LpMTG connection was significant

within the control network whereas PWA relied on the reverse connection. Last, within the patient group, we discovered that better performance on lexical-semantic tasks inside and outside the scanner was associated with greater coupling of LpMTG→LIFGtri as well as stronger activity within the LIFGtri. Each of the aforementioned results is considered below in greater detail in the context of findings from previous fMRI studies.

First, activation analyses that preceded DCM revealed similar patterns of left hemisphere activity in patients and controls, yet the spatial extent of activated clusters differed between groups (i.e., greater spatial extent in LMFG and domain-general cortex for PWA and in LIFGtri and LpMTG for controls) (see Supplemental Figure 1). Despite several PWA demonstrating a fair degree of damage to LIFGtri and LpMTG, the strength of activity within the anatomical bounding masks did not significantly differ between groups. It is possible that the surprisingly high activation in the patient group was driven by PWA with mostly spared ROIs. Alternatively, because contrast estimates in PWA were extracted from anatomical masks that accounted for lesion, the activation within the masks may be perilesional activity in PWA with damaged ROIs. If so, such perilesional activity may reflect some mechanism of earlier neural recovery that allowed for reinstatement of premorbid left hemisphere activation patterns by the chronic post-stroke stage (Saur et al., 2006). Critically, these results also lend credence to our activation localization approach in PWA and provide a basis for interpreting between-group comparisons of the connectivity results.

Turning to the DCM findings, the fact that the fit of Family #2: Input to LMFG models was so high in the PWA group indicates that the majority of patients, despite heterogeneous behavioral and lesion profiles, preferred this family of models. This finding aligns with our hypotheses and previous studies (Geranmayeh et al., 2017; Meier et al., 2016; Turkeltaub et al., 2011) that have demonstrated the importance of dorsal prefrontal cortex—and LMFG specifically—within the language network in individuals with chronic aphasia. By itself, this result also provides support for the theory that patients rely on MD regions for language processing when cognitive demands are high (Fedorenko, Duncan, & Kanwisher, 2013; Fedorenko et al., 2012; Fedorenko & Thompson-Schill, 2014). However, contrary to our hypotheses, Family #2: Input to LMFG was also the winning model family for the control group. Notably, model fit in controls was split evenly between three individual models, including one model from Family #1: Input to LIFGtri and two models from Family #2: Input to LMFG. Full, bidirectional task-modulated connections (excluding LIFGtri→LpMTG in one model) comprised each of these models. As such, it may be that the primary driving force behind model fit in the control group was the degree of connectivity between regions while the particular input region exerted a smaller—although still critical—impact. In general, the control results align with literature that reports a heightened reliance in older adults on prefrontal cortex for tasks requiring retrieval of lexical-semantic information (Baciu et al., 2016; Davis, Zhuang, Wright, & Tyler, 2014; Manenti, Brambilla, Petesi, Miniussi, & Cotelli, 2013; Meinzer et al., 2009; Obler et al., 2010). However, this is a tentative explanation given that the current results cannot be compared to connectivity findings from another, less cognitive-demanding task in this older adult sample nor did we enroll a group of younger healthy controls for comparison to our healthy control group.

At the connection level, both groups demonstrated significant task-modulated connectivity of LMFG→LpMTG and LMFG→LIFGtri. One possible interpretation of these findings is that modulation of LpMTG by LMFG assisted participants in rapidly activating candidate semantic features whereas modulation of LIFGtri by LMFG assisted in the selection of the correct features of the target item. The directionality of these connections suggests cognitive control mechanisms were at play during semantic decisions (Fedorenko, Duncan, & Kanwisher, 2013; Fedorenko et al., 2012). For example, the location of the LMFG bounding mask aligns with a dorsal anterior premotor region posited as a potential hub for domain-general cognitive control and implicated in contextual control across a variety of tasks (Badre & Nee, 2018). Along the same vein, Xu, Lin, Han, He, and Bi (2016) found that the same region of LMFG was one of two key hubs that connected three dissociable modules of the semantic network (i.e., perisylvian network, fronto-parietal network and DMN). Binder and Desai (2011) posited that the role of this portion of the prefrontal cortex is in the translation of internal states into “a plan for top-down activation of semantic fields relevant to the problem at hand” (p. 532). Although the exact role of LMFG for participants in either group cannot be ascertained for certain, these connection results further cement the central role of LMFG within this small network in both PWA and healthy controls.

Surprisingly, the test comparing the strength of all connections between patients and controls did not reach significance. It should be noted that trends of stronger connectivity of LMFG→LpMTG in controls (Ep.B in controls = 0.84 and patients = 0.46) and marginally stronger connectivity of LMFG→LIFGtri in patients (Ep.B in controls = 0.71 and patients = 0.80) were observed, and thus, the lack of significant between-group results could be an issue of statistical power. Given that the area of greatest brain damage in the patients spanned tissue between LMFG and LpMTG (see Figure 2C), the weaker LMFG→LpMTG connection in PWA may reflect the consequence of functional disconnect for some individuals. On the other hand, the slightly stronger LMFG→LIFGtri patient connection value may indicate a need for heightened semantic control for some PWA in making semantic judgments or may be a consequence of functional reorganization of the semantic system following prior language treatment that targeted the semantic system (e.g., Kiran et al., 2015).

By contrast, striking differences between PWA and controls were also observed in the coupling of LIFGtri and LpMTG. Specifically, the one-sample t-test in controls revealed LpMTG→LIFGtri connection was not signicantly involved in their task-based semantic network. However, for PWA, greater connectivity of LpMTG→LIFGtri was associated with better accuracy on lexical-semantic tasks inside and outside the scanner and was a significant network connection per the one-sample test. Interestingly, the reverse connection (i.e., LIFGtri→LpMTG) was not significantly modulated by the task in PWA—unlike in controls—and was not related to lexical-semantic abilities per either behavioral measure in the patient group. It is possible that the directionality difference in LpMTG-LIFGtri coupling reflects neural reorganization in the patients that occurred in the months after stroke. Alternatively, the between-group difference could purely be a consequence of structural damage and/or disconnect in some PWA.

For PWA, better lexical-semantic abilities (per PALPA 51) were also associated with stronger activation within the LIFGtri bounding mask but weaker activity in the LpMTG mask. The former result is unsurprising since spared tissue and activation within LIFG has been linked with greater spontaneous and treatment-induced recovery of language skills in numerous patient studies (Abel, Weiller, Huber, & Willmes, 2014; Abel et al., 2015; Fridriksson et al., 2010; Kiran et al., 2015; Marcotte et al., 2012; Rochon et al., 2010; Rosen et al., 2000; Sims et al., 2016; van Hees, McMahon, Angwin, de Zubicaray, Read, et al., 2014; van Oers et al., 2010). On the other hand, the latter finding is unexpected given that temporoparietal cortex is considered a convergence zone of structural and functional networks that are crucial to semantic processing (Buckner et al., 2009; Davey et al., 2016; Griffis, Nenert, Allendorfer, & Szaflarski, 2017a, 2017b; Turken & Dronkers, 2011; Wei et al., 2012; Xu et al., 2016). One potential explanation is that strong local activity within LpMTG without communication to *other* regions (e.g., LIFGtri in this subnetwork) may be the consequence of maladaptive activation patterns or structural disconnection that results in poorer semantic performance (Abel et al., 2015; Griffis, Nenert, Allendorfer, & Szaflarski, 2017b). Furthermore, it is reasonable to assume heavy reliance on LpMTG without recruitment of frontal regions might be detrimental to performance on PALPA 51 as this semantic association task requires subjects to select a target item in the presence of multiple —including semantic—distractors. However, this conclusion is tentative as explicit investigation of LIFGtri-LpMTG activation and connectivity patterns during a semantic association fMRI task was not undertaken in the present investigation.

Overall, these collective results suggest that the activation and connectivity of regions implicated in domain-general processing (e.g., LMFG) and domain-specific semantic mechanisms (e.g., LIFGtri) are critical for patients with chronic aphasia during semantic feature decision-making. While the particular cognitive mechanisms mediated by these regions cannot be definitively determined from this experiment, these results loan credence to the notion that the connectivity of left hemisphere regions that potentially mediate domain-general processing (e.g., LMFG) constitutes ideal neural organization patterns in chronic stroke-induced aphasia. Certainly, the positive relationships between patients' lexical-semantic abilities and LIFGtri activity and LpMTG→LIFGtri connectivity aligns with Heiss and Thiel's (2006) proposal that regions within the canonical language network must be recruited for optimal language task performance in chronic aphasia.

A final contribution of the present work is that, to our knowledge, no other study has incorporated a similar multipronged approach to account for individual lesion variability and also provided conclusions regarding task-based connectivity at the group level in patients with chronic aphasia. Several steps were taken to ensure reliability of the signal extracted for the effective connectivity analysis, including the creation of individualized anatomical bounding masks for each patient. As a result, we were able to successfully account for a diverse group of PWA with different lesion profiles, consistent with the greater population of PWA. One of the greatest challenges in investigating neural reorganization in post-stroke aphasia is the inherent heterogeneity of PWA. As such, despite our best efforts, P12 was still excluded from the connectivity analysis given the size of his lesion and damage to the ROIs. One way to accommodate such heterogeneity—including between-group differences in certain demographic variables (i.e., handness, gender)—would be to recruit a larger sample

of PWA so that participants could be split into subgroups according to behavioral, demographic and/or stroke profiles.

Future work could also mitigate such limitations of the present study by interrogating right hemisphere and interhemispheric connectivity in addition to left hemisphere interactions. Furthermore, it is possible that the inclusion of other regions implicated in semantic processing (e.g., posterior mPFC, ITG) would alter the present results. As such, follow-up investigations that pair exploratory functional connectivity and hypothesis-driven effective connectivity methods would be beneficial for providing further information regarding the most critical regions and connections for semantic processing in PWA. Last, while we accounted for the structural integrity of local regions, we did not incorporate metrics reflecting the integrity of white matter pathways connecting the three left hemisphere cortical nodes. As shown in emerging work (e.g., Pustina et al., 2017), multimodal investigations that measure both structural and functional connectivity may provide the best explanatory power of language skills in PWA and should be the focus of future work regarding the neural bases of lexical-semantic processing in PWA.

5. Conclusions

In sum, the present investigation revealed that at a high level, individuals with chronic aphasia with diverse behavioral and stroke profiles demonstrate some similarities to age-matched healthy controls in activation and connectivity patterns during lexical-semantic deicisions. Specifically, similar to controls, PWA recruited canonical left hemisphere language regions (i.e., LIFGtri, LpMTG) for the fMRI task although the extent of activation in such classic language regions was less for PWA compared to their healthy counterparts. By contrast, the extent of activity in regions associated with domain-general processing (e.g., LSFG, LMFG, left posterior mPFC) was greater in PWA relative to controls. Nonetheless, both groups relied on LMFG-driven connections during the fMRI task, a finding which aligns with work highlighting the importance of dorsolateral prefrontal cortex in cognitively-demanding tasks in healthy and disordered populations. Fine-grained differences in LIFGtri and LpMTG coupling and recruitment within each participant group further revealed neural reorganization patterns associated with healthy aging versus chronic aphasia. In particular, optimal lexical-semantic abilities in PWA were linked to greater excitatory modulation of LIFGtri by LpMTG, presumably resulting in beneficial heightened recruitment of LIFGtri for the task. Future work should endeavor to further disentangle beneficial LIFG-LMTG effective connectivity patterns for related tasks, determine the structural pathways most critical for mediating such connections, and determine the role of right hemisphere homologues of these regions from a network perspective.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AG	angular gyrus
ACC	anterior cingulate cortex
aSTG	anterior superior temporal gyrus
BMA	Bayesian model averaging
BPA	Bayesian parameter averaging
BMS	Bayesian model selection
CSC	controlled semantic cognition
DCM	dynamic causal modeling
DMN	default mode network
IFG	inferior frontal gyrus
op	pars opercularis of IFG
orb	pars orbitalis of IFG
tri	pars triangularis of IFG
ITG	inferior temporal gyrus
iOCC	inferior occipital cortex
GLM	general linear model
IPS	intraparietal sulcus
L prefix	denotes left hemisphere lateralization
mPFC	medial prefrontal cortex
MCA	middle cerebral artery
MCC	mid-cingulate cortex
MFG	middle frontal gyrus
MPO	months post-onset
MTG	middle temporal gyrus
pMTG	posterior portion of MTG

MD	multiple demand
PWA	persons with aphasia
R prefix	denotes right hemisphere lateralization
ROI(s)	region(s) of interest
RT	reaction time
SFG	superior frontal gyrus
SMA	supplementary motor area
SMG	supramarginal gyrus
VOI(s)	volume(s) of interest
xp	exceedance probability value

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Highlights

- Both patients with aphasia and age-matched healthy adults demonstrated left-lateralized frontotemporal activation during the semantic feature judgment task, including activity in the three regions (i.e., LIFGtri, LMFG, and LpMTG) selected *a priori* for effective connectivity analysis.
- Task-based effective connectivity was characterized by a similar reliance on LMFG-driven connections in patients and controls.
- Within the patient group, greater modulation of LIFGtri by LpMTG and greater local recruitment of LIFGtri for the semantic feature task was positively associated with lexical-semantic abilities inside and outside of the scanner.

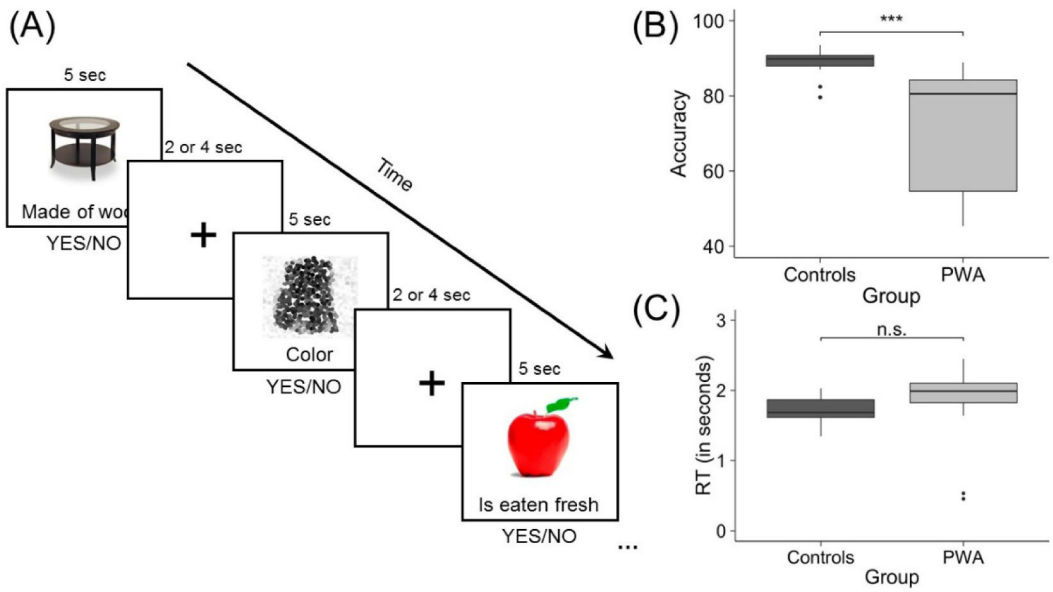

Figure 1.

fMRI task. (A) Example experimental and control trials and comparison of (B) fMRI task accuracy and (C) reaction times between participant groups

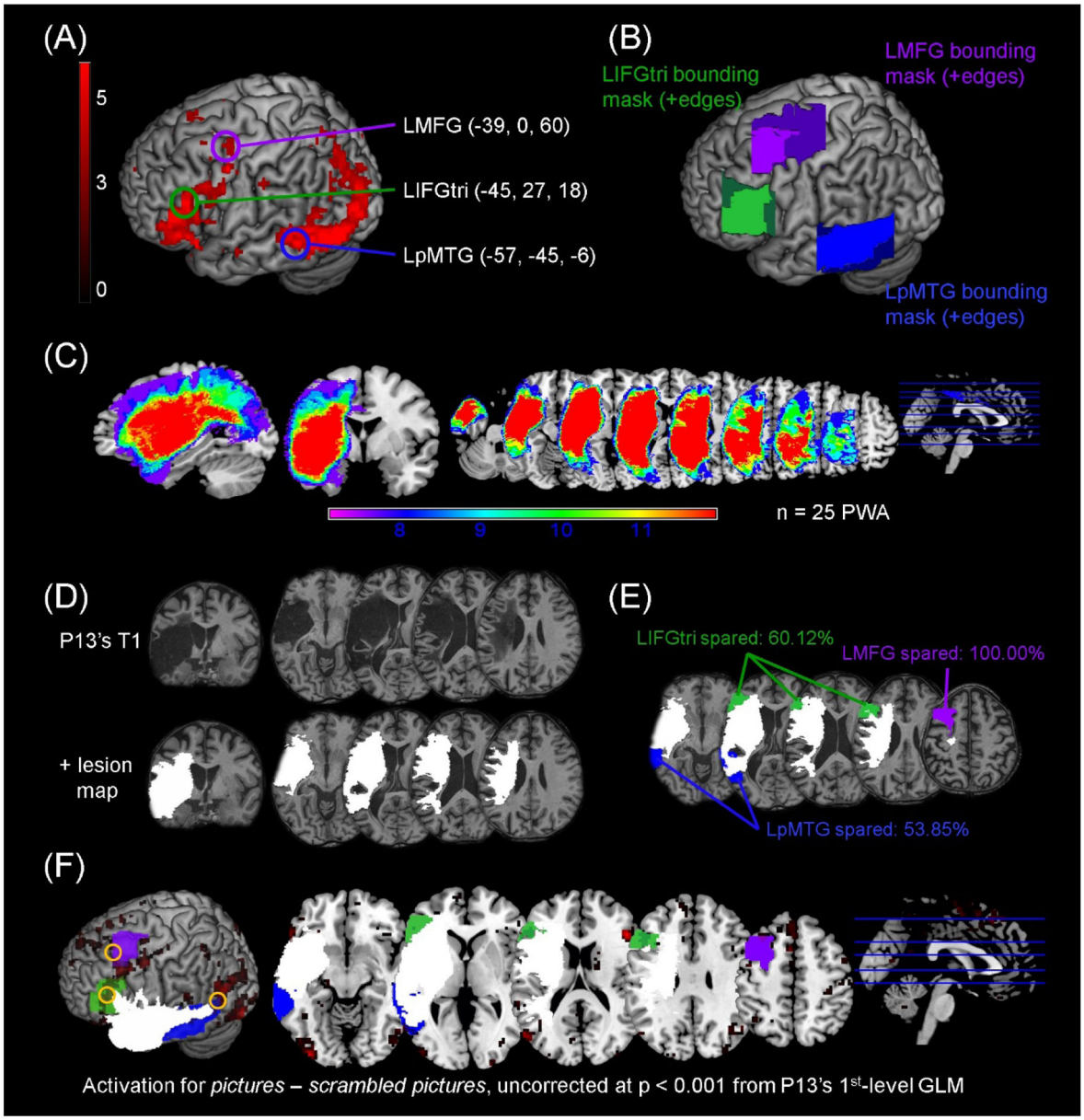

Figure 2.

Definition of anatomically-constrained bounding masks. (A) Rendered results of the control group 2nd-level analysis for *pictures – scrambled pictures*, uncorrected $p < 0.001$ are shown and activation peaks within each ROI that were used as the center input in the anatomically-constrained bounding masks are circled. (B) Rectangular bounding boxes at a search depth of 12mm are shown as dark edges. The edges were trimmed to constrain the masks to the anatomical boundaries of the ROIs, resulting in the three lightly-shaded masks used in other analyses. (C) Overlay of lesion maps from the patient group included in the DCM analysis are shown in sagittal, coronal and axial slices. (D) Lesion masks (in which lesioned voxels were deleted) were manually drawn slice-by-slice on each patient's T1 structural image in native space to create lesion maps (in which lesioned voxels were preserved). The

normalized lesion map overlaid on the normalized T1 structural image for one participant (i.e., P13) is shown to illustrate this process. (E) Each patient's lesion map was overlaid onto the anatomical bounding masks shown in (B) in order to create individually-tailored bounding masks reflecting the spared tissue within each mask. The percentage of residual tissue within each mask was determined by subtracting the patient's lesion volume from the volume of the anatomically-constrained bounding mask, divided by the volume of the mask. The lesion map (in white) and individually-tailored bounding masks are shown for P13. (F) Visual inspection of overlaid t maps for *pictures – scrambled pictures*, lesion maps, and individually-constrained bounding masks for each patient ensured that the extracted VOIs fell outside the lesion and within (or approximate to) the bounding mask borders. The location of P13's VOIs extracted for the connectivity analysis are denoted by the yellow circles.

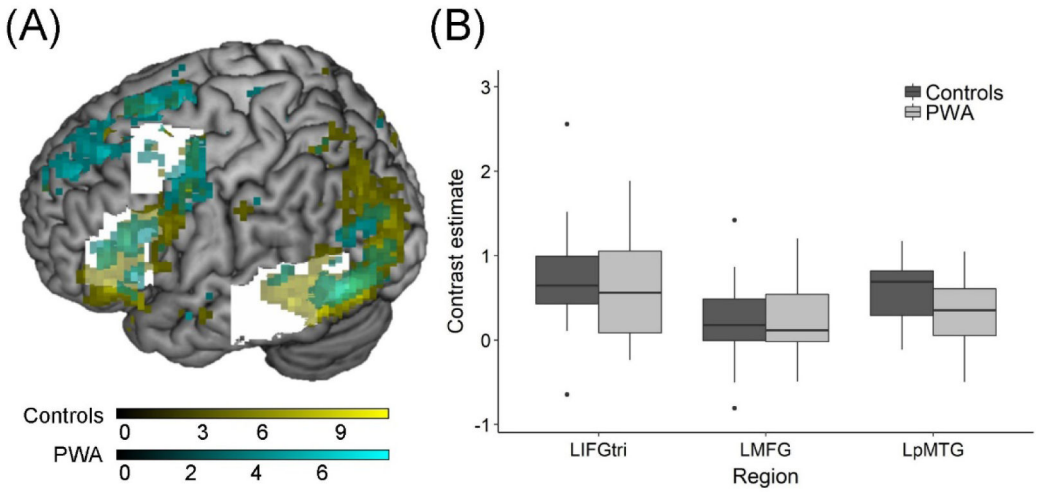

Figure 3.

Activity within bounding masks. (A) Rendered t-maps from the one-sample t-tests (at $p < 0.001$, uncorrected) in each group show activated clusters within the anatomical bounding masks (in white). (B) The comparison of contrast estimates extracted from the anatomical bounding masks for each participant revealed no significant differences.

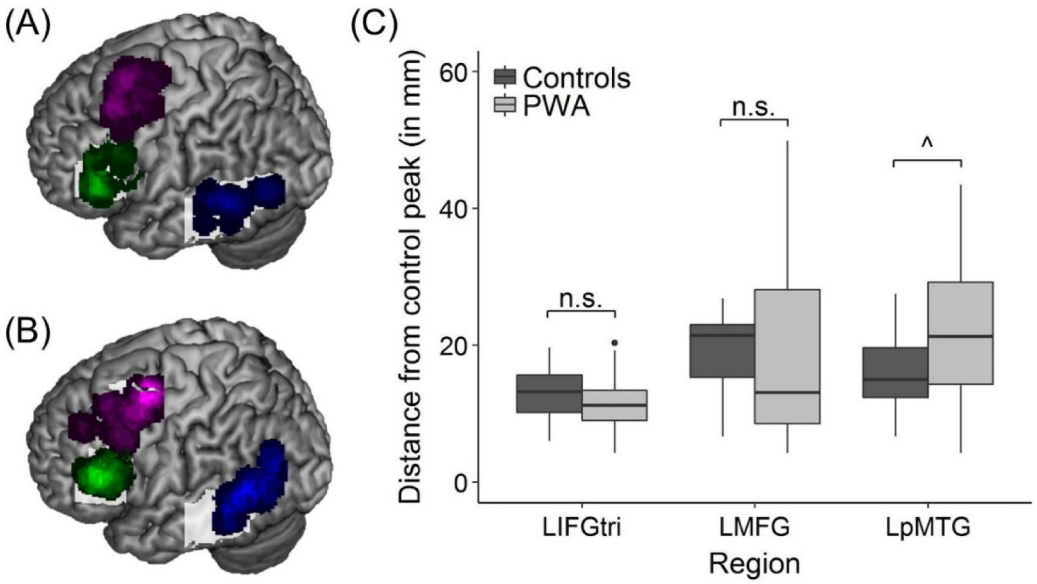

Figure 4.

VOI location. Overlays shown of all regional peaks for all (A) controls and (B) patients. (C) The results of the MANOVA revealed the distance between each subject's regional peak and the corresponding bounding mask peak did not differ between groups for LIFGtri and LMFG but approached significance for LpMTG. Note: for overlay of patients' VOIs, only functional spheres are shown (i.e., n = 21 LIFGtri VOIs, 24 LMFG VOIs, and 20 LpMTG VOIs)

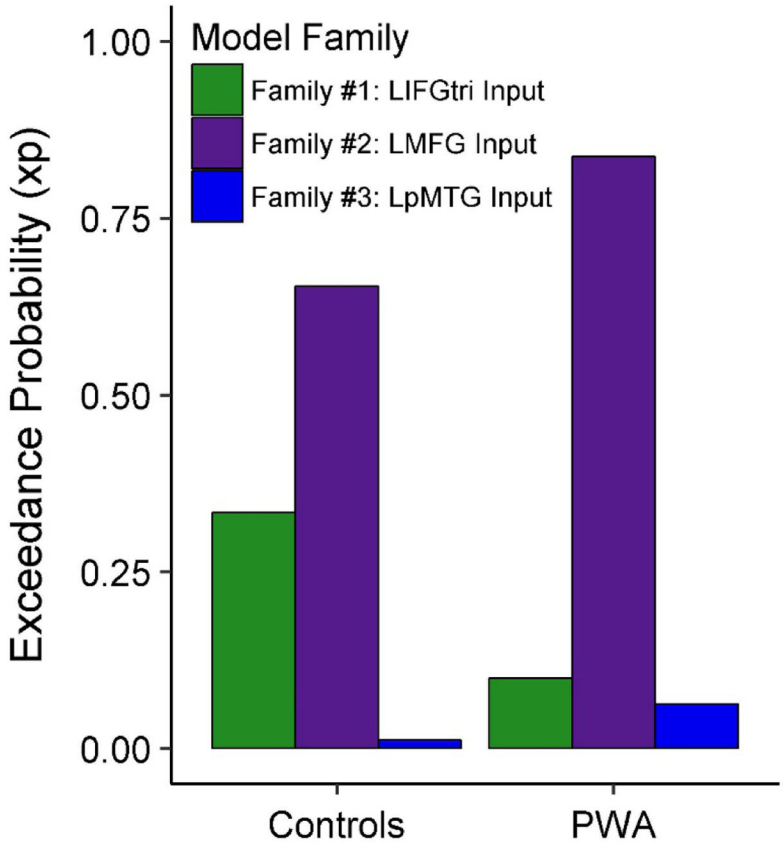

Figure 5.
Family-wise Bayesian model selection within each group

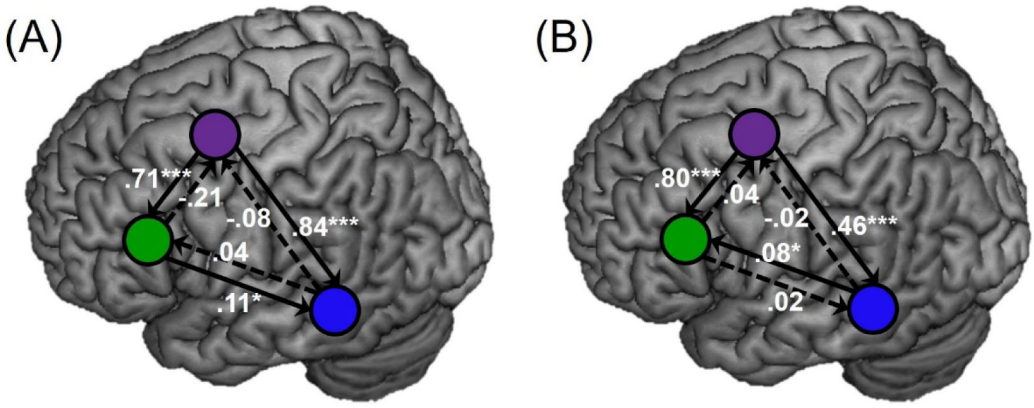

Figure 6.

Modulatory connections within the (A) controls and (B) PWA, with statistically significant and non-significant connections per one-sample t-tests denoted by solid and dashed lines, respectively. Purple = LMFG, blue = LpMTG, green = LIFGtri

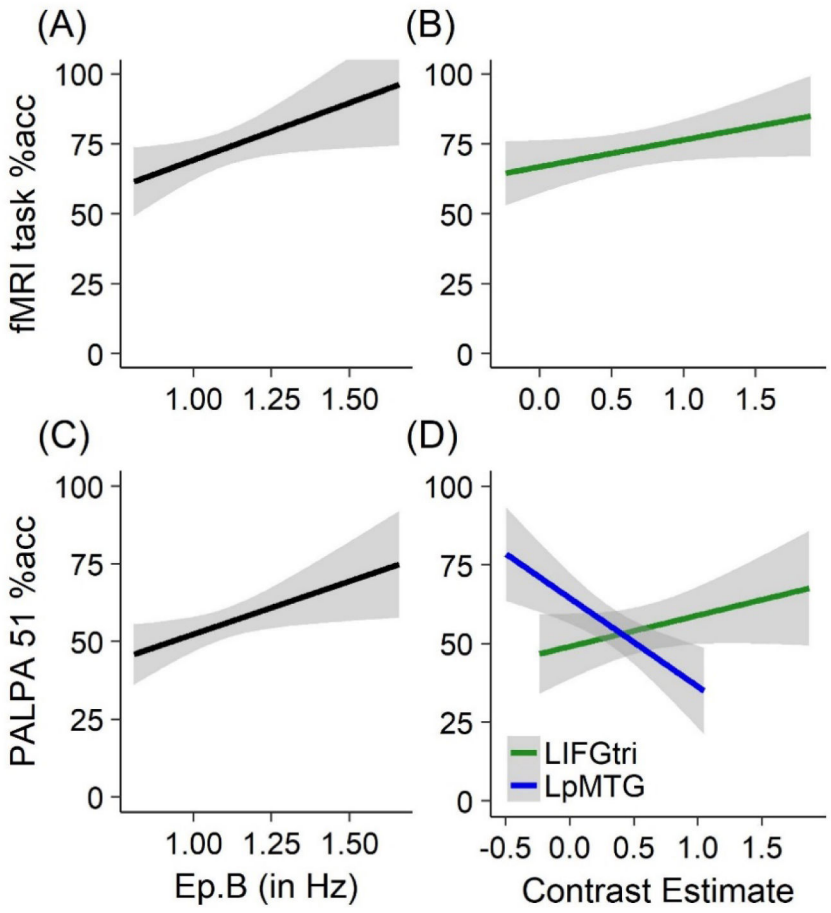

Figure 7.

Neural metrics predicting lexical-semantics showing relationships between (A) fMRI task accuracy and the influence of task-modulation on the strength of LpMTG→LIFGtri per Ep.B values (B) between fMRI task accuracy and contrast estimates within the LIFGtri bounding mask (C) between accuracy on PALPA 51 and the strength of LpMTG→LIFGtri (D) and between accuracy on PALPA 51 and contrast estimates extracted from the LIFGtri and LpMTG bounding masks.

Table 1.

Demographic, stroke, and behavioral data for PWA

ID	Gender	Age	Handedness	MPO	Lesion Volume*	WAB-R AQ	PPT	PALPA51
P1	M	55	R	12	74508	87.20	96.00	76.67
P2	M	79	R	13	92057	74.10	94.00	60.00
P3	M	67	R	8	172344	30.80	92.00	30.00
P4	M	49	R	113	324719	66.60	92.00	73.00
P5	M	55	R	137	210628	48.00	88.00	40.00
P6	F	71	R	37	11279	95.20	96.00	86.67
P7	F	53	R	12	68088	80.40	94.00	80.00
P8	M	68	R	104	210383	40.00	88.00	40.00
P9	M	42	L	18	8097	92.70	94.00	70.00
P10	F	64	R	24	59140	64.40	94.00	53.33
P11	F	70	R	62	130489	87.20	85.00	53.33
P12	M	50	R	71	321907	33.60	79.00	10.00
P13	M	61	R	152	159060	74.30	98.00	70.00
P14	F	70	R	152	154879	78.00	96.15	50.00
P15	M	80	R	22	87744	28.90	82.69	26.67
P16	F	48	R	20	257144	13.00	94.23	33.33
P17	M	69	R	164	235770	40.40	94.00	26.67
P18	F	76	R	33	136854	37.50	65.00	63.33
P19	F	64	R	115	279144	58.00	69.00	40.00
P20	M	63	R	22	111102	56.00	98.08	50.00
P21	M	49	R	49	79770	85.50	94.00	66.67
P22	M	82	R	12	57440	73.80	94.23	73.33
P23	M	39	R	18	13867	71.30	100.00	46.67
P24	M	64	L	13	56449	79.60	96.15	56.67
P25	M	62	L	21	5256	92.00	94.00	70.00
MEAN		**62.00**		**56.16**	**132724.72**	**63.54**	**90.70**	**53.85**
STDEV		**11.77**		**53.01**	**97283.45**	**23.49**	**8.65**	**19.53**

MPO = months post-onset; WAB-R AQ = Western Aphasia Battery-Revised Aphasia Quotient; PPT = Pyramids and Palm Trees Test; PALPA 51 = Psycholinguistic Assessment of Linguistic Processing in Aphasia, subtest 51;

*lesion volume in number of 1×1×1 mm voxels

Table 2.

Percentage of spared tissue per bounding mask

ID	LIFGtri	LMFG	LpMTG
P1	99.91	100.00	84.99
P2	100.00	100.00	36.30
P3	84.82	100.00	14.91
P4	15.88	68.24	11.44
P5	96.98	98.16	81.00
P6	100.00	100.00	100.00
P7	100.00	100.00	99.10
P8	34.49	100.00	85.78
P9	100.00	100.00	95.21
P10	77.86	95.61	87.10
P11	78.04	77.02	99.97
P12	36.03	28.01	10.99
P13	60.12	100.00	53.85
P14	84.26	100.00	52.53
P15	66.57	100.00	100.00
P16	2.60	98.48	42.82
P17	64.72	98.56	35.33
P18	95.17	100.00	65.60
P19	30.69	51.72	90.22
P20	71.36	100.00	25.66
P21	98.51	100.00	91.12
P22	100.00	100.00	41.57
P23	100.00	100.00	100.00
P24	98.24	100.00	100.00
P25	100.00	100.00	100.00
MEAN	**77.95**	**94.56**	**67.77**
STDEV	**28.38**	**15.82**	**31.98**