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## Tracking reorganization of large-scale effective connectivity in aphasia following right hemisphere stroke

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### Abstract

In this paper we demonstrate the application of new effective connectivity analyses to characterize changing patterns of task-related directed interaction in large (25–55 node) cortical networks following the onset of aphasia. The subject was a left-handed woman who became aphasic following a right-hemisphere stroke. She was tested on an auditory word-picture verification task administered one and seven months after the onset of aphasia. MEG/EEG and anatomical MRI data were used to create high spatiotemporal resolution estimates of task-related cortical activity. Effective connectivity analyses of those data showed a reduction of bilateral network influences on preserved right-hemisphere structures, and an increase in intra-hemispheric left-hemisphere influences. She developed a connectivity pattern that was more left lateralized than that of right-handed control subjects. Her emergent left hemisphere network showed a combination of increased functional subdivision of perisylvian language areas and recruitment of medial structures.

### Keywords

aphasia; recovery; effective connectivity; Granger causation; MEG; left-handed; right hemisphere

## 1. Introduction

Characterizing and examining the development of functional brain organization in people with aphasia (PWA) is of interest because of potential implications both to the recovery

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process and therapeutic approaches as well as to the general understanding of brain networks supporting language-related functions. While it is clear that PWA often show changing patterns of task-related activation in blood oxygenation level dependent (BOLD) functional MRI in the months following onset, it is less clear how those changes relate to the evolving structure of neural processing networks. This is in part because changes in the BOLD response may also be affected by factors other than functional reorganization of cortical language networks. These factors include decoupling of the hemodynamic response due to vascular damage, increased variance in BOLD measures due to changes in the hemodynamic response and increased motion artifacts in stroke patients, and the introduction of transcallosal disinhibition effects with unclear functional consequences (cf. Hartwigsen et al., 2013; Veldsman, Cumming, & Brodtmann, 2015).

Effective connectivity analyses help to alleviate some of these problems by quantifying the degree to which activation reflects a pattern of organized directed interactions between brain regions. Effective connectivity has been examined in several studies that have used model-based dynamic causal modeling and structural equation modeling techniques to analyze BOLD imaging data in recovering PWA (Kiran, Meier, Kapse, & Glynn, 2015; Sarasso et al., 2010; Vitali et al., 2010). However, model-based approaches of BOLD data are only practical for exhaustively examining small (<6 node) networks at low temporal resolution (~1 second) (Lohmann, Erfurth, Muller, & Turner, 2012; Wang et al., 2014). Here we introduce the use of model-free Kalman-filter based analyses of anatomically constrained source estimates of magneto- and electroencephalography (MEG/EEG) data as a powerful tool to characterize changes in effective connectivity in PWA. This approach supports analysis of large networks (>50 nodes) with a high temporal resolution (~1 msec) (Gow & Caplan, 2012; Milde et al., 2010). Moreover, because it does not depend on the BOLD signal, it is immune to hemodynamic artifacts. This technique has been successfully applied to analysis of unimpaired subjects in a series of experiments examining the interaction between speech perception and lexical processes (Gow & Nied, 2014; Gow & Olson, 2015a; Gow & Olson, 2015b). Here we apply these analyses to track the functional reorganization of task-driven language networks in a left-handed person who became aphasic following a right hemisphere stroke.

PWA with left hemisphere lesions often show increases in task-related activation during the subacute phase of recovery in the right hemisphere regions homotopic to affected left hemisphere regions. The extent of this activation depends on a number of factors including lesion size, location, and the amount of elapsed time since the initial insult (Anglade, Thiel, & Ansaldo, 2014; Karbe et al., 1998; Saur et al., 2006; Thomas, Altenmuller, Marckmann, Kahrs, & Dichgans, 1997). Several studies have shown that right hemisphere damage may impair language processing in some people recovering from left hemisphere aphasia (Barlow, 1887; Cambier, Elghozi, Signoret, & Henin, 1983; Kinsbourne, 1971). These results are often interpreted as evidence that the non-dominant hemisphere is recruited for language processing.

Left-handed aphasics with right hemisphere lesions may provide unique insight into some of the factors that guide the global network changes involved in the recruitment of the non-dominant hemisphere. Despite making up roughly 10% of the general population (Hardyck

& Petrinovich, 1977), left-handed subjects are routinely excluded from neuroimaging studies to reduce variance, and so relatively little is known about the functional organization of language processing in left-handers. However, the few studies that have examined language processing in both right and left-handed people suggest that both groups produce similar left hemisphere activation patterns, but left-handed people produce more right hemisphere activation (Findlay et al., 2012; van der Kallen et al., 1998). This may be connected with the observation that left-handed people who become aphasic after right hemisphere stroke tend to show stronger contralesional activation during the subacute period than their right-handed (left-hemisphere infarcted) counterparts. Moreover, these left-handed individuals show a reduced tendency towards increased perilesional (right hemisphere) activation, even when given contralesional repetitive inhibitory TMS therapy to encourage ipsilesional activity (Heiss et al., 2013). This suggests that people with non-crossed right hemisphere aphasia benefit from having integrated left hemisphere networks that are already well prepared to compensate for damage to the right hemisphere.

This hypothesis raises important questions about both the functional integration of lateralized language processing networks that may be directly resolved using effective connectivity analyses. Effective connectivity refers to patterns of directed influence between individual brain regions. Such analyses may be used to determine whether activation reflects organized and potentially effective processing, or disorganized and likely ineffective processing. Three studies have examined changes in effective connectivity in both hemispheres over the course of recovery from aphasia using model-driven analyses of fMRI data. All of them have focused exclusively on right-handed PWA with left-hemisphere infarcts (Kiran et al., 2015; Sarasso et al., 2010; Vitali et al., 2010). In each case, recovery was linked with strengthening of connections within the preserved portions of left hemisphere language networks. As a rule, the best outcomes were associated with the emergence of patterns of left hemisphere effective connectivity that resembled those found in unimpaired subjects. Critically, all of these studies employed right-handed subjects with left-hemisphere lesions, and so it is unclear whether this characterization applies to people with atypical patterns of language lateralization.

In the present study we tracked changes in task-related effective connectivity accompanying recovery from aphasia in a left-handed woman who became aphasic following a right hemisphere stroke affecting the middle cerebral artery. We assessed patterns of effective connectivity using Kalman-filter enabled Granger causation analysis of high spatiotemporal resolution estimates of cortical activity based on MRI-constrained MEG and EEG data (Gow & Caplan, 2012; Gow & Nied, 2014). Simultaneous MEG and EEG data were collected while the PWA performed an auditory word-picture verification task with semantic and phonological foils that was chosen to probe her impaired auditory word recognition and comprehension (Breese & Hillis, 2004). We tested her during the early stages of the subacute period (1 month post-onset) when activation of the non-dominant (left) hemisphere was relatively sparse, and again in the early stages of the chronic period (7 months post-onset) when task performance had improved and left hemisphere activation was well established. The purpose of the study was to describe the patterns of effective connectivity that supported processing with reorganized hemispheric lateralization. In addition, we tested

a cohort of unimpaired subjects to assess the contributions of both hemispheres to normative performance on the task.

## 2. Results

### Behavioral Results

In the auditory word-picture verification task, control subjects had an average accuracy of 90.2% (standard deviation = 3.3). The PWA performed with 69% accuracy on the first testing session, and 82% on the second.

### Regions of Interest

Our analyses focused on the development of within- and between- hemisphere effective connectivity. Cortical regions of interest (ROIs) with unique temporal patterns of estimated activation were identified using an automatic algorithm (Gow & Caplan, 2012; Gow & Nied, 2014). The algorithm was applied separately to the control subjects' data and the PWA's data gathered at each testing session (see Supplementary Material, Fig. S1 and Table S1). In the control data 38 ROIs were identified, including 21 in the left and 17 in the right hemisphere. In the PWA's data obtained one month after the onset of aphasia (subacute phase) the algorithm identified 25 ROIs, including 11 in the left and 14 in the right hemisphere. In the PWA's data collected 6 months later (chronic phase) 55 ROIs were identified, including 37 in the left and 18 in the right hemisphere. Of the ROIs identified in the control subjects, 15 fell under the same label in the FreeSurfer parcellation atlas with ROIs identified in the PWA's data collected during the subacute phase, and 29 collected during the chronic phase of recovery. In addition to the increase in the number of overlapping ROIs with the control subjects' data, the PWA's additional ROIs at 7 months suggest a combination of increased differentiation of activation patterns within brain structures associated with spoken language processing (supramarginal gyrus, superior temporal gyrus and inferior temporal gyrus), and the recruitment and increased differentiation of regions associated with metalinguistic and compensatory processing (pars triangularis, parahippocampal cortex, posterior and anterior cingulate, superior frontal gyrus).

### Effective connectivity

We examined broad patterns of effective connectivity among four types of within- and between-hemisphere connections (left-to-left, right -to left, right -to-right, and left-to-right) in the three subject cases (control subjects, patient at 1 month, and patient at 7 months) (see Supplementary Figure S2). Connectivity was quantified as the number of time points in directed interactions between ROIs for which the Granger Causation index had a significance level of  $p < 0.05$ . The results are summarized in Fig. 1. A 3-by-4 GLM analysis showed main effects for subject case ( $F(2,178) = 166.7, p < 0.001$ ) and connection type ( $F(3,178) = 166.0, p < 0.0001$ ), with an interaction between subject case and connection type ( $F(6,178) = 125.2, p < 0.001$ ). Focused comparisons of the connectivity patterns in the PWA data at 1 and 7 months were made using the Tukey-Kramer adjustment for multiple comparisons. These showed decreased influence at 7 months compared with 1 month on right-hemisphere ROIs by both other right hemisphere ROIs (right-to-right;  $p < 0.0001$ ), and

left hemisphere ROIs (left-to-right;  $p < 0.0001$ ). This was accompanied by increased influence on left hemisphere ROIs by other left hemisphere ROIs (left-to-left;  $p < 0.0001$ ) and decreased influence by right hemisphere ROIs (right-to-left;  $p < 0.0001$ ). At the time of the first testing, the patient showed more right-to-right hemisphere connections ( $p < 0.0001$ ), but less left-to-right connectivity ( $p < 0.0001$ ) than the control subjects. The patient showed no significant differences with the control subjects in left-to-left or right-to-left directed interactions. By the time of the second testing, the patient showed stronger intrahemispheric connectivity in the left hemisphere ( $p < 0.0001$ ) and weaker intrahemispheric connectivity in the right hemisphere ( $p < 0.001$ ) compared with the controls. This increase in connectivity within the left hemisphere is partially attributable to increases in the number of left hemisphere ROIs. However, the overall proportion of significant left-to-left influences (69%) is greater than would be predicted (45%) solely on the basis of the number of the number of directed pairs of ROIs that form potential left-to-left connections. At the same testing, the patient showed less interhemispheric connectivity compared with the control subjects (right-to-left;  $p < 0.05$ ; left-to-right;  $p < 0.001$ ).

### 3. Discussion

These results demonstrate the application of large-network, high spatiotemporal resolution effective connectivity analyses to single patient data. This approach provides a new tool for examining changing patterns of functional integration that support task performance in people recovering from stroke. The results provide some insight into both the hemispheric division of labor in language processing, and the determinants of adaptive contralesional processing during recovery from stroke. The PWA showed apparent behavioral improvement in the auditory word-picture verification task. The ROI identification relying on the high temporal resolution of the MRI-constrained MEG/EEG estimates of cortical activity allowed analyses suggesting that the apparent improvement was accompanied by an increasingly well articulated left hemisphere network (as evidenced by the number of strongly activated regions with contrastive activation timecourses). Effective connectivity analyses suggest that the emerging left hemisphere network was well-integrated, and influenced by input from both hemispheres. In contrast, the evolving right hemisphere network was less well-integrated, both in terms of patterns of internal influence and influence from the left-hemisphere.

The PWA's task-induced activation, network constituency and effective connectivity patterns at the time of the second testing resembled those of the right-handed controls in some, but not all respects. These suggest increased reliance on left hemisphere structures to perform the matching task. However, the left hemisphere network seen in this early chronic phase of recovery was more highly articulated, with a larger number of strongly activated regions showing temporally discriminable activation patterns (37 versus 21 ROIs), and a pattern of effective connectivity that was more elaborate in the left hemisphere than that seen in control subjects. This network involved the recruitment of brain areas outside of the modal language network including parahippocampal cortex, bilateral superior frontal cortex, and anterior and posterior cingulate reflecting extra-linguistic compensation. The increased functional differentiation of left hemisphere language areas, coupled with the decreased differentiation and network function of right hemisphere structures may suggest that the evolving left

hemisphere network preserves the complementary functional roles of left hemisphere brain regions and their former right hemisphere counterparts.

Several factors may support the development of a highly articulated and well-integrated left hemisphere during the subject's recovery. One factor is the bilateral pattern of processing and effective connectivity associated with normal performance on the task. We hypothesize that this pattern may have been reinforced by a premorbid pattern of bilateral language processing in left-handed individuals. Another likely factor is the contribution of a small set of preserved right superior frontal and anterior parietal structures that developed increasingly strong processing interactions with the strengthening distributed left hemisphere language network. The fact that the right superior frontal gyrus regions have no counterpart in either the normal controls or the PWA when observed one month after onset suggest that these regions play a primarily compensatory role in coordinating processing and perhaps maintaining attention

Although the PWA showed apparent behavioral improvement between the two testing sessions, it is important to note that she did not perform at the same level as unimpaired control subjects. This raises the possibility that while the emergence of the contralesional processing network may have enabled improved performance, still greater improvement could be attained with increased perilesional involvement in processing. The relative success of the contralesional network, measured in terms of behavior, neural activity and network development, may have played a role in the failure of the perilesional network to reassert itself during recovery.

## 4. Method

### 4.1 Participants

The PWA was a 53 year-old left handed woman with normal hearing and vision. Testing using the Edinburgh Handedness Inventory (Oldfield, 1971) showed her to be strongly left-handed (Laterality Quotient = -0.8) before her stroke. Her responses to questions on the inventory were independently confirmed by her spouse. She experienced a right middle cerebral artery infarct that produced two sizeable lesions (Figure 2). Lesion 1 extended in the coronal plane from the head of the caudate and anterior tip of the insula anteriorly to the end of the insula posteriorly. Throughout its extent it affected the head of the caudate, putamen, dorsal part of internal capsule, as well as the ventral parts of external and extreme capsules (Makris & Pandya, 2009). Lesion 2 affected the inferior bank of the superior temporal sulcus, i.e., middle temporal gyrus cortex and the core white matter of the temporo-occipito-parietal region.

Her medical history and MRI scans indicated that she had not had any prior strokes. Clinical notes describe her as showing left sided weakness with slurred speech, significant word-finding difficulty, and "intermittent complete aphasia" in the first week after her stroke. We tested her on two occasions on an auditory word-picture verification task, during which MEG/EEG data were recorded. The first testing occurred 33 days after the stroke, the second 6 months later (204 days after the stroke). At the time of the first testing she presented with frequent phonemic paraphasias, word-finding difficulty, and difficulty producing and

understanding meaningful speech. A behavioral screening battery with subtests from the Psycholinguistic Assessment of Language (PAL) battery (Caplan & Bub, 1990) revealed deficits in phoneme discrimination (77.5% accuracy on voice, 81.8% on place and 42.9% on manner discrimination), and auditory lexical decision (62%). Her performance on written word picture matching was at ceiling (100%). At the time of the second testing, only the word-picture verification task (with MEG/EEG recording) was administered. We also tested 12 unimpaired subjects (5 females) between the ages of 19 and 53 (mean age 24.7). All were self-reported right-handed native English speakers with no visual, auditory or motor impairments that would affect performance on the task. One additional subject was excluded because of poor performance due to a severe cold, and another due to technical problems encountered during data collection.

## 4.2 Procedure

MEG and EEG data were simultaneously collected during the performance of the word-picture verification task in a magnetically shielded room using a 306-channel whole head Neuromag Vector View System (Elekta, Helsinki, Finland). The system was equipped with 70-electrode EEG cap with nose reference and horizontal and vertical electro-oculograms (EOG) used for identifying eye-movement and blink artifacts. The MEG and EEG data were bandpass filtered at 0.1–400 Hz and sampled at 1200 Hz. All subjects underwent anatomical MR imaging after MEG/EEG recording using an MPRAGE sequence in a 1.5 T Siemens Avanto 32 channel TIM system. The imaging methods and parameters were the same as those described in Gow and Olson (Gow & Olson, 2015c).

In the auditory word-picture verification task, the stimuli were 100 imageable monosyllabic CVC words and accompanying line drawings. All words were produced by two speakers (one male, one female) in a quiet room and digitally recorded as 16 bit sound at a sampling rate of 44.1 Hz. These recordings were normalized for intensity, and their duration was manipulated using PRAAT (<http://www.praat.org>) so that all words were 500 ms in duration. Each word was accompanied by a line drawing that either depicted the word (50 items), a semantic associate (20 items), or a phonological foil that differed from the target word by a single phoneme (30 trials balanced by phoneme position). The final stimulus set was identified based on behavioral piloting testing with 19 subjects using a superset of 150 candidate word-image pairs.

Each trial began with the presentation of a spoken word. Two hundred milliseconds after the offset of the spoken word a line drawing was presented on a large projection screen for 500 milliseconds. Participants were instructed to press a button using their non-dominant hand if the picture matched the word they just heard. Up to one second was provided for a response beginning after the onset of the picture probe. There was a 500 ms intertrial interval between the end of the response period and the beginning of the next trial. Testing was conducted in two blocks. Participants heard each of the 100 words once per block, with stimuli equally divided between words produced by the male and female speakers. No pictures were repeated.

The unimpaired control subjects were tested after completing an unrelated task for a different study.

### 4.3 Analysis

All analyses of estimated cortical activation and effective connectivity were performed using the GPS processing stream (<https://www.martinos.org/software/gps>) (Gow & Caplan, 2012). GPS draws on the MNE software package (<https://www.martinos.org/mne/>) to create MRI-constrained minimum-norm estimates of the cortical sources of MEG and EEG data (Hämäläinen & Ilmoniemi, 1994). The MEG/EEG/MRI analysis procedures are described in depth in other work (Gow & Nied, 2014; Gow & Olson, 2015b, 2015c).

The estimates of cortical activation were submitted to Kalman-filter enabled Granger causation analysis (Gow & Caplan, 2012; Milde et al., 2010) to identify patterns of directed causal interaction between a large set of regions of interest (ROIs). Granger analysis is derived from the observation that causes both precede and uniquely predict their own effects (Granger, 1969). In Granger analysis, two types of predictive models are created; unrestricted models that include all variables to predict the behavior of one (included) variable, and restricted models that exclude one variable from that set. One variable is said to Granger cause changes in another if the error term associated the restricted model is significantly larger than the error term associated with the unrestricted model. This is formalized as the Granger causation index (GCi), which is calculated as the log ratio of these error terms (Milde et al., 2010). Our approach relies on Kalman filter methods to create new models at each time point. This approach makes the analysis less sensitive to measurement noise, eliminates the need to make biologically implausible assumptions about the stationarity of evoked brain activity, and makes it possible to assess GCi at every timepoint.

We identified comprehensive sets of ROIs based on the estimated cortical source activation at 100–400 ms after the onset of the spoken words. This time window was selected to capture the interval during which event related potentials associated with early auditory, phonological and lexical-semantic manipulations (e.g., the N1, MMN and N400 components) are typically observed. This interval ended before the presentation of picture probes, minimizing the influence of visual probe interpretation and response selection operations on processing. ROIs were selected automatically to meet Granger causation analysis' assumptions that all likely interacting regions with non-redundant temporal activation patterns are included (see Gow and Caplan, 2012 for complete description). In addition to ensuring the integrity of Granger analyses, this ROI identification algorithm allows for the segmentation of large patches of activated cortex into smaller units with different activation timecourses, suggesting different functional roles. Moreover, because the identification process is entirely data-driven, regions are identified that might not be in model-driven effective connectivity approaches such as dynamic causal modeling. Only trials that produced correct responses were used in ROI selection and effective connectivity analyses. All ROIs were labeled using Freesurfer's automatic parcellation utility based on the Desikan Killiany Atlas (Desikan et al., 2006). Because the ROI selection algorithm is based on the identification of different time courses of the estimated source activity, an increase in the number of ROIs between cases may be interpreted as an increased differentiation of activation patterns.

Granger analyses of the control subject data were performed as described previously (Gow & Nied, 2014; Gow & Olson, 2015b, 2015c). The estimated source activations were



averaged across trials within each control subject and submitted as individual supertrials to the Kalman filter Granger analysis. To accommodate single-subject analysis of the PWA's data, trials were randomly assigned to 10 different bins and averaged to form analogous supertrials for the Kalman Granger analysis. We used an oversampling strategy to ensure that all bins reflected the same number of trials across testing sessions.

We used a bootstrapping technique to create independent null distributions of the Granger measures at each timepoint and for each directed relationship between pairs of ROIs (Gow & Nied, 2014; Milde et al., 2010). Each distribution was based on 2000 re-sampled trials. As a measure of overall connectivity strength we used the cumulative Granger strength obtained by counting the number of GCi values with p-value less than 0.05 based on this bootstrapping technique.

In previous work (Gow & Nied, 2014; Gow & Olson, 2015b, 2015c) we compared patterns of effective connectivity between conditions by defining a common set of ROIs based on the activation data averaged over all conditions, and applying a binomial test to compare the number of time points for each directed connection in each condition that reach achieve a p-value less than 0.05. Given the limited overlap between ROIs found in the independent analyses of the control and the (subacute and chronic) patient data, this strategy would be problematic because the identification of individual ROIs would be subject to potential cross-subject class activation averaging artifacts, and because the overall set of ROIs that were identified would not meet Granger analysis assumption that all potentially meaningful ROIs contribute to the analysis. For that reason we adopted an alternate strategy. ROIs were determined separately for the three subject cases (control, subacute, and chronic), and the relative number of connections in four hemisphere-based connections types (left-to-left, right-to-left, right-to-right, and left-to-right) in each case was considered. Cumulative measures of connection strength were obtained by counting the number of timepoints within each connection type that achieved a Granger strength with a p-value less than 0.05. These data were compared using a 3-by-4 (subject case-by-connection type) general linear model (GLM) least squares model. The dependent variable was the number of significant GCi values among the connectivity types for individual ROIs. Focused comparisons were made using the Tukey-Kramer adjustment for multiple comparisons.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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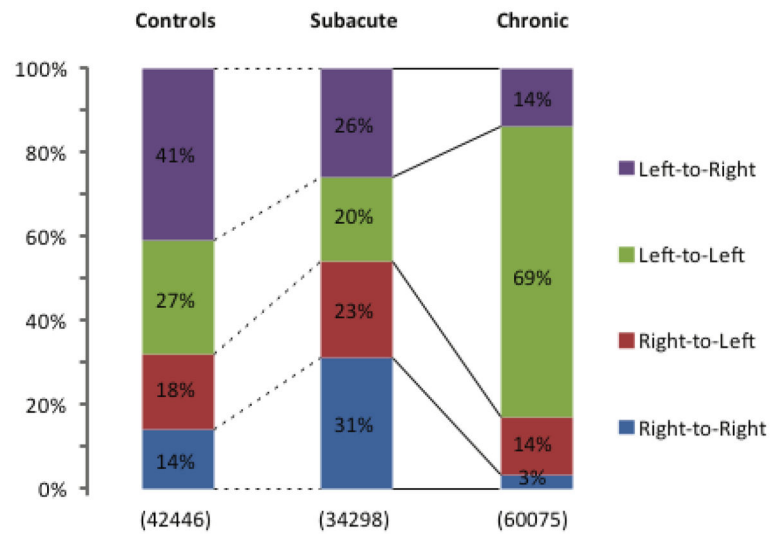
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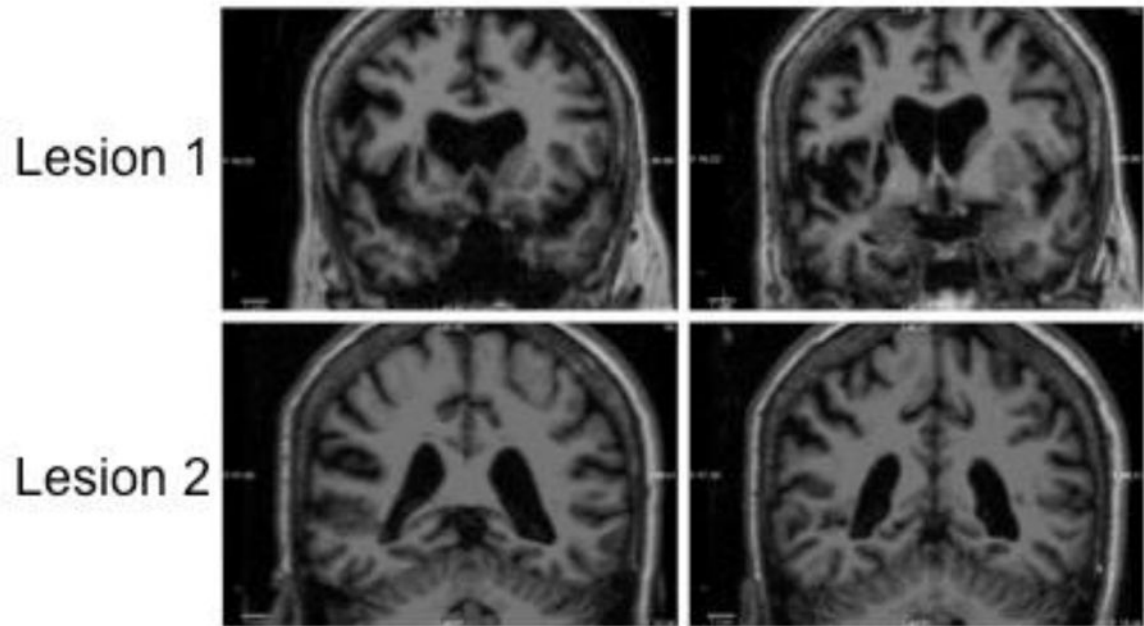
### Highlights

- A left-handed woman became aphasic following right hemisphere MCA stroke.
- During recovery there was a loss in RH and gain in LH ROIs supporting processing.
- During recovery more ROI dynamics drove LH ROIs, and fewer drove RH ROIs
- The resultant network was more left-lateralized than that of right-handed controls



**Figure 1.**

Cumulative effective connectivity within and between hemispheres for right-handed control subjects (*left*), for the patient 1 month after the onset of aphasia (subacute phase, *middle*), and for the patient 7 months after the onset (chronic phase, *right*). Connectivity visualized as the percentage of timepoints that show significant ( $p < 0.05$ ) GCi values. The total number of timepoints with significant GCi values for each connection type is shown in parentheses.



**Figure 2.** Coronal T1-weighted MRI showing the subject's lesions seven months after right middle cerebral artery (MCA) stroke. Images depict the anterior (left) and middle (right) aspect of lesion 1, and the anterior (left) and posterior (right) aspect of lesion 2.