



# Damage to white matter bottlenecks contributes to language impairments after left hemispheric stroke



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## ABSTRACT

Damage to the white matter underlying the left posterior temporal lobe leads to deficits in multiple language functions. The posterior temporal white matter may correspond to a bottleneck where both dorsal and ventral language pathways are vulnerable to simultaneous damage. Damage to a second putative white matter bottleneck in the left deep prefrontal white matter involving projections associated with ventral language pathways and thalamo-cortical projections has recently been proposed as a source of semantic deficits after stroke. Here, we first used white matter atlases to identify the previously described white matter bottlenecks in the posterior temporal and deep prefrontal white matter. We then assessed the effects of damage to each region on measures of verbal fluency, picture naming, and auditory semantic decision-making in 43 chronic left hemispheric stroke patients. Damage to the posterior temporal bottleneck predicted deficits on all tasks, while damage to the anterior bottleneck only significantly predicted deficits in verbal fluency. Importantly, the effects of damage to the bottleneck regions were not attributable to lesion volume, lesion loads on the tracts traversing the bottlenecks, or damage to nearby cortical language areas. Multivariate lesion-symptom mapping revealed additional lesion predictors of deficits. Post-hoc fiber tracking of the peak white matter lesion predictors using a publicly available tractography atlas revealed evidence consistent with the results of the bottleneck analyses. Together, our results provide support for the proposal that spatially specific white matter damage affecting bottleneck regions, particularly in the posterior temporal lobe, contributes to chronic language deficits after left hemispheric stroke. This may reflect the simultaneous disruption of signaling in dorsal and ventral language processing streams.

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## 1. Introduction

Damage to long-range white matter (WM) pathways likely contributes substantially to language deficits after left hemisphere stroke. Damage to the WM underlying the left posterior superior and middle temporal gyri (pSTG and pMTG) has been consistently implicated as a source of deficits in multiple language domains including comprehension (Dronkers et al., 2004; Geva et al., 2012; Henseler et al., 2014; Pustina et al., 2016; Yourganov et al., 2016), naming (Baldo et al., 2013; Harvey and Schnur, 2015; Henseler et al., 2014; Pustina et al., 2016; Yourganov et al., 2016), repetition (Butler et al., 2014; Henseler et al., 2014; Pustina et al., 2016; Yourganov et al., 2016), and phonology (Butler et al., 2014). The presence of lesions affecting the posterior temporal WM and disrupting posterior temporal connectivity also predicts

poor responses to language therapies (Bonilha et al., 2015; Fridriksson, 2010).

Why might damage to the WM in this area have such broadly negative impacts on language outcomes? Portions of the WM under the pSTG/pMTG contain projections associated with multiple long-range fiber pathways (Turken and Dronkers, 2011), including dorsal (sensori-motor) and ventral (associative) language pathways (Kümmerer et al., 2013; Saur et al., 2008). Fibers associated with at least three language-relevant tracts traverse this region – the arcuate fasciculus (AF – dorsal stream), inferior longitudinal fasciculus (ILF – ventral stream), and inferior fronto-occipital fasciculus (IFOF – ventral stream) (Catani and Mesulam, 2008; Turken and Dronkers, 2011). Thus, it has been proposed that the WM in this area corresponds to a structural weak point, or “bottleneck”, where multiple language-relevant pathways are vulnerable to simultaneous disruption by focal damage (Turken and Dronkers, 2011). The observation that fibers associated with the anterior thalamic radiations (ATR – thalamo-cortical), uncinate fasciculus (UF – ventral stream), and inferior fronto-occipital fasciculus (IFOF – ventral stream) form a bottleneck in the prefrontal WM near areas where damage is associated with chronic deficits in semantic recognition supports the proposal that damage to bottleneck regions may

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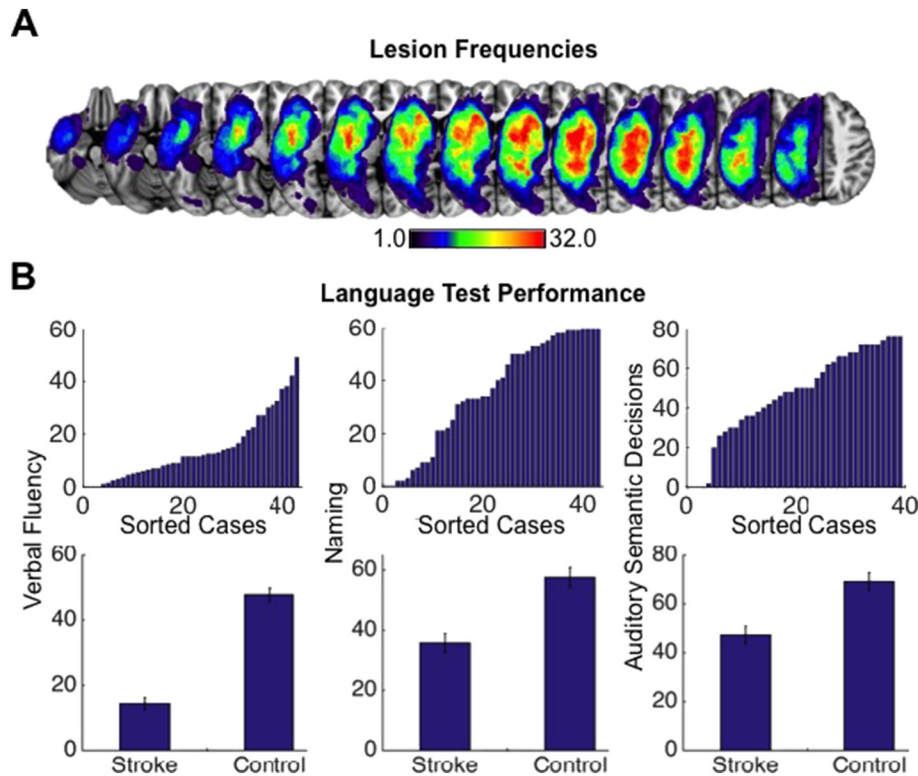
play a role in chronic language deficits after stroke (Mirman et al., 2015a). Indeed, this proposal is in accord with recent evidence suggesting that lesions affecting areas of high tract overlap are associated with post-stroke deficits in multiple cognitive domains (Corbetta et al., 2015).

However, the conclusions that can be drawn from previous studies linking bottleneck lesions to language deficits are limited because the bottleneck regions were identified as part of *post-hoc* exploratory analyses based on the results of voxel-wise lesion-symptom mapping (Dronkers et al., 2004; Mirman et al., 2015a; Turken and Dronkers, 2011). The effects of damage to *a priori* identified bottlenecks in these regions on language outcomes have not been investigated. We aimed to bridge this gap by characterizing how deficits in measures of verbal fluency, picture naming, and auditory semantic processing relate to lesions affecting the bottleneck regions described by previous reports. We expected that damage to the bottleneck underlying the left pSTG/pMTG would be associated with chronic impairments on all language measures, as broad deficits would be expected to follow the simultaneous disruption of both ventral and dorsal language streams. Based on the report by Mirman et al. (2015a), we expected that damage to the prefrontal bottleneck might be associated with deficits in picture naming and category judgments, which could influence performance on the other tasks. To enable stronger conclusions about our specific findings, we demonstrate that the effects of damage to these bottleneck regions are not attributable to lesion loads on the tracts traversing them or to concomitant cortical damage. In a second analysis using a data-driven approach, we thoroughly characterize the lesion-deficit relationships in these patients using multivariate lesion-symptom mapping with lesion volume control (Zhang et al., 2014). Exploratory fiber tracking was also performed to further characterize potential lesion effects on inter-regional connections.

## 2. Methods

### 2.1. Participants

All procedures were approved by the Institutional Review Boards of the participating institutions and performed in accordance with Declaration of Helsinki ethics principles and principles of informed consent. Data were collected from 43 patients with chronic left hemispheric stroke participating in different studies by our laboratory. Patients were excluded if they had diagnoses of degenerative/metabolic disorders, diagnoses of severe depression or other psychiatric disorders, were pregnant, were not fluent in English, or had any contraindication to MRI/fMRI. All patients had a single left hemispheric stroke and received a clinical diagnosis of aphasia following the initial insult, which occurred at least 1 year prior to data collection. Current scores on clinical aphasia measures (i.e. WAB/BDAE) were not available for all patients, but some patients were likely not aphasic at the time of data collection as indicated by their performance on the language tasks (i.e. some patients performed at levels comparable to healthy controls; see Fig. 1). This sample, which features patients with varying degrees of impairment, is well-suited for the lesion-behavior analyses employed in this study. No patients had right hemispheric stroke. The mean patient age was 53 (SD = 15; range = 23–90), 25 patients were male, and the mean pre-stroke handedness as determined by the Edinburgh Handedness Inventory (Oldfield, 1971) was 0.85 (SD = 0.43; range = –1.0–1.0). Data on educational background were not available for these patients. Behavioral data collected from a group of 43 age/sex/handedness-matched healthy controls were included as a reference. The mean control age was 54 (SD = 15; range = 19–74), 23 controls were male, and the mean control EHI was 0.80 (SD = 0.41; range = –0.9–1.0). A detailed



**Fig. 1.** Characterization of lesion and language test data. **A.** Lesion frequency overlaps are shown on axial slices from a template brain. Color bar values range from 1 to 32, and indicate the number of patients with lesions at each voxel. **B.** Plots on the top row show sorted scores (from low to high) for the Verbal Fluency (left), Naming (middle), and Auditory Semantic Decision (right) from the stroke patients. Bar graphs on the bottom row show mean scores for stroke patients and for 43 age/sex/handedness-matched healthy controls (error bars indicate standard error of the mean).

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