Cerebral perfusion in post-stroke aphasia and its relation to residual language abilities

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Running title: Cerebral perfusion in post-stroke aphasia

ABSTRACT

Stroke alters blood flow to the brain resulting in tissue loss. However, the disruption of cerebral blood flow (perfusion) can also be observed in surrounding tissue as well as distal areas. These structurally preserved but sub-optimally perfused regions may contribute less to recovery; thus, to better understand aphasia recovery the relationship between cerebral perfusion and language needs to be systematically examined. In the current study, we aimed to evaluate 1) how stroke affects perfusion outside of lesioned areas in chronic post-stroke aphasia, and 2) how perfusion in specific cortical areas and perilesional tissue relates to language outcomes in aphasia. We analyzed perfusion data from 43 participants with chronic aphasia due to left hemisphere stroke and 25 age-matched healthy controls. We used anatomically defined regions of interest that covered the frontal, parietal, and temporal areas of the perisylvian cortex in both hemispheres, along with several control regions, not implicated in language processing. For the aphasia group we also looked at three bands of perilesional tissue around the lesion. We compared perfusion levels between the two groups and investigated the relationship with between perfusion levels and language subtest scores while controlling for age, gender, time post-onset, scanning site, lesion volume, and lesion site. First, we observed that perfusion levels were significantly reduced in frontal and parietal areas in the left hemisphere in aphasia compared to the control group, while no differences were observed for right hemisphere regions. Second, we found that perfusion in the left temporal lobe (and most strongly in the posterior part of both superior and middle temporal gyri) and inferior parietal areas (supramarginal gyrus) was significantly related to residual language abilities. In contrast, perfusion in the frontal regions did not show such a relationship; no relationship with language was also observed for perfusion levels in control areas and all right hemisphere regions. Levels of perilesional perfusion were only marginally related to language production abilities. Cumulatively, the current findings demonstrate that blood flow is reduced beyond the lesion site in chronic post-stroke aphasia and hypoperfused neural tissue in critical temporo-parietal language areas may not be fully able to support recovery. These results underscore the critical and general role that left hemisphere posterior temporal regions play in various expressive and receptive language abilities. Overall, the study shows that slowed or reduced blood distribution can affect the functionality of regions beyond the lesion site and have a direct impact on behavioral outcomes.

Keywords: aphasia, language, perfusion, perilesional, temporo-parietal areas

1. INTRODUCTION

Stroke is a heterogeneous syndrome caused by multiple pathological mechanisms resulting in the disruption of cerebral blood flow (CBF). Decreases in the rate of delivery of blood to brain tissue (measured in units of ml blood/100 g tissue/min) result in subsequent cell death and tissue loss due to the lack of necessary oxygen (Markus, 2004). In human adults, normal CBF in different gray matter regions typically ranges from 35 to 80 mL/100 g/min depending on various factors such as age, sex, diet, cardiovascular fitness, and health status (Abbott, Baker, Chen, Liu, & Love, 2021; Joris, Mensink, Adam, & Liu, 2018; Leenders et al., 1990; Parkes, Rashid, Chard, & Tofts, 2004). Additionally, CBF is generally considered to be coupled with cerebral glucose metabolism (Newberg et al., 2005). Since blood carries oxygen and glucose to the brain that are both needed for aerobic metabolism underlying neural activity (Buxton, Uludağ, Dubowitz, & Liu, 2004), it is expected that lower perfusion may potentially impede normal functioning (Feeney & Baron, 1986; Girouard & Iadecola, 2006; Powers, Press, Grubb, Gado, & Raichle, 1987). Thus, perfusion may be a useful predictor of tissue status.

Beyond the core lesion, where a decline in blood flow also leads to cell death, a reduction in CBF has similarly been observed (Demeestere, Wouters, Christensen, Lemmens, & Lansberg, 2020). The most notable is the penumbra after ischemic stroke, a band of tissue that surrounds the core ischemic lesion. Penumbral tissue contains electrically unexcitable, but viable cells, which can regain their function if blood flow is promptly restored (Markus, 2004). Specifically, in animal models it was shown that brain tissue needs to be perfused at 10% of normal levels to survive, and at least at 30-50% for neuronal function (i.e., electrical signaling) to continue (Astrup, Symon, Branston, & Lassen, 1977; Sekhon, Morgan, Spence, & Weber, 1994). These thresholds are likely even higher for humans, though that remains to be ascertained (Hillis, 2007). Not only has altered perfusion been found in tissue surrounding the lesion after stroke, numerous reports have also described alterations in blood flow to distal areas as well (Brumm et al., 2011; Mimura et al., 1998), that could be due to a number of factors, including diaschisis (Carrera & Tononi, 2014).

Accumulating evidence suggests that there is a relationship between reduced regional perfusion and cognitive outcomes in chronic stroke (> 6 months post-stroke) (Boukrina, Barrett,

& Graves, 2019; Love, Swinney, Wong, & Buxton, 2002; Mimura et al., 1998; Richardson et al., 2011; Robson et al., 2017; Thompson et al., 2017). The impact of cerebral perfusion levels on cognitive and language outcomes in stroke have been observed in perilesional tissue, distant ipsilateral regions, as well as contralateral areas. This paper will review previous work related to cerebral blood perfusion in different brain regions post-stroke, and how CBF relates to language and cognitive performance, particularly in those individuals with aphasia. Foremost, we will present data from 43 participants with aphasia, evaluating patterns of perfusion in ipsilateral and contralateral regions in chronic aphasia and its relationship to language outcomes.

1.1 Perfusion of perilesional tissue

Research on acute stroke has demonstrated that CBF is typically disrupted in perilesional tissue, areas surrounding the neural regions that are permanently damaged (Chalela et al., 2000; Demeestere et al., 2020). These aberrant perfusion effects persist in the chronic phase, with perilesional perfusion reduced relative to homologous areas in the contralesional hemisphere and similar regions in age-matched healthy controls (Boukrina et al., 2019; Brumm et al., 2011; Richardson et al., 2011; Thompson et al., 2017). Interestingly, Richardson and colleagues (2011) demonstrated a strong relationship between infarct size and reduction in perilesional perfusion (defined as a 3 – 8 mm band around the original infarct) relative to the right hemisphere homologous regions in chronic ischemic stroke (n = 17), implying that individuals with larger infarcts might be doubly impacted both by larger structural lesions and by larger and more pronounced areas of hypoperfusion (but see Abbott et al., 2021 for contradictory findings). A recent study has argued for an individualized approach when determining hypoperfusion in perilesional tissue, with values falling below 1.5 standard deviations of the average right hemisphere CBF considered to be abnormal (Abbott et al., 2021). Using the proposed individualized criterion for determining functionally compromised brain tissue, in a small cohort of individuals with chronic aphasia (n = 6) Abbott and colleagues (2021) observed the most marked changes within a 0-3 mm band around the lesion, with perfusion returning to normal values outside of that ring.

Further, in stroke the extent of hypoperfusion of perilesional tissue has been shown to be associated with level of cognitive and language impairment (Brumm et al., 2011; Motta,

Ramadan, Hillis, Gottesman, & Leigh, 2015; Robson et al., 2017; Thompson et al., 2017) and recovery of motor function (e.g., Wiest et al., 2014). Motta and colleagues (2015) showed a statistical association between reperfusion of perilesional tissue (defined by a diffusion-perfusion mismatch based on MRI within 24 hours of onset) and cognitive outcomes at 2 weeks post onset in a large group of individuals with acute ischemic stroke (n = 38). In their study, a reduction in hypoperfused tissue volume (as defined by time-to-peak 4-5.9 second delay) was related to improvement in cognitive abilities (naming ability for left hemisphere patients and line cancelation for right hemisphere patients), further emphasizing the critical role perilesional tissue plays in stroke recovery. Specifically with regards to language outcomes in chronic stroke, Brumm et al. (2011) demonstrated that in three chronic ischemic stroke survivors lower perfusion in the ischemic penumbra was associated with more severe aphasia. Thompson and colleagues (2017) showed a strong positive relationship between perfusion levels in the perilesional tissue (defined as 0-6 mm band surrounding the core infarct) and naming, sentence comprehension and production abilities in a large group of individuals with chronic aphasia following ischemic stroke (n = 35). In twelve individuals with chronic Wernicke's aphasia, a strong association between language abilities and CBF in perilesional areas was demonstrated (Robson et al., 2017). However, in this study the definition of perilesional tissue was based on hypoperfusion values rather than a specific distance from the core lesion, making it harder to dissociate effects seen in perilesional areas from that of more distant ones.

However, not all studies find a systematic association between perilesional perfusion and functional outcomes. Fridriksson and colleagues were unable to demonstrate a significant relationship between pretreatment levels of CBF or change in CBF in perilesional cortex (3-15 mm around the lesion) and improvement in naming ability following anomia treatment in chronic stroke (n = 30) (Fridriksson, Richardson, Fillmore, & Cai, 2012). Similarly, perfusion of perilesional tissue (0-5 mm around the lesion) was not significantly associated with current reading deficits (although there was a positive trend) or recovery of reading abilities in a small longitudinal study (n = 15) (Boukrina et al., 2019). In the latter two studies, inclusion of individuals with both ischemic and hemorrhagic strokes might have additionally obfuscated the structure-function relationships.

Overall, failure to restore sufficient blood flow to perilesional tissue in acute stroke seems to result in persistent deficits even when it does not result in imminent progression to infarct and neuronal death. Discrepancies in observed findings in chronic stroke might be partially due to varying definitions of perilesional tissues, as currently there is no consensus on how far from the infarcted region should the tissue still be considered perilesional and whether partial volume effects potentially dilute the functional relationships (for a related argument see Abbott et al., 2021). Also, it is not clear whether right hemisphere areas that inevitably might fall into expanding perilesional masks are systematically excluded. So, while overall the evidence is in favor of perilesional perfusion being reduced and related to functional outcomes, the specific boundary for this underperforming tissue that may be critical for recovery still needs to be determined. Finally, it remains unknown to what extent changes in perilesional perfusion in chronic stroke can support language recovery.

1.2 Perfusion of distant ipsilateral areas

Disruption of perfusion in stroke goes beyond perilesional areas and has been observed in ipsilateral areas distant to the lesion in chronic stroke (Abbott et al., 2021; Mimura et al., 1998; Richardson et al., 2011). In the first study of perfusion in aphasia, Mimura and colleagues (1998) showed reduced CBF in the left hemisphere relative to the right hemisphere in subacute stroke (n = 20) and lower values relative to controls in chronic stroke (n = 16). Further those individuals with good language recovery showed higher left hemisphere perfusion and more pronounced changes in left hemisphere perfusion in the first year post-stroke, with similar associations with functional outcomes observed in the chronic stage as well. However important, this early study was restricted to one slice of single-photon emission computed tomography data, thus limiting generalizability and spatial accuracy.

Subsequently, several single case and small group studies in aphasia have documented abnormal vascular physiology and lowered perfusion in the left hemisphere. Love and colleagues demonstrated that lower perfusion in the left supramarginal and angular gyri in a patient with chronic stroke potentially led to functional impairment in reading ability, even when no damage to these areas was observed on structural scans (Love et al., 2002). Delayed time to peak of the hemodynamic response function – a potential indicator of impaired CBF – has been shown in

individuals with chronic aphasia across different perisylvian areas of the left hemisphere (Bonakdarpour, Parrish, & Thompson, 2007; Fridriksson, Morrow-Odom, Moser, Fridriksson, & Baylis, 2006). However, in these studies some individuals with post-stroke aphasia had a normal hemodynamic response function, indicating that blood flow dynamics are not always (or at least not always permanently) impacted by stroke. Brumm and colleagues (2011) documented both increased transit delays and decreased CBF in three individuals with chronic stroke. As expected, hypoperfusion was most notable in perilesional areas, but also documented in more distant regions from the lesion. However, the authors did not investigate relationships between functional outcomes and CBF levels in these distant left hemisphere regions. In one study focused on acute stroke, it was shown that language recovery was driven by reperfusion of frontal and temporal regions in the left hemisphere critical for language, but this effect was observed only in one patient out of five (Jarso et al., 2014).

A recent comprehensive study of perfusion in chronic aphasia showed a decrease in perfusion in several areas in the left hemisphere compared to healthy controls (and interestingly an increase in the superior frontal gyrus), however, these differences were not associated with functional language outcomes (Thompson et al., 2017). Based on the findings of this study, it appears that in the left hemisphere the ROIs falling within the distribution of the middle cerebral artery (MCA) are hypoperfused, while regions in the anterior cerebral artery (ACA) can be hyperperfused. A recent small cohort study employing individualized perfusion cutoffs based on right hemisphere perfusion values demonstrated a strong relationship between hypoperfusion of regions in the left posterior temporal and inferior parietal areas and general language ability and auditory comprehension (Abbott et al., 2021).

Further, perfusion levels have been identified as a prognostic factor in stroke recovery, with initially higher CBF predictive of better treatment outcomes in aphasia (Boukrina et al., 2019; Fridriksson et al., 2012; Thompson, Ouden, Bonakdarpour, Garibaldi, & Parrish, 2010). Thompson et al. (2010) found an association between baseline perfusion levels and propensity for upregulation of activity (as measured by the BOLD response in a task-based fMRI). Specifically, baseline perfusion was higher (i.e., closer to normal levels) in cortical regions that showed upregulation of neural activity in a small group of six patients who underwent treatment for

agrammatism, demonstrating that areas that are better perfused may have more treatment potential. Similarly, Fridriksson et al. (2012) found a comparable pattern in 30 patients who received treatment for anomia: pretreatment perfusion levels in undamaged regions within the left hemisphere language network (excluding infarcted and perilesional regions) predicted patients' naming accuracy, once again suggesting that higher baseline cerebral blood flow may be related to the potential for a better treatment outcome. Similarly in a recent longitudinal observational study (Boukrina et al., 2019), increased perfusion of intact areas within the reading circuit in the left hemisphere in the subacute stage predicted phonological and reading ability (but not semantic or orthographic abilities) at 6 months post-stroke in 15 patients. At the same time, as noted in the previous section, baseline perfusion levels in the perilesional tissue in the last two studies (Boukrina et al., 2019; Fridriksson et al., 2012) did not predict language recovery.

Cumulatively, the literature to date suggests that while perfusion in stroke will often be delayed and lowered in distant ipsilateral areas, there seems to be substantial individual variability, reflecting the influence of factors such as stroke type and severity, lesion site and size, time post-onset, age, as well as vascular and general brain health. Existing evidence suggests that hypoperfusion in left hemisphere regions is at least partially contributing to persistent language deficits. The available findings suggest that an adequate level of tissue perfusion in regions that support linguistic processing seems to be critical for upregulation of neural activity and promoting language recovery, with lower perfusion possibly limiting the region's contribution to functional recovery. However, there is a caveat to interpreting existing data. The causal directionality of disrupted neurovascular coupling remains unknown (for more on this see Girouard & Iadecola, 2006). It has been suggested that reduced CBF is secondary to decreased neuronal activity (Bundo et al., 2002). Accordingly, while it is likely that adequate perfusion levels are a prerequisite for restoration of respective function (Boukrina et al., 2019; Fridriksson et al., 2012; Thompson et al., 2010), a reverse interpretation of the data is also a possibility, i.e., that repeated activation of a region and its integration into existing networks is driving the restoration of blood flow to premorbid levels.

1.3 Perfusion of right hemisphere areas

In contrast to perfusion of ipsilateral areas, hypo- or hyperperfusion of homologous contralateral areas has not been consistently associated with functional outcomes in stroke. In individuals with good motor recovery following sensorimotor stroke, perfusion levels actually decreased in the contralesional hemisphere (Wiest et al., 2014). With regards to language, Mimura and colleagues (1998) showed that language recovery in the first year post-stroke was independent of changes in right hemisphere perfusion. However, in the same study in chronic stroke, those individuals with good language recovery had higher right hemisphere perfusion values compared to those with poor recovery and showed similar right hemisphere CBF to healthy controls. However, unlike that for regions in the left hemisphere, no association with language outcomes and right hemisphere perfusion was observed. Still another functional MRI study (Peck et al., 2004), showed that the time-to-peak values of the hemodynamic response in pre-SMA, Broca's area homologue, and motor and auditory cortices in the right hemisphere decreased following improvement in naming ability in three patients with chronic post-stroke non-fluent aphasia, substantiating the compensatory role of the right hemisphere in recovery. The authors concluded that the results reflect increased speed of language processing. However, a recent large group study in chronic stroke (Thompson et al., 2017) demonstrated that individuals with aphasia had increased perfusion in regions of the right hemisphere compared to the left hemisphere (once lesion was accounted for) and also compared to right hemisphere perfusion in age-matched healthy controls (although this difference was only borderline significant). However, the increased perfusion in the right hemisphere was not related to functional outcomes. The authors hypothesized that hyperperfusion of the right hemisphere likely indicates autoregulatory changes in blood flow following stroke and/or increases in general cognitive effort, rather than maladaptive language processing. In the same vein, Boukrina and colleagues (2019) showed increased perfusion in the right hemisphere reading network relative to the left hemisphere in a large group with subacute stroke (n=31). Interestingly, higher perfusion in the right hemisphere was associated with lower word reading accuracy both in the subacute and the chronic stages, but it was not related to performance on other language tasks involving phonological, semantic, and orthographic processing. Thus, there is inconclusive

evidence on whether reperfusion of right hemisphere areas to normal levels can support and promote recovery. It is more likely that increase in contralateral perfusion in the late chronic stages in stroke reflects largely vascular changes, rather than underlying reorganization of function. This observation likely undermines the proposed individualized approach (Abbott et al., 2021) for determining tissue perfusion based on contralateral perfusion values.

1.4 Aims of the current study

In general, functional compensation following stroke has been attributed to non-damaged tissue (Kiran & Thompson, 2019; Saur et al., 2006), with recent meta-analysis indicating stronger evidence for left hemisphere involvement in recovery (Stefaniak, Alyahya, & Ralph, 2021; Wilson & Schneck, 2021). However, structurally-preserved but sub-optimally perfused regions may also affect recovery (Fridriksson et al., 2012; Thompson et al., 2010, 2017). This purported relationship between perfusion and cognitive functioning needs further systematic investigation, especially in the context of language. The lack of consensus in prior perfusion studies in aphasia potentially has to do with small sample sizes and other methodological issues, such as different perfusion imaging sequences and processing algorithms, arbitrary cutoffs, varying definitions of perilesional areas, and different parcellations. Larger group studies using perfusion in chronic post-stroke aphasia are needed to address existing knowledge gaps.

In the current study we aimed to evaluate 1) how stroke affects perfusion outside of lesioned areas in chronic post-stroke aphasia, and 2) how perfusion in specific cortical areas and perilesional tissue relate to language outcomes in aphasia. Our work addresses several limitations of previous studies. First, we analyze the biggest sample to date of chronic patients with aphasia scanned with perfusion imaging. Next, we explore regions according to an anatomical atlas in both the left and the right hemispheres and we also systematically investigate perfusion in perilesional areas, looking separately at different bands of perilesional tissue at varying distances from the lesion. Finally, we explore the contribution of perfusion in multiple regions simultaneously to language abilities while accounting for structural damage.

2. METHODS

2.1 Participants

Forty-three participants with aphasia (PWA; 29 males, 14 females) following a left hemisphere stroke (M_{age} = 65.5 $\pm$ 11.1 years, from 43 to 88 years of age) were recruited for the study. All participants except three were strongly right-handed based on the Edinburgh Handedness Inventory (Oldfield, 1971), with these three participants reporting a right-hand preference but some ambidexterity. All passed screening tests for any hearing and visual deficits and had native-like proficiency in English prior to their stroke. All participants had suffered a single stroke, except for small (< 2 cm) asymptomatic secondary events, with the most recent incident being no less than 3 months prior to testing and scanning ($M_{time\ post\text{-}onset}$ = 52.2 $\pm$ 72.3 months). PWA in this sample presented with a wide range of speech and language deficits, some performing within normal limits on the Western Aphasia Battery (WAB; Kertesz, 1982, 2007), but still complaining of residual naming and/or comprehension deficits (see Results section for more information). All patients signed IRB-approved consent forms and were tested in accordance with the Helsinki Declaration.

A group of healthy age-matched controls was also recruited. Twenty-five participants (19 males, 6 females) with no neurological history participated (M_{age} = 61.6 $\pm$ 11.3 years, from 41 to 84 years of age). There was no significant difference in age between the control and aphasia groups (t (66) = -1.35, p = 0.18).

2.2 Behavioral assessments

The WAB (Kertesz, 1982, 2007) was administered to evaluate the language abilities of the PWA. Participants were assessed with the ten main language subtests, which contribute to the following subtest scores: Fluency, Information Content, Repetition, Naming, and Auditory Comprehension. Scores from these subtests comprise the WAB Aphasia Quotient (AQ), a general measure of aphasia severity.

2.3 MRI data: Acquisition, pre-processing, perfusion data analysis

Structural MRI (T1w) and perfusion data were acquired. The participants were scanned at two different sites – VA Martinez and UC Berkeley – with slightly differing protocols described below. All the processing steps were identical for the two groups. To account for possible

differences due to different sequences, scanning site was used as a covariate in all the correlation/regression analyses.

2.3.1 Data acquisition

2.3.1.1. VA cohort. All participants underwent anatomical and ASL scans on a 3T Siemens Verio scanner with a 12-channel phased-array head coil at the Veterans Affairs Hospital in Martinez, CA. For perfusion, a pseudo-continuous arterial spin labeling (pCASL) sequence was used with the following parameters: TR/TE = 4000/12ms, flip angle = 90°, bandwidth = 2.6 KHz/pixel, FOV = 22cm, voxel size = 3.4x3.4x6 mm, slice-selective gradient = 6mT/m, 20 axial slices in ascending sequential acquisition order using echo planar imaging (EPI) readout. The labeling duration was 1470ms with a post labeling delay of 1500ms. 80 images were acquired in the interleaved tag/control order for each subject. Since a separate M0 calibration image was not obtained, per current recommendations (Alsop et al., 2015), we used the first control image as a calibration image for the analysis of this cohort. One high-resolution anatomical image was acquired for each subject with the scan parameters: MP-RAGE sequence, TR/TE = 2200/1.62ms, TI = 900ms, flip angle = 9°, FOV = 256mm, voxel size 1x1x1 mm, 192 sagittal slices, bandwidth = 340Hz/voxel, GRAPPA factor = 2. Twenty-nine PWA and all twenty-five controls were scanned at this location.

2.3.1.2. UC Berkeley cohort.

All subjects underwent anatomical and ASL scans on a Siemens 3T Trio scanner with a 32-channel coil at the Brain Imaging Center, UC Berkeley. For perfusion imaging, a pCASL sequence with spiral read-out was used with the following parameters: TR/TE = 4600/8.7ms, flip angle = 90°, bandwidth = 400Hz/Pixel, FOV = 25cm, 40 slices, voxel size = 3×3×3 mm, phase encoding gradient = 6mT/m. The labeling duration was 1800ms with a post labeling delay of 2000ms. 16 images were acquired in the interleaved tag/control order for each subject. A stack-of-spirals readout was used with a 4-shot spiral interleave for each of the 3D phase encoding steps with background suppression on (Chang et al., 2017). An equilibrium magnetization (M0) image was also obtained and later used in the kinetic model to compute CBF values. One high-resolution anatomical image was also acquired for each subject with the following parameters: MP-RAGE sequence, TR/TE=2300/2.96ms, TI=900ms, flip angle = 9o, FOV = 256mm, voxel size 1x1x1 mm,

208 sagittal slices, bandwidth = 240Hz/voxel, GRAPPA factor = 2. Fourteen PWA were scanned at this location.

It is worth noting that there are differences between the two sequences: The UC Berkeley imaging sequence was obtained with a 3D stack-of-spirals readout while the VA used multi-slice 2D EPI. The post labelling delay and labeling duration were also different with the UC Berkeley being longer. We accounted for these inter-scanner variations by normalizing individual perfusion by whole-brain perfusion as well as adding scanning site as a covariate in our statistical analyses (see section 2.4 Statistical Analysis).

2.3.2 ASL data preprocessing

The processing steps were identical for the two cohorts. Tag-control images were motion corrected using FSL's function MCFLIRT (Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012). Cerebral blood flow (CBF) maps were obtained using FSL's command 'oxford_asl' on the motion corrected ASL data (Chappell, Groves, Whitcher, & Woolrich, 2009) with the parameters tailored to reflect each site's acquisition parameters. CBF maps were quantified in standard physiological units (ml blood/100mg tissue/min) using a standard kinetic model (Alsop et al., 2015). Labeling efficiency was set to α=0.72 and the longitudinal relaxation time of the blood was set to T1_b=1650ms. No further smoothing was performed.

2.3.3 Lesion segmentation and structural data preprocessing

The participants' lesions were traced directly onto the patient's native T1-weighted images using MRIcron software (Rorden & Brett, 2000) by trained research assistants, and then reviewed and verified by MI, IP, and ND. Next, we used the ANTs toolbox (Avants et al., 2011) to perform brain extraction on the structural T1s. We also used ANTs to segment the T1 images and obtain probability maps corresponding to different tissues (gray matter, white matter, and cerebrospinal fluid (CSF)). We then performed the following registrations to be able to bring regions of interest (ROIs) to native CBF space. (A) The CBF maps were registered to the brain extracted images (T1 native space) using an affine transformation (B) The brain-extracted T1 images were registered to the MNI-152 space. To do so we used ANTs with a transformation that consists of an initial rigid plus affine transformation followed by a diffeomorphic, "SyN" transformation, while cost-function masking the lesion. We used the MNI152NLin2009cAsym

version of the MNI image as the target MNI image (Fonov, Evans, McKinstry, Almli, & Collins, 2009). Using the inverse of the transformation obtained in (A) we were able to map ROIs that were in native T1 space to CBF space. Using the combined inverse transformations of (A) and (B) we were able to map atlas-based ROIs defined in MNI-152 to native T1 and then to CBF space. In the analysis we use the following ROIs:

i) *Atlas-based ROIs* – were taken from the Harvard-Oxford Cortical Structural Atlas in FSL (Desikan et al., 2006; Jenkinson et al., 2012). The segmentation from this atlas was selected as it contains ROIs of optimal size. Given the low-resolution of the perfusion data we needed ROIs large enough to minimize partial volume effects, but that would still have adequate spatial specificity and reflect distinct language regions. From the atlas we selected 11 ROIs that covered Perisylvian language areas (Inferior frontal gyrus (IFG) triangularis, IFG opercularis, Supramarginal anterior, Supramarginal posterior, Angular gyrus, Temporal pole, Superior temporal gyrus (STG) anterior, STG posterior, Middle temporal gyrus (MTG) anterior, MTG posterior, MTG temporal-occipital). We were interested whether perfusion levels in those ROIs would be related to residual language abilities. We also included four control ROIs (Frontal pole, Central, Superior frontal gyrus (SFG), Occipital pole) that included regions typically not related to language processing. See Figure 1 for representation of these ROIs. These ROIs in MNI-152 space were brought to native CBF space using the combination of transformations described previously in (A) and (B).

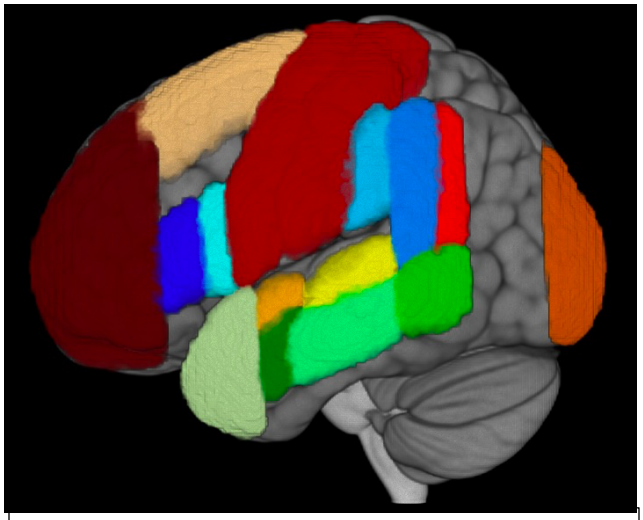

Figure 1. Representation of Atlas-based ROIs taken from the Harvard-Oxford atlas used in the current analysis.

ii) *Perilesional ROIs* – were obtained by eroding the lesion mask to 5mm and subtracting it from the original lesion mask. This process was repeated stepwise to obtain additional perilesional masks for 5-10mm and 10-15mm bands outside the lesion. The perilesional ROIs were brought to CBF space using the inverse affine transformation described previously in (A).

2.3.4 Region of interest (ROI) analysis of ASL data

For all the ROIs mean CBF values were obtained as the average CBF within each ROI. Because some ROIs overlapped with regions of no interest (e.g., perilesional ROIs could end up covering the ventricles or include voxels outside the brain), we required the CBF values of each ROI to exclude any CSF values or values outside the brain mask for all our calculations. Right hemisphere areas were excluded from all perilesional ROIs. Also, for the PWA cohort, lesioned voxel determined by the lesion mask were excluded from all the atlas-based ROIs at the participant level.

2.4 Statistical analysis

For all the statistical analyses, we divided perfusion values by the whole-brain perfusion signal (mean perfusion across the whole brain with the lesion site masked). This allowed for the accounting of individual variability in tagging efficiency and other potential session-specific and scanner-specific artifact. To control for multiple comparisons, we adjusted the *p*-value in each analysis by the number of atlas-based ROIs in each hemisphere. Thus, our critical significant threshold was $p < .0033$ (0.05/15) for both between-group comparisons and correlation analyses. All data analyses were performed in R ver. 4.1.2. (R Core Team, 2020) and figures were drawn in ggplot2 ver. 3.3.5 (Wickham, 2016).

For between-group comparisons of perfusion levels in different ROIs, the following procedure was implemented. First, we checked whether perfusion data for a specific ROI for each group followed a normal distribution (Shapiro test), and if the data were normally distributed in both groups for that ROI, we ran an F-test to test for homogeneity of variances. For those ROIs where all these assumptions were satisfied, we ran the standard independent samples t-tests to compare perfusion levels between groups. If the assumption of homogeneity of variances was violated, an unequal variances t-test (Welch's test) was performed. If in both or in one of the groups the data were not normally distributed, then the non-parametric two-samples Wilcoxon rank test was performed. This procedure was implemented for comparing PWA to age-matched controls and for checking whether perfusion levels differed between those PWA with lesion in a given atlas-based ROI and those without that lesion. Also, to explore the relationship between

perfusion levels and lesion status, we explored correlations between the two metrics – mean adjusted perfusion and lesion load – for each ROI.

For within-group comparisons of adjusted perfusion levels in left hemisphere ROIs to homologous right hemisphere ROIs, the following procedure was implemented. We first verified that the differences between homologous left and right ROIs were normally distributed. If that assumption was satisfied, then a standard paired samples t-test was run. If not, then we performed a paired two-samples Wilcoxon test.

Finally, to analyze the relationship between language measures and perfusion levels, we first performed a partial correlation analysis between mean adjusted perfusion in an ROI and language metrics, accounting for age, gender, time post-onset, scanning site, and lesion volume. Also, in addition to using the omnibus lesion volume, we accounted for lesion load to that specific ROI as well. Partial correlation analysis was done with package ppcor (Kim, 2015). This analysis was followed by a regularized lasso regression, so that we could analyze the impact of perfusion in all the ROIs simultaneously and outline in which regions perfusion levels were associated with different language abilities. Regularized regression allowed determination of salient relationships in complex datasets and has been successfully used previously in neuroimaging studies to select relevant neural predictors (Salvalaggio, de Filippo De Grazia, Zorzi, de Schotten, & Corbetta, 2020).

Specifically, lasso regression (alpha = 1) differs from traditional multiple linear regression as it employs L1-normalization to regularize model coefficients, so that unimportant features are eliminated, preventing overfitting and improving generalization on test data (Hastie, Tibshirani, & Friedman, 2009; Tibshirani et al., 2010). This approach is also recommended for instances when the number of cases is similar to the number of predictors, as in the present case. The regularization term provides a constraint on the size of weights, and it is controlled by parameter λ (lambda), with larger λ leading to more shrinkage. When there are many correlated variables in an ordinary linear regression model, the weights can be poorly determined and exhibit high variance. By imposing a size constraint on the coefficients, as is done by λ, this problem is alleviated, and a lasso (L1) regularized regression specifically will assign beta weights of 0 to weak predictors (Hastie et al., 2009). In this analysis, we included all the covariates from the partial

correlation above and all the perilesional and atlas-based ROIs. Predictors first had to be standardized, so that their absolute values would not influence the weights. Next, an optimal λ was selected through leave-one-out cross-validation, with the λ that minimized residual mean squared error in the model used in the analysis. These analyses were performed with the glmnet package (Friedman, Hastie, & Tibshirani, 2010).

3. RESULTS

3.1. Differences in perfusion levels between groups

Raw and adjusted (by the whole-brain perfusion) perfusion values for left and right hemisphere ROIs are presented in Figure 2A and 2B respectively (see Appendix, Table 1A for actual values). As can be seen from Figure 2A, all left hemisphere ROIs and most right hemisphere ROIs showed significantly lower raw perfusion values in PWA relative to controls as determined by independent samples t-tests/Wilcoxon rank tests. Whole-brain perfusion was also significantly lower in PWA compared to controls (M_{Controls} = 32.4, M_{PWA} = 26.2; t (66) = 3.42, p = .001). For the adjusted perfusion values (Figure 2, panel B), only left ROIs, specifically regions in the frontal and parietal regions, showed significantly decreased perfusion in the PWA group compared to age-matched controls. No differences were observed in the right hemisphere.

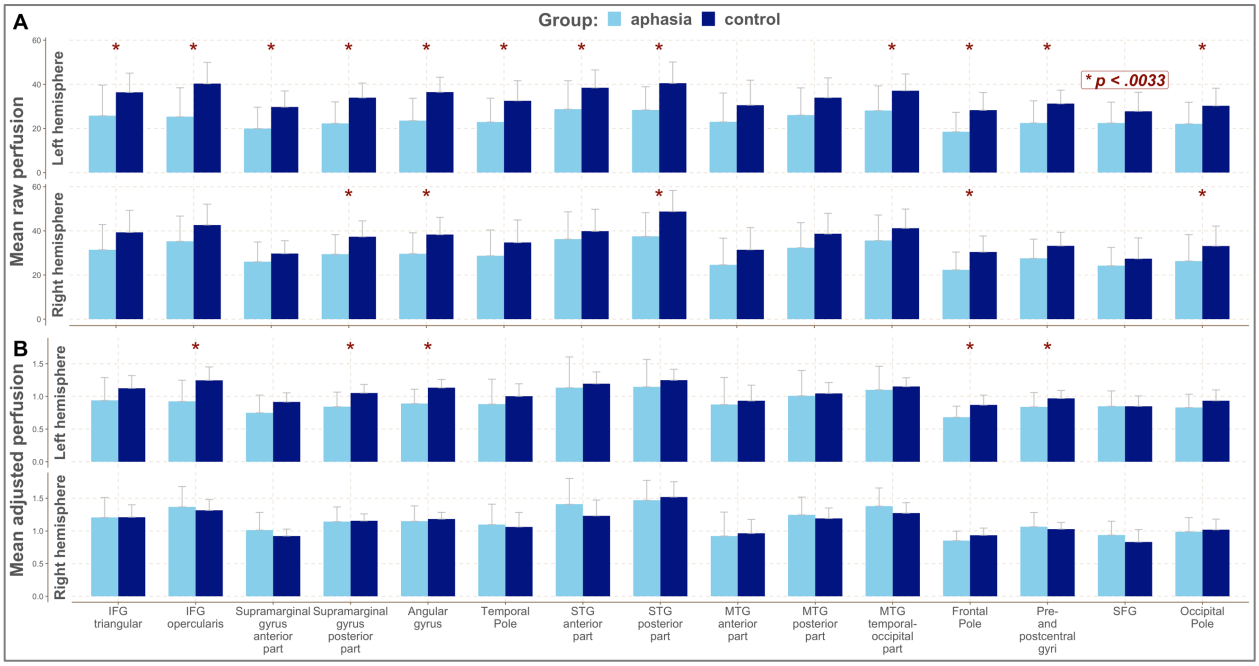

Figure 2. Mean perfusion values for the aphasia and the control groups across different left hemisphere ROIs. Red asterisks mark significant differences between groups for a given ROI. Panel A – Mean raw perfusion. Panel B – Mean adjusted perfusion. IFG – inferior frontal gyrus, STG – superior temporal gyrus, MTG – middle temporal gyrus, SFG – superior frontal gyrus.

3.2. Differences within groups: comparing perfusion levels in homologous regions in the left and right hemispheres

Next, we compared perfusion levels in the left hemisphere ROIs to homologous regions in the right hemisphere (see Figure 3) for both the control and aphasia groups. Lower perfusion across almost all regions of the left hemisphere was observed in the aphasia group, except the anterior part of the MTG and SFG. The control group showed interhemispheric differences for a limited set of regions, including the posterior portion of the supramarginal gyrus, the posterior part of the temporal lobe, and the area around the central sulcus, with left ROIs having lower perfusion compared to their right hemisphere counterparts.

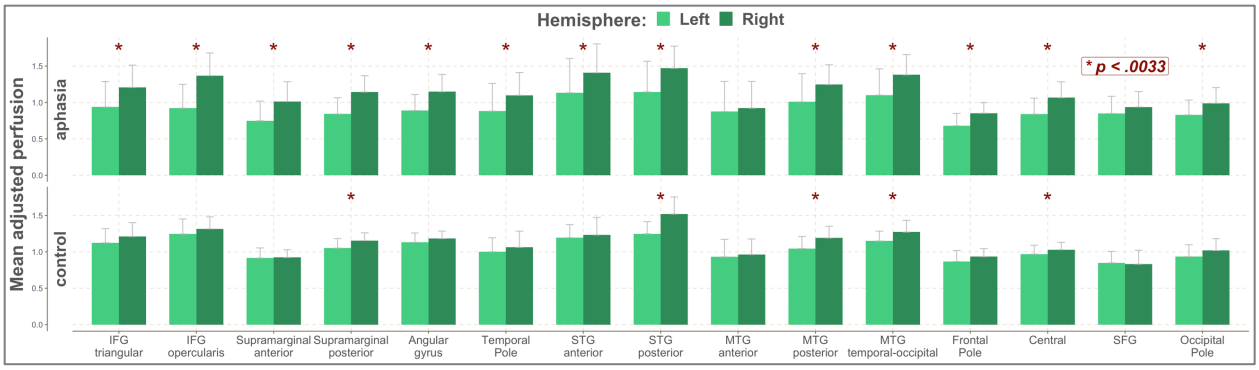

Figure 3. Mean adjusted perfusion for left and right hemisphere ROIs in the aphasia and the control groups. Red asterisks mark significant differences between homologous ROIs. IFG – inferior frontal gyrus, STG – superior temporal gyrus, MTG – middle temporal gyrus, SFG – superior frontal gyrus.

3.3 Impact of lesion on perfusion levels

Next, we investigated whether perfusion levels were impacted by having a lesion in a specific ROI. For each ROI, we split participants into two groups – those in whom the ROI was lesioned in the left hemisphere (lesion load greater than 0) and those in whom it was spared (lesion load equal to 0). We then compared the perfusion levels between these two groups in both hemispheres. This procedure was repeated across all the ROIs. In other words, for each

comparison we regrouped the participants based on their lesion status for that specific ROI in the left hemisphere. Numerically perfusion was higher in the 'Spared ROI' group compared to the 'Lesioned ROI' group across the left perisylvian regions, but the difference was statistically significant only for IFG opercularis and different parts of the MTG (see Figure 4). No significant or systematic differences were observed between the two groups for homologous right hemisphere ROIs.

Further, we explored the relationship between perfusion levels and lesion status by correlating perfusion levels in the left hemisphere with lesion load. Non-parametric spearman correlations were performed as the lesion load data was not distributed normally. Significant correlations were only detected for IFG opercularis (r = -.57, p < .001), posterior (r = -.48, p = .001) and temporal-occipital part of the MTG (r = -.6, p < .001). This indicated that, in these ROIs, having a higher lesion load (i.e., more damage) was associated with having lower perfusion levels.

Finally, we compared perfusion in the three different perilesional bands. Adjusted perfusion in the perilesional 0-5mm band ($M_{0\text{-}5mm}$=0.86 $\pm$ 0.19) was significantly lower than in the 5-10mm band ($M_{5\text{-}10mm}$=0.96 $\pm$ 0.16; t (42) = -7.5, p < .001), which in turn was lower than in the 10-15mm band ($M_{10\text{-}15mm}$=1.01 $\pm$ 0.12; t (42) = -3.14, p = .003). Only perfusion in 0-5 mm band was significantly lower compared to whole-brain perfusion (t (42) = -4.9, p < .001).

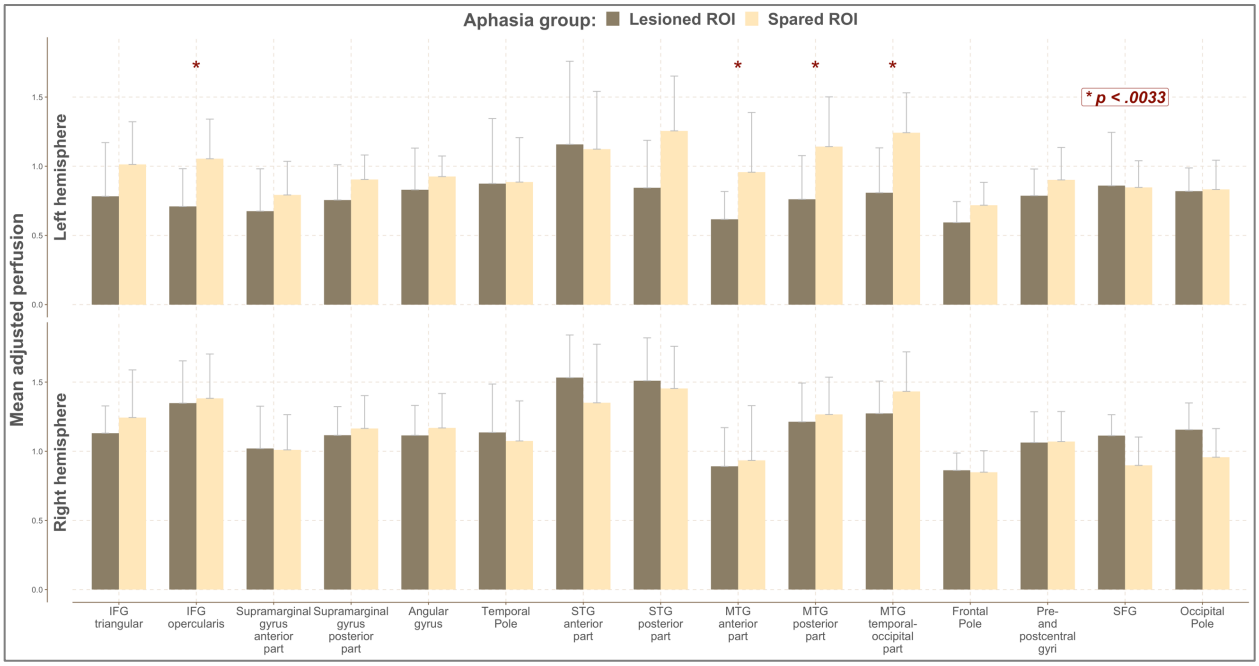

Figure 4. Mean adjusted perfusion for left and right hemisphere ROIs in the aphasia group with ('Lesioned ROI') and without a lesion ('Spared ROI') in a given ROI in the left hemisphere. Red asterisks mark significant differences between the two aphasia subgroups. IFG – inferior frontal gyrus, STG – superior temporal gyrus, MTG – middle temporal gyrus, SFG – superior frontal gyrus.

3.4 Correlation between language measures and perfusion levels

Mean WAB subtest scores for the PWA group are presented in Table 1. Note that while some participants had WAB AQ scores above the 93.8 cut-off for aphasia, they continued to experience minor language deficits, particularly for word finding.

Table 1. *Descriptive statistics for WAB subtest scores*

	Information Content	***Fluency***	***Repetition***	***Naming***	***Auditory Comprehension***	***WAB AQ***
Mean (SD)	8.7 (2)	8 (2.5)	7.9 (2.8)	7.6 (2.7)	9 (1.3)	82.3 (20.1)
Range (Min – Max)	3 - 10	0 - 10	0 - 10	0 - 10	5.4 - 10	22.8 - 100
Max score possible	10	10	10	10	10	100

Partial correlations were performed between language measures and perfusion levels in different atlas-based and perilesional ROIs in the aphasia group accounting for relevant demographic (age, sex, time post-onset, scanning site) and lesion variables (lesion volume or lesion load to a particular ROI). In Panel A of Figure 5, correlations between language and perfusion metrics accounting for demographic variables and lesion volume are presented, while in Panel B, correlations between language and perfusion metrics accounting also for lesion load to individual ROIs are shown. Note that the latter analysis is not applicable to perilesional ROIs, as perilesional bands by definition were not lesioned in any participants. No significant correlations were observed between perfusion levels in the right hemisphere ROIs and language abilities even prior to corrections for multiple comparisons. Accordingly, Figure 5 only includes left hemisphere ROIs.

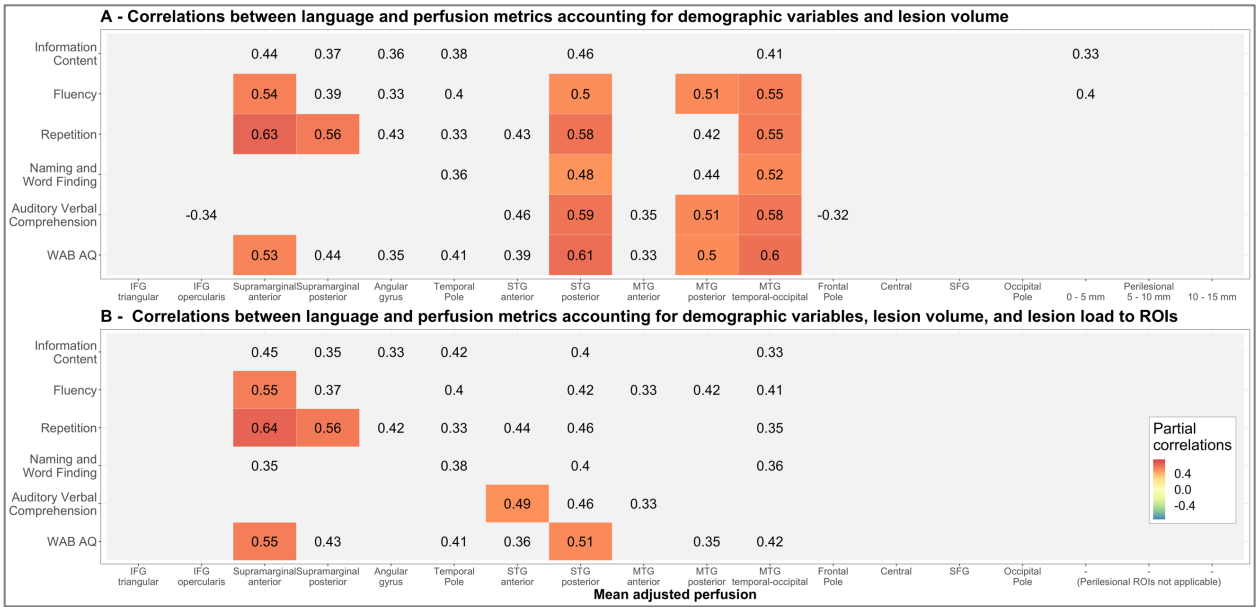

Figure 5. *Panel A:* Partial correlations between language and perfusion metrics in left hemisphere ROIs accounting for age, gender, time post-onset, scanning site, and lesion volume. *Panel B:* Partial correlations between language and perfusion metrics in left hemisphere ROIs accounting for age, gender, time post-onset, scanning site, lesion volume, and lesion load to individual ROIs. Correlations significant at $p < .05$ are printed, while significant correlations after adjusting for multiple comparisons ($p < .0033$) are color coded according to their values. IFG – inferior frontal gyrus, STG – superior temporal gyrus, MTG – middle temporal gyrus, SFG – superior frontal gyrus.

As can be seen from Figure 5, correlations remained significant and passed the threshold for multiple comparisons for inferior parietal areas (supramarginal gyrus) and posterior temporal areas. Since as shown previously, there was a significant relationship between lesion load and perfusion levels in posterior temporal areas, the analysis accounting for lesion load did not yield the same pattern of significant relationships between language measures and perfusion levels in the posterior temporal regions. Further, perfusion levels in perilesional areas were only marginally related to expressive language abilities and did not survive the correction for multiple comparisons. Overall, the data show that perfusion levels in areas beyond the lesion site in the left hemisphere significantly impacted performance on subtests of the WAB even after accounting for demographic and lesion variables (lesion volume and lesion load), while perfusion in the right hemisphere was not associated with residual language abilities.

3.5 Elastic net regression

To investigate the simultaneous impact of perfusion in different ROIs in the left hemisphere on language outcomes a regularized lasso regression was performed with each of the WAB subtest scores as the outcome variables. Respective regression coefficients are

presented in Table 2, with higher values indicative of stronger relationship with language measures. Overall, the analyses identified several ROIs in the parietal and temporal lobes simultaneously contributing to language processing, with posterior temporal areas playing a particularly prominent role. For the control regions, only the Central area was significantly associated with Fluency. As expected, other control areas showed no or a small negative relationship with language scores. Only perilesional tissue in the 0 – 5mm band showed a small relationship with expressive language abilities.

Table 2. *Results of Lasso regression analysis with WAB subtest scores as the dependent variables and perfusion in left hemisphere ROIs along with demographic variables and lesion load in left hemisphere ROIs as predictors.*

	Information Content	***Fluency***	***Repetition***	***Naming***	***Auditory Comprehension***	***WAB AQ***
Lesion volume	0	-0.176	0	-0.169	0	-0.081
Age	0	0	0	-0.052	0.082	0
Time post onset	0	0.143	0	0.153	0.256	0
Scanning site	0	0	0	0	0.058	0
Gender	0	0	0	0	0.061	0
IFG triangular perf	0	0	0	0	0	0
IFG opercularis perf	0	0	0	0	0	0
Supramarginal anterior perf	0.086	0.222	0.051	0	0.033	0.129
Supramarginal posterior perf	0	0	0.048	0	0	0
Angular gyrus perf	0.077	0	0	0	0	0
Temporal pole perf	0.098	0.053	0	0.021	0	0
STG anterior perf	0	0	0	0	0	0
STG posterior perf	0	0	0	0	0	0
MTG anterior perf	0	0	0	0	0	0
MTG posterior perf	0	0.121	0	0.102	0.157	0
MTG temporal-occipital perf	0	0.06	0	0	0	0.085
Frontal pole perf	0	0	0	0	0	0
Central perf	0	0	0	0	0	0
SFG perf	0	0.01	0	0	0	0
Occipital pole perf	0	0	0	0	0	0
Perilesional 0-5 mm perf	0.129	0.118	0	0.167	0	0.058
Perilesional 5-10 mm perf	0	0	0	0	0	0
Perilesional 10-15 mm perf	0	0	0	-0.09	0	0
IFG triangular LL	0	0	0	0	0	0
IFG opercularis LL	0.068	0	0	0.184	0.121	0
Supramarginal anterior LL	0	0	0	0	0	0
Supramarginal posterior LL	-0.044	-0.217	0	-0.297	-0.139	-0.203
Angular gyrus LL	-0.133	0	-0.047	0	0	-0.01
Temporal Pole LL	-0.24	-0.009	0	-0.156	-0.055	0
STG anterior LL	0	0	0	-0.125	0	0
STG posterior LL	-0.033	0	0	0	-0.097	0
MTG anterior LL	-0.054	0	0	-0.023	0	0
MTG posterior LL	0	0	0	-0.033	0	0

MTG temporal-occipital LL	0	-0.129	0	-0.127	-0.506	-0.123
Frontal Pole LL	0	-0.098	0	-0.022	0	0
Central LL	0	0	0	0	0	0
SFG LL	0	0	0	0	0	0
Occipital Pole LL	-0.126	-0.082	0	-0.254	0	0
Lambda	0.128	0.078	0.515	0.05	0.061	0.221
R^2	0.567	0.738	0.167	0.806	0.722	0.538
RMSE	0.65	0.506	0.902	0.436	0.521	0.672

Note. Perf – mean perfusion. LL – Lesion load.

4. DISCUSSION

In the current study, we first investigated how perfusion outside of lesioned areas was affected in chronic post-stroke aphasia in comparison to perfusion in age-matched controls. We then determined how perfusion in specific cortical and perilesional areas was related to language outcomes in aphasia. To investigate perfusion in aphasia we used anatomically-defined ROIs from the Harvard-Oxford atlas that covered the frontal, parietal, and temporal areas of the perisylvian cortex in both hemispheres, along with several control regions not implicated previously in language processing. For the PWA group, we also looked at three bands of perilesional tissue. We compared perfusion levels between the PWA and controls groups and investigated the relationship between perfusion levels and WAB subtest scores using both correlation and regularized regression analyses.

First, the current study clearly demonstrated that cerebral perfusion in chronic stroke is greatly reduced even beyond the lesion site, with overall whole-brain perfusion being significantly lower in the aphasia group compared to age-matched controls. Not surprisingly, the reduction in CBF is primarily noticeable in the lesioned hemisphere with raw perfusion reduced in most regions in the left hemisphere and some regions in the contralesional hemisphere. Once the whole-brain perfusion signal was accounted for (i.e., in the metric adjusted perfusion) perfusion levels in PWA remained significantly reduced in specific frontal and parietal areas in the left lesioned hemisphere compared to controls, while no statistically significant differences between PWA and controls were detected in homologous right hemisphere regions. This reduction in ipsilesional (left hemisphere) perfusion in areas distant from the lesion site has been observed in previous studies (Abbott et al., 2021; Brumm et al., 2011; Mimura et al., 1998; Richardson et al., 2011; Thompson et al., 2017). Perilesional tissue closer to the lesion, as

expected, showed lower perfusion compared to more distant perilesional areas, as has been documented in previous studies (Boukrina et al., 2019; Brumm et al., 2011; Richardson et al., 2011; Thompson et al., 2017). Outside of the 5 mm ring around the lesion, perfusion values returned to normal and were similar to the rest of the brain. Furthermore, perfusion levels in the left hemisphere ROIs in PWA were lower compared to homologous right hemisphere regions, as also demonstrated previously (Mimura et al., 1998; Thompson et al., 2017). A similar trend was observed for healthy controls, although to a lesser extent and the difference between hemispheres was only significant for four ROIs.

Second, we found that perfusion in the left temporal lobe (and most strongly in the posterior part of both superior and middle temporal gyri) and in inferior parietal areas (supramarginal gyrus) was significantly related to different WAB subtest scores. This relationship was present even when direct lesion damage to these areas was accounted for. This indicates that residual functionality in those areas is important for supporting language function and even if that tissue is preserved (as evidenced by an absence of a lesion on structural scans) it may display varying levels of functionality. Neurovascular coupling is disrupted in pathological conditions, such as stroke. Consequently, CBF might be no longer matched to the metabolic requirements of the tissue and thus sub-optimally perfused critical language areas might not be able to support residual processing. In contrast, perfusion in the frontal ROIs did not show such a relationship. This pattern is similar to a recent small study of perfusion in stroke patients, where perfusion levels – specifically in temporoparietal areas – were related to residual language abilities (Abbott et al., 2021). Further, our findings are aligned with results seen by Thompson et al., (2017), although their results did not survive correction for multiple comparisons. As expected, no relationship with language was observed for perfusion levels in control areas within the ipsilesional hemisphere.

In the perilesional analysis, only perfusion in the band of 0 – 5 mm was marginally related to language production abilities, particularly measures of fluency, but it did not survive the correction for multiple comparisons. In the Lasso regression analysis only perilesional perfusion in the 0 – 5 mm band was again related to language production abilities, including fluency and

naming ability, and overall aphasia severity. Thus, overall, perfusion in tissue directly adjacent to the lesion was pertinent for language outcomes.

Furthermore, aligned with most prior investigation of perfusion in the contralesional (right hemisphere) ROIs, no relationship with language abilities was observed (Mimura et al., 1998; Thompson et al., 2017). Interestingly, we did not observe a pattern of hyperperfused right hemisphere regions due to autoregulatory changes, as found by Thompson and colleagues (2017).

Cumulatively, our study showed that, as the language system reorganizes itself, the initial functional specialization of a region might be more pertinent than proximity to the lesion, with functionality of core parietotemporal language areas in the left hemisphere being most critical for determining residual language deficits. In other words, perfusion levels in language areas, rather than in perilesional tissue, determined language abilities. Surprisingly no consistent associations were found between perilesional perfusion and post-stroke language abilities. This is probably due to the fact that participants were scanned in the chronic stage of their aphasia, where changes in the perilesional space have already taken place (Lee & Donkelaar, 1995; Nudo, 2013). It may also be the case that perilesional perfusion is more relevant in cases of motor recovery, as the motor function is more modular and spatially-restricted, i.e. more distant areas are not capable of taking on functions of the motor cortex (Nudo, 1999).

Conclusions

Overall, the results demonstrate that blood flow is reduced beyond the lesion site in chronic post-stroke aphasia and hypoperfused neural tissue in critical temporo-parietal language areas may not be fully able to support recovery. The findings underscore the critical and general role that left hemisphere posterior temporal regions play in various expressive and receptive language abilities (Ivanova et al., 2016; Ivanova, Zhong, Turken, Baldo, & Dronkers, 2021; Turken & Dronkers, 2011; Wilson et al., 2022). Overall, the study shows that slowed or reduced blood distribution can affect the functionality of regions beyond the lesion site and have a direct impact on behavioral outcomes.

The current study highlights the importance of exploring CBF measures in stroke. Relative to task-based functional MRI, perfusion offers insights into functionality of all the brain regions

simultaneously, not just those involved in the execution of a given task. Furthermore, a perfusion protocol is easier to administer, and can be more readily standardized across sites and hence included in routine clinical assessments. Perfusion measures, while previously largely overlooked in multimodal neuroimaging studies (with the notable exception of Kristinsson et al., 2021), may offer valuable prognostic indicators of recovery potential and should be routinely included in future studies investigating the neural mechanisms of post-stroke recovery.

FUNDING

This work was supported by the National Institutes of Health (NIDCD R01DC016345, MH63901), Department of Veteran Affairs (VA RR&D RX002783), and the Wheeler Foundation. The content is solely the responsibility of the authors and does not necessarily represent the official views of the United States Department of Veterans Affairs, the National Institutes of Health, or the United States Government.

ACKNOWLEDGEMENTS

We would like to thank Brian Curran for his help with collection of neuroimaging data. We also extend our thanks to Dr. Robert Knight for his contribution to the anatomical accuracy of lesion reconstructions. As always, we are deeply grateful to all the participants with aphasia who make this research possible.

REFERENCES

Abbott, N. T., Baker, C. J., Chen, C., Liu, T. T., & Love, T. E. (2021). Defining hypoperfusion in chronic aphasia: An individualized thresholding approach. *Brain Sciences*, *11*(4), 491. https://doi.org/10.3390/brainsci11040491

Alsop, D. C., Detre, J. A., Golay, X., Günther, M., Hendrikse, J., Hernandez-Garcia, L., … Zaharchuk, G. (2015). Recommended implementation of arterial spin-labeled Perfusion mri for clinical applications: A consensus of the ISMRM Perfusion Study group and the European consortium for ASL in dementia. *Magnetic Resonance in Medicine*, *73*(1), 102–116. https://doi.org/10.1002/mrm.25197

Astrup, J., Symon, L., Branston, N. M., & Lassen, N. A. (1977). Cortical evoked potential and extracellular k+ and h+ at critical levels of brain ischemia. *Stroke*, *8*(1), 51–57. https://doi.org/10.1161/01.STR.8.1.51

Avants, B. B., Tustison, N. J., Song, G., Cook, P. A., Klein, A., & Gee, J. C. (2011). A reproducible evaluation of ANTs similarity metric performance in brain image registration. *NeuroImage*, *54*(3), 2033–2044. https://doi.org/10.1016/j.neuroimage.2010.09.025

Bonakdarpour, B., Parrish, T. B., & Thompson, C. K. (2007). Hemodynamic response function in patients with stroke-induced aphasia: Implications for fMRI data analysis. *NeuroImage*, *36*(2), 322–331.

Boukrina, O., Barrett, A. M., & Graves, W. W. (2019). Cerebral perfusion of the left reading network predicts recovery of reading in subacute to chronic stroke. *Human Brain Mapping*, (40), 5301–5314. https://doi.org/10.1002/hbm.24773

Brumm, K. P., Perthen, J. E., Liu, T. T., Haist, F., Ayalon, L., & Love, T. (2011). An Arterial Spin Labeling investigation of cerebral blood flow deficits in chronic stroke survivors. *NeuroImage*, *51*(3), 995–1005. https://doi.org/10.1016/j.neuroimage.2010.03.008.An

Bundo, M., Inao, S., Nakamura, A., Kato, T., Ito, K., Tadokoro, M., … Yoshida, J. (2002). Changes of neural activity correlate with the severity of cortical ischemia in patients with unilateral major cerebral artery occlusion. *Stroke*, *33*(1), 61–66. https://doi.org/10.1161/hs0102.101816

Buxton, R. B., Uludağ, K., Dubowitz, D. J., & Liu, T. T. (2004). Modeling the hemodynamic

response to brain activation. *NeuroImage*, *23*(SUPPL. 1), 220–233. https://doi.org/10.1016/j.neuroimage.2004.07.013

Carrera, E., & Tononi, G. (2014). Diaschisis: Past, present, future. *Brain*, *137*(9), 2408–2422. https://doi.org/10.1093/brain/awu101

Chalela, J. A., Alsop, D. C., Gonzalez-Atavales, J. B., Maldjian, J. A., Kasner, S. E., & Detre, J. A. (2000). Magnetic resonance perfusion imaging in acute ischemic stroke using continuous arterial spin labeling. *Stroke*, *31*(3), 680–687. https://doi.org/10.1161/01.STR.31.3.680

Chang, Y. V., Vidoretta, M., Wang, Z., & Detre, J. A. (2017). 3D-Accelerated, Stack-of-spirals Acquisitions and Reconstruction of Arterial Spin Labeling MRI. *Magnetic Resonance Imaging*, *78*(4), 1405–1419. https://doi.org/10.1002/mrm.26549.3D-Accelerated

Chappell, M. A., Groves, A. R., Whitcher, B., & Woolrich, M. W. (2009). Variational Bayesian inference for a nonlinear forward model. *IEEE Transactions on Signal Processing*, *57*(1), 223–236. https://doi.org/10.1109/TSP.2008.2005752

Demeestere, J., Wouters, A., Christensen, S., Lemmens, R., & Lansberg, M. G. (2020). Review of perfusion imaging in acute ischemic stroke: From time to tissue. *Stroke*, 1017–1024. https://doi.org/10.1161/STROKEAHA.119.028337

Desikan, R. S., Ségonne, F., Fischl, B., Quinn, B. T., Dickerson, B. C., Blacker, D., … Killiany, R. J. (2006). An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *NeuroImage*, *31*(3), 968–980. https://doi.org/10.1016/j.neuroimage.2006.01.021

Feeney, D. M., & Baron, J. C. (1986). Diaschisis. *Stroke*, *17*(5), 817–830.

Fonov, V., Evans, A., McKinstry, R., Almli, C., & Collins, D. (2009). Unbiased nonlinear average age-appropriate brain templates from birth to adulthood. *NeuroImage*, *47*, S102. https://doi.org/10.1016/S1053-8119(09)70884-5

Fridriksson, J., Morrow-Odom, L., Moser, D., Fridriksson, A., & Baylis, G. (2006). Neural recruitment associated with anomia treatment in aphasia. *NeuroImage*, *32*(3), 1403–1412. https://doi.org/10.1016/j.neuroimage.2006.04.194

Fridriksson, J., Richardson, J. D., Fillmore, P., & Cai, B. (2012). Left hemisphere plasticity and aphasia recovery. *NeuroImage*, *60*(2), 854–863.

https://doi.org/10.1016/j.neuroimage.2011.12.057

Friedman, J., Hastie, T., & Tibshirani, R. (2010). Regularization paths for generalized linear models via coordinate descent. *Journal of Statistical Software*, *33*(1), 1–22. https://doi.org/10.18637/jss.v033.i01

Girouard, H., & Iadecola, C. (2006). Neurovascular coupling in the normal brain and in hypertension, stroke, and Alzheimer disease. *Journal of Applied Physiology*, *100*(1), 328–335. https://doi.org/10.1152/japplphysiol.00966.2005

Hastie, T., Tibshirani, R., & Friedman, J. (2009). *The Elements of Statistical Learning* (2nd ed.). Springer Science+Business Media, LLC. Retrieved from https://hastie.su.domains/ElemStatLearn/printings/ESLII_print12_toc.pdf

Hillis, A. E. (2007). Magnetic resonance perfusion imaging in the study of language. *Brain and Language*, *102*(2), 165–175. https://doi.org/10.1016/j.bandl.2006.04.016

Ivanova, M. V., Isaev, D. Y., Dragoy, O. V., Akinina, Y. S., Petrushevskiy, A. G., Fedina, O. N., … Dronkers, N. F. (2016). Diffusion-tensor imaging of major white matter tracts and their role in language processing in aphasia. *Cortex*, *85*, 165–181. https://doi.org/10.1016/j.cortex.2016.04.019

Ivanova, M. V., Zhong, A., Turken, A., Baldo, J. V., & Dronkers, N. F. (2021). Functional contributions of the arcuate fasciculus to language processing. *Frontiers in Human Neuroscience*, *15*(June), 1–15. https://doi.org/10.3389/fnhum.2021.672665

Jarso, S., Li, M., Faria, A., Davis, C., Leigh, R., Sebastian, R., … Hillis, A. E. (2014). Distinct mechanisms and timing of language recovery after stroke. *Cognitive Neuropsychology*, *0*(0), 1–22. https://doi.org/10.1080/02643294.2013.875467

Jenkinson, M., Beckmann, C. F., Behrens, T. E. J., Woolrich, M. W., & Smith, S. M. (2012). FSL. *NeuroImage*, *62*(2), 782–790. https://doi.org/10.1016/j.neuroimage.2011.09.015

Joris, P. J., Mensink, R. P., Adam, T. C., & Liu, T. T. (2018). Cerebral blood flow measurements in adults: A review on the effects of dietary factors and exercise. *Nutrients*, *10*(5), 1–15. https://doi.org/10.3390/nu10050530

Kertesz, A. (1982). *Western Aphasia Battery*. New York: Grune & Stratton.

Kertesz, A. (2007). *Western Aphasia Battery - Revised*. San Antonio, TX: PsychCorp.

Kim, S. (2015). ppcor: An R Package for a Fast Calculation to Semi-partial Correlation Coefficients. *Communications for Statistical Applications and Methods*, *22*(6), 665–674. https://doi.org/10.5351/csam.2015.22.6.665

Kiran, S., & Thompson, C. K. (2019). Neuroplasticity of language networks in aphasia: Advances, updates, and future challenges. *Frontiers in Neurology*, *10*(295). https://doi.org/10.3389/fneur.2019.00295

Kristinsson, S., Zhang, W., Rorden, C., Newman-Norlund, R., Basilakos, A., Bonilha, L., … Fridriksson, J. (2021). Machine learning-based multimodal prediction of language outcomes in chronic aphasia. *Human Brain Mapping*, *42*(6), 1682–1698. https://doi.org/10.1002/hbm.25321

Lee, R. G., & Donkelaar, P. Van. (1995). Mechanisms Underlying Functional Recovery Following Stroke. *Canadian Journal of Neurological Sciences / Journal Canadien Des Sciences Neurologiques*, *22*(4), 257–263. https://doi.org/10.1017/S0317167100039445

Leenders, K. L., Perani, D., Lammertsma, A. A., Heather, J. D., Buckingham, P., Jones, T., … Frackowiak, R. S. J. (1990). Cerebral blood flow, blood volume and oxygen utilization: Normal values and effect of age. *Brain*, *113*(1), 27–47. https://doi.org/10.1093/brain/113.1.27

Love, T., Swinney, D., Wong, E., & Buxton, R. (2002). Perfusion imaging and stroke : A more sensitive measure of the brain bases of cognitive deficits, *16*(9), 873–883. https://doi.org/10.1080/02687030244000356

Markus, H. S. (2004). Cerebral perfusion and stroke. *Journal of Neurology, Neurosurgery and Psychiatry*, *75*(3), 353–361. https://doi.org/10.1136/jnnp.2003.025825

Mimura, M., Kato, M., Kato, M., Sano, Y., Kojima, T., Naeser, M., & Kashima, H. (1998). Prospective and retrospective studies of recovery in aphasia. Changes in cerebral blood flow and language functions. *Brain*, *121*(11), 2083–2094. https://doi.org/10.1093/brain/121.11.2083

Motta, M., Ramadan, A., Hillis, A. E., Gottesman, R. F., & Leigh, R. (2015). Diffusion – perfusion mismatch: An opportunity for improvement in cortical function. *Frontiers in Neurology*, *5*(280), 1–8. https://doi.org/10.3389/fneur.2014.00280

Newberg, A. B., Wang, J., Rao, H., Swanson, R. L., Wintering, N., Karp, J. S., … Detre, J. A. (2005). Concurrent CBF and CMRGlc changes during human brain activation by combined fMRI-PET scanning. *NeuroImage*, *28*(2), 500–506. https://doi.org/10.1016/j.neuroimage.2005.06.040

Nudo, R. J. (1999). Recovery after damage to motor cortical areas. *Current Opinion in Neurobiology*, *9*, 740–747.

Nudo, R. J. (2013). Recovery after brain injury: mechanisms and principles. *Frontiers in Human Neuroscience*, *7*(December), 1–14. https://doi.org/10.3389/fnhum.2013.00887

Oldfield, R. C. (1971). The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia*, *9*(1), 97–113.

Parkes, L. M., Rashid, W., Chard, D. T., & Tofts, P. S. (2004). Normal Cerebral Perfusion Measurements Using Arterial Spin Labeling: Reproducibility, Stability, and Age and Gender Effects. *Magnetic Resonance in Medicine*, *51*(4), 736–743. https://doi.org/10.1002/mrm.20023

Peck, K. K., Moore, A. B., Crosson, B. A., Gaiefsky, M., Gopinath, K. S., White, K., & Briggs, R. W. (2004). Functional Magnetic Resonance Imaging before and after Aphasia Therapy: Shifts in Hemodynamic Time to Peak during an Overt Language Task. *Stroke*, *35*(2), 554–559. https://doi.org/10.1161/01.STR.0000110983.50753.9D

Powers, W. J., Press, G. A., Grubb, R. L., Gado, M., & Raichle, M. E. (1987). The effect of hemodynamically significant carotid artery disease on the hemodynamic status of the cerebral circulation. *Annals of Internal Medicine*, *106*(1), 27–35. https://doi.org/10.7326/0003-4819-106-1-27

R Core Team. (2020). R: A Language and Environment for Statistical Computing. Vienna, Austria. Retrieved from https://www.r-project.org/

Richardson, J. D., Baker, J. M., Morgan, P. S., Rorden, C., Bonilha, L., & Fridriksson, J. (2011). Cerebral perfusion in chronic stroke: Implications for lesion-symptom mapping and functional MRI. *Behavioural Neurology*, *24*(2), 117–122. https://doi.org/10.3233/BEN-2011-0283

Robson, H., Specht, K., Beaumont, H., Parkes, L. M., Sage, K., Lambon, M. A., & Zahn, R. (2017).

Arterial spin labelling shows functional depression of non-lesion tissue in chronic Wernicke's aphasia. *Cortex*, *92*, 249–260. https://doi.org/10.1016/j.cortex.2016.11.002

Rorden, C., & Brett, M. (2000). Stereotaxic Display of Brain Lesions. *Behavioural Neurology*, *12*(4), 191–200. https://doi.org/10.1155/2000/421719

Salvalaggio, A., de Filippo De Grazia, M., Zorzi, M., de Schotten, M. T., & Corbetta, M. (2020). Post-stroke deficit prediction from lesion and indirect structural and functional disconnection. *Brain*, *143*(7), 2173–2188. https://doi.org/10.1093/brain/awaa156

Saur, D., Baumgaertner, A., Schraknepper, V., Willmes, K., Rijntjes, M., & Weiller, C. (2006). Dynamics of language reorganization after stroke. *Brain*, *129*, 1371–1384. https://doi.org/10.1093/brain/awl090

Sekhon, L. H. S., Morgan, M. K., Spence, I., & Weber, N. C. (1994). Chronic cerebral hypoperfusion and impaired neuronal function in rats. *Stroke*, *25*(5), 1022–1027. https://doi.org/10.1161/01.STR.25.5.1022

Stefaniak, J. D., Alyahya, R. S. W., & Ralph, M. A. L. (2021). Language networks in aphasia and health: A 1000 participant Activation Likelihood Estimation meta-analysis. *NeuroImage*, *233*(February), 117960. https://doi.org/10.1016/j.neuroimage.2021.117960

Thompson, C. K., Ouden, D. Den, Bonakdarpour, B., Garibaldi, K., & Parrish, T. B. (2010). Neural plasticity and treatment-induced recovery of sentence processing in agrammatism. *Neuropsychologia*, *48*(11), 3211–3227. https://doi.org/10.1016/j.neuropsychologia.2010.06.036

Thompson, C. K., Walenski, M., Chen, Y., Caplan, D., Kiran, S., Rapp, B., … Parrish, T. B. (2017). Intrahemispheric perfusion in chronic stroke-induced aphasia. *Neural Plasticity*, (Article ID 2361619), 1–15. https://doi.org/10.1155/2017/2361691

Tibshirani, R., Bien, J., Friedman, J., Hastie, T., Simon, N., Tay-, J., & Tibshirani, R. J. (2010). Strong rules for discarding predictors in lasso-type problems. *Journal of the Royal Statistical Society*, *74*(2), 245–266.

Turken, A. U., & Dronkers, N. F. (2011). The Neural Architecture of the Language Comprehension Network: Converging Evidence from Lesion and Connectivity Analyses. *Frontiers in System Neuroscience*, *5*(February), 1–20.

https://doi.org/10.3389/fnsys.2011.00001

Wickham, H. (2016). *ggplot2: Elegant Graphics for Data Analysis*. Springer-Verlag New York. Retrieved from https://ggplot2.tidyverse.org

Wiest, R., Abela, E., Missimer, J., Schroth, G., Hess, C. W., Sturzenegger, M., … Federspiel, A. (2014). Interhemispheric cerebral blood flow balance during recovery of motor hand function after ischemic stroke-A longitudinal MRI study using arterial spin labeling perfusion. *PLoS ONE*, *9*(9). https://doi.org/10.1371/journal.pone.0106327

Wilson, S. M., Entrup, J. L., Schneck, S. M., Onuscheck, C. F., Levy, D. F., Davis, T., … Kirshner, H. S. (2022). Recovery from aphasia in the first year after stroke. *Brain*.

Wilson, S. M., & Schneck, S. M. (2021). Neuroplasticity in Post-Stroke Aphasia: A Systematic Review and Meta-Analysis of Functional Imaging Studies of Reorganization of Language Processing. *Neurobiology of Language*, *2*(1), 22–82. https://doi.org/10.1162/nol_a_00025