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Structural white matter connectometry of word production in aphasia: an observational study

William D. Hula,[1,2] Sandip Panesar,[3] Michelle L. Gravier,[4] Fang-Cheng Yeh,[5] Haley C. Dresang,[2] Michael Walsh Dickey[1,2] and Juan C. Fernandez-Miranda[3]

While current dual-steam neurocognitive models of language function have coalesced around the view that distinct neuroanatomical networks subserve semantic and phonological processing, respectively, the specific white matter components of these networks remain a matter of debate. To inform this debate, we investigated relationships between structural white matter connectivity and word production in a cross-sectional study of 42 participants with aphasia due to unilateral left hemisphere stroke. Specifically, we reconstructed a local connectome matrix for each participant from diffusion spectrum imaging data and regressed these matrices on indices of semantic and phonological ability derived from their responses to a picture-naming test and a computational model of word production. These connectometry analyses indicated that both dorsally located (arcuate fasciculus) and ventrally located (inferior frontal-occipital, uncinate, and middle longitudinal fasciculi) tracts were associated with semantic ability, while associations with phonological ability were more dorsally situated, including the arcuate and middle longitudinal fasciculi. Associations with limbic pathways including the posterior cingulum bundle and the fornix were also found. All analyses controlled for total lesion volume and all results showing positive associations obtained false discovery rates < 0.05. These results challenge dual-stream accounts that deny a role for the arcuate fasciculus in semantic processing, and for ventral-stream pathways in language production. They also illuminate limbic contributions to both semantic and phonological processing for word production.

1 Geriatric Research, Education, and Clinical Center and Audiology and Speech Pathology Service, VA Pittsburgh Healthcare System, Pittsburgh PA, USA
2 Department of Communication Science and Disorders, University of Pittsburgh, Pittsburgh PA, USA
3 Department of Neurosurgery, Stanford University, Palo Alto, CA, USA
4 Department of Speech, Language, and Hearing Sciences, California State East Bay, Hayward, CA, USA
5 Department of Neurological Surgery, University of Pittsburgh, Pittsburgh, PA, USA

Correspondence to: William Hula
Audiology and Speech Pathology, VA Pittsburgh Healthcare System, University Drive 112SP-U
Pittsburgh Pennsylvania 15240, USA
E-mail: william.hula@va.gov

Introduction

Anomia is one of the defining characteristics of aphasia. Understanding the cognitive and neural bases of word production and its impairment is therefore important for aphasia rehabilitation. Analysis of picture-naming errors by persons with aphasia has also proven useful for constraining models of word production, and these errors also have significance for clinical diagnosis and decision-making. Integrating models that predict and explain aphasic language behaviour with current ideas about how brain structure and function are organized to support language production is thus key to enhancing the scientific basis for both diagnosis and treatment of anomia.

One prominent and highly productive computational psycholinguistic model of paraphasic naming errors is the semantic-phonological interactive two-step model (SP model; Foygel and Dell, 2000), an extension of Dell's (1986) model of word retrieval based on production errors in normal speech. The SP model is a localist connectionist network with three layers of units: semantic, lexical, and phonological. Activation spreads bi-directionally between related units across the three layers, governed by noise and decay terms, as well as two lesionable parameters. The first of these parameters, s, determines the strength of connection between units in the first layer (corresponding to conceptual semantic features) and lexical units in the second layer (corresponding to syntactically specified but phonologically empty word representations). The second parameter, p, determines the strength of the connections between the lexical units and phonological units in the third layer. Unlike other prominent computational models of aphasic language behaviour (Ueno et al., 2011; Roelofs, 2014), the model can be fit to person-level data from individuals with aphasia, providing estimates of s and p for each person depending on the pattern of responses to a confrontation naming test. Furthermore, given the SP model's notable success in modelling aphasic word-production performance (Schwartz et al., 2006; Dell et al., 2007) and evidence supporting its diagnostic value (Schwartz and Brecher, 2000; Abel et al., 2007, 2009; Dickey et al., 2016), identifying its potential neural correlates is of significant theoretical and clinical interest.

The SP model is consonant with prevailing neurocognitive dual-stream models of language function (Hickok and Poeppel, 2004, 2007; Saur et al., 2008; Ueno et al., 2011; Roelofs, 2014). Like dual-stream accounts of visual (Milner and Goodale, 2008) and auditory processing (Rauschecker and Scott, 2009), these models propose that the cortical organization of language function consists of two types of interface systems, in anatomically differentiated streams: a semantic sensory-conceptual ventral stream (sound to meaning mapping), and a phonological sensory-motor dorsal stream (sound to articulation mapping). Hickok and Poeppel (2004) proposed that the ventral stream projects ventrolaterally, connecting sensory speech input to bilateral middle and inferior temporal cortices, which are involved in speech recognition (Hickok and Poeppel, 2007). The ventral stream is proposed to have a weak left-hemisphere bias. In contrast, the more strongly left hemisphere dominant dorsal stream projects dorsoparietally to regions in the posterior frontal lobe, posterior-dorsal temporal lobe, and parietal operculum and is involved in translating speech sounds into articulatory representations. Importantly for the current discussion, these processing streams are hypothesized to be bidirectional (Hickok and Poeppel, 2004); thus, the ventral stream is proposed to support both auditory comprehension and the assignment of meaning to spontaneous speech.

In a voxel-based lesion parameter mapping study, Dell et al. (2013) found empirical support for the correspondence between the SP model and the dual-stream neurocognitive models. The SP model parameter p was associated with anterior dorsal stream cortical areas including the supramarginal gyrus, post-central gyrus, pre-central gyrus, and insula. These findings were similar to results produced by an earlier voxel-based lesion symptom mapping study of phonological errors (Schwartz et al., 2012), which are one of the major determinants of p. The association between p and damage to the anterior parietal cortex was taken as evidence that somatosensory areas play a role in the production of phonological errors in this context. The s parameter was associated with lesions to the anterior temporal lobe, frontal lobe, parietal-temporal junction, and angular gyrus. Based on these results, Dell et al. (2013) offered an expanded cognitive interpretation of s including not only semantic-lexical connections but also semantic control processes and semantic representations themselves.

These findings provide clear evidence regarding the grey matter correlates of dual-stream models and their mapping to Dell and colleagues' computational psycholinguistic model. However, they do not address the white matter correlates of either the dual-stream neurocognitive or the computational psycholinguistic model. The white matter substrates of the dorsal and ventral processing streams and their particular functional properties have been the subject of vigorous debate (Dick and Tremblay, 2012). There is broad agreement that the arcuate fasciculus (AF) is the major white matter component of the dorsal stream (Glasser and Rilling, 2008; Saur et al., 2008; Ueno et al., 2011; Isenberg et al., 2012; Roelofs, 2014; Fernández-Miranda et al., 2015) and participates in phonological and motor processing for speech output. However, some authors have also suggested that specific components of the AF contribute to semantic processing for language production (Catani et al., 2005; Glasser and Rilling, 2008; Roelofs, 2014; Fernández-Miranda et al., 2015). In particular, comparison of white matter cortical terminations with the results of functional imaging studies of language have led to the hypothesis that there is a strongly lateralized inner pathway of the left AF, specialized for phonology, and a less lateralized outer pathway specialized for semantic processing (Glasser and Rilling, 2008; Fernández-Miranda et al., 2015). However, other investigators have ascribed semantic processing for both comprehension and expression primarily to ventral stream pathways, including the middle longitudinal fasciculus (MdLF),

extreme capsule, the inferior fronto-occipital fasciculus (IFOF) and potentially the uncinate fasciculus (UF) (Ueno *et al.*, 2011; Duffau *et al.*, 2013; Han *et al.*, 2013; Almairac *et al.*, 2015). The MdLF was also identified by Saur *et al.* (2008) as participating in both the dorsal and ventral processing streams. The white matter correlates of these two aspects of word production, particularly semantic processing, thus remain unclear and controversial.

The white matter substrates of semantic processing are particularly relevant to a central distinction between two prominent neuroanatomically constrained computational models of language. The Lichtheim2 model (Ueno *et al.*, 2011) proposes that semantic and lexical processing for language production is supported primarily by ventral white matter pathways connecting the ventral anterior temporal lobe and the anterior superior temporal gyrus and superior temporal sulcus to Broca's area. Although simulations based on the Lichtheim2 model suggest a limited role for the dorsal pathway via the AF in semantically-driven word production, its authors make explicit the assumption that this functional arrangement can change with the recovery that occurs in response to a lesion, with a learning component formally instantiated in the model. By contrast, the WEAVER++/ARC model (Roelofs, 2014), following earlier tractographic studies (Catani *et al.*, 2005; Glasser and Rilling, 2008; Fernandez-Miranda *et al.*, 2012) locates the white matter substrate for the assignment of meaning to spoken output exclusively in a subcomponent of the left AF. Although ventral stream cortical areas in the anterior and posterior temporal lobe contribute to this processing, the white matter tracts connecting the temporal and inferior frontal cortices, primarily the UF, the IFOF, and portions of the MdLF, are assumed to play no role in mapping conceptual representations onto speech output for word production.

The purpose of the current study was to combine Dell *et al.*'s (2013) parameter mapping approach with diffusion MRI connectometry (Yeh *et al.*, 2016) to study the relationship between naming impairment in aphasia and white matter connectivity. Connectometry is a novel diffusion MRI analytic approach that utilizes permutation testing to identify white matter tracts associated with a variable of interest. It has shown greater sensitivity than conventional voxel-based or track-based analysis (Yeh *et al.*, 2016). In applying connectometry to the study of aphasic naming performance, we intended to identify the white matter correlates of lexical-semantic processing, indexed by the SP model parameter s, and phonological processing, indexed by the parameter p. We hypothesized that s would be associated with ventral-stream white matter pathways including the left IFOF, UF, as well as the outer pathway of the AF. We predicted that p would be associated primarily with the inner pathway of the left AF. Testing these predictions in the context of aphasic naming performance will shed valuable new light on the neurocognitive systems that support word production and underlie aphasic word-production impairments.

Materials and methods

Participants

This study was approved by the Institutional Review Boards of the University of Pittsburgh and the VA Pittsburgh Healthcare System. Each participant provided written informed consent to participate and authorization for release and review of relevant medical records for research purposes. All participants had aphasia due to unilateral left hemisphere stroke of >6 months post-onset, spoke English as a first language, had visual acuity sufficient for confrontation naming, and obtained a T-score of at least 32 on the Comprehensive Aphasia Test Recognition Memory Subtest (Swinburn *et al.*, 2004). Medical records and self-reports indicated no history of progressive neurological disease, dementia, or other cognitive impairment unrelated to aphasia, or developmental speech or language disorders unresolved by age 12. At the time of testing, no participants exhibited significant mood or behavioural disorders, dependence on drugs or alcohol, or chronic illnesses that were not stable or medically managed. Participants were excluded if any contraindication to MRI was present. Of 51 participants who passed an initial screening and were enrolled, three were unable to be scanned, one was determined not to have aphasia, one was found to have a right cerebellar lesion, two were found to have a lesion in the right cerebral hemisphere, and two had scan data that were not usable. Of the 42 participants included in the present analyses, nine (21%) were female and 33 (79%) were male. Seven (17%) participants were African American, one (2%) was Native American, and 34 (81%) were White. Two (5%) were left-handed. Participants' years of education ranged from 11 to 26 [mean = 15, standard deviation (SD) = 3.2]. Participants ranged from 31 to 82 years of age (mean = 59.5, SD = 11.7) at time of testing, and testing took place from 6 to 410 months (mean = 88, SD = 83.7) following aphasia onset. The aetiology of aphasia was ischaemic stroke in 28 (85%) cases, ischaemic stroke with haemorrhagic conversion in three (9%), and haemorrhagic stroke in two (6%). Eleven participants (26%) had apraxia of speech according to the diagnostic criteria outlined by McNeil *et al.* (2009).

Power analyses based on data reported by Marchina *et al.* (2011) suggested that a sample of 44 participants would provide power of at least 0.81 to detect the hypothesized relationships between naming behaviour and connectivity in the dorsal and ventral stream tracts of primary interest. Participants were recruited from the VA Pittsburgh Healthcare System Audiology and Speech Pathology clinic and Research Registry, the Western Pennsylvania Participant Registry, and the UPMC Stroke Institute. The present sample of 42 represents all of the eligible participants that the study team was able to identify, recruit, and test between January 2013 and December 2017. The most common reasons that potential participants were excluded from the study prior to enrolment were contraindications to MRI, lack of an aphasia diagnosis, and presence of a brain lesion outside the left hemisphere.

Behavioural data

All participants were administered the Philadelphia Naming Test (PNT; Roach *et al.*, 1996), which consists of 175 line drawings of high familiarity nouns drawn from a variety of

semantic categories. The target names range in length from one to four syllables and in frequency from 1 to 2110 tokens per million (Francis and Kucera, 1982). The PNT was administered and scored according to standardized procedures (http://mrri.org/philadelphia-naming-test/) in which the first complete attempt at naming each item was assigned one of seven categories. Responses were categorized as correct, semantically-related errors, formally- (phonologically) related errors, mixed semantically-and-formally-related errors, unrelated real words, and non-words. The response counts for each participant were fit to the SP model using a web-based application (Walker and Hickok, 2016) that provides estimates of s and p, and as an index of model fit, the root-mean-square difference between the observed and model-predicted response proportions. The s and p parameters take values ranging from 0 to 0.04, with values of 0.04 considered to be indicative of normal function.

Naming responses of 14 participants (33%) were independently scored by a second examiner to evaluate inter-rater reliability. The estimates of s and p obtained by the two raters correlated 0.91 and 0.87, respectively.

All participants were also administered the Comprehensive Aphasia Test (CAT; Swinburn et al., 2004), a general language battery that includes scales measuring naming, repetition, comprehension of spoken and written language, oral reading, and writing. Scores are reported as normalized T-scores (mean = 50, SD = 10) based on a large sample of subjects with aphasia. The average of these six scores was taken as an estimate of overall aphasia severity. The Comprehensive Aphasia Test also includes a semantic memory subtest, which requires participants to match a target picture to one of four semantically associated pictures. We took the score on this subtest as a measure of (pre-lexical) conceptual semantic ability. Complete data on the PNT and Comprehensive Aphasia Test were available for all 42 participants. Participants were also administered a standardized motor speech examination (Duffy, 2013) to assess for the presence of concomitant apraxia of speech. Finally, the three-pictures version of the Pyramids and Palm Trees Test (Howard and Patterson, 1992) was administered to a subset of the participants as a test of conceptual semantic processing ability. Participant data from the PNT, the SP model fits, and the Comprehensive Aphasia Test are summarized in Table 1.

MRI data acquisition and reconstruction

All neuroimaging data were collected at the University of Pittsburgh Medical Center Magnetic Resonance Research Center. The diffusion spectrum imaging (DSI) scans were acquired on a 3 T Siemens Tim Trio scanner using a 257-direction 2D EPI diffusion sequence (echo time = 150 ms, repetition time = 3439 ms, voxel size = 2.4 × 2.4 × 2.4 mm, field of view = 231 × 231 mm, b-max = 7000 s/mm²). The DSI data for nine subjects were collected using a slightly different scanning sequence, with echo time = 152 ms and repetition time = 9616. The diffusion data were reconstructed in the Montreal Neurological Institute (MNI) space using q-space diffeomorphic reconstruction (Yeh and Tseng, 2011). The normalization was done using the anisotropy map of the patients. This approach is more robust against large lesions because it focused only on core white matter. The reconstructed results of each subject were also inspected. We used forceps major and minor as key

anatomical benchmark to confirm the quality. Even in the participant with the largest lesion, the normalization results were still good when the reconstructed results and the goodness-of-fit metric were checked (R^2-value between the subject's anisotropy map and template). A diffusion sampling length ratio of 1.25 was used, and the output resolution was 2 mm. The restricted diffusion was quantified using restricted diffusion imaging (Yeh et al., 2017). The normalized spin distribution function (SDF) values were used in the connectometry analyses. Lesions were manually traced by research team members (M.L.G. and H.C.D. and a research assistant) with training and experience in the procedure. Tracings were done on individual participants' high-resolution T_1-weighted anatomical scans using ITK-SNAP software version 3.6.0 (Yushkevich et al., 2006) and reviewed by M.L.G. Images were then normalized to an age-appropriate template brain with Clinical Toolbox for SPM (Rorden et al., 2012) using enantiomorphic normalization (Nachev et al., 2008) and lesion volumes were calculated for each participant. A lesion overlay map is presented in Fig. 1.

Data analysis

Diffusion MRI connectometry (Yeh et al., 2016) analyses were conducted using DSI Studio (http://dsi-studio.labsolver.org). Two multiple regression models were used to identify local connectomes associated with s and p. Lesion volume was included as a covariate in both analyses. Also, because the DSI data for nine participants were collected using a different scanning protocol, a dummy variable indexing these cases was included as a covariate. Finally, analyses that also included the Comprehensive Aphasia Test semantic memory score or the Pyramids and Palm Trees score as covariates were conducted to evaluate whether controlling for conceptual semantic ability altered the results. The six cases with missing data on the Pyramids and Palm Trees test were excluded from the analysis that included it as a predictor.

Following Dell et al. (2013), the square roots rather than the raw estimates of s and p were analysed. This transformation has the effect of linearizing the relationship between s and p weight estimates and the number of naming errors, making interpretation of structure-behaviour relationships more straightforward. Local connectomes exceeding a t-statistic threshold of two were selected and tracked using a deterministic fibre tracking algorithm (Yeh et al., 2013). A length threshold of 20 voxels was used to identify associated tracks with a density of five tracks per voxel. Bootstrap resampling with 2000 randomized permutations was used to estimate the null distribution of track length and provide false discovery rates.

Once tract outputs were generated, they were subject to qualitative assessment by two expert clinical neuroanatomists (J.F.M. and S.P.) with extensive knowledge of tractographic white matter anatomy. The process for this analysis involved inspection of tracts, removal of fibres likely to have been identified due to statistical noise, and subsequent selection and separation of tracts.

Data availability

Anonymized data reported in this manuscript are available from the corresponding author upon reasonable request and subject to approval by the appropriate regulatory committees and officials.

Table 1 Demographic and clinical characteristics of the participant sample (*n* = 42)

	Mean	Median	SD	Min	Max
Philadelphia Naming Test (count)					
Correct	110.6	127.5	48.0	2	175
Semantic errors	8.9	6	8.9	0	32
Formal errors	6.5	3.5	8.3	0	40
Mixed errors	4.5	4	4.3	0	17
Unrelated errors	4	0.5	12.5	0	78
Non-word errors	20.5	11	24.2	0	109
SP model parameter estimates					
s	0.027	0.028	0.011	0.0001	0.04
p	0.022	0.022	0.008	0.005	0.04
Root-mean-square difference	0.027	0.016	0.031	0.002	0.159
Comprehensive Aphasia Test (T-score)					
Language modality mean	53.1	52.2	6.37	41.8	66.7
Comprehension of spoken language	51.7	52.5	7.6	35	68
Comprehension of written language	52.5	52	6.7	37	65
Repetition	52.6	53	6.9	39	64
Naming	54.4	55	6.9	40	74
Oral reading	52.1	50	8.1	38	71
Writing	54.7	54	7.4	41	69
Semantic memory	57.9	60	4.2	43	60
Pyramids and Palm Trees (correct /52)	48.1	49	3.0	40	52
Lesion volume, mm^3	120 863	109 963	74 432	8094	362 176

Results

Analysis of *s* parameter tracts

As shown in Fig. 2A–C, tracts identified as positively associated [false discovery rate (FDR) = 0.014] with the *s*-weight parameter included portions of the left AF, bilateral cinguli (posterior portions), and splenium of the corpus callosum. In addition, tracts resembling those traversing through the external capsule (namely bilateral IFOF and left UF) were positively associated with *s*-weight, as were fibres travelling via the posterior limb of the internal capsule to the parietal lobule. Fibres resembling the MdLF were also found on the left only. Fibres resembling the right-sided forniceal body were also identified as being positively associated with the *s* metric.

The analysis for *s* also showed several white matter tracts whose connectivity was negatively associated with the parameter (FDR = 0.089) (Fig. 2D–F). These included bilateral cinguli (anterior to the positively associated areas of the same tracts) and anterior (frontal) portions of the external capsule tracts. Likewise, middle-body and posterior-genual corpus callosum fibres were also negatively associated with the *s* parameter. On the left, internal capsular fibres were also negatively associated with *s*; these were distinctly anterior to positively associated internal capsular fibres, travelling to the precentral and frontal cortices. Other negatively associated tracts were the frontal aslant on the left and thalamo-cortical fibres on the right.

When viewed together, posterior and ventral tracts were strongly associated positively with *s*, including the perisylvian AF, posterior external capsule, MdLF, posterior internal capsule, cinguli, corpus callosum and MdLF. In contrast,
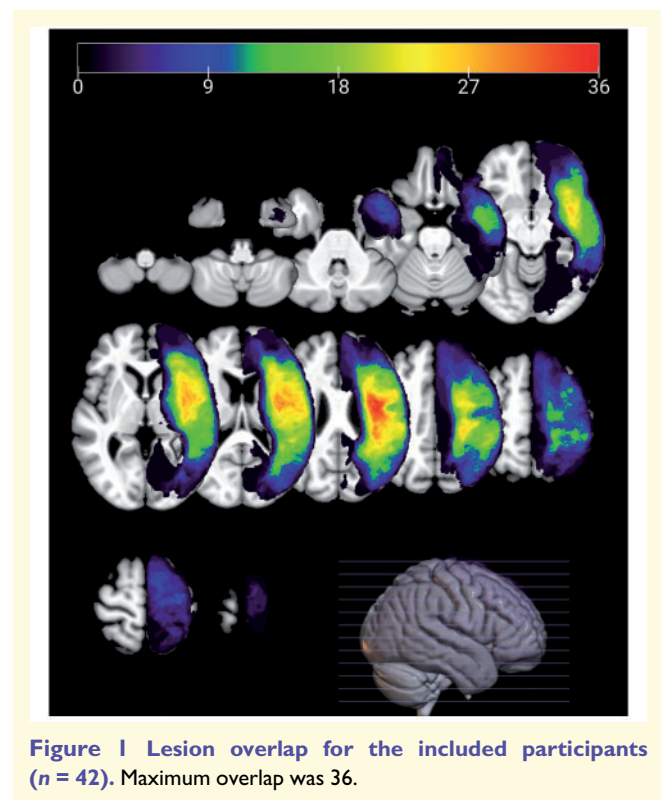

Figure 1 Lesion overlap for the included participants (*n* = 42). Maximum overlap was 36.

anterior tracts were negatively associated with *s*-weight, including the anterior internal capsular fibres, cinguli, external capsule, and corpus callosum. As expected, given the study inclusion criterion of unilateral left-hemisphere stroke, these positive and negative relationships between white
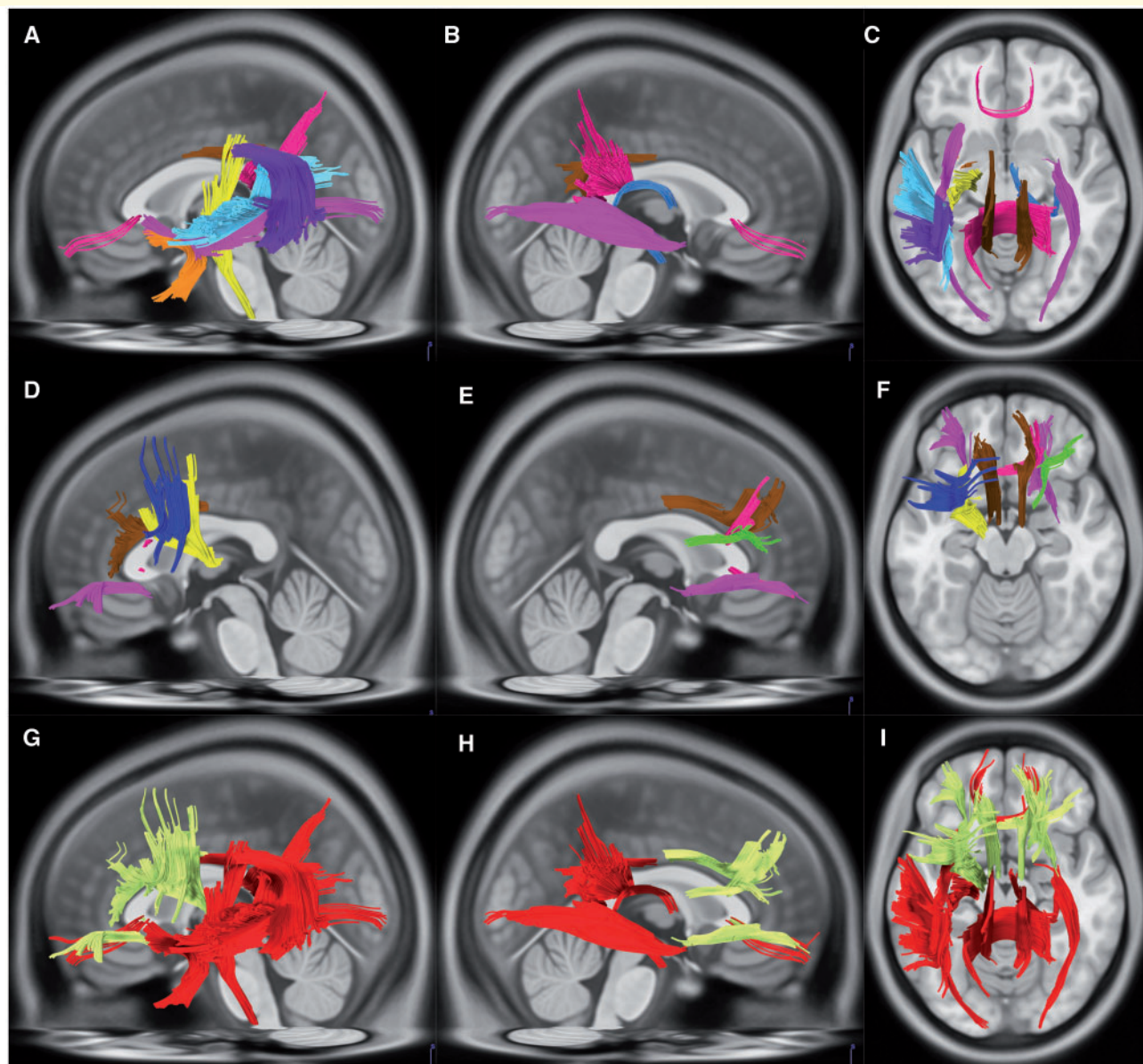
Figure 2 Positively and negatively associated semantic tracts. (**A**–**C**) Positively associated semantic tracts. (**D**–**F**) Negatively associated semantic tracts. (**G**–**I**) Comparison between white matter tracts positively (red) and negatively (light yellow) associated with the s parameter. Positively associated tracts lie more posteriorly and ventrally, while negatively associated tracts lie more dorsally and anteriorly. AF = purple; MdLF = light blue; UF = light orange; IFOF = magenta; internal capsule = yellow; cingulate cortex = pink, cingulum = dark orange; fornix = blue; frontal aslant tract = dark blue; anterior thalamocortical = bright green.

matter tract integrity and s-weight value appeared more prominently in the left than in the right hemisphere (Fig. 2G–I).

Follow-up analyses that included either the Comprehensive Aphasia Test semantic memory subtest or the Pyramids and Palm Trees score as a covariate along with total lesion volume did not materially alter the results.

Analysis of p parameter tracts

For p-weight, tracts identified as positively associated with the parameter (FDR = 0.047) (Fig. 3) included portions of the left AF, MdLF, and fornix. The bilateral cinguli (though a larger portion of the left cingulum) and the splenium segment of the corpus callosum were also positively associated with p. There were no reliable negative associations with the p parameter (FDR = 0.34).

Comparison of s versus p tracts

Positively associated tracts for s and p parameters were separated in an approximately ventral and dorsal arrangement, respectively (Fig. 4A–C). Notably, the AF was associated
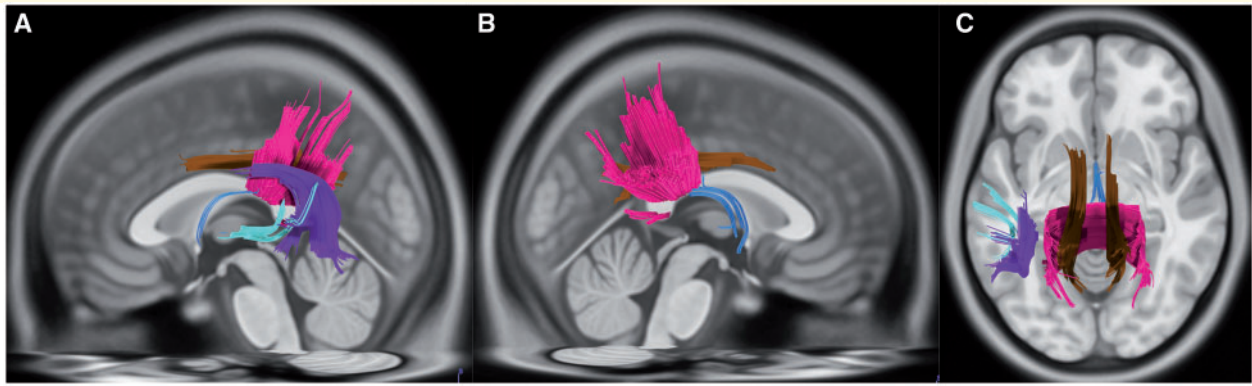
Figure 3 Positively associated phonological tracts. AF = purple; MdLF = bright blue; cingulate cortex = pink; cingulum = light orange; fornix = pale blue.

with both semantic and phonological metrics, as was the MdLF.

Individual tract comparison

The left AF (Fig. 5A) and splenium of the cingulate cortex (Fig. 5B) were notable for being positively associated with both *s* and *p* weights. Though the cingulum was also associated with both semantic and phonological function (Fig. 6A), the *p*-associated cinguli portions were much more anteriorly distributed compared to the *s*-associated portions of the cinguli, the latter lying dorsal to the splenium whereas the former were dorsal to the body of the cingulate cortex. Likewise, although the left MdLF was also associated with both *s* and *p* weight parameters, there were more MdLF fibres associated with *s*-weight versus *p*-weight values (Fig. 6B). In addition, the left-sided ventral external capsule white matter, namely the IFOF and UF tracts, were associated with the semantic function (Fig. 2A). The right temporo-occipital portion of the IFOF was also associated with the semantic measure (Fig. 2B).

Discussion

In this study, we sought to identify white matter pathways associated with distinct stages of word production using diffusion MRI connectometry, using *s* and *p* parameter values from the SP interactive two-step model for each of 42 participants with aphasia due to left-hemisphere stroke. Previous work has provided clear evidence regarding grey matter lesion correlates of semantic and phonological aspects of word-production impairments in aphasia (Dell *et al.*, 2013), consistent with dual-stream neurocognitive models (Hickok and Poeppel, 2007). However, the white matter correlates of dorsal and ventral stream processes remain unresolved (Glasser and Rilling, 2008; Saur *et al.*, 2008; Ueno *et al.*, 2011; Dick and Tremblay, 2012; Roelofs, 2014), as does the effect of damage to these pathways on semantic and phonological aspects of word production.

The *s*-weight parameter was taken as an index of semantic processing, including control processes, semantic representations, and lexical-semantic selection (Dell *et al.*, 2013). The *p*-weight parameter was taken as an index of the ability to select phonological representations, the integrity of the representations themselves, and potentially also aspects of motor speech processing (Dell *et al.*, 2013; Walker and Hickok, 2016). The present approach used the degree of connectivity between adjacent voxels to reconstruct a connectome for each participant (Yeh *et al.*, 2016), in contrast to connectometry methods that map pathways end-to-end between cortical parcels, permitting a more detailed and reliable connectome reconstruction. The connectome matrix for the group of participants was then related to *s* and *p*, controlling for total lesion volume.

The results for *s*-weight were in large part consistent with our predictions: connectivity of the major ventral stream pathways including the left IFOF, MdLF, and UF all demonstrated positive associations with this measure of semantic processing. Considering the functional interpretations of *s*-weight outlined above, and the evidence for a semantic network centred in the ventral anterior temporal lobe and including the inferior frontal gyrus, the posterior middle temporal gyrus, the angular gyrus, and the occipital lobe (Jackson *et al.*, 2016), our present results suggest that all three of these fibre pathways are involved in the construction and control of semantic representations (see Han *et al.*, 2013 for more extended discussion of the roles of the IFOF and UF in particular).

As predicted, based on prior tractography (Catani *et al.*, 2005; Glasser and Rilling, 2008; Fernández-Miranda *et al.*, 2015), connectivity of the temporal segment of the left AF was also positively associated with *s*-weight. The middle portion of the middle temporal gyrus, which is a cortical termination for the AF (Glasser and Rilling, 2008; Fernández-Miranda *et al.*, 2015) has been identified as being involved in lexical-semantic selection (Indefrey and Levelt, 2004). This finding is inconsistent with any neurocognitive account of language function that isolates semantic processing for
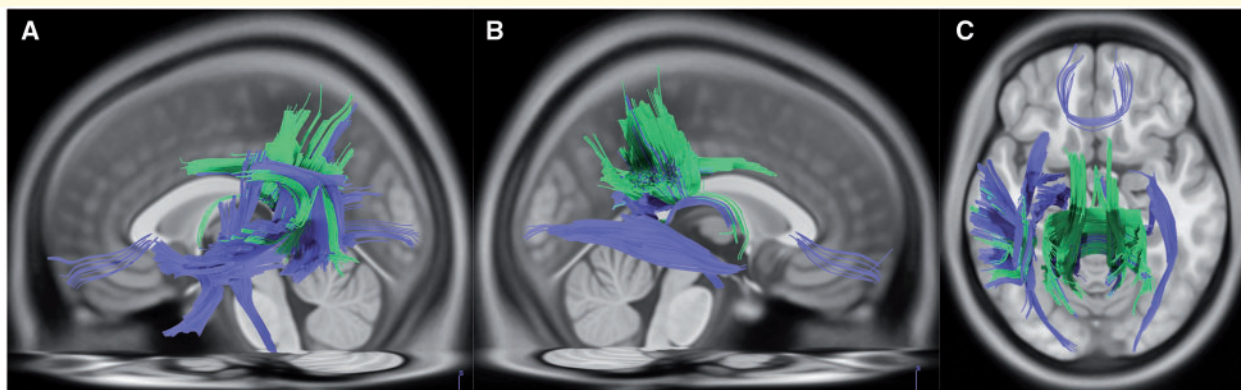
Figure 4 Comparison of semantic and phonological tracts. (**A–C**) Positively associated white matter tracts for *s* (purple) and *p* (green).
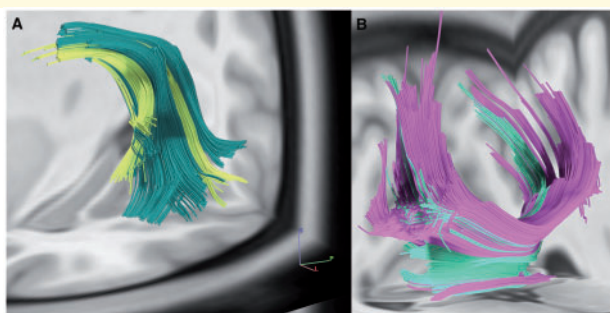

Figure 5 The AF portions associated with the *s* and *p* parameters. (**A**) The AF portions positively associated with *s* (green) and *p* (yellow) parameters. (**B**) The splenium of the corpus callosum portions positively associated with *s* (light green) and *p* (pink) parameters.
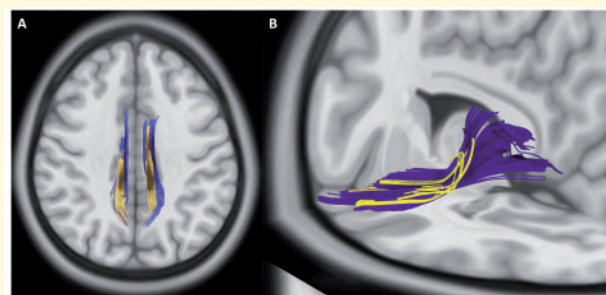

Figure 6 Portions of the splenium associated with the *s* and *p* parameters. (**A**) The cinguli portions positively associated with *s* (orange) and *p* (light purple) parameters. (**B**) The MdLF portions positively associated with *s* (yellow) and *p* (dark purple) parameters.

expression exclusively to the anatomical ventral stream pathways. Although relatively few accounts explicitly claim that semantic processing is uniquely subserved by ventral-stream structures (Duffau *et al.*, 2013), a strong, if not absolute, association between ventral pathways and semantic processes is at least implicitly assumed by many neurocognitive models of processing (Hickok and Poeppel, 2004, 2007; Indefrey and Levelt, 2004; Saur *et al.*, 2010; Ueno *et al.*, 2011; Harvey and Schnur, 2015). The current findings suggest a more prominent role for the left AF in the semantic aspects of conceptually-driven speech production.

Our analysis also found positive associations for parts of the left internal capsule, the posterior portion of the right IFOF, the splenium of the corpus callosum, the posterior cingulum bilaterally, and the right fornix. The demonstration of an association between semantic ability in aphasia and limbic white matter connectivity via the right fornix in particular is novel, and these results will be discussed in more detail below.

As predicted by neuroanatomically specified accounts of the dual-stream model (Glasser and Rilling, 2008; Saur *et al.*, 2008; Ueno *et al.*, 2011; Roelofs, 2014), positive

connectometric associations with *p*-weight included the left AF. The analysis for *p* also identified positive associations with portions of the left MdLF and fornix, the cinguli bilaterally, and the splenium of the corpus callosum. The positive associations between the phonological processing parameter *p* and both left AF and MdLF are also consistent with findings from meta-analyses of functional activation studies of word production (Indefrey and Levelt, 2004; Indefrey, 2011). These analyses have identified the middle and superior temporal gyri as key cortical regions for lexical-phonological access, and given that the AF terminates in both of these areas, and the MdLF in the latter, the present analysis confirms their role in this aspect of word production. In cases when streamlines within a tract showed positive associations with both *s* and *p*, streamlines associated with *p* were generally more anteriorly located (as in the corpus callosum), more dorsally situated (as in the MdLF), or more left-lateralized (as in the cinguli). Notably, the temporal portion of the left AF was positively associated with both *s* and *p*. While this result was consistent with our prediction, the present analysis did not demonstrate the predicted subdivision of the left AF into inner and outer pathways specialized

for phonological and semantic processing, respectively (Glasser and Rilling, 2008; Fernández-Miranda *et al.*, 2015).

These results are consistent with prevailing dual-stream models of language function (Hickok and Poeppel, 2004; Saur *et al.*, 2008), in which ventral networks involving the posterior and anterior temporal lobe and the inferior parietal lobe are active in assigning semantic value to phonological codes and a dorsal network with nodes in the posterior superior temporal lobe, the parietal lobe, and the posterior frontal lobe transforms phonological codes into motor speech commands. In addition to the clear dorsal-ventral arrangement of the tracts associated with *p* and *s*, respectively, predicted by the dual-stream model, *p*-associated tracts were more strongly left-lateralized (Hickok and Poeppel, 2004). Furthermore, the positive associations of *s*-weight with the posterior corpus callosum and the right IFOF point to the involvement of right hemisphere temporo-parieto-occipital regions in semantic processing, consistent with dual-stream model proposals that ventral-stream processing is only weakly left-lateralized (Hickok and Poeppel, 2004, 2007).

Aside from the cingulum, fornix, and corpus callosum, which are discussed below, the MdLF was the only fibre tract to demonstrate positive associations with both *s* and *p*. This tract runs medially to the AF and connects the superior temporal gyrus with the superior parietal lobule (Wang *et al.*, 2013). Our finding is consistent with Saur *et al.* (2008) conclusions that it participates in both dorsal and ventral stream processing. In our results, we observed that MdLF streamlines positively associated with *p* were essentially a subset of those associated with *s* that terminated more rostrally and posteriorly in the superior temporal gyrus. The anterior superior temporal lobe has been implicated in semantic processing, particularly of auditory and verbal stimuli (Visser *et al.*, 2010; Visser and Lambon Ralph, 2011), while the posterior superior temporal gyrus has been associated with phonological and lower level spatiotemporal processing (Buchsbaum *et al.*, 2001; Hickok and Poeppel, 2004).

This study also provides new evidence suggesting that in addition to its role in assigning meaning to phonological input, the ventral stream network also supports semantically-oriented stages of word production. In particular, the positive associations between *s*-weight and the anterior temporal lobe terminations of the UF and MdLF add to the current evidence that this region plays an important role in semantic processing for production (Duffau *et al.*, 2009; Schwartz *et al.*, 2009; Holland and Lambon Ralph, 2010). Despite their failure to confirm the existence of functionally distinct subfascicles of the left AF, the current results also provide new evidence complementing previous tractography studies suggesting that portions of the dorsal stream whose connections run through the left AF may be active in semantic aspects of word production (Glasser and Rilling, 2008; Fernández-Miranda *et al.*, 2015). This dual role of the AF goes against a 'strict' dual stream model (Duffau *et al.*, 2013) that proposes anatomically distinct phonological and semantic pathways (dorsal versus ventral), and favours

models where the AF plays a major role in both phonology and semantics, at least for language production.

The current finding that *s*-weight was positively associated with both dorsal and ventral stream white matter connectivity also informs an important distinction between two current computational neurocognitive models of language, Lichtheim2 (Ueno *et al.*, 2011) and WEAVER++/ARC (Roelofs, 2014). Given that WEAVER++/ARC locates the white matter substrate of semantic processing for spoken output exclusively in the (outer) MTG pathway of the left AF, this result is more consistent with Lichtheim2. Given the lack of any significant role for the left AF in semantically driven word production in the native version of Lichtheim2, this conclusion rests on the model's ability to reorganize in response to damage. Ueno *et al.* (2011) investigation of the model's recovery response demonstrated neuroplastic recruitment of ventral pathways for repetition following a supramarginal gyrus lesion, producing a conduction aphasia-type performance pattern (Ueno *et al.*, 2011). To our knowledge, it has thus far not been investigated whether lesions to Lichtheim2 resulting in large numbers of semantic and unrelated real-word paraphasias [and thus low *s*-weights in the context of Dell *et al.*'s (2013) SP model used in the current investigation] generally results in recruitment of the left AF pathway for spontaneous speech and naming. If confirmed, this novel prediction would significantly extend the empirical scope and coverage of the Lichtheim2 model.

Our results regarding the canonical dorsal and ventral stream pathways are also usefully compared with more recent structural connectivity and lesion-symptom mapping studies. Consistent with our conclusion that the left AF, MdLF, and IFOF all participate in the access and control of semantic representations, one such study demonstrated that dorsal and ventral-stream white matter connectivity between regions including the insula and the angular, superior temporal, middle temporal, and middle occipital gyri was positively associated with the ability to accurately produce verb argument structures, which govern the semantic relationships between nouns and verbs (den Ouden *et al.*, 2019). Another investigation found a negative relationship between left IFOF and UF lesion load and fluency benefit from speech entrainment procedures (Bonilha *et al.*, 2019). Bonilha and colleagues proposed that preservation of ventral-stream pathways supported better auditory comprehension of the entrained speech stimuli (and thus better access to their semantic content) and improved integration of dorsal and ventral-stream functioning.

A third recent study by Xing *et al.* (2018) found, in broad agreement with our present results, that fractional anisotropy of both dorsal and ventral left-hemisphere white matter pathways predicted the total-correct score on the PNT. Also, in agreement with our present results, they found that the integrity of a transcallosal pathway between the superior temporal gyri predicted naming ability. Xing and colleagues also investigated subprocesses of naming, but in contrast to our study, they used independent non-word repetition and picture association (Pyramids and Palm Trees) tasks to test

phonological and semantic processing, respectively. Perhaps unsurprisingly, they found that non-word repetition was predicted only by dorsal stream connectivity, while semantic picture association was predicted only by connectivity of ventral-stream pathways. We suspect that the discrepancy between this finding and our results showing that the left AF also participates in semantic processing can be explained by the fact that picture association is a primarily conceptual and receptive, as opposed to verbal and expressive, task.

A fourth recent investigation of structural connectivity in aphasia (Fridriksson et al., 2018) also included the PNT as part of a larger language assessment. Like Xing et al. (2018), Fridriksson and colleagues found that the overall PNT score was predicted by connectivity both dorsal and ventral stream pathways. They also regressed the number of semantic and phonological paraphasias produced on the PNT, which are the primary determinants of s and p-weight respectively, on their connectivity metric. Their results for semantic paraphasias agreed in large part with our own. Dorsal and ventral stream connectivity between regions in the parietal and frontal lobes and the occipital, parietal, and temporal lobes were predictive of semantic paraphasias. The results for phonological paraphasias were less consistent with our present findings. These analyses revealed only ventral-stream connections between the angular gyrus and the pole of the middle temporal gyrus, the inferior temporal gyrus and the insula, and between the inferior and posterior middle temporal gyri. If Fridriksson et al. (2018) included formal paraphasias in their counts of phonological errors, this might account for the discrepancy. This is because formal paraphasias, which are real words with a phonological relationship to the target, may arise from selection errors at either the lexical or the post-lexical, phonological level. If their phonological paraphasia counts were substantially influenced by lexical selection errors, it could account for the observed relationship with ventral-stream connectivity in the temporal lobe.

The positive associations of s with the posterior cingulum bundle and the right fornix were not specifically predicted. However, they are of significant interest because they are consistent both with other findings in aphasia and with current models of the neural bases of semantic processing. The cingulum streamlines found here appear to be part of the retrosplenial subdivision of the cingulum bundle, whose terminations include posterior cingulate cortex (PCC) and prefrontal cortex (Jones et al., 2013; Bubb et al., 2018). The PCC connection is interesting for two reasons. First, Binder et al. (2009) argued that the PCC functions to link neocortical semantic, perceptual, motor, and affective representations with the hippocampal system, enabling binding of this spatiotemporally distributed activity into unified episodic representations. Binder and colleagues' account focuses on the contribution of neocortical semantic processing to the strength of episodic encoding: connections of neocortical semantic memory representations with the hippocampus support formation of episodic memory traces. This view and our present results are consistent with previous findings of episodic memory deficits in subjects with aphasia, and a correlation between the ability to identify semantic associations between objects (drawing on semantic memory) and subsequent recognition of those same objects (Dalla Barba et al., 1996). Furthermore, findings that patients with frank amnesia due to hippocampal lesions also demonstrate semantic memory deficits (Klooster and Duff, 2015) and that the hippocampus participates in online semantic processing (Piai et al., 2016) suggest that this relationship between the episodic and semantic systems is bi-directional.

Second, the PCC participates in the default mode network (DMN), a resting state functional network defined by task-related decreases in activity (Binder et al., 1999; Buckner et al., 2008). One function of this network, which overlaps substantially with the functional semantic network and is not deactivated by engagement in a semantic decision task, may be to support task-independent retrieval of conceptual knowledge for offline problem-solving or integration of prior experiences (Binder et al., 1999, 2009). In line with our current finding of a relationship between structural connectivity of the PCC and semantic processing ability, prior studies have found reduced DMN connectivity in patients with aphasia (Balaev et al., 2016; Sandberg, 2017), a negative correlation between aphasia severity and DMN connectivity (Sandberg, 2017), and increases in posterior DMN connectivity associated with semantic feature analysis treatment for aphasia (Marcotte et al., 2013).

The current findings also revealed a positive association between the p parameter and the posterior cingulum bundles bilaterally (with leftward bias in the number of streamlines identified) and the left fornix (a major white matter component of the hippocampal system). These results suggest that connections between multimodal neocortical representations and the hippocampal system are also key to lexical-phonological processes, an interpretation supported by psycholinguistic evidence demonstrating that episodic information is encoded and used by the phonological system for both perception and production (Goldinger, 1998; Papesh et al., 2016; Pierrehumbert, 2016). The importance of the hippocampal system for phonological encoding was also suggested by Meinzer et al. (2010) finding that left hippocampal volume and fractional anisotropy of the adjacent white matter predicted the acquisition of treated items, but not generalization to untreated items, in a sample of 10 patients with chronic aphasia due to left hemisphere stroke. Although they found behavioural evidence of generalization, improvement on items not specifically treated was unrelated to the integrity of the hippocampal system. The treatment included a high number of repetitions of each trained item and focused on phonemic and graphemic cueing, and thus promoted binding of the visual stimuli, written forms, and phonological forms, likely mediated through the hippocampal system (Meinzer et al., 2010). Previous work with the same treatment approach also found a correlation between short-term improvement on treated items and increases in blood oxygen level-dependent signal in the hippocampus and cingulate (Menke et al., 2009).

In addition to the positive associations discussed thus far, we found negative associations between semantic abilities and the connectivity of many fibre tracts: individuals with greater white matter damage in these tracts had higher *s*-weight values. It is possible that adaptation to an aphasia-producing left-hemisphere stroke could lead to a situation where decreased connectivity is causally associated with better behavioural function. Such 'Sprague effects' have sometimes been observed in neurologically impaired individuals, for example for visuospatial function (see discussion in Valero-Cabré *et al.*, 2020). However, we prefer an alternative explanation. We believe instead that the negative associations observed in this study are an artefact of the distribution of lesions in our sample, resulting from the inherent asymmetries in how stroke affects different brain regions, reflecting cerebral vasculature (Sperber, 2020). Ischaemic occlusion of superior branches of the middle cerebral artery will result in damage to anterior left-hemisphere regions but leave posterior regions (and associated white matter) relatively intact, and vice versa. This may give rise to the appearance of a negative relationship between anterior structural connectivity and semantic processing. That is, more damage to anterior white matter is associated with better *s* weight in a given sample of stroke survivors, but this association is because more anterior damage is in turn associated with more intact posterior, ventral-stream structure. The positive and negative associations for *s*, shown in Fig. 3, are consistent with this interpretation. The positive associations are, with very few exceptions, situated posteriorly and ventrally to the negative associations. The individuals in our sample with greater anterior/dorsal white matter damage were relatively more likely to have less posterior/ventral white matter damage, which is what is responsible for their higher *s* weight. We believe that this artefact explains the negative *s*-weight associations, rather than any direct or causal link between reduced anterior connectivity and better semantic processing.

Another feature of our results that we attribute to an artefact of our sample is the lack of any positive associations between behavioural function and dorsal fibre pathways within the frontal lobe. This is perhaps most striking in the case of the left AF, where one would expect the connectivity of fronto-parietal portions of the tract to correlate positively with *p* in particular. We attribute this to the fact that the area of greatest lesion overlap was in the posterior inferior frontal lobe, thus reducing statistical power to detect associations in this area. This may also explain the lack of association between behavioural function and the superior longitudinal fascicle, a fibre tract interconnecting the inferior and middle frontal gyri with the inferior parietal lobule, which has been related to speech function particularly in the dominant hemisphere (Wang *et al.*, 2016).

Limitations

The major limitation of this work stems from the fact that we studied a sample composed exclusively of chronic left-hemisphere stroke survivors with aphasia. Because of this, the observed associations between behaviour and structural connectivity may be due to native organization of the brain functions underlying picture naming or to adaption in response to the aphasia-producing lesion. Also, because the observed relationships are conditional on the presence of left-hemisphere stroke and aphasia, the negative correlations between connectivity and behavioural function cannot be interpreted unambiguously, for reasons discussed above. Finally, the high lesion overlap in the posterior inferior frontal lobe limited our power to detect associations with fibre tracts in this region.

Conclusions

The results of this study relating semantic and phonological abilities underlying word production in chronic aphasia to white matter connectivity are broadly consistent with current dual-stream models of language function. They add new evidence supporting the involvement of the AF in semantic processing of conceptually-driven speech, and of the ventral stream pathways in the same. The study also provides new evidence for the role of the hippocampal system and the PCC in both semantic and phonological processing of spoken language.

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Competing interests

The authors report no competing interests

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