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Predicting Recovery in Acute Post-stroke Aphasia

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Abstract

Objective—Many stroke patients show remarkable recovery of language after initial severe impairment, but it is difficult to predict which patients will show good recovery. We aimed to identify patient and lesion characteristics that together predict the best naming outcome in four studies.

Methods—We report two longitudinal studies that identified two variables at onset that were strongly associated with good recovery of naming (the most common residual deficit in aphasia) in the first six months after stroke: damage to left posterior superior temporal gyrus (pSTG) and/or superior longitudinal fasciculus/arcuate fasciculus (SLF/AF) and selective serotonin reuptake inhibitor (SSRI) use. We then tested these variables in two independent cohorts of chronic left hemisphere stroke patients, using chi squared tests and multivariable logistic regression for dichotomous outcomes and t-tests for continuous outcomes.

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Author Contributions:

The authors contributed to study concept and design (AEH, YYB, JF); data acquisition and analysis (AEH, YYB, AB, AW, SS, BB, LB, CR, GY, JF); and drafting the manuscript and figures (AEH, YYB, AB, RS, DCT, LB, BB, CR, JF).

Potential Conflicts of Interest

No authors have conflicts to report.

Results—Lesion load in left pSTG and SLF/AF was associated with poorer naming outcome. Preservation of these areas and use of SSRIs were associated with naming recovery, independent of lesion volume, time since stroke, and depression. Patients with damage to these critical areas showed better naming outcome if they took SSRIs for three months after stroke. Those with preservation of these critical areas achieved good recovery of naming regardless of SSRI use.

Interpretation—Lesion load in left pSTG and SLF/AF at onset predicts later naming performance. Although based on a small number of patients, our preliminary results suggest outcome might be modulated by SSRIs, but these associations need to be confirmed in a larger randomized controlled trial.

Keywords

aphasia; ischemic stroke; recovery; lesion studies

Aphasia is among the most common and disabling consequences of stroke.[1] At stroke onset, it is not possible to predict which individuals will show substantial recovery of language and which individuals will show little recovery or even decline.

Studies of aphasia recovery have evaluated people at different times post-stroke to identify variables associated with good versus poor recovery.[2–6] One large cross-sectional study showed that aphasia severity was associated with stroke volume, time post-onset, and percentage of damage to 35 brain regions.[2] Three studies have shown a strong association between lesion load in the AF (along with the integrity of right hemisphere white matter tracts[5]) and outcome of naming and speech fluency in post-stroke aphasia.[4–6] One longitudinal study of 21 aphasic individuals showed that age, initial severity, and the pattern of activation on functional imaging at baseline were associated with degree of impairment at six months.[7] Other longitudinal aphasia studies have shown that lesion volume,[2, 8,] initial severity,[9, 10, 11, 12] and education[11] influence recovery. However, variables associated with outcome have not been prospectively evaluated in an independent population to determine if the same variables predict later recovery.

To our knowledge, no previous study has evaluated the independent contributions of lesion site and medications. There are several mechanisms by which SSRIs, which elevate synaptic serotonin, might enhance recovery by augmenting synaptic plasticity.[13,14] SSRIs increase brain-derived neurotrophic factor,[15] which may be a critical modulator of recovery.[16] These mechanisms might account for the positive effect of an SSRI on human motor recovery[17] and cognitive performance.[18] Other small studies have reported positive effects of antidepressants on aphasia[3, 19–21] (but see[22]).

Here we report novel evidence to improve prediction of aphasia recovery. We report two longitudinal studies in which we identify variables associated with the degree of language recovery over the first six months. We then use these data to predict which individuals are likely to have made the best recovery of language later after stroke, in two independent samples of chronic stroke patients who initially had aphasia. Based on our initial longitudinal studies, we hypothesized that individuals without lesions involving two critical areas were more likely to show recovery of naming than those with these lesions. The

critical areas were: left superior temporal gyrus posterior to the pole (areas STG and the posterior pSTG on the JHU-MNI atlas - cmrm.med.jhmi.edu - Figure 3, Panel C) and superior longitudinal fasciculus (SLF in the JHU-MNI atlas - equivalent to the AF in the Catani atlas - https://www.natbrainlab.co.uk/atlas-maps, Figure 3, Panel D). Results confirmed the influence of lesion load in left AF on aphasia outcome[4–6], and revealed an additional influence of lesion load in left pSTG. We also hypothesized that, among aphasic individuals whose lesions involved left pSTG or SLF/AF, recovery would be greatest in those who took an SSRI daily for at least three months after stroke. We focused on naming because impaired naming is the most common and important residual language deficit in post-stroke aphasia. This deficit impedes effective and efficient communication in daily interactions.

Methods

The protocol for this study received prior approval by the Institutional Review Boards of Johns Hopkins, University of South Carolina, and Medical University of South Carolina. Informed consent was obtained from each participant or their Legally Authorized Representative (LAR, for individuals with impaired language comprehension). We conducted four independent, complementary studies, summarized in Table 1.

Participants

Longitudinal studies—Participants were enrolled at Johns Hopkins Hospital in the first 48 hours after left hemisphere ischemic stroke. Exclusion criteria included: impaired level of consciousness or ongoing sedation, lack of premorbid competence in English, previous neurological disease affecting the brain, and contraindication for MRI (e.g. implanted ferrous metal, claustrophobia). For these studies, we included only those who initially had aphasia as scored on the NIH Stroke Scale.[23] In our first longitudinal study of 19 patients, the mean age was 54.8 (± SD 13.2) years; 36.8% were female (Table 2). The second longitudinal study began when we started recording antidepressant use. We enrolled 30 aphasic patients, the mean age was 57.5 (±12.2) years; 29.0% were female. Both studies were a consecutive series of patients who met all inclusion criteria and returned for follow up testing at 6 months. They represent subsets of 207 patients who completed the language testing and had MRI at the acute time point, of whom 128 had aphasia at onset. The most frequent reason for failure to follow up was that the participant could not be reached. At least two had died, and at least three had new strokes in the 6 month interval.

Cross-sectional studies—Participants in our cross-sectional studies were assessed to validate the variables associated with best recovery in two independent groups enrolled at separate centers. These studies involved retrospective analyses of prospectively collected data. Participants in the first cross-sectional group (n=159) were enrolled at the University of South Carolina or Medical University of South Carolina at least 6 months after left hemisphere ischemic stroke. Mean months post-stroke at time of testing was 34 (± 40; range 6–276). The mean age was 59.8 (± 11) years; 37.7% were female. Mean lesion volume was 118.1 (± 97) cc, and mean aphasia quotient (AQ; measured using the Western Aphasia Battery-Revised, WAB-R[24]) was 63.3 (± 28.9). In this cohort, we tested only the first

hypothesis, i.e., that lesions in left pSTG and/or SLF/AF are associated with poorer recovery of naming in chronic stroke compared to individuals without damage to these areas, because medication information was not available.

Participants in the second cross-sectional group included 43 patients recovering from left hemisphere ischemic stroke who were enrolled at Johns Hopkins Hospital at mean of 39 (± 36) months post stroke. The mean age was 56.1 (±15.1) years; 51.1% were female. Mean lesion volume was 188.8 (± 200.7) cc, and mean AQ was 74.5 (± 30.9). For this group, both imaging and medication use were available. Therefore, in this group, we evaluated our second hypothesis, that among individuals with damage to left pSTG and/or SLF/AF, those who continuously take SSRIs during the first three months show better recovery than non-users of SSRIs.

Each of these study populations was a convenience sample of individuals who met inclusion and exclusion criteria and had the available data. The populations were similar in aphasia severity at the chronic stage. The mean object naming accuracy at the chronic stage (> 6 months post stroke) was 76.6% (±25.5) in Study 1; 75.2% (±18.2) in Study 2; 63.9 % (± 36.6) in Study 3, and 81.8% (±34.5) in Study 4.

Language Testing

Longitudinal studies of aphasia recovery in the first year—All participants underwent a comprehensive battery of language tests, including the Boston Diagnostic Aphasia Examination (BDAE)[25] or the WAB-R, to classify patients by vascular aphasia syndrome. However, we focused on assessments of naming because testing and scoring is reliable,[24–27] with a wide range of scores in aphasic individuals, and because it is the most commonly reported residual deficit. In the first longitudinal study, we evaluated performance on the Boston Naming Test short form (BNTsf; 30 items)[28] within 48 hours and six months (range=5–7 months) after stroke onset.

In the second longitudinal study, we evaluated performance on the Boston Naming Test (BNT)[26] and also evaluated naming in the context of picture description at the same three time points. For the latter, participants were asked to describe everything they could see in the Cookie Theft picture (part of the Boston Diagnostic Aphasia Examination,[25] and more recently incorporated in the National Institutes of Health Stroke Scale used world-wide.[23] Picture descriptions were scored for the number of Correct Content Units (Cookie Theft: Correct Content Units; items mentioned by 31 healthy controls in describing the same picture). This measure correlates with aphasia severity measured by more extensive batteries,[27] and correlates with performance on the BNTsf in our first longitudinal cohort (r^2=0.72; p=0.0005). Two independent speech language pathologists scoring Cookie Theft: Correct Content Units achieved point-to-point agreement of 96.7%.

Cross-sectional studies of chronic aphasia—Participants in both cross-sectional groups described above were administered the WAB-R. Our primary outcome variable of interest was naming, tested with the object naming subtest. Accuracy is measured by percentage correct out of 60 items. This score was highly correlated with the BNT score in participants at the University of South Carolina or Medical University of South Carolina

who had both tests at the same time point (r^2=0.88). However, not all participants had been administered the BNT (n=118/159). We also evaluated naming outcome using the WAB-R word fluency subtest (naming items rapidly in a given category) and overall language outcome using the WAB-R AQ (a summary score based on all auditory-verbal language subtests).

Medication Use

We recorded use of antidepressants (which included: SSRIs, tricyclic antidepressants, venlafaxine, duloxetine, and bupropion) continuously for the first three months after stroke, by interview of participants, confirmed with information from the individual's pharmacy (available through medical records).

Depression Assessment

In both the longitudinal study and the cross-sectional study that evaluated the effect of antidepressants, we also evaluated for depression using the Patient Health Questionnaire-9.[29] In a study of 200 stroke patients within one month of onset, a score of ≥ 10 on the PHQ-9 had 91% sensitivity and 87% specificity for depression, compared to structured psychiatric interview.[30]

Imaging and Statistical Analyses

For the two studies that used Parcel-based Lesion Symptom Mapping (PSLM) to identify (longitudinally) or validate (cross-sectionally) areas associated with recovery, participants underwent high-resolution (voxel size=1mm^3) structural MRI that included T1-MRI and T2-MRI. For acute patients, MRI also included Diffusion Weighted Images (DWI) and Apparent Diffusion Coefficient (ADC) maps to identify acutely infarcted areas. The stroke lesion was demarcated on DWI trace image (for acute patients) or T2-weighted images (for chronic patients) by a neurologist highly experienced in lesion studies or by a study team member supervised by a neurologist. For acute patients, the normalization transforms were computed for the DWI B=0 image (which does not yet show stroke-related abnormalities) to a template based on age-matched controls.[31] The normalization parameters were then applied to the DWI trace based lesion. A different approach was used for chronic patients, as lesion-based abnormalities are seen in all modalities. For chronic patients the lesion was drawn on a high-resolution T2 image which was co-registered to the T1 image. The resliced lesion maps were smoothed with a 3mm full-width at half-maximum Gaussian kernel to remove jagged edges associated with manual drawing. To align the T1 image to standard space, we used enantiomorphic normalization [32] as implemented in the Clinical Toolbox[31] for SPM12. First, a mirrored image of the T1 image (reflected around the midline) was coregistered to the native T1 image. Then, we created a chimeric image based on the native T1 image with the lesioned tissue replaced by tissue from the mirrored image (using the smoothed lesion map to modulate this blending, feathering the lesion edge). SPM12's unified segmentation-normalization[33] was used to warp this chimeric image to standard space, with the resulting spatial transform applied to the actual T1 image as well as the lesion map. The normalized lesion map was then binarized, using a 50% probability threshold.

Parcel-based Lesion-Symptom Mapping analyses were completed to identify localized brain damage associated with naming outcome. Each analysis related naming performance to proportional damage to regions included in the JHU-MNI atlas.[34] The threshold level of significance selected was 0.05. In the first longitudinal study from the acute stage of stroke (with 19 patients), associations between lesioned brain regions and naming deficits were computed using general linear model (least squares' linear regression) and corrected for multiple comparisons using Bonferroni correction. As parcels that are infrequently damaged will have low statistical power while increasing the number of comparisons, only parcels where at least eight participants had any damage were included in the analyses. To control for lesion volume, it was regressed out of behavioral scores. In the cross-sectional study of 159 participants, multiple comparisons were corrected using permutation thresholding, with 4,000 permutations; Freedman-Lane testing was applied to correct for lesion volume (as a nuisance regressor within permutation thresholding). Only parcels where at least ten participants had any damage were included in the analyses. Note that inclusion of lesion volume as well as excluding rarely injured regions have been shown to attenuate some of the spatial biases inherent to lesion-symptom mapping.[35] The lesion-symptom analysis for both acute and chronic patients relied on routines integrated into the NiiStat toolbox for Matlab (http://www.nitrc.org/projects/niistat).

In addition to the PSLM to determine the areas where damage was associated with poorer outcome of naming in a longitudinal study and a cross-sectional study of chronic stroke, described above, we evaluated the influence of using SSRIs continuously for the first 3 months, lesion volume, and lesion site in both a longitudinal study and a cross-sectional study. We also recorded use of other antidepressants, but did not evaluate their influence, because other antidepressants were used by only eight (five: duloxetine, three: buproprion) of 30 patients in the longitudinal study, and only four (two: duloxetine, two: buproprion) of 43 patients in the cross-sectional study. In the longitudinal study, we tested the hypothesis from earlier studies[9, 36] that stroke patients typically achieve 70% of their maximal potential recovery, when maximum potential recovery is defined as the maximum score minus the initial score. We identified Pearson correlations (and absolute differences) between expected recovery (70% of maximal recovery) and observed recovery. For remaining analyses, naming improvement was measured by change in object naming divided by the initial score on object naming. We then tested the predictions based on this longitudinal study in a cross-sectional study of chronic stroke in which medication use from the acute stage was available. We evaluated the independent contributions of antidepressant use, lesion variables, and time post onset of stroke with logistic regression. We also evaluated associations between dichotomized naming outcomes and each antidepressant medication with Pearson chi squared tests. Behavioral differences between participants who took each antidepressant versus those who did not take that antidepressant in naming recovery using Student's t-tests. These statistical analyses were carried out using STATA version 12.4.

Results

Longitudinal study: Johns Hopkins (n=19; PSLM)

In the first longitudinal study from the acute period (<48 hours) through month six, the only regions where percent damage (lesion load) was associated with naming outcome at month 6, after controlling for lesion volume and multiple comparisons, were left pSTG and SLF/AF. SLF/AF here refers to a bundle of white matter tracts in the dorsolateral corona radiata that includes connections between the frontal, parietal, temporal, and occipital lobes. It includes all three subcomponents of the AF described by Markris et al.[37]

There was a significant correlation between expected recovery (70% of maximal recovery) and observed recovery (r^2=0.50; p=0.001). However, deviation from expected recovery varied from −34% to 30% of total score (Table 1; see also Figure 2); 42% deviated from expected recovery by more than 10% of the maximum score.

Longitudinal study: Johns Hopkins (n=30 ; SSRI use)

In this study, we identified the effects of antidepressants and lesion variables on change in BNT and change in Cookie Theft: Correct Content Units. We found that 71% showed improvement on the BNT, 5% showed no change at all, and 21% showed decline. Likewise, 69% showed improvement in Cookie Theft: Correct Content Units, 9% showed no change, and 22 % showed decline. That is, roughly the lowest quartile of change on language tests were negative values (decline); the next lowest was little or no change. Good improvement was defined as the upper 50th percentile. In the entire cohort, 11 participants (37%) used SSRIs, 5 (17%) used duloxetine, 3 (10%) used bupropion, and only one individual each used tricyclic antidepressants or venlafaxine. Of the SSRI users, 9 took fluoxetine; 1 took escitalopram; 1 took sertraline. No other antidepressants were prescribed in this cohort.

Continuous SSRI use in the first three months (compared to SSRI non-use) was associated with greater frequency of obtaining good improvement in both the BNT score (88% versus 33%; X^2_1 = 5.1; p=0.04) and in Cookie Theft: Correct Content Units (100% versus 44% X^2_1 = 6.9; p=0.018) after correction for multiple comparisons. SSRI users showed a greater mean improvement in BNT score than SSRI non-users (10.7 versus −0.5; p=0.032) after correction. The effect size for this analysis (d=1.34) was found to exceed Cohen's[38] convention for a large effect (d = .80).

There were no differences between SSRI users and non-users in age, education, lesion volume, initial severity (BNT score) or depression (PHQ-9 scores at outcome). None of these variables alone or together predicted SSRI use (Table 3). In multivariable analysis, SSRI use, age, and education were associated with improvement in BNT (p=0.019), but only SSRI use was associated with good improvement (OR 95% CI: 1.63–12329; p=0.030) independently of the other variables. Regarding effect size, 47% of the variability in this primary outcome measure was accounted for by SSRI use, age, and education. There were too few users of other antidepressants to evaluate their effects on recovery.

Cross-sectional Study: South Carolina (n=159)

Two cross-sectional studies were carried out to test predictors of recovery identified in the longitudinal studies in independent populations. The first examined chronic stroke patients from the University of South Carolina or Medical University of South Carolina, we tested the hypothesis derived from the first longitudinal study, that damage to left pSTG or SLF/AF is associated with worse naming outcome. Using PSLM, the only lesion locations that predicted poor naming accuracy were left superior temporal gyrus (between STG pole and pSTG; r= −0.63). pSTG (r= −0.53), and SLF/AF (r= −0.65), all of which were significant associations at the level of $p<0.001$), which suggests that these regions need to be intact for patients to experience good recovery of naming abilities (see Figure 3 for results in left panel, and the demarcations of these areas in the JHU-MNI atlas). Damage to the postcentral gyrus, anterior cingulate gyrus, and thalamus had the opposite effect, as patients with damage to those regions tended to name more items correctly compared to those participants who had damage elsewhere.

Cross-sectional Study: Johns Hopkins (n=43)

In this study we tested the hypothesis derived from the second longitudinal study (Johns Hopkins, n=30) that preservation of left pSTG and/or SLF/AF and SSRI use are associated with better naming outcome.

Effect of lesion site—We confirmed that damage to left pSTG and/or SLF/AF was associated with lower chance of achieving the highest quartile of naming (6% versus 92%; $X^2_1=19.5$; $p<0.0001$) after correcting for multiple comparisons. However, damage to pSTG and/or SLF/AF was not significantly associated with lower chance of achieving the highest quartile of WAB Aphasia Quotient (0% vs. 83%; ns) or highest quartile word fluency (17% vs. 57%; ns) after correction. There was no difference in SSRI use between participants with and without left pSTG/SLF lesions (40% versus 35%; ns). In multivariable analysis, damage to left pSTG/SLF was associated with lower odds of achieving the highest quartile of object naming, after controlling for lesion volume, SSRI use, and months since onset (OR:0.034; 95% CI 0.0033–0.35; p=0.005). Regarding effect size, these variables together accounted for 36% of the variance in the primary outcome.

The effect of lesion site cannot be explained by differences in antidepressant use. There was no difference in the rate of antidepressant use after acute stroke between those with and without pSTG/SLF lesions. Of the 20 people with pSTG/SLF lesions, 10 were prescribed antidepressants (8 SSRIs, 2 other). Of the 23 people without pSTG/SLF lesions, 10 were prescribed antidepressants (8 SSRIs, 2 other). ($X^2(1) = 0.18$; $p = 0.67$).

Effect of SSRI use (continuously in the first 3 months post-stroke) in patients with left pSTG/SLF lesions—There was no difference between SSRI users and SSRI nonusers in age, lesion volume, months post-stroke, or percent with damage to left pSTG/SLF. Of the 16 people who took SSRIs, 8 had pSLF/STG lesions and 8 did not. None of these variables alone or together predicted SSRI use (Table 4). Among patients with pSTG/SLF lesions, SSRI users attained a higher accuracy on object naming than non-users (mean 85.7% vs. 45.5% correct; t(18)=2.3; p=0.017). The effect size for this analysis

(d=1.16) exceeded Cohen's convention for a large effect (d = .80). Those without pSTG/SLF lesions achieved excellent object naming accuracy with or without SSRIs (highest quartile object naming: 93.3% versus 87.5%; mean object naming: 99.7% versus 99.3% correct; ns; Cohen's d<0.00001). For illustrative cases, see Figure 4.

Discussion

Although we confirmed previous findings that degree of recovery of naming is proportional to initial severity, the relationship was not as strong as reported in previous studies (particularly for motor recovery). Initial severity accounted for only 50% of the variance in recovery. Our data indicate that recovery of naming in post-stroke aphasia is negatively influenced by lesion load in left pSTG and/or SLF/AF, and positively influenced by SSRI use in participants with lesions to these areas. We did not have sufficient numbers to evaluate the influence of other antidepressants. The effects could not be explained by the effects of lesion volume, depression, or initial severity, as we controlled for these variables. Although, as expected, there was a significant correlation between the degree of improvement and the degree of possible improvement, the change in naming divided by the initial score was influenced by SSRI use and damage to left pSTG and/or SLF/AF.

The negative effect of left pSTG and/or SLF/AF damage on naming recovery is consistent with other studies indicating that these areas are critical to naming. Three studies have demonstrated that naming outcome depends on lesion load in the AF.[4–6] Damage to various parts of SLF/AF was also associated poorer recovery of various aspects of language in a previous longitudinal study[11]. Our results confirm the critical role of left SLF/AF and extend those findings by showing that lesion load in left pSTG is also critical to naming outcome. Three other studies showed dysfunction of left pSTG was associated with impairments in naming in stroke;[39–41] and yet another showed that production of semantic errors in naming was associated with dysfunction in left pSTG or damage to left posterior inferior temporal cortex[42].

However, another study found that other areas of infarction (left middle and inferior temporal gyrus anterior to the fusiform, as well as left STG posterior to STG pole are associated with production of semantic errors in chronic stroke.[43] Differences between that study and our study include the fact that we did not evaluate lesions associated with different types of naming errors and that we used different tests of naming. The main difference between the naming test used in the earlier study (the Philadelphia Naming Test, PNT) and those in the current study is that feedback is provided in the PNT. Furthermore, the two studies used different lesion-symptom mapping approaches.

Our results reveal the influence of lesion load in left pSTG and SLF/AF on naming outcome, but do not rule out the influence of damage to other areas of language cortex, such as left posterior inferior frontal gyrus (pIFG), anterior temporal lobe (ATL), fusiform gyrus (FG), or angular gyrus (AG), where lesions cause naming deficits acutely.[39] Other areas may not have been found to have a independent influence on naming outcome because of inadequate power to detect their influence. Alternatively, it is possible that other areas of the brain can assume the functions of areas such as pIFG and ATL more readily than the functions of

pSTG and SLF/AF. Larger longitudinal studies are needed to reveal the role of these other areas in naming outcome.

Our results regarding SSRIs, while preliminary, are consistent with findings of a positive effect of SSRIs in the first three months after stroke on motor recovery[44] and cognitive function[18], independently of depression. Results are also consistent with a previous cross-over trial of SSRI use in 10 aphasic patients, which showed greater gains in naming in the SSRI condition, independently of the effects on depression.[45] Many patients are now prescribed SSRIs after acute ischemic stroke irrespective of depression, because results of this randomized controlled trial, which indicated that SSRI is associated with better motor recovery. Nevertheless, there is high rate of post-stroke depression, ranging from 30 – 60%; [46, 47] and post-stroke depression can be significantly reduced with pharmacotherapy.[48] There may be several positive effects of SSRIs after stroke; the effects on mood (as assessed by this screening test) and language recovery appear to be relatively independent.[17,49]

Limitations of our research include the fact that we did not evaluate the effects of SSRIs at different time periods after stroke or the influence of duration, dose, or type of SSRI. We also did not compare SSRIs to other antidepressants because the number of participants taking various other antidepressants was low. Another limitation is that we relied on convenience samples of patients who met inclusion and exclusion criteria and had the available data (who prospectively enrolled in larger studies of aphasia recovery). Finally, our longitudinal studies were relatively small. Larger prospective studies are needed to determine the extent to which damage to left pSTG and/or SLF/AF can prospectively predict recovery by a particular time point after stroke. A multicenter, randomized clinical trial is needed to determine whether SSRI use in the first three months after stroke or later is associated with better aphasia recovery, compared to placebo.

Despite its limitations, our results provide new information that will be useful in predicting at onset an individual's potential for good recovery from post-stroke aphasia based on the location of damage.

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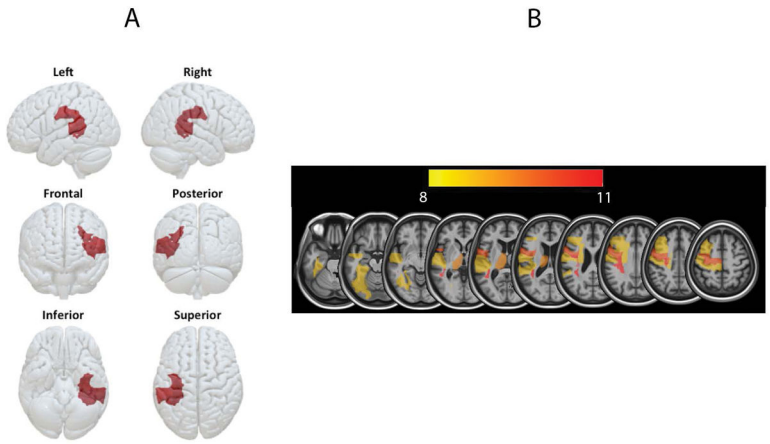

Figure 1.

Panel A. Areas (in red) where damage was significantly associated with impaired object naming in the first longitudinal study. The brain template is partially transparent so lesion locations associated with naming performance can be viewed from different orientations. Red represents areas where more damage is significantly associated with lower accuracy in object naming. Note that the Right orientation image in the top right panel shows results in the left hemisphere as viewed “through” the right hemisphere.”

Panel B. Lesion overlay map showing the number of patients with damage to each area. Color denotes number of individuals who had at least partial damage to the given parcel. The lower threshold (N>8) for the map is set so that only regions where at least 8 patients had damage are included. Slices correspond to −24, −16, −8, 0, 8, 16, 24, 32, 40 and 50mm in MNI coordinates.

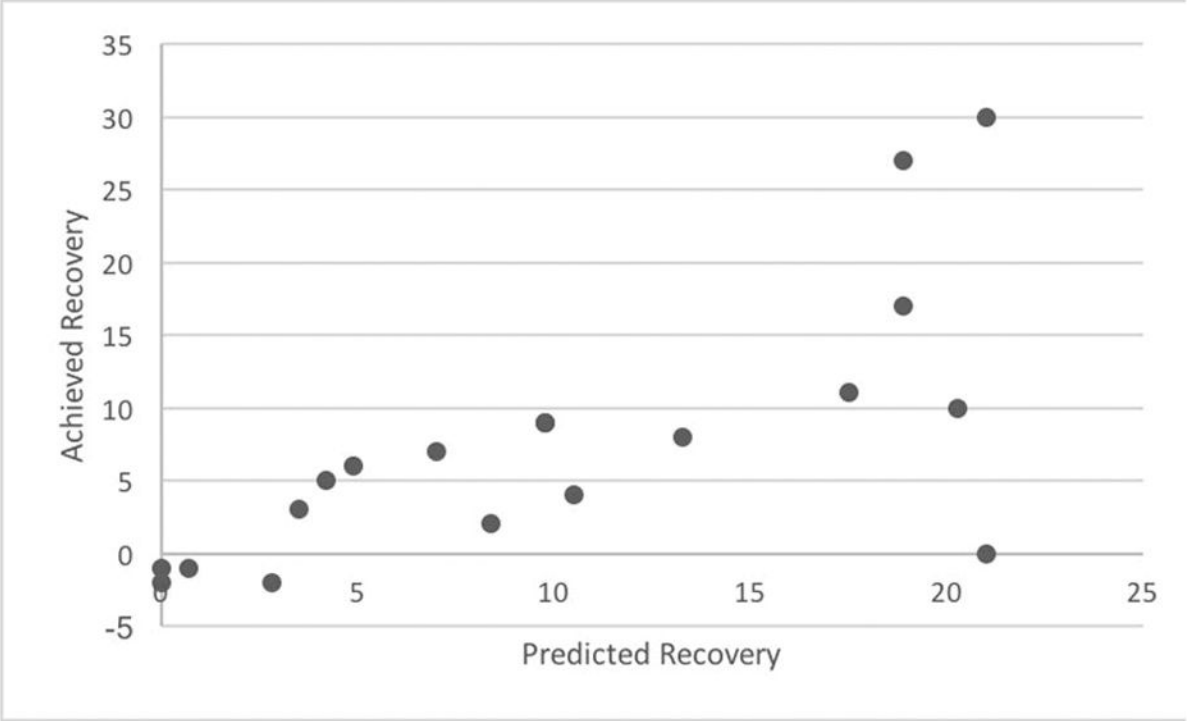

Figure 2.
Scatterplot showing the relationship between potential recovery on the BNTsf and achieved recovery on the BNTsf.

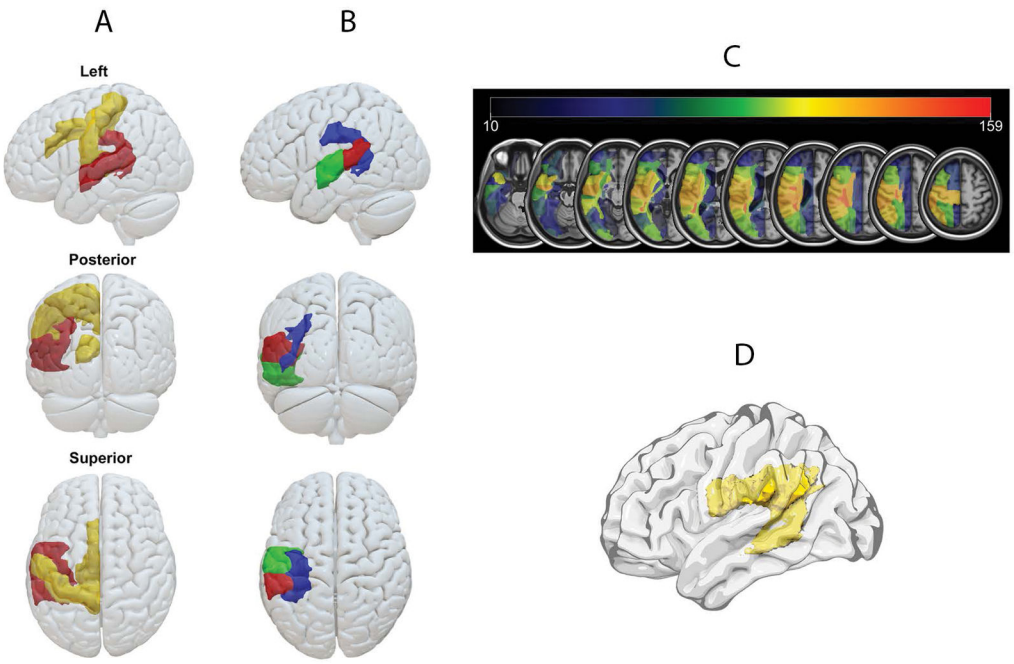

Figure 3.

Panel A. Areas where damage was significantly associated with impaired object naming in chronic post-stroke aphasia. The brain template is partially transparent so lesion locations associated with naming performance can be viewed from different orientations.

Red represents areas where more damage is significantly associated with lower accuracy in object naming, and yellow represents areas where more damage is associated with higher accuracy in picture naming. Note that the Right orientation image in the top right panel shows results in the left hemisphere as viewed “through” the right hemisphere.”

The three parcels where the correlation was significant ($p<0.001$) were left superior temporal gyrus (STG) (−0.63), left posterior STG (−0.53) and left superior longitudinal fasciculus (SLF) (−0.65) on the JHU-MNI atlas

Panel B. JHU-MNI Atlas Demarcation of Parcels of Interest (where percentage of damaged voxels was significantly associated with error rate in naming)

Green=left STG; Red=left posterior STG; Blue=SLF

Panel C. Lesion overlay map for the 159 patients included in the chronic study. The lower threshold (N>10) for the map is set so that only regions where at least 10 patients had damage are included. Coordinates are the same as Figure 1B.

Panel D. The arcuate fasciculus from the Catani atlas (https://www.natbrainlab.co.uk/atlas-maps)

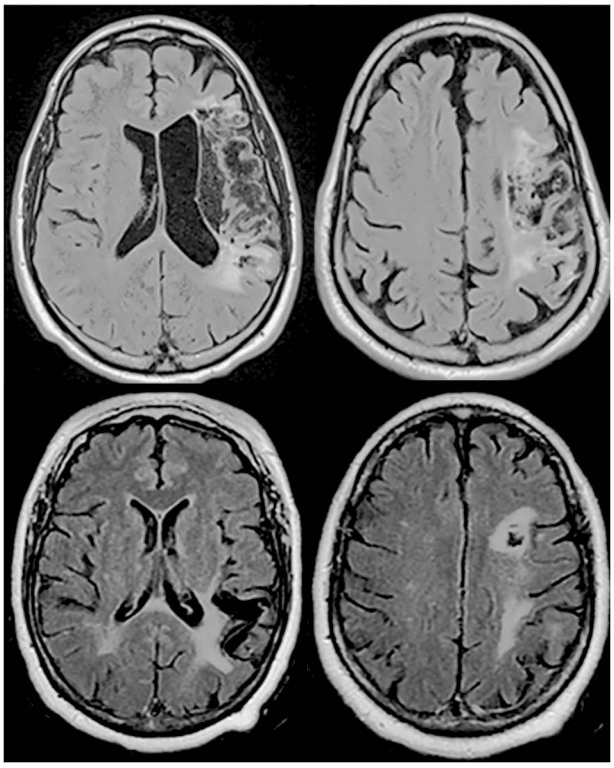

Figure 4.

Divergent outcomes at 12 months post-stroke in two 56 year old right handed men with damage to left pSTG/SLF.

Top panel. FLAIR images of initially aphasic man who achieved the highest quartile of recovery of naming (98.3% correct) after taking an SSRI continuously for three months after stroke. Lower panel: FLAIR images of an initially aphasic man of the same age who failed to achieve the highest quartile of recovery of object naming at the same time point after stroke. He did not take an SSRI (or any antidepressant) after the stroke, and was not depressed

Table 1

Summary of the Four Studies

Study Design and Location	Population	Primary (& Secondary) Outcome Measures	Primary Statistic	Variables Evaluated
Longitudinal study: Johns Hopkins (n=19; PSLM)	19 patients 0 – 6 months post-stroke	Change in BNTsf	PSLM	% Damage to Parcels of Interest, Lesion Volume
Longitudinal study: Johns Hopkins (n=30)	30 patients 0 – 6 months post-stroke	Change in BNTsf (Cookie Theft: Content Units)	Logistic Regression	Damage to Parcels of Interest, SSRI use, age, lesion volume
Cross-sectional Study: South Carolina (n=159)	159 patients, at mean 34 months post-stroke	WAB-R Naming	PSLM	% Damage to Parcels of Interest
Cross-sectional Study: Johns Hopkins (n=43)	43 patients, at mean 39 months post-stroke	WAB-R Naming (WAB-R Aphasia Quotient, fluency)	Logistic Regression	Damage to Parcels of Interest, SSRI use, age, PHQ-9 score

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Table 2

Demographics and Scores of the 19 Patients in the First Longitudinal Study

Aphasia Type	Age	Educ	Acute NIHSS Score	Acute BNTsf Score	6 Month BNTsf* Score	Predicted Change in BNTsf**	Achieved Change in BNTsf	Difference Between Predicted & Achieved BNTsf (% of 30)	
Anomic	46	12	4	26	24	2.8	−2	−4.8	−16%
Anomic	60	14	5	30	29	0	−1	−1	−3.3%
Broca	74	16	5	16	25	9.8	9	−0.8	−2.7%
Global	42	12	11	1	11	20.3	10	−10.3	−34%
Broca	50	16	7	16	25	9.8	9	−0.8	−2.7%
Broca	65	18	4	24	29	4.2	5	0.8	2.7%
Anomic	49	15	3	25	28	3.5	3	−0.5	−1.7%
Global	60	12	23	0	0	21	0	−21	−7.0%
Wernicke	59	9	1	18	20	8.4	2	−6.4	−21.3%
Anomic	54	15	3	0	30	21	30	9	30%
Wernicke	61	16	4	3	20	18.9	17	−1.9	−6.3%
Broca	48	12	2	29	28	0.7	−1	−1.7	−5.7%
Anomic	54	18	6	3	30	18.9	27	8.1	27%
Broca	28	12	2	9	16	17.5	11	−6.5	−21.7%
Anomic	49	12	3	23	29	4.9	6	1.1	3.7%
Broca	63	18	1	15	19	10.5	4	−6.5	−21.7%
Wernicke	54	12	3	11	19	13.3	8	−5.3	−17.7%
Anomic	60	14	5	30	28	0	−2	−2	−6.7%
Anomic	87	20	1	20	27	7	7	0	0%

BNTsf= Boston Naming Test, short form.

** Predicted recovery = 70% of maximum possible improvement (maximum accuracy minus initial accuracy)

Table 3

The (Lack of) Influence of Independent Variables on SSRI Use (Longitudinal Study, Johns Hopkins, n=30)

Logistic Regression Model with SSRI use at the Dependent Variable (p = 0.72)					
Independent Variables	**Coefficient**	**Standard Error**	**z**	**p**	**95% Confidence Interval**
Depression Severity (PHQ-9 score)	0.092	0.19	0.47	0.64	−0.29 – 0.47
Age	−0.83	0.37	−0.68	0.50	−0.71 – 0.35
Education	0.35	0.89	0.39	0.70	−1.39 – 2.09
Lesion Volume	0.000053	0.000051	1.03	0.30	−0.000048 – 0.00015
Initial Severity (Day 1 BNTsf Score)	−0.0053	0.040	−0.13	0.90	−0.084 – 0.073

*PHQ-9: Patient Health Questionnaire-9; BNTsf= Boston Naming Test short form

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Table 4

The (Lack of) Influence of Independent Variables on SSRI Use (Cross-Sectional Study, Johns Hopkins, n=43)

Logistic Regression Model with SSRI use at the Dependent Variable (p = 0.95)					
Independent Variables	**Coefficient**	**Standard Error**	**z**	**p**	**95% Confidence Interval**
Age	0.014	0.026	0.56	0.56	−0.036 – 0.065
Months Post-Onset	0.0050	0.010	0.47	0.64	−0.016 – 0.026
Lesion Volume	1.20e-06	2.24e-06	0.54	0.59	−3.19e-06 – 5.59e-06
Damage to Left pSTG/SLF	−0.24	0.91	−0.26	0.80	−2.02 – 1.55

* pSTG/SLF = posterior Superior Temporal Gyrus and/or Superior Longitudinal Fasciculus

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