Damage to the anterior arcuate fasciculus predicts non-fluent speech production in aphasia

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Non-fluent aphasia implies a relatively straightforward neurological condition characterized by limited speech output. However, it is an umbrella term for different underlying impairments affecting speech production. Several studies have sought the critical lesion location that gives rise to non-fluent aphasia. The results have been mixed but typically implicate anterior cortical regions such as Broca’s area, the left anterior insula, and deep white matter regions. To provide a clearer picture of cortical damage in non-fluent aphasia, the current study examined brain damage that negatively influences speech fluency in patients with aphasia. It controlled for some basic speech and language comprehension factors in order to better isolate the contribution of different mechanisms to fluency, or its lack. Cortical damage was related to overall speech fluency, as estimated by clinical judgements using the Western Aphasia Battery speech fluency scale, diadochokinetic rate, rudimentary auditory language comprehension, and executive functioning (scores on a matrix reasoning test) in 64 patients with chronic left hemisphere stroke. A region of interest analysis that included brain regions typically implicated in speech and language processing revealed that non-fluency in aphasia is primarily predicted by damage to the anterior segment of the left arcuate fasciculus. An improved prediction model also included the left uncinate fasciculus, a white matter tract connecting the middle and anterior temporal lobe with frontal lobe regions, including the pars triangularis. Models that controlled for diadochokinetic rate, picture-word recognition, or executive functioning also revealed a strong relationship between anterior segment involvement and speech fluency. Whole brain analyses corroborated the findings from the region of interest analyses. An additional exploratory analysis revealed that involvement of the uncinate fasciculus adjudicated between Broca’s and global aphasia, the two most common kinds of non-fluent aphasia. In summary, the current results suggest that the anterior segment of the left arcuate fasciculus, a white matter tract that lies deep to posterior portions of Broca’s area and the sensory-motor cortex, is a robust predictor of impaired speech fluency in aphasic patients, even when motor speech, lexical processing, and executive functioning are included as co-factors. Simply put, damage to those regions results in non-fluent aphasic speech; when they are undamaged, fluent aphasias result.

Keywords: aphasia; speech production; non-fluent speech; arcuate fasciculus; uncinate fasciculus
Abbreviations: ASAF = anterior segment of the arcuate fasciculus; VLSM = voxel-based lesion-symptom mapping; WAB = Western Aphasia Battery
Introduction

Among the most basic distinctions to be found in the aphasia literature is that between fluent and non-fluent speech production. As defined by Albert et al. (1981), non-fluent speech is:

‘...laboriously produced, with abnormal speech rhythm and melody, poor articulation, shortened phrase length, and preferential use of substantive words (such as nouns and main verbs) rather than the grammatical words (such as conjunctions and auxiliary verbs). Non fluent speech, often called telegraphic or agrammatic is frequently associated with anterior lesions.’

In contrast, these authors define fluent aphasic speech as being produced: ‘...at a normal or hypernormal phrase length. When fluent speech is part of a dysphasic syndrome, the lesion is usually located posteriorly in the cerebral hemisphere.’

The fluent/non-fluent distinction in speech production has been a common one since the pioneering work of Broca and Wernicke and their followers in the mid to late 1800s. Although definitions may be unclearly operationalized, and speech and language processes are often conflated, it is a practical distinction, and is still used in most contemporary tests for aphasia, such as the Western Aphasia Battery (WAB; Kertesz, 1982) or the Boston Diagnostic Aphasia Examination (Goodglass et al., 2000).

This practice is not without problems and several well-justified critiques have been posed (McNeil, 1982; Schwartz, 1984; Poeck, 1989). Many patients fall somewhere in the middle and cannot be clearly classified as being either fluent or non-fluent. Moreover, there is no consensus regarding how speech fluency should be qualified (or quantified) and there are several speech characteristics, and combinations thereof, by which speech non-fluency could be defined, including typical utterance length, articulatory agility, disturbed prosody, and difficulty in initiating speech.

One of the reasons for classifying aphasic patients based on similar speech or language impairments results from the assumption that similar language impairments result from similar underlying patterns of brain damage. In regard to non-fluent speech, several studies have attempted to identify a common lesion location. Broca (1861) famously demonstrated the first well-known assumption of this kind in his patient, Leborgne, who had an impairment of speech production, and at autopsy was shown to have incurred damage to the left inferior frontal gyrus, insula, parietal lobe and the white matter at the anterior horn of the lateral ventricle. Although it is far from clear whether Leborgne actually had Broca’s aphasia (Code, 2013), later descriptions would often refer to the lesion location that causes Broca’s aphasia as involving Broca’s area (Hills et al., 2004; Ochfeld et al., 2010).

In contrast, in a study that included multiple case examinations, Mohr et al. (1978) revealed that patients whose cortical damage was mostly confined to Broca’s area did not present with chronic Broca’s aphasia. Based on visual inspection of CT images of stroke patients, Naeser et al. (1989) concluded that the brain damage that was most consistent across patients with non-fluent aphasia involved anterior white matter structures in the left hemisphere, especially the subcallosal fasciculus and approximately one-third of the left peri-ventricular white matter. Bates et al. (2003) found that poor speech fluency, as measured using the WAB, is associated with damage to the left anterior insula and surrounding structures. This study was remarkable for several reasons. It was the first to use parametric statistics and to implement voxel-based lesion-symptom mapping (VLSM) in relating localized brain damage to specific behavioural impairment. Most current VLSM studies use methods similar to those developed by Bates et al. (2003). The Bates et al. (2003) study was also significant in that it failed to find a significant relationship between Broca’s area damage (as compared to damage to the left anterior insula) and non-fluent speech. Taken together, the evidence suggests that brain damage that gives rise to non-fluent speech occurs in left anterior cortical regions, probably involving parts of the dorsal pathway, which, according to the dual-stream model, is hypothesized to map auditory representations to articulatory motor maps (Hickok and Poeppel, 2007). However, a specific lesion location that typically results in impaired speech fluency has not yet been defined.

In the current study, we attempted to relate structural brain damage to speech fluency in patients with aphasia. Instead of targeting only speech fluency, as measured on the WAB, we included three factors in the lesion analyses that could contribute to non-fluent speech—motor speech production (diadochokinetic rate), a rudimentary lexical processing task (auditory word-picture recognition), and an executive functioning task (matrix reasoning). We used these measures as cofactors in our analyses, permitting us to identify brain damage associated with non-fluent speech with and without the influence of factors that may contribute to speech fluency. In addition to the fluent/non-fluent distinction, individuals with aphasia are often referred to by their aphasia type (e.g. Broca’s, Wernicke’s, etc.). Accordingly, a secondary analysis compared brain damage across the two predominant non-fluent aphasias, namely Broca’s and global aphasia.

Unlike most previous VLSM studies, the current work relied mostly on image preprocessing and analysis methods developed by Tyler et al. (2005) who outlined a method in which brain damage is not directly demarcated on brain images in native space or on a brain template, but instead is defined by image intensity. This method does not require an expert to make a subjective decision about lesion boundaries, in that it directly relates specific behavioural impairment to image intensity of high-resolution T1-MRI images where brain damage is typically associated with hypointensity (Tyler et al., 2005, 2011; Acres et al., 2009).

To measure speech fluency, we used the 10-point rating scale incorporated into the WAB (Kertesz, 1982). On this scale, a score of 0 signifies mutism or only limited sound making or unintelligible words; a score of 10 suggests no impairment of speech fluency. Patients who are assigned a score between 0 and 4 are deemed to have non-fluent speech, whereas scores from 5 to 10 denote fluent speech. There are many criticisms of this scale, including the plotting of essentially qualitative data on an interval scale, lack of careful reliability assessment, and failure to take features such as articulatory agility and prosody into account [see Gordon (1998), for a discussion of these issues]. Even with these limitations the WAB has gained considerable acceptance within the clinical and scientific communities as a flawed but usable shorthand for characterizing fluent speech in aphasic patients.
Materials and methods

Participants

The data for this research were obtained from a database that includes patients enrolled in various studies conducted during the past 10 years in the Aphasia Lab, University of South Carolina. To qualify for the current study, patients needed to have undergone testing with the WAB and a high-resolution T1-MRI. Out of 76 patients included in the database, data from 64 patients (29 females) who had incurred a single left hemisphere stroke (60 ischaemic; four haemorrhagic) resulting in chronic aphasia (>6 months post-stroke) were included in this research (Supplementary material). The greatest lesion overlap among the patients (Fig. 1) was in the anterior portion of the left insula where 45 of 64 patients had damage [Montreal Neurological Institute (MNI) coordinate, –35, 1, 18]. These patients were recruited from aphasia support groups associated with the Aphasia Lab, University of South Carolina, by word-of-mouth among local neurologists and speech-language pathologists, and through newspaper advertising in Columbia, South Carolina. The mean patient age was 61.6 years (SD = 12.27), and the mean time post-stroke was 39.86 months (SD = 49.24).

Each patient was tested by either of two staff speech-language pathologists who each had at least 15 years of comprehensive experience with aphasic patients. Behavioural testing included the WAB (Kertesz, 1982), the Apraxia Battery for Adults, 2nd ed. (Dabul, 2000), and the Matrix Reasoning subtest from the Wechsler Adult Intelligence Scale, 3rd edition (WAIS III; Wechsler, 1997). Although all 64 patients were tested with the WAB, only 54 patients underwent testing with the Apraxia Battery for Adults, 2nd Edition and 46 with the Matrix Reasoning Test. The mean Aphasia Quotient, a measure of aphasia severity on the WAB where a score >93.8 implies no language impairment, was 60.23 (SD = 26.64). Based on the WAB aphasia classification system, the distribution of aphasia types across the 64 patients was as follows: anomic aphasia = 25; Broca’s aphasia = 20; conduction aphasia = 7; global aphasia = 6; and Wernicke’s aphasia = 6. Each patient agreed to study inclusion, and this research was approved by the University of South Carolina Institutional Review Board. The primary dependent factor, speech fluency, was defined as the clinical rating on the WAB’s 10-point fluency rating scale. Three other factors of interest were also included in the data analyses: (i) rudimentary lexical processing was measured as performance on the auditory word-picture matching subtest of the WAB. This subtest includes 60 items and relies on matching single spoken words to objects, pictures, and body parts; (ii) motor speech agility was measured as patients’ diadochokinetic rate (subtest 1 on the Apraxia Battery for Adults, 2nd Edition); and (iii) an aspect of executive functioning was measured using the Matrix Reasoning subtest from the Wechsler Adult Intelligence Scale. This test is similar to the commonly used Raven’s Progressive Matrices Test (Raven, 1976) and is commonly considered to be a test of inductive reasoning, with slightly less verbal and cultural dependence than the Raven’s test (Dugbartey et al., 1999).

Magnetic resonance imaging data collection and analyses

MRI was acquired with a 3 T Siemens Trio system fitted with a 12-channel head-coil. All patients were scanned with the same 3D T1-MRI sequence using a MP-RAGE (turbo field echo) sequence: field of view = 256 × 256 mm, 160 sagittal slices, 9° flip angle, repetition time = 2250 ms, inversion time = 900 ms, echo time = 4.2 ms. For the purpose of lesion demarcation, all patients were scanned with a high-resolution T2-MRI, yielding a 1 mm isotropic image. This sequence uses a 3D SPACE (Sampling Perfection with Application Optimized Contrasts by using different flip angle Evolutions) protocol with the following parameters: field of view = 256 × 256 mm, 160 sagittal slices, variable flip angle, repetition time = 3200 ms, echo time = 352 ms, using the same slice positioning and angulation as the T1 sequence.

Preprocessing of structural images

Preprocessing of images relied on the clinical toolbox (Rorden et al., 2012) for Statistical Parametric Mapping (SPM8; Friston et al., 1995). Consistent with Andersen et al. (2010), lesion masking was implemented for normalization. Note that the lesions demarcated on the T2-MRI images were used for the purpose of normalization, visualization of lesion overlay maps in Fig. 1, and to estimate lesion size (which was included as a factor in the multiple regression analyses). The lesions were manually demarcated using MRicron (Rorden & Brett, 2000) by the author (J.F.) or by graduate students or post-doctoral fellows who were closely supervised by J.F. The first step of the pre-processing involved co-registration of the T1-MRI and T2-MRI images (and yoking of the binary lesion into common space with the native T1-MRI images). Then, using cost-function masking (Brett et al., 2005), the lesion-MRI images were segmented and normalized to the 2 mm3 ICBM standard brain template. This process relied on the following parameters: (i) [2 2 2] Gaussians per class; (ii) 6 mm bias full-width at half-maximum; (iii) very light regularization; (iv) 3 mm sampling distance; and (v) trilinear interpolation.

Consistent with methods proposed by Tyler et al. (2005), the lesion-symptom mapping analysis related image intensity on the normalized T1-MRI scans, and not, as is typically the case for VLSM analysis, binary lesions, to the behavioural measures. In their paper, Tyler et al. (2005) compared the utility of conventional VLSM (predicting behaviour with binary lesions) versus relating image intensity on T1-
MRI to behaviour and found the latter method to yield better prediction. In short, the deficit-intensity mapping method relies on first normalizing and smoothing (10mm Gaussian kernel) patients’ T1-MRI scans. Then, image intensity is related to behaviour on a voxel-by-voxel basis and corrected for multiple comparisons (Tyler et al., 2005, 2011; Acres et al., 2009). As the overall signal intensity of T1-MRI can vary significantly across patients, the mean signal intensity for the whole brain image is included as a co-factor of no interest in the analyses. We made one modification to the methods proposed by Tyler et al. (2005) instead of including the mean image intensity value as a co-factor, Z-scores were calculated on voxel-by-voxel basis for each patients’ T1-MRI based on the mean and standard deviation of the structurally intact (right) hemisphere. Specifically, using an in-house code implemented in Matlab (The Mathworks), the mean and standard deviation of voxels included in a standard right hemisphere mask were calculated. Then, the whole brain T1-MRI image was converted to Z-scores based on the right hemisphere mean and standard deviation. This procedure does not alter the appearance of the images or the relative intensity values of the voxels. The Z-score images were used in the subsequent region of interest and whole brain VLSM analyses. We chose this option over the method espoused by Tyler et al. (2005) as we found that it improves overall statistical power. Essentially, the Z-score step is similar to what was suggested by Tyler et al. (2005), except that our modification standardizes image intensity based on the average image intensity observed in the grey and white matter of the intact hemisphere rather than the overall image intensity of the whole volume which includes the lesion in the affected hemisphere and non-brain tissue (e.g. scalp fat).

Region of interest analyses

The primary analyses of this study related mean image intensity (measured as Z-scores on voxel-by-voxel basis) in 21 a priori selected regions of interest to the behavioural measures. The regions of interest included in our analyses consisted of both cortical areas and white matter tracts in the left hemisphere, and were selected based on a review of the relevant literature, to encompass areas that have been historically associated with speech and language processing. Cortical areas included: the superior, middle and inferior temporal gyrri (Démonet et al., 1992; Howard et al., 1992; Damasio et al., 1996; Binder et al., 1997) and the temporal pole (Mazoyer et al., 1993; Visser et al., 2012), the angular gyrus (Nielsen, 1939; Binder et al., 1997), the anterior and posterior supra-marginal gyrus (Kertesz et al., 1979; Binder et al., 1997; Celsis et al., 1999), the middle and inferior temporal-occipital junctions (Démonet et al., 1992; Xu et al., 2001), the pars opercularis (Tonkonogy and Goodglass, 1981; Richardson et al., 2012) and pars triangularis (Desmond et al., 1995), the middle frontal (Wise et al., 1991; Binder et al., 1997) and precentral gyri (Levine and Sweet, 1982), and the anterior and posterior insulae (Price, 2000; Bates et al., 2003). White matter tracts included: the anterior, posterior and long segments of the arcuate fasciculus (Wernicke, 1908; Dick and Tremblay, 2012), the inferior longitudinal fasciculus (Vigneau et al., 2006), the inferior frontal-occipital fasciculus (Vigneau et al., 2006; Dick and Tremblay, 2012), and the uncinate fasciculus (Wernicke, 1908; Dick and Tremblay, 2012). Two separate brain atlases were consulted to define the regions of interest: for the cortical regions, the regions of interest were selected from the Harvard-Oxford standard brain atlas that includes probabilistic maps of different cortical regions based on identification and demarcation of each region by multiple experts in neuroanatomy (Desikan et al., 2006). The white matter tracts were obtained from a recent white matter atlas published by Catani et al. (2012). A probability threshold for each region was set at 0.50 so that at least 50% of the participants whose data were included to construct a given brain atlas overlapped in the specific region. This threshold was set to minimize overlap between the regions of interest in grey and white matter included in the two separate brain atlases. Note that there was some overlap between different regions of interest [e.g. the anterior segment of the arcuate fasciculus (ASAF) and pars opercularis], but we chose not to make arbitrary divisions between different anatomical regions. The cortical regions and white matter tracts comprised a neuroanatomical model where the mean intensity value in each region of interest, as well as lesion size, was entered into a stepwise regression analysis to predict the speech and language measures (Fig. 2). The stepwise regression analyses were implemented in SPSS (Version 20, IBM Corp.). To control for multiple comparisons, the stepwise regression analyses were Bonferroni corrected where \( P = 0.05 \) was divided by the number of predictors: 21 regions of interest and one factor for lesion size (for 22 total predictors). Thus, a critical alpha level for a statistically significant prediction model (as identified in the stepwise regression analyses) was set at \( P < 0.002 \). An exploratory region of interest analysis was conducted to examine differences in cortical damage between the two main types of non-fluent aphasia represented in our study sample, Broca’s aphasia \((n = 20)\) and global aphasia \((n = 6)\). For this purpose, multiple t-tests (two-tailed; equal variances in the two groups not assumed) were run where image intensity in each region of interest was compared across the two groups. As this analysis was exploratory only, no correction for multiple comparisons was applied.

Whole brain analyses

To more thoroughly investigate brain damage that gives rise to non-fluent speech production, we also conducted whole brain VLSM analyses. Thereby, we hoped to corroborate the results found in the region of interest analyses and, perhaps, give insight in regard to critical brain damage that cuts across two or more regions of interest. In the whole brain statistical analyses image intensities (voxel values represented as Z-scores in normalized T1-MRI scans) were related to the behavioural measures using linear regression analyses implemented in Non-Parametric Mapping, a statistical tool for neuroimaging distributed as part of the MRIcon software package (Rorden et al., 2009). Non-Parametric Mapping allows for multivariate analyses where the relation between image intensity and a given predicted factor can be modulated by one or more co-factors. The regression analyses were corrected for multiple comparisons using permutation thresholding with 1000 permutations (Rorden et al., 2009).

Results

Region of interest analyses

The primary region of interest analysis (using stepwise regression) revealed that speech fluency ratings on the WAB are best predicted by damage to the ASAF, \( P < 0.0001, R^2 = 0.40 \) (Fig. 3). The results from each of the region of interest analyses are included in Table 1. A second model that included the ASAF as well as the uncinate fasciculus (Fig. 3) improved the prediction of speech fluency, \( P < 0.0001, R^2 = 0.50 \). An F-change test revealed a statistically significant improvement in \( R^2 \) for the second model compared to the first \((P = 0.001)\). To understand if including lexical processing in the regression model improves prediction of speech fluency, a separate analysis included auditory word-picture
recognition as a cofactor. This analysis yielded three models: Model 1 comprised the ASAF, \( P < 0.0001, R^2 = 0.39 \); Model 2 included ASAF and pars opercularis, \( P < 0.0001, R^2 = 0.48 \) (F-change test for improvement in \( R^2, P = 0.003 \)); and Model 3 also involved the temporal pole, \( P < 0.0001, R^2 = 0.52 \) (F-change test for improvement in \( R^2, P = 0.03 \)). A separate regression analysis included diadochokinetic rate as a cofactor and revealed involvement of the uncinate fasciculus as the single best predictor of speech fluency, \( P < 0.0001, R^2 = 0.51 \). A second fluency prediction model included the uncinate fasciculus and the added proportional reduction in error provided by the ASAF, \( P < 0.0001, R^2 = 0.60 \) (F-change test for improvement in \( R^2, P = 0.003 \)). The final regression analysis for speech fluency included scores from the Matrix Reasoning subtest on the WAIS III as a cofactor and yielded only one model with the ASAF as the single best predictor, \( P < 0.0001, R^2 = 0.45 \). Two models predicted auditory word-picture recognition ability: Model 1 included the inferior longitudinal fasciculus, \( P < 0.0001, R^2 = 0.42 \), and Model 2, which also included the posterior portion of the middle temporal gyrus, provided additional error reduction, \( P < 0.0001, R^2 = 0.47 \) (F-change test for improvement in \( R^2, P = 0.02 \)) (Fig. 4). Diadochokinetic rate was predicted by involvement of the lateral precentral gyrus, \( P = 0.003, R^2 = 0.16 \) (Fig. 4). However, note that this model was not statistically significant at the Bonferroni corrected alpha-level of 0.002. No statistically significant prediction model was generated in the regression analysis that would account for matrix reasoning scores.

Differences in image intensity across different regions of interest among patients with Broca’s versus global aphasia were also explored. This analysis revealed a difference in only two regions of interest, the uncinate fasciculus, \( t(24) = 2.34, P = 0.03 \), and the temporal pole, \( t(24) = 2.67, P = 0.01 \), where there was lower
Table 1 Results from the region of interest analyses

<table>
<thead>
<tr>
<th>Predicted factor</th>
<th>Model</th>
<th>Co-factor</th>
<th>F</th>
<th>P</th>
<th>R²</th>
<th>Predictor(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Speech fluency</td>
<td>1</td>
<td>None</td>
<td>41</td>
<td>&lt;0.0001</td>
<td>0.40</td>
<td>ASAF</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td></td>
<td>29.41</td>
<td>&lt;0.0001</td>
<td>0.50</td>
<td>Model 1 and uncinate fasciculus</td>
</tr>
<tr>
<td>Speech fluency</td>
<td>1</td>
<td>Picture-word recognition</td>
<td>37.71</td>
<td>&lt;0.0001</td>
<td>0.39</td>
<td>ASAF</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td></td>
<td>26.33</td>
<td>&lt;0.0001</td>
<td>0.48</td>
<td>Model 1 and pars opercularis</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td></td>
<td>20.34</td>
<td>&lt;0.0001</td>
<td>0.52</td>
<td>Model 2 and temporal pole</td>
</tr>
<tr>
<td>Speech fluency</td>
<td>1</td>
<td>Diadochokinetic rate</td>
<td>41.83</td>
<td>&lt;0.0001</td>
<td>0.51</td>
<td>Uncinate fasciculus</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td></td>
<td>30.36</td>
<td>&lt;0.0001</td>
<td>0.60</td>
<td>Model 2 and ASAF</td>
</tr>
<tr>
<td>Speech fluency</td>
<td>1</td>
<td>Matrix reasoning</td>
<td>34.73</td>
<td>&lt;0.0001</td>
<td>0.45</td>
<td>ASAF</td>
</tr>
<tr>
<td>Picture-word recognition</td>
<td>1</td>
<td>None</td>
<td>41.33</td>
<td>&lt;0.0001</td>
<td>0.42</td>
<td>Inferior longitudinal fasciculus</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td></td>
<td>24.96</td>
<td>&lt;0.0001</td>
<td>0.47</td>
<td>Model 1 and posterior middle temporal gyrus</td>
</tr>
<tr>
<td>Diadochokinetic rate</td>
<td>1</td>
<td>None</td>
<td>9.73</td>
<td>0.003</td>
<td>0.16</td>
<td>Precentral gyrus</td>
</tr>
<tr>
<td>Matrix reasoning</td>
<td></td>
<td>No statistically significant model</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Each model is selected in the stepwise regression analyses, which are optimized for maximum error reduction (R²). The first column includes the predicted factors, the second column lists the number of statistically significant prediction models identified in the stepwise regression analyses, the third column includes cofactors included in each analysis, columns 4–6 include model parameters, and the final column includes the strongest predictive factors identified in the regression analyses.
overall image intensity in the global aphasia group. A Levene’s test suggested that the variance in image intensity in different regions of interest across patients with Broca’s and global aphasia was not different. Although the patients with global aphasia had \( \sim 20\% \) greater lesion volume than their counterparts with Broca’s aphasia, this difference was not statistically significant, \( t(24) = 1.28, P = 0.24 \). Likewise, there was not a statistically significant difference in time post-stroke between the two groups, \( t(24) = 0.047, P = 0.96 \). The crucial difference that distinguishes between patients with Broca’s and global aphasia on the WAB is based on patients’ auditory comprehension scores. A linear regression analysis that only included patients with Broca’s or global aphasia revealed that damage to the uncinate fasciculus is the single best predictor of the auditory comprehension subscore on the WAB, \( F(1,25) = 11.98, P = 0.002, R^2 = 0.324 \).

**Whole brain analyses**

Each of the whole brain analyses for speech fluency, including those that incorporated cofactors, yielded statistically significant results (corrected for multiple comparisons). Impaired speech fluency is associated with damage mostly involving the Rolandic operculum, pars opercularis, pars triangularis, insula, precentral gyrus, middle frontal gyrus, and the white matter underlying Broca’s area and surrounding structures (Fig. 5A). The voxel with the highest Z-score (Z = 7.29) was located in the Rolandic operculum (MNI: \(-55, -1, 6\)). Subsequent analyses that separately included auditory word-picture matching, diadochokinetic rate, and scores from the Matrix Reasoning test as cofactors revealed approximately the same lesion location as when no cofactors were included; albeit, with lower overall Z-scores. Impaired auditory word-picture matching was associated with involvement of the middle and anterior inferior longitudinal fasciculus as well as the posterior horn of the uncinate fasciculus (Fig. 5B). The voxel with the highest Z-score (Z = 5.5) was located in the inferior longitudinal fasciculus (MNI: \(-41, -15, -22\)). Finally, the whole brain analyses for diadochokinetic rate and Matrix Reasoning test scores did not yield statistically significant results.

**Discussion**

The results from this study suggest that damage to anterior structures, especially the ASAF, has a particularly negative impact on speech fluency in patients with aphasia, at least when speech fluency is defined and measured according to the WAB. It is also notable that involvement of the uncinate fasciculus contributes to improved prediction of speech fluency. Damage to the ASAF seems to be a particularly robust predictor of speech fluency even when measures related to rudimentary auditory comprehension, motor speech agility, and executive functioning are included as cofactors in the regression analyses. Not surprisingly, impaired auditory word-picture recognition was associated with damage to the left temporal lobe, particularly in the underlying white matter tracts. Slower diadochokinetic rate was associated with damage to the left lateral precentral gyrus. Neither the region of interest nor the whole brain analyses yielded statistically significant results for Matrix Reasoning scores, likely because impaired performance in patients is typically associated with right hemisphere damage (Gla¨ scher et al., 2009; Barbey et al., 2013), and the current study only included those with left hemisphere damage.

Although it is common to discuss the neural architecture that supports speech in relation to cortical regions (e.g. Broca’s area), the current findings highlight the importance of specific white matter tracts for speech production. The ASAF connects anterior areas such as the pars opercularis and lateral middle and inferior precentral gyrus with the posterior, inferior parietal lobe, a region...
identified as ‘Geschwind’s area’ by Catani et al. (2005). It is also important to note that damage to the short white matter fibres that connect the anterior speech areas to each other has a particularly negative effect on speech fluency, especially as highlighted in our whole brain analyses. This does not diminish the importance of specific cortical regions that potentially comprise the anterior speech network (e.g. the inferior lateral precentral gyrus, premotor cortex, and pars opercularis) but, rather, highlights the importance of the connections between these regions for fluent speech production.

We attempted to control for the influence of impaired lexical processing, motor agility and executive functioning in our analyses. However, the added value of including these factors is probably related to how well each represents basic levels of processing. For example, we included auditory word-picture matching as representing rudimentary lexical processing. However, it is clear that this task does not specifically isolate lexical and semantic processing. Nevertheless, it is a task that relies on processes such as lexical decision and semantic control, which, based on the dual stream model, are supported by the ventral pathway (Hickok and Poeppel, 2007). We decided to include a measure of diadochokinetiic rate, a task that probably places only minimal demands on lexical or semantic processing, in that it is also a rudimentary task. Whereas patients with apraxia of speech have reduced diadochokinetiic rate, it is not a measure that clearly adjudicates between those who do or do not have motor speech impairment. Nevertheless, it appears that reduced diadochokinetic rate is associated with involvement of the left lateral precentral gyrus, whereas non-fluent aphasia is marked by more widespread damage, primarily involving the ASAF, pars opercularis, and uncinate fasciculus. According to the hierarchical state feedback control model, a framework that specifically addresses speech production and could be viewed as the hierarchical state feedback control model, a framework that the ASAF, pars opercularis, and uncinate fasciculus. According to the dual stream model in real time (Fridriksson et al., 2012), we decided to include a measure of diadochokinetic rate, a task that probably places only minimal demands on lexical or semantic processing, in that it is also a rudimentary task. Whereas patients with apraxia of speech have reduced diadochokinetiic rate, it is not a measure that clearly adjudicates between those who do or do not have motor speech impairment. Nevertheless, it appears that reduced diadochokinetic rate is associated with involvement of the left lateral precentral gyrus, whereas non-fluent aphasia is marked by more widespread damage, primarily involving the ASAF, pars opercularis, and uncinate fasciculus. According to the hierarchical state feedback control model, a framework that specifically addresses speech production and could be viewed as an extension of the dual stream model, motor-phoneme programs rely on the left motor cortex and ventral portions of Brodmann’s area 6 (Hickok, 2012, also see Guenther et al., 2006). Accordingly, the current findings regarding reduced diadochokinetic rate appear to reflect impaired storage or access to motor-phoneme programs.

The data set on which the study is based does not include a detailed measure of agrammatism. Accordingly, the findings presented here do not account for the potential influence of impaired grammatical processing. Typically, patients who are agrammatic also present with reduced speech fluency (Thompson et al., 2012). However, there is little evidence to suggest that agrammatism actually causes non-fluent speech rather than being a condition that typically coexists with impaired speech fluency.

The study is also limited by its lack of explicit measures of patients’ ability to initiate or to maintain fluent speech. These factors are underexplored, and could reflect a mechanism that is crucial for fluent speech production. Goodglass (1993) discussed the importance of speech initiation and flow but did not explicitly expound on a potential mechanism. Luria (1966), however, described impaired speech initiation as one of the central features of dynamic aphasia, a syndrome characterized by severely reduced speech output but less impairment of motor speech commands. In a recent study, our group showed that some patients with Broca’s aphasia could produce relatively fluent speech when mimicking an audio-visual speech model in real time (Fridriksson et al., 2012). As suggested in Fridriksson et al. (2012) it could be the case the audio-visual speech model provides external gating for speech initiation and maintenance of the flow of speech. However, in cases where the primary problem is rooted in impaired speech articulation, this kind of audio-visual gating does not provide the same benefit as in cases where the primary impairment manifests as a problem with speech initiation and flow, a mechanism that may rely on Broca’s area rather than the precentral gyrus and premotor cortex (for further discussion of this issue; Fridriksson et al., 2012). Accordingly, it could be the case that involvement of Broca’s area (and the underlying white matter, including the ASAF), on one hand, and the left precentral gyrus and premotor cortex, on the other, results in different speech impairments that often coexist among the same patients whose brain damage encompasses both crucial regions.

Our data suggest that greater involvement of the uncinate fasciculus and the left temporal pole distinguishes patients with global aphasia from their counterparts who have Broca’s aphasia. Many of the patients with Broca’s aphasia included here presented with quite extensive involvement of the temporal lobe. In fact, excluding the temporal pole, differences in temporal lobe involvement never achieved statistical significance in other regions of interest. Given that among patients who have Broca’s or global aphasia, involvement of the uncinate fasciculus was a robust predictor of auditory comprehension impairment, we tentatively suggest that the uncinate fasciculus plays a crucial role in maintaining relatively spared auditory comprehension in patients with Broca’s aphasia. We emphasize that our findings regarding differences in brain damage between patients with global and Broca’s aphasia should be interpreted with utmost caution; especially as the sample size for global aphasia (n = 6) was particularly small and a larger sample could potentially have revealed an overall difference in lesion size among the two groups.

In conclusion, it seems clear that several factors can contribute to decreased speech fluency in aphasia and that the influence of these factors may be related to localized cortical and/or subcortical white matter damage. Future studies are required to determine which are the actual causative factors among those that coexist with non-fluent speech. Based on the current findings, it appears that damage to the anterior segment of the arcuate fasciculus has a particularly negative effect on speech fluency. Furthermore, when we control for the influence of three potential culprits that could affect speech fluency, lexical processing, motor speech agility, and executive functioning, the same region, the anterior segment of the arcuate fasciculus, still remains as a robust predictor of non-fluent speech in aphasia.

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**Supplementary material**

Supplementary material is available at *Brain* online.
References


