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Stroke 2011, 42:2251-2256: originally published online June 30, 2011
doi: 10.1161/STROKEAHA.110.606103

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Impairment of Speech Production Predicted by Lesion Load of the Left Arcuate Fasciculus

Sarah Marchina, PhD*; Lin L. Zhu, BA*; Andrea Norton, BM; Lauryn Zipse, PhD; Catherine Y. Wan, PhD; Gottfried Schlaug, MD, PhD

Background and Purpose—Previous studies have suggested that patients’ potential for poststroke language recovery is related to lesion size; however, lesion location may also be of importance, particularly when fiber tracts that are critical to the sensorimotor mapping of sounds for articulation (eg, the arcuate fasciculus) have been damaged. In this study, we tested the hypothesis that lesion loads of the arcuate fasciculus (ie, volume of arcuate fasciculus that is affected by a patient’s lesion) and of 2 other tracts involved in language processing (the extreme capsule and the uncinate fasciculus) are inversely related to the severity of speech production impairments in patients with stroke with aphasia.

Methods—Thirty patients with chronic stroke with residual impairments in speech production underwent high-resolution anatomic MRI and a battery of cognitive and language tests. Impairment was assessed using 3 functional measures of spontaneous speech (eg, rate, informativeness, and overall efficiency) as well as naming ability. To quantitatively analyze the relationship between impairment scores and lesion load along the 3 fiber tracts, we calculated tract–lesion overlap volumes for each patient using probabilistic maps of the tracts derived from diffusion tensor images of 10 age-matched healthy subjects.

Results—Regression analyses showed that arcuate fasciculus lesion load, but not extreme capsule or uncinate fasciculus lesion load or overall lesion size, significantly predicted rate, informativeness, and overall efficiency of speech as well as naming ability.

Conclusions—A new variable, arcuate fasciculus lesion load, complements established voxel-based lesion mapping techniques and, in the future, may potentially be used to estimate impairment and recovery potential after stroke and refine inclusion criteria for experimental rehabilitation programs. (Stroke. 2011;42:2251-2256.)

Key Words: aphasia ■ brain imaging ■ brain infarction ■ brain recovery ■ Broca’s aphasia ■ diffusion tensor imaging ■ diffusion-weighted imaging ■ functional recovery ■ speech disorders ■ speech therapy ■ stroke recovery ■ voxel-based lesion mapping ■ non fluent aphasia

Aphasia is a devastating complication of stroke that is characterized by an impairment in or loss of verbal communication ability. Although researchers have long attempted to identify the major predictors of recovery from this condition, it remains difficult for clinicians to make accurate prognoses regarding speech and language deficits after stroke. In particular, the extent to which lesion size affects speech production remains unclear. Although some researchers have reported lesion size to be a significant determinant of fluency after stroke, others have found no significant differences in lesion size between patients who recover fully and those who do not. Indeed, recent study found no significant correlations between lesion size and severity of initial impairment or performance at 90 days. Furthermore, a regression model combining age, lesion size, and severity of initial impairment, although statistically significant, predicted <30% of the variance in speech outcome at 90 days.

In their efforts to delineate the relationship between lesion size/location and degree of impairment, several recent studies have used voxel-based lesion–symptom mapping techniques to investigate the anatomic correlates of aphasia. Some of these studies have suggested that the degree of white matter involvement plays a role in language deficits and recovery; however, the extent to which aphasia severity and recovery potential are affected by specific white matter damage—for example, the involvement of language-related fiber tracts—has not been assessed.

In this study, we examined 3 major language tracts previously identified by researchers: the arcuate fasciculus (AF), uncinate fasciculus (UF), and extreme capsule (EmC). The
AF connects the superior and middle temporal gyri with the posterior inferior frontal lobe. Recent studies have suggested that the AF may be primarily involved in the mapping of sounds to articulation. In contrast, the UF and the EmC, which connect the temporal lobe to more anterior portions of the inferior frontal gyrus, are thought to be more involved in the mapping of sounds to meaning. Thus, the aim of our study was to quantitatively examine the relationship between lesion size and location—as measured by extent of damage to these 3 language tracts—and impairment of fluent speech production. Speech fluency—a multidimensional parameter of speech production that encompasses various elements such as speech rate, phrase length, pauses, articulatory struggle and accuracy, prosody, syntactic structure, and so on—is notoriously difficult to measure and lacks a widely accepted standard measure. In the absence of such an assessment tool, we chose to evaluate fluency using 3 functional measures of conversational speech; this is in contrast to using clinical measures of speech production, which do not necessarily capture all aspects of speech and language that may be of importance to the patient or for recovery.

Accordingly, we overlaid lesion maps of 30 patients with chronic stroke and with probabilistic maps of the AF, UF, and EmC derived from diffusion tensor images of healthy, age-matched subjects. Lesion loads (ie, volume of tract affected by a patient’s lesion) of these tracts were then calculated and related to 3 functional measures of speech production: words per minute (WPM), number of correct information units (CIUs) per total words uttered (%CIUs), and CIUs per minute. WPM reflects the rate of speech but includes uninformative “filler” words, circumlocutions, and incorrect words. A high WPM score therefore requires relatively intact articulatory abilities but does not necessarily require accurate retrieval of phonological word forms. Percent CIUs measures the informativeness of speech. This measure relies on retrieval of correct phonological word forms; semantic-to-phonological connections must be relatively intact in order for %CIUs to be high. CIUs/min measures the efficiency of speech; a high score on this measure requires both adequate articulatory abilities and good retrieval of phonological word forms. In keeping with our interpretation of these 3 fluency measures, we hypothesized that lesion load would be a better predictor of impairment than lesion size alone and, furthermore, that AF lesion load would predict WPM, whereas UF and EmC lesion load would predict %CIUs.

### Methods

#### Subjects

The study group consisted of 30 right-handed patients, all of whom had left-hemispheric strokes in the middle cerebral artery territory and were at least 11 months post stroke at the time of testing (6 females and 24 males; mean age 58.5 years [SD 10.0]; mean time poststroke 35.0 months [SD 28.7]). Although all patients had been diagnosed with severe nonfluent aphasia in the acute/subacute phase (based on assessments conducted during the initial hospitalization period), they had recovered to varying degrees at the time of study enrollment (see Supplemental Table I for details on patients; http://stroke.ahajournals.org). Exclusion criteria included bifrontal or frontoparietal infarcts, primary intracerebral hemorrhages, previous or subsequent strokes, concomitant neurological diseases/disorders, and other aphasic syndromes such as pure anoma

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### Table. Patient Data and Normative Values

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Normative values:

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RCPM indicates Raven’s Colored Progressive Matrices; WPM, words per min; CIUs, correct information units; BNT, Boston Naming Test; BDAE, Boston Diagnostic Aphasia Evaluation; SD, standard deviation.

### Behavioral Assessments

Spontaneous speech was elicited using conversational interviews regarding biographical data, medical history, daily activities, descriptions of complex pictures (eg, the Cookie Theft picture from the Boston Diagnostic Aphasia Examination), and descriptions of simple routine procedures (eg, “Explain how you would make a peanut butter sandwich, cook a favorite dish, work on a hobby, do a simple repair”). Videotapes of patient assessments were transcribed, timed, and scored by blinded coders with backgrounds in communication disorders and speech language pathology.

Because there is no standard definition for fluency and, as a result, no widely accepted means of assessing spontaneous speech, we chose to evaluate speech production by using 3 measures of functional relevance: WPM (rate of speech), percent CIUs of total words uttered (informativeness), and CIUs per minute (overall efficiency of speech). To be counted as CIUs, words had to be intelligible in context as well as accurate, relevant, and informative with respect to the stimulus; meaningless utterances, exclamations, inappropriate information, and perseverations were counted as words but not as CIUs. Intraobserver reliability as well as interobserver (2 coders) reliability for these 3 items was >0.9.

In addition to assessing spontaneous speech, we also evaluated each patient’s naming ability using an untimed version of the Boston Naming Test. Patients were given a full point (1.0) for items they could name unassisted, 0.5 points for items named with help of a semantic or phonemic cue, and 0.25 points for items they could identify by choosing the correct written word (from a set of 4 words presented in conjunction with the picture stimulus).
acquired and spatially normalized into images of isotropic voxel size (2×2×2 mm³) using SPM5 (Wellcome Department of Neurology, London, UK) implemented in Matlab (The Mathworks Inc, Natick, MA). For patients with extensive lesions, masks were drawn in MRicro22 to exclude the lesion from the cost function calculation of the spatial normalization process.22

The control subjects underwent diffusion tensor imaging using a single-shot, spin-echo echoplanar imaging sequence with the following parameters: TR=10 seconds; TE=86.9 ms; resolution 2.6×2.6×2.6 mm³; 30 noncollinear diffusion directions with a b-value of 1000 s/mm²; and 6 acquisitions with a value of 0 s/mm². A total of 56 slices covered the entire brain, including the brain stem.

Postprocessing of diffusion tensor imaging images and fiber-tracking were done as detailed in Zhu et al.23 For the AF, a curved fiber bundle that connects the posterior portion of the temporoparietal junction with the frontal cortex,24 we drew 1 region of interest on the Fractional Anisotropy (FA) map in the white matter underlying the pars opercularis of the posterior inferior frontal gyrus.

The UF is a hook-shaped fiber bundle that links the anterior portion of the temporal lobe with the orbital and inferior frontal gyri.25,26 To reconstruct this tract, we drew coronal regions of interest in the anterior region of the corona radiata (y=-37), the anterior part of the temporal lobe where the UF adjoins the inferior fronto-occipito fasciculus,26,27 and in the white matter underlying the pars opercularis of the posterior inferior frontal gyrus.

Lesion Load Calculation

The reconstructed fiber tracts of the control subjects were transformed into binary images and then spatially normalized using SPM5. Overlaps between lesions and fiber tracts were calculated using the previously described raw lesion load method.23 In brief, the binary fiber tracts of the 10 healthy control subjects were summed to generate a fiber map using Matlab (Figure 1). Voxel intensities ranged from I=0 (ie, voxel is not part of the tract in any of the subjects) to I=10 (ie, voxel is part of the tract in all 10 subjects); thus, the probability that a particular voxel would be part of the tract was calculated as one tenth of the voxel’s intensity. For each lesion, a raw lesion–tract overlap volume (Vraw) was calculated by overlaying the lesion map onto the probabilistic fiber tract and summing the intensities of all intersecting voxels. This calculation is denoted by the equation

\[
V_{raw} = \sum_{i=1}^{n_{max}} \left[ \frac{1}{10} \cdot I(i) \cdot \text{(voxel volume)} \right],
\]

where \(n_{max}\) is the total number of intersecting voxels between the lesion map and fiber map and \(I(i)\) is the intensity of the \(i^{th}\) voxel (as represented in the fiber map).

Results

Rate of Speech

A regression analysis was first conducted using lesion size and lesion loads of all 3 tracts (ie, AF, EmC, and UF) as predictors of words/min (adjusted \(R^2=0.301, P=0.011\)). AF lesion load proved to be the best variable (partial \(R^2=0.175, P=0.030\); Figure 2A), whereas EmC lesion load (partial \(R^2=0.087, P=0.135\), UF lesion load (partial \(R^2=0.098, P=0.112\), and lesion size (partial \(R^2=0.002, P=0.829\) were shown to be nonsignificant predictors.

Informativeness of Speech

A second regression analysis was conducted using the same 4 variables to predict %CIUs (adjusted \(R^2=0.496, P<0.001\)). Again, AF lesion load was shown to be a significant predictor (partial \(R^2=0.336, P=0.002\); Figure 2B), whereas EmC lesion load (partial \(R^2=0.052, P=0.520\), UF lesion load (partial \(R^2=0.058, P=0.227\), and lesion size (partial \(R^2=0.002, P=0.844\) were nonsignificant.

Overall Efficiency of Speech

A third regression analysis was conducted using lesion size as well as AF, EmC, and UF lesion loads as predictors of

Lesion Mapping

We used MRicro to define each patient’s chronic lesion in the spatially normalized T1-weighted images while referring to the coregistered fluid-attenuated inversion recovery images for additional guidance. In some cases, we found marked ventricular dilatation due to extensive ischemic lesions and subsequent hemispheric atrophy. However, no part of the dilated ventricle was included in the lesion area. Lesions were drawn by a single rater who was blind to the patients’ fluency/behavioral scores. A second rater, also naïve to the patients’ speech impairment scores, drew lesions in a subset of 10 patients to calculate an interobserver reliability, which was 0.93 for lesion volume.
CIUs/min (adjusted $R^2=0.610$, $P<0.001$). Once again, AF lesion load proved to be a significant predictor (partial $R^2=0.450$, $P<0.001$; Figure 2C), whereas EmC lesion load (partial $R^2=0.086$, $P=0.138$), UF lesion load (partial $R^2=0.106$, $P=0.100$), and lesion size (partial $R^2=0.034$, $P=0.358$) remained nonsignificant.

**Discussion**

AF lesion load, but not EmC or UF lesion load, significantly predicted rate, informativeness, and overall efficiency of speech in patients with impairments of speech production after stroke. Lesion size, despite showing a substantial correlation with these lesion load measures, was shown not to be a significant predictor of speech production after stroke (Figure 3).

Our results are in accordance with previous lesion–behavior mapping studies indicating a critical role for white matter tracts in the production of fluent speech. In 1 such study, CT images of 27 chronic patients were used to rate extent of lesion damage within specific regions on a scale from 0 (no lesion) to 5 (entire area has lesion). Although severity of impairment was not predicted by the amount of lesion damage in any single area, the authors did report that extent of lesion within 2 subcortical regions (the subcallosal fasciculus and the middle third of the periventricular white matter) could, when used together, discriminate severely affected patients from mildly affected patients. It should be noted that the periventricular white matter contains fibers of the arcuate fasciculus, which we have examined in this study and associated with speech production. More recently, lesion–behavior mapping techniques have been used on a voxel-by-voxel basis to implicate white matter tracts in the production of fluent speech. In particular, studies have suggested involvement of the arcuate/superior longitudinal fasciculus to be related to impaired performance on the fluency subtest of the Western Aphasia Battery and decreased word production during conversational interviews; however, the voxel-based lesion–symptom mapping method used in these studies does not allow differentiation between white and gray matter damage and their relation to speech impairment.
Despite the emergence of diffusion tensor imaging as a means of tracing white matter tracts in vivo and, as a result, a growing body of evidence for the importance of fiber tract integrity in fluent speech production,30–32 very few researchers have investigated the predictive value of lesion size and location with respect to major fiber tracts. Several studies have related speech and language impairment after stroke to the extent of lesion damage within specific cortical and subcortical structures30,33–35; however, the aforementioned study by Naeser and colleagues29 remains the only 1 that has examined the relationship between white matter damage and impairment of speech production. In contrast to the qualitative nature of their investigation, our study is the first to quantitatively relate the extent of lesion damage within white matter tracts to verbal fluency.

Our results are of particular interest when considered in light of the dual-stream framework of auditory language processing originally proposed by Hickok and Poeppel.36 In this dual-stream model, the dorsal stream, which is thought to be serviced by the AF, is responsible for the mapping of sound onto articulatory-based representations, whereas the ventral stream, which includes the UF and EmC, is involved in the mapping of sound onto meaning.11–13,36–38 According to this model, speech rate should be more related to AF lesion load, whereas measures of semantic processing and function (eg, informativeness of content) should be more related to UF and/or EmC lesion load. However, we found that all 3 of our measures were predicted by AF lesion load, but neither EmC nor UF lesion load.

Possible explanations might be that our measures do not purely reflect 1 neural circuit or the other (eg, WPM relies in part on retrieval of phonological word forms, although not as heavily as %CIUs does). As a result, all of the behavioral measures may correlate most strongly with damage to the most vulnerable tract of the 3 we considered. This tract is likely the AF. Furthermore, as was suggested by Hickock and Poeppel,39 the dorsal stream (ie, the AF) is more strongly left lateralized than the ventral stream and does not have the same degree of bihemispheric redundancy as the ventral stream. Finally, the AF mainly runs dorsal to the sylvian fissure, which is supplied by the superior division of the middle cerebral artery, and the region of the brain supplied by the superior division of the middle cerebral artery is the area most frequently affected by a stroke. Regardless of the explanation, our results highlight the critical role played by the AF in the feed-forward and feedback loops for the efficient mapping of articulatory-based representations onto phonemic representations.40

![Lesion–diffusion tensor imaging fiber tract overlap](http://stroke.ahajournals.org/)

**Figure 3.** Lesion–diffusion tensor imaging fiber tract overlap. Shown here are examples of 3 patients’ behavioral scores, lesion sizes, and AF lesion loads as well as their individual lesion maps (depicted in blue) overlaid onto the probabilistic AF map (depicted in red). Overlap between lesion and AF is displayed in purple. The axial slices depicted correspond to z = −10, −2, 8, 18, 26, 34, and 42 in Talairach space. Comparison of Patients A and B shows how 2 patients can display comparable AF lesion loads and behavioral scores despite drastically different overall lesion volumes. Similarly, comparison of Patients B and C shows how a similar lesion size can produce 2 markedly different AF lesion loads and, accordingly, result in very different levels of impairment. AF indicates arcuate fasciculus.
results are in accordance with those of a recent study, in which stimulation and resection of the UF in epileptic patients did not produce any deficits in performance on the naming subtest of the Boston Diagnostic Aphasia Examination.

In the future, automation of AF lesion load calculations may allow physicians and researchers to make more accurate prognoses regarding impairment of speech production after stroke and recovery potential, possibly even in the subacute stroke phase, and thus, identify optimal interventions for patients based on their lesion–behavior profiles.

Sources of Funding
This work was supported by grants from the National Institutes of Health (1RO1 DC008796, 3RO1 DC008796-02S1 ARRA), the Rosalyn and Richard Sfikas Family Foundation and the Matina R. Proctor Foundation.

Disclosures
None.

References
Supplementary Table: All biographical, language testing, lesion volume, and lesion load data.

Abbreviations: G=Gender; Mo_P = Months post stroke; Age_T = age at testing; RCPM = Raven’s Coloured Progressive Matrices Test (24 items, performance expressed as % correct of all); WPM = words per minute; %CIU = percent CIUs; CIU/m = CIUs per minute; BNT = Boston Naming Test (60 items, performance expressed as % correct of all); BDAE_R = Repetition subtest of the BDAE (max performance=10); Les_V = Lesion volume in cc; AF_Vol = AF lesion load in cc; %AF = AF lesion load in %; EMC_V = EMC lesion load in cc; %EMC = EMC lesion load in %; UF_V = UF lesion load in cc; %UF = UF lesion load in %. Med=median, Mea=mean, SD=standard deviation.
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