CORTEX 155 (2022) 90–106

Available online at www.sciencedirect.com

ScienceDirect

Journal homepage: www.elsevier.com/locate/cortex

Clinical Neuroanatomy

Structural disconnections associated with language impairments in chronic post-stroke aphasia using disconnectome maps

Anne Billot [a,b,*], Michel Thiebaut de Schotten [c,d], Todd B. Parrish [e], Cynthia K. Thompson [f], Brenda Rapp [g], David Caplan [h] and Swathi Kiran [a]

[a] Sargent College of Health & Rehabilitation Sciences, Boston University, Boston, MA, USA
[b] School of Medicine, Boston University, Boston, MA, USA
[c] Brain Connectivity and Behaviour Laboratory, Sorbonne Universities, Paris, France
[d] Groupe d'Imagerie Neurofonctionnelle, Institut des Maladies Neurodégénératives-UMR 5293, CNRS, CEA University of Bordeaux, Bordeaux, France
[e] Department of Radiology, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA
[f] Department of Communication Sciences and Disorders, Northwestern University, Evanston, IL, USA
[g] Department of Cognitive Science, Johns Hopkins University, Baltimore, MD, USA
[h] Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

ARTICLE INFO

Article history:
Received 15 April 2021
Reviewed 16 July 2021
Revised 14 September 2021
Accepted 10 June 2022
Action editor Olga Dragoy
Published online 19 July 2022

Keywords:
Aphasia
Disconnection
Mapping
Stroke
White matter

ABSTRACT

Inconsistent findings have been reported about the impact of structural disconnections on language function in post-stroke aphasia. This study investigated patterns of structural disconnections associated with chronic language impairments using disconnectome maps.

Seventy-six individuals with post-stroke aphasia underwent a battery of language assessments and a structural MRI scan. Support-vector regression disconnectome-symptom mapping analyses were performed to examine the correlations between disconnectome maps, representing the probability of disconnection at each white matter voxel and different language scores. To further understand whether significant disconnections were primarily representing focal damage or a more extended network of seemingly preserved but disconnected areas beyond the lesion site, results were qualitatively compared to support-vector regression lesion-symptom mapping analyses.

Part of the left white matter perisylvian network was similarly disconnected in 90% of the individuals with aphasia. Surrounding this common left perisylvian disconnectome, specific structural disconnections in the left fronto-temporo-parietal network were significantly associated with aphasia severity and with lower performance in auditory comprehension, syntactic comprehension, syntactic production, repetition and naming tasks. Auditory comprehension, repetition and syntactic processing deficits were related to disconnections in areas that overlapped with and extended beyond lesion sites significant in SVR-LSM analyses. In contrast, overall language abilities as measured by aphasia

Abbreviations: AF, arcuate fasciculus; IFOF, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; UF, uncinate fasciculus; SLF, superior longitudinal fasciculus; SVR, support vector regression; DSM, disconnectome-symptom mapping; LSM, lesion-symptom mapping.

* *Corresponding author*. Boston University Sargent College, Rm 326, 635 Commonwealth Ave., Boston, MA 02215, USA.
E-mail address: abillot@bu.edu (A. Billot).

https://doi.org/10.1016/j.cortex.2022.06.016

severity and naming seemed to be mostly explained by focal damage at the level of the insular and central opercular cortices, given the high overlap between SVR-DSM and SVR-LSM results for these scores.

While focal damage seems to be sufficient to explain broad measures of language performance, the structural disconnections between language areas provide additional information on the neural basis of specific and persistent language impairments at the chronic stage beyond lesion volume. Leveraging routinely available clinical data, disconnectome mapping furthers our understanding of anatomical connectivity constraints that may limit the recovery of some language abilities in chronic post-stroke aphasia.

1. Introduction

Individuals with aphasia may present with various language impairments following an acquired brain injury such as a stroke. Multiple interdependent neurobiological events occur during and after a stroke, resulting in brain tissue death in the gray and white matter (Quillinan, Herson, & Traystman, 2016) and critical disruption of connections between brain regions responsible for language processing. Over the last decades, neuroimaging studies have provided insight into the pathophysiology of these language deficits, and the findings can be broadly categorized into two sets: 1) the effect of focal brain damage on language function, 2) the influence of network-level disruptions on language behavior (Kiran & Thompson, 2019). Here, we will first review these observations in the context of their methodology, focusing on studies using structural data, and then propose a complementary analysis of structural connectivity disruptions that can further our understanding of language impairments in post-stroke aphasia.

Voxel-based lesion-symptom mapping has revealed the relationship between cortical injury and language impairment (VLSM, Bates et al., 2003). Lesion topography is associated with a range of linguistic abilities after stroke, such as speech production and speech comprehension (Borovsky, Saygin, Bates, & Dronkers, 2007; Henseler, Regenbrecht, & Obrig, 2014; Kümmerer et al., 2013; Mirman, Chen, et al., 2015; Price, Seghier, & Leff, 2010), and more specifically verbal fluency (Baldo, Schwartz, Wilkins, & Dronkers, 2006), picture naming (Akinina et al., 2019; Døli, Helland, Helland, & Specht, 2020; Henseler et al., 2014; Piras & Marangolo, 2010), semantic processing (Halai, Woollams, & Lambon Ralph, 2017; Henseler et al., 2014; Mirman, Chen, et al., 2015; Schumacher, Halai, & Lambon Ralph, 2019; Schwartz et al., 2009; Walker et al., 2011), phonological processing (Halai et al., 2017; Ripamonti et al., 2018; Schumacher et al., 2019), repetition (Døli et al., 2020; Fridriksson et al., 2010; Henseler et al., 2014; Kümmerer et al., 2013; Ripamonti et al., 2018), syntactic processing (den Ouden et al., 2019; Dronkers, Wilkins, Van Valin, Redfern, & Jaeger, 2004; Lukic et al., 2020; Magnusdottir et al., 2013; Rogalsky et al., 2017), number and word reading (Døli et al., 2020; Piras & Marangolo, 2009) and spelling (Rapp, Purcell, Hillis, Capasso, & Miceli, 2016). Traditionally, VLSM uses t-statistics at each voxel of the brain to determine whether the degree of injury is related to the language performance (Bates et al., 2003). Lesion-symptom mapping analyses, therefore, provide information on the role of different brain areas in language performance. Nevertheless, they present inherent limitations. First, lesion coverage is heterogeneous across voxels and restricted to particular vascular territories in most studies (Karnath, Sperber, & Rorden, 2019; Rudrauf et al., 2008) which influences the statistical power at each voxel (Rudrauf et al., 2008). Consequently, the analysis may include a spatial bias toward the center of the vascular territory affected by the stroke (Karnath et al., 2019; Mah, Husain, Rees, & Nachev, 2014). Second, damage to different regions can cause the same language impairment if these regions belong to the same structural or functional network (Fridriksson et al., 2018; Karnath et al., 2019; Price, Hope, & Seghier, 2017). For these reasons, the prediction power and the interpretation of standard lesion–outcome associations are limited (Karnath et al., 2019; Kimberg, Coslett, & Schwartz, 2007; Price et al., 2017).

Furthermore, stroke damage can disrupt distant regions' structure and function by modifying their metabolism (Carrera & Tononi, 2014). Von Monakow has defined this neurobiological phenomenon as diaschisis (von Monakow, 1914). Carrera and Tononi have recently extended this notion to 'connectomal diaschisis' to describe remote "changes in the structural and functional connectomes, including disconnections and reorganization of subgraphs" (Carrera & Tononi, 2014, p. 2419). Hence, language deficits might arise from seemingly undamaged but disconnected regions involved in language processing (Catani & Mesulam, 2008; Price et al., 2017). Interestingly, structural disconnection measures seem to better predict functional connectivity disruption within and between large-scale networks than region-based or voxel-based damage measures (Griffis, Metcalf, Corbetta, & Shulman, 2019). Recent studies examining affected anatomical networks in stroke survivors have provided a richer understanding of the relationship between aphasia and its neural underpinnings.

Following the assumption that network-level analyses provide a more comprehensive interpretation of the relationship between clinical symptoms and physiological disruptions caused by the stroke lesion (Catani & Mesulam, 2008), several studies have examined the impact of infarcts on structural network connectivity and how white matter

disruptions relate to language dysfunction. This paper focuses on methods that measure direct lesions' effect on anatomical connections (see Zhang et al., 2021 for a meta-analysis of studies using diffusion metrics to investigate white matter integrity in spared tracts). In post-stroke aphasia studies, researchers have mainly used two types of measurements based on white matter tractography data to investigate structural disconnections: (i) reduction in connection density (i.e., percentage number of fibers connected to a cortical region compared to the homologous cortical area), and (ii) a binary measure of tract discontinuity. In the first approach, Bonilha and colleagues found that reduced fiber density at two left hemisphere cortical regions (i.e., Brodmann areas 45 and 22) was associated with the degree of impairment in specific language tasks, but not with the overall aphasia severity (Bonilha, Rorden, & Fridriksson, 2014). The second approach calculates binary measures of disconnection. It considers a tract to be disconnected "if a lesion either disconnects one part of the tract from another or completely destroys one end of the tract" (Hope & Price, 2016, p. 1171). Two studies demonstrated that binary disconnection of the left arcuate fasciculus was associated with deficits in naming (Geller, Thye, & Mirman, 2019; Hope, Seghier, Prejawa, Leff, & Price, 2016). However, since this technique relies on a single value for a whole tract, it may be more sensitive to image processing errors, such as misregistration between the lesion map and the probabilistic white matter atlas needed for this method. An error of measurement at one portion of the tract would lead to the opposite category definition for the whole tract (i.e., from disconnected to spared and vice versa) (Geller et al., 2019). Mapping disconnected white matter fibers at the voxel level in the whole brain is one way to overcome this limitation. Specifically, detailing the topological distribution of structural network disruption voxel by voxel in post-stroke aphasia provides information to elucidate clinical-anatomical relationships at the level of the affected connectome, from and beyond the lesion site. It also enables one to identify and trace pathways that may be affected by the distal effects of stroke damage that are not easily measurable with actual MRI techniques (Carrera & Tononi, 2014). The most direct way to identify structural disconnections in the whole brain would be to trace fibers that cross each patient's brain's damaged area using diffusion-weighted imaging data and fiber-tracking algorithms (Basser, Mattiello, & LeBihan, 1994; Mori & van Zijl, 2002). However, when white matter tracts are directly damaged, reconstruction of the tract's remaining portions may not be possible (Auriat, Borich, Snow, Wadden, & Boyd, 2015). Here, we apply an alternative and complementary approach to examine the anatomical substrates of neural disruption in aphasia by constructing disconnectome maps (Foulon et al., 2018). By using a large reference set of high-quality tractograms from healthy controls, these disconnectome maps provide the probability of structural disconnection at each voxel without the need to acquire diffusion-weighted images (Foulon et al., 2018). Specifically, in this work, the probability of disconnection refers to the voxel-wise probability of tracking a white matter fiber in healthy controls. These fibers are then considered disconnected if they enter the infarcted area when overlaid with the patient's lesion map. This tool was first used to identify potentially disconnected tracts related to deficits in language processing, decision making, and memory in three well-studied historical patients (Thiebaut de Schotten et al., 2015). Subsequently, this technique has been used in patients following an acquired brain injury to identify disconnected networks related to the overall language behavior (Salvalaggio, De Filippo De Grazia, Zorzi, Thiebaut de Schotten, & Corbetta, 2020) or specific language impairments, such as poor fluency performance (Foulon et al., 2018) and repetitive verbal behaviors (Mandonnet et al., 2019; Torres-Prioris et al., 2019). Three of these studies included individuals who underwent a brain resection due to a brain tumor or suffered a traumatic brain injury, and each examined one language component only (Foulon et al., 2018; Mandonnet et al., 2019; Torres-Prioris et al., 2019). Using multivariate analyses, Salvalaggio et al. (2020) demonstrated that disconnectome maps can predict overall language behavior variability in stroke survivors at a similar level as lesion maps, with slightly less accuracy (i.e. 41% vs 48%). A previous study from the same group using the same method found similar results with 44% of language behavior variability explained by lesion maps (Corbetta et al., 2015). Using a similar method, Kuceyeski et al. (2015) evaluated disconnections at each cortical region and found that disconnections at medial regions predicted language scores. Notably, these studies measured language behavior either with screening tests or as a composite score obtained from multiple subtests of a language battery and, thus, did not identify disconnections related to specific language impairments in individuals with chronic post-stroke aphasia.

In the present study, we implement a comprehensive clinical-neuroanatomical investigation of the impact of white matter disconnections on a range of language abilities in a large cohort of patients with different types of chronic post-stroke aphasia. We then compare the results from disconnectome-symptom mapping (DSM) analyses to more standard lesion-symptom mapping (LSM) analyses to further distinguish between the remote pathological effects and the loss of brain tissue on chronic language deficits. We hypothesize that overall aphasia severity and specific language impairments, such as naming, repetition, syntactic processing, and auditory comprehension, will be associated with disconnections in the left perisylvian connectome due to long-range fiber pathways affected by the lesions. Further, these language impairments will be explained by disconnections that overlap and extend beyond lesion sites associated with each impairment.

2. Materials and methods

2.1. Patients

We report how we determined our sample size, all data exclusions, all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established before data analysis, all manipulations, and all measures in the study. Eighty-one participants with a single left-hemisphere ischaemic stroke at least six months post-stroke were recruited from three

research sites (Boston University, Johns Hopkins University and Northwestern University) between 2015 and 2018 as part of a large-scale study of the Center for the Neurobiology of Language Recovery (http://cnlr.northwestern.edu/). All participants were native English speakers, at least high school educated, and had normal or corrected-to-normal vision and hearing. Demographics and neurological history were obtained from medical records and study-specific questionnaires. Exclusion criteria included contraindication for MRI, history of neurological disorder other than a stroke, history of multiple infarcts, history of drug or alcohol abuse and articulatory disorders (apraxia of speech or dysarthria). Five participants out of the 81 have been excluded due to poor imaging data ($n = 1$), different acquisition parameters ($n = 2$), and withdrawal during testing ($n = 2$). A total of 76 individuals with chronic aphasia have been included in the analyses. Participants provided informed consent according to the Declaration of Helsinki. Additional information was provided when needed to ensure participants' understanding of the study protocol before obtaining their written consent. The Institutional Review Boards approved the study at all three universities. No part of the study procedures and analyses was pre-registered before the research was conducted. The conditions of our ethics approval and HIPAA law do not permit public archiving of anonymised study data. Readers seeking access to the data should contact author S.K. Access will be granted to named individuals in accordance with ethical procedures governing the reuse of sensitive data, including completion of a formal data-sharing agreement.

2.2. Language assessment

An extensive battery of language assessments was administered to the participants by speech-language pathologists or trained research assistants: the Western Aphasia Battery-Revised (WAB-R) (Kertesz, 2007), Northwestern Naming Battery (NNB) (Thompson, Lukic, King, Mesulam, & Weintraub, 2012) and Northwestern Assessment of Verbs and Sentences (NAVS) (Cho-Reyes & Thompson, 2012). Only specific subtests have been included in the analyses of this study: Aphasia Quotient (AQ) to investigate aphasia severity, auditory verbal comprehension and repetition scores from the WAB-R; Confrontation Picture Naming (Nouns) total score from the NNB; and Sentence Comprehension Test (SCT) and Sentence Production Priming Test (SPPT) total scores from the NAVS. Legal copyright restrictions prevent public archiving of the WAB-R, NNB and NAVS, which can be obtained commercially from the copyright holders in the cited references.

2.3. Imaging data acquisition and preprocessing

Imaging data were collected from four different 3 Tesla MRI scanners: a Siemens TIM Trio with a 32-channel head coil and a Siemens Prisma with a 64-channel head/neck coil at Northwestern University, a Siemens TIM Trio with a 20-channel head/neck coil at the Athinoula A. Martinos Center for Boston University, and a Philips Intera with a 32-channel head coil at Johns Hopkins University. Imaging parameters were consistent across the three sites, with the cross-site harmonization verified by the neuroimaging team. High resolution, T1-weighted 3D sagittal volumes were acquired using an MPRAGE sequence (parameters: T1/TE[1]/TR = 900/2.98/2300 ms, FOV = 256 × 256mm, voxel resolution = 1x1x1mm^3, 176 sagittal slices, phase encoding direction = A/P).

2.3.1. Lesion mapping

The lesions were traced using a semi-automated procedure on T1-weighted images. First, for each participant, multiple lesion masks were generated by the quality assurance anatomical pipeline available within the Northwestern University Neuroimaging Data Archive (Alpert, Kogan, Parrish, Marcus, & Wang, 2016) through the application of a deep convolutional neural network approach (Wang, Katsaggelos, Wang, & Parrish, 2016). This approach uses information about 3D structural image intensity in surrounding voxels and contralateral (i.e., right hemisphere) voxels to classify each voxel as belonging to normal or pathological tissue. Second, for each participant, two trained members of the research team independently chose the best lesion mask, and a third member helped resolve any disagreement. When necessary, lesion masks were manually edited in native space using MRIcron software (Rorden & Brett, 2000) (https://people.cas.sc.edu/rorden/mricron/). Spatial normalization of the lesion maps to the MNI space, filtering and resampling to 1x1x1 mm voxels were performed using the 3dQwarp function of the AFNI software through a pipeline in the Northwestern University Neuroimaging Data Archive. Specifically, each pseudo-T1 image with the lesion removed was nonlinearly warped to the MNI template (Brett, Leff, Rorden, & Ashburner, 2001). The warp field was then applied to the lesion mask to generate the lesion mask in template space. Due to technical issues, the lesion maps of three participants[2] were manually drawn using MRIcron software and normalized to the MNI space using SPM 12 instead of this pipeline. The volume of each lesion map was calculated using the *volume* function in MATLAB.

2.3.2. Disconnectome mapping

A probability map of white matter tracts' disconnection was computed for each participant with aphasia with the "Disconnectome map" tool of the BCBToolkit (Foulon et al., 2018). Disconnectome maps provide an indirect estimate of the degree of structural disconnection at each voxel. This estimate is computed from healthy controls' tractograms representing white matter fibers that pass through each lesion. These tractograms were produced using a set of 178 healthy controls of the Human Connectome Project diffusion-weighted imaging database (Thiebaut de Schotten, Foulon, & Nachev, 2020). More specifically, for each individual with aphasia, the lesion map in MNI space was used as a seed to track healthy controls' fibers passing through the lesion in TrackVis (Wang & Wedeen, 2007). A percentage overlap map was then produced by computing, at each voxel in MNI space, the proportion of controls who had a tract that crossed the lesioned area (Fig. 1). Hence, in the resulting disconnectome map, the value in each voxel takes into account

[1] There were slight variations in TE values at NU and JHU (<.07) and TR values at JHU (<325) based on the different scanners used.
[2] P10, P17, P26.

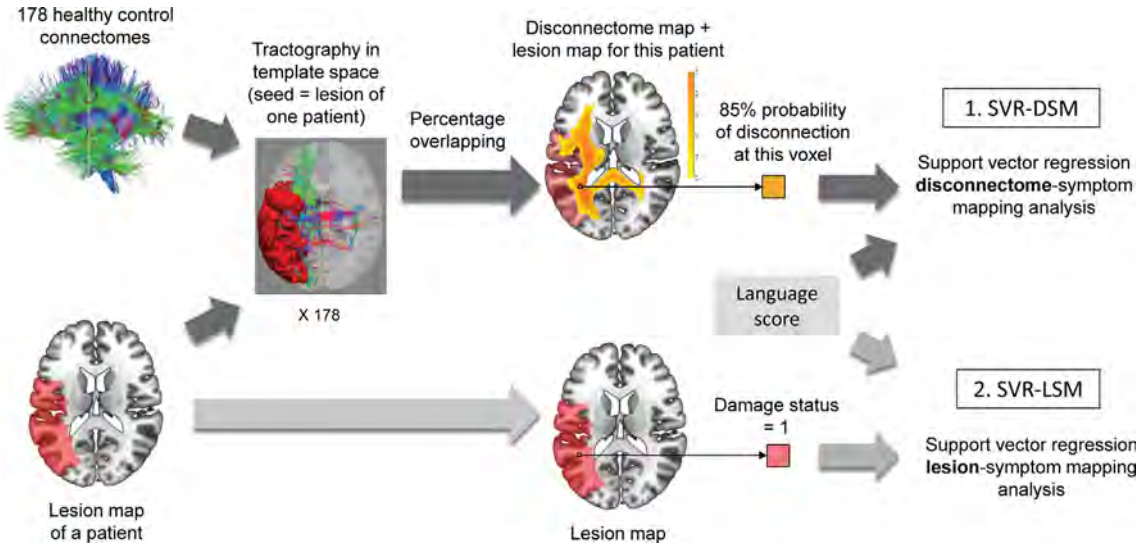

Fig. 1 – Support Vector Regression Disconnectome-Symptom Mapping (SVR-DSM) and Support Vector Regression Lesion-Symptom Mapping (SVR-LSM) methodological procedures. For each patient, a disconnectome map was created by overlapping the lesion map of the individual with post-stroke aphasia with healthy control tractograms from the HCP diffusion-weighted images dataset using the Disconnectome map tool of the BCBToolkit. The probability of disconnection at each voxel (e.g., 85% at the voxel highlighted) was then entered into the SVR-DSM analysis. As a subsequent investigation, the binary value of presence (1) or absence (0) of damage at each voxel was entered into the SVR-LSM analysis.

the interindividual variability of tract reconstruction across controls and indicates the probability of disconnection from 0 to 100% for a given lesion (Thiebaut de Schotten et al., 2015). In other words, "probability of disconnection" refers to the voxel-wise probability of tracking a healthy control fiber that enters the infarcted area when overlayed with the lesion map of a patient. Thus, each disconnectome map includes both the white matter pathways that overlap with the infarcted area (i.e., damaged) and the part that extends beyond the infarcted area (i.e., seemingly spared). In accordance with previous studies (Foulon et al., 2018; Mandonnet et al., 2019), a threshold of 50% was applied for this study to ensure generalizability of the results (i.e., at each voxel labeled as disconnected, at least 50% of healthy controls fibers passed through the lesion). For a given lesion, this threshold ensures that at least the majority of controls had a tract where the disconnection was being calculated. It excludes voxels with low probability of disconnection from the disconnectome maps as they reflect individual differences in the white matter tractograms of controls. After thresholding the disconnectome maps, values at each voxel were either zero (no disconnection) or within the range of 50–100% probability of disconnection.

2.4. *Statistical analysis*

The study aimed to investigate whether and where white matter disconnections were related to aphasia severity and other specific language deficits. To this end, support vector regression disconnectome-symptom mapping (SVR-DSM) analyses were performed as described below.

Notably, disconnectome maps include disconnected white matter voxels that can be either directly damaged (i.e., direct overlap with the lesion map) or seemingly spared (i.e., part of the fibers not damaged but connected to the lesioned area). To understand whether the significant relationships between disconnections and language deficits were only driven by the lesioned voxels or by disconnected voxels from and beyond the lesioned areas, results that emerged from SVR-DSM were compared to traditional lesion-symptom mapping analyses (SVR-LSM).

2.4.1. *Support vector regression disconnectome-symptom mapping*

Disconnectome-symptom mapping analyses were performed using support vector regression (SVR-DSM) to investigate the relationship between individuals' language scores and the probability of disconnection. Support vector regression has been used and validated as a multivariate method to model lesion-symptom associations in multiple lesion-symptom mapping studies (DeMarco & Turkeltaub, 2018; Fama, Hayward, Snider, Friedman, & Turkeltaub, 2017; Griffis, Nenert, Allendorfer, & Szaflarski, 2017; Mirman, Kraft, Harvey, Brecher, & Schwartz, 2019; Mirman, Zhang, et al., 2015; Wiesen, Karnath, & Sperber, 2020). Instead of investigating brain-behavior relationships at the voxel-level such as in traditional mass-univariate voxel-based lesion-symptom mapping (VLSM) analyses, this multivariate method uses a high dimensional feature space to evaluate the entire brain-behavior association simultaneously (Zhang, Kimberg, Coslett, Schwartz, & Wang, 2014). In this study, disconnectome maps serve as the input to the SVR models. In

accordance with previous lesion-symptom mapping literature (Binder et al., 2016; Borovsky et al., 2007; den Ouden et al., 2019; Dronkers et al., 2004; Klingbeil, Wawrzyniak, Stockert, Karnath, & Saur, 2020; Lukic et al., 2020), only voxels with sufficient disconnection involvement were assessed in the SVR-DSM analyses. Before the analyses, upper and lower thresholds were set on the disconnectome maps to ensure sufficient variance of the sample at each voxel. Specifically, only voxels disconnected in 10%–90% of the patients (n = 8–68) were included. The six language scores were included as dependent variables in separate SVR-DSM analyses. In addition, several factors may influence language function in aphasia, such as lesion volume (Døli et al., 2020; Hope, Seghier, Leff, & Price, 2013; Kertesz, Harlock, & Coates, 1979; Naeser et al., 1998; Plowman, Hentz, & Ellis, 2011; Watila & Balarabe, 2015), age (Ellis & Urban, 2016; Wallentin, 2018), time post-stroke onset (Holland, Fromm, Forbes, & MacWhinney, 2017; Naeser et al., 1998; Pedersen, Vinter, & Olsen, 2004) and handedness (Knecht et al., 2000). Therefore, these variables were regressed out of both the language scores and the disconnectome data, as recommended by DeMarco and Turkeltaub (2018). The study center was also covaried out of both the language scores and disconnectome data to account for potential differences across testing facilities.

The resulting SVR-β values represent the strength of the association between the disconnection status and the language deficit at each voxel. They were thresholded at $P < .05$ based on continuous permutation-based family-wise error (CFWE) correction configured to permit 100 mm^3 of false positive voxels (5000 permutations, $v = 100$), given that SVR-DSM results are not expected to be interpreted at the single voxel level (Mirman et al., 2018; Winkler, Ridgway, Webster, Smith, & Nichols, 2014). This method allows quantifying the rate of multi-voxel false positives, resulting in the transparent reporting of the strength of the evidence within a less stringent framework (Mirman et al., 2018). Bonferroni correction was also applied to thresholded β-maps to control for the number of language scores tested. Results were considered significant below an alpha level of .05 (i.e., less than 5% of the permutations had v voxels that exceeded the β value). The analyses were run using the svrlsmgui in MATLAB, version 2019b (parallelized, run from the GUI), with default parameters gamma = 5 and cost = 30 (DeMarco & Turkeltaub, 2018).

2.4.2. *Support Vector Regression Lesion-Symptom Mapping (SVR-LSM)*

Following the same method as in the SVR-DSM analyses, multivariate analyses using support vector regression models were performed to assess the relationship between brain damage (lesioned versus non-lesioned voxels) and each language score separately (SVR-LSM). Similarly to the SVR-DSM analyses, only gray and white matter voxels lesioned in at least 10% of individuals ($n > 8$) were included to ensure a sufficient number of participants with a lesion at each voxel. However, the second upper thresholding was unnecessary because the maximum lesion overlap (76% of participants) was below 90%. Lesion volume, age, months post-stroke onset, handedness, and site were also covaried out of both lesion data and language scores in each analysis. The same multiple comparison correction techniques (continuous permutation-based FWER at $v = 100$ to correct for multiple comparisons across voxels), toolbox and software as in SVR-DSM analyses were used.

2.4.3. *Validation of results across brain-behavior mapping approaches*

Support vector regression has been shown to better account for functional dependencies in lesion-symptom mapping analyses and seems to be more appropriate for network-level analyses than univariate analyses (Ivanova, Herron, Dronkers, & Baldo, 2021; Xu, Jha, & Nachev, 2018). However, there is still an ongoing debate on the best approach to use to map behavior to specific brain regions (Ivanova et al., 2021; Sperber, Wiesen, & Karnath, 2019) and no systematic methodological study has compared univariate and multivariate methods in the context of disconnectome maps. Therefore, in addition to multivariate analyses, traditional mass-univariate voxel-based disconnectome-symptom (VDSM) and lesion-symptom mapping (VLSM) analyses were performed in order to confirm the robustness of the results across methodological approaches and to compare them across studies. Methodological details on these analyses and results are included in the supplementary material.

2.5. *Labeling of white matter pathways and gray matter areas*

We further characterized which white matter pathways were involved in the thresholded β-maps (cFWER $P < .05$, $v = 100$) of both SVR-DSM and SVR-LSM analyses by overlaying them onto the PANDORA probabilistic atlas of white matter pathways (Hansen et al., 2021). In this study, we used the atlas compiled from the Baltimore Longitudinal Study of Aging tractography data ($n = 963$) extracted via the Automated Fiber-tract Quantification technique. This atlas was selected for the close proximity in age of its population (mean age = 66.2) with the population of individuals with aphasia included in the present study (mean age = 58.3). Second, the Automated Fiber-tract Quantification technique was chosen because its 20 reconstructed tracts include tracts of interest for our research that are thought to be involved in language processing based on previous literature. The resulting probabilistic white matter atlas was thresholded at 25%, binarized and overlaid onto the statistical maps. The 25% probability threshold ensures a large enough sample size to generalize the atlas labels to our sample while limiting the inter-individual variability that can occur during fiber tracing. The intersection volume between the atlas mask of each fiber pathway and the thresholded β-map was computed for both SVR-DSM and SVR-LSM. In addition, the Harvard Oxford cortical structural atlas (Desikan et al., 2006) thresholded at a probability of 25%, was used to identify disconnected gray matter regions significantly associated with language deficits at the edges of the thresholded β-maps

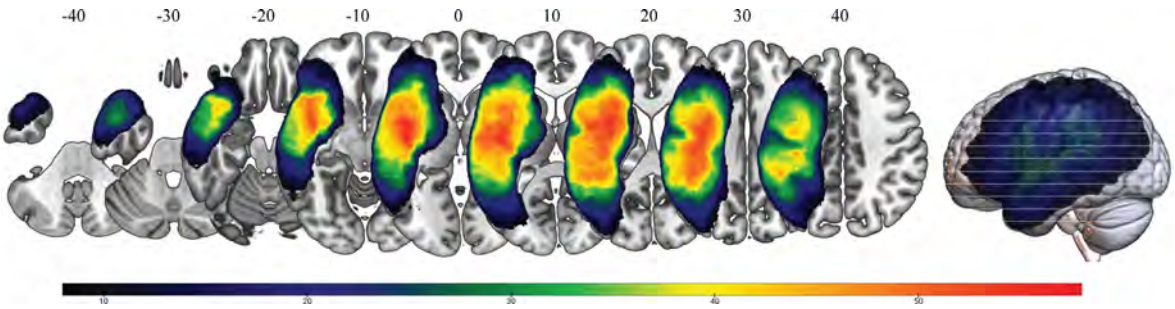

Fig. 2 – Lesion overlay. Plot representing the distribution of lesions in all patients. Slice numbers represent z coordinates of the MNI 152 brain template. Color shades illustrate the increasing number of patients with overlapping lesions (range: 8–58, from cold to warm colors).

(cFWER $P < .05$, $v = 100$) by overlapping each statistical map to each gray matter ROI mask. These steps were performed with FSL (*fslmaths* and *fslstats* functions), version 6.0.2 (Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012).

3. Results

3.1. Behavioral results

Participants' demographics and behavioral scores are available in Supplementary Table 1. Results are presented for the 76 individuals with chronic aphasia who completed the full battery of language assessments and had good quality imaging data (52 males/24 females; mean age = 58.3, sd = 11.6; mean time post-stroke onset = 65.1 months, sd = 68.5, range = 8–467). One participant had missing data for NAVS – SPPT and NNB – Confrontation Naming scores but was included for the other analyses.

3.2. Structural maps

Fig. 2 displays the overlay of the 76 lesion maps showing an extensive coverage of the left hemisphere. The maximum lesion coverage included left periventricular white matter pathways, left perisylvian white matter (AF) and cortical

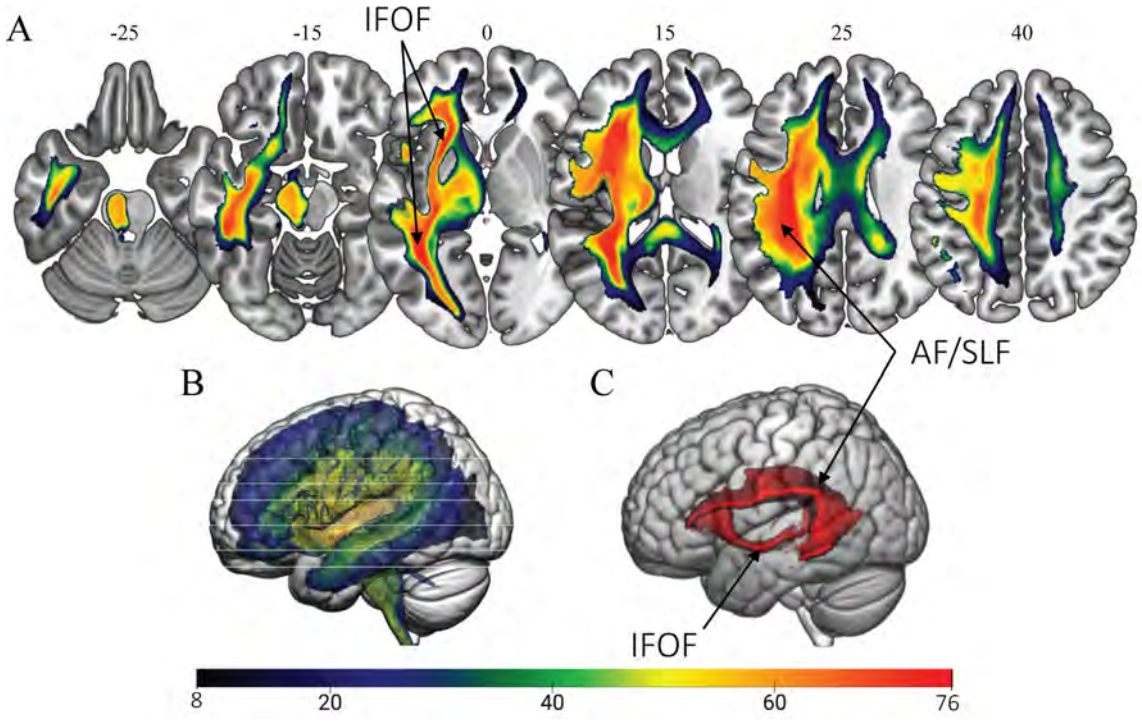

Fig. 3 – Disconnectome overlay. Color shades illustrate the increasing number of patients with overlapping disconnectomes (range: 8–76, from cold to warm colors). A) Plot representing the distribution of disconnections for all patients. Slice numbers represent z coordinates of the MNI 152 brain template. B) Sagittal view of the disconnectome overlay. C) Overlap of disconnections occurring in more than 90% of the participants. IFOF = inferior fronto-occipital fasciculus, AF = arcuate fasciculus, SLF = superior longitudinal fasciculus.

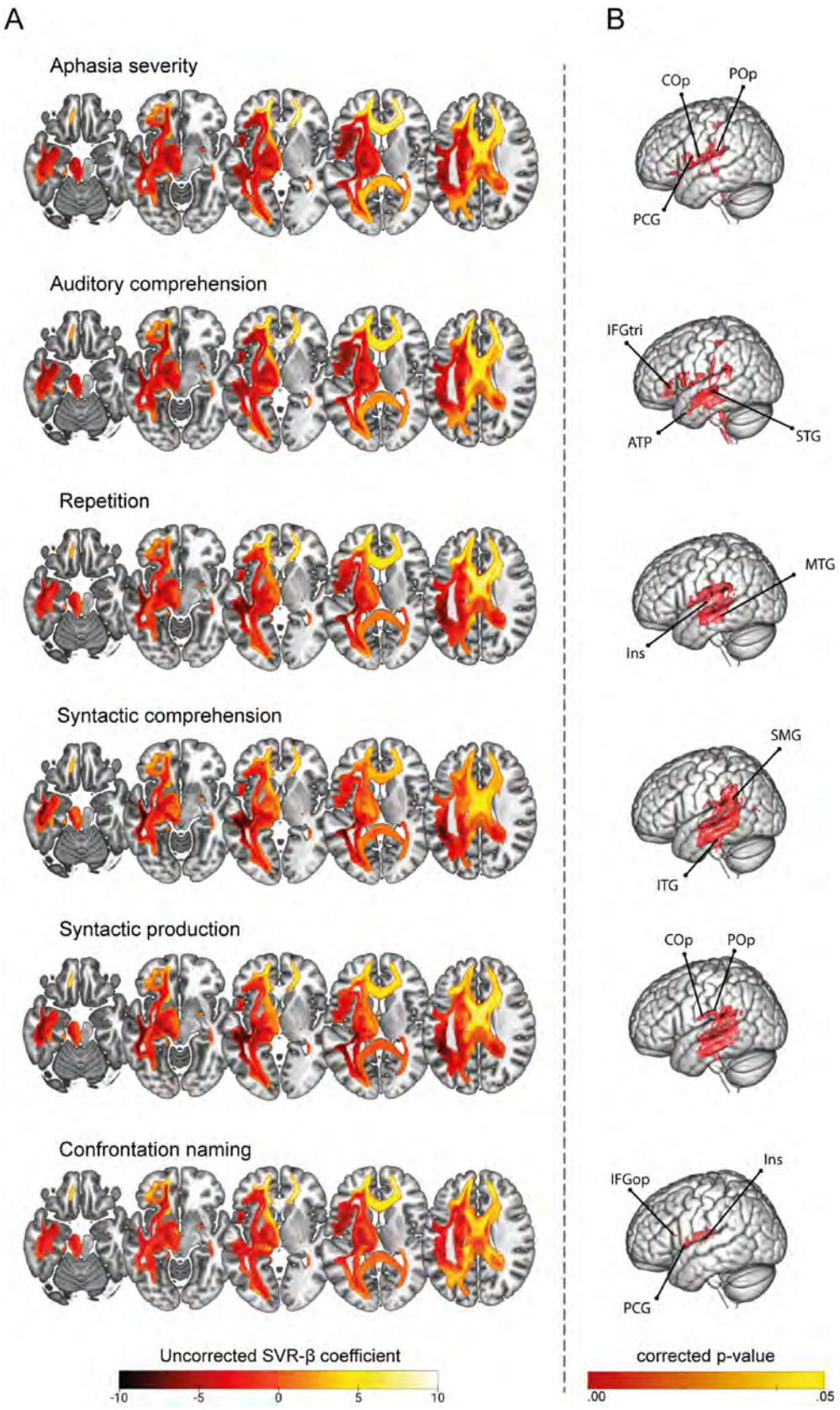

Fig. 4 – Structural maps of disconnections associated with persistent language impairments in individuals with chronic aphasia. Results of the SVR-DSM analyses investigating the relationship between language impairments and the voxel-wise probability of disconnection. A) Uncorrected β-maps. B) β-maps thresholded at $p < .05$, corrected for multiple comparisons (maximum of 100 mm^3 of false positive voxels) and adjusted for lesion volume and other covariates. Statistical

areas (insula, rolandic operculum). Fig. 3 displays the overlay of disconnectome maps for 76 individuals. The major white matter pathways disconnected in more than 90% of the participants were the left arcuate fasciculus (AF, 23% of the total volume of the tract per the PANDORA atlas), superior longitudinal fasciculus (SLF, 14%), inferior fronto-occipital fasciculus (IFOF, 20%) and posterior part of the inferior longitudinal fasciculus (ILF, 10%) (Fig. 3 C). Given that parts of the AF, SLF, IFOF and ILF were disconnected in almost all individuals with aphasia included in this study, voxels that had greater than 90% of subjects with disconnections were excluded from the SVR-DSM analyses to ensure sufficient variance in the sample analyzed at each voxel, as described in the methods.

3.3. SVR-DSM results: disconnections associated with chronic language impairments

In SVR-DSM analyses, all language scores were negatively associated with the probability of disconnection in left perisylvian and corticobulbar networks after accounting for lesion volume, demographic information and correcting for multiple comparisons ($P < .005$). The higher the probability of disconnection in these white matter pathways, the lower the language performance across linguistic skills. Uncorrected and thresholded β-maps of each SVR-DSM analysis are displayed in Fig. 4. All language scores, except naming, were associated to different extents with disconnections along both dorsal and ventral left hemisphere white matter tracts, such as the arcuate, superior longitudinal, inferior longitudinal, inferior fronto-occipital, and uncinate fasciculi, as well as thalamic radiations and cortico-spinal/cortico-bulbar tract. The volume of overlap between thresholded statistical maps and white matter and gray matter regions from each respective atlas are available in Table 2 and 4 in the supplementary material. Specifically, aphasia severity was mostly associated with disconnections of the central and parietal opercular cortices, the inferior part of the precentral gyrus and the inferior frontal gyrus. Disconnections related to naming deficits were restricted to fibers between the insular cortex and the central operculum. The other language scores were related to disconnections in a more extended network. Repetition, auditory comprehension and syntactic processing (comprehension and production) deficits were similarly related to disconnections of temporo-parietal areas. More specifically, these disconnections were located i) dorsally, along the arcuate fasciculus and underlying the precentral and supramarginal gyri, as well as the central, parietal opercular, and insular cortices, and ii) ventrally, along the inferior longitudinal and the inferior fronto-occipital fasciculi, also including short-range disconnections between the superior and middle temporal cortices. In addition, disconnections associated with syntactic production deficits specifically extended to the inferior temporal gyrus, and disconnections associated with auditory comprehension deficits specifically extended to the inferior frontal (pars triangularis and opercularis), the frontal-orbital and the anterior temporal cortices. Patterns of disconnections significantly related to aphasia severity, auditory comprehension and syntactic comprehension and production also included a few white matter voxels in the brain stem.

3.4. Differences and overlap between disconnectome-symptom and lesion-symptom mapping results

Since the disconnectome maps used in the SVR-DSM analyses mentioned above encompassed both infarcted white matter tissue and potentially spared white matter areas connected to the lesion, we compared the SVR-DSM to more classical SVR-LSM analyses. Fig. 5 shows that, when examining infarcted areas only (i.e., SVR-LSM), all language deficits were negatively associated with damage in restricted white matter clusters surrounding the left lateral sulcus ($P < .005$). By contrast, when investigating white matter disconnections (i.e., SVR-DSM), significant structural pathways negatively associated with language deficits not only included damaged white matter areas significant in the SVR-LSM analyses but encompassed a more extended network of fiber bundles that extended to the left temporal pole, the inferior lateral temporal regions, the inferior frontal gyrus, the orbitofrontal area, the temporo-parietal junction and the brain stem. More specifically, disconnected white matter areas significantly related to repetition, syntactic comprehension and syntactic production deficits extended into the temporo-parietal junction while damaged white matter voxels significantly related with these scores were located in focal white matter clusters underlying the left superior temporal gyrus. In addition, disconnections of the left middle and inferior temporal gyri showed significant associations with syntactic comprehension and production deficits, whereas damage to the same regions did not show a significant association with these language scores. Further, auditory comprehension deficits were related to damage of the left central operculum, insula and superior temporal gyrus and to disconnections between the inferior frontal gyrus and the anterior temporal lobe, along the uncinate fasciculus. Conversely, significant disconnections associated with aphasia severity and confrontation naming, did not extend beyond the damaged white matter areas related to these language scores.

Relative to the SVR-LSM results, SVR-DSM results suggest that post-stroke chronic language impairments may be related to the disruption of function via focal white matter damage and disconnections in language networks from and

maps were also corrected for multiple comparisons across language tests using Bonferroni correction. Language scores include aphasia severity (WAB-R Aphasia Quotient), auditory comprehension (WAB-R auditory verbal comprehension), syntactic comprehension (NAVS-SCT), syntactic production (NAVS-SPPT), repetition (WAB-R repetition) and naming (NNB naming). Z coordinates for panel A: -20 -10 0 10 25. Only clusters with a size >10 mm^3 are displayed. ATP = anterior temporal pole, COp = central opercular cortex, IFGtri = inferior frontal gyrus-pars triangularis, IFGop = inferior frontal gyrus-pars opercularis, ITG = inferior temporal gyrus, Ins = insula, MTG = middle temporal gyrus, PCG = precentral gyrus, POp = parietal opercular cortex, SMG = supramarginal gyrus, STG = superior temporal gyrus.

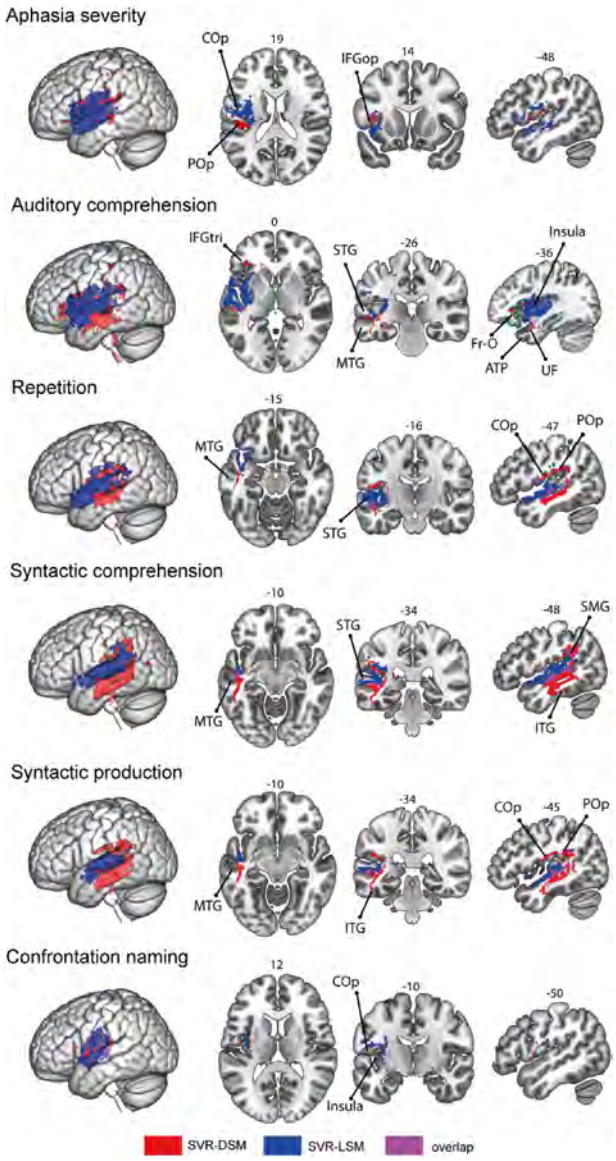

Fig. 5 – Overlay and overlap of thresholded and binarized ß-maps from the SVR-DSM and SVR-LSM analyses. Results of the SVR-DSM and SVR-LSM analyses investigating the relationship between language impairments and the voxel-wise probability of disconnection and damage, respectively. β-maps were thresholded at $p < .05$, corrected for multiple comparisons (maximum of 100 mm^3 of false positive voxels) and adjusted for lesion volume and other covariates. Statistical maps were also corrected for multiple comparisons across language tests using Bonferroni correction. Language scores include aphasia severity (WAB-R Aphasia Quotient), auditory comprehension (WAB-R auditory verbal comprehension), syntactic comprehension (NAVS-SCT), syntactic production (NAVS-SPPT), repetition (WAB-R repetition) and naming (NNB naming). Only clusters with a size >10 mm^3 are displayed. Numbers correspond to MNI 152 coordinates. ATP = anterior temporal pole, COp = central opercular cortex, Fr-O = frontal-orbital cortex, IFGtri = inferior frontal gyrus-pars triangularis, IFGop = inferior frontal gyrus-pars opercularis, ITG = inferior temporal gyrus, MTG = middle temporal gyrus, PCG = precentral gyrus, POp = parietal opercular cortex, SMG = supramarginal gyrus, STG = superior temporal gyrus, UF = uncinate fasciculus.

beyond these damaged areas. Second, SVR-DSM identifies remote regions that may not be frequently damaged by infarcts in patients with aphasia but whose disconnection may limit language recovery. Disconnection of such areas, namely the middle and inferior temporal gyri and the anterior temporal lobe, seem to play a significant role in chronic language deficits.

4. Discussion

In this study, using a large dataset of healthy control tractograms as comparison, structural mapping of white matter disconnections was carried out to understand the extended neuroanatomical and behavioral impact of stroke lesions in a relatively large sample of individuals with chronic aphasia. Prior work in aphasia examining the disconnection paradigm has been chiefly used to describe relationships between the AF and repetition deficits (Catani & Mesulam, 2008). Our results show that specific language impairments such as syntactic or repetition deficits observed in chronic aphasia are related to structural disconnections in left temporo-parietal perisylvian networks beyond the lesion site related to the same deficits, while deficits in general language processing, as measured by aphasia severity and naming, were mainly related to the focal site of damage. A typical left perisylvian connectome was identified as disconnected in more than 90% of individuals with aphasia resulting from different stroke lesions. While previous studies have looked at (a) white matter integrity in tracts that were not affected by the lesion, (b) reduction in fiber density in spared cortical regions, or (c) binary measures of tract disconnection, this is the first study, to our knowledge, to map whole-brain disconnections in white matter fibers that are associated with the severity of a range of language impairments in chronic post-stroke aphasia.

4.1. *White matter disconnections associated with language impairments*

By first overlaying the structural disconnectome maps of all participants with chronic aphasia, a consistent anatomical network was identified as similarly disconnected across more than 90% of individuals despite heterogeneity in language abilities, lesion location, and lesion volume (Fig. 3C). It included parts of dorsal and ventral left white matter tracts previously described as involved in language processing (Dick, Bernal, & Tremblay, 2014; Dick & Tremblay, 2012; Gierhan, 2013): the AF, SLF, IFOF, and ILF. Due to the low variance in the disconnection probability, portions of these tracts could not be investigated with SVR-DSM. Surrounding this common disconnectome, results of SVR-DSM analyses showed that specific disconnections along left perisylvian tracts play a role in both speech production and speech comprehension deficits, even after accounting for lesion volume (Fig. 4).

Structural disconnections significantly explained lower abilities in syntactic comprehension and syntactic production beyond focal damage. While our SVR-LSM analyses are in line with previous findings showing that focal lesions in the left superior temporal gyrus are associated with syntactic comprehension and production deficits (den Ouden et al., 2019; Dick & Tremblay, 2012; Lukic et al., 2020), SVR-DSM illustrates an extension of this brain-behavior relationship such that disconnections in the left temporo-parietal network, from the superior temporal gyrus to the middle and inferior temporal and inferior parietal cortices, may also explain persistent syntactic processing difficulties in individuals with chronic aphasia. Importantly, structural disconnections explain variance in syntactic deficits above and beyond what is already explained by the lesion volume. In contrast, in a previous connectome-based study investigating the predictive power of connection strength using the number of streamlines between cortical regions, none of the associations with syntactic processing deficits survived correction for the lesion size (den Ouden et al., 2019). This discrepancy demonstrates that the methodology used to characterize connectivity disruption may play an essential role in revealing specific clinical-anatomical associations.

Repetition and auditory comprehension scores were also significantly related to disconnections in left perisylvian white matter tracts that extended beyond the damaged regions found significant in SVR-LSM analyses. These structural disconnections were mainly located in the dorsal and ventral stream processing routes, respectively for repetition and auditory comprehension performance, mostly consistent with findings from Saur and colleagues using functional and diffusion tensor imaging (2008). Specifically, repetition deficits were primarily affected by disconnections of the temporo-parietal junction, along the left AF, extending similar findings from previous studies using diffusion metrics or lesion load (Berthier, Lambon Ralph, Pujol, & Green, 2012; Breier, Hasan, Zhang, Men, & Papanicolaou, 2008; Dick et al., 2014; Fridriksson et al., 2010; Kümmerer et al., 2013) and confirmed the importance of temporo-parietal connections in repetition (Baboyan et al., 2021; Forkel et al., 2020). Regarding auditory comprehension, disconnectome mapping showed that a higher probability of disconnection of tracts underlying the left inferior frontal gyrus and the anterior temporal pole was associated with lower auditory comprehension performance, which involves semantic processing abilities. These results are consistent with the anatomical components of the controlled semantic cognition framework that includes the anterior temporal pole (cross-modal representational system) as well as frontal and temporo-parietal regions (control network) (Lambon Ralph, Jefferies, Patterson, & Rogers, 2017). Although the dual-stream model does not include the anterior temporal pole in the ventral stream (Hickok & Poeppel, 2007), previous evidence from diffusion imaging, electrostimulation, and lesion-mapping studies demonstrated that ventral neural pathways (IFOF and ILF) that connect these two frontal and temporal regions to posterior parts of the brain play a role in semantic processing (Almairac, Herbet, Moritz-Gasser, de Champfleur, & Duffau, 2015; Duffau, Moritz-Gasser, & Mandonnet, 2014; Ivanova et al., 2016; Xing, Lacey, Skipper-Kallal, Zeng, & Turkeltaub, 2017). In our analyses, the disconnected frontotemporal pathway significantly associated with auditory comprehension impairments could be identified as the left UF on a white matter atlas. However, whether and how the UF disruption affects auditory comprehension and semantic processing remains a matter of debate as findings have been inconsistent (Dick et al., 2014) and need further investigation.

Lastly, most disconnections related to aphasia severity and naming performance did not survive correction for multiple comparisons. One possible explanation may be that distributed representations of language function are associated with aphasia severity and naming abilities (Baldo, Arévalo, Patterson, & Dronkers, 2013; Hope & Price, 2016). Thus, while SVR-DSM revealed some degree of anatomical specificity for the other language impairments investigated in this study, heterogeneous presentations of aphasia severity and naming deficits could involve the disconnection of multiple white matter pathways, resulting in lower statistical power in any specific area of the brain and the detection of significant relationships only at a bottleneck of fibers surrounding the insula along the extreme capsule. Additionally, most of the left AF was excluded from SVR-DSM analyses because it was disconnected in almost all participants. Disconnection of this tract may play a role in these language behaviors, but this relationship could not be investigated in the present study because of limited variance in our data. In another study that examined binary disconnections in individuals with aphasia, only 67% of the participants showed a disconnection of the AF. The authors found a significant relationship between the disconnection of the AF and aphasia severity and naming scores (Geller et al., 2019). Other methods have also shown that the integrity of this tract does play a role in the overall aphasia severity at the tract level. A tractography study from our group on a subset of the same data demonstrated that participants whose left AF could not be delineated had more severe aphasia (Braun et al., 2022). More work is needed to understand the exact contribution of left frontotemporal disconnections in language impairments related to particularly distributed representations of language function.

Surprisingly, we also found associations between disconnections along the corticobulbar/corticospinal pathway and language scores. We can hypothesize that disconnection of the corticobulbar pathway may burden patients with additional dysarthria (Urban, Hopf, Fleischer, Zorowka, & Müller-Forell, 1997), hampering some of the language recovery after a stroke.

4.2. *Disconnectome-symptom mapping identifies network disruptions critical in specific language processes after stroke beyond the infarcted area*

This study shows that language performance after stroke may be predicted by structural disconnections from and beyond the lesion site to different extents. While focal damage seemed to be sufficient to explain broad measures of language performance such as aphasia severity or naming, disconnectome-symptom mapping identified a network of areas where disconnections were associated with specific linguistic deficits such as syntactic comprehension and production or repetition. Importantly, this study did not aim at comparing the predictive power of each method but instead

aimed at identifying the complementary information that each approach can provide. In this study, disconnectome-symptom mapping revealed connections that may be essential for functional reorganization. Their disruption may limit the potential for recovery and results in deficits that persist at the chronic stage, after the period of spontaneous recovery. As described by Karnath and colleagues, when a cognitive function is distributed over a large number of voxels in the brain, the statistical power of lesion-symptom mapping is limited due to mutual exclusion between patients who will have the same impairment from an injury in different brain regions that are part of the same network (Karnath et al., 2019). We speculate that this 'partial injury problem' was overcome to a certain extent by disconnectome mapping, as it includes information from lesions that affect the same pathway in a single unit (i.e., disconnected pathway). Specifically, patients with the same language impairment and stroke damage located at different areas along the same anatomical pathway will show distinct lesion-symptom patterns in lesion-symptom mapping and a similar disconnection-symptom pattern in disconnectome-symptom mapping. For instance, in this study, in addition to confirming the importance of damage in the superior temporal gyrus in persistent syntactic processing deficits with lesion-symptom mapping, disconnectome-symptom mapping allowed us to identify that disconnections between this region and the middle and inferior temporal gyri as well as the supramarginal gyrus may also play a role in the degree of chronic syntactic impairments. Two recent studies using multivariate predictive models, including one using disconnectome maps, showed that structural connectivity disruptions predicted language performance at a level as good as lesion models using damage location only as input features (Salvalaggio et al., 2020; Yourganov, Fridriksson, Rorden, Gleichgerrcht, & Bonilha, 2016). Despite a potential similar prediction power, mapping clinical-anatomical associations at the disconnectome level allows us to identify the disrupted networks that may impact specific language skills.

Interestingly, disconnectome-symptom mapping reveals brain-behavior relationships in areas not typically detected in lesion-symptom mapping studies due to the biased spatial distribution of stroke lesions. For instance, our results confirmed the involvement of tracts underlying the superior and middle temporal gyri in syntactic processing, as previously described in a VLSM study published as part of the same multi-site project (Lukic et al., 2020), and additionally suggest that syntactic deficits could also be explained by disrupted connections with the inferior temporal gyrus which may correspond to terminations of fibers from the AF (Lin et al., 2020). We showed that these disconnections might impact language processing even at the chronic stage. This hodological approach (Catani & Ffytche, 2005) informs us on the topological distribution of potential structural modifications in regions remote but directly linked to the infarcted area associated with chronic language deficits after a stroke. For instance, disconnection-symptom associations presented here may indicate dysfunctional neural mechanisms such as diaschisis (Carrera & Tononi, 2014; Fornito, Zalesky, & Breakspear, 2015). However, this interpretation remains speculative and needs further investigation. Further, the continued relationship between left-hemisphere structural disconnection topology and behavior at the chronic stage may reflect anatomical constraints limiting brain reorganization and language recovery.

4.3. *Methodological considerations*

One advantage of the disconnectome-symptom mapping technique is that it provides valuable information on the neural basis of language deficits with data easily accessible from a routine clinical scan (Karnath et al., 2019). Disconnectome-symptom mapping partly accounts for brain-behavior relationships in structural networks unified by function (i.e., 'partial injury problem'). Specifically, if two different lesions affected the same tract and therefore the same function but at different parts of this tract, the relationship with the language deficit may have better chances to be detected in disconnectome-symptom mapping due to stronger statistical power along the tract. However, similarly to lesion-symptom mapping, the anatomical pattern of stroke damage may induce some localization bias due to non-random disconnections in adjacent voxels (Ivanova et al., 2021; Sperber et al., 2019; Xu et al., 2018). In addition, a high overlap in disconnection patterns across participants limited the analysis in parts of the language network (i.e., core of the AF (anterior, posterior, and long segments) and IFOF (from the posterior temporal lobe to the inferior frontal lobe), see Fig. 3C). A bigger sample size including stroke survivors without aphasia may help overcome this caveat in future studies.

Finally, disconnectome probabilistic maps are derived from the HCP data, which is a large set of high-resolution diffusion imaging data of healthy controls that have been preprocessed into tractograms. While tracts disconnected in patients are hardly traceable with present tractography techniques, it is essential to note that the probability of disconnection is an indirect estimate for characterizing white matter stroke disruptions and may not fully account for changes in white matter integrity that occur after a stroke. Further, the Human Connectome Project dataset contains a majority of young, healthy individuals, which could reduce the validity of our study due to a mismatch of anatomical data in older individuals. However, three studies have demonstrated that the shape of tracts in disconnectome maps does not significantly change with age (Foulon et al., 2018; Rojkova et al., 2016; Thiebaut de Schotten et al., 2020).

5. Conclusion

In this innovative study, most of the individuals with chronic aphasia presented consistent disconnections in a left perisylvian structural network including parts of the arcuate, superior longitudinal, inferior fronto-occipital and inferior longitudinal fasciculi. All language scores were significantly related to disconnections in the left perisylvian network. However, while the relationships with aphasia severity and naming seemed to be driven by focal damage only, disconnections significantly related to repetition, auditory comprehension, syntactic comprehension and syntactic production

impairments demonstrated remote pathological effects extending beyond lesion sites related to the same deficits. Mapping disconnectome-symptom associations in chronic aphasia is a complementary approach to better understand the neural basis of some persistent language impairments by extending previous lesion-symptom mapping findings to network-level anatomical disruptions that can hinder specific language functions. These results provide complementary information on anatomical connectivity constraints limiting neural reorganization and language recovery.

Funding

This work was supported by the NIH - National Institute on Deafness and Other Communication Disorders (grant No. 1P50DC012283) and from the European Research Council under the European Union's Horizon 2020 research and innovation programme (grant No. 818521 to MTS).

Declaration of competing interest

Dr. Kiran is a scientific advisor for Constant Therapy Health, but there is no overlap between this role and the submitted investigation. The authors have no other financial or non-financial conflicts of interest.

Author contributions

Anne Billot: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing; Michel Thiebaut de Schotten: Conceptualization, Formal analysis, Funding acquisition, Methodology, Software, Supervision, Validation, Writing – review & editing; Todd B. Parrish: Data curation, Funding acquisition, Project administration, Resources, Writing – Review & editing; Cynthia K. Thompson: Funding acquisition, Project administration, Resources, Writing – Review & editing; Brenda Rapp: Funding acquisition, Project administration, Resources, Writing – Review & editing; David Caplan: Funding acquisition, Project administration, Resources, Writing – Review & editing; Swathi Kiran: Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Supervision, Validation, Writing – review & editing.

Acknowledgments

We would like to thank the individuals with aphasia who participated in this study for their time and effort. We additionally express our gratitude to past and present members of the Boston University Aphasia Research Laboratory, especially Erin Meier, Jeffrey Johnson, Maria Dekhtyar, Natalie Gilmore and Yue Pan for their work on this project. We also acknowledge the work of our collaborators through the Center for the Neurobiology of Language Recovery, in particular Ajay Kurani.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cortex.2022.06.016.

REFERENCES

Akinina, Y., Dragoy, O., Ivanova, M. V., Iskra, E. V., Soloukhina, O. A., Petryshevsky, A. G., et al. (2019). Grey and white matter substrates of action naming. *Neuropsychologia, 131*, 249–265. https://doi.org/10.1016/j.neuropsychologia.2019.05.015

Almairac, F., Herbet, G., Moritz-Gasser, S., de Champfleur, N. M., & Duffau, H. (2015). The left inferior fronto-occipital fasciculus subserves language semantics: A multilevel lesion study. *Brain Structure & Function, 220*(4), 1983–1995. https://doi.org/10.1007/s00429-014-0773-1

Alpert, K., Kogan, A., Parrish, T., Marcus, D., & Wang, L. (2016). The Northwestern university neuroimaging data archive (NUNDA). *Neuroimage, 124*, 1131–1136. https://doi.org/10.1016/j.neuroimage.2015.05.060

Auriat, A. M., Borich, M. R., Snow, N. J., Wadden, K. P., & Boyd, L. A. (2015). Comparing a diffusion tensor and non-tensor approach to white matter fiber tractography in chronic stroke. *NeuroImage: Clinical, 7*, 771–781. https://doi.org/10.1016/j.nicl.2015.03.007

Baboyan, V., Basilakos, A., Yourganov, G., Rorden, C., Bonilha, L., Fridriksson, J., & Hickok, G. (2021). Isolating the white matter circuitry of the dorsal language stream: Connectome-Symptom Mapping in stroke induced aphasia. *Human Brain Mapping*. https://doi.org/10.1002/hbm.25647. *n/a*(n/a).

Baldo, J. V., Arévalo, A., Patterson, J. P., & Dronkers, N. F. (2013). Grey and white matter correlates of picture naming: Evidence from a voxel-based lesion analysis of the Boston Naming Test. *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior, 49*(3), 658–667. https://doi.org/10.1016/j.cortex.2012.03.001

Baldo, J. V., Schwartz, S., Wilkins, D., & Dronkers, N. F. (2006). Role of frontal versus temporal cortex in verbal fluency as revealed by voxel-based lesion symptom mapping. *Journal of the International Neuropsychological Society, 12*(6), 896–900. https://doi.org/10.1017/S1355617706061078

Basser, P. J., Mattiello, J., & LeBihan, D. (1994). MR diffusion tensor spectroscopy and imaging. *Biophysical Journal, 66*(1), 259–267. https://doi.org/10.1016/S0006-3495(94)80775-1

Bates, E., Wilson, S. M., Saygin, A. P., Dick, F., Sereno, M. I., Knight, R. T., et al. (2003). Voxel-based lesion-symptom mapping. *Nature Neuroscience, 6*(5), 448–450. https://doi.org/10.1038/nn1050

Berthier, M. L., Lambon Ralph, M. A., Pujol, J., & Green, C. (2012). Arcuate fasciculus variability and repetition: The left sometimes can be right. *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior, 48*(2), 133–143. https://doi.org/10.1016/j.cortex.2011.06.014

Binder, J. R., Pillay, S. B., Humphries, C. J., Gross, W. L., Graves, W. W., & Book, D. S. (2016). Surface errors without semantic impairment in acquired dyslexia: A voxel-based lesion–symptom mapping study. *Brain: a Journal of Neurology, 139*(5), 1517–1526. https://doi.org/10.1093/brain/aww029

Bonilha, L., Rorden, C., & Fridriksson, J. (2014). Assessing the clinical effect of residual cortical disconnection after ischemic strokes. *Stroke; a Journal of Cerebral Circulation, 45*(4), 988–993. https://doi.org/10.1161/STROKEAHA.113.004137

Borovsky, A., Saygin, A. P., Bates, E., & Dronkers, N. (2007). Lesion correlates of conversational speech production deficits.

Neuropsychologia, 45(11), 2525–2533. https://doi.org/10.1016/j.neuropsychologia.2007.03.023

Braun, E. J., Billot, A., Meier, E. L., Pan, Y., Parrish, T. B., Kurani, A. S., & Kiran, S. (2022). White matter microstructural integrity pre- and post-treatment in individuals with chronic post-stroke aphasia. *Brain and Language, 232*, 105163. https://doi.org/10.1016/j.bandl.2022.105163

Breier, J. I., Hasan, K. M., Zhang, W., Men, D., & Papanicolaou, A. C. (2008). Language dysfunction after stroke and damage to white matter tracts evaluated using diffusion tensor imaging. *AJNR. American Journal of Neuroradiology, 29*(3), 483–487. https://doi.org/10.3174/ajnr.A0846

Brett, M., Leff, A. P., Rorden, C., & Ashburner, J. (2001). Spatial normalization of brain images with focal lesions using cost function masking. *Neuroimage, 14*(2), 486–500. https://doi.org/10.1006/nimg.2001.0845

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

Catani, M., & Ffytche, D. H. (2005). The rises and falls of disconnection syndromes. *Brain: a Journal of Neurology, 128*(10), 2224–2239. https://doi.org/10.1093/brain/awh622

Catani, M., & Mesulam, M. (2008). The arcuate fasciculus and the disconnection theme in language and aphasia: History and current state. *Cortex, 44*(8), 953–961. https://doi.org/10.1016/j.cortex.2008.04.002

Cho-Reyes, S., & Thompson, C. K. (2012). Verb and sentence production and comprehension in aphasia: Northwestern assessment of Verbs and Sentences (NAVS). *Aphasiology, 26*(10), 1250–1277. https://doi.org/10.1080/02687038.2012.693584

Corbetta, M., Ramsey, L., Callejas, A., Baldassarre, A., Hacker, C., Siegel, J., et al. (2015). Common behavioral clusters and subcortical anatomy in stroke. *Neuron*. https://doi.org/10.1016/j.neuron.2015.02.027

den Ouden, D., Malyutina, S., Basilakos, A., Bonilha, L., Gleichgerrcht, E., Yourganov, G., et al. (2019). Cortical and structural-connectivity damage correlated with impaired syntactic processing in aphasia. *Human Brain Mapping, 40*(7), 2153–2173. https://doi.org/10.1002/hbm.24514

DeMarco, A. T., & Turkeltaub, P. E. (2018). A multivariate lesion symptom mapping toolbox and examination of lesion-volume biases and correction methods in lesion-symptom mapping. *Human Brain Mapping, 39*(11), 4169–4182. https://doi.org/10.1002/hbm.24289

Desikan, R. S., Ségonne, F., Fischl, B., Quinn, B. T., Dickerson, B. C., Blacker, D., et al. (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

Dick, A. S., Bernal, B., & Tremblay, P. (2014). The language connectome: New pathways, new concepts. *The Neuroscientist: A Review Journal Bringing Neurobiology, Neurology and Psychiatry, 20*(5), 453–467. https://doi.org/10.1177/1073858413513502

Dick, A. S., & Tremblay, P. (2012). Beyond the arcuate fasciculus: Consensus and controversy in the connectional anatomy of language. *Brain: A Journal of Neurology, 135*(Pt 12), 3529–3550. https://doi.org/10.1093/brain/aws222

Døli, H., Helland, W. A., Helland, T., & Specht, K. (2020). Associations between lesion size, lesion location and aphasia in acute stroke. *Aphasiology*, 1–19. https://doi.org/10.1080/02687038.2020.1727838, 0(0).

Dronkers, N. F., Wilkins, D. P., Van Valin, R. D., Redfern, B. B., & Jaeger, J. J. (2004). Lesion analysis of the brain areas involved in language comprehension. *Cognition, 92*(1), 145–177. https://doi.org/10.1016/j.cognition.2003.11.002

Duffau, H., Moritz-Gasser, S., & Mandonnet, E. (2014). A re-examination of neural basis of language processing: Proposal of a dynamic hodotopical model from data provided by brain stimulation mapping during picture naming. *Brain and Language, 131*, 1–10. https://doi.org/10.1016/j.bandl.2013.05.011

Ellis, C., & Urban, S. (2016). Age and aphasia: A review of presence, type, recovery and clinical outcomes. *Topics in Stroke Rehabilitation, 23*(6), 430–439. https://doi.org/10.1080/10749357.2016.1150412

Fama, M. E., Hayward, W., Snider, S. F., Friedman, R. B., & Turkeltaub, P. E. (2017). Subjective experience of inner speech in aphasia: Preliminary behavioral relationships and neural correlates. *Brain and Language, 164*, 32–42. https://doi.org/10.1016/j.bandl.2016.09.009

Forkel, S. J., Rogalski, E., Drossinos Sancho, N., D'Anna, L., Luque Laguna, P., Sridhar, J., et al. (2020). Anatomical evidence of an indirect pathway for word repetition. *Neurology, 94*(6), e594–e606. https://doi.org/10.1212/WNL.0000000000008746

Fornito, A., Zalesky, A., & Breakspear, M. (2015). The connectomics of brain disorders. *Nature Reviews Neuroscience, 16*(3), 159–172. https://doi.org/10.1038/nrn3901

Foulon, C., Cerliani, L., Kinkingnéhun, S., Levy, R., Rosso, C., Urbanski, M., et al. (2018). Advanced lesion symptom mapping analyses and implementation as BCBtoolkit. *GigaScience, 7*(3), 1–17. https://doi.org/10.1093/gigascience/giy004

Fridriksson, J., den Ouden, D.-B., Hillis, A. E., Hickok, G., Rorden, C., Basilakos, A., et al. (2018). Anatomy of aphasia revisited. *Brain: a Journal of Neurology, 141*(3), 848–862. https://doi.org/10.1093/brain/awx363

Fridriksson, J., Kjartansson, O., Morgan, P. S., Hjaltason, H., Magnusdottir, S., Bonilha, L., et al. (2010). Impaired speech repetition and left parietal lobe damage. *Journal of Neuroscience, 30*(33), 11057–11061. https://doi.org/10.1523/JNEUROSCI.1120-10.2010

Geller, J., Thye, M., & Mirman, D. (2019). Estimating effects of graded white matter damage and binary tract disconnection on post-stroke language impairment. *Neuroimage, 189*, 248–257. https://doi.org/10.1016/j.neuroimage.2019.01.020

Gierhan, S. M. E. (2013). Connections for auditory language in the human brain. *Brain and Language, 127*(2), 205–221. https://doi.org/10.1016/j.bandl.2012.11.002

Griffis, J. C., Metcalf, N. V., Corbetta, M., & Shulman, G. L. (2019). Structural disconnections explain brain network dysfunction after stroke. *Cell Reports, 28*(10), 2527–2540. https://doi.org/10.1016/j.celrep.2019.07.100. e9.

Griffis, J. C., Nenert, R., Allendorfer, J. B., & Szaflarski, J. P. (2017). Damage to white matter bottlenecks contributes to language impairments after left hemispheric stroke. *NeuroImage: Clinical, 14*, 552–565. https://doi.org/10.1016/j.nicl.2017.02.019

Halai, A. D., Woollams, A. M., & Lambon Ralph, M. A. (2017). Using principal component analysis to capture individual differences within a unified neuropsychological model of chronic post-stroke aphasia: Revealing the unique neural correlates of speech fluency, phonology and semantics. *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior, 86*, 275–289. https://doi.org/10.1016/j.cortex.2016.04.016

Hansen, C. B., Yang, Q., Lyu, I., Rheault, F., Kerley, C., Chandio, B. Q., et al. (2021). Pandora: 4-D white matter bundle population-based atlases derived from diffusion MRI fiber tractography. *Neuroinformatics, 19*(3), 447–460. https://doi.org/10.1007/s12021-020-09497-1

Henseler, I., Regenbrecht, F., & Obrig, H. (2014). Lesion correlates of patholinguistic profiles in chronic aphasia: Comparisons of syndrome-, modality- and symptom-level assessment. *Brain: a Journal of Neurology, 137*(3), 918–930. https://doi.org/10.1093/brain/awt374

Hickok, G., & Poeppel, D. (2007). The cortical organization of speech processing. *Nature Reviews Neuroscience, 8*(5), 393–402. https://doi.org/10.1038/nrn2113

Holland, A., Fromm, D., Forbes, M., & MacWhinney, B. (2017). Long-term recovery in stroke accompanied by aphasia: A reconsideration. *Aphasiology, 31*(2), 152–165. https://doi.org/10.1080/02687038.2016.1184221

Hope, T. M. H., & Price, C. J. (2016). Why the left posterior inferior temporal lobe is needed for word finding. *Brain: a Journal of Neurology, 139*(11), 2823–2826. https://doi.org/10.1093/brain/aww240

Hope, T. M. H., Seghier, M. L., Leff, A. P., & Price, C. J. (2013). Predicting outcome and recovery after stroke with lesions extracted from MRI images. *NeuroImage. Clinical, 2*, 424–433. https://doi.org/10.1016/j.nicl.2013.03.005

Hope, T. M. H., Seghier, M. L., Prejawa, S., Leff, A. P., & Price, C. J. (2016). Distinguishing the effect of lesion load from tract disconnection in the arcuate and uncinate fasciculi. *Neuroimage, 125*, 1169–1173. https://doi.org/10.1016/j.neuroimage.2015.09.025

Ivanova, M. V., Herron, T. J., Dronkers, N. F., & Baldo, J. V. (2021). An empirical comparison of univariate versus multivariate methods for the analysis of brain–behavior mapping. *Human Brain Mapping, 42*(4), 1070–1101. https://doi.org/10.1002/hbm.25278

Ivanova, M. V., Isaev, D. Y., Dragoy, O. V., Akinina, Y. S., Petrushevskiy, A. G., Fedina, O. N., et al. (2016). Diffusion-tensor imaging of major white matter tracts and their role in language processing in aphasia. *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior, 85*, 165–181. https://doi.org/10.1016/j.cortex.2016.04.019

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

Karnath, H.-O., Sperber, C., & Rorden, C. (2019). Reprint of: Mapping human brain lesions and their functional consequences. *Neuroimage, 190*, 4–13. https://doi.org/10.1016/j.neuroimage.2019.01.044

Kertesz, A. (2007). WAB-R: Western aphasia battery-revised. *PsychCorp*.

Kertesz, A., Harlock, W., & Coates, R. (1979). Computer tomographic localization, lesion size, and prognosis in aphasia and nonverbal impairment. *Brain and Language, 8*(1), 34–50. https://doi.org/10.1016/0093-934X(79)90038-5

Kimberg, D. Y., Coslett, H. B., & Schwartz, M. F. (2007). Power in voxel-based lesion-symptom mapping. *Journal of Cognitive Neuroscience, 19*(7), 1067–1080. https://doi.org/10.1162/jocn.2007.19.7.1067

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

Klingbeil, J., Wawrzyniak, M., Stockert, A., Karnath, H.-O., & Saur, D. (2020). Hippocampal diaschisis contributes to anosognosia for hemiplegia: Evidence from lesion network-symptom-mapping. *Neuroimage, 208*, 116485. https://doi.org/10.1016/j.neuroimage.2019.116485

Knecht, S., Dräger, B., Deppe, M., Bobe, L., Lohmann, H., Flöel, A., et al. (2000). Handedness and hemispheric language dominance in healthy humans. *Brain: a Journal of Neurology, 123*(12), 2512–2518. https://doi.org/10.1093/brain/123.12.2512

Kuceyeski, A., Navi, B. B., Kamel, H., Relkin, N., Villanueva, M., Raj, A., et al. (2015). Exploring the brain's structural connectome: A quantitative stroke lesion-dysfunction mapping study. *Human Brain Mapping, 36*(6), 2147–2160. https://doi.org/10.1002/hbm.22761

Kümmerer, D., Hartwigsen, G., Kellmeyer, P., Glauche, V., Mader, I., Klöppel, S., et al. (2013). Damage to ventral and dorsal language pathways in acute aphasia. *Brain: a Journal of Neurology, 136*(2), 619–629. https://doi.org/10.1093/brain/aws354

Lambon Ralph, M. A., Jefferies, E., Patterson, K., & Rogers, T. T. (2017). The neural and computational bases of semantic cognition. *Nature Reviews Neuroscience, 18*(1), 42–55. https://doi.org/10.1038/nrn.2016.150

Lin, Y.-H., Young, I. M., Conner, A. K., Glenn, C. A., Chakraborty, A. R., Nix, C. E., et al. (2020). Anatomy and white matter connections of the inferior temporal gyrus. *World Neurosurgery, 143*, e656–e666. https://doi.org/10.1016/j.wneu.2020.08.058

Lukic, S., Thompson, C. K., Barbieri, E., Chiappetta, B., Bonakdarpour, B., Kiran, S., et al. (2020). Common and distinct neural substrates of sentence production and comprehension. *Neuroimage, 224*, 117374. https://doi.org/10.1016/j.neuroimage.2020.117374

Magnusdottir, S., Fillmore, P., den Ouden, D. B., Hjaltason, H., Rorden, C., Kjartansson, O., et al. (2013). Damage to left anterior temporal cortex predicts impairment of complex syntactic processing: A lesion-symptom mapping study. *Human Brain Mapping, 34*(10), 2715–2723. https://doi.org/10.1002/hbm.22096

Mah, Y.-H., Husain, M., Rees, G., & Nachev, P. (2014). Human brain lesion-deficit inference remapped. *Brain: a Journal of Neurology, 137*(9), 2522–2531. https://doi.org/10.1093/brain/awu164

Mandonnet, E., Herbet, G., Moritz-Gasser, S., Poisson, I., Rheault, F., & Duffau, H. (2019). Electrically induced verbal perseveration: A striatal deafferentation model. *Neurology, 92*(6), e613–e621. https://doi.org/10.1212/WNL.0000000000006880

Mirman, D., Chen, Q., Zhang, Y., Wang, Z., Faseyitan, O. K., Coslett, H. B., et al. (2015a). Neural organization of spoken language revealed by lesion–symptom mapping. *Nature Communications, 6*(1), 6762. https://doi.org/10.1038/ncomms7762

Mirman, D., Kraft, A. E., Harvey, D. Y., Brecher, A. R., & Schwartz, M. F. (2019). Mapping articulatory and grammatical subcomponents of fluency deficits in post-stroke aphasia. *Cognitive, Affective, & Behavioral Neuroscience, 19*(5), 1286–1298. https://doi.org/10.3758/s13415-019-00729-9

Mirman, D., Landrigan, J.-F., Kokolis, S., Verillo, S., Ferrara, C., & Pustina, D. (2018). Corrections for multiple comparisons in voxel-based lesion-symptom mapping. *Neuropsychologia, 115*, 112–123. https://doi.org/10.1016/j.neuropsychologia.2017.08.025

Mirman, D., Zhang, Y., Wang, Z., Coslett, H. B., & Schwartz, M. F. (2015b). The ins and outs of meaning: Behavioral and neuroanatomical dissociation of semantically-driven word retrieval and multimodal semantic recognition in aphasia. *Neuropsychologia, 76*, 208–219. https://doi.org/10.1016/j.neuropsychologia.2015.02.014

Mori, S., & van Zijl, P. C. M. (2002). Fiber tracking: Principles and strategies – a technical review. *NMR in Biomedicine, 15*(7–8), 468–480. https://doi.org/10.1002/nbm.781

Naeser, M. A., Palumbo, C. L., Prete, M. N., Fitzpatrick, P. M., Mimura, M., Samaraweera, R., et al. (1998). Visible changes in lesion borders on CT scan after five years poststroke, and long-term recovery in aphasia. *Brain and Language, 62*(1), 1–28. https://doi.org/10.1006/brln.1997.1866

Pedersen, P. M., Vinter, K., & Olsen, T. S. (2004). Aphasia after stroke: Type, severity and prognosis. *Cerebrovascular Diseases, 17*(1), 35–43. https://doi.org/10.1159/000073896

Piras, F., & Marangolo, P. (2009). Word and number reading in the brain: Evidence from a voxel-based lesion-symptom mapping

study. *Neuropsychologia, 47*(8), 1944–1953. https://doi.org/10.1016/j.neuropsychologia.2009.03.006

Piras, F., & Marangolo, P. (2010). When "Crack walnuts" lies in different brain regions: Evidence from a voxel-based lesion-symptom mapping study. *Journal of the International Neuropsychological Society : JINS, 16*(3), 433–442. https://doi.org/10.1017/s1355617710000068

Plowman, E., Hentz, B., & Ellis, C. (2011). Post-stroke aphasia prognosis: A review of patient-related and stroke-related factors. *Journal of Evaluation in Clinical Practice, 18*(3), 689–694. https://doi.org/10.1111/j.1365-2753.2011.01650.x

Price, C. J., Hope, T. M., & Seghier, M. L. (2017). Ten problems and solutions when predicting individual outcome from lesion site after stroke. *Neuroimage, 145*, 200–208. https://doi.org/10.1016/j.neuroimage.2016.08.006

Price, C. J., Seghier, M. L., & Leff, A. P. (2010). Predicting language outcome and recovery after stroke: The PLORAS system. *Nature Reviews. Neurology, 6*(4), 202–210. https://doi.org/10.1038/nrneurol.2010.15

Quillinan, N., Herson, P. S., & Traystman, R. J. (2016). Neuropathophysiology of brain injury. *Anesthesiology Clinics, 34*(3), 453–464. https://doi.org/10.1016/j.anclin.2016.04.011

Rapp, B., Purcell, J., Hillis, A. E., Capasso, R., & Miceli, G. (2016). Neural bases of orthographic long-term memory and working memory in dysgraphia. *Brain: A Journal of Neurology, 139*(Pt 2), 588–604. https://doi.org/10.1093/brain/awv348

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

Rogalsky, C., LaCroix, A. N., Chen, K.-H., Anderson, S. W., Damasio, H., Love, T., et al. (2017). The Neurobiology of agrammatic sentence comprehension: A lesion study. *Journal of Cognitive Neuroscience, 30*(2), 234–255. https://doi.org/10.1162/jocn_a_01200

Rojkova, K., Volle, E., Urbanski, M., Humbert, F., Dell'Acqua, F., & Thiebaut de Schotten, M. (2016). Atlasing the frontal lobe connections and their variability due to age and education: A spherical deconvolution tractography study. *Brain Structure & Function, 221*(3), 1751–1766. https://doi.org/10.1007/s00429-015-1001-3

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

Rudrauf, D., Mehta, S., Bruss, J., Tranel, D., Damasio, H., & Grabowski, T. J. (2008). Thresholding lesion overlap difference maps: Application to category-related naming and recognition deficits. *Neuroimage, 41*(3), 970–984. https://doi.org/10.1016/j.neuroimage.2007.12.033

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

Saur, D., Kreher, B. W., Schnell, S., Kümmerer, D., Kellmeyer, P., Vry, M.-S., et al. (2008). Ventral and dorsal pathways for language. *Proceedings of the National Academy of Sciences of the United States of America, 105*(46), 18035–18040. https://doi.org/10.1073/pnas.0805234105

Schumacher, R., Halai, A. D., & Lambon Ralph, M. A. (2019). Assessing and mapping language, attention and executive multidimensional deficits in stroke aphasia. *Brain: a Journal of Neurology, 142*(10), 3202–3216. https://doi.org/10.1093/brain/awz258

Schwartz, M. F., Kimberg, D. Y., Walker, G. M., Faseyitan, O., Brecher, A., Dell, G. S., et al. (2009). Anterior temporal involvement in semantic word retrieval: Voxel-based lesion-symptom mapping evidence from aphasia. *Brain: a Journal of Neurology, 132*(12), 3411–3427. https://doi.org/10.1093/brain/awp284

Sperber, C., Wiesen, D., & Karnath, H.-O. (2019). An empirical evaluation of multivariate lesion behaviour mapping using support vector regression. *Human Brain Mapping, 40*(5), 1381–1390. https://doi.org/10.1002/hbm.24476

Thiebaut de Schotten, M., Dell'Acqua, F., Ratiu, P., Leslie, A., Howells, H., Cabanis, E., et al. (2015). From phineas gage and monsieur Leborgne to H.M.: Revisiting disconnection syndromes. *Cerebral Cortex, 25*(12), 4812–4827. https://doi.org/10.1093/cercor/bhv173

Thiebaut de Schotten, M., Foulon, C., & Nachev, P. (2020). Brain disconnections link structural connectivity with function and behaviour. *Nature Communications, 11*(1), 5094. https://doi.org/10.1038/s41467-020-18920-9

Thompson, C. K., Lukic, S., King, M. C., Mesulam, M. M., & Weintraub, S. (2012). Verb and noun deficits in stroke-induced and primary progressive aphasia: The Northwestern Naming Battery. *Aphasiology, 26*(5), 632–655. https://doi.org/10.1080/02687038.2012.676852

Torres-Prioris, M. J., López-Barroso, D., Roé-Vellvé, N., Paredes-Pacheco, J., Dávila, G., & Berthier, M. L. (2019). Repetitive verbal behaviors are not always harmful signs: Compensatory plasticity within the language network in aphasia. *Brain and Language, 190*, 16–30. https://doi.org/10.1016/j.bandl.2018.12.004

Urban, P. P., Hopf, H. C., Fleischer, S., Zorowka, P. G., & Müller-Forell, W. (1997). Impaired cortico-bulbar tract function in dysarthria due to hemispheric stroke. Functional testing using transcranial magnetic stimulation. *Brain: A Journal of Neurology, 120*(Pt 6), 1077–1084. https://doi.org/10.1093/brain/120.6.1077

von Monakow, C. (1914). Die lokalisation im grosshirn und der abbau der funktion durch kortikale herde. *J.F. Bergmann*.

Walker, G. M., Schwartz, M. F., Kimberg, D. Y., Faseyitan, O., Brecher, A., Dell, G. S., et al. (2011). Support for anterior temporal involvement in semantic error production in aphasia: New evidence from VLSM. *Brain and Language, 117*(3), 110–122. https://doi.org/10.1016/j.bandl.2010.09.008

Wallentin, M. (2018). Sex differences in post-stroke aphasia rates are caused by age. A meta-analysis and database query. *PLOS ONE, 13*(12), Article e0209571. https://doi.org/10.1371/journal.pone.0209571

Wang, Y., Katsaggelos, A. K., Wang, X., & Parrish, T. B. (2016). A deep symmetry convnet for stroke lesion segmentation. In *2016 IEEE international conference on image processing (ICIP)* (pp. 111–115). https://doi.org/10.1109/ICIP.2016.7532329

Wang, R., & Wedeen, V. J. (2007). TrackVis. http://www.trackvis.org/.

Watila, M. M., & Balarabe, S. A. (2015). Factors predicting post-stroke aphasia recovery. *Journal of the Neurological Sciences, 352*(1–2), 12–18. https://doi.org/10.1016/j.jns.2015.03.020

Wiesen, D., Karnath, H.-O., & Sperber, C. (2020). Disconnection somewhere down the line: Multivariate lesion-symptom mapping of the line bisection error. *Cortex, 133*, 120–132. https://doi.org/10.1016/j.cortex.2020.09.012

Winkler, A. M., Ridgway, G. R., Webster, M. A., Smith, S. M., & Nichols, T. E. (2014). Permutation inference for the general linear model. *Neuroimage, 92*, 381–397. https://doi.org/10.1016/j.neuroimage.2014.01.060

Xing, S., Lacey, E. H., Skipper-Kallal, L. M., Zeng, J., & Turkeltaub, P. E. (2017). White matter correlates of auditory comprehension outcomes in chronic post-stroke aphasia. *Frontiers in Neurology, 8*, 54. https://doi.org/10.3389/fneur.2017.00054

Xu, T., Jha, A., & Nachev, P. (2018). The dimensionalities of lesion-deficit mapping. *Neuropsychologia, 115*, 134–141. https://doi.org/10.1016/j.neuropsychologia.2017.09.007

Yourganov, G., Fridriksson, J., Rorden, C., Gleichgerrcht, E., & Bonilha, L. (2016). Multivariate connectome-based symptom mapping in post-stroke patients: Networks supporting language and speech. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience, 36*(25), 6668–6679. https://doi.org/10.1523/JNEUROSCI.4396-15.2016

Zhang, J., Zhong, S., Zhou, L., Yu, Y., Tan, X., Wu, M., et al. (2021). Correlations between dual-pathway white matter alterations and language impairment in patients with aphasia: A systematic review and meta-analysis. *Neuropsychology Review*. https://doi.org/10.1007/s11065-021-09482-8

Zhang, Y., Kimberg, D. Y., Coslett, H. B., Schwartz, M. F., & Wang, Z. (2014). Multivariate lesion-symptom mapping using support vector regression. *Human Brain Mapping, 35*(12), 5861–5876. https://doi.org/10.1002/hbm.22590