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Short communication

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.

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 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 to 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 s) (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 ms) (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

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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 transcranial magnetic stimulation (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

2.1. 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.

2.2. 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).

2.3. 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 Fig. 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