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Research report

Role of the precentral gyrus of the insula in complex articulation

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ABSTRACT

Previous research has suggested that the left anterior insula, specifically the superior precentral gyrus of the insula (SPGI), is a critical brain region for the coordination of complex articulatory movements. However, previous studies have not determined which articulatory factors are specifically dependent on this brain region. In the current study, 33 left hemisphere stroke patients with varying degrees of speech impairment were asked to perform multiple repetitions of single words that varied along three separate dimensions: number of syllables, degree of articulatory travel (i.e., change between places of articulation for consonants), and presence/absence of an initial consonant cluster. The role of the SPGI in performance across the three conditions was determined using voxel-based lesion symptom mapping (VLSM), a statistical approach to lesion analysis that does not require separating patients based on lesion site or symptom profile. Rather, continuous performance data are entered, along with lesions reconstructed in normalized space. Based on preliminary analyses, there was adequate power to detect differences in the SPGI, which was the focus of our predictions. We found that the SPGI was critical for performance on the articulation task across all three conditions, namely, when words were multi-syllabic, required a high degree of travel, or involved an initial consonant cluster. As a control, we also generated a VLSM map for articulation of words with minimal articulatory complexity (i.e., single-syllable words with no initial cluster and a minimal change in place of articulation). In this case, the SPGI was not implicated. The current results suggest that the left SPGI is a critical area for intra- and inter-syllabic coordination of complex articulatory movements, prior to end-stage execution of speech commands.

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Articulation is a complex process that involves rapid, precise, orchestrated coordination of a large number of muscles. Previous research has attempted to delineate the specific

cognitive and neural processes involved in this complex and uniquely human ability (Ackermann and Riecker, 2004; Blank et al., 2002; Dronkers, 1996; Levelt, 2001; Murphy et al., 1997;

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Nota and Honda, 2004; Riecker et al., 2000a, 2000b; Vargha-Khadem et al., 1998; Wildgruber et al., 1996; Wise et al., 1999). One way to analyze the processes involved in articulation is to study patients who have specific articulatory deficits, such as apraxia of speech (AOS; Ogar et al., 2005). AOS is an articulatory impairment at the level of the motor speech coordinator, an intermediate stage between language formulation and speech execution (Darley et al., 1975; Duffy, 1995). The motor speech coordinator is critical for implementing the abstract phonologic representation of an utterance by creating a coordinated motor plan for the various articulators (i.e., lips, tongue, palate, etc.) and then sending that plan to motor execution centers (Duffy, 1995). In addition, the motor speech coordinator is thought to monitor the execution of that utterance and update it as necessary. When the motor speech coordinator is disrupted, as in patients with AOS, speech becomes slow and halting with a large number of inconsistent articulation errors, commonly involving distortions and perceived substitutions (Duffy, 1995; Kirshner, 1995; McNeil et al., 1997; Wertz et al., 1991). For example, in an attempt to say the word *grief*, one of our patients with AOS said /gris...riss... riff./ As is typical in AOS, there is an effort to correct each attempt with a modified utterance, but each utterance is unique. This pattern is in contrast to a motor execution disorder like dysarthria, in which repeated utterances exhibit more consistent distortions (Duffy, 1995; Wertz et al., 1984).

Previous studies have attempted to determine the neural basis for AOS, and thus, for articulatory coordination. Dronkers (1996) showed that a critical brain region underlying AOS is the anterior insula, specifically, the left superior precentral gyrus of the insula (SPGI). Critically, all 25 patients with AOS in that study had lesions encapsulating this region, while 19 patients without AOS all spared this region (though they had similarly large middle cerebral artery lesions). A number of case studies of AOS with anterior insular damage have also been reported in the literature. Nagao et al. (1999) reported a patient with a small infarct restricted to the left anterior insula (precentral gyrus) who presented with a speech coordination impairment but no aphasia. The patient had difficulty initiating speech and produced inconsistent errors in repetition, hallmarks of AOS. Also, Shuren (1993) described a case of a left antero-inferior insular stroke that resulted in a chronic speech initiation problem with intact language. Finally, Marien et al. (2001) reported a case of a left anterior insular stroke who suffered a severe AOS, marked by groping and struggling, and articulatory distortions, with errors increasing along with word length. Taken together, these studies suggest that anterior portions of the insula are critical for articulatory coordination.

Recently, Ogar et al. (2006) analyzed the types of errors made by AOS patients on a standardized test, the Motor Speech Evaluation (MSE; Wertz et al., 1984). They found that AOS patients with insula lesions were most impaired on items requiring the coordination of complex articulatory movements (e.g., when repeating /pataka pataka pataka/). Even the most mildly affected AOS patients were impaired on such items, although they (unlike more severely affected AOS patients) were much less impaired on items requiring only simple articulatory movements (e.g., sequential

diadochokinesis or saying /ka ka ka ka/). In this and previous studies, however, the various factors that might contribute to articulatory complexity (e.g., number of syllables, travel, etc.) could not be systematically teased apart.

In the present study, we tested a group of left hemisphere stroke patients on an experimental paradigm that allowed us to manipulate three articulation complexity factors: number of syllables, degree of articulatory travel, and presence of an initial consonant cluster. We wanted to determine which of these factors would be related to the integrity of the SPGI. Unlike previous studies that separated patients a priori based on motor speech profiles, we examined a group of patients with a wide range of AOS severity from none to severe and used voxel-based lesion symptom mapping (VLSM) to relate articulation errors to lesion site. VLSM is a statistical approach that involves comparing performance between patients with and without a lesion in every voxel on a given performance measure. Thus, rather than dividing patients into AOS and non-AOS groups, we could relate the continuous range of performance to voxel-based lesion maps. We hypothesized that lesions in the SPGI would be associated with increased rates of apraxic errors in articulation when stimuli involved a greater degree of articulatory travel, initial consonant clusters, or multiple syllables.

1. Methods

1.1. Participants

The study included 33 patients (27 males) who had a history of a single, left hemisphere stroke. Other study criteria included that patients be right-handed and native English speakers, with no prior history of psychiatric or neurologic disorders. Patients were included in the current study based on availability for testing and were not chosen based on symptomatology or deficit profile. Three additional patients with severe aphasia, two Wernicke's and one global, were initially tested but were not included in the study because they were unable to comply with task instructions. This decision to exclude these three patients was made prior to data analysis on the recommendation of the examiners who were blind to the imaging data. Patients' mean age was 58.6 (standard deviation – SD = 9.9), mean years of education were 15.9 (SD = 2.4), and mean months post-onset of stroke was 60.3 months (SD = 54.3). A subset of the patients tested in the current study was included in an earlier paper that tested performance on a clinical motor speech battery (Ogar et al., 2006).

1.2. Methods and procedures

All patients were assessed with a battery of speech and language instruments. The primary measure of language competence was the Western Aphasia Battery (WAB; Kertesz, 1982), which assesses a variety of speech and language functions including fluency, naming, repetition, and comprehension. The mean score was 85.4 out of 100 (SD = 19.9; range 16.2–100). Based on the subtest cut-off scores on the WAB, the sample included 7 patients with anomia, 4 patients with Broca's aphasia, 1 patient with global aphasia, 1 patient

with transcortical sensory aphasia, 5 patients who were unclassifiable, and 15 patients who scored within normal limits. Patients were also assessed with a motor speech evaluation (MSE; Wertz et al., 1984) by a trained speech-language pathologist. The mean MSE score of the entire group was 1.1 out of 7 (SD = 1.8, range 0–6). Of the 33 patients, 12 exhibited symptoms of AOS: 7 mild (MSE score of 1–3), 4 moderate (MSE score of 4–5), and 1 severe (MSE score of 6–7). The other 21 patients scored in the normal range. Because the current study employed a voxel-based lesion approach, patients were not separated into groups based on lesion site or presence of AOS, but rather all patients' behavioral scores and lesion data were entered into the analyses.

In a separate testing session, patients were administered an experimental test of articulation by two different licensed speech pathologists who were blind to the lesion analysis data. This test required patients to repeat an auditorily-presented word five times in succession. For example, the examiner would say *spaghetti*, and the patient was asked to repeat the word five times. There were 48 words in total (see Table 1 for stimuli), and they varied on three dimensions: number of syllables, initial consonant cluster, and degree of travel. We chose to look at these three aspects of articulation, because they were suggested to be critical factors in a previous study on AOS (Ogar et al., 2006). The stimuli were all low frequency nouns (Kucera–Francis count < 34), with word frequency matched across the three condition comparisons (i.e., low- vs high-travel, initial cluster vs no initial cluster, and 1-syllable vs 3-syllable words; all $ps < .05$). Data regarding other variables such as familiarity and age of acquisition were

not available for all stimuli due to the use of low frequency words. Half of the stimuli were 1-syllable words, and the other half were 3-syllable words. Half of the words began with a consonant cluster (e.g., *drill*), and the other half did not (e.g., *zeal*). Half of the words had a low degree of travel (i.e., the consonants were in a similar place of articulation, e.g., *nicety*), and the other half, a high degree of travel (e.g., *tobacco*). The low-travel condition consisted of words ranging between zero travel (e.g., *sanity*) and one place transition (e.g., *flattery*), while the high-travel condition included words with one, two (e.g., *tobacco*), and three place transitions (e.g., *spaghetti*). The degree of travel was based on the number of movements only; we did not factor in the “distance” (i.e., /pa/ to /ta/ was considered the same as /pa/ to /ka/).

The test was videotaped, and the speech pathologist scored any apraxic errors in the patient's performance. Patients received a score of 0 or 1 for each stimulus word (i.e., trial of 5 repetitions). If there were no errors on the 5 repetitions, it was scored as 0, and if there were 1 or more errors on the 5 repetitions, it was scored as 1 (i.e., whether the patient made 1 or 5 errors on the 5 repetitions, it was scored as a single error). Other errors such as those due to dysarthria or perseveration were not scored as errors. There were two different orders of stimuli, each given to half of the examinees. Stimuli were pseudo-randomly ordered so that no two successive stimuli came from the same condition.

Patients were scanned with CT or MRI at least three months post-onset of their stroke. For those patients who were tested months after their CT/MRI scan, neurologic status was monitored for changes via medical records, clinical observation, and caregiver report. Most of the patients' lesions (67%) were reconstructed based on high-resolution T1-weighted structural 3D MRI scans obtained from a 1.5 T Phillips Eclipse scanner. T1-weighted images were acquired with a Spoiled Gradient Recall (SPGR) sequence (TR/TE = 15/4.47 msec, FOV = 240 mm, 256 × 256 imaging matrix, flip angle = 35°, .94 × 1.3 × .94 mm³ voxels, 212 coronal slices). If patients were unable to undergo MRI scanning (e.g., due to the presence of magnetic materials), they were scanned with a Picker 3D CT scanner. For patients who had digital MRI images available, lesions were traced directly onto T1 scans using MRicro software (Rorden and Brett, 2000). A board-certified neurologist (blind to the patients' symptoms and study goals) reviewed the reconstructions for accuracy. The scans were then non-linearly transformed into MNI space (152-MNI template) in SPM5 (see Brett et al., 2001). Lesion masks were used for each reconstruction during the normalization procedure (i.e., cost function masking). When digital MRI images were not available, the same board-certified neurologist reconstructed patients' lesions from hard-copy images onto an 11-slice, standardized template (based on the atlas by DeArmond et al., 1989). Reliability has been demonstrated previously using this technique (Friedrich et al., 1998; Knight et al., 1988). These templates were then digitized and non-linearly transformed into MNI space (Collins et al., 1994) using SPM5. For this transformation, slices from the two templates were aligned using 50 control point pairs to match anatomical features on the two templates, and the slices were then aligned using a local weighted mean transformation implemented by the *cpselect*, *cp2tform* and *imtransform* functions in Matlab 6.5. These

Table 1 – Experimental stimuli in articulation task.

		No initial cluster	Initial cluster		
1-syllable words	Low-travel	zeal (8)	drill (33)		
		loot/lute (3/1)	stool (8)		
		ruse (2)	truce (5)		
		dune (1)	sleet (1)		
		dud (1)	snout (1)		
		soot (1)	drone (3)		
		loop (21)	gloom (14)		
	High-travel	rouge (7)	grief (10)		
		doom (3)	throng (3)		
		wreath (8)	scum (0)		
		kite (1)	flak (0)		
		shoal (0)	quail (0)		
		3-syllable words	Low-travel	sonata (9)	clarity (28)
				sanity (4)	florida (20)
retina (1)	trinity (5)				
nicety (0)	flattery (3)				
detainee (0)	glossary (3)				
tyranny (11)	granada (0)				
tobacco (19)	gravity (7)				
High-travel	therapy (12)		spaghetti (1)		
	canopy (2)		schemata (1)		
	machete (0)		fricassee (0)		
	cassava (0)		plethora (0)		
	vagary (0)		glaucoma (1)		

Note. The Kucera and Francis word frequency rating is provided in parentheses.

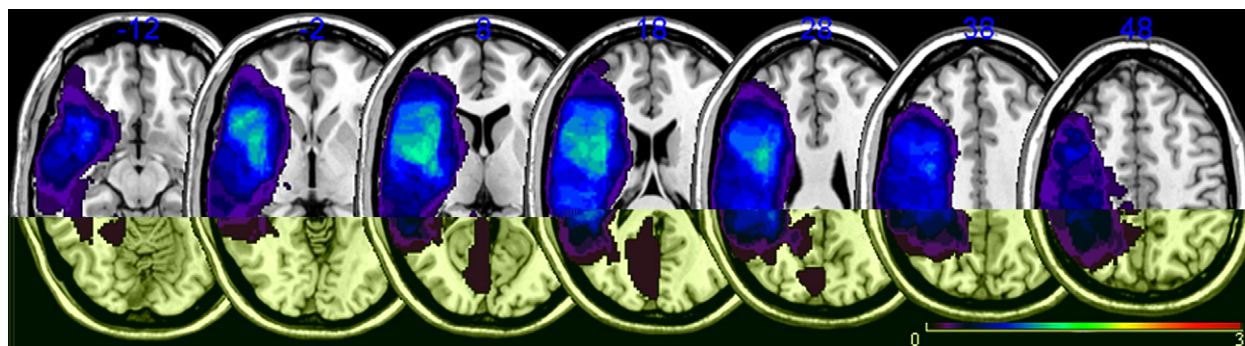


Fig. 1 – Overlay of all patients' lesions. Brighter areas indicate areas of greater lesion overlap.

algorithms were then used to warp all the lesion reconstructions from the 11-slice template into MNI space.

An overlay map of the patients' lesions is shown in Fig. 1. Patients' lesions were primarily in the left middle cerebral artery distribution. A power map was generated in order to determine those voxels in which there was enough power to detect significant differences (see Fig. 2). Power was based on an alpha of .05 and an effect size of .8 (Cohen, 1988, 1992; Kimberg et al., 2007). As can be seen in Fig. 2, there was sufficient power in the region of the insula, which was the main focus of comparisons in the current study.

Next, we used VLSM to relate lesion site to patients' performance on the three articulatory conditions (see Bates et al., 2003). VLSM provides a voxel-by-voxel analysis of brain regions involved in performance and uses all patient data, rather than dividing patients based on performance or lesion location. Only voxels containing at least 10 patients with and without a lesion were included in the analysis, in order to avoid spurious results. That is, if a voxel was lesioned in too few patients (<10), it was not included in the VLSM analysis, and if a voxel was lesioned in too many patients (i.e., in all patients but a few), it was also not included in the analysis.

The VLSM procedure involved running a general linear model (GLM) on the data, where the predictor variable was lesion (present or not in that voxel), and the outcome variable was the number of errors on the different conditions. The VLSM analysis was subjected to permutation testing using Matlab, in order to determine a critical t cut-off (at $p < .05$), based on 1000 random permutations of the data. This procedure has been recommended for the analysis of lesion data and has been

compared to other types of statistical corrections (see Kimberg et al., 2007). The permutation testing involved randomly reassigning the data to patients 1000 times, and for each permuted dataset, the GLM was refit. VLSM maps were then generated, based on the resultant t values for those voxels reaching the critical t value ($t = 4.10$ for the high-travel condition, $t = 3.98$ for low-travel, $t = 3.86$ for initial cluster, $t = 4.02$ for no initial cluster, $t = 3.90$ for 1-syllable, and $t = 4.17$ for the 3-syllable condition). In order to quantify the degree of involvement of the SPGI, we drew a volume of interest (VOI) for this region and calculated the percentage of voxels in this region that were significantly related to performance in each condition.

2. Results

2.1. Behavioral analysis

Error rates across the six different stimulus conditions were calculated and paired samples t -tests were run comparing the three main contrasts. Articulation of 3-syllable words produced significantly more errors than articulation of 1-syllable words, $t(32) = -4.03$, $p < .001$ ($M = 28\%$ vs 17% , respectively). Similarly, articulation of words with a high degree of travel produced more errors than words with less travel, $t(32) = -3.24$, $p < .01$ ($M = 26\%$ vs 20% , respectively). Articulation of words with initial clusters also produced numerically more errors than words with no initial cluster ($M = 24\%$ vs 22%), but this difference was not statistically significant, $t(32) = -.87$, ns.

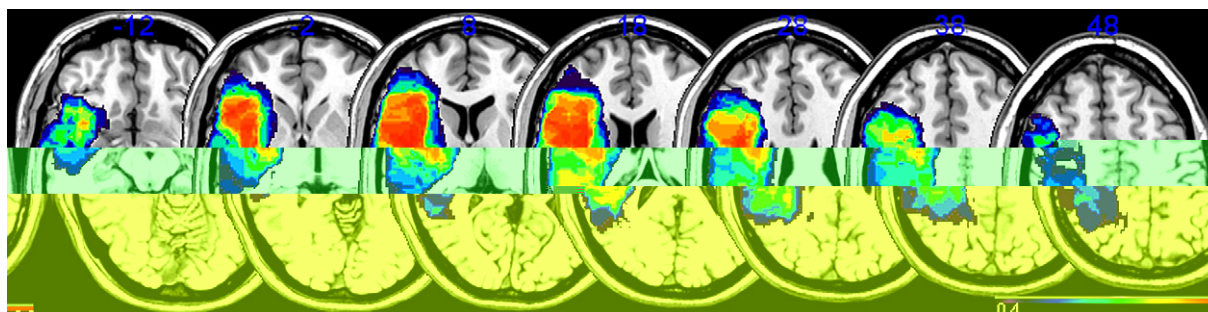


Fig. 2 – Map showing distribution of power, ranging from .4 (purple) to .8 and higher (red). Predictions for the current study were restricted to these brain regions.

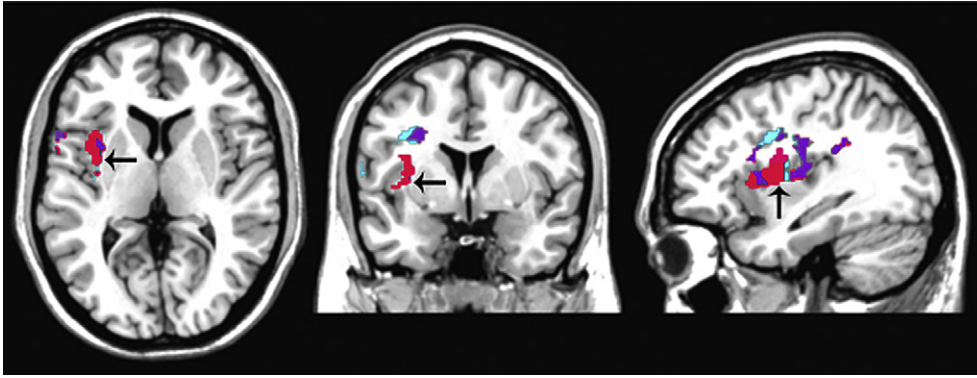


Fig. 3 – VLSM map showing voxels associated with repeating 1-syllable words (in light blue) versus 3-syllable words (in red). Areas associated with both conditions are shown in purple. The arrows indicate the location of the SPGI.

2.2. Lesion analysis

VLSM maps were generated for all three articulatory comparisons (number of syllables, degree of travel, and presence of initial consonant cluster), where the number of errors was the dependent measure. Only significant voxels reaching the critical *t* cut-off threshold are shown in the VLSM maps.

First, we generated VLSM maps to determine areas significantly associated with articulating 1-syllable and 3-syllable words (shown in light blue and red in Fig. 3, respectively, with regions of overlap shown in purple). As predicted, performance on the 3-syllable condition was associated with a large area of significance in the SPGI (centered at MNI $-36, 1, 10$). Specifically, the percentage of voxels in the SPGI that were significantly related to performance was much greater for the 3-syllable (22%) versus the 1-syllable condition (3%). Both conditions were also associated with a small number of significant voxels in pre-motor cortex ($-32, 2, 33$), rolandic operculum (inferior motor strip; $-59, -3, 11$), frontal inferior operculum ($-44, 15, 11$), superior temporal gyrus ($-57, -28, 16$), and supramarginal gyrus ($-45, -34, 25$), as well as white matter superior to the insula ($-35, -14, 26$).

The VLSM maps for articulation of words with low- versus high-travel revealed a similar pattern (see Fig. 4). Again, articulation of high-travel words showed a greater

dependence specifically in the SPGI (centered at $-36, 1, 10$), relative to the low-travel condition (significant voxels in 28% vs .8% of SPGI, respectively). Again, both conditions were associated with a small number of significant voxels in pre-motor cortex ($-32, 2, 33$), rolandic operculum ($-63, -4, 11$), frontal inferior operculum ($-44, 15, 11$), superior temporal gyrus ($-57, -28, 16$), and supramarginal gyrus ($-45, -34, 25$), as well as white matter superior to the insula ($-35, -14, 26$).

Next, we generated VLSM maps for articulation of words with an initial consonant cluster versus no initial consonant cluster (see Fig. 5). Again, as can be seen, articulation of words with an initial cluster (shown in red) was associated with a much larger area of significance in the left SPGI relative to articulation of words with no initial cluster (28% vs 6% of the SPGI; $-36, 1, 10$). As above, both cluster conditions were also associated with a small number of significant voxels in pre-motor cortex ($-32, 2, 33$), rolandic operculum (inferior motor strip; $-62, -3, 11$), frontal inferior operculum ($-44, 15, 11$), superior temporal gyrus ($-57, -28, 16$), and supramarginal gyrus ($-45, -34, 25$), as well as white matter superior to the insula ($-35, -14, 26$).

Last, given that all three complexity factors (number of syllables, degree of travel, and initial cluster) appeared to have similar effects in terms of their reliance on the SPGI, we also generated maps to compare articulation of words with minimal

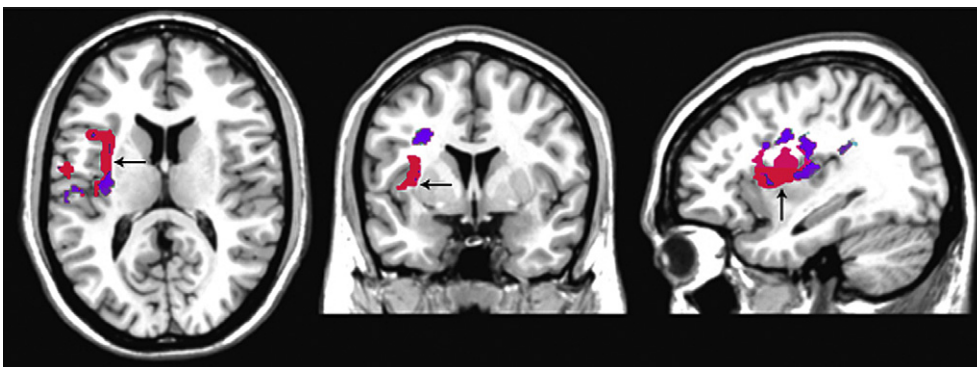


Fig. 4 – VLSM map showing voxels significantly associated with repeating words with low-travel (in light blue) versus high-travel (in red). Regions of overlap between the two conditions are shown in purple. The arrows indicate the location of the SPGI.

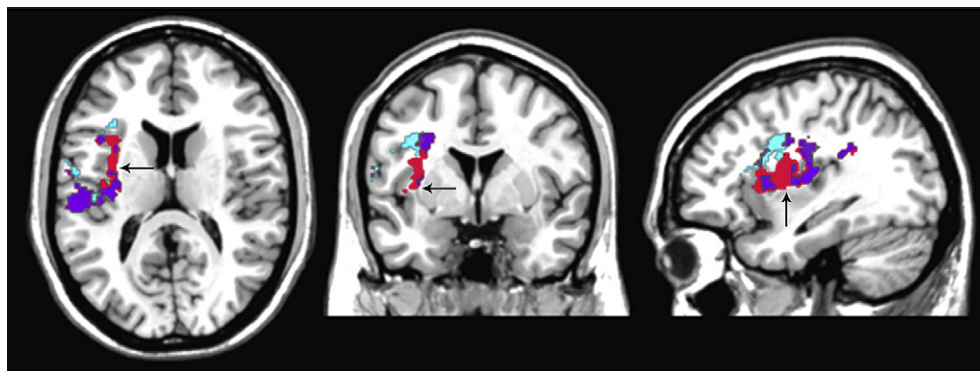


Fig. 5 – VLSM map showing significant voxels associated with articulation of words with no initial consonant cluster (shown in light blue) and articulation of words with an initial cluster (in red). Regions of overlap between the two conditions are shown in purple. The arrows indicate the location of the SPGI.

complexity such as *soot* (i.e., single-syllable, low-travel, no initial cluster) versus articulation of words with all three complexity factors combined such as *fricassee* (i.e., 3-syllable, high-travel, initial cluster).

When all three complexity factors were combined, the SPGI (centered at $-36, 1, 10$) was again critical for performance (see Fig. 6), whereas when articulatory complexity was minimal, the SPGI showed almost no involvement (50% vs 2% of SPGI, respectively). Thus, this analysis shows that having a lesion in the SPGI versus not having a lesion in the SPGI leads to differential performance on the most difficult articulation condition, suggesting that this region is critical for complex articulation. The fact that the SPGI shows minimal involvement for the easy articulation condition suggests that having a lesion in the SPGI is not likely to disrupt performance with such easy articulation demands.

3. Discussion

The current study assessed the role of the left SPGI in complex articulation based on three factors: number of syllables, degree of travel, and initial cluster. We used VLSM,

a technique that statistically relates lesion site to performance on a continuous measure without requiring any a priori division of patients into groups based on speech profile or lesion site. We found that the SPGI was critical for complex articulatory movements in all three cases: when the stimuli were multi-syllabic, had a high degree of travel between places of articulation, and began with a consonant cluster. Moreover, when articulatory complexity was minimized (i.e., when articulating single-syllable words with minimal travel and no initial cluster), performance was minimally dependent on the SPGI. The current findings expand upon prior lesion studies of patients with articulatory deficits such as AOS that suggest that the left SPGI is critical for both intra- and inter-syllabic coordination of the articulators during complex speech production (Dronkers, 1996; Marien et al., 2001; Nagao et al., 1999; Ogar et al., 2006; Shuren, 1993). Specifically, the results suggest that the SPGI is necessary for the coordination of rapidly-changing articulatory movements. Words with more syllables, words whose consonants change in place of articulation, or words with consonant clusters all require rapid tongue or lip alterations from one position to another. As these demands increase, the need for the SPGI also appears to increase.

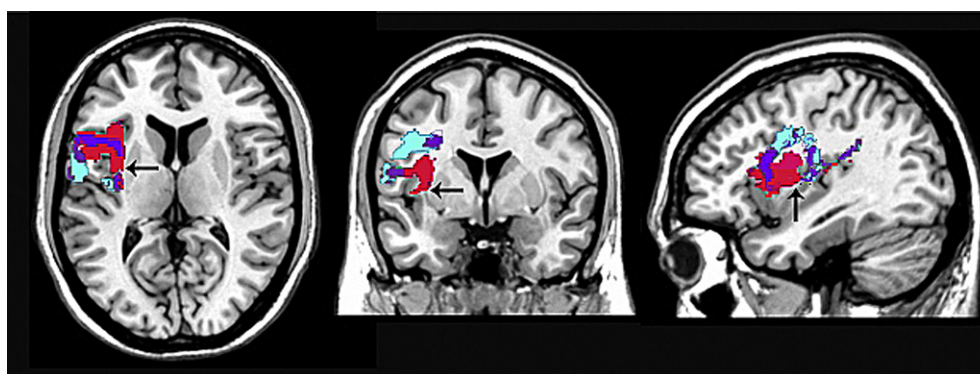


Fig. 6 – VLSM maps showing significant voxels associated with articulation of words with a high degree of articulatory complexity (3-syllable, high-travel, initial cluster) shown in red and articulation of words with minimal articulatory complexity (1-syllable, low-travel, no initial cluster) shown in light blue. Regions of overlap between the two conditions are shown in purple. The arrows indicate the location of the SPGI.

The current findings are not only consistent with previous lesion studies implicating this area in the coordination of complex articulatory movements (reviewed above) but are also consistent with findings from a number of functional imaging studies (Bohland and Guenther, 2006). For example, Wise et al. (1999) conducted a PET study in which articulation (using word repetition) was associated with activation in the left anterior insula and bilateral sensorimotor cortex, as well as the left basal ganglia, anterior cingulate, and right cerebellum. An functional magnetic resonance imaging (fMRI) study by Nota and Honda (2003) found that the anterior insula was activated when normal participants uttered various CVCVCV syllables in a random fashion, although the region was not active in a repetition block when participants repeated the same syllables over and over. Riecker et al. (2000a) reported anterior insula activation during automatic speech (recitation of months of the year), which was only significant during overt, not covert, speech. Because the anterior insula was only active during overt speech, they concluded that this brain region was more directly involved in muscle control during articulation, as opposed to playing a role in the planning aspect of articulation (see review by Ackermann and Riecker, 2004). However, the distinction between the processes involved in overt and covert speech is poorly understood. It is possible that covert speech does not engage the same articulatory planning processes as overt speech. For example, a PET study by Sakurai et al. (2001) found that the insula was active when participants were reading out loud (along with sensorimotor and supplementary motor areas) but not when they read covertly.

At the same time, a number of papers have failed to find insula activation during articulation tasks (e.g., Murphy et al., 1997; Nota and Honda, 2004). Riecker et al. (2000b) manipulated syllable structure and did not observe insula activation in an fMRI study, even with multi-syllabic stimuli. However, the authors themselves suggest that the slowed rate of recitation used in the study could have caused this failure to observe insula activation, since that reduced the articulatory load. Activations were predominantly in sensorimotor cortex, with monosyllables being bilateral and polysyllables being more left hemisphere lateralized. Murphy et al. (1997) had participants repeat the bilabial phrase *Buy Bobby a poppy* in a PET study and found that such *speaking without language* resulted in predominantly bilateral activations, primarily in sensorimotor cortex and the cerebellum. Broca's area was not activated; nor was the insula highlighted, although there was a region associated with articulation that was in the vicinity of Dronkers' (1996) SPGI coordinates. It is possible that the insula was not more directly involved due to the fact that the same stimulus was repeated over and over, and it was a completely bilabial, overlearned phrase that involved no travel or consonant clusters. Bilabial sounds are the least likely to be affected in AOS (LaPointe and Johns, 1975). Last, Nota and Honda (2004) failed to find insular activation in their fMRI study of articulation that required participants to repeat overlearned phrases (*Good morning, Good afternoon, and Good evening*). In a recent review, Ackermann and Riecker (2004) posited that more automatic articulation is subserved by classic motor and premotor regions, while sequencing less automatic and longer syllables requires a separate set of neural processes (possibly

instantiated in the insula). Indeed, AOS patients commonly have much less difficulty with automatic phrases (Kirshner, 1995; Wertz et al., 1991).

Limitations of the current study include the fact that we were not able to fully sample the left hemisphere in the VLSM analyses. This was in part due to the nature of the patients' lesions (arising from predominantly middle cerebral artery strokes) and the statistical requirements of our lesion analysis (i.e., at least ten patients with and without a lesion in every voxel to be sampled). However, there was adequate power in the insular region, which was the focus of our predictions. It should be noted that the insula findings here are very specific to the current articulation task and do not reflect an artifact of the nature of the patients' lesions: A number of recent studies from our lab using similar groups of patients and the same VLSM methodology to study neural correlates of other cognitive processes that do not involve complex articulation have not found any association with the SPGI (e.g., Baldo et al., 2010).

It is also important to note that, due to the constraints of English phonetics, it was difficult to create articulation conditions that were "pure" (e.g., 3-syllable words with absolutely no travel). Therefore, we focused on the relative difference between the critical comparisons (i.e., 1- vs 3-syllable words, initial cluster vs no initial cluster, and low- vs high-travel). As predicted, the critical conditions showed more dependence specifically on the SPGI, relative to their respective baseline conditions. Another final issue to consider is that it is very likely that a certain degree of brain reorganization occurs following stroke due to natural recovery and rehabilitation efforts. Such reorganization may affect the results of such a study completed in the chronic phase of stroke. It is important to note, however, that participants were tested in the post-acute phase of stroke, when both lesion site and behavioral profile were relatively stable. Thus, the current results reflect a stabilized brain-behavior relationship that is quite robust and consistent.

In short, the current study is a confirmation of the role of the left SPGI in complex articulation using a novel, voxel-based technique that did not have the same limitations as previous lesion overlay studies. Unlike traditional lesion studies, what the VLSM analysis shows are those voxels most critical for a particular condition, rather than the pattern of lesions in patients with a particular deficit. The study also expands on previous findings by identifying the critical factors associated with complex articulation that engage the left SPGI. Specifically, we found that the SPGI is critically involved in the ability to articulate multi-syllabic words with a high degree of travel and initial consonant clusters. Articulation of simple, single-syllable words was minimally dependent on this region. Therefore, the SPGI appears to be preferentially recruited under difficult articulation conditions, prior to end-stage execution of speech production.

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REFERENCES

- Ackermann H and Riecker A. The contribution of the insula to motor aspects of speech production: A review and a hypothesis. *Brain and Language*, 89: 320–328, 2004.
- Baldo JV, Bunge SA, Wilson SM, and Dronkers NF. Double dissociation of regions underlying distinct forms of visual reasoning. *Brain and Language*, 113: 59–64, 2010.
- Bates E, Wilson S, Saygin A, Dick F, Sereno MI, Knight RT, et al. Voxel-based lesion-symptom mapping. *Nature Neuroscience*, 6: 448–450, 2003.
- Blank S, Scott S, Murphy K, Warburton E, and Wise R. Speech production: Wernicke, Broca and beyond. *Brain*, 125: 1829–1838, 2002.
- Bohland JW and Guenther FH. An fMRI investigation of syllable sequence production. *NeuroImage*, 32: 821–841, 2006.
- Brett M, Leff AP, Rorden C, and Ashburner J. Spatial normalization of brain images with focal lesions using cost function masking. *NeuroImage*, 14: 486–500, 2001.
- Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. 2nd ed. Hillsdale, NJ: Earlbaum, 1988.
- Cohen J. A power primer. *Psychological Bulletin*, 112: 155–159, 1992.
- Collins DL, Neelin P, Terrence P, and Evans A. *Journal of Computer Assisted Tomography*, 18: 192–205, 1994.
- Darley FL, Aronson AE, and Brown JR. *Motor Speech Disorders*. Philadelphia: Saunders, 1975.
- DeArmond SJ, Fusco MM, and Dewey MM. *Structure of the Human Brain*. New York: Oxford University Press, 1989.
- Dronkers NF. A new brain region for coordinating speech articulation. *Nature*, 384: 159–161, 1996.
- Duffy J. *Motor Speech Disorders: Substrates, Differential Diagnosis, and Management*. St. Louis: Mosby, 1995.
- Friedrich FJ, Egly R, Rafal RD, and Beck D. Spatial attention deficits in humans: A comparison of superior parietal and temporal-parietal junction lesions. *Neuropsychology*, 12: 193–207, 1998.
- Kertesz A. *Western Aphasia Battery*. New York: Grune and Stratton, 1982.
- Kimberg DY, Coslett HB, and Schwartz MF. Power in voxel-based lesion-symptom mapping. *Journal of Cognitive Neuroscience*, 19: 1067–1080, 2007.
- Kirshner HS. Apraxia of speech. In Kirshner H (Ed), *Handbook of Neurological Speech and Language Disorders*. Informa Health Care, 1995: 41–55.
- Knight RT, Scabini D, Woods DL, and Clayworth C. The effects of lesions of superior temporal gyrus and inferior parietal lobe on temporal and vertex components of the human AEP. *Electroencephalography and Clinical Neurophysiology*, 70: 499–509, 1988.
- LaPointe L and Johns D. Some phonemic characteristics in apraxia of speech. *Journal of Communicative Disorders*, 8: 259–269, 1975.
- Levelt WJM. Spoken word production: A theory of lexical access. *Proceedings of the National Academy of Sciences USA*, 98: 13464–13471, 2001.
- Marien P, Pickut BA, Engelborghs S, Martin JJ, and De Deyn PP. Phonological agraphia following a focal anterior insulo-opercular infarction. *Neuropsychologia*, 39: 845–855, 2001.
- McNeil M, Robin D, and Schmidt R. Apraxia of speech: Definition, differentiation, and treatment. In McNeil MR (Ed), *Clinical Management of Sensorimotor Speech Disorders*. New York: Thieme Medical Publishers, 1997: 311–344.
- Murphy K, Corfield DR, Guz A, Fink GR, Wise R, Harrison J, et al. Cerebral areas associated with motor control of speech in humans. *Journal of Applied Physiology*, 83: 1438–1447, 1997.
- Nagao M, Takeda K, Komori T, Isozaki E, and Hirai S. Apraxia of speech associated with an infarct in the precentral gyrus of the insula. *Neuroradiology*, 41: 356–357, 1999.
- Nota Y and Honda K. Possible role of the anterior insula in articulation. In Proceedings of the 6th International Seminar on Speech Production, Sydney, 2003.
- Nota Y and Honda K. Brain regions involved in motor control of speech. *Acoustical Science and Technology*, 25: 286–289, 2004.
- Ogar J, Slama H, Dronkers NF, Amici S, and Gorno-Tempini M. Apraxia of speech: An overview. *Neurocase*, 11: 427–432, 2005.
- Ogar J, Willock S, Baldo JV, Wilkins D, Ludy C, and Dronkers NF. Clinical and anatomical correlates of apraxia of speech. *Brain and Language*, 97: 343–350, 2006.
- Riecker A, Ackermann H, Wildgruber D, Dogil G, and Grodd W. Opposite hemispheric lateralization effects during speaking and singing at motor cortex, insula and cerebellum. *NeuroReport*, 11: 1997–2000, 2000a.
- Riecker A, Ackermann H, Wildgruber D, Mayer J, Dogil G, Haider H, et al. Articulatory/phonetic sequencing at the level of the anterior perisylvian cortex: A functional magnetic resonance imaging (fMRI) study. *Brain and Language*, 75: 259–276, 2000b.
- Rorden C and Brett M. Stereotaxic display of brain lesions. *Behavioural Neurology*, 12: 191–200, 2000.
- Sakurai Y, Momose T, Iwata M, Sudo Y, Ohtomo K, and Kanazawa I. Cortical activity associated with vocalization and reading proper. *Cognitive Brain Research*, 12: 161–165, 2001.
- Shuren J. Insula and aphasia. *Journal of Neurology*, 240: 216–218, 1993.
- Vargha-Khadem F, Watkins KE, Price CJ, Ashburner J, Alcock KJ, Connelly A, et al. Neural basis of an inherited speech and language disorder. *Proceedings of the National Academy of Sciences USA*, 95: 12695–12700, 1998.
- Wertz T, LaPointe L, and Rosenbek J. *Apraxia of Speech: The Disorders and Its Management*. New York: Grune and Stratton, 1984.
- Wertz T, LaPointe L, and Rosenbek J. *Apraxia of Speech in Adults: The Disorder and Its Management*. San Diego: Singular Publishing Group, 1991.
- Wildgruber D, Ackermann H, Klose U, Kardatzki B, and Grodd W. Functional lateralization of speech production at primary motor cortex: A fMRI study. *NeuroReport*, 7: 2791–2795, 1996.
- Wise RJ, Greene J, Buchel C, and Scott SK. Brain regions involved in articulation. *Lancet*, 353: 1057–1061, 1999.