Patterns of Poststroke Brain Damage That Predict Speech Production Errors in Apraxia of Speech and Aphasia Dissociate

Alexandra Basilakos, MA; Chris Rorden, PhD; Leonardo Bonilha, MD, PhD; Dana Moser, PhD; Julius Fridriksson, PhD

Background and Purpose—Acquired apraxia of speech (AOS) is a motor speech disorder caused by brain damage. AOS often co-occurs with aphasia, a language disorder in which patients may also demonstrate speech production errors. The overlap of speech production deficits in both disorders has raised questions on whether AOS emerges from a unique pattern of brain damage or as a subelement of the aphasic syndrome. The purpose of this study was to determine whether speech production errors in AOS and aphasia are associated with distinctive patterns of brain injury.

Methods—Forty-three patients with history of a single left-hemisphere stroke underwent comprehensive speech and language testing. The AOS Rating Scale was used to rate speech errors specific to AOS versus speech errors that can also be associated with both AOS and aphasia. Localized brain damage was identified using structural magnetic resonance imaging, and voxel-based lesion-impairment mapping was used to evaluate the relationship between speech errors specific to AOS, those that can occur in AOS or aphasia, and brain damage.

Results—The pattern of brain damage associated with AOS was most strongly associated with damage to cortical motor regions, with additional involvement of somatosensory areas. Speech production deficits that could be attributed to AOS or aphasia were associated with damage to the temporal lobe and the inferior precentral frontal regions.

Conclusions—AOS likely occurs in conjunction with aphasia because of the proximity of the brain areas supporting speech and language, but the neurobiological substrate for each disorder differs. (Stroke. 2015;46:00-00. DOI: 10.1161/STROKEAHA.115.009211.)

Key Words: aphasia • apraxia, articulatory • neuroimaging • stroke

Apraxia of speech (AOS) is a disorder of motor speech planning that can occur after brain damage to the language-dominant hemisphere. Generally, agreed-on characteristics of AOS include articulatory imprecision, atypical prosody, frequent errors with consonants when compared with vowels, and distinct from speech production deficits that occur in aphasia and dysarthria, distorted sound additions and substitutions.1,2 The nature of these behaviors differs from that of aphasia, as AOS is neither a linguistic impairment (ie, a problem with the conceptualization of verbal symbols used to communicate thoughts) nor a problem with speech motor execution (ie, dysarthria). Rather, it is a deficit in planning speech motor movements.3

The study of AOS has been plagued by controversy since its description by Darley in 1968.4,5 This can be attributed to the fact that the behavioral presentation of AOS is often difficult to distinguish from the speech production deficits that can occur in aphasia and dysarthria,6-9 and because the anatomy of brain damage leading to AOS is similar to the pattern of damage leading to aphasia.10,11 A seminal study by Dronkers12 in 1996 localized AOS to damage to the left insula, specifically the superior precentral gyrus of the insula (SPGI). Twenty-five poststroke patients with chronic AOS had SPGI damage, whereas patients without AOS did not have a lesion in this area. This double dissociation between SPGI damage and AOS has been argued as strong support for the role of the insula in AOS.6,12,13 However, in the study by Dronkers,12 none of the patients in the group without AOS were reported to have Broca aphasia or other speech impairment (eg, dysarthria). These patients were classified with Wernicke, anomic, conduction, or unclassifiable/no aphasia. In addition, lesion distribution maps for this group indicate that areas of maximal overlap occurred in posterior perisylvian areas; therefore, it can be argued that the lesion distribution of this group is too different to serve as an adequate comparison.14

Furthermore, mounting evidence does not support the role of the insula in speech production generally and AOS specifically, as such work has found that AOS can occur in the
absence of insula damage. This work argues for the involvement of the inferior frontal gyrus pars opercularis (IFGpo) or primary and supplementary motor areas, and it has suggested that the maximum overlap in the SPG1 can be attributed to vascular distribution and the likelihood of insula damage after a left middle cerebral artery stroke.

Differences between the anatomic localization originally proposed by Dronkers and that suggested by subsequent studies may be explained by outdated diagnostic criteria for AOS or the method of analysis used. Richardson et al compared results from lesion overlap (replicating Dronkers) and voxel-based lesion symptom mapping using the same diagnostic criteria implemented by Dronkers.

Results from the lesion overlap analysis showed that a subregion of the insula was indeed the greatest area of overlap in individuals with AOS. However, in the group with aphasia without AOS, some patients (12/24) had damage to the same subregion of the insula, contradicting previously reported double dissociations between this site of damage and AOS. In addition, results from the voxel-based lesion symptom mapping analysis showed that damage to the IFGpo was the greatest predictor of AOS. Therefore, comparison between these 2 studies, along with other evidence from patients with AOS as the primary impairment (eg, stroke-induced and primary progressive AOS) suggests that original findings on the SPG1 may be explained by diagnostic criteria or analysis methods implemented.

Here, we classified speech production errors in a cohort of patients with chronic poststroke as errors that exclusively occur in AOS and those that can occur in both AOS and aphasia. The goal of this study was to test the hypothesis that speech production deficits characteristic of AOS are caused by unique anatomic patterns of damage that can be distinguished from patterns of damage related to production deficits that can occur in aphasia. We hypothesized that (1) speech errors unique to AOS are associated with damage in cortical motor and somatosensory areas and (2) speech errors that can occur in aphasia are predominantly represented by patterns of damage along the ventral stream and dorsal areas that are responsible for higher level production processes.

Methods

Participants

Forty-three patients who incurred a single-event left-hemisphere stroke (17 women; mean age, 59.2±10.7) were included. Patients were recruited as part of a larger stroke study at the University of South Carolina, in which inclusion criteria included single-event ischemic stroke. Patients were selected for the current sample if they had experienced a left-hemisphere stroke. No patients had a history of other neurological disease or developmental language abnormalities.

All were tested at the chronic phase of recovery (ie, >6 months post stroke; mean month post onset, 52.5±38.9).

Patients varied in the presence/absence of aphasia type and severity as follows: no aphasia: n=14; anomic: n=11; Broca: n=11; conduction: n=4; Wernicke: n=2; and global: n=1. Mean Western Aphasia Battery score for all patients with aphasia was 72.5±18.7 and 97.8±1.6 for those without aphasia. A lesion overlap map for all patients is presented in Figure 1. All patients provided informed consent in accordance with the Institutional Review Board of the University of South Carolina.

Procedure

Behavioral Tasks

Speech production was rated using the AOS Rating Scale (ASRS). Speech samples were obtained from audiovisual recordings of 3 picture description tasks, a reading passage, diadochokinetic rates, and conversation. The speech characteristics included on the ASRS classify speech abnormalities into 4 categories: (1) features that occur in AOS but not in dysarthria or aphasia; (2) features that can occur because of AOS or dysarthria; (3) features that can occur because of AOS or aphasia; and (4) features that can occur because of AOS/dysarthria/aphasia. In general, AOS-specific behaviors include segment-level articulatory errors characterized by distorted sound substitutions/additions, whereas speech production errors that can also be attributed to aphasia include initiation difficulty, false starts/restarts, audible/visible groping, and difficulties with sequential motor rates. Additional details about the scale’s items, and the scale itself, can be found in the study by Strand et al.

ASRS ratings for all patients were completed by an American Speech-Language-Hearing Association–certified speech-language pathologist with experience using this scale for classifying speech production behaviors as related to AOS, aphasia, and dysarthria. Each patient was rated on the presence/absence of all ASRS speech characteristics, based on a 5-point scale (0=not present; 1=detected but not frequent; 2=frequent but not pervasive; 3=nearly always evident but not marked in severity; 4=nearly always evident and marked in severity).

According to ASRS criteria, a patient must have at least 1 primary distinguishing feature rated for AOS diagnosis. In addition, an overall score >8 is most reliably associated with AOS. On the basis of each patient’s ratings, clinical judgment about the presence/absence of AOS was determined. If AOS was present, then the overall severity was rated (1–4). If AOS was not present, then the patient receives a score of 0 for AOS severity. This score was determined by specific ratings from the ASRS items and the overall effect of these production difficulties on each patient’s communication abilities.

An overall severity score for production errors related to aphasia severity was assigned to each patient as applicable, using the same aforementioned 5-point scale. Patients’ Western Aphasia Battery scores were additionally used to determine aphasia presence/absence and severity ratings. Items that can occur in dysarthria were rated but not used in subsequent analyses, as the focus of this study was aphasia and AOS.

Reliability

Inter-rater reliability was established using a 2-way mixed, consistency single-measures intraclass correlation coefficient with the primary rater and another American Speech-Language-Hearing...
Association–certified speech-language pathologist who rated patients by independently viewing the video-recorded speech and language samples for a subset of patients (n=10). Intraclass correlation coefficient was computed for ratings on each of the 16 items on the ASRS and overall severity ratings for both AOS and aphasia. The intraclass correlation coefficient was 0.884, indicating good reliability between the 2 raters.

MRI Data Acquisition
Magnetic resonance imaging (MRI) data were acquired using a Siemens 3T Trio System with a 12-channel head coil. All patients underwent scanning with the following imaging sequences: (1) T1-weighted sequence using a magnetization-prepared rapid acquisition gradient echo (turbo field echo) sequence with a field of view of 256×256 mm, 192 sagittal slices, flip angle of 9°, retention time of 2250 ms, inversion time of 925 ms, echo time of 4.15 ms, generalized autocalibrating partially parallel acquisitions (GRAPPA) of 2, and 80 reference lines; (2) T2-weighted MRI for the purpose of lesion-demarcation with a 3-dimensional (3D) Sampling Perfection with Application optimized Contrasts by using different flip angle Evolutions protocol with the following parameters: field of view of 256×256 mm, 160 sagittal slices, variable flip angle, retention time of 3200 ms, TE of 352 ms, and no slice acceleration. The slice center and angulation were the same as with the T1 sequence.

Preprocessing of Structural Images
The Clinical Toolbox (http://dbm.neuro.uni-jena.de/CRNL/tools/niistat) was used for the preprocessing of images. Stroke lesions were demarcated by a neurologist (L.B.) in MRICron on individual T2-MRIs (in native space), using the T1-MRI and diffusion sequences for guidance. Preprocessing began with the coregistration of the T2-MRI to match the T1-MRI, aligning the lesions to native T1 space. Lesion cost-function masking was then used for segmentation and normalization with the stroke-control template image included with the Clinical Toolbox. The cost-function normalization process registered T1-weighted images into standard space. The hand-drawn T2 lesion masks were used for cost-function normalization. However, once the T1 weighted images were registered onto standard space, the location of poststroke gliosis was assessed by T1-signal intensity, which was used as a continuous measure of anatomic damage as chronic stroke, as opposed to the hand-drawn lesion masks. Because stroke is associated with hypointense signal on chronic T1-MRI, this method of analysis uses hypointense signal as a continuous quantification of structural damage to predict behavior. The use of continuous data has been suggested to be superior in increasing sensitivity of correlations when compared with binary lesion classifications in whole-brain analyses.

To account for individual differences in overall signal intensity, we calculated z-scores for each patient’s T1-MRI on a voxel-by-voxel basis based on the mean and SD of the right-hemisphere image intensity of that patient using an in-house code written in Matlab (The Mathworks, Natick, MA). This method allows for standardization based on the image intensity of the structurally intact right hemisphere (using a brain mask from the clinical toolbox corresponding to the entire right hemisphere thresholded for >50% combined probability of the voxel belonging to gray or white matter). This approach has been used previously in our lab and in other work as a surrogate measure of damage in other studies. It is possible that for some individuals, stroke-related changes occurred in the right hemisphere (eg, diaschisis), introducing greater error in the overall analysis. On the basis of first principles, this error should have decreased the likelihood of finding significant results.

Lesion Symptom Mapping Analysis
We conducted Freedman–Lane regression where each behavioral variable acted as a nuisance regressor for the other using Matlab routines developed by Ged Ridgway. Of note, we chose to use a regression analysis, as opposed to logistic regression or ANCOVA because we used images with continuous voxel-based measures instead of binary lesions and conducted permutation thresholding. Whole-brain analyses were completed with the threshold for statistical significance set to P<0.05, using 4000 permutations to control for multiple comparisons. Threshold-free cluster enhancement (TFCE) was used to improve signal-to-noise detection of significant clusters using routines developed by Christian Gaser (http://dbm.neuro.uni-jena.de/ tface). Specifically, for each permutation, we transformed the 3D z-score map using the TFCE formula that emphasizes voxels that are both bright (strong z-scores) and in a bright neighborhood (strong support). For each permutation, we scrambled all voxels in a given volume, identified the single brightest resulting voxel, and rank-ordered these values. The 200th most significant value (5%) was used as the subsequent statistical threshold, robustly controlling for familywise error. Accordingly, our threshold is based on the peak of all voxels for each permutation. All of these routines are integrated into our NiStat toolbox for Matlab (http://www.mccauslandcenter.sc.edu/CRNL/tools/nimstat).

We aimed to identify clusters of voxels where there was a contiguous significant correlation between the voxel intensity and the behavioral measure. By reducing the variability across contiguous voxels, TFCE increases the statistical power of voxel-lesion based analysis, preserving the identification of clusters composed by voxels with a strong relationship with behavior.

Results

Behavioral Measures
Eighteen patients were classified with AOS (mean ASRS score, 2.8±1.1). Two of these patients did not have concomitant aphasia. For the remaining patients with AOS (n=16), their aphasia was classified as follows: Broca: 12; anomic: 3; global: 1. Six patients had concomitant dysarthria (mean severity, 1.83). Twelve were classified with aphasia only (mean ASRS aphasia severity, 1.33), and 11 did not classify with any speech or language deficits.

Neuroimaging
All 189,008 voxels inside the 2-mm isotropic brainmask were included in the whole-brain analysis. A total of 15,639 voxels survived thresholding for severity of speech errors typically associated with aphasia (defined by the TFCE threshold, 12.86), and 2508 voxels survived thresholding for severity of speech errors associated with AOS (defined by the TFCE threshold, 12.49). Statistical maps (herein referred to as clusters) associated with speech errors in AOS and aphasia are overlaid on a standard brain map and presented in Figure 2, with clusters predictive of AOS speech errors in blue and aphasic speech errors in red. There was a small region (34 voxels) where damage predicted both AOS and aphasic errors (after treating the other behavior as a nuisance variable). This small area is displayed in yellow in Figure 2. Because TFCE identifies clusters of voxels homogeneously associated with behavior, we report each cluster as a single element, without the voxel-wise breakdown of statistical values.

The 3 thresholded clusters were subsequently scrutinized using the Johns Hopkins University atlas and a custom Matlab script to identify the extent to which each cluster occupied different anatomic brain areas. The cluster common to AOS–specific speech errors was distributed across the precentral and postcentral gyri, whereas the cluster associated with aphasic speech errors was distributed across many anatomic regions in the inferior prefrontal and temporal regions. For the clusters associated with AOS and aphasic errors independently, regions of interest (ROIs) that contributed to at least

Downloaded from http://stroke.ahajournals.org/ by guest on June 10, 2017
3% of the respective cluster are listed in Tables 1 and 2 (the specific percentage is listed in column 2). The percentage of damage to each specific ROI is also provided (column 3).

**Discussion**

We demonstrated that speech errors in AOS and aphasia result from unique patterns of brain damage. Specifically, we identified regions in cortical motor and somatosensory areas that predict AOS errors, even after removing variability explained by errors that could also occur in aphasia (and vice versa). The study of AOS has been built on different definitions of the disorder, complicating the interpretation of findings about its localization and theoretical bases and hindering the generalizability of conclusions pertaining to speech motor planning in general. On the most fundamental level, the current practices for AOS diagnosis are largely ambiguous and subject to variability in interpretation. Furthermore, the one published and widely used AOS battery, the Apraxia Battery for Adults-2, is subject to failure in the differential diagnosis between AOS and aphasia.

Importantly, these results add to a growing body of evidence attempting to rectify many debates surrounding AOS by using the ASRS, a descriptive scale created by researchers who have extensive experience with AOS and motor speech disorders. The ASRS provides a more detailed description...
and classification of production errors, based on expert opinion, and development of a response to decades of debate about the description of AOS. The ASRS itself is based on perceptual ratings but shows high reliability and validity in distinguishing between production errors that can occur in AOS, aphasia, and dystartria. It has also been used in many studies to explicitly describe and further localize production deficits in AOS\textsuperscript{6,18,20} and progressive AOS.\textsuperscript{16–18,20}

Although previous work has localized AOS to the left SPGI of the insula\textsuperscript{2,13} or the left IFG,\textsuperscript{10,11} this study provides converging evidence between the neuroanatomical underpinnings of severity ratings of AOS using the ASRS and neuroimaging findings with recent investigations into the localization of poststroke AOS\textsuperscript{19} and primary progressive apraxia of speech.\textsuperscript{17,18} Furthermore, a recent functional MRI study in neurologically intact individuals\textsuperscript{15} found that the SPGI is not involved in complex articulation tasks as previously suggested by patient data.\textsuperscript{12,13} Clearly, our methods were sufficient for detecting statistically significant results in the insula, as damage to this area was a significant predictor for speech errors that can occur in aphasia but did not survive thresholding for severity of speech errors that are characteristic of AOS. In addition, the cohort of patients in this study demonstrated lesion coverage of the left hemisphere, with maximum overlap in key regions that have been associated with speech production (eg, insula, IFGpo, and precentral/postcentral areas). The Johns Hopkins University atlas does not divide the insula into specific regions; rather, the entirety of the insula boundary is included in the Johns Hopkins University atlas’s insula ROI. Regardless, if damage to any portion of the insula was to be predictive of AOS, this would have been evident in the ROI analysis.

Finally, this study did not replicate previous work that has credited the IFGpo with damage crucial for AOS. The IFGpo accounted for <1% of the AOS cluster (0.05%), with only 0.14% damage to this ROI; however, the IFGpo accounted for 2.23% of the aphasia severity cluster, with 33.69% IFGpo damage associated with aphasia. These results do not discount the role of the IFGpo or the insula in motor speech production in general but instead implicate both the insula and IFGpo in higher levels of verbal output, before speech motor planning. This notion is supported further by an electrocorticographic study by Flinker et al.,\textsuperscript{43} who revealed that Broca area itself is not involved in articulation per se but serves as a relay between auditory representations of words (stored in ventral stream areas\textsuperscript{44}) and articulatory programs that are executed in cortical motor areas.\textsuperscript{43}

Conclusions

These results implicate the role of cortical motor and somatosensory areas in the primary localization of AOS. Theoretically, this study provides additional support for the role of low-level somatosensory and motor control in AOS.\textsuperscript{44} Clinically, evidence provided here suggests that using structural neuroimaging in addition to a valid rating scale may improve the differential diagnosis of speech production errors resulting from AOS versus those that could be attributed to aphasia. Such work will ultimately further the study of speech production in general, and clinically, support the development of more valid assessments for AOS.

Acknowledgments

We also thank Dr Joe Duffy et al for use of the Apraxia of Speech Rating Scale.

Sources of Funding

We are grateful for the generous funding provided by the National Institutes of Health (National Institute of Deafness and Communication Disorders) through award R01DC009571. The content is solely the responsibility of the authors and does not necessarily represent the views of the National Institutes of Health.

Disclosures

None.

References


Patterns of Poststroke Brain Damage That Predict Speech Production Errors in Apraxia of Speech and Aphasia Dissociate
Alexandra Basilakos, Chris Rorden, Leonardo Bonilha, Dana Moser and Julius Fridriksson

Stroke. published online April 23, 2015;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2015 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/early/2015/04/23/STROKEAHA.115.009211

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/