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.

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. 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.

**Key Words:** aphasia, apraxia of speech, articulatory, neuroimaging, stroke

**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;46:1561-1566. DOI: 10.1161/STROKEAHA.115.009211.)
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 SPGI 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 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 SPGI 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/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/severity of all ASRS speech characteristics, based on a 5-point scale (0=not present; 1=detectable 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 with experience using this scale for classifying speech production behaviors as related to AOS, aphasia, and dysarthria. Each patient was rated on the presence/severity of all ASRS speech characteristics, based on a 5-point scale (0=not present; 1=detectable 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).

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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.28

**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 256x256 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 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 256x256 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 Toolbox27 for SPM8 was used for the preprocessing of images. Stroke lesions were demarcated by a neurologist (L.B.) in MRIcon30 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 masking29 was then used for segmentation and normalization30 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 decreased the likelihood of finding significant results. In other work as a surrogate measure of damage in other studies.33,34 It is possible that for some individuals, stroke-related changes occurred in the right hemisphere (eg, diaschisis), introducing greater error in the voxel-wise breakdown of statistical values. On the basis of first principles, this error should have decreased the likelihood of finding significant results.

**Lesion Symptom Mapping Analysis**

We conducted Friedman–Lane regression where each behavioral variable acted as a nuisance regressor for the other using Matlab routines developed by Ged Ridgway.26 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 <0.05, using 4000 permutations to control for multiple comparisons.36 Threshold-free cluster enhancement (TFCE)37 was used to improve signal-to-noise detection of significant clusters using routines developed by Christian Gaser (http://dbm.neuro.uni-jena.de/tfce/). 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 NiiStat toolbox for Matlab (http://www.mccauslandcenter.sc.edu/CRNL/tools/niiStat).

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 dystartria (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 189,005 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 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 University38 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
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.

**Table 1. Anatomic Regions Associated With Aphasia**

<table>
<thead>
<tr>
<th>ROIs Associated With Aphasia Characteristics</th>
<th>Percent of the Aphasia-Related Cluster Within Each ROI</th>
<th>Percent of the ROI Damaged</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superior temporal gyrus</td>
<td>9.66</td>
<td>76.05</td>
</tr>
<tr>
<td>Posterior middle temporal gyrus</td>
<td>8.53</td>
<td>67.51</td>
</tr>
<tr>
<td>Posterior superior temporal gyrus</td>
<td>5.73</td>
<td>76.13</td>
</tr>
<tr>
<td>Insula</td>
<td>4.74</td>
<td>93.46</td>
</tr>
<tr>
<td>Superior temporal pole</td>
<td>3.72</td>
<td>46.04</td>
</tr>
<tr>
<td>Inferior frontal gyrus pars orbitalis</td>
<td>3.46</td>
<td>49.37</td>
</tr>
<tr>
<td>Posterior thalamic radiation</td>
<td>3.42</td>
<td>70.67</td>
</tr>
<tr>
<td>Inferior frontal gyrus pars triangularis</td>
<td>3.32</td>
<td>41.13</td>
</tr>
<tr>
<td>Middle occipital gyrus</td>
<td>3.22</td>
<td>12.57</td>
</tr>
<tr>
<td>Angular gyrus</td>
<td>3.14</td>
<td>18.10</td>
</tr>
<tr>
<td>Middle temporal gyrus</td>
<td>3.13</td>
<td>43.43</td>
</tr>
<tr>
<td>Inferior temporal gyrus</td>
<td>3.12</td>
<td>35.14</td>
</tr>
<tr>
<td>Thalamus</td>
<td>3.11</td>
<td>39.07</td>
</tr>
</tbody>
</table>

The first column lists ROIs (defined by the JHU atlas) in which damage was identified to be associated with the behavioral speech characteristics of aphasia. The second column displays the percent of each behaviorally related statistical map (ie, cluster) that was distributed within each identified ROI. The third column displays the proportion of each ROI compromised. For example, the superior temporal gyrus was associated with aphasia, accounting for 9.66% of the voxels associated with this deficit and a total of 76.05% of the voxels in this region. JHU indicates Johns Hopkins University; and ROI, region of interest.

**Table 2. Anatomic Regions Associated With AOS**

<table>
<thead>
<tr>
<th>ROIs Associated With AOS Characteristics</th>
<th>Percent of the AOS-Related Cluster Within Each ROI</th>
<th>Percent of the ROI Damaged</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precentral gyrus</td>
<td>48.65</td>
<td>29.91</td>
</tr>
<tr>
<td>Postcentral gyrus</td>
<td>21.05</td>
<td>13.82</td>
</tr>
<tr>
<td>Superior corona radiata</td>
<td>10.80</td>
<td>26.95</td>
</tr>
<tr>
<td>Superior longitudinal fasciculus</td>
<td>9.78</td>
<td>25.07</td>
</tr>
<tr>
<td>Supramarginal gyrus</td>
<td>4.59</td>
<td>4.51</td>
</tr>
</tbody>
</table>

The first column lists ROIs (defined by the JHU atlas) in which damage was identified to be associated with the behavioral speech characteristics of AOS. The second column displays the percent of each behaviorally related statistical map (ie, cluster) that was distributed within each identified ROI. The third column displays the proportion of each ROI compromised. For example, the precentral gyrus was associated with AOS, accounting for 48.65% of the voxels associated with this deficit and a total of 29.91% of the voxels in this region. AOS indicates apraxia of speech; JHU, Johns Hopkins University; and ROI, region of interest.

**Figure 2.** Patterns of damage related to apraxia of speech (blue) and aphasia (red) and shared by both disorders (yellow). Colored regions survived a $P$ value of <0.05 threshold controlling for both multiple comparisons and the variability described by the other deficits.
and classification of production errors, based on expert opinion, and development of a tool for 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 dysarthria. It has also been used in many studies to explicitly describe and further localize production deficits in AOS19 and progressive AOS.16-18,20

Although previous work has localized AOS to the left SPG of the insula2,13 or the left IFG,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 AOS19 and primary progressive apraxia of speech.16-20 We did not find evidence of insula involvement in predicting AOS, similar to recent studies with primary progressive apraxia of speech.17,18 Furthermore, a recent functional MRI study in neurologically intact individuals 15 found evidence of insula 12,13 or the left IFG, 10,11 this study provides converging evidence between auditory representations of words (stored in ventral stream areas24) and articulatory programs that are executed in precentral 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 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,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 areas44) and articulatory programs that are executed in cortical motor areas.45

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.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.

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Disclosures

None.

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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

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