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# Changes in functional connectivity related to direct training and generalization effects of a word finding treatment in chronic aphasia

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The neural mechanisms that underlie generalization of treatment-induced improvements in word finding in persons with aphasia (PWA) are currently poorly understood. This study aimed to shed light on changes in functional network connectivity underlying generalization in aphasia. To this end, we used fMRI and graph theoretic analyses to examine changes in functional connectivity after a theoretically-based word-finding treatment in which abstract words were used as training items with the goal of promoting generalization to concrete words. Ten right-handed native English-speaking PWA (7 male, 3 female) ranging in age from 47 to 75 (mean = 59) participated in this study. Direct training effects coincided with increased functional connectivity for regions involved in abstract word processing. Generalization effects coincided with increased functional connectivity for regions involved in concrete word processing. Importantly, similarities between training and generalization effects were noted as were differences between participants who generalized and those who did not.



## 1. Introduction

Aphasia is a language deficit which often occurs following a cerebrovascular accident (CVA) of the language dominant hemisphere of the brain. The majority of spontaneous recovery after a CVA occurs within the acute and subacute stages, reaching a plateau during the chronic stage (Cramer, 2008). *Importantly, even in the chronic stage, after spontaneous recovery has ceased, treatment can induce neuroplasticity*. Neuroplasticity related to treatment for aphasia in the chronic phase has been shown in a number of neuroimaging studies in the last decade (e.g., Cornelissen et al., 2003; Fridriksson, Richardson, Fillmore, & Cai, 2012; Marcotte, Perlbarg, Marrelec, Benali, & Ansaldo, 2013; Meinzer et al., 2008; Rochon et al., 2010; van Hees et al., 2014; Vitali et al., 2010).

An important feature of successful therapy in aphasia is generalization from trained to untrained items, leading to more efficient and cost-effective therapies. While many neuroimaging studies have examined treatment-induced neuroplasticity in aphasia, few have systematically examined and reported neural changes associated with behavioral improvements due to both direct training and generalization effects of treatment (Meinzer et al., 2008; Vitali et al., 2010). The current study examines neural changes related to direct training and generalization effects of a theoretically based treatment for word finding difficulties. We hypothesized that changes to the semantic processing system would emerge as modifications in the functional pathways between a distributed set of brain areas, and that such changes would mirror behavioral changes associated with therapy. Given these hypotheses and the relatively large network of brain regions involved in word finding, we adopted a network-based functional connectivity analysis of fMRI data obtained before and after therapy.

While fMRI activation studies provide valuable insight into local effects of treatment-induced neuroplasticity, functional connectivity analyses can capture changes in task-specific coupling of brain areas related to treatment gains, which may not be evident from activation-based contrasts. Analyses of changes in functional connectivity allow researchers to make inferences not only about the coupling among brain regions while subjects engage certain processes, but also about how that coupling is influenced by changes in the experimental context or over time. Examining changes in functional connectivity is relatively new in aphasia treatment research, with only a few studies published to date (Abutalebi, Rosa, Tettamanti, Green, & Cappa, 2009; Marcotte et al., 2013; Sarasso et al., 2010; van Hees et al., 2014; Vitali et al., 2010). These studies utilize techniques such as Structural Equation Modeling (SEM; Sarasso et al., 2010; Vitali et al., 2010) and Dynamic Causal Modeling (DCM; Abutalebi et al., 2009), and examine both resting state (van Hees et al., 2014) and task-based (Abutalebi et al., 2009;

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Marcotte et al., 2013; Sarasso et al., 2010; Vitali et al., 2010) functional connectivity.

These studies have shown increased functional connectivity related to direct training, and in one case, to generalization effects. Using SEM, Vitali et al. (2010) found that direct training effects of a phonological cueing treatment in two patients with phonological anomia were evident immediately following treatment, while generalization effects were observed at a six-month follow-up test, when the trained versus untrained conditions showed similar levels of performance. The authors suggest that these patients eventually adopted a strategy for lexical retrieval of untrained items that mirrored their training-induced lexical retrieval strategy.

Based on these recent studies of changes in functional connectivity following treatment in aphasia, we hypothesize that direct training effects will coincide with increased functional connectivity within networks engaged by the trained items (Abutalebi et al., 2009; Sarasso et al., 2010; Vitali et al., 2010) and that generalization effects will coincide with increased functional connectivity in networks engaged by the untrained items (Vitali et al., 2010). Here we adopt a graph theoretic approach, novel to aphasia treatment research, to test these hypotheses related to treatment-induced changes in functional connectivity in the language system.

Graph theory has been used to characterize complex systems ranging from social networks to molecular interactions and is gaining popularity in cognitive neuroscience as it provides meaningful insights into the organization and dynamics of complex networks such as the brain. Neuroimaging studies that utilize graph theory have begun to identify changes in intrinsic network properties, for example, after motor training (e.g., Sami & Miall, 2013). However, such approaches are currently underutilized in the study of neuroplastic changes related to treatment outcomes, and no study to date has used graph theoretical measures to characterize changes in task-based networks after language treatment. The current study utilizes node degree, which expresses the importance of a region via the quantity of its incoming and outgoing connections within a network, and allows a comparison across participants, while taking into account individual variability of network composition (functional regions of interest included within the network).

One hurdle in examining neural changes related to direct training and generalization effects, especially in a word-finding treatment, is that both the trained and the untrained items are expected to activate the same regions in the semantic network. This is especially true in picture-naming paradigms, which necessarily use concrete words for both trained and untrained items. One way to separate the effects of direct training and generalization is to choose stimuli that have been shown to be dissociable, both behaviorally and neurophysiologically, such as abstract and concrete words. Recent neuroimaging research suggests that abstract and concrete words are preferentially processed in different cortical regions (Binder, Desai, Graves, & Conant, 2009; Wang, Conder, Blitzer, & Shinkareva, 2010). In a meta-analysis of 17 imaging studies, Binder et al. (2009) found preferential activation for concrete concepts in bilateral angular gyrus (AG), left fusiform gyrus (L FFG), left dorsomedial prefrontal cortex (L DMPFC) – which includes portions of superior medial gyrus (SupMed), superior frontal gyrus (SFG), and middle frontal gyrus (MFG) – and left posterior cingulate cortex (L PCC). Preferential activation for abstract concepts was found in left inferior frontal gyrus (L IFG) and left anterior superior temporal sulcus (L aSTS).

In a separate meta-analysis, Wang et al. (2010) examined 19 functional neuroimaging studies of abstract and concrete concept processing, ten of which overlapped with the Binder et al. (2009) study. They found consistent activation in left precuneus (L PCN), L PCC, L FFG, and left parahippocampal gyrus (L PHG) for the [concrete > abstract] contrast and activation in L IFG, L aSTG, left anterior middle temporal gyrus (L aMTG), and left posterior middle temporal gyrus (L pMTG) for the [abstract > concrete] contrast. Similar to the Binder et al. (2009) study, abstract words preferentially activated verbal regions while concrete words preferentially activated nonverbal regions, although the exact regions differed somewhat.

In our own work, we have shown that training abstract words (i.e., *justice*) in a particular context-category (i.e., *courthouse*) promotes generalization to concrete words (i.e., *jury*) in the same context-category, but not vice versa (Kiran, Sandberg, & Abbott, 2009; Sandberg & Kiran, 2014). This treatment is based on the complexity account of treatment efficacy (Thompson, Shapiro, Kiran, & Sobecks, 2003), and suggests that training semantic features of abstract words – the more complex items – promotes spreading activation to a large distributed network of associated words, including concrete words, whereas training semantic features for concrete words – the less complex items – results in spreading activation to a more confined network of related concrete words. We hypothesize that training abstract words will increase functional connectivity of the abstract network and that generalization to concrete words will increase functional connectivity of the concrete network. However, the underlying neural mechanism of generalization from abstract to concrete words is currently unknown.

Thus, the goal of this study is to shed light on the underlying neural mechanism of generalization from abstract to concrete words by comparing the functional connectivity patterns of abstract and concrete word processing in PWA before and after a successful word generation treatment. This study builds upon the current literature by systematically examining both direct training and generalization effects of treatment, incorporating a functional connectivity analysis, and utilizing graph theoretical measures to characterize changes in functional connectivity related to treatment gains. We also use a sample size of 10 PWA in response to the prevalence of single- or multiple-case studies with fewer than eight PWA, which makes it difficult to examine consistent patterns across PWA. Additionally, we include a no-treatment within-patient control subgroup, as only one study to date has included a no-treatment patient control, albeit not within-patient controls (Rochon et al., 2010), and patient controls, especially within-patient controls are an ideal baseline for measuring treatment gains.

Our specific aims and hypotheses were as follows:

(a) *Examine changes in functional connectivity during a no-treatment control period*. We analyzed scan-to-scan changes in functional connectivity for a subgroup of PWA who participated in a no-treatment control period before beginning treatment as a baseline comparison for the effects of treatment. Based on Rochon et al. (2010) and Meinzer et al. (2006), who found scan-to-scan stability in activation for healthy control subjects, we expected scan-to-scan stability in functional connectivity for this subgroup of PWA during the control period, as all PWA were in the chronic stage of recovery.

(b) *Examine changes in functional connectivity related to direct training effects of treatment*. We analyzed pre- to post-treatment changes in functional connectivity for the trained items (abstract words) for the group of PWA who improved on the trained abstract words. Based on Abutalebi et al. (2009), Sarasso et al. (2010), and Vitali et al. (2010), we expected direct training effects to coincide with increased functional connectivity in the abstract word network. Based on the neuroimaging literature of abstract and concrete words (e.g., Binder et al., 2009; Wang et al., 2010), we expected that the regions with the largest network-level changes would include L IFG, L STG, and/or L MTG.