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Regional Brain Dysfunction Associated with Semantic Errors in Comprehension

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Abstract

Here we illustrate how investigation of individuals acutely after stroke, before structure/function reorganization through recovery or rehabilitation, can be helpful in answering questions about the role of specific brain regions in language functions. Although there is converging evidence from a variety of sources that left posterior superior temporal gyrus plays some role in spoken word comprehension, its precise role in this function has not been established. We hypothesized that this region is essential for distinguishing between semantically related words, because it is critical for linking the spoken word to the complete semantic representation. We tested this hypothesis in 127 individuals with 48 hours of acute ischemic stroke, before the opportunity for reorganization or recovery. We identified tissue dysfunction (acute infarct and/or hypoperfusion) in grey and white matter parcels of the left hemisphere, and evaluated the association between rate of semantic errors in a word/picture verification tasks and extent of tissue dysfunction in each region. We found that after correcting for lesion volume and multiple comparisons, the rate of semantic errors correlated with the extent of tissue dysfunction in left posterior superior temporal gyrus and retrolenticular white matter.

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Keywords

aphasia; stroke; comprehension; semantics; brain mapping

Introduction

The types of errors individuals make after lesions to different regions of the brain can reveal the structure of cognitive and language mechanisms as well as the neural circuitry that supports these mechanisms^{1–3}. Semantic errors in naming, such as calling a sock “shoe” are quite common acutely after left hemisphere stroke, but can arise from different sources, including impairment in accessing semantics from vision^{4–8}, damage to the semantic system^{1,9,10} damage to access to lexical representations for output^{11–13}, or damage to an output buffer¹⁴. Crucially, these different mechanisms lead to different patterns of impairment, allowing careful behavioral testing to reveal the systems that are compromised. In the case of a lexical access deficit, the aphasic individual understands the word (e.g., as demonstrated by word/verification tasks) and can name the word in one modality (e.g., written naming) but not another (e.g., spoken naming). These data indicate that a semantically related phonological or orthographic representation can be accessed when the target is not accessible for output. In contrast, semantic errors in word/picture verification (i.e., accepting a semantically related word as the label of a picture) or in forced word-picture matching with semantically related foils, can be due to impaired access to semantics from vision^{4–8} or access to an incomplete semantic representation itself (e.g., <worn> <protect feet> for sock)^{10,13}. In the latter case, the underspecified semantic information might be equally compatible with both the target (sock) and semantically related foils (shoes, boots, slippers), so the participant will accept any of these words as the name of the picture (e.g., <worn> <protect feet> would also be compatible with “sock”, “shoe”, “boots”, etc.)¹⁵. Furthermore, the underspecified semantic information would activate both phonological representations and orthographic representations to which it corresponds (/sak/, /but/, makasin/, as well as sock, boot, moccasin, etc.), so the aphasic person would make semantic errors in both oral and written naming regardless of the input modality (e.g., tactile or visual)⁹. In contrast, in the rare cases of impaired access to the complete semantic representation from vision (cases of optic aphasia), the aphasic individuals make semantic errors in word/picture verification (or word-picture matching) and naming visual stimuli, but correctly name from tactile or auditory stimuli and correctly answer questions about objects (e.g., Do cats bark?) that they cannot name visually. The magnitude of impairment in either case can be measured by spoken word/picture verification with semantic foils, which is more sensitive than forced choice word/picture matching¹⁵.

While several studies have evaluated areas of brain damage associated with production of semantic errors in naming^{3,16–18}, only a few have accounted for distinct underlying deficits as the cause of semantic errors in naming. Also, many studies have evaluated brain damage associated with errors in word comprehension, but few have focused on semantic errors in spoken comprehension tasks. However, one seminal detailed study of chronic post-stroke aphasia¹⁹ reported that errors in spoken word comprehension that are specifically due to semantic impairment (ruling out visual-to-semantic impairment and lexical deficits as the

cause) were associated with damage to left posterior superior temporal gyrus (pSTG). However, this study was carried out before the development of sophisticated lesion-deficit mapping approaches, such as voxel-wise lesion symptom mapping^{20,21}. Furthermore, participants were studied long after stroke, so that some may have undergone reorganization of structure-function relationships or recovery, such that some areas critical to accessing complete semantics from spoken words for comprehension might have been missed.

Quite a few studies of chronic post-stroke aphasia have identified an association between impaired auditory word comprehension and lesions in left pSTG^{19,22–27}. Given this evidence, this area could be one where damage prevents recovery of word comprehension, or it could be a primary area supporting word comprehension in the intact brain. By studying participants acutely after stroke, we can identify areas of dysfunctional brain tissue associated with deficits before recovery or the opportunity for substantial structure-function reorganization. Magnetic resonance imaging (MRI) techniques of diffusion weighted imaging (DWI) and perfusion weighted imaging (PWI) can identify both infarcted and hypoperfused tissue (either of which can be responsible for acute deficits) a few hours after onset of stroke^{28–30}.

Word/picture verification requires accessing a complete semantic representation from both a spoken word and from a picture, as well as deciding whether the information accessed from the two stimuli is the same. Here we evaluate areas where acute ischemia is associated with different types of errors in auditory word/picture verification in order to evaluate whether the role of areas like pSTG in word comprehension is in distinguishing phonologically similar words, or rather distinguishing semantically related words. Specifically, we tested the hypotheses that acute infarct and/or hypoperfusion in left pSTG is associated with errors in distinguishing between semantically related spoken words (e.g., due to impaired access to the complete semantic representation).

Materials and Methods

Participants

We retrospectively analyzed prospectively collected data from 127 right-handed, English speaking individuals with an acute ischemic left hemisphere stroke who were enrolled in a language processing study at Johns Hopkins Hospital or Johns Hopkins Bayview Medical Center. Exclusion criteria included: uncorrected hearing loss or vision loss; age < 18 years; or impaired level of consciousness or ongoing sedation. For this analysis, we also excluded participants who made significantly more errors with visual relative to tactile or purely auditory stimuli on language testing (evidence of optic aphasia or visual agnosia); which excluded one person). All participants or their legally authorized representatives (for those with impaired comprehension) provided informed consent to participate. All enrolled participants had language testing and an MRI scan within 48 hours of onset of stroke symptoms. For the 127 included patients, mean age was 59 (SD 12.2) years; 52% were women. Mean education was 12.3 (SD 3.3) years.

Auditory Word Comprehension Test

The auditory word comprehension test consisted of a word/picture verification task. The task included 17 items, each presented three times in random order: once with a semantically related foil (e.g., sock/shoe); once with a phonologically related foil (e.g., sock/rock); and once with the target (e.g., sock/sock). The same target item was presented only once every 17 items (not consecutively), each time with a different foil or the target, in random order (for details see ¹⁵). The testing was completed at bedside, within 48 hours of admission, by a trained research assistant who was a native English speaker.

Imaging

MRI sequences included diffusion weighted imaging (DWI) with computation of apparent diffusion coefficient (ADC) maps to identify acute infarct, as well as T2 and Fluid Attenuation Inversion Recovery (FLAIR) sequences to permit the identification of chronic ischemic or other structural lesions. Susceptibility Weighted Images (SWI) were acquired to evaluate for macroscopic hemorrhage. DWI trace images were acquired using a multi-slice, isotropic, single shot EPI sequence, with $b_{max} = 1000 \text{ s/mm}^2$, TR/TE of 10,000/120 msec, and slice thickness of 5 mm. DWI b_0 images were also acquired using the same parameters for normalization (see below). Perfusion weighted imaging (PWI) with power injection of contrast was obtained to identify hypoperfusion, or PWI. Single shot gradient echo EPI perfusion images (TR/TE of 2000/60 msec, 5 mm slices) were obtained with 20 cc GdDTPA (Gadolinium) bolus power injected at 5 cc/sec at the start of the scan. PWI was obtained by power injection of 10 cc of contrast at a rate of 5 cc/sec. Areas of significant hypoperfusion corresponding to dysfunction were defined as areas with >4 sec delay in time to peak (TTP) relative to the homologous region of interest in the right hemisphere. This threshold was chosen based on studies using PET³¹ or impairment in function^{32,33}. For all sequences, we obtained whole brain coverage with trans-axial planes parallel to the AC-PC line.

Statistical Analysis

One-way analysis of variance was conducted (STATA version 12) to evaluate the differences in the volume of dysfunctional tissue in patients with various error types in word/picture verification. Pearson correlations between volume of dysfunctional tissue and rate of each type of error in word/picture verification were also evaluated.

To identify the *site* of tissue dysfunction associated with rate of each error type, infarcted tissue was drawn on DWI trace images and regions of hypoperfusion were drawn on PWI images using MRICron (www.mccauslandcenter.sc.edu) by a trained physician who was unaware of the language scores. A map of “dysfunctional tissue”, including areas that were abnormal on DWI and/or PWI TTP map (i.e., the combined abnormality) was drawn for each patient by a physician, without knowledge of the clinical scores. It was essential to include all areas that were either infarcted (on DWI) and/or hypoperfused (on PWI) in the area of dysfunctional tissue due to the occurrence of “luxury perfusion” of the infarct in some cases. That is, there can be normal (presumably restored) perfusion where there is infarction (as well as hypoperfusion where there is no infarct) in acute stroke. All images were normalized to standard space using SPM12. First, the normalization transforms were computed for the DWI $B=0$ image to a template based on age-matched controls³⁴. Then, the

normalization parameters were applied to the DWI Trace based lesion and TTP images. This method takes advantage of the fact that abnormalities visible on DWI Trace images and TTP maps are not generally apparent on acute DWI B=0 images, allowing a normalization that is not disrupted by abnormal signal³⁵. Proportions of dysfunctional tissue in all of the anatomical parcels in the JHU-MNI atlas (cmrm.med.jhmi.edu) were calculated for each patient. Thus, we identified the percentage of voxels in each anatomical parcel that were affected by stroke. We entered this proportion into our analyses. We identified associations between behavior and tissue dysfunction (i.e. the association between severity of deficit and percentage of voxels that were damaged in each parcel) using GLM (pooled-variance t-test, linear regression). We included in each analysis regions where at least 10 patients had damage/tissue dysfunction. The t-scores were transformed to z-scores to facilitate interpretation (using SPM12's `spm_t2z` function). The benefit of this transformation is that knowledge of the degrees of freedom is not needed to interpret z-scores. The resulting statistical maps were then thresholded to correct for multiple comparisons using 5000 permutations using our open source NiiStat (https://github.com/neurolabusc/NiiStat/blob/master/nii_stat_core.m) routines and the methods described by Rorden et al.²¹. We used a corrected alpha level of one-tailed $p < 0.05$, as we assumed that injury would correlate with impaired (not better) performance.

Results

Data from all 127 patients were included in the analyses. Sixty-four patients made no errors in word/picture verification. Sixty-three patient made errors. Some individuals made combinations of error types and others made only one error type. A total of 51 participants made semantic errors, 50 made phonological errors, and 37 made target errors. Twenty-eight participants made all three types of errors. Only five patients made exclusively semantic errors, 11 made exclusively phonological errors, and no participants made exclusively errors of incorrectly rejecting the target.

Lesion volume varied significantly by error pattern. Except in the case of the one participant who made phonological and target errors, the smallest areas of tissue dysfunction were in participants who made no errors (mean 23.9 cc), exclusively semantic errors (mean 25.3 cc) or phonological errors (mean 24.2 cc), and the largest areas of dysfunctional tissue were in those who made all three types of errors (mean 130.9 cc; $F(6, 120) = 9.0$, $p < 0.0001$) (Table 1).

The range of semantic errors on the word/picture verification test was 0 – 17 (mean = 3; SD 5). After controlling for lesion volume, there were two regions where greater extent of tissue dysfunction was significantly associated with higher rate of semantic errors: pSTG ($z = 4.49$) and retrolenticular white matter ($z = 3.96$) (correcting for multiple comparisons) (Figure 1). Greater extent of tissue dysfunction in precuneus was associated with fewer semantic errors ($z = -2.48$), indicating that individuals with these lesions (usually due to posterior cerebral artery stroke, which preserves the persylvian cortex) were less likely than other participants to make semantic errors in word comprehension.

The range of phonological errors in word/picture verification was 0 – 17 (mean=2; SD 5). There were no areas where greater extent of tissue dysfunction was associated with higher rate of phonological errors, after correcting for multiple comparisons. However, greater tissue dysfunction in left cuneus was related to fewer phonological errors ($z = -2.67$), indicating that participants with cuneus lesions were less likely than other left hemisphere stroke participants to make phonological errors in word/picture verification.

Error rate on the target (incorrect rejection of the correct word/picture match) ranged from 0 – 17 (mean 2; SD 5). There were no areas where dysfunctional tissue was associated with either higher or lower rate of rejection of targets, after correcting for lesion volume and controlling for multiple comparisons.

Regardless of lesion site, volume of dysfunctional tissue significantly correlated with rate of semantic errors ($r^2 = 0.48$; $p < 0.0001$), phonological errors ($r^2 = 0.39$; $p < 0.0001$), and target errors ($r^2 = 0.42$; $p < 0.0001$). As indicated above, the site of lesion was an independent predictor of error rate only for semantic errors.

Discussion

Impairment in distinguishing semantically related errors in word comprehension was associated with acute tissue abnormality in left pSTG and retrolenticular white matter. Participants with cuneus and precuneus (usually from posterior cerebral artery strokes) made fewer semantic or phonological errors relative to other acute left hemisphere stroke participants (who mostly had middle cerebral artery strokes). We did not find areas where tissue dysfunction was associated with rate of phonological errors or rate of incorrect rejection of the target, after correcting for lesion volume, likely because a large percent of the variance in these types of errors was explained by lesion volume. Only participants with the largest strokes made all types of errors in word/picture verification.

These results do not imply that that left pSTG and retrolenticular white matter are the only areas critical for word comprehension, or the only areas needed for distinguishing between semantically related words. There is evidence from both lesion studies and functional imaging studies that there is a circuit of gray matter regions and white matter tracts that supports word comprehension³⁶, which includes left pSTG^{19,22,23,24,26,37,38} as well as middle and inferior temporal gyri, temporal pole, and tracts that connect them. However, our results do indicate that left pSTG and retrolenticular white matter are critical for linking the spoken word to one of a set of semantically related meanings.

Our results are also consistent with studies that have identified pSTG as critical for both word comprehension and naming^{39,40}. Both word comprehension and naming require linking a semantic representation and a specific word or phonological representation.

Limitations of the study include the fact that relatively few participants made only semantic errors in word/picture verification. Note that incorrect rejection of the target could also reflect impaired access to the semantic representation, and many participants made both types of errors. Another limitation is that we could not factor out how much of the deficit was due to an impaired amodal concept versus impairment in linking the spoken word to the

concept because we did not evaluate amodal or nonverbal semantic processing. However, previous studies that have separately evaluated areas critical for nonverbal semantics (e.g., with picture-picture association), have found that anterior temporal lobe is associated with nonverbal semantics, while posterior middle temporal gyrus³⁶ or pSTG³⁸ remain associated with word comprehension after controlling for performance on picture-picture association.

Future Directions

Additional investigations are planned to identify areas of acute tissue dysfunction (infarct and/or hypoperfusion) that are associated with phonological errors in naming. It is possible that we did not have adequate power to identify these areas, after correcting for lesion volume. Alternatively, there may be a very extensive network involved in differentiating spoken words from phonologically similar words, such that aphasic individuals who make this type of error have many different lesion sites.

For aphasic individuals who have damage to pSTG or retrolenticular white matter, and others who make semantic errors in word comprehension task, treatment to improve comprehension might involve teaching distinctions between the target and semantically related words¹⁰. Although single case studies have shown the effectiveness of this approach^{10,41}, further studies are needed to evaluate the efficacy of treatment across individuals. This study indicates that such a treatment study should target individuals with damage to left pSTG or retrolenticular white matter.

In conclusion, the extent of dysfunction in left pSTG and retrolenticular white matter region is specifically associated with rate of semantic errors in spoken word comprehension. Thus, these areas are among the areas critical for distinguishing between semantically related words. This specificity helps narrow the role of pSTG to one aspect of accessing a complete semantic representation from spoken words.

Clinical Implications

The results of this study provide insights into the comprehension deficits of people with strokes to the left posterior temporal gyrus (one of the most commonly damaged areas in people with post-stroke aphasia). People with damage to this area have difficulty distinguishing between semantically related words. When they hear “horse” they may access an under-specified semantic representation (e.g. <domesticated> <eats grass>, <runs>), which would be compatible with several concepts, including “cow”, “goat”, and “horse”. Deficits of this type can be detected using word-picture verification tasks like the one we describe here, if they include semantically-related foils, or word-picture matching tasks with semantically related foils, which are included in most standard aphasia batteries. Treatment of this deficit might optimally focus on teaching distinctions between semantically related items. For example, if an individual points to cow instead of horse in a word-picture matching task, the clinician can point out differences between cow and horse, pointing to the mane, discussing milk from the horse (using drawings and gestures), drawing a saddle on the horse, etc. Alternatively, in naming tasks, if the person with aphasia says “goat” for a pictured horse, the clinician can provide a picture of a goat (e.g., using Google images), and

again point out differences between goats and horses (see references 10 and 41 for details of such a treatment). Understanding the nature of the comprehension deficit in people with this common lesion can also provide the basis for counseling the family. To facilitate comprehension, providing pictures or drawings or gestures that emphasize the distinctive features of a target word (e.g. when one says banana, gesture how it is peeled or its characteristic shape) should help the individual understand the word and relearn its meaning.

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Figure 1. Areas where the extent of tissue dysfunction (abnormality on DWI and/or PWI) in that region was positively correlated with the rate of semantic errors in word/picture verification (in pink or yellow) or negatively correlated with the rate of semantic errors in word/picture verification (in purple)

Table 1

Volume of Infarct Observed in Participants with each Pattern of Errors

Error Pattern	Number of Participants (percent)	Mean ($\pm$ SD) Volume of Tissue Dysfunction in cc
Semantic Errors	5 (4)	25.3 $\pm$ 34.2
Phonological Errors	11(9)	24.2 $\pm$ 24.5
Rejection of Target Errors	0 (0)	Not applicable
Semantic & Phonological Errors	10 (8)	54.9 $\pm$ 41.5
Semantic & Target Errors	8(6)	75.9 $\pm$ 80.1
Phonological & Target Errors	1(1)	6.5
Semantic, Phonological & Target Errors	28 (22)	136.9 $\pm$ 116.6
No Errors	64 (50)	23.9 $\pm$ 32.1