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Anatomy of aphasia revisited

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In most cases, aphasia is caused by strokes involving the left hemisphere, with more extensive damage typically being associated with more severe aphasia. The classical model of aphasia commonly adhered to in the Western world is the Wernicke-Lichtheim model. The model has been in existence for over a century, and classification of aphasic symptomatology continues to rely on it. However, far more detailed models of speech and language localization in the brain have been formulated. In this regard, the dual stream model of cortical brain organization proposed by Hickok and Poeppel is particularly influential. Their model describes two processing routes, a dorsal stream and a ventral stream, that roughly support speech production and speech comprehension, respectively, in normal subjects. Despite the strong influence of the dual stream model in current neuropsychological research, there has been relatively limited focus on explaining aphasic symptoms in the context of this model. Given that the dual stream model represents a more nuanced picture of cortical speech and language organization, cortical damage that causes aphasic impairment should map clearly onto the dual processing streams. Here, we present a follow-up study to our previous work that used lesion data to reveal the anatomical boundaries of the dorsal and ventral streams supporting speech and language processing. Specifically, by emphasizing clinical measures, we examine the effect of cortical damage and disconnection involving the dorsal and ventral streams on aphasic impairment. The results reveal that measures of motor speech impairment mostly involve damage to the dorsal stream, whereas measures of impaired speech comprehension are more strongly associated with ventral stream involvement. Equally important, many clinical tests that target behaviours such as naming, speech repetition, or grammatical processing rely on interactions between the two streams. This latter finding explains why patients with seemingly disparate lesion locations often experience similar impairments on given subtests. Namely, these individuals' cortical damage, although dissimilar, affects a broad cortical network that plays a role in carrying out a given speech or language task. The current data suggest this is a more accurate characterization than ascribing specific lesion locations as responsible for specific language deficits.

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Abbreviations: CLSM = connectome lesion-symptom mapping; PNT = Philadelphia Naming Test; RLSM = region-wise lesion-symptom mapping; SMG = supramarginal gyrus; STG = superior temporal gyrus

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Introduction

Stroke is the most common cause of aphasia, with approximately 20–40% of all strokes resulting in acute aphasia (Engelter *et al.*, 2006). The general pattern of speech and language impairment that results from stroke is somewhat predictable as the type of aphasia is associated with specific lesion patterns (Yourganov *et al.*, 2015). Despite the heterogeneity of lesion locations in people with the same aphasia type, there is enough similarity in lesion patterns within a given aphasia type to differentiate it from other aphasia types. The overall pattern of speech and language impairment is similar in patients classified as having the same type of aphasia (e.g. Broca's aphasia) compared to those who have different kinds of aphasia (e.g. Wernicke's aphasia or conduction aphasia). Nevertheless, even among patients who are classified as having the same kind of aphasia, there is considerable variability in impairment and task performance. Two primary factors contribute to the predictability of aphasic impairment: the first factor pertains to the fact that the anatomy of cerebrovascular perfusion territories is relatively similar across individuals and, as a result, a stroke that affects the territory of a given segment of a cerebral artery results in somewhat similar damage across patients (Caviness *et al.*, 2002). Aphasia is most commonly the result of an occlusion within the middle cerebral artery (MCA) territory. After its origin from the internal carotid artery, the MCA bifurcates into a superior and an inferior branch. Occlusions involving the superior division tend to lead to similar lesion patterns, which are different than the patterns yielded by strokes resulting from occlusion of the inferior division of the MCA. The second factor is that although there is some degree of variability between individuals in the cortical organization of speech and language processing (Ojemann and Whitaker, 1978; Amunts *et al.*, 1999; Fischl *et al.*, 2008; Fedorenko *et al.*, 2010), the overall regional distribution of language is fairly consistent across healthy individuals. That is, cortical activation studies commonly reveal remarkable similarities across healthy individuals in cortical areas recruited to execute a given speech or language task. As a result, damage to a given brain region tends to result in somewhat similar patterns of speech and language impairment across individuals.

The classical typology of aphasia, which has its roots in the Wernicke-Lichtheim model (Wernicke, 1874, Lichtheim, 1885) and was later refined by Geschwind (1970), associates the major aphasia types with specific lesion locations. For example, Wernicke's and Broca's aphasia were associated with damage to Wernicke's and Broca's areas, respectively. However, as has been amply discussed elsewhere (Mohr *et al.*, 1978; Dronkers *et al.*, 2007; Lazar and Mohr, 2011; Fridriksson *et al.*, 2014), localized damage to these regions rarely results in complete Wernicke's or Broca's aphasia. The Wernicke-Lichtheim model has been highly influential and is still being taught in clinical curricula today. However, it is an oversimplification of how speech and language are rooted in the brain as extensive research has shown how many other cortical and subcortical regions besides Broca's and Wernicke's areas are involved in processing speech and language (Hickok and Poeppel, 2007; Tourville and Guenther, 2011; Ueno *et al.*, 2011).

One of the most influential contemporary neuropsychological models of speech and language organization in the brain is the dual stream model (Hickok and Poeppel, 2004, 2007), which is associationist, like the Wernicke-Lichtheim model, but places the main emphasis on the connections between cortical regions. The dual stream model describes two large-scale processing streams. A ventral stream, rooted in the bilateral temporal lobes, supports the processing of auditory-to-meaning information and is essential for successful auditory comprehension. A dorsal stream processes auditory-to-articulation information and is unilaterally organized across left-hemisphere frontal speech areas and a region located at the temporal-parietal junction. The dorsal stream provides *ad hoc* auditory and proprioceptive feedback that is crucial for producing fluent speech. In a recent paper, our group performed an extensive evaluation of language deficits in relation to post-stroke lesion location, mapping the grey matter localization of the ventral and dorsal streams (Fridriksson *et al.*, 2016). In line with the theoretical predictions by Hickok and Poeppel (2007), the dorsal stream involves fronto-parietal regions, including the pars opercularis, pars triangularis, pre- and postcentral regions, as well as portions of the parietal lobe. In contrast, the ventral stream involves much of the lateral temporal lobe, extending into the posterior-inferior frontal gyrus pars orbitalis via the uncinate fasciculus. This study provided strong support for the cortical boundaries of two anatomical streams that support speech and language processing. Notably, our study revealed the anatomical boundaries of the dorsal and ventral streams to be more in line with Hickok and Poeppel's framework than with other dual stream models of speech processing proposed in the literature (Rauschecker and Tian, 2000; Rauschecker and Scott, 2009).

Although it is possible to infer aphasic symptomatology from the dual stream model, it is important to point out that the model describes the anatomical foundations of normal, and not disordered, speech and language processing. Given the outdated utility of the Wernicke-Lichtheim model and the contemporary emphasis on the dual stream model, the purpose of the current study was to investigate how damage to the ventral and dorsal streams identified by Fridriksson *et al.* (2016) relates to performance on tests commonly used to assess aphasia. As such, the current study represents a follow-up study to our previous work (Fridriksson *et al.*, 2016). We expected that measures that address relative isolation of speech comprehension and motor speech processes would load strongly onto the ventral and dorsal streams, respectively. We further expected

Table 1 List of measures included in RLSM and CLSM analyses and the domain of communication assessed

Test/scale	Domain assessed	Participants completed
WAB Aphasia Quotient	Overall deficit severity	159
WAB Speech Fluency	Speech production	159
WAB Speech Repetition	Speech perception/production	159
WAB Word Recognition	Speech comprehension	159
WAB Reading	Reading comprehension	55
WAB Writing	Written language	55
Pyramids and Palm Trees	Semantic processing (non-verbal)	117
PNT Correct	Verbal naming	105
PNT Semantic Errors	Verbal naming	105
PNT Phonemic Errors	Verbal naming	105
Syllable Identification	Speech Perception	42
Sentence Comprehension	Grammatical processing (all sentence types)	57
Non-Canonical Comprehension	Grammatical processing (non-canonical relative to canonical)	57
ASRS AOS Severity	Speech production/articulation	65
Speech rate	Speech production	103
Articulatory rate	Speech production/articulation	103

AOS = apraxia of speech; ASRS = Apraxia of Speech Rating Scale; WAB = Western Aphasia Battery.

that tests requiring the involvement and coordination of several different processes would involve both streams.

The methodology used here involved both region-wise lesion symptom mapping (RLSM) and connectome lesion-symptom mapping (CLSM; Yourganov *et al.*, 2016). CLSM uses the same statistical approach as traditional lesion-symptom mapping methods with one major exception: instead of relating a given lesion location to impairment, CLSM associates damage involving white matter connections between anatomical regions and behavioural impairment. Thus, rather than isolating lesion locations, CLSM makes it possible to reveal cortical networks that are crucial for performing a given task. For both RLSM and CLSM, we carried out univariate and multivariate analyses to provide slightly different perspectives based on different data analysis approaches of the same data.

Materials and methods

Participants

The data for this project were obtained from an archival database in the Aphasia Lab, University of South Carolina and Medical University of South Carolina. Participants had sustained a single-event stroke to the left hemisphere at least 6 months prior to study inclusion and were tested either as part of an aphasia treatment study or strictly for the purpose of lesion-symptom mapping research. A lesion overlay map is included in Supplementary Fig. 1. The average time post-stroke was 36.4 months [standard deviation (SD) = 43.1]. The total sample size was 159 chronic stroke survivors and the number of tested participants varied across the different assessment batteries used here to assess speech and language impairment. All participants were native speakers of English with a mean age of 60.0 years (SD = 11.2), and 68 were female. Participants were excluded if they had a history of dementia or other neurological problems (as per self/caregiver or medical report). All participants were recruited through local advertisement and were enrolled at the University of South Carolina or at the Medical University of South Carolina. They provided informed consent to participate in this study, which was approved by the Institutional Review Boards at the University of South Carolina and at the Medical University of South Carolina.

Speech and language testing

The behavioural battery included 16 tests and tasks selected to reflect speech and language impairments typically included as part of the clinical management of aphasia in the USA (Table 1). It was not meant to reflect in-depth assessment of linguistic processing or neurophysiology of speech, as the intended audience here consists of clinicians and clinician-scientists who might be more interested in the effects of stroke-related brain damage on communication skills that might reflect real-life situations (e.g. speech fluency and overall severity of aphasia). However, we selected tests and tasks that primarily tax motor speech processes with relatively minimal speech comprehension requirements as well as the opposite; tests that focus specifically on speech recognition and comprehension with little or no input from motor speech. This allowed us to compare and contrast cortical network damage that primarily affects motor speech versus auditory comprehension, two aspects of processing that are commonly assessed as part of a comprehensive aphasia work-up. In addition, other typical subtests included on aphasia test batteries were used to test functions such as reading, writing, speech repetition, verbal naming, and grammatical processing of sentences. Unfortunately, our dataset did not include a comprehensive measure of phonological input, something that is clearly a focus of Hickok and Poeppel's dual stream model.

The speech and language battery included six tests or rating scales from the Western Aphasia Battery (Kertesz, 1982): Aphasia Quotient, a 0–100 point aphasia severity scale; Speech Fluency, a 10-point qualitative rating scale of speech

production; Speech Repetition, a 60-point test of speech repetition of real words and progressively longer sentences; Auditory Word Recognition, a 60-point test where the participant is required to point to a picture or object that corresponds to spoken words presented by a clinician (picture and object targets are presented along with five distractors); Reading ability, a collection of nine subtests with a maximum possible score of 20 points; and Writing ability, a collection of seven subtests with a maximum possible score of 20 points. Three scores were derived from the Philadelphia Naming Test (PNT), a 175-item test of picture naming (Roach *et al.*, 1996): correct naming; phonological errors; and semantic errors. Assessment of auditory sentence comprehension relied on a 45-item test where participants were required to match a clinician-spoken sentence to a target picture that was presented along with a semantic foil and an unrelated foil (Magnusdottir *et al.*, 2013). Two scores from this sentence comprehension test were analysed: overall sentence comprehension accuracy and scores for non-canonical sentences (in comparison to canonical sentences). To assess speech rate and articulation rate, we relied on discourse measures of picture descriptions where speech rate was defined as the number of words spoken per minute and articulation rate reflected speaking time minus pauses. A 30-item in-house speech perception task (syllable identification) was included where participants listened to one of three syllables (/pa/, /ta/, /ka/) and indicated which syllable they heard by pointing to its written representation ('PA', 'TA', 'KA') on a computer screen. Other tests included ratings of apraxia of speech on the Apraxia of Speech Rating Scale (Strand *et al.*, 2014), and the Pyramids and Palm Trees Test, which permits the assessment of amodal semantic processing based on 52-item matching of semantically related pictures (Howard and Patterson, 1992). A correlation matrix that shows the relation between the behavioural tasks and tests is included in Supplementary Fig. 2.

Brain imaging

All participants underwent an extensive MRI work-up using a Siemens Trio 3 T scanner equipped with a 12-element head coil either at the University of South Carolina or at the Medical University of South Carolina. For the purpose of this study, three kinds of images were used: (i) T_1-weighted MRI using an MP-RAGE sequence with 1 mm isotropic voxels, a 256 × 256 matrix size, and a 9° flip angle. T_1 images used either a 160 slice sequence with repetition time = 2250 ms, inversion time = 900 ms, echo time = 4.52 ms or a 192 slice sequence with repetition time = 2250 ms, inversion time = 925 ms, echo time = 4.15 with parallel imaging (GRAPPA = 2, 80 reference lines); (ii) T_2-weighted MRI using a sampling perfection with application optimized contrasts using a different flip angle evolution (3D-SPACE) sequence. This 3D TSE scan uses a repetition time = 2800 ms, an echo time of 402 ms, variable flip angle, 256 × 256 matrix scan with 192 slices (1 mm thick), using parallel imaging (GRAPPA = 2, 120 reference lines); and (iii) diffusion EPI scan that uses 30 directions with b = 1000 s/mm^2 and b = 2000 s/mm^2, repetition time = 6100 ms, echo time = 101 ms, 82 × 82 matrix, 222 × 222 mm field of view, with parallel imaging GRAPPA = 2, 80 45 contiguous 2.7 mm axial slices. This sequence was acquired twice, as well as a third series that was identical in all respects but only included nine B = 0 s/mm^2. Therefore, in total we acquired 60 volumes with B = 1000, 60 with B = 2000 and 11 with B = 0.

Image preprocessing

Lesions

The chronic stroke lesion was demarcated on T_2-weighted images by a neurologist (L.B.), who was blinded to the participants' language scores. The T_2 image was co-registered to the T_1 image, and these parameters were used to reslice the lesion into the native T_1 space. The resliced lesion maps were smoothed with a 3 mm full-width at half-maximum Gaussian kernel to remove jagged edges associated with manual drawing. Enantiomorphic normalization (Nachev *et al.*, 2008) relied on SPM12 and MATLAB scripts developed by two authors (C.R., G.Y.). A mirrored image of the T_1 image (reflected around the midline) was coregistered to the native T_1 image. We then created a chimeric image based on the native T_1 image with the lesioned tissue replaced by tissue from the mirrored image (using the smoothed lesion map to modulate this blending, feathering the lesion edge). SPM12's unified segmentation-normalization (Ashburner and Friston, 2005) was used to warp this chimeric image to standard space, with the resulting spatial transform applied to the actual T_1 image as well as the lesion map. The normalized lesion map was then binarized, using a 50% probability threshold.

Once the lesion data had been transformed to standard space, each image was divided into 118 anatomical grey matter brain regions based on a standardized brain atlas (Faria *et al.*, 2012). This step was included because the connectome is constructed for each individual by determining the density of white matter fibres extending from one anatomical region of interest to another. To compute lesion load, we aligned the anatomical brain atlas containing the parcellation with each individual's T_1-weighted images. The T_1-weighted images were segmented into probabilistic grey and white matter maps, and the grey matter map was divided into regions according to the atlas. Then, lesion load was computed as the proportion of intact (i.e. not lesioned) voxels per each grey matter region. For both lesion and connectome-based analyses, cerebellar regions were excluded.

Connectome

Connectome-based damage was computed as the number of diffusion tensor imaging (DTI) tracts that connected each pair of the grey matter regions. The following steps were used to build each participant's connectome: (i) segmenting the T_1-weighted images using SPM12's unified segmentation-normalization process to determine the probabilistic grey and white matter maps; (ii) dividing the probabilistic grey matter map into anatomical regions, using the parcellation scheme described in the previous section; (iii) registering the white matter and cortical parcellation maps into the DTI space; (iv) computing grey matter pairwise probabilistic DTI fibre tracking; (v) measuring the weight of each pairwise connectivity link as a function of the number of streamlines connecting the grey matter region pair, and correcting it based on the distance travelled by each streamline and by the total volume of the connected regions; and (vi) constructing an adjacency matrix to summarize the individual connectome. Of note, we used an approach described by Bonilha *et al.* (2014*a*) to

attenuate the distorting effects of stroke-related necrotic changes on the brain anatomy and fibre tracking. The preprocessing approach also excluded the lesion site from all tractography tracings (including cortical seeding, cortical waypoints or white matter tracking regions) thus controlling for lesion influence on the final tract tracing. For this reason, steps to control for the overall lesion size were not included in subsequent statistical analyses. These steps are described in more detail below.

To align the diffusion image with the lesion map, the T_2-weighted image (co-registered to match the T_1-weighted image, and therefore in the same space as the native T_1 image) was normalized to match the non-diffusion weighted image from the diffusion MRI sequence (the B0 image) and the resulting spatial transform was used to register the probabilistic maps of white and grey matter (the latter divided into regions of interest) and the stroke lesion into the diffusion MRI space. All subsequent calculations were performed in diffusion space.

Probabilistic tractography was applied to evaluate pairwise grey matter structural connectivity. Tractography was estimated through the FMRIB Diffusion Toolbox (FDT) probabilistic method (Behrens *et al.*, 2007) with FDT's BEDPOST being used to build default distributions of diffusion parameters at each voxel, followed by probabilistic tractography using FDT's probtrackX (parameters: 5000 individual pathways drawn through the probability distributions on principle fibre direction, curvature threshold set at 0.2, 200 maximum steps, step length 0.5 mm and distance correction). The white matter probabilistic map excluding the stroke lesion was used as a waypoint mask. The connectivity between regions was defined as the number of streamlines arriving in one region when another region was seeded and vice versa. Thus, the weighted connectivity between regions A and B was defined as the number of probabilistic streamlines arriving at region B when region A was seeded, averaged with the number of probabilistic streamlines arriving at region A when region B was seeded. The calculation of the probabilistic streamlines was corrected based on the distance travelled by the streamline connecting regions A and B ('distance correction' built into probtrackX). To compensate for the unequal size of grey matter regions, the number of streamlines connecting each pair of regions was divided by the sum of the volumes of these regions. When a given region was completely destroyed, the number of streamlines between that region and other regions was automatically set to zero.

Data analyses

All univariate statistical analyses that related brain damage to speech and language impairment were implemented using the NiiStat toolbox for MATLAB (https://www.nitrc.org/projects/niistat/). The lesion and connectome analyses focused on grey matter regions of interest within the dual streams defined in Fridriksson *et al.* (2016). Regions of interest in the dorsal stream included pars opercularis, pars triangularis, anterior insula, posterior insula, precentral gyrus, postcentral gyrus, middle frontal gyrus, supramarginal gyrus (SMG), globus pallidus, and putamen. The ventral stream included posterior middle temporal gyrus (pMTG), posterior superior temporal gyrus (pSTG), MTG, STG, superior temporal pole, angular gyrus, middle temporal pole, pars orbitalis, inferior temporal gyrus, and middle occipital gyrus. The univariate lesion analyses relied on conventional lesion symptom mapping: General Linear Model (GLM) (pooled variance *t*-test) with $P < 0.05$ (one-tailed) and control for multiple comparisons used permutation threshholding (4000 permutations). Similarly, the univariate CLSM analyses also relied on GLM with $P < 0.05$ and 4000 permutations to control for multiple comparisons. A handful of studies have shown that aphasia severity changes considerably among some patients, even in the chronic phase (Naeser *et al.*, 1998; Holland *et al.*, 2017; Hope *et al.*, 2017). To verify that time post-stroke would not influence the results, we examined the correlation between each of the 16 tasks and tests and time post-stroke. No statistically significant correlations were revealed. Therefore, the lesion-symptom analyses were not adjusted for time post-stroke.

For multivariate analyses, we relied on stepwise regression implemented in the 'Automatic Linear Modeling' module in SPSS (Edition 24.0) were the dorsal and ventral stream regions of interest and links between those regions of interest were included as predictors for RLSM and CLSM, respectively. Criteria for entry and removal of factors in a step-wise model selection used $P < 0.05$ for factor inclusion and $P > 0.10$ for factor removal. Unlike the univariate analyses, the multivariate analyses did not rely on permutation thresholding. At this time, we are not aware of comparable methods that enable both univariate and multivariate analyses of RLSM or CLSM data. Hence, a direct comparison between the univariate and multivariate results should be considered with this caveat in mind.

Principal component analysis (PCA) was used in an attempt to isolate behavioural components that primarily reflect impaired speech comprehension versus speech production. To demonstrate cortical damage associated with poor speech production or speech comprehension, univariate and multivariate analyses were carried out with patients' components scores included as dependent factors. The PCA included Varimax rotation and only components with an eigenvalue of 1 and above were considered for further analyses. As was the case for the multivariate analyses, the PCA relied on SPSS.

Results

Region-wise lesion-symptom mapping results

All univariate RLSM analyses yielded statistically significant results (Fig. 1 and Supplementary Fig. 3A–D), with the exception of 'phonological naming errors' on the PNT. Not surprisingly, performance on some of the speech and language tests included here was related to damage to the same set of cortical regions. For example, a few of the Western Aphasia Battery scores such as 'aphasia quotient,' 'speech fluency,' 'auditory-word recognition,' and 'speech repetition' were predicted by each of the 20 analysed regions of interest even though the strongest predictors varied across tests (Table 2 presents the three strongest predictors; for a complete list of damaged regions that predicted test performance see Supplementary Table 1). Performance on other tests was predicted by a subset of the regions of interest. The regions that most often emerged

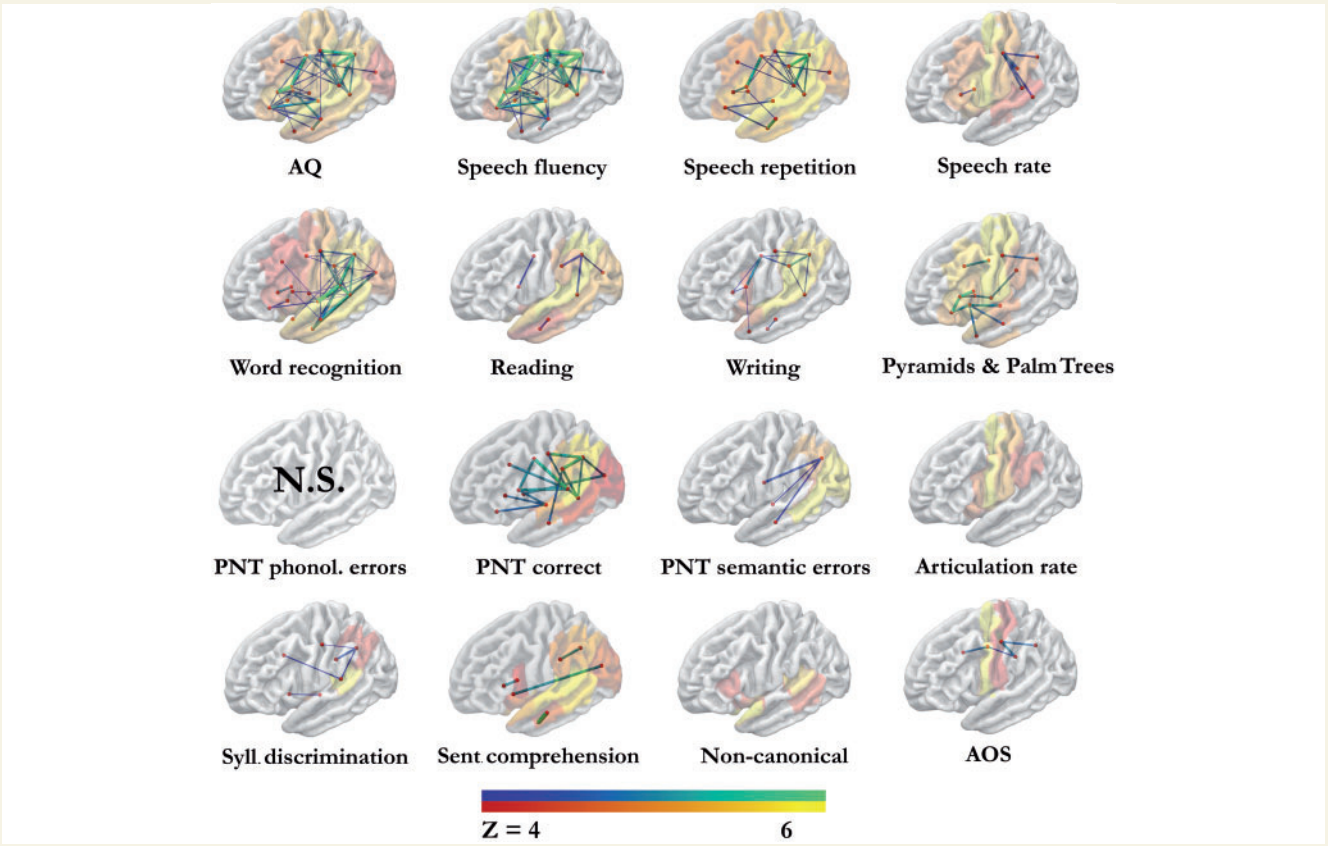

Figure 1 Univariate RLSM (red-yellow) and CLSM (blue-green) results for each of the speech and language tests. For CLSM, both colour intensity and link thickness denote how strongly damage to a given link predicts speech or language test performance. AQ = aphasia quotient; AOS = apraxia of speech; N.S. = non-significant.

as predictors of speech and language performance in the univariate RLSM were: (i) pars opercularis; (ii) STG; and (iii) SMG. Damage to each of these three regions was a statistically significant predictor of performance on 14 of the 16 speech and language tests.

Because of the nature of multivariate analyses where the best predictor (region of interest damage) tends to have no or low correlation with subsequent model factors that reduce prediction error, considerably fewer regions were revealed in the multivariate analyses compared to the univariate analyses (Fig. 2 and Supplementary Fig. 4A–D). Nevertheless, all 16 multivariate RLSM analyses yielded statistically significant results. The regions that most often predicted performance on the 16 speech and language measures in the multivariate analyses were: (i) pSTG (predictor on eight tests); (ii) precentral gyrus (predictor on seven tests); and (iii) posterior insula (predictor on six tests). Table 3 includes all statistically significant predictors for each multivariate RLSM analysis. It is worth noting that the best predictor of each speech and language measure explained proportionally far greater proportion of the variance than subsequent predictors included in each model. This fact is illustrated in Fig. 2 as well as listed in Table 3.

Connectome lesion-symptom mapping results

As was the case for the univariate RLSM analyses, not all univariate CLSM analyses yielded statistically significant results, including 'phonological naming errors' on the PNT (Fig. 1 and Table 4). In addition, impaired 'comprehension of non-canonical sentences' (in comparison to canonical sentences) and slower 'articulation rate' were not associated with damage to specific network connections. The overall severity of aphasia ('aphasia quotient') and 'speech fluency' were predicted by damage to an extensive network primarily involving the dorsal stream, with somewhat fewer connections to the ventral stream. 'Auditory word recognition', 'correct naming', and 'speech repetition' were also predicted by damage to an extensive cortical network. Much of the damage associated with 'auditory word recognition' involved the ventral stream with relatively fewer links involving the dorsal stream, whereas 'speech repetition' and 'correct naming' were associated with both dorsal and ventral stream damage. Accuracy on the Pyramids and Palm Trees test was mostly associated with damage to a fronto-temporal network with the pars triangularis being the region most often included as part of a

Table 2 The top three brain regions predictive in the univariate analyses of each test/task and the z-score associated with brain damage and each given region

Test/scale	Region	Z-Score
Aphasia Quotient	STG	−7.84
	Posterior Ins	−7.65
	Posterior STG	−7.61
Speech Fluency	STG	−7.74
	IFG opercularis	−7.73
	Posterior Ins	−7.71
Speech Repetition	Posterior STG	−7.78
	STG	−7.69
	SMG	−7.41
Auditory Word Recognition	STG	−7.17
	Posterior STG	−6.99
	Posterior MTG	−6.77
Reading	Posterior STG	−5.72
	STG	−5.71
	AG	−5.65
Writing	SMG	−5.75
	Posterior Ins	−5.72
	Posterior STG	−5.65
Pyramids and Palm Trees	PrCG	−4.34
	PoCG	−4.12
	Ins	−3.75
PNT Correct	Posterior STG	−5.13
	AG	−4.96
	SMG	−4.75
PNT Semantic Errors	Posterior MTG	4.64
	MOG	4.57
	AG	4.33
Syllable Identification	Posterior STG	−4.67
	Posterior Ins	−4.25
	AG	−4.05
Sentence Comprehension	Posterior STG	−7.06
	STG	−6.58
	Posterior MTG	−6.40
Non-Canonical	STG-pole	−4.08
	Posterior STG	−3.92
	Posterior Ins	−3.73
AOS	PrCG	4.56
	PoCG	4.01
	SMG	3.90
Speech Rate	PrCG	−6.72
	IFG opercularis	−6.15
	Posterior Ins	−6.05
Articulation rate	PrCG	−6.20
	Posterior Ins	−5.44
	Putamen	−5.24

No regions of interest survived the analysis that included phonemic errors on the PNT.
AG = angular gyrus; AOS = apraxia of speech; IFG = inferior frontal gyrus; Ins = insula; MOG = middle occipital gyrus; MTG = middle temporal gyrus; PoCG = post-central gyrus; PrCG = precentral gyrus.
A full list of regions significantly predictive of each test/scale is presented in Supplementary Table 1.

damaged link. Other functions such as 'auditory syllable discrimination', 'speech rate' and 'apraxia of speech' involved relatively few links. Not surprisingly, the number of cortical regions implicated in the univariate RLSM analyses was correlated with the number of links revealed in the CLSM analyses, $r = 0.86$, $P < 0.0001$. However, the number of participants included in the analyses of each behavioural test or task was not correlated with the number of regions revealed by RLSM ($r = 0.38$, $P = 0.17$) or CLSM ($r = 0.46$, $P = 0.075$). To appreciate which cortical regions were most often included as part of a damaged link related to test performance, we counted how often each region of interest occurred in the CLSM results. Three regions stood out: (i) pars triangularis ($n = 69$) and pars opercularis ($n = 68$); (ii) SMG ($n = 74$) and angular gyrus ($n = 76$); and (iii) MTG ($n = 73$).

Similar to the RLSM analyses, far fewer links were identified in the multivariate CLSM analyses compared to the univariate CLSM analyses (Fig. 2). Nonetheless, the multivariate CLSM analyses revealed damage associated with extensive cortical networks for performance on tests and tasks such as speech repetition, ratings of 'speech fluency', 'speech rate', 'articulation rate', correct naming on the PNT, and overall severity of aphasia (aphasia quotient). The areas that most often were included as parts of damaged links in the multivariate analyses were: (i) pars opercularis ($n = 21$); (ii) precentral gyrus ($n = 19$); (iii) angular gyrus ($n = 19$); and (iv) posterior STG ($n = 12$).

Principal components analysis

Consistent with our previous research suggesting phonological form-to-articulation and phonological form-to-meaning processing primarily rely on the dorsal and ventral streams, respectively, we explored what regions and links are primarily associated with speech production and speech comprehension. For this purpose, we carried out a principal components analysis (PCA) of four tests or tasks included in our battery that primarily reflect speech production ability (speech rate, speech articulation, speech fluency, and apraxia of speech) and three tests or tasks that primarily reflect speech perception or comprehension (auditory word recognition, auditory syllable identification, and sentence comprehension).

The PCA yielded two main components that largely reflect speech production and speech comprehension abilities (Supplementary Fig. 5). The primary loadings for component 1 were the four tests we had identified as primarily reflecting speech production ability. Component 2 was not as clear-cut in that 'speech fluency' was the second strongest influence after 'word recognition'. Yet, three of the four highest loadings for component 2 involved the tests or tasks that primarily reflect speech perception or speech comprehension ability. The univariate RLSM analyses of components 1 and 2 revealed a fairly clear division between regions included in the dorsal and ventral streams, respectively (Fig. 3). However, one region, the SMG, was included

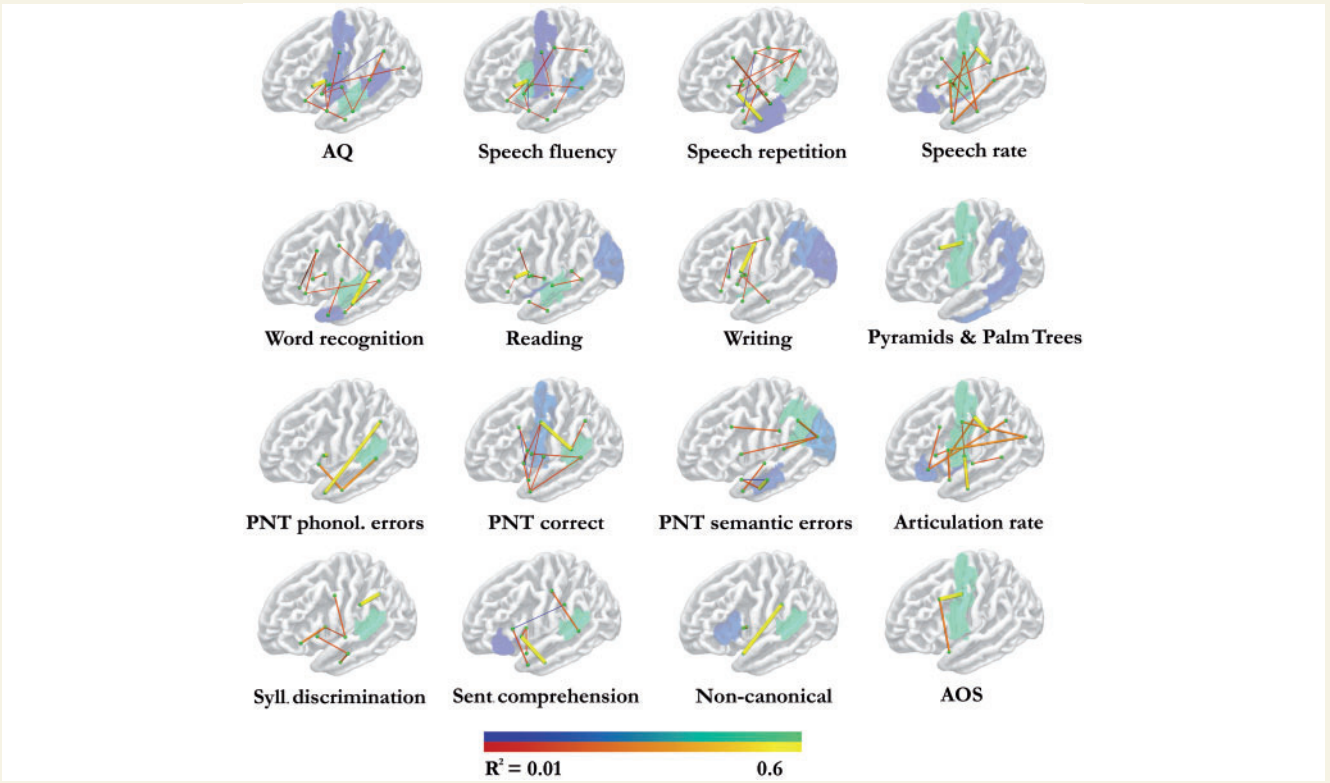

Figure 2 Multivariate RLSM (blue-green) and CLSM (red-yellow) results for each of the speech and language tests. Note that the colour scales represent amount of variance (R^2) explained by each region of interest or link. AQ = aphasia quotient; AOS = apraxia of speech.

in both lesion maps. The multivariate RLSM analysis of components 1 and 2 also revealed regions that mostly loaded onto the dorsal and ventral stream regions of interest with only one region, middle frontal gyrus, included in both lesion maps. For both the univariate and multivariate RLSM analyses, the precentral gyrus was the strongest predictor of component 1 and the posterior STG was the strongest predictor of component 2. Somewhat less convergence across the univariate and multivariate analyses was revealed for the CLSM results. A link between the precentral gyrus and the middle frontal gyrus was the best predictor of component 1, whereas two different links were identified as the strongest predictor of component 2 in the univariate (angular gyrus ↔ SMG) and multivariate analyses (posterior STG ↔ MTG). Both the univariate and multivariate CLSM analyses for component 1 mainly highlighted links between dorsal stream regions. Although the multivariate CLSM analysis mostly revealed links across ventral stream regions, this was not the case for the univariate results, which included links between both dorsal and ventral stream regions.

Discussion

The current study demonstrates that overall aphasia severity, as reflected by the 'aphasia quotient' on the Western Aphasia Battery, is associated with extensive cortical network damage, mostly involving the dorsal stream and, to a lesser extent, the ventral stream. This is perhaps not surprising as the aphasia quotient is heavily weighted for speech production where three out of the four factors that comprise aphasia quotient (speech fluency, speech repetition, and naming) rely on speech production. Given that the rating of 'speech fluency' and 'speech repetition' ability are two of the subtests that comprise aphasia quotient, it stands to reason that there would be considerable overlap among the regions and connections that predict each of these factors. Aphasia can involve different degrees of impairment to multiple speech and language processes that subserve communication functioning. As such, even relatively smaller strokes that affect the cortical language network, especially if the affected areas involve links between the dorsal and ventral streams, seem likely to cause aphasia lasting beyond the subacute stage.

Whereas traditional RLSM can reveal damage that predicts a given speech or language impairment, CLSM provides complementary information highlighting links between regions that, when damaged, have a particularly detrimental effect on functioning. CLSM and RLSM are inter-related since CLSM is also dependent on lesion location: white matter pathways related to areas of cortical damage are more commonly lesioned. Nonetheless, the specific white matter projections from the areas of cortical

Table 3 All regions surviving multivariate lesion analyses for each test/task, along with corresponding R^2 and R^2 change values

Test/scale	Region	R^2	R^2 change
Aphasia Quotient	STG	0.43	0.43
	PrCG	0.48	0.05
	Posterior STG	0.50	0.02
	Posterior Ins	0.51	0.01
Speech Fluency	IFG opercularis	0.40	0.40
	Posterior STG	0.53	0.13
	Putamen	0.56	0.02
	PrCG	0.57	0.02
Speech Repetition	Posterior STG	0.42	0.42
	Posterior Ins	0.47	0.05
	ITG	0.48	0.02
	MTG	0.49	0.01
Auditory Word Recognition	STG	0.31	0.31
	AG	0.36	0.05
	MTG pole	0.39	0.03
Reading	STG	0.42	0.42
	MOG	0.51	0.08
	Posterior Ins	0.54	0.03
Writing	Posterior Ins	0.43	0.43
	AG	0.52	0.10
	GP	0.56	0.04
	MOG	0.60	0.03
PPTT	PrCG	0.18	0.18
	ITG	0.22	0.04
	AG	0.24	0.03
	Posterior MTG	0.27	0.03
PNT Correct	Posterior STG	0.22	0.22
	PrCG	0.29	0.06
PNT Semantic Errors	AG	0.21	0.21
	GP	0.31	0.10
	MOG	0.37	0.07
	MTG	0.41	0.04
PNT Phonological Errors	Posterior STG	0.06	0.06
Syllable Identification	Posterior STG	0.34	0.34
Sentence Comprehension	Posterior STG	0.60	0.60
	IFG orbitalis	0.63	0.03
Non-Canonical	Posterior STG	0.22	0.22
	IFG triangularis	0.27	0.05
AOS	PrCG	0.21	0.21
Speech Rate	PrCG	0.31	0.31
	Posterior Ins	0.38	0.06
	Putamen	0.40	0.02
	IFG orbitalis	0.42	0.02
Articulation Rate	PrCG	0.26	0.26
	Posterior Ins	0.31	0.05
	IFG orbitalis	0.36	0.05
	Putamen	0.38	0.02

AG = angular gyrus; AOS = apraxia of speech; GP = globus pallidus; IFG = inferior frontal gyrus; Ins = insula; ITG = inferior temporal gyrus; MOG = middle occipital gyrus; MTG = middle temporal gyrus; PrCG = precentral gyrus.

damage are not systematically mapped by RLSM. CSLM can thus define the anatomy of subcortical networks that are related to behaviour. Importantly, CLSM can also disclose the relationship between cortical disconnection and behaviour. Post-stroke cortical damage can be understood as the combination of direct vascular injury (necrosis or gliosis) and disconnection (Bonilha *et al.*, 2014*a*, *b*). However, disconnected areas that are seemingly preserved are not mapped by RLSM. By disclosing crucial pathways extending beyond the stroke lesion, CLSM can identify which remotely disconnected areas are directly related to cognitive function.

In this context, it is worth noting that cortical damage seen on clinical scans does not only show a given lesion location associated with speech and language processing but also reflects disconnections to regions that may be important as parts of a cortical speech and language network. This point is well demonstrated by damage that predicts naming impairment, anomia. In the current study, 'correct naming' was predicted in the univariate analysis by a lesion location mostly involving posterior structures, including the posterior STG and angular gyrus. However, CLSM showed that anomia is associated with extensive network damage that includes various regions that make up the ventral and dorsal streams. The involvement of multiple regions associated with anomia is further demonstrated in the multivariate analyses, which highlighted both posterior (posterior STG) and anterior structures (precentral gyrus) and connections involving those regions as being crucial for correct naming on the PNT. Anomia has often been deemed the hallmark impairment of aphasia—patients who have no word-finding problems at all are highly unlikely to have aphasia (Goodglass and Wingfield, 1997). Anomic aphasia, the least severe form of aphasia, is characterized by fluent speech and good auditory comprehension but poor lexical retrieval and, in the more severe cases, empty speech (Helm-Estabrooks and Albert, 1991). As demonstrated in Yourganov *et al.* (2015), unlike Wernicke's, Broca's, conduction, or global aphasia, anomic aphasia has no specific lesion location. Based on the current data, it makes sense that various different lesion locations would result in anomia as naming relies on such an extensive cortical network. From a clinical standpoint, a patient's difficulty to name could be caused by impairment at several different levels of processing—phonology, lexical, semantic, or motor speech—that are impaired to different degrees depending on what parts of the cortical network that supports naming were affected (DeLeon *et al.*, 2007).

The findings presented here demonstrate an important clinical point: speech and language processing relies on an extensive cortical network and damage to different subcomponents of this network can result in difficulty with the same communication task. This does not mean that different parts of the network are equipotential. Quite the contrary; our data suggest that the dorsal stream is very much motor speech-driven, whereas speech comprehension relies much more on the ventral stream. It is the harmony of stream interaction that makes communication possible, and the location of damage, both structural and

Table 4 The top 10 connections surviving in the univariate analyses for each test/task and the corresponding z-score

Test/scale	Connections	Z-score
Aphasia Quotient	IFG opercularis ↔ IFG triangularis	5.65
	IFG opercularis ↔ PrCG	5.39
	SMG ↔ AG	5.35
	PoCG ↔ AG	5.34
	AG ↔ posterior STG	5.06
	MTG ↔ ITG	5.06
	IFG orbitalis ↔ STG	4.98
	MTG ↔ putamen	4.89
	PoCG ↔ posterior MTG	4.77
	PoCG ↔ posterior STG	4.73
Speech Fluency	IFG opercularis ↔ PrCG	6.47
	IFG opercularis ↔ IFG triangularis	6.23
	SMG ↔ AG	5.71
	PoCG ↔ AG	5.61
	IFG orbitalis ↔ IFG triangularis	5.30
	MFG ↔ PrCG	5.26
	PoCG ↔ pMTG	5.14
	PrCG ↔ SMG	5.09
	IFG opercularis ↔ PoCG	5.05
	IFG orbitalis ↔ STG	5.05
Speech Repetition	MTG ↔ ITG	5.30
	IFG opercularis ↔ PrCG	5.29
	SMG ↔ AG	5.26
	AG ↔ posterior STG	5.16
	IFG opercularis ↔ IFG triangularis	4.80
	PoCG ↔ AG	4.77
	AG ↔ posterior MTG	4.61
	IFG orbitalis ↔ ITG	4.53
	PrCG ↔ posterior STG	4.45
	IFG orbitalis ↔ STG	4.44
Aud Word Recognition	STG ↔ posterior STG	4.75
	AG ↔ posterior STG	4.29
	MTG ↔ posterior MTG	4.18
	Posterior STG ↔ posterior MTG	4.17
	MTG ↔ ITG	4.07
	IFG opercularis ↔ IFG triangularis	3.97
	ITG ↔ MOG	3.97
	ITG ↔ posterior MTG	3.91
	MOG ↔ posterior MTG	3.80
	MTG ↔ posterior STG	3.80
Reading	SMG ↔ AG	4.21
	AG ↔ posterior MTG	4.18
	MTG ↔ ITG	4.18
	IFG opercularis ↔ PrCG	4.07
	AG ↔ MOG	4.07
	IFG opercularis ↔ IFG triangularis	3.69
	IFG triangularis ↔ PrCG	3.69
	PrCG ↔ SMG	3.67
	SMG ↔ pMTG	3.58
	PrCG ↔ AG	3.56
Writing	IFG opercularis ↔ PrCG	4.97
	SMG ↔ AG	4.80
	MTG ↔ ITG	4.52
	PrCG ↔ SMG	4.50
	AG ↔ pMTG	4.36
	PoCG ↔ AG	4.34
	IFG opercularis ↔ IFG triangularis	4.29
	SMG ↔ posterior MTG	4.24
	IFG triangularis ↔ PrCG	4.15
	PrCG ↔ AG	4.07
Pyramids and Palm Trees	IFG opercularis ↔ IFG triangularis	3.36
	IFG orbitalis ↔ IFG triangularis	3.28
	STG ↔ Ins	3.02
	IFG orbitalis ↔ Ins	3.00
	MFG ↔ PrCG	2.93
	MTG pole ↔ Ins	2.82
	Putamen ↔ posterior Ins	2.77
	PoCG ↔ AG	2.76
	SMG ↔ posterior Ins	2.74
	MTG ↔ Ins	2.73
PNT Correct	PrCG ↔ posterior STG	4.21
	SMG ↔ AG	3.91
	PoCG ↔ AG	3.84
	IFG opercularis ↔ posterior STG	3.74
	IFG opercularis ↔ PrCG	3.64
	MFG ↔ posterior STG	3.51
	MOG ↔ GP	3.50
	SMG ↔ posterior MTG	3.45
	IFG opercularis ↔ STG	3.32
	AG ↔ MOG	3.27
PNT Semantic Errors[a]	SOG ↔ Thal	−3.47
	MTG ↔ SOG	−3.24
	STG ↔ SOG	−3.05
Syllable Identification[a]	SMG ↔ AG	3.64
	AG ↔ posterior STG	3.26
	MFG ↔ posterior STG	3.20
	STG ↔ Ins	3.09
	PoCG ↔ AG	3.01
	MTG ↔ Ins	2.98
	Ins ↔ posterior Ins	2.98
	SMG ↔ MOG	2.91
	PrCG ↔ MOG	2.86
Sentence Comprehension[a]	MTG ↔ ITG	3.92
	MOG ↔ Ins	3.11
	IFG opercularis ↔ IFG triangularis	3.06
	SMG ↔ AG	3.03
AOS[a]	PoCG ↔ SMG	−2.92
	MFG ↔ PrCG	−2.75
	PoCG ↔ AG	−2.73
	PrCG ↔ SMG	−2.42
Speech Rate[a]	PoCG ↔ SMG	4.02
	PoCG ↔ pSTG	3.69
	PoCG ↔ pMTG	3.59
	PoCG ↔ AG	3.51
	IFG opercularis ↔ IFG triangularis	3.44

[a]Behaviours that were predicted by 10 or fewer connections; in these cases, all predictive connections are listed. All connections are between interhemispheric, left hemisphere grey matter regions.

No connections survived analyses that included 'phonemic errors' on the PNT, 'grammatical processing for non-canonical sentences,' or 'articulation rate.'

AG = angular gyrus; AOS = apraxia of speech; GP = globus pallidus; IFG = inferior frontal gyrus; Ins = insula; ITG = inferior temporal gyrus; MFG = middle frontal gyrus; MTG = middle temporal gyrus; MOG = middle occipital gyrus; PoCG = post-central gyrus; PrCG = precentral gyrus; SOG = superior occipital gyrus; Thal = thalamus.

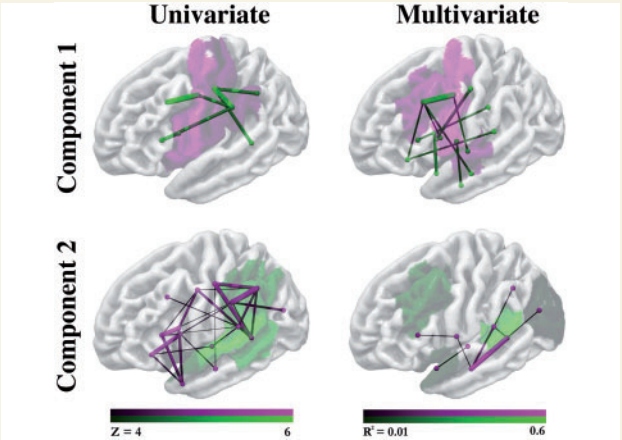

Figure 3 Univariate and multivariate analyses of RLSM and CLSM data derived from the PCA analysis of speech comprehension and speech production tests/tasks. The *top* panel shows results from component 1 and the *bottom* panel shows component 2. The *left* images show univariate results whereas the *right* images show multivariate results. Note that the scales form the univariate (Z-scores) and multivariate (R^2) analyses are different.

physiological, determines the pattern of speech and language impairment. Figure 3 shows that damage to the dorsal regions has major effects on speech production, including articulation rate and apraxia of speech severity. Not surprisingly, apraxia of speech, an impairment of speech motor planning, is predicted by damage to links between multiple cortical regions, almost exclusively within the dorsal stream. Conversely, patients' inability to comprehend speech is far more related to damage to the ventral stream. Impaired grammatical processing of sentences, which has been suggested to rely on the dorsal stream and not the ventral stream (Friederici, 2009; Wilson *et al.*, 2011; Bornkessel-Schlesewsky and Schlesewsky, 2013; Mesulam *et al.*, 2015), was primarily explained by damage to regions such as the posterior STG and Broca's area in the current dataset. Whereas patients with frontal damage have been shown to have difficulty with processing grammatically complex sentences (Caramazza and Zurif, 1976; Tyler *et al.*, 2011), this impairment seems likely to be related to disconnection of frontal lobe regions from temporal lobe structures (see also Tyler and Marslen-Wilson, 2008). Indeed, a functional network analysis by Den Ouden *et al.* (2012) suggests that the ventral and dorsal streams contribute to grammatical processing in healthy speakers, in an interactive manner.

Although the dorsal and ventral streams provide an organizational framework on which human communication relies, not all the cortical regions within the streams are equally important for speech and language processing. This notion is demonstrated by the RLSM results that suggest damage to pars opercularis, angular gyrus, and posterior STG is more harmful, overall, to speech and language processing compared to damage to other regions. The univariate and multivariate connectome results revealed a similar, albeit not identical, picture with damage to links that included regions such as Broca's area (pars opercularis and pars triangularis), SMG/angular gyrus, as well as MTG having particularly negative effects. These regions could be considered especially important hubs in the cortical speech and language network as damage to connections that terminate here has proportionally greater effects on the different aspects of speech and language processing assessed by clinical tests of aphasia. Area Spt (Sylvian fissure, parietal-temporal junction), a posterior region and a part of the dorsal stream (Hickok *et al.*, 2003, 2009), is located in the JHU atlas at the junction of the posterior STG, SMG, and angular gyrus. This area has been proposed to play an important role in coordinating activity across the dorsal and ventral streams (Hickok and Poeppel, 2007; Hickok *et al.*, 2011; Hickok, 2012). As such, it is not surprising that damage to this region has general effects on speech and language. The roles of Broca's area and the posterior STG in speech and language processing have been amply discussed elsewhere and readers are referred to a rich literature on the neurobiology of language for further details regarding human communication (Hillis *et al.*, 2001, 2006; DeLeon *et al.*, 2007; Cloutman *et al.*, 2009; Binder and Desai, 2011; Rogalsky and Hickok, 2011; Friederici, 2012; Poeppel *et al.*, 2012; Dick *et al.*, 2014; Fedorenko and Thompson-Shill, 2014; Hagoort and Indefrey, 2014). In relation to patients, damage to any of the hubs identified here should result in greater overall impairment of speech and language. However, this does not suggest that the remaining regions of interest analysed here are not crucial for specific processes. For example, atrophy of the temporal pole has been associated with impaired semantic processing (Hodges *et al.*, 1992; Mummery *et al.*, 2000; Galton *et al.*, 2001; Ogar *et al.*, 2011; Faria *et al.*, 2014) and damage to the inferior temporal gyrus predicts poor single word comprehension (Bonilha *et al.*, 2017). Nevertheless, damage to the hubs identified here seems likely to have long-term effects on overall communication ability. As such, future studies should consider damage to these regions as important for prognosis of aphasia.

In addition to highlighting areas that could be considered hubs for speech and language processing, the current data also emphasize the role of shorter white matter fibres. Explicitly, it is clear from Figs 1 and 2 that many of the links that, when damaged, give rise to speech and language impairment connect adjacent cortical regions. To be clear, there is nothing that disadvantages longer-range connections in our analyses. It would seem that shorter fibres, for example, between the angular gyrus, posterior STG, and MTG probably play a crucial role in some aspects of speech and language processing. This notion was specifically raised in a paper by Mesulam and colleagues (2015). Moreover, it would seem odd if only the most distal regions of the major tracts (e.g. arcuate fasciculus, superior longitudinal fasciculus, and inferior fronto-occipital fasciculus) were crucial for speech and language processing instead of also connections between more proximal regions.

Table 5 The top 10 connections surviving multivariate connectome analyses, along with corresponding R^2 and R^2 change values

Test/scale	Connections	R^2	R^2 change
Aphasia Quotient	IFG triangularis ↔ IFG opercularis	0.22	0.22
	Posterior STG ↔ AG	0.28	0.06
	ITG ↔ IFG orbitalis	0.32	0.04
	STG pole ↔ PrCG	0.35	0.03
	Putamen ↔ Ins	0.38	0.03
	IFG orbitalis ↔ IFG opercularis	0.41	0.03
	Ins ↔ AG	0.40	−0.01
	GP ↔ MOG	0.43	0.03
	Posterior Ins ↔ MTG	0.45	0.02
	Posterior Ins ↔ Ins	0.47	0.02
Speech Fluency	IFG triangularis ↔ IFG opercularis	0.25	0.25
	IFG orbitalis ↔ IFG opercularis	0.31	0.05
	Posterior ITG ↔ GP	0.33	0.03
	AG ↔ PoCG	0.37	0.04
	Ins ↔ STG pole	0.39	0.03
	Putamen ↔ Ins	0.41	0.02
	L ITG ↔ IFG orbitalis	0.43	0.02
	Posterior STG ↔ MTG	0.45	0.02
	STG pole ↔ IFG opercularis	0.44	−0.01
	Ins ↔ PoCG	0.46	0.01
Speech Repetition	Ins ↔ ITG	0.20	0.20
	Medial lemniscus ↔ MFG	0.26	0.06
	Posterior Ins ↔ MTG pole	0.29	0.04
	Posterior STG ↔ AG	0.33	0.03
	AG ↔ PoCG	0.36	0.03
	PrCG ↔ PoCG	0.39	0.03
	STG pole ↔ PrCG	0.38	−0.01
	AG ↔ IFG opercularis	0.41	0.03
	SMG ↔ PrCG	0.44	0.02
	Posterior Ins ↔ STG	0.45	0.02
	Putamen ↔ IFG triangularis	0.47	0.01
Auditory Word Recognition[a]	Posterior STG ↔ MTG	0.17	0.17
	IFG triangularis ↔ IFG opercularis	0.21	0.04
	IFG orbitalis ↔ MFG	0.25	0.03
	Posterior MTG ↔ ITG	0.28	0.03
	MTG pole ↔ MFG	0.30	0.03
	Posterior Ins ↔ MTG pole	0.33	0.03
	Posterior STG ↔ PrCG	0.36	0.03
	Posterior MTG ↔ IFG orbitalis	0.38	0.02
Reading[a]	IFG triangularis ↔ IFG opercularis	0.32	0.32
	Posterior Ins ↔ GP	0.39	0.07
	Posterior MTG ↔ pSTG	0.44	0.04
	Putamen ↔ MFG	0.49	0.05
	IFG triangularis ↔ IFG orbitalis	0.49	0.00
	ITG ↔ STG pole	0.54	0.05
	Posterior MTG ↔ STG	0.60	0.06
Writing[a]	PrCG ↔ IFG opercularis	0.40	0.40
	Putamen ↔ MTG	0.47	0.07
	SMG ↔ MFG	0.51	0.04
	IFG orbitalis ↔ MFG	0.56	0.05
	IFG triangularis ↔ MFG	0.54	−0.02
	STG pole ↔ PrCG	0.58	0.04
	GP ↔ IFG opercularis	0.62	0.04
	Putamen ↔ Ins	0.65	0.04
PPTT[a]	PrCG ↔ MFG	0.12	0.12
PNT Correct	Posterior STG ↔ PrCG	0.18	0.18
	IFG opercularis ↔ MFG	0.22	0.04
	Posterior STG ↔ AG	0.26	0.04
	Ins ↔ PrCG	0.28	0.03
	Posterior MTG ↔ GP	0.32	0.04
	Ins ↔ MTG pole	0.37	0.05
	Posterior MTG ↔ MTG pole	0.40	0.04
	Ins ↔ IFG opercularis	0.43	0.03
	Posterior Ins ↔ MTG pole	0.46	0.03
	STG pole ↔ PrCG	0.48	0.02
PNT Semantic Errors[a]	ITG ↔ MTG	0.13	0.13
	MOG ↔ AG	0.19	0.06
	Posterior STG ↔ MOG	0.25	0.05
	MTG pole ↔ STG	0.28	0.04
	SMG ↔ MFG	0.33	0.04
	Putamen ↔ MOG	0.36	0.03
	ITG ↔ STG pole	0.40	0.05
	MTG ↔ STG pole	0.38	−0.02
PNT Phonological Errors[a]	GP ↔ Putamen	0.08	0.08
	MTG pole ↔ AG	0.15	0.07
	Ins ↔ ITG	0.19	0.04
	pMTG ↔ ITG	0.23	0.04
Syllable Identification[a]	AG ↔ SMG	0.26	0.26
	GP ↔ IFG orbitalis	0.38	0.12
	ITG ↔ MTG	0.46	0.09
	STG ↔ PrCG	0.53	0.07
	Ins ↔ MTG	0.59	0.06
	GP ↔ STG	0.64	0.04
Sentence Comprehension[a]	Ins ↔ ITG	0.26	0.26
	Posterior MTG ↔ PoCG	0.34	0.08
	Putamen ↔ Ins	0.40	0.07
	Putamen ↔ STG pole	0.45	0.05
	SMG ↔ IFG triangularis	0.43	−0.02
	MTG pole ↔ IFG triangularis	0.50	0.07
Non-Canonical[a]	STG pole ↔ SMG	0.12	0.12
	GP ↔ Putamen	0.18	0.07
AOS[a]	PrCG ↔ MFG	0.16	0.16

(continued)

Table 5 Continued

Test/scale	Connections	R^2	R^2 change
	STG pole ↔ MFG	0.22	0.07
Speech Rate	SMG ↔ PoCG	0.16	0.16
	Posterior STG ↔ MOG	0.22	0.06
	Posterior STG ↔ MTG pole	0.29	0.07
	IFG triangularis ↔ IFG opercularis	0.33	0.04
	STG pole ↔ IFG opercularis	0.41	0.07
	MTG ↔ PrCG	0.45	0.05
	Putamen ↔ PoCG	0.49	0.04
	GP ↔ IFG opercularis	0.53	0.04
	MTG pole ↔ PrCG	0.56	0.04
	Posterior Ins ↔ MFG	0.59	0.03
Articulation Rate	SMG ↔ PoCG	0.12	0.12
	Posterior Ins ↔ ITG	0.21	0.09
	MOG ↔ IFG opercularis	0.27	0.06
	MOG ↔ PrCG	0.32	0.05
	Putamen ↔ PoCG	0.37	0.05
	AG ↔ IFG orbitalis	0.42	0.05
	STG pole ↔ IFG opercularis	0.47	0.05
	IFG orbitalis ↔ MFG	0.50	0.03
	IFG triangularis ↔ IFG opercularis	0.53	0.03
	pMTG ↔ STG	0.55	0.03

[a]Behaviours that were predicted by 10 or fewer connections; in these cases, all predictive connections are listed.

AG = angular gyrus; AOS = apraxia of speech; GP = globus pallidus; IFG = inferior frontal gyrus; Ins = insula; ITG = inferior temporal gyrus; MFG = middle frontal gyrus; MTG = middle temporal gyrus; MOG = middle occipital gyrus; PoCG = post-central gyrus; PrCG = precentral gyrus.

It could be the case that larger lesions that cause the most severe impairments do so not only because of greater grey matter damage but also because of destruction of a number of underlying white matter tracts, which are crucial for speech and language processing.

The reading and writing subtests on the Western Aphasia Battery provide a somewhat shallow picture of alexia and agraphia, respectively. Much more sensitive tasks are needed to understand specifically why a given patient struggles with reading and writing (Kay *et al.*, 1996; Rapcsak *et al.*, 2007). Yet, both the RLSM and CLSM analyses yielded statistically significant results for the reading and writing subtests on the Western Aphasia Battery. Some of the same regions and connections that predict poor reading performance also predict poor writing. As both subtests tax a broad cortical network, brain damage that causes reading and writing impairment can involve several different regions and connections.

The number of different statistically significant cortical areas and links varied considerably across the 16 different subtests included here. One reason why this was the case is that some tests or tasks simply recruit input and coordination of a larger set of cortical regions relative to other tests. For example, it is reasonable to expect that speech fluency, a construct that theoretically relies on many different processes, would recruit more regions than speech syllable discrimination. However, other possibilities need to be considered. As demonstrated in Table 1, the number of participants who completed each test or task varied. Therefore, statistical power was not equal across all univariate analyses. Nevertheless, the number of regions and links revealed in the univariate RLSM and CLSM analyses, respectively, was not associated with the number of participants that completed each test or task. This suggests that the number of regions and links associated with poor task performance was not primarily driven by statistical power. It is also possible that error responses on individual tasks reflected impaired processes rooted in different cortical locations. A case in point is 'phonological naming errors': it is not so straightforward to determine the source of a given sound error. It could be the case that an error arose because of impaired phonological retrieval or assembly. Yet, a similar error caused by impaired motor planning may sound similar and scoring on the PNT is not typically based on detailed acoustic analyses. Therefore, the non-result for the univariate RLSM analysis of phonological naming errors may reflect different sources of impairment rather than insufficient statistical power. Nevertheless, the multivariate RLSM analysis did reveal an association between posterior STG damage and phonological naming errors, a result that is not in agreement with Schwartz and colleagues (2012), who revealed a relationship between more anterior dorsal stream damage and phonological naming errors.

The current study is somewhat unique in that it relied on univariate and multivariate analyses of both lesion and connectome data. One of the differences between univariate and multivariate analyses is that the univariate analysis does not take into account covariance across predictors (regions of interest). Therefore, in the current study, adjacent regions were quite often predictors of performance on a given test in the univariate analyses whereas this rarely occurred in the multivariate analyses. This is because the extent of damage to adjacent regions is correlated in stroke. For example, patients who have damage to pars opercularis also tend to have damage to pars triangularis, and vice versa, which means that these regions are highly correlated as predictors in our statistical analyses. Therefore, it was unlikely that both pars triangularis and pars opercularis would be included in the same prediction model in a multivariate analysis due to their high covariance. This notion is demonstrated in Fig. 2, which clearly demonstrates that the multivariate RLSM analyses rarely identified spatially contiguous regions. We suggest the univariate and multivariate results should be considered complementary instead of contradictory. The univariate analyses highlight larger contiguous regional clusters that, when damaged, are very likely to cause impairment. In contrast, the multivariate analyses reveal smaller overall damage but more distal modules as being independent predictors of performance on a given test.

In conclusion, our findings reveal that clinical tests typically used to assess aphasia recruit a cortical network composed of the dorsal and ventral streams underlying phonological form-to-articulation (dorsal stream) and phonological form-to-meaning (ventral stream), respectively. Speech production is impaired primarily as a result of damage to the dorsal stream whereas speech comprehension is more likely associated with ventral stream damage. Nevertheless, many clinical tests of aphasia involve multiple processes that rely on both streams, which can result in poor performance due to damage affecting different sections of the cortical speech and language network. Damage to specific cortical hubs such as Broca's area, SMG/angular gyrus, and posterior STG affects performance at least 6 months after stroke on several different aphasia tests and should be explored in future studies of prognosis in aphasia.

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Supplementary material

Supplementary material is available at *Brain* online.

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